



## Original Research

# Multidisciplinary interventions in a specialist Drug Development Unit to improve family history documentation and onward referral of patients with advanced cancer to cancer genetics services



Cathryn A. Moss<sup>a</sup>, Elena Cojocaru<sup>b</sup>, Janet Hanwell<sup>b</sup>, Simon Ward<sup>a</sup>, Wen Xu<sup>b</sup>, Mary van Zyl<sup>b</sup>, Lorraine O’Leary<sup>b</sup>, Johann S. de Bono<sup>b</sup>, Udai Banerji<sup>b</sup>, Stan B. Kaye<sup>b</sup>, Anna Minchom<sup>b</sup>, Angela J. George<sup>a,c</sup>, Juanita Lopez<sup>b</sup>, Terri P. McVeigh<sup>a,\*</sup>

<sup>a</sup> Cancer Genetics Unit, Royal Marsden NHS Foundation Trust, Fulham Road, London, UK

<sup>b</sup> Drug Development Unit, Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK

<sup>c</sup> Gynaecological Oncology Unit, Royal Marsden NHS Foundation Trust, Fulham Road, London, UK

Received 22 February 2019; received in revised form 26 March 2019; accepted 2 April 2019

Available online 16 May 2019

## KEYWORDS

Germline genetic testing;  
Germline predisposition;  
Cancer predisposition syndrome;  
Mismatch repair;  
Mainstreaming;  
Somatic testing;  
Drug development;  
Phase 1;  
Advanced cancer

**Abstract Background:** Molecular aberrations in cancer may represent therapeutic targets, and, if arising from the germline, may impact further cancer risk management in patients and their blood relatives. Annually, 600–700 patients are referred for consideration of experimental drug trials in the Drug Development Unit (DDU) in our institution. A proportion of patients may merit germline genetic testing because of suspicious personal/family history or findings of tumour-based testing. We aimed to assess the impact of different multidisciplinary interventions on family history taking and referral rates from DDU to Cancer Genetics Unit (CGU).

**Methods:** Over 42 months, three interventions were undertaken at different intervals: (1) embedding a genetics provider in the DDU review clinic, (2) ‘traffic light’ system flagging cancers with a heritable component and (3) virtual multidisciplinary meeting (MDM). Comparative analyses between intervals were undertaken, including referral rates to CGU, investigations and patient outcomes. Family history taking in a sample of 20 patients managed in each interval was assessed by a retrospective chart review.

**Results:** Frequency of family history taking and referral to CGU, increased with each intervention, particularly, the virtual MDM (40% vs 85%). Referral rates increased over the study

\* Corresponding author: Consultant Clinical Geneticist Cancer Genetics Unit, Royal Marsden NHS Foundation Trust, Orchard House, Downs Road, Sutton, SM2 5PT, UK. Fax: +0044 208 770 1489.

E-mail address: [terri.mcveigh@icr.ac.uk](mailto:terri.mcveigh@icr.ac.uk) (T.P. McVeigh).

period, from 0.1 referral/week (5/year, 0.36% total referrals) to 1.2/week (projected 63/year, 3.81%). Forty-four (52%) patients referred required germline testing; in three of whom, variants were identified. Non-attendance rates were low (6, 7%).

**Conclusion:** Patients in the DDU are unique, with long cancer histories and often short estimated life expectancy. Multidisciplinary working between CGU and DDU facilitates germline testing of those patients who may otherwise miss the opportunity.

© 2019 Elsevier Ltd. All rights reserved.

## 1. Introduction

‘Cancer’ refers to a group of heterogeneous diseases of disordered cell growth caused by driver mutations in key proto-oncogenes or tumour suppressor genes. The vast majority of such variants are acquired in somatic cells over time, but a small proportion (~5–10%) of cancer is attributable to heritable variation in the germline. Recognition of individuals with germline variants in cancer predisposition genes may not only facilitate personalisation of cancer treatment in affected individuals, but also facilitate risk estimation and prevention in the proband and their blood relatives. Inherited cancer predisposition should be suspected in individuals affected by rare cancers, multiple primaries or cancer at younger than expected age, or individuals with a positive family history of cancers with a shared genetic aetiology. Criteria for National health service (NHS)-funded genetic testing are dynamic, changing over time in response to increasing evidence from research [1], increasing availability of targeted treatments, and rapidly decreasing costs of genetic testing [2], meaning that patients who were unable to avail of testing at a one-off genetics assessment may later become eligible for germline genetic testing over time.

The Drug Development Unit (DDU) in the Royal Marsden NHS Foundation Trust represents one of the largest phase 1 trial units in Europe, with approximately 600–700 patients assessed each year. Referrals are accepted from anywhere in the United Kingdom, meaning that patients may travel long distances to attend for clinical review. Patients attending this unit comprise a unique, heterogeneous group. Most patients have long cancer histories and are heavily pre-treated with standard therapies, before embarking on an experimental phase 1 trial. A proportion of patients, conversely, have relatively short cancer histories, presenting with rare cancers for which standard options are limited. In light of the experimental nature of the trials, enrolled patients must be of good physiological fitness, leading to an over-representation of younger patients with relatively little medical comorbidity.

