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SPECIAL ARTICLE

Breast cancer germline multigene panel testing in mainstream oncology based on clinical—public health utility: ESMO Precision Oncology Working Group recommendations

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Background: With widening therapeutic indications, germline genetic testing is offered to an increasing proportion of patients with breast cancer (BC) via mainstream oncology services. However, the gene set tested varies widely from just *BRCA1/BRCA2* through to 'pan-cancer' panels of nearly 100 genes. If a germline pathogenic variant (GPV) is detected, the BC proband and other family GPV-carriers may be offered interventions such as risk-reducing surgery and intensive surveillance over decades for the various cancers linked to that gene.

Methods: The European Society for Medical Oncology (ESMO) Precision Oncology Working Group established an international expert working group (EWG) in BC germline genetics. This EWG firstly established a framework of criteria by which to evaluate each breast cancer susceptibility gene (BCSG) for potential inclusion on a breast cancer multigene panel test (BC-MGPT) for universal mainstream testing for BC cases. Next, the EWG scored BCSGs for impact regarding (i) BC risk estimation, (ii) clinical actionability and (iii) cancer-related mortality.

Results: The group agreed that they would constitute a BC-MGPT based on net clinical—public health utility, as quantified by likelihood of impact on cancer-related mortality. Judged as of high or moderate impact on this basis were six BCSGs: *BRCA1, BRCA2, PALB2, RAD51C, RAD51D* and *TP53* (for BC diagnosed <40 years of age), with possible addition of *BRIP1*. While potentially informative for BC risk estimation, *CHEK2* and *ATM* were judged to offer insufficient evidence for improving cancer-related mortality. The EWG recommended strongly against inclusion of 'syndromic' genes such as *STK11*, *PTEN*, *NF1* and *CDH1*.

Conclusions: With expanded germline testing in patients with BC (and cascade testing into families), the number and nature of resultant GPV-carriers identified will be dictated by the genes included on the upfront BC-MGPT. The potential

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harms, opportunity and economic costs of decades of surveillance of multiple organs and risk-reducing surgeries for GPV-carriers should be justified by strong evidence of meaningful improvement in cancer-related mortality (or health-related quality of life).

Key words: breast cancer, multigene panel test, mainstream, germline, cancer-related mortality

INTRODUCTION

The only breast cancer susceptibility genes (BCSGs) that had been identified at the turn of the century were those of sufficiently high penetrance to have generated a linkage signal.[1,2] Clinical genetic testing was expensive, low throughput and accordingly restricted to a small number of families with multiple cases of breast (BC) and ovarian (OC) cancers (for *BRCA1* and *BRCA2*) or characteristic syndromic features (for genes such as *PTEN* and *STK11*). Testing involved just the specific gene(s) that was most likely to 'confirm' the suspected diagnosis already manifest in the patient or family. Predictive testing of the germline pathogenic variant (GPV) was then offered to family members to provide a dichotomous result of their being either at very high risk of or spared from the familial predisposition.

Subsequent linkage analyses in hereditary breast—ovarian cancer (HBOC) families were unfruitful, confirming there to be no additional genes with a risk—frequency profile comparable to *BRCA1*/*BRCA2*.[3] With accordant shift to case-control studies of genes in candidate pathways (often related to DNA repair), association with BC has been reported for multiple additional genes over the following two decades. *PALB2*, *CHEK2* and *ATM* were established early as BCSGs with BC risks being (reasonably) reproducible over time.[4-8] By contrast, only with large population-based case-control studies (and meta-analysis thereof) have we been able to confirm the association of GPVs in *BARD1*, *RAD51C* and *RAD51D* with BC. Inconsistency of earlier association study results is unsurprising, given the very low frequency of GPVs in these genes and their subtype-specific association with triple-negative breast cancer (TNBC).[9-11] These well-powered population-based case-control studies (BRIDGES and CARRIERS) have also refuted a multitude of other previously reported BC associations, including genes involved in DNA repair pathways (e.g. *NBN*, *RAD50*, *RECQL*, *XRCC2*, *XRCC3*, *SLX4* and *GEN1*) and mismatch repair genes.[12-16] Notably, for *TP53*, *PTEN*, *STK11* and *CDH1*, BCSGs identified via their distinctive syndromes of pleomorphic susceptibility to rare cancers (hereafter termed 'syndromic BCSGs'), the association signals in these population-based BC case-control studies were markedly lower than estimates from earlier familial-based analyses.

The initial identification of *BRCA1* and *BRCA2* was based on epidemiologically observed co-susceptibility for BC and OC. Additional studies in *BRCA1/BRCA2* families have suggested association with prostate and pancreatic cancers; relative risks (RRs) are of more modest magnitude than for BC and OC but reproducible for *BRCA2*. The other BCSGs functioning in DNA repair pathways with *BRCA1/BRCA2* (*PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, *BARD1*) have thus also been extensively studied for association with these cancers (with varying reproducibility of findings) and have been grouped under the umbrella of 'HBOPP (hereditary breast—ovarian—prostate—pancreatic cancer) genes'. Numerous associations with other rare and common cancers have been reported from studies of both the HBOPP and syndromic BCSGs.

Clinical management protocols for GPV-carriers have evolved, aimed at mitigating the elevated risks for BC and other implicated cancers via surveillance, prevention and early detection (SPED) interventions. Surveillance for GPV-carriers typically (i) is of greater frequency, (ii) is initiated at a younger age and continued for a greater duration and (iii) involves multi-modal approaches (e.g. combining serum biomarker testing with imaging modalities), as compared with the population-level screening (if any) recommended for the given cancer type. Programmes of population-level screening are typically only implemented following randomised trials in which cancer-specific mortality benefit has been established (quantified against false-positive and overdiagnosis rates). By contrast, the intensive surveillance recommendations for GPV-carriers have typically evolved via expert opinion and modelling (due to lack of direct evidence from longitudinal clinical studies, let alone randomised trials).

