

# Delivering improved access to genetic testing in epithelial ovarian cancer

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## Authors:

Louise Cameron, Inga Plaskocinska, Mark Kroese and Marc Tischkowitz

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Correspondence to:  
[mdt33@medschl.cam.ac.uk](mailto:mdt33@medschl.cam.ac.uk)

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## 1. Executive summary

This report describes our experiences of implementing a clinical genetics-coordinated service in our region to allow improved access to *BRCA1/BRCA2* testing for epithelial ovarian cancer patients. We describe the GTEOC research study which informed the design of our regional NHS service, as well as local influences and general drivers for change which led us to offer this service. We hope that this description of our experiences of implementation may be useful for other providers considering setting up such a service for patients in their region.



### Epithelial ovarian cancer (EOC)

- Around 7,300 patients diagnosed with ovarian cancer annually in the UK
- Fifth commonest cancer-related cause of mortality in women
- Well-established prognostic and therapeutic associations with *BRCA1/BRCA2* mutations
- Risk-reducing options for unaffected family members
- The 2015 CRUK Cancer Taskforce recommends that '*NHS commissioners should ensure that: all women with non-mucinous epithelial ovarian cancer are offered testing for BRCA1/BRCA2 at the point of diagnosis*'



### GTEOC research study findings

- 83% of eligible women accepted *BRCA1/BRCA2* genetic testing
- Median turnaround time from consent to results delivered was 46 days
- Diagnostic yield of 8% in all unselected women (not selected on basis of family history) and 12% in unselected women under 70 years
- No significant additional distress reported as a result of being offered testing



## Benefits of the NHS GTEOC model

- Increased diagnostic yield - identification of a larger numbers of patients with mutations, leading to better outcomes from use of more targeted treatments, and the ability to offer cascade testing to unaffected family members
- Improved care experience for affected individuals - ease of accessing testing via telephone appointment, and faster turnaround of results
- Clinical genetics involvement throughout the care pathway but with a more efficient approach - assessing risk through family history in clinical genetics is resource intensive and can be a poor discriminator of risk
- The GTEOC model improves access to appropriate genetic testing, but with a clinical genetics-coordinated approach which ensures patients have access to the clinical genetics service
- Healthcare professionals were satisfied with being able to offer testing to more of their patients



## Key considerations for NHS service delivery

- No additional financial resources required to implement the service, as the financial impact of the service changes, including an increased number of tests and decreased clinic overheads, were managed in one directorate budget
- In the East Anglia region (population 2.4 million), where access to testing is fully implemented, this has resulted in approximately 100 patients with EOC being referred for *BRCA1/BRCA2* testing per annum
- Communication with local referral centres is important to highlight the benefits of testing, and maintain referral rates

## 2. Background

### 2.1 Epithelial ovarian cancer and genetic testing

Ovarian cancer affects 1.5% of women during their lifetime. Almost 7,300 new cases are diagnosed in the UK each year <sup>[1]</sup>, with epithelial ovarian cancer accounting for the largest proportion of the disease. A number of environmental and genetic factors play a part in the aetiology of ovarian cancer; it is estimated that around 15-20% of all ovarian cancer cases arise from inherited mutations, with *BRCA1*/*BRCA2* mutations the most common <sup>[2]</sup>.

*BRCA1* and *BRCA2* mutations are found in 8 to 22% of unselected women (i.e. unselected on the basis of age or family history) with epithelial ovarian cancer, the variability reflecting the presence of founder mutations in some populations <sup>[3], [4], [5], [6]</sup>. The association between germline mutations in *BRCA1* and *BRCA2* and epithelial ovarian cancer was first established in the 1990s, and since then over 1600 mutations in the *BRCA1* gene, and over 1800 in the *BRCA2* gene, have been identified. Mutations result in reduced expression levels or diminished function of the *BRCA1* and *BRCA2* proteins which play an important role in DNA repair, thereby increasing the risk of DNA damage and tumour formation. Estimates of penetrance vary depending on the cohort analysed, but it is estimated that women with a *BRCA1* mutation have a 40-60% lifetime risk of developing ovarian cancer <sup>[7]</sup>, and women with a *BRCA2* mutation have a 10-30% lifetime risk of developing the disease <sup>[8]</sup>. NICE guidelines (CG164) on the management of patients at risk of familial breast cancer and related risks recommend testing in women with a greater than 10% risk of having a mutation, as judged through clinical assessment with tools such as BOADICEA or the Manchester score <sup>[9]</sup>. However, a significant proportion of women with *BRCA1* and *BRCA2* mutations are not identified because they are not referred for risk assessment, sometimes because of a lack of a significant family history.

#### Testing methods

Depending on the reason for testing, a number of different molecular techniques may be employed. The assay may be *BRCA1*/*BRCA2*-specific or, in the form of a panel test, include a larger number of cancer-associated genes, opening up the possibility of subsequent analysis of additional genes. Diagnostic testing examines the entire *BRCA1* and *BRCA2* genes where there is no prior knowledge of a known mutation, and now commonly utilises next generation sequencing of DNA, coupled with multiple ligation-dependent probe amplification (MLPA) for detection of larger (exonic) deletions and duplications. Predictive testing where a familial mutation has already been identified involves a more focused approach utilising Sanger sequencing for small mutations or MLPA for larger deletions and duplications.

## *Benefits of testing*

Over the past few decades, there has been a growth in understanding of different subtypes of cancer, based on the features of the tumour cells and their underlying genetic differences. This knowledge has underpinned an expansion in novel therapeutic approaches and more personalised prognostic advice. As a subgroup of patients with ovarian cancer, studies have suggested that women with *BRCA1* and *BRCA2* mutations may have slightly higher short- to medium-term survival but this may not translate into significantly higher long-term survival <sup>[10], [11]</sup>. Differences in response to treatment have been observed, both in comparing *BRCA1/BRCA2* mutation carriers with non-carriers, and also between *BRCA1* and *BRCA2* mutation carriers. *BRCA2* mutation carriers show a slightly better response to treatment than both *BRCA1* mutation carriers and non-carriers, most likely due to the increased frequency of genetic mutations in *BRCA2* mutation-positive malignant cells, increasing cell instability and therefore vulnerability to chemotherapeutic agents <sup>[12]</sup>. *BRCA1* and *BRCA2* mutation carriers appear to be more responsive to both platinum agents and poly ADP ribose polymerase (PARP) inhibitors <sup>[13], [14]</sup>. A more detailed understanding of the cellular processes afforded by genetic testing allows the development of therapeutic agents which may provide not just a superior response, but are exclusively effective in particular groups of patients.

Therefore, knowledge of *BRCA1/BRCA2* mutation status is of value to the patient and clinician in understanding better the likely prognosis and in selecting the most effective therapeutic options (and avoiding treatment which is unlikely to be effective). Patients are supported in communicating the results of testing to family members, as the presence (or absence) of a *BRCA1/BRCA2* mutation has important implications for unaffected family members who may then consider testing. Unaffected individuals who are found to have a *BRCA1/BRCA2* mutation may then consider increased surveillance or options to reduce their risk of developing breast or ovarian cancer, such as selective oestrogen receptor modulator treatment (e.g. tamoxifen), mastectomy or bilateral salpingo-oophorectomy.

