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Impact of NICE Guideline NG241 'Ovarian Cancer: identifying and managing familial and genetic risk' on a regional NHS family history and clinical genetics service

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ABSTRACT

Background NICE Guideline NG241: identifying and managing familial and genetic risk of ovarian cancer (OC) was published by the National Institute for Health and Care Excellence (NICE) in March 2024. NG241 advises germline genetic testing of genes predisposing to OC in unaffected individuals with an OC family history at different mutation likelihood thresholds depending on age and sex, ranging from 2% to 10% likelihood of finding a germline pathogenic variant (GPV). Prior to implementation of NG241, updates to the NHS England National Genomic Test Directory would be required. Clinical genetics services have to consider equity of access to assessment and testing across all familial cancer types, best use of their limited resources and other factors such as complexity of delivery of clinical pathways.

Methods We analysed data from 8011 patients who provided digital family histories to the South West Thames Centre for Genomics between October 2019 and June 2024.

Results We estimate 527/782 (68%) females and 28/77 (36%) males would meet test criteria for NICE NG241. We estimate we would reject 2919/5485 (53%) females and 135/1208 (11%) males with the same likelihood of carrying a GPV, but with a breast cancer rather than OC family history. Testing the familial OC cohort at a universal 5% threshold in OC families would detect ~11 carriers for 229 tests compared with ~8 carriers for 278 tests following NG241 criteria.

Conclusion Our data highlight additional factors needing to be considered before the NICE Guideline NG241 can be implemented by regional genetics services.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Identifying unaffected individuals at genetic risk of developing cancer is known to improve clinical outcomes by facilitating access to screening, prevention and early detection programmes. The National Institute for Health and Care Excellence (NICE) published NICE Guideline NG241: identifying and managing familial and genetic risk of ovarian cancer in March 2024. These guidelines recommend changes to germline genetic testing pathways across the UK.

WHAT THIS STUDY ADDS

⇒ NICE guidelines are developed on the basis of health economic analysis and do not take into account broader issues around implementation into the healthcare system. This study uses data from a UK regional genetics service with a population of around 3.8 million people to analyse the real-world impact of full implementation of NICE Guideline NG241 by considering required changes to the national infrastructure and implications for clinical and administrative resource and equity of access.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study demonstrates the potential challenges that arise when implementation of NICE guidelines is not feasible within current National Health Service service delivery. This study provides data which can be used by the National Genomic Medicine Service and UK Clinical Genetics Services to enable development of robust, equitable and resourced testing pathways to broaden access to testing for cancer susceptibility genes.

INTRODUCTION

In March 2024, the National Institute for Health and Care Excellence (NICE) published guidance on identifying and managing familial and genetic risk of ovarian cancer (OC), NICE Guideline NG241.[1] This is the first NICE guideline specifically for familial OC, although individuals with a family history of OC were already partly indirectly covered by the NICE Guideline CG164: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer.[2] Following NG241 guideline publication, there followed an article in the *British Medical Journal* aimed at primary and secondary care providers which stated 'Refer for genetic counselling and testing people who have a first or second degree relative diagnosed with OC…'.[3]

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NICE Guideline NG241 advises undertaking germline genetic testing of genes predisposing to OC in unaffected individuals with a family history of OC at different mutation likelihood thresholds depending on their age and sex, ranging from 2% to 10% likelihood of finding a germline pathogenic variant (GPV). The rationale for this age/sex stratification is that these meet NICE health economic thresholds for implementation.[1] Individuals considered to be at increased risk can be offered the option of surgery to significantly reduce the chance of OC. The guidelines specifically state that the eligibility criteria apply only to those with a first-degree or second-degree relative (FDR/SDR) with OC and do not apply in families with other cancers which can also be caused by GPV in the same genes, such as breast, pancreatic or prostate cancer. The guidelines recommend confirmation of the OC diagnoses in the family due to high rates of misreporting of OC diagnoses and the improvement in accuracy through cancer registry confirmation.[4 5]

Testing for heritable GPVs in cancer susceptibility genes in the NHS England is only accessible through the National Genomic Medicine Service (GMS). The GMS specifies who is eligible for genetic testing through the National Genomic Test Directories (NGTD)[6 7] and who can request the testing. Of note, while diagnostic testing (genetic testing undertaken in patients with cancer) is offered in the mainstream (typically through oncology and surgery), due to the complexities of the implications in unaffected individuals, those without cancer are currently only offered genetic testing via regional clinical genetic services.