Over the past decade, embedding of next generation sequencing (NGS) within diagnostic laboratories now means that the wet-laboratory cost for testing of 200 genes differs little from 2 or 20 genes. This technological economy has catalysed a dramatic shift in clinical testing practice. Previously, expensive, low-throughput testing necessitated that clinicians undertake individualised selection of the gene(s) for testing based on patient phenotype and clinical context (even, for example, strategic sequencing of *BRCA2* ahead of *BRCA1*). Now, we typically 'tick-box order' a routine 'panel' of genes pre-defined as relevant to BC susceptibility, a so-called breast cancer multigene panel test (BC-MGPT). The number and range of genes included on such a BC-MGPT varies widely between countries and providers (varying from 7 to 37 genes) (Table 1). Depending on local protocols and reimbursement, a newly diagnosed BC patient may instead be offered a pan-cancer panel (typically >50 genes) to obviate other testing requirements emerging downstream.

Extended therapeutic indications for poly (ADP-ribose) polymerase inhibitors (PARPi) have increased the proportion of patients with BC offered germline testing, adding momentum to arguments for broader or even universal germline testing for all female BC presentations. Indeed, the American Society of Clinical Oncology (ASCO) recently

Table 1. Survey of genes included on 12 commercial and 3 health-service multigene panel tests designated for breast cancer (± ovarian/gynaecological cancers)

	Panel type	Total genes	*BRCA1*	*BRCA2*	*PALB2*	*CHEK2*	*ATM*	*RAD51C*	*RAD51D*	*BARD1*	*TP53*	*NF1*	*PTEN*	*CDH1*	*BRIP1*	*STK11*	*MLH1*	*MSH2*	*MSH6*	*PMS2*	*APC*	*BAP1*	*BLM*	*BMPR1A*	*CDK4*	*CDKN2A*	*DICER1*	*EPCAM*	*FAM175A*	*FANCC*	*FANCM*	*GREM1*	*MEN1*	*MITF*	*MRE11*	*MUTYH*	*NBN*	*POLD1*	*POLE*	*RAD50*	*RECQL*	*RNF139*	*SMAD4*	*SMARCA4*	*XRCC2*
Ambry Genetics; BRCANext	B-G/O	18	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔		✔	✔	✔	✔								✔									✔							
Centogene; CentoBreast	B	27	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔							✔	✔		✔			✔		✔	✔	✔			✔			✔	✔
Check4Cancer (BreastHealthUK); *BRCA1* & *BRCA2* Plus	B	11	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔			✔																												
Everything Genetics; 12 Gene Breast Cancer Panel	B	12	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔		✔																												
Fulgent Diagnostics; Breast Cancer Focus	B	13	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔																												
GeneDx; Breast/Gyn Cancer Panel	B-G/O	24	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔								✔		✔	✔					✔		✔		✔				
Illumina; AmpliSe BRCA Plus, Extended HBOC Research Panel	B-G/O	11	✔	✔	✔	✔	✔	✔	✔		✔			✔																						✔							✔	
Informed Genomics (UK); Breast Cancer Panel	B	11	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔			✔																												
Invitae; Breast Cancer STAT Panel	B	9	✔	✔	✔	✔	✔				✔		✔	✔		✔																												
Oxford Gene Technology (OGT); SureSeq	B	7	✔	✔	✔	✔	✔				✔		✔																															
Paragon Genomics; CleanPlex® HBOC Panel v2	B-G/O	37	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔			✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Randox; Genetic Breast and Ovarian Cancer Risk	B-G/O	8	✔	✔	✔	✔	✔				✔		✔	✔																														
Radbound UMC; DNA-first hereditary breast cancer	B-G/O	10	✔	✔	✔	✔	✔	✔	✔	✔			✔		✔																													
Servei Català de la Salut; Perfil genètic de les síndromes hereditàries de càncer en l'adult i pediatria	B-G/O	15	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔		✔	✔	✔																									
UK NHSE National Test Directory; R208	B	7	✔	✔	✔	✔	✔	✔	✔																																		

B, breast; B-G/O, breast plus gynaecological/ovarian.

recommended that germline genetic testing be offered routinely to all female BC diagnoses age <65 years (and also to many BC cases age >65 years).[17]

However, as an increasing proportion of BC cases are tested upfront, more GPVs will be detected in the probands. In turn, there will be more relatives with GPVs identified on familial cascading. In turn, there will be commensurate expansion in the volume of SPED interventions offered to probands and their relatives. The resultant volume of GPV-carriers identified, the scale of concomitant SPED activity and the overall impact on cancer mortality will be predicated on the number and specifics of the genes included upfront in the BC proband panel.

Aims

An expert working group (EWG) was convened at the recommendation of the European Society for Medical Oncology (ESMO) Precision Oncology Working Group, via individual invitation based on expertise and representation across health care settings. The overarching aim for the EWG was to consider which genes should be included on a germline BC-MGPT, in the context of anticipating incipient expansion of patients with BC being offered germline genetic testing relating to therapeutic indications.

The EWG established in early discussions that the criteria by which genes are currently included for germline testing, as per Box 1, are (i) clinical validity (i.e. GPV is associated with BC and therefore can inform BC risk estimation) and (ii) clinical actionability (i.e. existence of SPED recommendations for associated cancers). The EWG agreed that while these two parameters in combination may broadly be taken to be a proxy for impacting survival (mortality), available evidence was often lacking or contrary to this presumption. The EWG thus agreed on a first aim to consider BCSGs for potential inclusion on a BC-MGPT judged against each of these three measures of impact/utility, namely (i) BC risk estimation, (ii) actionability for SPED interventions for associated cancers and (iii) improving cancer-related mortality.

Box 1. Measures of clinical impact/utility for evaluation of genes for potential inclusion on a germline breast cancer multigene panel test (BC-MGPT)

(i) **Clinical validity:** Is there a robust reproducible association for GPVs with breast cancer? If so, the gene can be judged to offer utility in informing BC risk estimation.
(ii) **Clinical actionability:** Are there society or national clinical guidelines advising SPED interventions for the cancers (reported to be) associated with GPVs in this gene? If so, the gene can be judged to offer utility in regard to 'clinical actionability' (or 'altering of clinical management').
(iii) **Cancer-related mortality benefit[a]:** Is there evidence that the oncological interventions and/or SPED interventions implemented in GPV-carriers reduce the likelihood of dying from the corresponding cancer(s)[a] without causing undue harms? If so, the gene can be judged to confer 'net clinical—public health utility'.[b]

BC, breast cancer; EWG, expert working group; GPV, germline pathogenic variant; SPED, surveillance, prevention and early detection.

