Evaluation of a Streamlined Oncologist-Led *BRCA* Mutation Testing and Counseling Model for Patients With Ovarian Cancer

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ABSTRACT

Purpose

There is a growing demand for *BRCA1/2* mutation (*BRCAm*) testing in patients with ovarian cancer; however, the limited number of genetic counselors presents a potential barrier. To facilitate more widespread *BRCAm* testing in ovarian cancer, pretest counseling by the oncology team could shorten testing turnaround times and ease the pressure on genetic counselors.

Patients and Methods

The prospective, observational Evaluating a Streamlined Onco-genetic *BRCA* Testing and Counseling Model Among Patients With Ovarian Cancer (ENGAGE) study evaluated a streamlined, oncologist-led *BRCAm* testing pathway. The analysis population comprised 700 patients with ovarian cancer at 26 sites in the United States, Italy, and Spain. The primary objectives were to assess turnaround time and, using questionnaires, to evaluate stakeholder satisfaction (patients, oncologists, and geneticists or genetic counselors) with the oncologist-led *BRCAm* testing pathway.

Results

The median overall turnaround time was 9.1 weeks (range, 0.9 to 37.1 weeks), with median turnaround times in the United States, Italy, and Spain of 4.1 weeks (range, 0.9 to 37.1 weeks), 20.4 weeks (range, 2.9 to 35.4 weeks), and 12.0 weeks (range, 2.0 to 36.7 weeks), respectively. Patient satisfaction with the oncologist-led *BRCAm* testing pathway was high, with > 99% of patients expressing satisfaction with pre- and post-*BRCAm* test counseling. Oncologist satisfaction with the *BRCAm* testing pathway was also high, with > 80% agreeing that the process for performing *BRCAm* testing worked well and that counseling patients on *BRCAm* testing was an efficient use of their time. Oncologists expressed higher levels of satisfaction with the *BRCAm* testing pathway than did geneticists or genetic counselors.

Conclusion

The results of the ENGAGE study demonstrate that an oncologist-led *BRCAm* testing process is feasible in ovarian cancer. Development of local *BRCAm* testing guidelines similar to the one used in this study could allow faster treatment decisions and better use of resources in the management of patients with ovarian cancer.

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INTRODUCTION

BRCA1/2 mutation (*BRCAm*) status is an established predictive biomarker of potential benefit from treatment with poly(ADP-ribose) polymerase (PARP) inhibitors.¹ Maintenance therapy with oral PARP inhibitors prolongs progression-free survival and overall survival in patients with platinum-sensitive relapsed ovarian cancer and a *BRCAm*.²⁻⁴ The PARP inhibitor olaparib is available for the

treatment of advanced ovarian cancer with or without a *BRCAm*^{5,6}; rucaparib and niraparib are also available.^{7,8}

A *BRCAm* is found in approximately 15% of newly diagnosed ovarian cancers^{9,10} and is associated with earlier disease onset.¹¹ Establishing the *BRCAm* status of patients with ovarian cancer provides useful information regarding the prognosis and clinical course of the disease, and it is essential in identifying patients most likely to benefit from PARP inhibitor therapy.¹

ASSOCIATED CONTENT

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Data Supplement
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Previously, *BRC*Am testing was offered only to patients with a family history of breast and/or ovarian cancer; however, recent evidence shows that > 40% of women with a *BRC*Am have no such family history.^{1,9} National guidelines now recommend that *BRC*Am testing be provided to all patients diagnosed with epithelial ovarian cancer,¹²⁻¹⁴ although some variation between guidelines remains.¹⁵ Despite these recommendations, genetic testing is currently underused in women with ovarian cancer.¹⁶

Genetic counseling is recommended both when genetic testing is offered to the patient and after genetic test results are disclosed to the patient.¹² However, the capacity of genetic counselors is rate limiting and presents a potential barrier to the implementation of *BRC*Am testing for patients with ovarian cancer.^{17,18} For example, in the United Kingdom, the average waiting time for a genetics appointment is 12 to 15 weeks.¹⁹ Given the high volume of *BRC*Am tests now being ordered, a new, more streamlined testing approach is needed to shorten testing turnaround times and to ease the pressure on genetic counselors.