NHS England does not fund laboratories to provide genetic testing outside of the scope of the NGTD. Similar pathways specifying specific clinical criteria to access genetic testing also exist in the devolved nations.[6] For patients to access genetic testing according to the new NICE Guideline NG241, the NGTD and/or equivalent guidelines would need to be updated accordingly. Therefore, clinical genetics services cannot currently offer testing according to the recommendations in NICE Guideline NG241. Discrepancies between what is currently available in the National Health Service (NHS) clinical service versus NICE recommendations can lead to significant frustrations for patients and difficulties for clinicians.

Updates to the NGTD to increase access to testing can be requested via a formal update process.[7] For cancer susceptibility genes this process is coordinated by the UK Cancer Genetics Group[8] in collaboration with UK-wide clinical cancer genetics services. The review committee then considers the resource implications, any potential impact on equity and the clinical benefit of these requests before rejecting the proposal or updating the NGTD accordingly.

At time of writing (August 2024), the NGTD germline OC panel (R207) contains the following genes associated with a predisposition to OC: *BRCA1, BRCA2, BRIP1, PALB2, MLH1, MSH2, MSH6, RAD51C, RAD51D*. Currently there is not an available risk assessment model which can calculate the likelihoods of a GPV for all the genes on this panel to map to the NICE Guideline NG241. The closest approximation of likelihood of finding a variant in a gene included on R207 is through use of the CanRisk/BOADICEA tool[9–12] which calculates the likelihood of identifying a clinically actionable variant in *BRCA1, BRCA2, BRIP1, PALB2, RAD51C* and *RAD51D*. This approach is not unreasonable given that in unselected OC cases, clinically actionable variants in the mismatch repair genes (*MLH1, MSH2, MSH6*) are rare[13] but CanRisk will underestimate pick-up in families with additional Lynch-related tumours.

All women with a diagnosis of high-grade non-mucinous epithelial OC can already access R207 germline genetic testing, as their likelihood of identifying a pathogenic variant is greater than the 10% testing threshold regardless of family history. Women with a breast cancer (BC) diagnosis must currently meet criteria either based on their personal diagnosis (age <40, triple negative <60 or bilateral status <60) or additional family history reaching 10% mutation likelihood threshold prior to being offered germline genetic testing. These eligibility criteria are specified in the NGTD.

To provide some evidence for the NGTD review process, and to enable any potential service development work to be undertaken, the South West Thames Centre for Genomics (SWTCG) analysed real-world data from patients referred to their service for family history assessment collected over 55 months using a digital tool for family history collection, the Family History Questionnaire Service (FHQS).[14] We analysed the number of R207 germline genetic tests which could be offered plus the estimated carrier pick-up for the following categories of individual:

1. Unaffected patients *with* an FDR/SDR with OC who would meet the new genetic testing criteria outlined in NICE Guideline NG241.
2. Unaffected patients *without* an FDR/SDR with OC who would meet the genetic testing criteria outlined in NICE Guideline NG241 but would be excluded from meeting testing eligibility by not having a relative with OC.
3. All adult patients (≥18) at a 5% mutation likelihood from the following groups:
   a. Unaffected patients *with* an FDR/SDR with OC.
   b. Unaffected patients *without* an FDR/SDR with OC.
   c. Affected patients with invasive BC diagnosed aged 40–49 in the UK.