## *Provision of testing across the UK*

Genetic testing for *BRCA1* and *BRCA2* is currently commissioned by NHS England according to the Medical Genetics Service Specification, based on a pre-test probability of having a *BRCA1* or *BRCA2* mutation of greater than 10%, following the publication of updated NICE guidelines on testing in breast cancer patients in 2013 <sup>[9]</sup>. The previous threshold was set at 20%, and clinical practice has not evolved uniformly in line with the lowering of the threshold, one factor which contributes to variability in testing referral rates. Figures from the literature cite rates of referral for testing of between 15% and 30% <sup>[15], [16], [17], [18]</sup> which may be due in part to the fact that only around 50% of patients report a significant family history <sup>[3], [6]</sup>. Our experience prior to the GTEOC study would suggest higher rates of referral in our region, of around 50% of eligible patients, but with some intra-regional variability and still representing an unmet need amongst this group of patients.

The NHS England Specialised Commissioning team report <sup>[19]</sup> gives estimates of *BRCA1/BRCA2* testing in ovarian and breast cancer produced prior to the publication of the updated NICE guidelines in 2013, based on a survey by the NICE Guideline Development Group (GDG), taking into account *BRCA1/BRCA2* prevalence and test uptake. This report suggests that a substantial number of affected women and unaffected relatives are not referred for testing <sup>[19]</sup>. Although this includes individuals not just with ovarian cancer, but breast cancer also, the report does serve to highlight the need to ensure provision of adequate laboratory resources and suitable clinical genetics capacity to undertake risk assessment and counselling. In the resource-limited environment of the NHS, this is a challenging task. The GTEOC study takes a novel approach and finds a workable solution to deliver enhanced care for patients with more efficient use of clinical genetics resources.

The 2015 Cancer Taskforce report <sup>[20]</sup> notes the importance of understanding *BRCA1/BRCA2* mutation status in informing treatment and enabling family members to access risk-reducing options and makes a specific recommendation that '*NHS commissioners should ensure that: all women with non-mucinous epithelial ovarian cancer are offered testing for BRCA1/BRCA2 at the point of diagnosis.*'

## 2.2 Current service models in the UK

There is currently no consensus in the UK regarding testing for *BRCA1/BRCA2* in ovarian cancer patients and therefore service models vary across regions. Different models of service delivery have evolved following the publication of the NICE guidelines on *BRCA1/BRCA2* testing in breast cancer patients, with the aim of offering testing to ovarian cancer patients with a risk greater than 10%. Given differences in infrastructure, resources, and methods to assess risk, it is perhaps not surprising that service models differ across the UK. A review of service models by George <sup>[21]</sup> showed variability in practice, but with the majority of centres ordering tests after an initial assessment of risk by the clinical genetics service. The review noted a small but increasing number of centres beginning to offer *BRCA1/BRCA2* testing to all patients with a relevant diagnosis. In addition to the East Anglian GTEOC model, The Royal Marsden's 'oncogenetic' testing model has trained oncology clinicians to allow them to obtain consent from patients for testing. Describing the landscape of testing in the UK in 2015, the review by George <sup>[21]</sup> showed that centres in Liverpool and Birmingham were offering testing to all patients at diagnosis, and in Oxford to patients on request, whilst in Manchester *BRCA1/BRCA2* testing is offered on request to selected patients. Following publication of the Scottish Intercollegiate Guidelines Network (SIGN), services in Scotland are offering *BRCA1/BRCA2* testing at diagnosis to all patients, with consent obtained by oncologists in a fully integrated service.

Outside the UK, there is similar variability in service models, with a number of initiatives: for example, the DNA-BONus study in Norway <sup>[4]</sup>, and a study in the Netherlands that recently examined the benefits of automatic access to *BRCA1/BRCA2* testing for epithelial ovarian cancer patients <sup>[22]</sup>.



## 2.3 Mainstreaming and drivers for change

Genetic testing has traditionally been regarded as a highly specialised service and, owing to the need for resource-intensive pre- and post-test counselling and relatively high test costs, has been delivered through the clinical genetics service with risk assessment being an important aspect of service delivery. In recent years a number of factors have come to bear on this situation:

- A growing awareness that a genetic aetiology underlies a far greater proportion of disease than previously understood, and that this genetic influence in disease can be harnessed to provide more effective, personalised care
- The advent of higher throughput, faster, lower cost genetic testing
- A greater awareness of, and therefore demand for, testing amongst patients and their relatives and a desire to address inequity of access.

Policy initiatives and practical programmes to support wider testing such as the Mainstreaming Cancer Genetics programme <sup>[23]</sup> and, most recently, the high profile NHS-wide 100,000 Genomes Project <sup>[24]</sup> all highlight the belief that patients and the health service have much to be gained from responsible widening of access to genomic services in the UK. The rise in demand for genetic testing by these drivers cannot easily be serviced by the existing NHS clinical genetics infrastructure, and therefore novel solutions which may overcome the potential 'bottleneck' in access are critical if the benefits of wider testing are to be fully realised.

### 3. The evidence for change - the GTEOC research study

#### 3.1 Study overview

##### *Purpose of study*

The GTEOC research study recruited women with newly diagnosed epithelial ovarian cancer in the East Anglia region between July 2013 and June 2015, with the aim of assessing the acceptability and feasibility of testing for *BRCA1* and *BRCA2* mutations without initial assessment of risk in the clinical genetics service.