The Evaluating a Streamlined Onco-genetic *BRCA* Testing and Counseling Model Among Patients With Ovarian Cancer (ENGAGE) study evaluated a streamlined, oncologist-led *BRC*Am testing model. ENGAGE builds on a pilot study initiated as part of the Mainstreaming Cancer Genetics program by the Institute of Cancer Research and the Royal Marsden Hospital, London, United Kingdom.¹⁹ In the pilot study, use of a streamlined, oncologist-led

(ie, mainstream) *BRC*Am testing model was associated with a fourfold reduction in the 20-week average turnaround time of the conventional testing pathway.¹⁹

PATIENTS AND METHODS

Study Design and Patient Population

The ENGAGE study is an international, multicenter, prospective, observational study designed to evaluate the feasibility of a streamlined *BRC*Am testing model in patients diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer. The study was conducted at 26 sites in the United States ($n = 11$), Italy ($n = 8$), and Spain ($n = 7$).

Eligible patients were ≥ 18 years of age and had a diagnosis of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients were excluded if they had low-grade epithelial ovarian cancer or nonepithelial ovarian cancer, had undergone prior *BRC*Am testing, or were enrolled in an interventional clinical trial for any malignancy.

The institutional review boards or independent ethics committees of all investigational sites approved the protocol. The study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice, and the applicable legislation on noninterventional studies.

Procedures

The clinical team (ie, oncologists and oncology nurses) received training on discussing the role of *BRC*Am testing and on genetic counseling techniques and provided patients with pre-*BRC*Am test counseling (Fig 1 and Data Supplement). If requested by the patient, additional pre-*BRC*Am

Fig 1. ENGAGE trial procedures. (*) Blood sample collected and sent to an external laboratory or participating site for germline *BRCA1/2* mutation testing, followed by genetics review; (†) clinical team includes the oncologist and/or nursing staff; (‡) end-of-study form is filled in by the clinical team to confirm the patient's study status as either completed or not completed (includes loss to follow-up, death, patient decision).

test counseling was provided by a geneticist or genetic counselor. After testing, the oncologist and/or geneticist reviewed and interpreted the test results and reported them to the patient. An appointment with a geneticist or genetic counselor was recommended for patients with a positive *BRCAM* test.

Patient satisfaction with pre- and post-*BRCAM* test counseling was assessed using the Satisfaction with Genetic Counseling Scale (SGCS), which comprises 12 items and assesses six dimensions (Data Supplement).²⁰ The quality of pre-*BRCAM* test counseling was also assessed by patients using the Oncogenetic Counseling Elements Questionnaire (14 questions; Data Supplement). After the *BRCAM* test, patient satisfaction was also assessed using the Modified Royal Marsden Satisfaction Questionnaire (15 questions; Data Supplement).

Oncologists (or oncology nurses) and geneticists or genetic counselors evaluated the *BRCAM* testing pathway using the Oncologist Satisfaction Survey (14 questions) and the Genetic Counselor Satisfaction Survey (seven questions; Data Supplement). Satisfaction questionnaires were completed after one, five, and 10 patients had been counseled. All treatment decisions and clinical assessments were made at the discretion of the treating physician, in accordance with usual care.

Outcomes

The three primary objectives were assessment of turnaround time, patient assessment of pre-*BRCAM* test counseling quality and satisfaction with the streamlined *BRCAM* testing pathway, and evaluation by the oncologist (or oncology nurse) and geneticist or genetic counselor of their satisfaction with the *BRCAM* testing pathway.

The overall turnaround time was defined as the time from initial clinical team counseling until provision of the *BRCAM* test result to the patient by the oncologist, geneticist or genetic counselor, or testing laboratory, or provision of post-*BRCAM* test counseling by an oncologist or geneticist or genetic counselor (whichever occurred later). Turnaround times for each step in the pathway were also assessed.

