Title: Mainstreamed genetic testing for women with ovarian cancer: first year experience

Rahman B[1], Lanceley A[1], Kristeleit R[2,3], Ledermann J[2,3], Lockley M[3,4], McCormack M[2,3], Mould T[2,3], Side L[5]

1 EGA Institute for Women's Health, University College London, UK
2 UCL Cancer Institute, University College London, UK
3 UCL Hospitals, London, UK
4 Bart's Cancer Institute, Queen Mary University of London, UK
5 Wessex Clinical Genetics Service, Southampton, UK

Abstract:

Background: Ovarian cancer is the fifth most common cause of cancer death for women in the UK. Up to 18% of cases can be attributed to germline mutations in BRCA1 and BRCA2 genes. Identifying patients who carry a BRCA mutation provides important information about potential response to treatment and eligibility for therapies such as PARP-inhibitors. Implementation of systematic genetic testing of ovarian cancer patients via oncology clinics (mainstreamed genetic testing, MGT) is increasing.
Methods and results: This service evaluation reports on the first year of MGT at a tertiary oncology centre in London, UK. In total, 122 patients with high grade non-mucinous ovarian cancer underwent BRCA germline testing via MGT. Eighteen patients (14.8%) were found to carry a deleterious BRCA1/2 mutation. Four BRCA carriers did not meet previous criteria for genetic testing and would have been missed. Six BRCA carriers accessed PARP-inhibitors post-MGT. Only 22% of patients with a VUS were referred to clinical genetics services.
Conclusions: MGT appears to be a feasible way of providing BRCA testing to ovarian cancer patients. Greater clarity of how oncologists use VUS results is needed, as well as further research on psychosocial implications of MGT for ovarian cancer patients which may include somatic testing in the future.

Introduction:

One in 70 women will develop ovarian cancer over their lifetime, leading to over 4000 deaths per year in the UK.[1] There is an inherited component to ovarian cancer; between 5.8–24.8% of cases can be attributed to germline mutations in BRCA1 and BRCA2 genes.[2] Until recently, BRCA genetic testing has been provided by clinical genetics services. Ovarian cancer patients could access testing if they had a significant family history of breast and/or ovarian cancer or Ashkenazi Jewish ancestry. Consequently, genetic testing was only offered to a minority of patients; however, up to 44% of BRCA mutation carriers do not have a significant family history.[3] Furthermore, barriers to referral and uptake of genetic counselling for both clinicians and patients have been reported.[4-7] A review of current ovarian cancer and BRCA genetic testing guidelines found only five from 15 guidelines recommend testing regardless of family history, Ashkenazi Jewish ancestry or cancer histology.[2]

Identifying ovarian cancer patients with a BRCA mutation is increasingly important for treatment decisions, in particular for accessing poly adenosine diphosphate ribose polymerase (PARP)-inhibitors (such as olaparib, rucaparib and niraparib*), targeted therapies for relapsed, BRCA-mutated ovarian cancer. Recent changes to the UK National Institute for Health and Care Excellence (NICE) guidelines mean that women with high grade epithelial ovarian cancer (EOC) but without a family history should be able to access BRCA genetic testing.[8] Integrating BRCA testing into oncology clinics, referred to as 'mainstreamed' genetic testing (MGT), is key to providing testing to more women. Systematic genetic testing for all women with high grade non-mucinous EOC is increasing, either via oncology (MGT) or clinical genetics services. However, there is a lack of consensus as to how BRCA testing should be provided to ovarian cancer patients[9] and this will lead to inequities in accessing testing in this group.

At University College London Hospital (UCLH), a tertiary referral centre in North London, MGT was introduced within the gynaecological oncology department in February 2015 with

* Olaparib was approved by the UK NICE guidelines in January 2016 for relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1/2 mutations and whose disease has responded to platinum based chemotherapy after three or more courses of platinum based chemotherapy.
Rucaparib was approved by the U.S. Food and Drug Administration in December 2016 for treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Rucaparib is currently accessed via Clovis named patient compassionate use programme or clinical trials; niraparib via Clinigen and TESARO managed access programme.

funding for BRCA germline testing provided by The UCLH Charity for an initial period of 12 months.