This final category was analysed to look at equity across patient groups, with a simplified universal assessment criterion in all adults. The 5% threshold was set as this approximates to the overall mutation pick-up in NG241 and the minimum mutation likelihood for women with BC between 40 and 49,[15] but can be easily universally applied regardless of sex/age/cancer status. Testing below the age of 30 would enable carriers of high-risk variants (in *BRCA1, BRCA2* or *PALB2*) to potentially enter breast screening from age 25 and therefore has clinical utility.

METHODS

Region and cohort

The SWTCG serves a population of approximately 3.8 million people across South West London, Surrey and West Sussex. In October 2019, SWTCG implemented a patient-facing online tool for collection of personal and family history of cancer to enable risk analysis, the FHQS.[14] This cohort of patients comprises all patients who were referred to SWTCG or the aligned Virtual Family History Clinic Service from 1 October 2019 to 31 May 2024 who completed the FHQS after their NHS referral. This cohort represents individuals concerned about their family history of cancer who sought advice from their general practitioner or secondary care provider who then requested expert analysis from a family history assessment service. It only includes patients who responded to the request for online family history information. FHQS asks patients about their sex assigned at birth and their preferred gender.

Risk assessment

Risk assessment was performed using the CanRisk/BOADICEA tool[9–12] on 10 June 2024. FHQS generates CanRisk input files from the data provided by patients allowing batch generation of CanRisk output. Mutation probabilities were obtained under

the OC model for *BRCA1, BRCA2, BRIP1, PALB2, RAD51C* and *RAD51D*. The OC model was used even for patients with a personal or family history of BC to allow direct comparison between groups. No analysis of mutation probability was undertaken of other genes on the R207 panel (*MLH1, MSH2, MSH6*).

OC confirmations

In order to estimate the accuracy of reporting of family history of OC, records were ascertained for all patients inputting into FHQS that they had a first-degree or second-degree family member(s) with OC between 1 April 2024 and 31 June 2024. Where confirmation of the diagnosis had been requested through the National Cancer Registration and Analysis Service (NCRAS)[16] these results were reviewed. NCRAS submissions can only be fulfilled without consent for deceased patients.

BC incidence

The average number of new cases of BC in females per year was taken from Cancer Research UK data 2017–2019.[17]

RESULTS

8011 patients completed FHQS between October 2019 and June 2024. 932/8011 (12%) reported at least one FDR/SDR with OC with a total number of 1094 reported relatives with OC. 7552/8011 (94%) patients were aged 30 or older and mutation likelihood and test eligibility could be assessed against NICE Guideline NG241. Review of NCRAS submission data from April 2024 to June 2024 identified 28 fulfilled requests for information from deceased relatives. OC was confirmed in 14/28 (50%). 10/28 (36%) had a confirmed different diagnosis, most commonly cervical cancer, and 4/28 (14%) had no NCRAS record available. All included patients stated their preferred gender was the same as their sex assigned at birth and are therefore referred to as females and males throughout.

1. *Unaffected patients meeting test criteria for NICE NG241*

859/7552 (11%) (782 females, 77 males) reported at least one FDR/SDR with OC, of which we extrapolated 50% would be confirmed. 527/782 (68%) females and 28/77 (36%) males (555 in total) met test criteria for NICE NG241, leading to an estimated 278 genetic tests over 55 months, or approximately five per month (figure 1, table 1). This equates to a half-day clinic per month within a clinical genetics service for discussion of genetic testing. We would expect to identify 8/278 (3%) patients with a clinically actionable variant, taking into account numbers referred from each group and mutation likelihood in different sex/age groups (figure 1, table 1).

2. *Unaffected patients at equivalent mutation thresholds but without an FDR/SDR with OC*

2919/5485 (53%) females and 135/1208 (11%) males met testing criteria on mutation likelihood but did not have an FDR/SDR with OC. According to NICE Guideline NG241 these individuals would not be eligible for testing despite the comparable level of risk. The majority of risk was conferred by familial BC diagnoses. Without performing any cancer confirmations this would include 3054 people in total in 55 months (figure 1). This equates to ~55 per month and ~11 half-day clinics per month (as a minimum) which would be expected to identify ~100 carriers.

