STUDY REPORT SUMMARY (ABSTRACT)

Evaluating a Novel Onco-genetic *BRCA* Testing Counseling Model Among Patients with Ovarian Cancer

Prospective observational study of patients diagnosed with epithelial ovarian/fallopian tube/primary peritoneal cancer

Background/Rationale:

Approximately 15% of all ovarian cancer patients will harbor a germline mutation in Breast cancer susceptibility gene 1 and 2 (*BRCA1* and *BRCA2*). Who *BRCA* gene testing is performed on, and when and how *BRCA* testing is done, is becoming an important component of the diagnostic process for ovarian cancer for prognostic, family assessment, and treatment decision purposes. Additionally, there is a growing public awareness and demand for genetic testing in breast and ovarian cancer.

The Mainstreaming Cancer Genetics programme (www.mcgprogramme.com), a Wellcome funded initiative led by The Institute of Cancer Research, London (ICR) and the Royal Marsden Hospital (RMH), developed and implemented a streamlined *BRCA* testing model (the "mainstream" testing model) in which trained members of the cancer team directly consent cancer patients for genetic testing. Together with faster testing using a Next Generation Sequencing (NGS) methodology, this model allows a much faster testing turnaround time of 3-4 weeks. Patients with a mutation get a genetics clinic appointment time with their result, in addition to written information. Patients without a mutation receive their result as written information only, though they or their cancer team can request a genetics appointment if required. The pathway was well received by both participating physicians and patients. Shortened turnaround times for the *BRCA* testing will aid physicians in making timely decisions about patient treatment now drugs specifically indicated for *BRCA* positive patients are available. The findings of the proposed study were expected to provide evidence to inform discussions on *BRCA* testing guidance and standards across the United States (US) and Europe for streamlined onco-genetic *BRCA* testing pathways in clinical practice.

Objectives and Hypotheses:

The overall objective of this study was to assess turnaround time, pre-*BRCA* test counseling quality and satisfaction with a new streamlined *BRCA* testing model. The specific primary and secondary objectives of this study were as follows:

The primary objectives included a) assessing turnaround time with the new streamlined *BRCA* testing pathway; b) patient's assessment of pre-*BRCA* test counseling quality and satisfaction with the streamlined *BRCA* testing pathway; c) oncologists, and genetic counselor's assessment of the streamlined *BRCA* testing process.

The secondary study objectives included a) assessing the association between turnaround time and patient satisfaction and quality of pre-test counseling; b) among patients following a *BRCA* testing pathway alternative to the primary one (i.e., requesting additional pre-test counseling by a genetic counselor), turnaround time, satisfaction and quality among these patients were descriptively compared with patients following the primary pathway proposed in the study.

Methods:

This was a prospective observational study of patients diagnosed with epithelial ovarian/fallopian tube/primary peritoneal cancer prior to, or at enrolment in this study. The study was descriptive in nature and did not attempt to test any specific a priori hypotheses.

Clinical teams (physicians and nurses) were trained to discuss *BRCA* testing with ovarian cancer patients who met eligibility criteria and consented to participate in the study. Patients were recruited from participating sites in the US and Europe. Patients selected per the study inclusion and exclusion criteria were consented for participation in the study. Patients were recruited during an estimated 12 month period and participating patients were followed from enrollment in the study until provision of *BRCA* test results, final genetics counseling, and completion of a satisfaction survey or death. A case report form was developed to collect information on the primary variable of interest (i.e., turnaround time), patient and disease characteristics, medical history, treatment patterns and outcome of the *BRCA* test. In addition, a survey was developed to evaluate patient's assessment of pre-*BRCA* counseling quality and satisfaction with the streamlined testing process. Finally, surveys were developed to evaluate oncologist (or oncology nurse) and genetic counselor's assessment of the processes associated with the streamlined testing pathway.

Target subject population

Patients with a diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer prior to or at enrollment in this study and who needed to receive a *BRCA* test were considered for inclusion in the study (patients who had received a *BRCA* test previously were not to be included). The study was expected to enroll 800 patients.