The objective of this evaluation was to examine clinical outcomes from the first year of MGT which could be used to inform development of this service.

Methods:

A service evaluation was approved by the UCLH Applied Health Research in Governance Group.

All women with a diagnosis of high grade non-mucinous EOC currently under the care of UCLH were eligible for BRCA testing with no age or family history restrictions. Testing was provided by medical/clinical oncologists who completed an online training course via the Marsden Mainstreamed Genetic Testing in Cancer (MCG) Programme.[10] Timing of testing was guided by clinician and patient preference. Testing was discussed at the patient's oncology appointment alongside other treatment decisions. Women who agreed to BRCA testing received their results from their oncologist. Where a BRCA mutation or variant of unknown significance (VUS) was identified, patients were referred to their local clinical genetics service. Referrals were also recommended for women without a mutation but with a relevant family history.

Clinical files were reviewed for all patients who had MGT, including genetic reports. If histopathology was unclear from medical records, these were reviewed with an expert gynaecology oncology pathologist. Two local clinical genetics services were contacted to review referral patterns, family history data and referral of at-risk relatives for predictive testing.

Results:

Patient characteristics:

Between February 2015 and April 2016, 122 eligible patients had BRCA testing via MGT. Most (100/122, 82%) had high grade serous ovarian cancer, and were diagnosed with stage III or IV disease (95/122, 78%). The median age at diagnosis was 62 years (range 28-88); 68 women (56%) were younger than 60 years at diagnosis.

BRCA mutation carriers:

18 women with a BRCA mutation were identified from MGT; 10 BRCA1 and 8 BRCA2 mutations. Ashkenazi Jewish/Polish founder mutations comprised 11% of pathogenic mutations (2/18). Nine VUS were identified.

The prevalence of BRCA mutations in our cohort was 14.8% which is similar to other studies of large cohorts of women with EOC.[3] Two UK sites offering systematic BRCA testing to ovarian cancer patients reported a prevalence of 7.8% and 15.9% (Table 1).[9, 11]

	Site		
	UCLH	East Anglia	Royal Marsden
Patients tested, n	122	232	207
BRCA1 mutation, n	10	12	17
BRCA2 mutation, n	8	6	16
VUS, n	9	15	Not reported
Overall BRCA mutation prevalence	14.8%	7.8%	15.9%

Table 1. Prevalence of BRCA mutations from systematic genetic testing in the UK

The median age at diagnosis of BRCA mutation carriers was 57 years (range 42-74 years), compared to 66 and 62 years in the VUS and no mutation groups, respectively. There was no significant difference in age between women with a BRCA mutation and those with either a normal result or VUS (p=0.171). BRCA1 mutation carriers were younger at diagnosis than BRCA2 carriers (p=0.012). One BRCA carrier had a carcinosarcoma; 17 had high grade serous cancer. Most BRCA carriers had stage III or IV disease (17/18, 94%).

	BRCA1/2 mutation positive (n=18)	**BRCA1/2 VUS (n=9)**	**No mutation (n=95)**
Age (years), median (range)	58 (42-74)	66 (55-70)	62 (28-88)
BRCA1, n	10	3	0
BRCA2, n	8	6	0
Pathology, n			
Clear cell	0	0	5
Carcinosarcoma	1	0	4
Endometrioid	0	0	9
High grade serous	17	9	74
Mixed	0	0	2
Other	0	0	1

Stage, n			
I	0	1	14
II	1	1	9
III	10	4	45
IV	7	2	27
Not classified	0	1	0

Table 2. Summary of patient characteristics

During this evaluation it was noted two patients who had received normal BRCA germline results from MGT were identified as carrying BRCA somatic mutations during clinical trial participation.