Secondary objectives included assessment of the association between the *BRCAM* testing turnaround time and patient satisfaction with pre-*BRCAM* test counseling, site characteristics, patient demographic and disease characteristics, and outcome of the test.

Statistical Analysis

All patients who consented to participate in the study and who met the eligibility criteria were included in the analysis population. All data were summarized using descriptive statistics, and no statistical tests were performed.

The main analysis of pre-*BRCAM* test questionnaires was conducted on questionnaires completed within 14 days after clinical team counseling. The main analysis of post-*BRCAM* test questionnaires was conducted within 14 days of one of the following: the date on which *BRCAM* test results were given to the patient, the date of consultation with an oncologist, or the date of counseling by a geneticist or genetic counselor after receipt of *BRCAM* test results.

Because satisfaction questionnaires were not completed consistently by oncologists and geneticists or genetic counselors after one, five, and 10 patients had been counseled, the assessment points were amended to after two or fewer, three to seven, and eight or more patients had been counseled, respectively.

RESULTS

Oncologist and Geneticist or Genetic Counselor Characteristics

Overall, 52 oncologists completed 110 oncologist satisfaction survey questionnaires (35, 43, and 32 questionnaires were completed after one, five, and 10 patients had been counseled, respectively, with one or more oncologists involved in patient counseling per site). Pre-*BRCAM* test counseling was provided only by oncologists in Europe but by either oncologists (40.7%) or oncology nurses (59.3%) in the United States.

Overall, 18 geneticists or genetic counselors completed 27 genetic counselor satisfaction survey questionnaires (15, eight, and four surveys were completed after one, five, and 10 patients had been counseled, respectively).

Patient Population

ENGAGE was conducted between April 21, 2015, and September 30, 2016, and 710 patients were enrolled. The analysis population comprised 700 patients; 10 patients were excluded because they did not comply fully with the inclusion criteria.

The study was completed by 634 patients (90.6%); reasons for premature discontinuation were death (n = 24), loss to follow-up (n = 19), patient voluntary discontinuation (n = 14), and other reasons (n = 9).

The main analysis included 530 SGCS questionnaires at pre-*BRCAM* testing, 414 SGCS questionnaires at post-*BRCAM* testing, 514 Oncogenetic Counseling Elements Questionnaires at pre-*BRCAM* testing, and 414 Modified Royal Marsden Patient Satisfaction Questionnaires after *BRCAM* testing.

Table 1. Patient Demographic and Clinical Characteristics

Parameter	Analysis Population (N = 700)
Age, mean $\pm$ SD, years	62.0 $\pm$ 11.0
Country (n = 700)	
United States	317 (45.3)
Spain	146 (20.9)
Italy	237 (33.9)
Ovarian cancer status at enrollment (n = 700)	
New diagnosis	255 (36.4)
Relapse	128 (18.3)
Remission or stable	317 (45.3)
Ovarian cancer histology at diagnosis (n = 700)	
Serous	516 (80.6)
Mucinous	10 (1.6)
Endometrioid	55 (8.6)
Clear cell	38 (5.9)
Transitional cell	2 (0.3)
Malignant mixed mesodermal	7 (1.1)
Unclassified	12 (1.9)
Missing	60
Known personal history of malignant cancers (n = 700)	
Breast cancer	19 (2.7)
Uterine cancer	13 (1.9)
Lung cancer	2 (0.3)
Cervical cancer	1 (0.1)
Other cancer	13 (1.9)
Family history of breast or ovarian cancer (n = 654)	
Yes	232 (35.5)
No	422 (64.5)
Missing or unknown*	46
History of other cancers (eg, pancreas, prostate) in relatives (n = 644)	
Yes	319 (49.5)
No	325 (50.5)
Missing or unknown*	56
History of <i>BRCA1</i> or <i>BRCA2</i> mutations in relatives (n = 551)	
Yes	12 (2.2)
No	539 (97.8)
Missing or unknown*	149

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviation: SD, standard deviation.