[a]All-cause mortality benefit (thus including potential off-target harms and competing risks) may be considered a more rigorous metric of impact.
[b]Net clinical—public health utility would also encompass evidenced benefit in health-related quality-of-life outcomes, but these are seldom robustly measured.

The EWG next sought to define more clearly the 'routine-mainstream' BC probands for whom our recommended BC-MGPT would be applicable. The EWG recognised that eligibility criteria for BC-MGPT relating to age, BC histology/characteristics and/or personal and/or cancer family history are implemented in most health care settings, but that these vary widely. The EWG agreed that we should seek to define a single, universal BC-MGPT that would be applicable for (virtually) all eligible BC cases, meaning that:

(i) the BC-MGPT would be applicable regardless of the health care settings and of threshold of eligibility (i.e. whether 10% or 100% of presenting BC cases were eligible for testing).
(ii) the genes on the BC-MGPT would be a sufficient and complete test for >99% of these eligible BC patients. The BC-MGPT should thus be readily implementable in the urgent diagnostic mainstream oncology setting (without additional algorithms of individualised patient assessment being required to determine gene selection).
(iii) additional genetic assessment would only be indicated in a tiny minority (<1%) of BC cases. These individuals could be identified non-urgently downstream of the routine early BC-MGPT via questionnaire and referred to clinical genetics.

We thus use the term 'routine-mainstream' BC probands to describe the totality of recently diagnosed BC patients being offered this BC-MGPT in a mainstream oncology setting (encompassing stricter, looser or unrestricted eligibility).

The EWG agreed that in the context of (i) incipient expansion of germline genetic testing in BC and (ii) the scale of SPED activity across a family consequent from a GPV being identified in the proband, greater focus was required regarding evidenced impact on cancer-related mortality. The EWG thus agreed on a second aim to make explicit recommendations regarding genes for inclusion on a BC-MGPT, based on evaluation of impact on cancer-related mortality (hereafter termed clinical—public health utility). Namely that the BC-MGPT should include genes on the basis of available evidence that (i) associated cancer risks and concomitant SPED intervention number will result in improvement to cancer mortality for GPV-carriers and/or (ii) systemic oncology management offers survival benefit in the proband. While the EWG sought also to consider health-related quality of life alongside cancer-related mortality, robust evidence of this type is extremely infrequent.

Objectives

The EWG established four objectives by which to address their aims:

(i) To review genes currently included on BC-MGPTs to identify a set of genes for review
(ii) To define and assemble evidence relevant for per-gene evaluations
(iii) To undertake individual evaluations (by each EWG member) of each gene against a range of different measures of impact/utility
(iv) To integrate individual-level evaluations to provide consensus recommendations regarding genes for inclusion for a BC-MGPT applicable for 'routine-mainstream' BC cases in mainstream oncology, as judged by net clinical—public health utility (evidenced impact on cancer-related mortality)

METHODS

We convened four meetings of the EWG, with development of recommendations based on quantitative polls conducted between the meetings (see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.04.012).

OUTCOMES FROM OBJECTIVES

Objective 1: To review genes currently included on BC-MGPTs

The EWG identified 12 BC-MGPTs offered by commercial providers and 3 from health services which were specified for either (i) BC, (ii) BC and/or OC or (iii) BC and/or gynaecological cancers (Table 1). Through this review, the EWG agreed on a core set of 13 widely included BCSGs for evaluation, which we grouped into two broad categories:

1. **HBOPP-related genes:** *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D* and *BARD1*. These genes are grouped together on the basis of (i) being identified through common pathways related to DNA repair and/or (ii) broad commonality of spectrum of additional reported cancer associations (potentially including ovarian, prostate and/or pancreatic cancer). *BRIP1,* an ovarian-only susceptibility gene, was subsequently included by the EWG for consideration.
2. **Rare 'syndromic' genes:** *TP53*, *CDH1*, *NF1*, *STK11* and *PTEN*. These genes are grouped together on the basis of each causing a rare cancer susceptibility syndrome for which non-malignant features would typically precede cancer onset (*NF1*, *STK11* and *PTEN*) and/or the constellation/sub-types of rare cancers are typically distinctive (*TP53*, *CDH1*).

Objective 2: To assemble evidence for consideration in per-gene evaluations

The EWG agreed on five categories of evidence for consideration within the per-gene evaluations (for additional details of EWG review, see Table 2 and Supplementary Tables S1-S4, available at https://doi.org/10.1016/j.annonc.2025.04.012).

1. *Frequency of GPVs in unselected (population-type) BC and magnitude of BC association*

The EWG surveyed GPV frequencies for the 13 genes in unselected (population-type) BC versus population controls (UK Biobank, BRIDGES, CARRIERS, Table 2). The EWG noted for *BRCA1* and *BRCA2* high odds ratios (ORs) for BC association with enrichment for TNBC and younger-onset disease (in particular for *BRCA1*). The EWG recognised a high but lesser BC risk for *PALB2* (OR 4-5) with some enrichment for TNBC. The EWG noted *ATM* and *CHEK2* to have moderate association with BC (OR 2-3), with risk largely restricted to estrogen receptor (ER)-positive disease. The EWG noted low GPV frequencies and very modest metrics for association in unselected BC cases for *RAD51C* and *RAD51C* (OR $<$ 2), albeit with enrichment for TNBC.

The EWG noted that for the 'syndromic' BCSGs, the frequency of GPVs in unselected BC cases was very low and only modestly greater than that in the population, resulting in quite modest ORs for association. However, while these population-based BC studies are spared the upward bias in association estimates inherent to familial, phenotype-based ascertainment, these BC series are likely depleted for precisely the atypical and/or very young-onset types of BC cases characteristically linked to these genes.[18]

The EWG agreed that a very low GPV frequency in unselected (population-type) BC would not preclude inclusion of the gene on the BC-MGPT. The EWG noted nevertheless that clinical testing of genes in contexts in which there is a very low rate of true GPVs results in an elevated ratio of variants of uncertain significance (VUSs) to true GPVs. This has implications for complex, time-consuming variant interpretation, challenging clinical management and patient anxiety.