Testing process and timing:

All BRCA germline testing was performed by the NE Thames Regional Genetics Laboratories. Median time from sample receipt to result was 26 working days (range 14-48 days).

Timing of testing ranged from at diagnosis to up to 104 months post-diagnosis. Approximately half of patients in this cohort had been newly diagnosed within the previous 12 months (56/122, 46%). From this group, 20/56 (36%) women underwent MGT within one month of diagnosis. Amongst 18 women carrying a BRCA mutation, ten (56%) were newly diagnosed with ovarian cancer in the 12 months prior to genetic testing, six of whom were tested within one month of diagnosis. Eight carriers (44%) were diagnosed 21-104 months prior to BRCA testing.

Clinical genetics and family history:

After MGT, women with a BRCA mutation or VUS should have been referred to their local clinical genetics service by their oncologist. Most patients were referred between 12 and 43 working days after their MGT results were reported. at the time of this evaluation, 22% (4/18) of BRCA mutation carriers had not yet been referred to clinical genetics. Two of these patients were subsequently referred, 98 and 127 working days from date of MGT results. Of nine patients with a BRCA VUS, only two had been referred to clinical genetics.

Family history data documented at the time of genetic counselling was available for 13 BRCA carriers. Nine patients had a family history of breast, ovarian and/or other cancers;

four patients had no significant family history and did not meet previous criteria for BRCA genetic testing (i.e. Manchester score <15).[12] Fifteen relatives of BRCA carriers were referred to clinical genetics services, with 11 undergoing predictive testing.

Patient management BRCA carriers:

Of the 18 BRCA mutation carriers, there was no change to treatment for 67% (11/18); seven patients completed first line chemotherapy with three of these patients on maintenance bevacizumab, and four completed or were undergoing second line chemotherapy. One patient was deceased eight months after MGT. Thirty-three percent (6/18) of patients were subsequently able to access PARP-inhibitors. Four patients commenced olaparib, one patient accessed rucaparib via a compassionate use programme, and one patient was participating in an olaparib clinical trial. Family history data were available for five patients in this group, and of these three did not meet previous criteria for BRCA genetic testing.

Discussion:

The MGT service at UCLH provided BRCA germline testing to 122 ovarian cancer patients and identified 18 women with BRCA mutations (prevalence 14.8%). The variation in mutation rates between the three UK sites with published BRCA testing data may be due to several factors. The lower rate in East Anglia (of 7.8%) could result from testing only newly diagnosed patients, and ethnicity; no Ashkenazi/Polish founder mutations were found in their cohort. The higher prevalence (15.9%) at the Royal Marsden may be due to a younger cohort; an age cut-off of <65 years was used for the first nine of 16 months of MGT. The higher prevalence at both UCLH and the Royal Marsden may be due to retrospective testing of patients several years from their initial diagnosis. This may indicate enrichment based on treatment response, i.e. increased prevalence of BRCA mutations in platinum-sensitive disease.

Currently there is no consensus as to the best time to offer BRCA testing to women with ovarian cancer, although many clinicians choose to do this early in the treatment pathway. At UCLH, germline testing of all patients more than 12 months after diagnosis identified 44% of BRCA carriers. MGT should be offered to patients regardless of time elapsed since diagnosis as results may inform not only clinical decisions but identification of at risk relatives for patients identified as mutation carriers, first degree blood relatives will have a 50% risk of carrying the same mutation.

Patient management was reviewed for the 18 women identified as BRCA mutation carriers. Six patients were able to access a PARP-inhibitor therapy or trial; most patients had received MGT results between 6-14 months earlier. For 11 patients, there was no change to treatment. The lack of immediate impact on clinical management is largely due to timing, as olaparib is available only for platinum-sensitive relapsed ovarian cancer after three or more lines of treatment and the niraparib managed access programme was not yet available at the time of this evaluation. Clarifying BRCA mutation status whilst patients are still on first or second line chemotherapy would identify those who are eligible for PARP-inhibitor therapies or trials in the future.