The eligibility criteria were as follows:

Inclusion Criteria

The patient population was to fulfill all of the following criteria:

1. Patients diagnosed with epithelial ovarian/fallopian tube/primary peritoneal cancer
2. Patients aged 18 years or older at ovarian cancer diagnosis
3. Provision of written informed consent
4. Patient is able to read, write, and understand the material presented to them as part of this study, per the discretion of the physician

Exclusion Criteria

The exclusion criteria considered for this study were as follows:

1. Patients with low grade epithelial ovarian cancer or non-epithelial ovarian cancer
2. Patients enrolled in an interventional clinical trial for ovarian cancer or other malignancy at the time of conduct of this study
3. Patients with *BRCA* testing any time prior to the study enrolment

Results:

This prospective non-interventional study has been initiated in 2 European countries (Spain and Italy) and in the US in order to assess turnaround time, pre-*BRCA* test counseling quality and satisfaction with a new streamlined *BRCA* testing model.

The study was conducted between 21 April 2015 (First Patient First Visit) and 30 September 2016 (Last Patient Last Visit) by 26 active physicians (7 in Spain, 8 in Italy and 11 in the US) who enrolled a total of 710 patients in the study (146 in Spain, 243 in Italy and 321 in the US).

All active physicians but one were oncologists or gynecologists/oncologists and only 1 was a genetic counselor. The active physicians generally worked at an academic/university hospital (73.1%) and/or a clinic/hospital (30.8%), and a small proportion (11.5%) had a private practice. Most of the active physicians had a long experience treating patients with ovarian cancer (17.6 years on average).

Of the 710 patients enrolled, 700 patients (98.6%) were included in the analysis population. Ten patients were excluded from the analysis population because they were not diagnosed with an epithelial ovarian/fallopian tube/primary peritoneal cancer (5 patients) or because they were also enrolled in an interventional clinical trial for ovarian cancer or other malignancy (5 patients).

Of the 700 patients in the analysis population, 634 (90.6%) completed the study and 66 (9.4%) prematurely discontinued. The reasons for premature study discontinuation were death (24 patients), lost to follow-up (19 patients), patient voluntary discontinuation (14 patients) and other reasons (9 patients). Overall, the mean duration of follow-up was 3.2 (standard deviation (SD): 2.1) months.

Patient Characteristics

The mean age of women included in the analysis population was 62.0 (SD: 11.0) years, with slight differences between participating regions: 59.6 (SD: 11.3) years in Europe and 64.8 (SD: 10.1) years in the US. The proportion of Hispanic patients was 24.0%. Overall, 84.9% of patients were white, 8.1% black and 7.0% were of another race. More than 80% of patients had a national health system and/or a private health insurance coverage.

Most of the patients had a good functional status (94.4% had a grade 0 or grade 1 ECOG Performance Status) and minimal comorbidity (90.0% had a Charlson Co-morbidity Index ≤3). The mean 10-year survival probability as assessed by the Charlson Co-morbidity Index probability was 84.6% (SD: 18.0%).

The median time since initial diagnosis was 0.7 (interquartile range (IQR): 0.2-3.0) years. At enrollment, 36.4% of patients had a newly diagnosed ovarian cancer, 45.3% were in remission or stable and 18.3% had a relapse. Respectively 90.1% had an ovarian cancer, 6.3% a fallopian tube cancer and 3.6% a primary peritoneal cancer. Approximately 81% of patients had a serous tumor and 92.2% had a high grade tumor (G2 or G3). At initial diagnosis, 13.2% of patients had a stage I, 9.8% a stage II, 58.0% a stage III and 19.0% a stage IV disease. Almost 90% of patients received prior lines of chemotherapy and/or biologic agents for the treatment of the primary ovarian cancer (from 1 to 10 lines of treatments). Additionally, 88.7% of patients had prior surgery for the treatment of the primary ovarian cancer and prior radiotherapy was reported in 3.4% of patients.