2. *Per-gene associations with other cancers*

Co-aggregation of BCs and OCs had been empirically observed long before linkage analyses enabled localisation of *BRCA1* and *BRCA2* and quantitation of commensurately high penetrance for these cancer types. For *BRCA1* the risk to age 80 years for developing OC is estimated at ∼44% [standardised incidence ratio (SIR) ∼50] and for *BRCA2* ∼17% (SIR ∼14).[19]

Studies associating *BRCA1*/*BRCA2* with other cancer types, as well as those investigating cancer associations for other BCSGs, have been more challenging. Studies based on familial/phenotypic ascertainment may suffer upwardly biased estimates of effect size; there may also be inflated cancer incidences against background rates where extra pre-emptive surveillance has been implemented. Early case-control studies were often distorted due to differential molecular analyses for controls versus cases with added variability due to case definition and the spectrum of variants included. However, overarching these methodological limitations is the impact of statistical variation where (i) effect sizes are modest, (ii) GPVs are comparatively rare

Table 2. **Frequency of pathogenic variants, cancer associations and efficacy of gene-stratified systemic oncological management for 13 breast cancer susceptibility genes**

	Evaluation of unselected BC (meta-analysis of BRIDGES, CARRIERS, UKBIOBANK)[11]					**Ovarian cancer association**	**Mortality benefit: systemic oncological management (stratified by gene GPV)**	**Other cancer associations (non-breast/ovarian)**		
	Frequency of pathogenic variants		Association of GPVs with breast cancer					Tumours reported as associated	Instability between studies for reported associations	Uncertainty of risk estimates due to ascertainment
	In unselected BC cases	In the control population	Overall odds ratio for BC	Triple-negative BC enrichment	ER-positive BC enrichment					
BRCA1	0.99% 1 in 101	0.088% 1 in 1134	8.73 (7.47-10.20)	✔✔✔✔		✔✔✔✔✔	✔✔✔✔✔	Prostate, stomach, pancreas, male breast	✔✔	✔
BRCA2	1.48% 1 in 68	0.25% 1 in 400	5.68 (5.13-6.30)	✔		✔✔✔✔	✔✔✔✔	**Prostate, pancreas, male breast,** stomach, (melanoma)	✔✔✔	✔
PALB2	0.54% 1 in 187	0.14% 1 in 726	4.30 (3.68-5.03)	✔✔		✔✔	✔	**Pancreas, male breast**	✔✔	✔
CHEK2	1.36% 1 in 73	0.58% 1 in 172	2.40 (2.21-2.62)		✔✔✔✔			**Prostate,** kidney, thyroid, (osteosarcoma, colorectal)	✔✔✔✔	✔
ATM	0.76% 1 in 132	0.35% 1 in 287	2.16 (1.93-2.41)		✔✔✔✔	✔		**Prostate, pancreas**	✔✔✔✔	✔
BARD1	0.15% 1 in 672	0.062% 1 in 1621	2.34 (1.85-2.97)	✔✔✔				[nil of note]		
RAD51C	0.11% 1 in 913	0.055% 1 in 1819	1.53 (1.15-2.04)	✔✔✔		✔✔✔		[nil of note]		
RAD51D	0.093% 1 in 1079	0.048% 1 in 2100	1.76 (1.29-2.41)	✔✔✔		✔✔✔		[nil of note]		
TP53	0.054% 1 in 1844	0.0073% 1 in 13 606	3.62 (1.98-6.61)			✔		**Sarcomas, adrenocortical, neurological,** other epithelial	✔✔✔	✔✔✔✔
PTEN	0.027% 1 in 3755	0.0067% 1 in 14 902	2.63 (1.38-5.02)					**Thyroid, kidney, endometrial, colorectal, hamartomas**	✔✔✔	✔✔✔✔✔
NF1	0.068% 1 in 1470	0.033% 1 in 3068	2.01 (1.43-2.83)					**Neurofibromas, (mainly benign) neurological**	✔✔	✔✔✔✔✔
STK11	0.0087% 1 in 11 525	0.0019% 1 in 52 157	1.60[a] (0.48-5.30)					**Hamartomas, gonadal, pancreas,** other epithelial	✔✔✔	✔✔✔✔✔
CDH1	0.037% 1 in 2668	0.015% 1 in 6658	2.01 (1.25-3.24)					**Diffuse gastric**	✔	✔✔✔✔✔

Associated cancers reported as per EWG consensus (bold: well established; non-bold: less well established; brackets: reported but equivocated; see Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.04.012, for source references. Other fields (✔✔✔✔✔: highest); scored as per EWG consensus.

BC, breast cancer; ER, estrogen receptor; EWG, expert working group.

[a]Data available for UK Biobank and BRIDGES only.

and/or (iii) the cancer type is of low population frequency and/or late onset.

The EWG noted robust reproducible associations with OC for *RAD51C* and *RAD51D* (OR 6-9; risk to age 80 years 11%-13%).[20,21] However, for other HBOC genes, there has been less reproducibility for reported associations across studies. *PALB2* and *ATM* have been more frequently associated with OC with risks approximately two- to fourfold elevated (Table 2, Supplementary Tables S3 and S4, available at https://doi.org/10.1016/j.annonc.2025.04.012).[20,22-27]

Of the multitude of cancer associations reported in studies of *BRCA1/BRCA2* families, elevated risks of male breast, prostate and pancreatic cancers in *BRCA2* families have been the most reproducible. Recent prospective analyses in *BRCA2* GPV-carriers from the international CIMBA consortium estimate risk to age 80 years at 2.5% for pancreatic cancer [RR 3.34, 95% confidence interval (CI) 2.21-5.06] and at 27% for prostate cancer (RR 2.22, 95% CI 1.63-3.03).[28] Because of their links to *BRCA1/BRCA2*, pancreatic and prostate cancers have been a particular focus of study for the other HBOC genes. Although with considerable variability between studies, the EWG noted relatively consistent reported association with pancreatic cancer for *ATM* GPVs (OR/RR 4-8), with less reproducible estimates of association for *PALB2*.[25,29-32] Albeit with widely varying estimates, prostate cancer has also been relatively consistently reported for *ATM* and *CHEK2,* with recent analysis in the UK Biobank suggesting respective ORs of 2.35 (95% CI 1.78-3.11) and 1.92 (95% CI 1.59-2.32).[25]

For rare cancer types linked to highly rare 'syndromic' susceptibility genes, well-powered case-control studies using unselected case series are not typically feasible. Accordingly, for the 'syndromic' BCSGs, working risk estimates for the implicated rare cancers are typically still based on phenotype-driven ascertainment of families. The EWG agreed there to be great uncertainty regarding true prospective risks of rarer cancers when a GPV is identified outside of the characteristic personal/familial phenotype, as illustrated in several recently published population-based penetrance analyses.[33,34]

3. *Evidence of cancer-related mortality benefit from available SPED interventions*

The EWG noted that where there was direct evidence from longitudinal (albeit largely non-randomised) clinical studies, these data typically related to carriers of *BRCA1/BRCA2* GPVs only. Thus, the EWG noted requirement for extrapolation of these data to GPV-carriers of other genes (necessarily taking into account differences in cancer risk and subtype associations).