##### *Methodology*

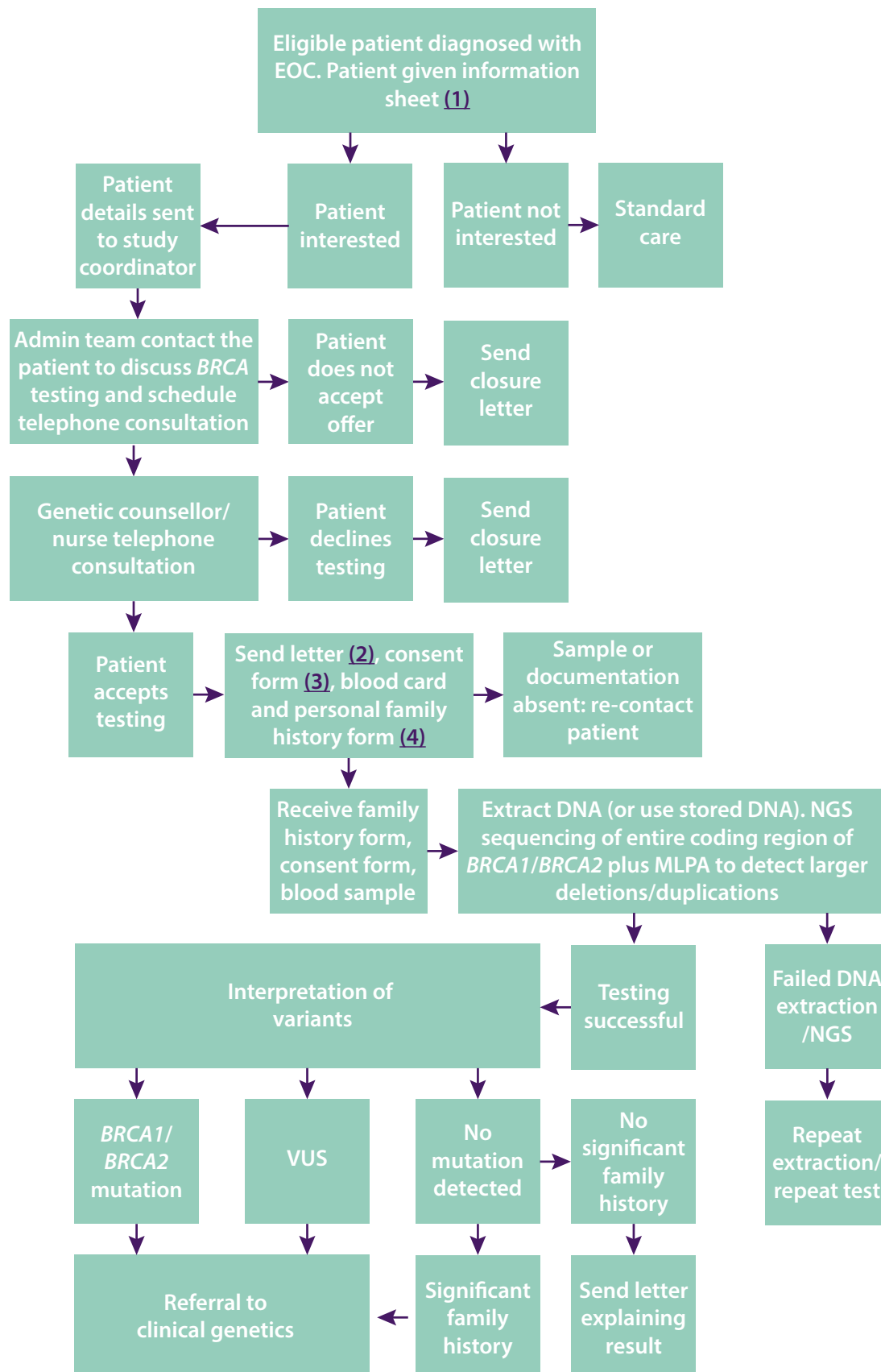
Patients were eligible if they were aged 18 years and over and diagnosed with serous, endometrioid or mixed type ovarian cancer within the last 12 months. Patients with mucinous ovarian cancer types and clear cell tumours were not included in the study as they are not part of the *BRCA1/BRCA2* phenotype.

All women with newly diagnosed epithelial ovarian cancer were made aware of the GTEOC study during their oncology appointment and, if they expressed an interest, their details were passed to the study coordinator. Detailed study information was sent to the patient, but instead of a face to face genetic counselling appointment as previously occurred, the patient was offered a telephone consultation with the study genetic counsellor/nurse, with the focus on information-giving and consent. No prior assessment of the risk of being a mutation carrier was performed. These telephone consultations covered elements considered to be key to effective genetic counselling, including provision of relevant and objective information to support autonomous decision-making and ensure informed consent. However, some aspects of counselling were not routinely explored with patients as part of the study approach, for example, offering psychological support or exploring familial implications in detail, unless patients explicitly requested support in these areas. If the patient decided to go ahead with testing, a consent form was sent along with instructions to provide a 5ml EDTA blood sample, which could be taken in the most convenient setting for the patient, for example the local hospital phlebotomy service or GP practice, or at a forthcoming out-patient appointment. The patient was also asked to complete a demographic survey and personal/family history form.

*BRCA1/BRCA2* testing was carried out by the East Anglian Genetics Service using NGS and MLPA. The results were fed back to the referring clinician: patients with a mutation or variant of uncertain significance (VUS) were then invited for a genetic counselling appointment with the clinical genetics service. Mutation-negative patients with a clinically relevant family history were also advised to seek a referral to the clinical genetics service. [Figure 1](#) shows the GTEOC research study pathway.

# Genetic testing in epithelial ovarian cancer

Figure 1 GTEOC research study pathway



For the health economic analyses, the original testing pathway and GTEOC research study pathway were mapped and individual costs were included. (More details are provided in the GTEOC research study publication [\(link\)](#)).

To assess the psychological impact of testing, all participants were asked to complete a short questionnaire which included the Depression, Anxiety and Stress Scale (DASS-21) <sup>[25]</sup> and the Impact of Event Scale (IES) <sup>[26]</sup>. Each scale was administered in relation to both the impact of diagnosis of cancer and impact of genetic testing.

## 3.2 Results

### *Uptake and patient characteristics*

A total of 232 out of 281 (83%) eligible women accepted the offer of testing. Almost all women (97%) reported their ethnicity as white, reflecting the demographic profile of the area. The mean age of participants was 63 years (range 28-89 years). Eighty-two percent of participants had high-grade serous ovarian cancer, 9% had endometrioid ovarian cancer, 6% had unspecified or poorly differentiated adenocarcinomas, and 2.5% had mixed types.

### *Reporting*

The target turnaround time for the clinical reporting of samples was 56 working days, and the actual median turnaround time from receiving the consent form to test results being returned to patients was 46 working days. The range was 15-117 days, which included some samples where testing was delayed at the patient's request.

### *Diagnostic yield*

Eighteen clinically significant *BRCA1/BRCA2* mutations were detected, twelve in *BRCA1* and six in *BRCA2*, giving an overall prevalence of 8% in unselected women of all ages which is concordant with the NICE guidelines on risk threshold for testing in breast cancer patients. Fifteen out of the sixteen mutations observed were in patients with high-grade serous ovarian cancer, the other case had a high-grade adenocarcinoma with features suggestive of endometrioid adenocarcinoma.

None of the mutations observed were common founder mutations seen in other populations. The mean age of mutation carriers was 49.5 years (range 40-75 years). In unselected women under 70 years, the mutation prevalence was 12%, and in unselected women aged over 70 years the prevalence was 1%. The mutation prevalence in women under 70 years with a positive family history was 17%, but notably one quarter of mutation carriers had no significant family history.

Seventeen variants of uncertain significance (VUS) were observed in fifteen patients, fourteen in *BRCA1* and three in *BRCA2*.

## Psychological impact

Questionnaires were returned from 75% of patients, and the results showed that distress was not significantly increased as a result of genetic testing in this study, above that already experienced as a result of the cancer diagnosis. Younger participants reported an increase in intrusive thoughts, and higher levels of cognitive avoidance were noted in women with *BRCA1/BRCA2* mutations as opposed to women without *BRCA1/BRCA2* mutations.

## Test acceptability

High levels of acceptability were reported, with patients reporting sufficient information and time to make the decision regarding testing. Most participants noted that they had talked with their family about the test, and felt that the test helped them to understand their family's risk.