A family history of breast or ovarian cancer was reported in 35.5% of patients, with notable differences between countries (41.9% in the US, 34.3% in Italy and 23.6% in Spain). In addition, 2.2% of patients had a history of a *BRCA1* or *BRCA2* mutation among their relatives.

No patients had genetic mutations previously identified by genetic testing.

***BRCA* Testing**

Counseling prior to *BRCA* testing was generally conducted in outpatient or office settings. In Europe, pre-*BRCA* test counseling was provided only by oncologists, whereas in the US, it was provided by nurses (59.3%) or oncologists (40.7%).

All women consented to have *BRCA* testing. Only 2 women requested an appointment for an additional counseling by a genetic counselor/geneticist prior to testing.

BRCA testing was performed in 99.6% of patients as 3 patients in the US had no *BRCA* testing and prematurely discontinued from the study.

In Europe, blood samples were mainly sent to an ENGAGE study sponsored central laboratory (76.2%) or the hospital/site affiliated local laboratory (23.5%) for *BRCA* testing, whereas in the US, they were sent to the hospital/site affiliated local laboratory (54.8%) or to a commercial laboratory (central laboratory provider specialized in genetic cancer testing) (45.2%).

Main Results

The median overall turnaround time from the initial clinical team counseling to the provision of the test results to the patient or to the provision of counseling by the oncologist or the geneticist was 9.1 (IQR: 4.1-19.4) weeks. The analysis of each step of the streamlined testing pathway showed the overall turnaround time was mainly driven by the time from the collection of the blood sample for *BRCA* testing to provision of the test results to the patient (median: 8.6 (IQR: 4.0-17.7) weeks): over this time period, a median time of 4.7 (IQR: 2.4-11.0) weeks was necessary to perform the *BRCA* test and provide the oncology team with the *BRCA* testing results.

The overall turnaround time was very variable across participating countries: the median overall turnaround time was longer in the European countries (20.4 (IQR: 13.4-26.6) weeks in Italy and 12.0 (IQR: 7.6-19.1) weeks in Spain) than in the US (4.1 (IQR: 2.4-7.1) weeks).

The time needed to perform the *BRCA* test and provide the oncology team with the *BRCA* testing results was highly variable between participating countries: 2.7 (IQR: 1.7-3.9) weeks in the US vs. 14.6 (IQR: 7.0-18.6) weeks in Italy and 5.9 (IQR: 4.1-11.0) weeks in Spain. It should be noted that the analyzer of the ENGAGE study sponsored central laboratory in Italy broke down 2 times during the study period, which may have caused significant delays.

The time necessary to provide the patient with the test results was also shorter in the US than in Europe: the median time from taking the *BRCA* test sample to provision of test results to the patient was 3.9 (IQR: 2.3-6.7) weeks in the US vs. 19.0 (IQR: 11.7-25.3) weeks in Italy and 10.4 (IQR: 7.1-17.0) weeks in Spain.

The turnaround time from the collection of the blood sample to providing the patient with the test results and the overall turnaround time were not improved in Europe for positive *BRCA* test results.

The between-country differences in sample processing may be partly explained by the differences in *BRCA* testing location: the median overall turnaround time was markedly longer with the ENGAGE study sponsored central laboratory (16.7 (IQR: 9.4-24.0) weeks) than with the hospital-site affiliated local laboratory or commercial laboratory (4.9 (IQR: 2.7-15.1) weeks and 6.0 (IQR: 3.1-9.6) weeks, respectively).

The between-country differences in terms of the time to provide test results may be explained by the fact that negative *BRCA* test results were more frequently provided remotely (e.g., phone call, letter, e-mail) in the US than in Europe, which reduces the time to deliver the test results to the patients. In Europe, 88.3% of patients had a consultation with a member of the oncology team and 28.4% had a counseling with a genetic counselor/geneticist after receiving the *BRCA* test results vs. respectively 59.1% and 11.4% in the US. In the event of positive results, 74.6% of patients in Europe and only 42.9% of patients in the US had a consultation with a genetic counselor or a geneticist. As the oncologist or geneticist consultations are the last step of the *BRCA* testing pathway, the higher rate of consultations with an oncologist and/or with a genetic counselor/geneticist in Europe tended to increase the time to communicate the test results to the patients.