*The missing or unknown category refers to data that were not provided or were collected as "unknown" at enrollment.

Fig 2. Turnaround times for each step of the streamlined *BRC*Am testing pathway. (*) Negative durations correspond to patients who consented to a *BRC*Am test before initial oncology team counseling or for whom the blood sample was taken before initial oncology team counseling. *BRC*Am, *BRCA1/2* mutation.

Patient demographic and clinical characteristics are presented in Table 1. The proportion of patients with a family history of breast or ovarian cancer differed among countries (41.9% in the United States, 34.3% in Italy, and 23.6% in Spain). Two women received additional counseling by a geneticist or genetic counselor after the oncologist-led counseling and before *BRC*Am testing; in both cases, this was conducted less than 1 week after the initial oncology team counseling.

Assessment of *BRC*Am Test Turnaround Time

The turnaround times expected by participating physicians using standard procedures are presented in the Data Supplement. Using the streamlined *BRC*Am testing pathway, the median overall turnaround time was 9.1 weeks (range, 0.9 to 37.1 weeks; Fig 2). Analysis of each step of the testing pathway revealed that the overall turnaround time was driven mainly by the time from the collection of the blood sample for *BRC*Am testing to the provision of the test results to the patient (median, 8.6 weeks [range, 0.7 to 35.6 weeks]; Fig 2). The median time from collection of the blood sample to receipt of the test results by the referring clinician was 4.7 weeks (range, 0.0 to 32.1 weeks). In terms of the other steps, patient consent to a *BRC*Am test was usually obtained during initial oncology team counseling, and the blood sample for *BRC*Am testing was usually taken shortly after the initial oncology team counseling (Fig 2). Oncologist counseling usually occurred at the same time as the provision of the *BRC*Am test results to the patient

(Fig 2). Counseling by a geneticist or genetic counselor was provided a median of 0.0 weeks (range, 0.0 to 30.9 weeks) after patients received a positive *BRC*Am result.

Turnaround times differed among countries (Fig 2). The median overall turnaround time was longer in Europe than the United States, which is reflected in the longer median time from performing the *BRC*Am test to providing the result either to the referring clinician or to the patient.

Patient Assessment of the Streamlined *BRC*Am Testing Model

Patient satisfaction with streamlined *BRC*Am testing was high. Mean SGCS scores at both pre- and post-*BRC*Am testing were > 3.5 for all six dimensions, with minimal differences seen between pre- and post-*BRC*Am testing (Data Supplement). Overall, 99.2% of patients were satisfied with pre-*BRC*Am test counseling (Fig 3), and 99.8% of patients were satisfied with post-*BRC*Am test counseling by a geneticist or genetic counselor or oncologist.

Patients considered the quality of pre-*BRC*Am test counseling to be high, with > 90% of patients recording on their Oncogenetic Counseling Elements Questionnaire that their oncologist or nurse discussed the purpose of the *BRC*Am test, how the *BRC*Am test could affect their treatment, the *BRCA* gene and its function, the implications of a positive *BRC*Am test result, and the impact their test result could have on their family (Fig 3 and Data Supplement). In addition, pre-*BRC*Am test counseling was comprehensive, with

Fig 3. Patient satisfaction with pre-*BRCA1/2* mutation (*BRCAm*) test counseling. Results shown for eight questions from the patients' assessment of quality report form (Oncogenetic Counseling Elements Questionnaires) and for one summary question from the patients' satisfaction report form (Satisfaction with Genetic Counseling Scale) before *BRCAm* testing. Q, question; VUS, variant of uncertain significance.

oncologists or nurses spending a median of 20.0 minutes (range, 2 to 115 minutes) discussing the *BRCAm* test.