## Health economic evaluations

The health economic evaluations are summarised in Table 1. More details are available in the GTEOC study paper ([link](#)).

Table 1\*

Metric	Original pathway	GTEOC research study pathway	GTEOC study pathway testing women <70 yrs
Overall cost	£142,702	£253,617	£148,429
Average cost per <i>BRCA1/BRCA2</i> positive	£11,892	£14,919	£9,895
Average cost per test offered	£2,265	£1,093	£1,091
Average cost per patient (excluding genetic test cost)	£383	£243	

\*The figures in Table 1 are based on a test price of £850

The greater overall costs for the GTEOC research study pathway reflect the increased volume of tests, but when genetic test costs are excluded, the GTEOC pathway costs less than the original pathway, reflecting the decreased costs attributable to clinical genetics personnel time. The non-genetic test costs represent 22% of the GTEOC pathway budget compared with 62% of the original pathway budget. Therefore any change in cost of genetic testing has a large impact on the budget and this was reflected in the sensitivity analyses. If the test price was reduced from the base case of £850 to £190, then the overall budget for the GTEOC pathway would be equivalent to the standard pathway. The health economic models show that offering testing to women under the age of 70, in whom the mutation prevalence is higher, impacts significantly on the overall costs, as can be seen in Table 1 above, without impacting significantly on mutation detection rates. The overall cost when testing is offered to women under 70 is comparable (£148,429) to that for the original pathway (£142,702), and the cost per *BRCA1/BRCA2* positive result is lower (£9,895 versus £11,892). These analyses assume a relatively high test price of £850, and a trajectory of lowering test prices will therefore impact significantly on the overall cost of increased levels of testing in a 'real-life' implementation context.

## *Study limitations*

Further work to establish the acceptability of this model of testing in more ethnically diverse regions would be beneficial, as the GTEOC research study was limited in this regard due to the lack of ethnic diversity in the study population. Also, the assessment of cost implications associated with clinical management of patients identified through cascade testing was outside the remit of the study, but may yield important data. The study focused on women with newly diagnosed disease, but an understanding of *BRCA1/BRCA2* mutation status may prove useful at other points in the disease course, particularly prevention.

## **3.3 Significance of GTEOC research study findings for service delivery**

The GTEOC research study is of interest to service providers and commissioners as it has shown that the diagnostic yield when offering *BRCA1/BRCA2* testing to unselected women with epithelial ovarian cancer is in line with existing guidelines on assessing risk. (i.e. NICE guidelines on *BRCA1/BRCA2* testing in patients with breast cancer.) The study showed that the service model is workable across a regional service with numerous referral sites in district general hospitals. Patients reported high acceptability, and no significant levels of distress above that already experienced in relation to the cancer diagnosis. By limiting testing to women under 70 years of age, testing can be offered in a cost neutral manner, without impacting negatively on mutation detection rates. With a trajectory of lowering laboratory costs and increasing personnel costs, the shift in resource consumption embodied by the GTEOC pathway will likely become increasingly efficient in economic terms.

Whilst improving access to genetic testing the GTEOC research study approach represents a move from a genetics-led to a genetics-coordinated service with numerous advantages of maintaining clinical genetics involvement in patient care, as shown in [Box 1](#).

## Box 1 Advantages of maintaining clinical genetics involvement in models to improve access to genetic testing

- ✓ Access to genetic counselling for all patients prior to and throughout the testing process
- ✓ Easy access to genetic advice at any stage in the care pathway for participants and their families
- ✓ Direct liaison with the regional genetics laboratory
- ✓ Accurate clinical interpretation of VUS
- ✓ As mutation carriers will be known to the clinical genetics service there is seamless offering of cascade (presymptomatic) testing to family members of mutation carriers
- ✓ Identification and further investigation of individuals who do not have *BRCA1/BRCA2* mutations but do have a suggestive family history
- ✓ Overview of genetic testing activity within a region, and the ability to make comparisons between genetics centres to get a UK-wide perspective

Therefore the GTEOC approach extracts the greatest benefit from clinical genetics expertise, allowing cases which need more careful consideration to be prioritised, but without overly prescriptive involvement. Models of clinical genetics care have been founded on testing for conditions such as Huntington's disease, and therefore a re-evaluation is warranted in the context of a broader range of conditions, including more common diseases with a genetic basis, such as cancer. The introduction of a model such as this is dependent on close working between oncology and clinical genetics but in this context the potential benefits include:

- Improved access to testing, especially for the substantial proportion of women with *BRCA1/BRCA2* mutations without a family history
- Improved quality of care informed by knowledge of mutation status
- More efficient use of clinical genetics personnel time, potentially allowing reallocation of resources

# 4. Implementing an NHS GTEOC service in the East Anglia region

## 4.1 The process of setting up the service and key changes

For those wishing to implement a GTEOC based model of *BRCA1/BRCA2* testing in their own regional service, we describe the process of transitioning from our original NHS testing pathway to an NHS GTEOC service within our region.

### *Background*

We recognised a need for improvement in the access to genetic testing in the East Anglia region which was mostly driven by the large discrepancy between the number of patients diagnosed with ovarian cancer and the number of referrals to clinical genetics for *BRCA1/BRCA2* testing. Awareness amongst the oncology community of the effectiveness of new targeted therapies, like PARP inhibitors, which have proven to be more effective for patients with mutations, has driven a desire to redefine the patient population who might benefit from *BRCA1* and *BRCA2* testing. Initial discussions took place with key members of staff, such as surgeons, oncologists and specialist gynaecological-oncology nurses, who were keen to improve service delivery for their patients through expanded access to testing.

### *NHS GTEOC service eligibility criteria*

In order to optimise delivery of the NHS GTEOC service, the distribution of mutations and VUS in the GTEOC research study participants was taken into account to define the eligibility criteria for testing. In the research study, 17 of the 18 mutations observed were in women aged under 70 years, whilst almost 50% of VUS were found in women aged over 70 years. In our NHS service, testing is therefore offered to all women with epithelial ovarian cancer aged under 70 years as the mutation prevalence is above the current threshold of 10% used to define eligibility for testing breast cancer families in the UK, as per the NICE guidelines (NICE CG164). This age cut-off also improves the mutation: VUS ratio from 1:1 to 2:1. By not testing women aged over 70 years it is possible to reduce the number of tests by around 37%. Although the eligibility criteria are important to ensure an effective service, in all cases clinical judgement is essential to ensure patients are assessed according to their individual characteristics, and any woman over 70 years with a significant family history or personal history of breast cancer would be offered testing. Therefore the one woman with a mutation in the GTEOC research study aged over 70 would have been offered testing in our NHS service model on the basis of clinical judgement, despite not meeting the initial eligibility criteria.