3. *Simplifying eligibility criteria to universal testing at 5% mutation likelihood*

a. *Testing at 5% mutation likelihood for unaffected patients with an FDR/SDR with OC*

Making the same assumptions around cancer confirmations as in (1) but assessing all adult (≥18) patients equally, 229 patients are eligible for testing, and we would identify approximately 11 carriers (figure 1, table 1). This would be around four patients per month equating to a half-day clinic per month.

b. *Testing at 5% mutation likelihood for patients without an FDR/SDR without OC*

2338 females and 184 males meet testing criteria prior to any cancer confirmations being undertaken, with approximately 126 carriers identified (figure 1). This would equate to ~46 patients per month.

c. *Testing at 5% mutation likelihood for patients with BC*

All women with a BC diagnosis under the age of 50 meet a testing threshold of 5% mutation likelihood.[14] Approximately 4884 women between the ages of 45 and 49 are diagnosed with BC in the UK each year.[17]. 2573 women between 40 and 44 are diagnosed with BC in the UK each year[17] (figure 1). With a population of 3.8 million people, SWTCG covers ~6% of the UK population, with ~447 newly diagnosed women with BC per year or ~37 per month. If we assume at least a 5% mutation pick-up across this cohort,[14] testing would detect around 22 carriers.

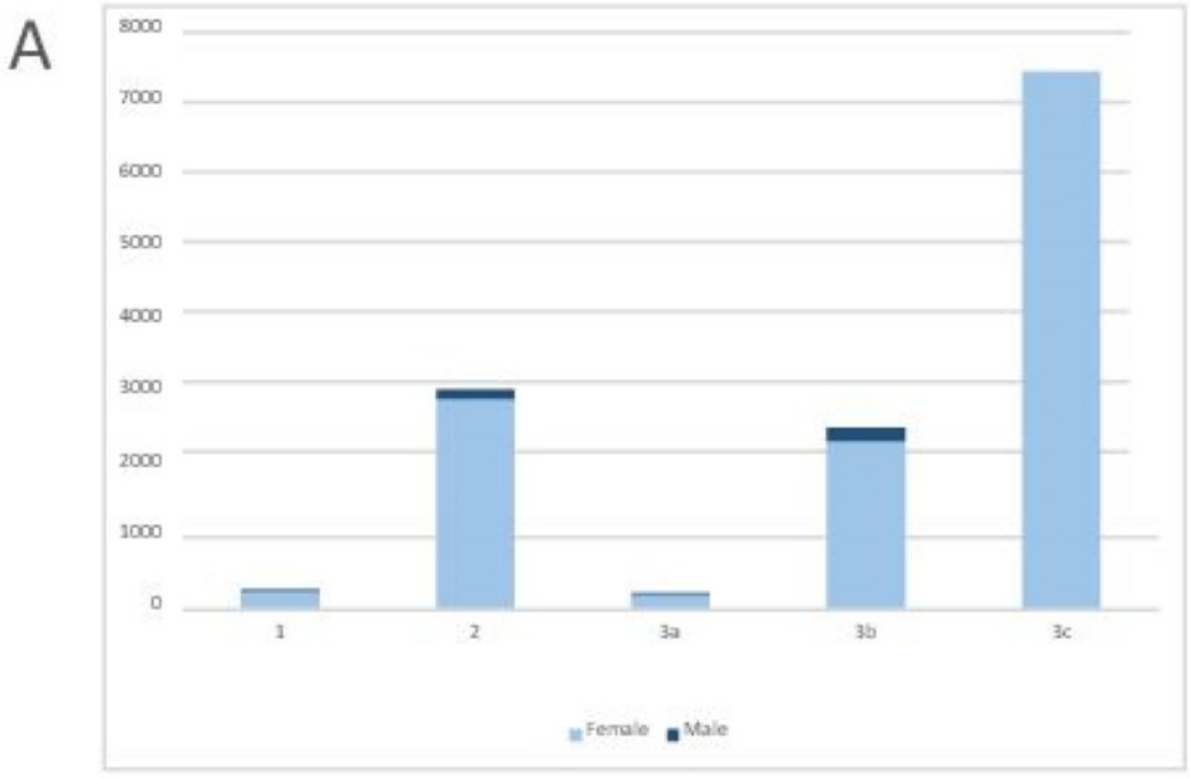
DISCUSSION

This study uses real-world data to provide some evidence of the impact of full implementation of NICE Guideline NG241 in a regional genetics service with a population of approximately 3.8 million, and to put this into context against the other competing referrals for genetic testing within the resource-limited NHS and GMS.

The authors recognise the limitations of the data. The patient cohort is historical and before publication of NG241. This would likely significantly underestimate the number of additional referrals which might be expected as a result of publication of the guidelines. Historical referral criteria provided to local primary and secondary care would not have included