The EWG noted consistent demonstration of sizeable OC-specific mortality benefit for risk-reducing bilateral salpingo-oophorectomy (RRBSO) in *BRCA1/BRCA2* GPV-carriers, with benefit in BC-specific mortality and all-cause mortality also reported in some studies.[35-39] The EWG noted absence of data for mortality benefit from RRBSO for genes such as *RAD51C/RAD51D/BRIP1*. Based on (i) the sizeable OC-specific mortality benefit from RRBSO for *BRCA1/BRCA2* GPV-carriers and (ii) modelling analyses that the mortality benefit from RRBSO would extend to those with a lifetime risk of OC of $\geq$5%, the EWG concurred that mortality benefit from RRBSO could reasonably be extrapolated to *RAD51C*, *RAD51D* and *BRIP1* GPV-carriers (albeit with a commensurately lower predicted impact on mortality).[40,41]

The EWG noted recently published internationally amalgamated follow-up studies of breast magnetic resonance imaging (MRI) in unaffected women with GPVs in *BRCA1/BRCA2*. The EWG noted a statistically significant sizeable hazard ratio for BC mortality reduction for *BRCA1* only (albeit the absolute number of deaths was overall low).[42] Studies of risk-reducing bilateral mastectomy (RRBM) have typically reported dramatic reduction in the incidence of BC but have generally reported a low number of events (deaths) meaning that in most studies the incidence reduction has failed to translate into mortality benefit.[43-46] The EWG noted the Dutch multicentre HEBON study of unaffected GPV-carriers in which BC-specific mortality was significantly lower in the RRBM group compared with the MRI group for both *BRCA1* and *BRCA2* (but only statistically significant for *BRCA1*).[43] The EWG agreed that published data overall supported RRBM and MRI as likely conferring BC-related mortality benefit for *BRCA1* GPV-carriers; the EWG permitted extrapolation of possible benefit to *BRCA2*, *TP53* and *PALB2*, albeit that direct evidence was lacking. The EWG noted that the treatment-related improvements in BC outcomes over recent decades necessarily have significantly extended the follow-up required to quantify mortality benefit from RRBM and MRI surveillance.

The EWG noted the lack of clinical data quantifying mortality impact for enhanced breast surveillance or RRBM in unaffected *CHEK2/ATM* GPV-carriers. Based on (i) data for *BRCA2* versus *BRCA1*, (ii) lower BC risks of *CHEK2/ATM* compared with *BRCA2*, (iii) predominant association of *CHEK2/ATM* with ER-positive BC and (iv) recent modelling analyses, the EWG concurred that the BC-related mortality benefit for enhanced breast surveillance (above routine breast screening) or RRBM for unaffected *CHEK2/ATM* GPV-carriers was likely to be at best minimal.[47]

Regarding the impact of bilateral mastectomy in management of the presenting BC in *BRCA1/BRCA2* GPV-carriers, the EWG noted evidence supporting reduced incidence of new BCs but mixed data supporting mortality impact. The EWG noted that recent international analysis from 11 countries in *BRCA1* GPV-positive BC cases failed to show mortality benefit for bilateral mastectomy versus unilateral surgery.[48] The EWG concurred that for BC probands with *CHEK2/ATM* GPVs (where BC risks are lower and association is with ER-positive BC), mortality benefit from bilateral mastectomy was therefore likely to be at best minimal. The EWG noted the wide variation in reported estimates of elevation in contralateral BC risk associated with GPVs in *CHEK2/ATM*.[49-51]

The EWG noted that public health bodies such as the United States Preventive Services Task Force (USPSTF) and UK National Screening Committee (UK-NSC) currently recommend against screening at population level for either prostate cancer (due to excessive overdiagnosis) or pancreatic cancer (due to lack of proven impact on mortality of available technologies).[52,53] The EWG noted that while regimens of surveillance for pancreatic and prostate cancer are widely implemented for GPV-carriers of various BCSGs, evidence is currently lacking as to whether these surveillance regimens confer any net benefit in cancer mortality and/or adequate mitigation of cancer overdiagnosis in these groups.[54-56]

The EWG noted various intensive protocols for multi-organ system surveillance implemented for individuals with GPVs in 'syndromic' BCSGs. The EWG noted that such surveillance regimens had (unsurprisingly) never been evaluated via randomised trials, meaning that perceived earlier detection may just represent lead time rather than any genuine improvement in mortality. Likewise, it remains impossible to quantify the extent and impact of overdiagnosis.