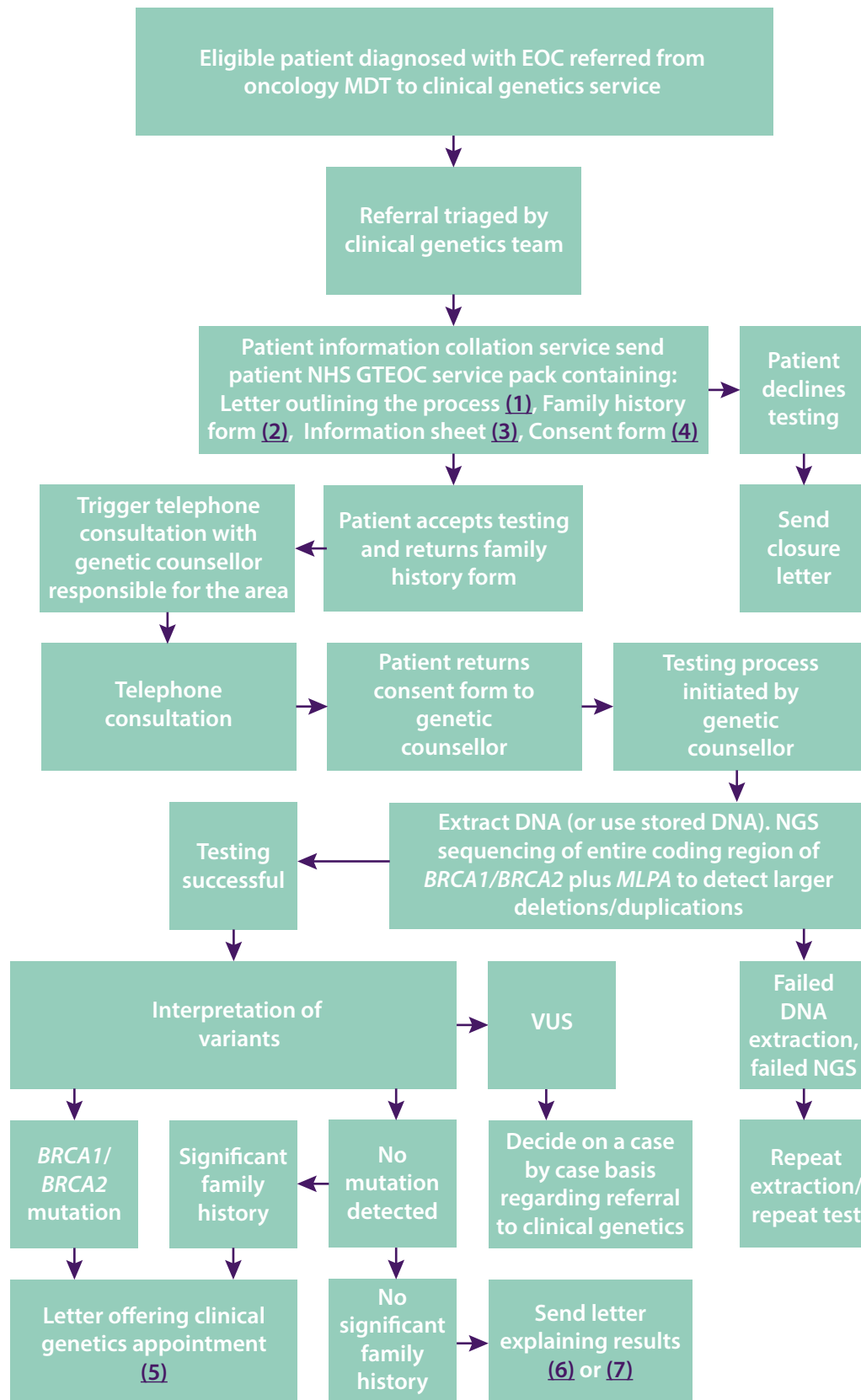
## *Setting up the NHS GTEOC service*

The first step to establishing the NHS GTEOC service was to discuss the service proposal with laboratory staff, the genetic counselling team, surgeons, oncologists and the specialist gynaecological-oncology nursing staff in the region. This occurred through face to face meetings and, in order to disseminate important service information, through more formal approaches such as presentations at regional network meetings. This ensured complete coverage with dissemination beyond networks of colleagues where there was regular interaction, to include professionals with whom there may not have been existing contact. The NHS GTEOC service proposal was met with enthusiasm, as professionals across the region were keen to increase access to *BRCA1/BRCA2* testing for their ovarian cancer patients.

[Figure 2](#) shows the testing pathway for the NHS GTEOC service.