a family history of only one relative with OC. However, the proportion of referrals at different ages is likely to be a fair representation of the cohort we would expect to assess and key findings around carrier pick-up will remain with increased referral levels. While the cohort used to confirm accuracy of OC diagnoses is small, this is consistent with other published studies.[5]

In families without OC, fewer cancer confirmations are undertaken but most regional genetics services would also attempt to confirm young BCs under 40 and bilateral BC[16] which would potentially reduce the numbers testable in this group, although we do not have good data on the number of accurate confirmations in the BC cohort. Germline genetic testing in BC families would be undertaken using a slightly different gene panel (R208) containing *BRCA1, BRCA2, PALB2, ATM, CHEK2, RAD51C* and *RAD51D*. Therefore, these estimates using the R207 panel in this cohort will likely underestimate the numbers of carriers who would be identified in BC families as *ATM* and *CHEK2* GPVs have a higher frequency in this cohort than GPVs in the *BRIP1, MLH1, MSH2* and *MSH6* genes.

While we have focused on the number of genetic testing appointments required in each category, it should not be forgotten that prior additional administrative time for cancer confirmations would also be required as well as post-test clinical and administrative time for return of results. It is also worth noting that while SWTCG has a digital FHQS which can automatically generate CanRisk files, most clinical genetics services have to manually input data into CanRisk to calculate mutation



1 = Number of unaffected patients eligible for germline genetic testing according to NG241, 2 = Number of unaffected patients with equivalent GPV likelihood to cohort 1 but without an FDR/SDR with OC, 3a = Number of unaffected patients at 5% risk of a GPV with an FDR/SDR with OC, 3b = Number of patients at 5% risk of a GPV without an FDR/SDR with OC, 3c = Number of patients diagnosed yearly with BC between ages 40-49 who would meet at least 5% chance of having GPV