For the Modified Royal Marsden Patient Satisfaction Questionnaire, 96.6% of patients agreed or strongly agreed that they were pleased to have had the genetic test, and 93.7% of patients agreed or strongly agreed that they were happy to have had the genetic test at one of their existing oncology appointments, rather than at a separate appointment with the genetics team (Data Supplement).

Oncologists and Genetic Counselors' Assessment of the Streamlined *BRCAm* Testing Pathway

Oncologist satisfaction with the streamlined *BRCAm* testing pathway was high. Of the oncologists who completed surveys after 10 patients had been counseled, 90.6% agreed or strongly agreed that it is very important for patients with ovarian cancer to be offered *BRCAm* testing, and 84.3% agreed or strongly agreed that the process for performing *BRCAm* testing worked well (Data Supplement).

Oncologists expressed higher levels of satisfaction with the *BRCAm* testing pathway than did geneticists or genetic counselors. When all surveys were considered, 48.1% of geneticists or genetic counselors welcomed having oncologists conducting pre-

BRCAm test counseling, and 46.2% of geneticists or genetic counselors agreed or strongly agreed that patients seemed to receive accurate information during the pre-*BRCAm* test counseling (Data Supplement).

Secondary Outcomes

The overall *BRCAm* testing turnaround time did not have a notable impact on the dimension scores of the SGCS. No clear associations were found between the turnaround time and the instrumental, affective, satisfaction with the information provided during counseling, fulfillment of expectations, and overall feeling of satisfaction dimensions. An association was found between the turnaround time and the procedural dimension score, with a shorter turnaround time associated with higher patient satisfaction with administrative procedures.

Additional analyses demonstrated that the median overall turnaround time was longer with local versus central laboratory providers, and with the use of a study-sponsored central laboratory versus a local hospital-affiliated or commercial laboratory (Data Supplement).

Remote delivery of negative *BRCAm* test results was more common in the United States than in Europe, thereby reducing the time to delivery of results (Data Supplement).

Fig 4. Breakdown of *BRCA*1/2 mutation test results. VUS, variant of uncertain significance; Wt, wild type.

Data on which team member provided the *BRCA*m test result to the patient are summarized in the Data Supplement. Regardless of the result (positive, negative, or variant of uncertain significance [VUS]), patients in Europe were more likely than those in the United States to have a consultation with the oncology team or with a geneticist or genetic counselor after receiving their *BRCA*m test results, which would tend to increase the turnaround time.

A *BRCA*m was identified in 95 of 690 evaluable patients (13.8%; Fig 4). The prevalence of *BRCA*1 mutations (65.3%) was higher than that of *BRCA*2 mutations (33.7%), with one patient (1.1%) having both *BRCA*1 and *BRCA*2 mutations. Of 91 evaluable patients with a *BRCA*m, 53.8% had a family history of breast or ovarian cancer, whereas 46.2% did not.

DISCUSSION

The streamlined oncologist-led *BRCA*m testing pathway we report here was associated with high levels of acceptance and satisfaction among patients with ovarian cancer. Patient satisfaction was high regardless of testing outcome, and the overall turnaround time did not have a notable impact on patient satisfaction. Patients' therapies were not dependent on *BRCA*m test results because most patients were either in remission or stable, or undergoing primary chemotherapy for newly diagnosed ovarian cancer, meaning that any delays may have been less likely to cause dissatisfaction. By contrast, rapid receipt of test results is more critical in cancers such as breast cancer, where prophylactic surgical decisions must be made.

There was low uptake of pre-*BRCA*m test counseling with a geneticist or genetic counselor, with only two patients requesting this additional counseling, which suggested high patient satisfaction

with the oncologist-led pretest counseling. It is not feasible to train enough genetic counselors to meet the growing demand for genetic testing,²¹ and use of an oncologist-led *BRCA*m testing pathway has the potential to avoid the substantial delays associated with waiting for an appointment with a geneticist or genetic counselor.¹⁹ In this study, *BRCA*m testing usually occurred shortly after the initial oncology team counseling (Fig 2), whereas the average time from patient consent to *BRCA*m testing was expected to be > 1 month in approximately 25% of patients using standard procedures (Data Supplement).