# Genetic testing in epithelial ovarian cancer

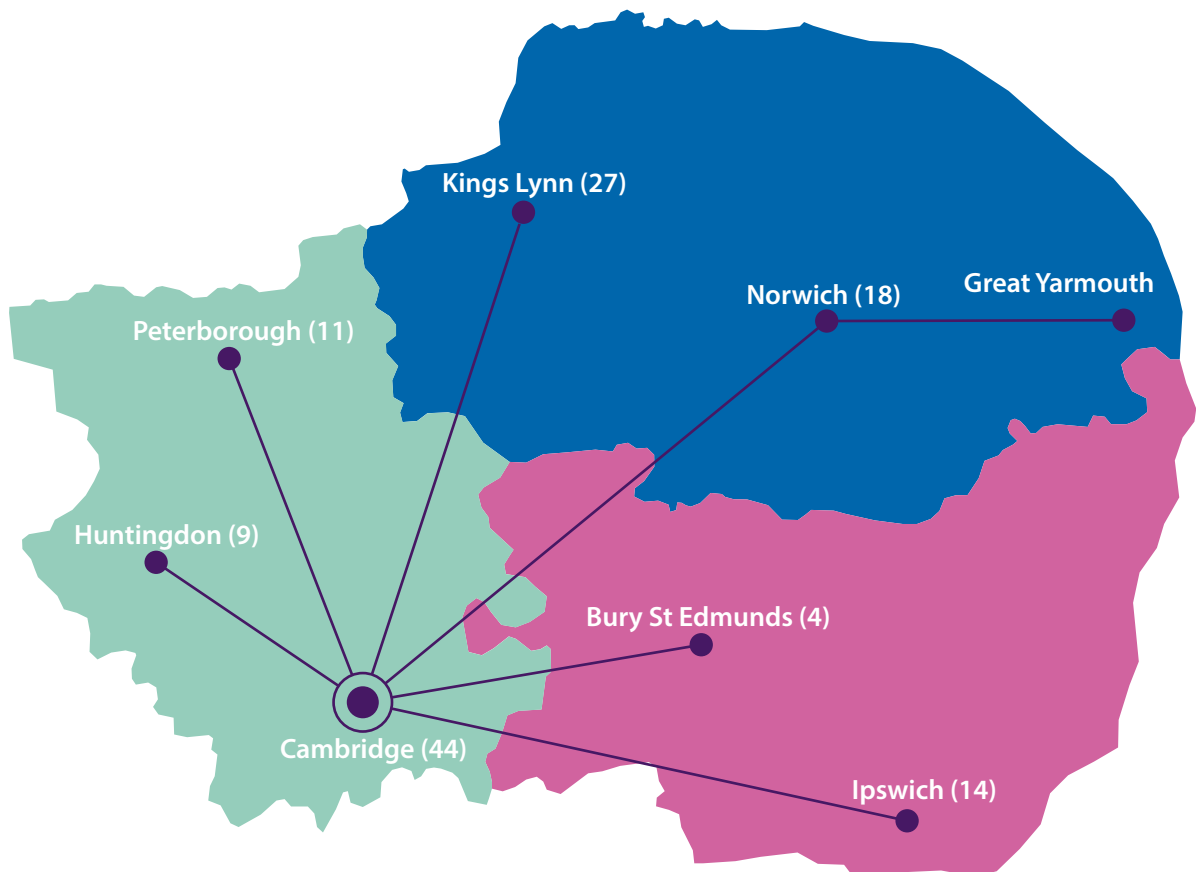
Figure 2 NHS GTEOC service pathway



## *Scale of the East Anglia regional NHS GTEOC service*

[Figure 3](#) shows the hub and spoke regional service in East Anglia, and gives numbers of patients referred for testing at each site since the introduction of the NHS GTEOC service. For the population of 2.4 million in East Anglia, the NHS GTEOC service received 127 referrals for *BRCA1/BRCA2* testing across the region from June 2015-November 2016. This group of patients constitutes a relatively small proportion in the context of the total number of referrals within clinical genetics, therefore changes made to the offer of testing may be made without substantial impacts on resources/logistics.

Figure 3 Epithelial ovarian cancer patients referred for *BRCA1/BRCA2* testing (June 2015-November 2016) in the NHS GTEOC service in the East Anglia region



## 4.2 Changes to interactions, referral and reporting structures and responsibilities

Setting up an effective clinical service is reliant on on-going dialogue between departments to define new reporting structures and responsibilities. Here we outline our experiences.

### *Interactions*

The biggest challenge and most important part of setting up the service was ensuring the links between each oncology department and clinical genetics. First steps included designating one consultant and one specialist nurse in each hospital to be responsible for the identification of new patients and sharing the knowledge and experience with their colleagues. We ensured staff at the sites had the necessary knowledge through presentations and regular updates and provided them with support if any uncertainties arose. Within a short period of time we noticed that the network of professionals contributing to the *BRCA1/BRCA2* testing expanded with increasing interest in testing amongst both professionals and patients.

### *Referral structure*

Oncology multi-disciplinary teams (MDTs) are critical to the referral process. By creating a *BRCA1/BRCA2* test-specific referral document ([link](#)) that applied specifically to ovarian cancer patients, the referral process was simplified and this made it easier for oncologists to refer patients. Referrals from Addenbrooke's Hospital are made through its electronic health record and referrals from other hospitals to the service are made using a standard one-page proforma that can be faxed or posted to the genetics service.

### *Reporting structures*

The reporting approach for the NHS GTEOC service did not change from that of the original service, but the list of people to whom reports were sent grew as the number of clinicians referring patients increased. Sharing the results of testing allows timely confirmation of mutation status for referring clinicians for a larger number of patients with potential to consider the implications.

### *Responsibilities*

The responsibility for delivering the NHS GTEOC service is shared between the people involved in all aspects of the process. In the current system, weekly cancer genetics meetings involving genetic counsellors and clinicians provide a forum to discuss any GTEOC cases where further consideration is deemed necessary. In the initial stages of the NHS GTEOC service, a designated coordinator was included in correspondence between the patients and the genetic counsellor. This person was responsible for collecting data on new patients and the outcomes of testing. Currently, the genetic counsellor or consultant involved in the patient's care is directly responsible for updating records on patients who have undergone testing.

## 4.3 Impact on care

Apart from removing the referral for the initial risk assessment in clinical genetics, the care pathway for patients has remained largely the same. However, the change in approach to testing has impacted on the patients' experiences of care, and the operation of the service.

### *Impact of reduced travel*

Patients do not incur any additional travel costs, or time spent travelling to clinical genetics appointments. The waiting time for the telephone clinic is much shorter as none of the parties involved (genetic counsellor, consultant or patient) have to travel. For face to face meetings, for example to discuss a positive result, patients are seen either in the peripheral hospitals once monthly as part of the general NHS clinical genetics outreach clinics (King's Lynn, Peterborough, Bury St Edmunds, Huntingdon, Ipswich) or at weekly clinics at Cambridge or Norwich.

### *Patient experience*

Our experiences of offering a telephone service to patients were positive, and support findings in the literature which have shown the equivalence of telephone and face to face counselling in terms of psychosocial and informed decision-making outcomes <sup>[27]</sup>. There is no time limit for testing following diagnosis so this allows patients time to come to terms with their diagnosis first and then consider the option to have testing. Testing can be carried out at any time to facilitate treatment.

### *Therapeutic approach*

The initial therapeutic approach remains the same. Patients are usually offered first line treatment for ovarian cancer as per NICE guidelines. That may be followed by more personalised treatment (such as PARP inhibitors) if a mutation is detected.

## 4.4 Impact on resources

As described earlier, the number of patients to whom the change applies, in the context of the regional clinical genetics service, is relatively small. Therefore, whilst setting up the NHS GTEOC service we could be confident, based on this, and the health economic analyses in the GTEOC research study, that the overall magnitude of the impact on resources would be modest.

Prior to implementing the new service our considerations focused on novel aspects of the service:

- Setting up the telephone clinic tariff

As a new element within the NHS GTEOC service, we conducted local negotiations with commissioners regarding setting up the telephone clinic and agreeing a tariff for this service, to accurately reflect the nature of the telephone clinic appointment: e.g. setting a tariff higher than that for a follow-up call. The tariff also factored in the resource implications of follow up care for the proportion of mutation-positive cases.

- Creating new documentation

New documents were created following the criteria of existing hospital templates and involved meetings to approve format and content.

The on-going impact on resources now the NHS GTEOC service is running have been quite marginal, but the main areas of change to note have been:

- Triaging time. The clinical genetics team reviews all referrals for the NHS GTEOC service within 48 hours of them being received, to ensure that the correct patients enter the NHS GTEOC pathway. For NHS GTEOC referrals this does not constitute a large time burden as most referrals are appropriate.
- Genetic counsellors' telephone consultations. This represents a redistribution of resources from face to face pre-test genetic counselling and risk assessment in clinic with associated overheads for clinic space and bookings to shorter telephone clinic appointments which can be arranged more easily (and do not include risk assessment). As part of the transformation to the clinical service, the NHS service telephone consultations are very much client-driven and therefore often encompass more in-depth genetic counselling. This has been easily accommodated within the context of the telephone clinic approach. We have not experienced difficulties with staffing capacity in terms of genetic counsellors and the telephone clinic approach has alleviated any potential delays associated with accessing clinic space.
- There is some additional laboratory time and resources for an increased number of tests.
- Cascade testing. The impact of this is difficult to quantify in terms of local resources. In all cases, if a mutation is found, the importance of testing family members is highlighted and the proband is supported to inform relatives so that testing may be offered to all first degree family members (aged 18 and over) in the first place. However, the resource impact from testing relatives depends on a number of factors including family makeup in terms of gender/age, geographic location of relatives, and their feelings about testing.