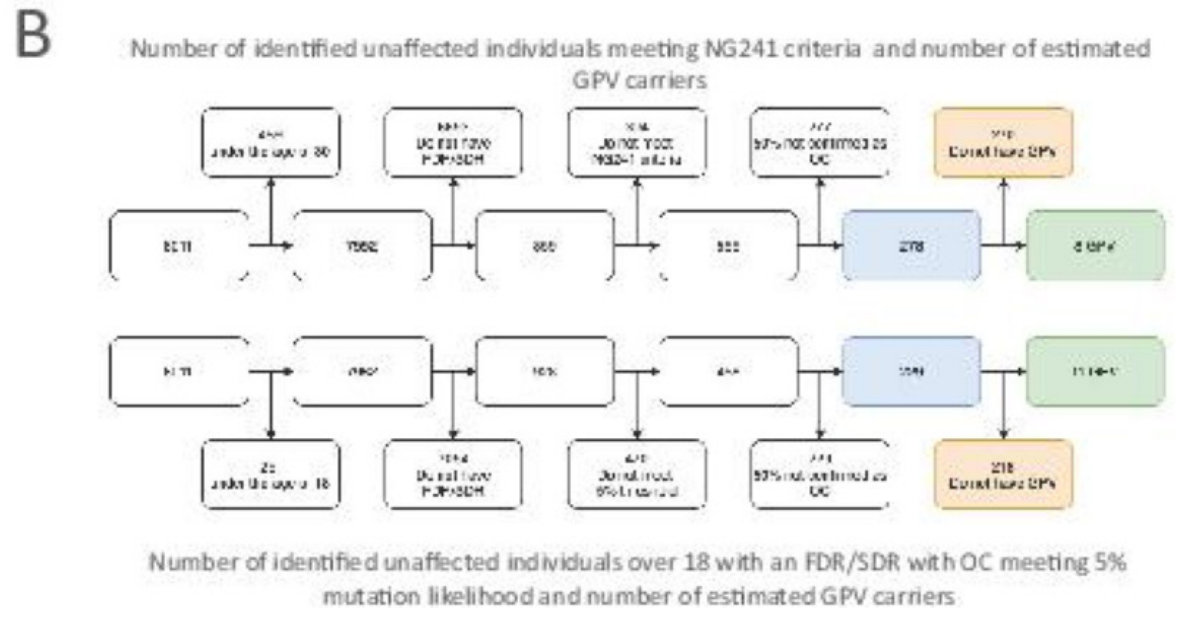


Figure 1 (A) Comparison of numbers of individuals from our family history cohort who are eligible for germline genetic testing of R207: BRCA1, BRCA2, PALB2, BRIP1, RAD51C, RAD51D, MLH1, MSH2, MSH6 with different germline pathogenic variant (GPV) likelihood thresholds, family history and cancer status. (B) Flow diagram showing numbers of unaffected individuals who have a first-degree or second-degree relative (FDR/SDR) with ovarian cancer (OC) eligible for germline genetic testing of R207 and subsequent estimated numbers of carriers identified through NG241 pathway versus testing at universal 5% threshold. BC, breast cancer. 1 = Number of unaffected patients eligible for germline genetic testing according to NG241, 2 = Number of unaffected patients with equivalent GPV likelihood to cohort 1 but without an FDR/SDR with OC, 3a = Number of unaffected patients at 5% risk of a GPV with an FDR/SDR with OC, 3b = Number of patients at 5% risk of a GPV without an FDR/SDR with OC, 3c = Number of patients diagnosed yearly with BC between ages 40-49 who would meet at least 5% chance of having GPV.

Table 1 Comparison of numbers of patients meeting testing criteria and estimated numbers of carriers which would be detected by testing using NG241 criteria versus simplifying to universal 5% testing criteria

		Test eligibility	Number eligible	Estimated carrier detection	Test eligibility	Number eligible	Estimated carrier detection
Age range	Sex	NG241 testing criteria			5% testing criteria		
18–19	Female	NA	NA	NA	5%	1	0.1
18–19	Male	NA	NA	NA	5%	1	0.1
20–29	Female	NA	NA	NA	5%	20	1.0
20–29	Male	NA	NA	NA	5%	2	0.1
30–39	Female	2%	70	1.4	5%	54	2.7
30–39	Male	6%	2	0.1	5%	5	0.3
40–49	Female	2%	109	2.2	5%	69	3.4
40–49	Male	9%	3	0.3	5%	4	0.2
50–59	Female	3%	64	1.9	5%	45	2.2
50–59	Male	10%	4	0.4	5%	3	0.2
60–69	Female	6%	17	1.0	5%	18	0.9
60–69	Male	10%	3	0.3	5%	3	0.1
70+	Female	10%	4	0.4	5%	4	0.2
70+	Male	10%	2	0.2	5%	0	0
Total			278	8.2		229	11.5

likelihoods and this is very time consuming.[18] Carriers require a follow-up appointment and subsequent cascade testing of relatives would also be indicated.