Knowledge of BRCA status provides important cancer risk information for families. Patients found to carry a BRCA mutation or VUS should be referred to clinical genetics services to discuss the implications of their results, including communicating results to relatives. In this service evaluation, although most women with a BRCA mutation were referred immediately to clinical genetics by their oncologist, for some the referral was delayed. Most women with a BRCA VUS were not referred to clinical genetics. It is unclear how oncologists interpret VUS, and/or use them for clinical management. The interpretation of VUS results are challenges for genetics and other areas of clinical medicine.[13] The pathogenicity of a VUS should be reviewed periodically, as in time it may be reclassified as either deleterious or benign. This is usually carried out within a clinical genetics service. In some families segregation analysis of the variant amongst cancer affected relatives may help clarify pathogenicity.[14]

Future directions for MGT:

Offering BRCA testing to women with high grade EOC in the oncology setting (MGT) is being adopted across the UK. Research continues to identify other genes that contribute to epithelial ovarian cancer. Testing for moderate risk genes conferring lifetime risks of 6-13% (RAD51C, RAD51D and BRIP1) is now offered alongside BRCA1/2.[15, 16] Testing of multiple cancer susceptibility genes using next generation sequencing panels is increasingly being offered. However there remain counselling issues; the penetrance of some of these genes is uncertain, as well as how they might influence ovarian cancer management.

Currently UK clinical genetics services are commissioned to provide BRCA germline testing in individuals with a pre-test BRCA1/2 carrier probability of 10% or more as recommended in NICE guidance.[8, 17] This includes all women with high grade non-mucinous EOC. Tumour BRCA testing is available in Europe, but is not offered routinely in the UK. Within this cohort of MGT patients, two with a normal BRCA germline result were later found to carry somatic

BRCA mutations. It is estimated 5-7% of women with high grade serous ovarian cancer who do not carry a BRCA germline mutation are found to have a somatic BRCA mutation.[18] These patients would be eligible for olaparib therapy or other PARP-inhibitor clinical trials, calling for greater access to tumour testing in ovarian cancer.

This evaluation demonstrates that MGT is a feasible way of providing BRCA testing to ovarian cancer patients and led to 33% of mutation carriers accessing targeted therapies. Greater clarity of how oncologists use VUS results is needed, as is ensuring these are reviewed. Timing of MGT may be important to ensure all eligible patients are offered BRCA testing, including newly diagnosed women and those some years from diagnosis. Further research is needed to explore the psychosocial experiences of women with ovarian cancer who have MGT, in particular those who receive mutation positive results.

Funding: No funding was received for this service evaluation and short report.

Declaration of interest: The authors declare that they have no competing interests.

Contribution to authorship: BR conducted the service evaluation. BR, AL and LS and wrote the report. RSK, JAL, ML, MMC, TM contributed to drafting the report and participated in final draft revisions.

Acknowledgements: The first 12 months of BRCA germline testing for ovarian cancer patients at UCLH were kindly funded by The University College London Hospitals Charity (Grant 7146).

References:

1 CRUK. Ovarian cancer statistics http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-One Access date 4 Oct 2016.

2 Eccles D, Balmana J, Clune J, Ehlken B, Gohlke A, Hirst C, Potter D, Schroeder C, Tyczynski J, Gomez Garcia E. Selecting Patients with Ovarian Cancer for Germline BRCA Mutation Testing: Findings from Guidelines and a Systematic Literature Review. *Adv Ther* 2016;33:129-50.

3 Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer M, al e. BRCA mutation frequency and patterns of treatment response in BRCA mutation positive women with ovarian cancer. *J Clin Oncol* 2012;30:2654-63.