4. *Potential physical harms, psychological implications and problems with uncertainty*

The EWG noted that mainstream oncology clinicians (and consequently their patients) may not appreciate the potential harms of genetic testing and downstream management, in particular (i) the potential physical harms from long-term intensive regimes of surveillance, including overdiagnosis and overtreatment, (ii) negative physical, aesthetic and/or psychosexual sequelae from risk-reducing surgery, (iii) the psychological burden of lifelong genetic assignation of elevated cancer risk and (iv) opportunity costs.[57] The EWG were in strong agreement that the benefit—harm trade-off varied according to (i) the robustness of cancer risk estimates, (ii) the clinical context in which the genetic test was carried out and (iii) quality of evidence underpinning the mortality benefits of concomitant SPED interventions.[58,59] The EWG agreed that harms would most commonly outweigh benefits where aggressive surveillance/surgery was implemented for GPV-carriers of 'syndromic' BCSGs ascertained in contexts in which cancer risks were highly uncertain. For example, for a GPV in *CDH1* or *STK11* detected in a BC proband in the absence of any manifestation of relevant familial disease and/or syndromic features.[59-63]

5. *Evidence for gene-based stratification in systemic oncological management*

The EWG noted that clinical trials in the metastatic and adjuvant setting have demonstrated impact on progression-free survival and, in the adjuvant setting, overall survival from use of PARPi and/or platinum following stratification by *BRCA1/BRCA2* mutational status.[64,65] The EWG noted also demonstration of improved clinical outcomes in the metastatic setting from treatment stratification by *PALB2* mutational status.[66,67]

Objective 3: To generate scores for genes against different measures of impact/utility

Following EWG review of the evidence items assembled for Objective 2, the 18 members of the EWG independently awarded integer scores of 0-5 for each gene for the impact of identifying GPV in the context of testing of 'routine-mainstream' BC probands. Thirteen (subsequently 14) genes were scored for their impact/utility regarding:

(i) estimation of BC risk in the proband (contralateral breast management)
(ii) estimation of BC risk in unaffected female relatives
(iii) alteration of clinical management (actionability) in the proband
(iv) alteration of clinical management (actionability) in unaffected relatives
(v) clinical—public health utility: evidenced impact on cancer-related mortality in the proband and/or relatives. Evidence of improved health-related quality-of-life outcomes would also be included in this category but are seldom robustly measured.

The mean and interquartile range for the scores of the 18 contributing EWG members are presented in Table 3.

Objective 4: To generate consensus recommendations for genes to be included on a BC-MGPT

Reflective of the consensus scoring, the EWG agreed that a BC-MGPT based on evidenced likelihood of cancer-related mortality benefit (clinical—public health utility) for application in 'routine-mainstream' BC probands would include the following genes: *BRCA1*, *BRCA2*, *PALB2*, *TP53* (<40 years of age), *RAD51C*, *RAD51D* and *BRIP1*.

Evaluated in regard to clinical—public health utility, the EWG recommended against inclusion on the BC-MGPT of *ATM*, *CHEK2*, *BARD1*, *PTEN*, *NF1*, *CDH1* and *STK11* (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.04.012, for additional EWG discussion).

The only additional germline genetic testing in the diagnostic BC pathway recommended by the EWG would be for the very small proportion of BC cases exhibiting features strongly suggestive of one of the rare 'syndromic' genes, and only after (non-urgent) detailed review within clinical genetics. Namely, testing of *PTEN*, *NF1* or *STK11* where relevant syndromic manifestations of disease were present in the proband and of *CDH1* and *TP53* (in women over 40 years of age) where a strong history of relevant canonical cancers is present in the family or patient.

BRIP1, an OC susceptibility gene, was recommended by the EWG for inclusion on the BC-MGPT on the basis of extending the utility of the BC-MGPT to enable more comprehensive evaluation of OC susceptibility (see 'Discussion').

Table 3. Mean and interquartile range of individual scores from 18 EWG members for five measures of impact/utility for 14 genes

	Prediction of breast cancer risk				Altering management				Cancer mortality impact (proband and relatives)	
	in BC proband (contralateral)		in unaffected female relatives		in BC proband		in unaffected relatives			
BRCA1	5.00	(5-5)	5.00	(5-5)	5.00	(5-5)	5.00	(5-5)	4.94	(5-5)
BRCA2	4.89	(5-5)	4.94	(5-5)	4.89	(5-5)	4.89	(5-5)	4.83	(5-5)
PALB2	4.17	(4-5)	4.22	(3.25-5)	4.17	(4-5)	4.47	(4-5)	3.44	(3-4)
CHEK2	2.83	(2-3)	3.00	(3-3)	2.06	(1.25-2.75)	2.44	(2-3)	1.33	(1-2)
ATM	2.17	(2-2.75)	2.72	(2-3)	1.94	(1-2)	2.28	(2-3)	1.22	(0.25-2)
BARD1	1.78	(1-2)	2.11	(1-3)	1.50	(1-2)	1.72	(1-2)	1.06	(1-1)
RAD51C	1.94	(1-2.75)	2.17	(2-3)	3.11	(2-4)	3.11	(2-4)	2.17	(1-3)
RAD51D	1.94	(1-2.75)	2.11	(2-2.75)	3.11	(2-4)	3.11	(2-4)	2.17	(1-3)
TP53 (under 40)	4.56	(4.25-5)	4.33	(4-5)	4.44	(4-5)	4.39	(4-5)	3.22	(3-4)
PTEN	2.78	(2-3)	2.67	(2-3)	3.28	(2.25-4.75)	3.22	(2.25-4)	1.22	(0.25-2)
NF1	1.89	(2-2)	1.72	(2-2)	2.00	(1-3)	2.00	(1-3)	0.83	(0-1)
STK11	1.67	(1-2)	1.72	(1-2)	2.44	(2-3)	2.44	(2-3)	1.00	(0-1.75)
CDH1	2.06	(1.25-3)	2.50	(2-3)	3.11	(2.25-4)	3.06	(2.25-4)	1.94	(1-3)
BRIP1	0.94	(1-1)	1.00	(1-1)	3.28	(3-4)	3.28	(3-4)	2.44	(2-3.75)

The impact/utility relates to identification of a GPV on testing of the gene in 'mainstream-routine' BC proband. Mean scores are presented to 1 dp: 4-5 (very high, dark green), 3-3.99 (high, pale green), 2-2.99 (moderate, dark orange), 1-1.99 (low, pale orange), 0-0.99 (very low, uncoloured). *TP53* was scored specifically in the context of testing only BC probands diagnosed <40 years of age.
BC, breast cancer; EWG, expert working group; GPV, germline pathogenic variant.

DISCUSSION

The EWG members were in agreement that genetic testing in patients with BC (i) was likely to expand in volume, (ii) will increasingly be carried out in the mainstream oncology setting and (iii) requires delivery in a time-sensitive fashion to inform immediate surgical and systemic oncological management. The EWG agreed that within mainstream oncology it is already becoming infeasible to implement at scale complex protocols involving (i) selection of genes for testing based on detailed family history scoring rules, (ii) algorithmic sequential gene testing and (iii) time-sensitive assessment within clinical genetics ahead of testing. Such time-consuming complexities have incentivised clinicians to default to larger pan-gene panels. This strategy obviates clinician concerns around 'missing something' present within the family history (or that might subsequently emerge) and is particularly attractive (i) in settings of 'single-shot reimbursement' for genetic testing, (ii) regarding potential litigiousness for failed adherence to society recommendations and (iii) to seemingly offer a better 'value-for-money' service.