The NICE Guideline NG241 specifically prioritises health economic evaluation of germline genetic testing in familial OC, followed by specific management interventions. However, in practice, clinicians offering germline genetic testing have to consider equity of access to assessment and testing across all familial cancer types, best use of their limited resources and other factors such as complexity of delivery of clinical pathways. Unaffected women with a strong family history of BC but not OC with equivalent or higher mutation likelihoods as their counterparts eligible through NG241 are likely to feel it is inequitable that they are denied a test when they will equally benefit from the same interventions. However, the much higher numbers of women with BC family histories meeting NG241 criteria would overwhelm family history and clinical genetics services if they were all referred for testing. While the health economic analyses are compelling and important, from a clinical perspective the rationale to prioritise one group compared with another group with a differing cancer, but at equivalent risk of the same genetic condition and equal propensity to benefit from subsequent intervention, is hard to understand. It also leads to complex communication with patients and referrers.

Women between 40 and 49 with BC may also feel rightly aggrieved that they are not eligible for genetic testing, despite having a cancer diagnosis and a mutation likelihood of >5%, if their unaffected age-equivalent peers who have a mother or grandmother with OC may access testing at a 2% mutation likelihood threshold. As these individuals already have a diagnosis of cancer and would meet testing thresholds on the basis of their personal diagnosis, this testing would not require separate referral to clinical genetics but could be undertaken by mainstream oncology services or via innovative novel testing pathways such as BRCA Direct[19] without any complex calculation of eligibility. However, these figures only model the number of additional tests/appointments for new diagnoses and the cohort who would become eligible is much larger if prevalent cases were considered.

Eligibility for genetic testing for women with BC in other countries varies according to the healthcare system and presumably reflects population size, test access and funding arrangements. For example, in the USA it has been suggested that all women with BC should access germline genetic testing,[20] but this is funded by private health insurance arrangements. In other European countries criteria to stratify patients according to likelihood of carrying a GPV are applied but vary significantly between countries for affected women from testing available to those <35 to those <60 years old.[21] This highlights that access to germline genetic testing is complex and reliant on many unique healthcare system dependencies. Thoughtful consideration of testing pathways in the broader context of service delivery should be an essential component of clinical/laboratory guidelines development.

It is of note that in our data, simplifying testing to a 5% mutation threshold identified more carriers with an FDR/SDR with OC for fewer tests. While women over 60 may have fewer quality-adjusted life years remaining following bilateral salpingo-oophorectomy and therefore require a higher mutation likelihood in NG241, the NHS cost advantage due to age-related stratified testing is unlikely to be comforting to women who have a higher mutation likelihood than their younger counterparts and a higher risk of developing OC. Restricting testing to patients ≥30 years old delays high-risk gene carriers from entering Very High Risk Breast screening programmes which may be available from age 25 depending on 10-year BC risk.[22] However, the numbers of individuals who would meet 5% testing threshold on the basis of a BC diagnosis or a BC and/or OC family history are high and would require significant investment and innovation in testing pathways for testing all individuals at a 5% mutation risk to be feasible.

Healthcare practitioners working in inherited cancer pathways are passionate about improving detection and management of enhanced cancer risk. This should be equitable, properly resourced and delivered in the most streamlined, effective clinical pathways. We should be smart and innovative to ensure we put our limited resource where we are most likely to benefit the majority of patients. This could include new testing pathways for patients with cancer which are scalable, like BRCA Direct,[19] but would need to consider the increased complexity of counselling for unaffected well individuals. This includes the administrative infrastructure to confirm and clarify familial diagnoses and the

clinical infrastructure, taking into account that well individuals without a phenotype are not under any specific clinical service and require specialised clinical genetics advice.

This study highlights additional factors needing to be considered before the NICE Guideline NG241 can be implemented by regional genetics services and we look forward to working with the NGTD to improve access to germline genetic testing for all our patients.

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Patient consent for publication Not applicable.

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