4 Metcalfe K, Fan I, McLaughlin J, Risch H, Rosen B, Murphy J, Bradley L, Armel S, Sun P, Narod S. Uptake of clinical genetic testing for ovarian cancer in Ontario: A population-based study. *Gynecol Oncol* 2009;112:68-72.

5 Bell K, Scott M, Pond G, Piccinin C, Amer M, Elit L, Bordeleau L. Genetic Counselling Referral Rates and Uptake of BRCA1 and BRCA2 Testing among Women Diagnosed with Serous Ovarian Cancer in a Tertiary Care Cancer Centre. *J Genet Syndr Gene Ther* 2013;4:156.

6 Powell CB, Littell R, Hoodfar E, Sinclair F, Pressman A. Does the Diagnosis of Breast or Ovarian Cancer Trigger Referral to Genetic Counseling? *Int J Gynecol Cancer* 2013;23:431-6.

7 Lanceley A, Eagle Z, Ogden G, Gessler S, Razvi K, Ledermann J, Side L. Family History and Women With Ovarian Cancer: Is it Asked and Does it Matter? An Observational Study. *Int J Gynecol Cancer* 2012;22:254-9.

8 National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). 2013.

9 George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, Cloke V, Slade I, Kemp Z, Gore M, Strydom A, Banerjee S, Hanson H, Rahman N. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci Rep* 2016.

10 Mainstreaming Cancer Genetics Programme. Mainstreaming Cancer Genetics 22 March 2016;Available from: https://mcgprogramme.com/brcatesting.

11 Plaskocinska I, Shipman H, Drummond J, Thompson E, Buchanan V, Newcombe B, Hodgkin C, Barter L, Ridley P, al e. New paradigms for *BRCA1/BRCA2* testing in

women with ovarian cancer: results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study. *J Med Genet* 2016;53:655-61.

12 North East Thames Regional Genetics Service. BRCA1 and BRCA2 mutation testing guidelines. London: Pan Thames, 2012.

13 Eccles D, Mitchell G, Monteiro A, Schmultzer R, Couch F, Spurdle A, Gomez Garcia E. BRCA1 and BRCA2 genetic testing - pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann Oncol* 2015;26:1057-65.

14 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody W, al e. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine* 2015;17 405–23

15 Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, Fraser L, Gentry-Maharaj A, Hayward J, Philpott S, Anderson C, Edlund CK, Conti D, Harrington P, Barrowdale D, Bowtell DD, Alsop K, Mitchell G, Group AS, Cicek MS, Cunningham JM, Fridley BL, Alsop J, Jimenez-Linan M, Poblete S, Lele S, Sucheston-Campbell L, Moysich KB, Sieh W, McGuire V, Lester J, Bogdanova N, Dürst M, Hillemanns P, Ovarian Cancer Association Consortium, Odunsi K, Whittemore AS, Karlan BY, Dörk T, Goode EL, Menon U, Jacobs IJ, Antoniou AC, Pharoah PDP, Gayther SA. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J Natl Cancer Inst* 2015;107.

16 Song H, Dicks E, Ramus SJ, Tyrer JP, Intermaggio MP, Hayward J, Edlund CK, Conti D, Harrington P, Fraser L, Philpott S, Anderson C, Rosenthal A, Gentry-Maharaj A, Bowtell DD, Alsop K, Cicek MS, Cunningham JM, Fridley BL, Alsop J, Jimenez-Linan M, Høgdall E, Høgdall CK, Jensen A, Kjaer SK, Lubiński J, Huzarski T, Jakubowska A, Gronwald J, Poblete S, Lele S, Sucheston-Campbell L, Moysich KB, Odunsi K, Goode EL, Menon U, Jacobs IJ, Gayther SA, Pharoah PDP. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. *J Clin Oncol* 2015;33:2901-7.

17 NHS England. Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 mutations. 2015.

18 Moschetta M, George A, Kaye S, Banerjee S. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. *Annals of Oncology* 2016;27:1449-55.