Patient and Clinician Satisfaction

Overall, patient satisfaction with the streamlined *BRCA* testing pathway was high, irrespective of the outcome. All dimension scores of the Satisfaction with Genetic Counseling Scale were on average >3.5 (1: lowest satisfaction to 4: highest satisfaction), with no notable changes between pre- and post-*BRCA* testing. These results were consistent with those of the modified Royal Marsden satisfaction questionnaire, which showed that a vast majority of patients were pleased to have the genetic test and were happy to access testing through a routine oncology appointment. In addition, the results of the onco-genetic counseling elements questionnaire showed that the pre-*BRCA* test counseling was comprehensive with a mean duration of almost 25 minutes.

The overall turnaround time had no notable impact on the dimension scores of the Satisfaction with Genetic Counseling Scale. However, patient satisfaction was not impacted probably because the overall turnaround time had no direct influence on the patient therapeutic management.

Oncologist satisfaction was also high. The majority of oncologists considered that it is very important for ovarian cancer patients to be offered *BRCA* gene testing, that the process for carrying out *BRCA* gene testing worked well and that counseling patients on *BRCA* testing was an efficient use of their time. Although the number of genetic counselor satisfaction surveys was limited (N=18 survey questionnaires completed), the satisfaction of genetic counselors was more mitigated. Only 33% of them were pleased having oncologists conduct *BRCA* pre-test counseling. Moreover, only half of them considered that the patients received accurate information during the pre-test counseling and only 36% considered that the oncologists were able to identify patients who needed additional psycho-social counseling about the test.

***BRCA* Results**

Overall, a *BRCA* mutation (positive test result) was identified in 13.8% of patients, with a higher prevalence of *BRCA1* mutations (65.3%) (vs. *BRCA2* mutations (33.7%) and both *BRCA1* and *BRCA2* mutations (1.1%)). The rate of *BRCA* mutations observed was lower than expected in patients with high-grade serous ovarian cancer, in particular in the US (9.0%).

Among the patients with a *BRCA* mutation, approximately 54% had a family history of breast/ovarian cancer and approximately 13% had a family history of a *BRCA1* or *BRCA2* mutation (8.2% in Europe and 21.7% in the US).

Conclusion:

BRCA testing is becoming an important component of the ovarian cancer management process as it provides substantial prognostic and therapeutic information for patients with ovarian cancer and may improve cancer risk information for patient family members. The ENGAGE study aimed to evaluate a streamlined, oncologist-led *BRCA* testing model, previously implemented by the Institute of Cancer Research and the Royal Marsden Hospital, London, UK. The results of the ENGAGE study confirmed the findings of the previous study that the mainstream *BRCA* testing model can offer short turnaround time for combined genetic testing and counselling with high acceptance and satisfaction levels in patients and staff. However, the turnaround time was noticeably longer in Europe than in the US, mainly at testing laboratory level. Compared to the study of George et al., the turnaround time in counselling was shorter, but the *BRCA* testing process was longer. It should be noted that George at al. modified their process to allow for patients with negative results to be informed by post, as was the practice in many sites in the USA in the ENGAGE study. Further improvements should therefore include a better access to testing laboratories in Europe, which may deliver the *BRCA* test results in a shorter time to enable a better scheduling of the follow-up visits with the patients, and the remote provision of negative test results to the patients by phone call, letter or e-mail. All patients with a positive result should see a genetic counsellor, so the implementation of such an streamlined *BRCA* testing pathway should also include a good collaboration between oncologists and genetic counsellors, with a clear definition of their role, to allow genetic testing and counselling to be performed in the most efficient and consistent way.