The EWG recognised however that many mainstream oncologists (physicians/surgeons) managing patients with BC and ordering these upfront panel tests would typically have minimal experience in the downstream management of the unaffected familial GPV-carriers. These oncologists therefore might not appreciate the management complexities regarding uncertainty of cancer risks and consequent management quandaries, long-term (lifelong) surveillance, reproductive decisions and concomitant potential psychological issues for GPV-carriers in particular for 'syndromic' genes.

Using panels of an increasingly large number of genes, alongside testing of these large panels in an increasing proportion of BC probands, and then cascading out to their family members will have exponential implications for the proportion of the population assigned as being a carrier of a GPV in one gene or the other. Given the intensive protocols of decades-long, multi-organ surveillance typically triggered by assignment of individuals as GPV-carriers, there are also substantial considerations regarding health care costs and resource allocation.

Such concerns would be addressed to some extent by our recommendations for inclusion on the upfront BC-MGPT of only those genes with evidence of likely clinical—public health utility (cancer-related mortality benefit). The EWG has delineated a seven-gene BC-MGPT based on net clinical—public health utility, which we propose as appropriate and sufficient for >99% of 'routine-mainstream' BC cases, noting simple binary inclusion/exclusion of *TP53* based on age at BC diagnosis.

There was full consensus of the EWG that testing of rare 'syndromic' BCSGs should not be carried out in 'routine-mainstream' BC cases, on the basis that identifying GPVs in this context offers minimal clinical—public health utility and is likely of net harm. The EWG agreed that rare 'syndromic' BCSGs should only be tested where strong active indicators of a syndromic diagnosis existed. This small group of BC cases could be identified via simple questionnaire and referred for clinical genetics review downstream of their

routine upfront BC-MGPT. Given that across BRIDGES, CARRIERS and UK Biobank, the GPV frequency for *TP53, PTEN*, *NF1*, *STK11* and *CDH1* combined is <0.2% (1 in 520), the proportion of BC cases requiring referral for assessment in clinical genetics will likely be <1%.

BRCA1 and *BRCA2* were agreed unanimously by the EWG as being of very high clinical—public health utility (driven primarily by the OC risk). Scoring for *PALB2* was lower, but still attained a mean rating of 3.44/5 (high), on the basis of TNBC association, moderate OC risk and possible therapeutic potential. *TP53* was included for testing in BC cases <40 years of age only, both to reduce detection of clonal haematopoiesis of indeterminate potential and also to target ascertainment. Nevertheless, there were residual concerns within the EWG relating to uncertainty regarding the penetrance for rare cancers (especially paediatric) even in this context of ascertainment. Several EWG members advocated for clinical genetics review ahead of any testing of *TP53*; counter-weighing were concerns regarding expediency of mainstream testing at the time of BC diagnosis.

RAD51C and *RAD51D* each attained mean scores for clinical—public health utility within the moderate range (2.17). The EWG equivocated over their inclusion on the BC-MGPT, recognising the weak overall BC association (OR < 2) and very low detection rate of GPVs in unselected BC. However, with a focus on clinical—public health utility, the EWG was motivated by the opportunity for OC prevention (albeit that evidence of mortality benefit was extrapolated from studies in *BRCA1/BRCA2* GPV-carriers rather than directly observed). Also factored into this assessment was the low morbidity of RRBSO in postmenopausal women, modest numbers of GPV-carriers and lack of equivocal additional cancer associations for these genes. As a logical sequel to inclusion of *RAD51C* and *RAD51D*, the EWG noted *BRIP1* as having a very similar risk profile for high-grade serous OC to *RAD51C*/*RAD51D*. Recognising absence of significant association with BC, the EWG saw potential merit in inclusion of *BRIP1* on the BC-MGPT (thus reflecting how BC and OC are tightly interwoven in regard to genetic risk assessment). Furthermore, the EWG members noted from recent data (and their own experience), a negligible frequency of mismatch repair gene GPVs in unselected OCs.[20] Accordingly, the EWG hypothesised that the proposed BC-MGPT of *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D* and *BRIP1* (with *TP53* duly excluded) could equivalently serve as an OC susceptibility panel.

Notably excluded from our BC-MGPT are *CHEK2* and *ATM*. *CHEK2/ATM* results have in recent years been keenly incorporated within the surgical consultation to 'explain' (in part) why the BC arose and to inform individualised contralateral risk estimation. However, disparate published estimates for contralateral risk notwithstanding, as discussed under Objective 2iii, the BC-related mortality impact of risk-reducing contralateral mastectomy in *CHEK2/ATM* GPV-carriers is likely to be at best minimal.[49-51] While direct evidence from longitudinal surveillance studies in *CHEK2/ATM* GPV-carriers is lacking, again it is unlikely that RRBM or regimens of additional surveillance (sometimes including MRI) for unaffected *CHEK2*/*ATM* GPV-carriers add significant absolute BC mortality benefit over and above population-level breast screening (see Objective 2iii, Supplementary Tables S1-S3, available at https://doi.org/10.1016/j.annonc.2025.04.012).[47]

The EWG noted furthermore that the reported associations for *ATM/CHEK2* with OC were not sizeable or reproducible. The risk estimates for other cancers have also varied widely over time; for prostate and pancreatic cancers, the concomitant surveillance regimens lack evidence for net benefit in cancer-related mortality (see Supplementary Tables S1 and S4, available at https://doi.org/10.1016/j.annonc.2025.04.012). The EWG noted that the population frequency of *CHEK2* GPVs is relatively high (even just considering truncating variants where RR for BC is better established as >2). In addition, there are a number of common *CHEK2* missense variants for which BC RR <1.5 (e.g. I157T and S428F), the widespread reporting of which creates additional clinical management quandaries. Thus, the EWG judged testing *CHEK2/ATM* to offer low clinical—public health benefit overall in regard to impact on cancer-related mortality (albeit agreeing that the results could be informative for BC risk estimation, in particular as part of multifactorial risk analysis).