The streamlined *BRCA*m testing pathway also has convenience implications, with the vast majority of patients in ENGAGE agreeable to having the *BRCA*m test at an existing oncologist appointment, rather than having to make a separate appointment with a genetic counselor.

Although clinicians expressed high satisfaction with the streamlined *BRCA*m testing pathway, geneticists or genetic counselors showed less enthusiasm for this approach. For example, ≤ 50% of surveyed geneticists or genetic counselors responded that patients seemed to receive accurate information about the *BRCA*m test in the pretest counseling session. For the streamlined *BRCA*m testing pathway to succeed, it is important that oncologists and geneticists or genetic counselors work collaboratively and that oncologists receive high-quality training on how to conduct pre-*BRCA*m test counseling. To achieve streamlining, oncologists may wish to adapt and tailor the testing process to their institution in collaboration with geneticists or genetic counselors. It should be noted that the purpose of the oncologist-led pretest counseling was to provide enough information on why the patient should have the test, rather than full genetic counseling, which is appropriate once the test result is known. In addition, counseling was provided in the context of an existing cancer diagnosis, where there is general agreement that *BRCA*m testing is appropriate, rather than in the context of a theoretical risk.

Variations in turnaround times were observed among the participating countries. One factor underlying the differences in sample processing time was the longer overall turnaround time seen with the use of a study-sponsored central laboratory than with a local laboratory affiliated with a hospital site or a commercial laboratory. Methods of communicating results to patients also differed among countries, with patients in the United States more likely to have negative results delivered remotely. Even if negative results are delivered remotely, patients should still be offered a face-to-face appointment to discuss their results.

The results of ENGAGE support the premise that *BRCA*m status should be based on patient criteria rather than on family history alone.¹ Among women in ENGAGE who were found to have a *BRCA*m, only 54% had a family history of breast or ovarian cancer. Various factors may limit the usefulness of a family history, including a small family size, early deaths in family members, prophylactic surgeries, and a lack of communication among family members.¹²

Given that the ENGAGE study was not limited to a specific *BRCA*m test, the streamlined oncologist-led *BRCA*m testing pathway is feasible regardless of the test used. Somatic *BRCA*m testing is increasingly common and of growing importance; some institutions prefer to test for somatic mutations first, with those patients found to have a mutation in a tumor subsequently undergoing germline

testing.¹ Although *BRCAm* constitute the majority of deleterious mutations associated with an increased risk of epithelial ovarian, fallopian tube, and primary peritoneal cancer, multigene panel testing may be appropriate in some settings to evaluate for all currently known mutations.¹²

BRCA VUS was identified in 11.2% of patients in ENGAGE, with approximately 70% of surveyed patients responding that their oncologist or nurse had discussed the implications of VUS during pre-*BRCAm* test counseling. The level of understanding of both oncologists and patients with regard to the complexities of VUS must be evaluated adequately when adopting novel *BRCAm* testing pathways.²²

Strategies are needed to meet the growing demand for genetic testing.²¹ One suggested approach is that after brief training, clinicians perform the initial genetic testing, after which patients with a positive result or VUS could be referred to a geneticist or genetic counselor as needed.²¹ The results of the ENGAGE study support such a strategy.

The results of the ENGAGE study demonstrate that an oncologist-led *BRCAm* testing process is feasible in patients diagnosed with ovarian, fallopian tube, and primary peritoneal cancer. The streamlined *BRCAm* testing model can shorten turnaround times by providing combined genetic testing and counseling, with high acceptance and satisfaction among both patients and clinical staff. Development of local *BRCAm* testing guidelines, involving oncologists, oncology nurses, and geneticists or genetic counselors and following a pathway similar to the

one used in this study, could allow faster treatment decisions and better use of resources in the management of patients with ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer

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