## 4.5 New documentation

In order to set up the clinical service, a number of new documents were created, including:

- Patient Information Sheet (document that includes all the basic information about the purpose of testing, testing outcomes and implications of the outcomes) ([link](#))
- Patient Information Collation Service referral letter outlining the process of testing ([link](#))
- Request form for telephone clinic with referral criteria ([link](#))
- Letters to patients with information about the outcome of testing ([link1](#)) ([link2](#)) ([link3](#))

## 4.6 Funding

The health economic data from the GTEOC research study showed that, for testing in women under 70 years of age, the overall impact on resources approaches cost neutral. The changes in expenditure resulting from the NHS service i.e. a reduction in spending on clinical genetics clinic time, with a concomitant increase in telephone clinic time/increased costs of laboratory testing, are contained within the clinical genetics service budget, without resources moving across budgetary divisions. We therefore did not need to request for additional resources from our Trust for setting up the NHS GTEOC service.

## 4.7 Update on the NHS GTEOC service

Since the introduction of the NHS GTEOC service in our region, 127 women have been offered testing, and full data on the outcome of testing will be reported in subsequent updates on the service. The median reporting time for testing from sample receipt to final report was 27 days (range 13-50 days).

This is in line with our expectations given the GTEOC research study findings and the impact of the eligibility criteria. In the NHS GTEOC service women can be tested at any point following diagnosis so, in contrast to the GTEOC research study, there is the potential for women with a longer clinical history to come forward for testing, which may impact on numbers in the initial stages of setting up a service.

### *Challenges*

The NHS GTEOC service does not have the same level of oversight of the number of patients referred for testing as in the GTEOC research study, so we remain vigilant to ensure patients are not missed through intra-regional variability in test referring practice. Maintenance of an optimal service is reliant on on-going communication and we therefore plan to provide service updates for all our local sites within the region.

### *Further developments*

In order to appraise the introduction of the service, a clinical audit is planned to assess the impact of the NHS service against predictions from the GTEOC research study, and to invite feedback from patients and clinicians about their experiences of the new testing approach.

We are considering the application of the GTEOC model of care for other groups of patients to improve access to testing where prior assessment of risk in clinical genetics may not be the most appropriate approach. This includes *BRCA1/BRCA2* testing for women aged under 50 years with triple negative breast cancer, and testing for Lynch syndrome genes for patients aged under 50 years with uterine or colon cancer.



## 5. Discussion

### *Current testing provision and influencing factors*

Genetic testing for *BRCA1/BRCA2* mutations in patients with epithelial ovarian cancer has demonstrable benefits yet referral rates are still surprisingly low, with recent estimates suggesting rates of between 15% and 30% of eligible patients being offered testing <sup>[15], [16], [17], [18]</sup>. The NICE guidelines for *BRCA1/BRCA2* testing in breast cancer have served as a starting point for offering testing, the lack of consensus guidelines specifically for genetic testing in epithelial ovarian cancer has resulted in local approaches filling this void, with resultant variability in practice. Professionals have raised concerns regarding capacity, both in terms of laboratory resources to realise testing, and the ability of clinical genetics services to provide adequate pre- and post-test counselling and to deal with the interpretation of an increased number of variants. However, our experience of offering expanded NHS testing in our regional service has not resulted in significant challenges in terms of resource and capacity demands. To encourage a sustained increase in referral rates, education is essential to ensure professionals are aware of the potential risk-reducing and therapeutic benefits of testing for patients and their families. Adequate support is also needed to enable them to confidently discuss the implications and outcomes of testing. Within our own NHS service, we have demonstrated the importance of this on-going dialogue to ensure optimal service delivery. But even with adequate capacity and a motivated and well-informed workforce, it is worth noting that there still exist some other more complex factors which may impact on local initiatives to make changes to service delivery. Existing organisational structures, governance, commissioning and reimbursement policies are likely to reflect the situation that inherited genetic testing remains an NHS highly specialist service. However, for some patients, as in the NHS GTEOC service model, access to genetic testing should be regarded as an essential integrated part of clinical management.

### *Drivers for change*

Despite the challenges, in oncology at least, mainstreaming models are becoming more widespread with 73% of UK cancer genetic services surveyed in a recent consultation exercise <sup>[18]</sup> describing local arrangements where non-geneticists could order specific tests. The UK Genetic Testing Network (UKGTN) review of genetic testing activity for inherited diseases showed that the majority of testing was initiated by professionals outside of clinical genetics <sup>[28]</sup>. Indeed the consultation by Slade *et al.* <sup>[18]</sup> supports the idea that clinicians are keen to improve appropriate access to genetic testing, whilst making efficient use of clinical genetics resources. As mentioned previously, there are a number of drivers impacting upon this, including the decreasing cost and turnaround time for genetic testing, scientific developments demonstrating the prognostic and therapeutic significance of certain genetic mutations and increased patient awareness and willingness to engage in different models of care.

The current drivers are described below in [Figure 4](#), along with outstanding areas for change which, if addressed, could help to support even more widespread applications of mainstream genetic testing.

Figure 4 Issues around mainstream clinical application of genetic testing



Traditional models of genetic service provision were derived when test assays were relatively labour-intensive and provision was therefore carefully managed to make efficient use of limited resources. In addition, there has been a tendency to use a standard approach to genetic testing and counselling across all genetic testing domains, rather than considering the needs of patients with different diseases or in different personal or clinical scenarios. For example, patients with cancer will differ in their need for genetic counselling from unaffected individuals and in this more time-sensitive milieu, where mutation status may affect therapeutic options, a testing strategy which can deliver timely information may be of critical importance.

The prognostic and therapeutic significance of *BRCA1/BRCA2* mutations means that *BRCA1/BRCA2* testing should now be considered an important element in the diagnostic work-up, alongside other standard components such as tumour staging. The advantages are clear in terms of identifying increased numbers of mutation carriers amongst affected individuals and allowing access to cascade testing for unaffected family members. This has resultant benefits as testing unaffected relatives for a known mutation is more efficient than screening for larger numbers of potential mutations. Aside from the benefits for patients and their families in terms of access to the most appropriate therapeutic and risk-reducing options, such an approach brings efficiency savings both in managing affected individuals and their unaffected relatives. In thinking about clinical genetics services as a whole, any improvement in efficiency represents an opportunity to reallocate resources to other priority areas within these services.

Patients have become increasingly aware of the significance of genetic mutations in cancer, as a result of charity campaigns, support groups and reporting in the media of, for example, Angelina Jolie's experience of *BRCA1/BRCA2* testing. A more general cultural shift towards acceptance of online or telephone provision of services as opposed to face to face interaction is perhaps influencing change in this area. In a study in the Netherlands<sup>[22]</sup> to evaluate provision of testing without face to face counselling, some patients who were already visiting hospital numerous times felt an extra visit would be a burden at this time and therefore readily took up the offer of a telephone consultation.