BARD1 was likewise deemed of low clinical—public health benefit for inclusion on the BC-MGPT, based on its very low GPV frequency, modest BC risk and lack of association with OC.

Considerations of resource allocation are important across health care systems, in both high- and low-middle-income economies. Regardless of setting, the greatest system-level benefit is likely to be gained from maximising identification of GPV-carriers for the genes for which SPED interventions offer the highest cancer-related mortality benefit. If, for a given gene, associated cancer risks are not robust and/or evidence is lacking that concomitant SPED interventions result in improvement to cancer-related mortality for the GPV-carriers, testing of that gene may just result in clinical harms and diversion of health care resource. Especially within a competitive diagnostic and clinical marketplace, the scaled economies of NGS testing have rendered it attractive to offer increasingly large panels of genes. However, the economic (and other) costs of downstream management of a GPV will generally dwarf by scales of magnitude the cost of identifying the GPV, especially where decades of surveillance are initiated for multiple organ systems for multiple family members. Recognising the inevitable cautions about 'putting genies back in bottles', this incipient expansion in BC germline testing is a critical inflection point at which to reflect. As the reach of germline genetic testing is further expanded, circumspection regarding clinical—public health utility, evidenced impact on mortality, avoidance of harms and health-economic benefit are of course applicable beyond the context of testing in BC patients.

DISCLOSURE

MIA reports receipt of a fee for participation in advisory board from Pfizer; receipt of a fee as an invited speaker from AstraZeneca, Daiichi Sankio, MSD, Roche. JB reports receipt of a fee as an invited speaker from AstraZeneca; educational programmes to institution from AstraZeneca, MSD; financial interest to institution as a steering committee member from AstraZeneca; financial interest to institution as a local principal investigator from MedSir. EC reports receipt of a fee for participation in advisory board from AstraZeneca, Bayer, Daiichi Sankyo, Janssen, Eli Lilly, Medscape, MSD, Novartis, Pfizer; receipt of a fee as an invited speaker from Astellas, AstraZeneca, Janssen, Medscape, PeerVoice, Pfizer; receipt of a fee for writing engagement from Pfizer; financial interest from receipt of research grants to institution from Bayer, Janssen, Pfizer; receipt of a fee as a steering committee member from Janssen, Pfizer, Telix; financial interest to institution as a local principal investigator from AstraZeneca, Janssen, Macrogenics, MSD, Pfizer. GC reports receipt of a fee for participation in advisory board from AstraZeneca, BMS, Celcuity, Daiichi Sankyo, Exact Sciences, Gilead, Eli Lilly, Menarini, Merck, Pfizer, Roche, Veracyte, Ellipsis; receipt of a fee as an invited speaker from AstraZeneca, Daiichi Sankyo, Novartis, Pfizer, Roche; receipt of a fee for writing engagement from Pfizer; receipt of funding to institution for running phase I studies from Astellas, AstraZeneca, Blueprint Medicine, BMS, Daiichi Sankyo, Kymab, Novartis, Phylogen, Roche, Sanofi; receipt of a research grant to institution for running an investigator-initiated trial from Merck; receipt of a fee to institution as a coordinating principal investigator from Relay Therapeutics; non-financial interest for advisory role as an officer in Consiglio Superiore di Sanità, Italian National Health Council as an Advisor for Ministry of Health, as an Editor-in-Chief of the ESMO Open, in EuropaDonna as a Member of the Scientific Council, in EUSOMA as a Member of the Advisory Council and in Fondazione Beretta. SMD reports receipt of a fee for providing consultancy from GSK, Intellia; no financial interest to institution as a local principal investigator from AstraZeneca. DGE reports receipt of a fee for participation in advisory board from EverythingGenetic Ltd, Recursion, Springworks, Syanatra; receipt of a fee for writing engagement from AstraZeneca. WDF reports no financial interest for a leadership role in organising a biennial BRCA symposium which is supported by AstraZeneca. He reports holding a research grant from AstraZeneca. HH reports receipt of a fee for participation in advisory board from AstraZeneca; no financial interest for leadership role as a Chair of the UK Cancer Genetics Group. NH reports non-financial interest for leadership role in the European Commission as a Chair of the European Reference Network Genetic Tumour Risk Syndromes (ERN GENTURIS). JNYY reports non-financial interest from receipt of a research grant to institution from AstraZeneca. MR reports receipt of a fee for participation in advisory board from MyMedEd; receipt of a fee as an invited speaker from Clinical Care Options, MJH Holdings, Physician's Education Resource; receipt of a fee for review of guideline pathways from Change Healthcare; financial interest to institution as a co-principal investigator from Merck; financial interest to institution as a local principal investigator from Artios Pharma, AstraZeneca, Merck; financial interest to institution as a local co-principal investigator from Merck, Pfizer; no financial interest as a steering committee member from AstraZeneca, Merck; no financial interest for advisory role from Foundation Medicine, Tempus Labs, Zenith Pharmaceuticals; no financial interest for editorial services from AstraZeneca, Merck. CT reports receipt of fees to charities for participation in advisory board from Roche and as an invited speaker from AstraZeneca. BW reports receipt of a fee for participation in advisory board from BMS, Celgene, Incyte, Rafael, RedHill, Roche, Shire/Baxalta; receipt of a fee as an invited speaker from Amgen, AstraZeneca, Bayer, BMS, Celgene, Chugai, Falk, GSK, Janssen, Lilly, Merck, MSD, QuIP GmbH, Roche, Servier, Sirtex, Taiho; receipt of a fee for an expert testimony from Janssen; receipt of travel support from Bayer, Celgene, Janssen, RedHill, Roche, Servier, Taiho; non-financial interest from receipt of research grant both personal and to institution from Roche; non-financial interest for serving as an officer in AIO-Arbeitsgemeinschaft Internistische Onkologie (Germany); non-financial interest for advisory role in EU Commission—DG RTD as a member of the EU Commission Mission Board for Cancer, non-financial interest for advisory role in German Federal Ministry of Education and Research, Member Forum Zukunftsstrategie. All other authors have declared no conflicts of interest.

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