## *The impact of wider genetic testing - issues to be considered*

Wider use of genetic testing brings important considerations regarding its clinical utility. The sensitivity and specificity of the test should be well-established and there needs to be sufficient evidence of clinical utility to support using such a test in a clinical setting. The ease with which variants can be interpreted is critical and automated bioinformatics pipelines are necessary to handle the majority of results, allowing expert interpretation to be focused on a minority of variants, and thereby keeping VUS results to a minimum. Given the potential for variability in practice, consensus-based national guidelines covering interpretation of variants are important to support initiatives to provide increased genetic testing nationwide. The ACGS recently issued a consensus statement supporting adoption of the ACMG guidelines for sequence variant classification and interpretation in the UK for rare disease and familial cancers<sup>[29]</sup>.

Consideration needs to be given to the timing of testing, and the acceptability and clinical utility of testing women at diagnosis versus further along in the therapeutic process, as well as the resource implications of access to testing for a much broader group, including women who are not in an active phase of disease.

Any change to the structure, culture and practice of clinical genetics services must be supported by adequate training, education and clinical audit to ensure a smooth reallocation of new roles and responsibilities amongst clinical geneticists and other clinical specialists and appropriate service development.

## *Future developments*

The NHS GTEOC service has demonstrated the feasibility and potential for improving access to genetic testing, and is therefore aligned with the overarching drive to improve outcomes for patients, as evidenced by the government's commitment to initiatives in this area including the 100,000 Genomes Project and NHS England's vision for improving outcomes through personalised medicine. While the prognostic and therapeutic significance of *BRCA1/BRCA2* mutations is relatively well characterised, ongoing work is likely to yield greater information about existing and novel mutations. Therefore, given the pace at which understanding of genetic aetiology and tailored therapeutics is developing, it is imperative that systems build in a degree of flexibility to cope with possible increases in mainstream genetic testing and the GTEOC model of care represents an approach which could support the clinical application of these future scientific developments.

The increasingly widespread routine use of genetic analysis in tumour samples must also be considered within the context of individuals with inherited mutations. Genetic testing of tumours may identify individuals with germline mutations, and this will need to be coordinated with clinical genetics services to ensure proper counselling and access to testing for family members.

## *Summary*

The NHS GTEOC service is designed to address an identifiable clinical need resulting from a shortfall in access to genetic testing for patients with epithelial ovarian cancer. Our service design reduces the burden on the clinical genetics service - and bypasses the bottleneck - to allow improved access to testing, whilst maintaining the benefits of a genetics-coordinated service, which we feel is very important in optimising care for patients and their families. Implementation of the NHS service has been straightforward, and given the number of patients referred, has not had a significant impact on resources. The benefits for patients are clear and supported by data from the GTEOC research study,;

- Improvements in diagnostic yield
- Enhanced patient experience
- Better quality of care
- More efficient service

We continue to monitor the impact of the service to help maintain optimal patient care, but we feel that the NHS GTEOC service is already working well within the structure of our regional oncology/genetics service, with a central hub and local referral centres. We believe it provides a successful service model which other providers in the UK could apply within their own service.

## Glossary

### Founder mutations

Mutations which are found at a relatively high frequency within a specific population as a result of them being present in one or more individuals who are founders of a distinct population.

### Germline mutation

A heritable mutation present in all cells of the body.

### Multiple ligation-dependent probe amplification (MLPA)

In PCR, probes are designed to bind to specific DNA sequences and initiate the amplification process. Multiplex Ligation dependent Probe Amplification (MLPA) makes use of split probes which can only ligate and function when a specific DNA sequence is present. Therefore the PCR product is only visible when the complete target sequence is present. MLPA can identify larger (exonic) deletions and duplications which may not be detectable by Sanger or next generation sequencing.

### Poly ADP ribose polymerase (PARP) inhibitor

The pharmacological inhibitor prevents the enzyme PARP from repairing breaks in DNA. In *BRCA* mutation-positive cancer cells, PARP function is essential to prevent breaks in the DNA and cell death. By inhibiting the action of PARP, PARP inhibitors can cause selective cell death of *BRCA* mutation-positive cancer cells.

### Penetrance

The proportion of individuals who have a mutation and express symptoms of the disease.

### Somatic mutation

An acquired mutation arising in some cells of the body as opposed to an inherited germline mutation which is present in all of a person's cells.

### Variant of uncertain significance (VUS)

A VUS is a variant whose pathogenicity, at the current time, can neither be confirmed nor ruled out. This may be due to a lack of data on identical variants, a lack of knowledge regarding the function of the gene affected, or a lack of understanding regarding the functional impact of the mutation.

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# Additional information

Target Ovarian Cancer's Genetic testing and hereditary ovarian cancer guide provides a useful resource for women with ovarian cancer and their families describing inherited mutations in ovarian cancer and the implications for families [\(link\)](#)

# Appendix

## 1. Form for referral to clinical genetics telephone clinic

Cambridge University Hospitals   
NHS Foundation Trust

NHS – Genetic Testing in Epithelial Ovarian Cancer

**Referral to Clinical Genetics telephone clinic - Epithelial Ovarian Cancer**

**Eligibility for BRCA1/BRCA2 testing**  
 <70 with Epithelial Ovarian Cancer, EOC (Serous, Endometrioid, Adenocarcinoma)  
 >70 with Epithelial Ovarian Cancer and a previous history of breast cancer or history of breast or ovarian cancer in a first degree relative  
**NOT** eligible - Mucinous, clear cell or any borderline tumours

<div style="border: 1px solid black; border-radius: 10px; padding: 10px; margin-bottom: 10px;"> <b>Patient demographics:</b>  <b>Hospital no:</b>  <b>Surname:</b>  <b>First names:</b>  <b>Date of birth:</b>  <b>NHS No:</b> ____ / ____ / ____                  (Use hospital identification label)             </div>	<b>Consultant:</b> <b>Department:</b> <b>Hospital:</b> <b>Requesting Dr:</b> <b>Patient tel no (include <u>all</u> available H/W/M):</b>
<b>Is this family already known to Clinical Genetics?</b> Yes / No <b>Family number or name of person seen:</b>	
<b>Is the patient aware of this referral, including the reasons for it &amp; potential implications?</b> Yes / No <i>We would generally expect the patient to be prepared for our telephone contact</i>	
<b>Relevant medical history:</b> (age at diagnosis, histology)	<b>Relevant family history:</b> (breast, ovarian or prostate cancer)
<b>Has DNA been stored?</b>	Yes / No
<b>Any special requirements?</b> e.g. need for foreign language interpreter	<b>Consultant signature (essential):</b>  <b>Print name:</b> <b>Designation:</b> <b>Bleep/Contact no:</b> <b>Date:</b> DD / MM / YYYY

*If urgent or special requirements, please can the consultant telephone the on call genetic counsellor to discuss? 01223 216446*

Please ensure that all the requested details are provided in legible writing.

Please either send referral by fax (01223 217054) or post to:

Department of Clinical Genetics  
 Box 134, Addenbrooke's Hospital  
 Hills Road  
 Cambridge, CB2 0QQ

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2 Worts Causeway  
Cambridge  
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