A significant proportion of young patients with cancer, particularly those with rare cancers, will have an underlying germline predisposition, and are likely to benefit

from a review by a Clinical Geneticist. Patients with long cancer histories may similarly benefit from a review to determine their eligibility for genetic testing according to current criteria. The ascertainment of a patient’s family history of cancer is critical in identifying patients who may benefit from a genetics review. We have previously demonstrated that attempts to record family history in clinics in the DDU in our institution are suboptimal, even for those patients affected at young ages [3]. Pedigree drawing in the Cancer Genetics Unit (CGU) in our institution is undertaken using departmental software, and familial pedigrees are stored separately from individual electronic patient records (EPRs). Family history documentation on the hospital’s electronic record is limited to a free text comment, and there is significant variability in the manner in which it is recorded, with some individuals restricting their comments to first-degree relatives, others to first- and second-degree relatives, and some individuals focussing on only family history of the specific cancer type of the proband. Such issues are not unique to our institution [4–8]. Close multidisciplinary working between Clinical Genetics and other clinical teams can improve identification of patients eligible for genetic testing. One approach includes embedding of genetics clinicians in multidisciplinary clinics [9–12], which has been shown to improve referral rates and uptake of genetic testing. It has also been shown that virtual multidisciplinary meetings (MDMs) involving clinical genetics can also have a positive impact [13]. In the absence of availability of clinicians to participate in clinics or multidisciplinary team (MDT) meetings, clear guidelines should be provided to help non-genetic professionals identify patients in need of onward referral. We implemented a number of different interventions to investigate their impact on family history documentation and referral rates from the DDU to the CGU.

## 2. Methods

Over a 42-month period, different interventions were implemented to encourage recognition and referral of patients suspected to have an underlying germline predisposition to cancer. Interventions included the following:

1. Embedding of a clinical geneticist in one clinic in DDU per week

2. Adoption of a ‘traffic light’ system to highlight cancer types with strong association to underlying germline predisposition
3. Virtual MDT review of patients attending DDU clinics

### 3. Interventions

#### 3.1. Intervention 1: embedding a genetics clinician in one clinic per week

For a period of one year, a clinician from the CGU attended one clinic in the DDU per week. In advance of their appointment, the cases of those patients due to attend the clinic were discussed in a MDT meeting. Patients who would benefit from genetics review based on age at diagnosis, cancer type or recorded family history were identified and reviewed in clinic in real time by the genetics clinician, without the need for formal referral from DDU clinicians.

#### 3.2. Intervention 2: ‘traffic light’ system

The Clinical Genetics Unit devised and provided all DDU clinicians with a three-tiered classification of the most common types of cancers managed in the DDU ([Supplementary Table 1](#)). Cancers listed in the ‘green’ category were those cancers more commonly associated with somatic aberrations or viral or environmental factors rather than germline predisposition (e.g. cervical cancer, lung cancer), for which the patient was unlikely to be eligible for NHS-funded genetic testing. Cancers listed in the ‘red’ category were those cancers strongly associated with germline variation (e.g. high-grade serous ovarian cancer, adrenocortical cancer), for which the patient would be offered a germline genetic test regardless of family history. Cancers in the ‘orange’ category were cancers moderately associated with germline predisposition, for which affected patients *may* be offered germline testing if they fulfilled other criteria. DDU clinicians were encouraged to refer patients with cancers in the red category, irrespective of family history, and patients with cancers in the orange/green category, if there was a positive family history of cancer or the patient was younger than expected age at diagnosis. It was not possible to make a fully comprehensive classification system, and clinicians were encouraged to discuss and/or refer patients with rare cancer types not included on the pro forma.

#### 3.3. Intervention 3: virtual multidisciplinary review of patient history

As part of pre-clinic preparation, the electronic record of patients attending clinics in the DDU was reviewed by a

genetics professional. Patients with personal or documented family history, suggestive of an underlying germline predisposition, were highlighted for onward referral to the CGU. Formal referral by DDU clinicians to the CGU was required before appointments were offered.

#### 3.4. Comparative analyses

Comparisons were made between five periods: the year preceding any interventions (52 weeks), the period in which intervention 1 was undertaken (53 weeks), the period after intervention 1 where no active intervention was undertaken (30 weeks), the period in which the ‘traffic light’ system was piloted (22 weeks) and the period during which new patients were virtually prospectively assessed by a clinician from the CGU (19 weeks). Given the small patient numbers, formal statistical analysis was not undertaken.

#### 3.5. Family history taking and onward referral from the DDU to CGU

Referral rates from the DDU to CGU were prospectively recorded over the study period. Data were recorded with respect to absolute number of referrals from the DDU to CGU, as well as relative number of referrals from the DDU as proportion of all referrals to the CGU. The EPRs for 100 patients were reviewed to determine whether or not family history was documented in any way.

This represented 20 consecutive new patients reviewed in DDU clinics in each study period.

## 4. Results

### 4.1. Unselected patients ( $n = 100$ )

#### 4.1.1. Genetic assessment before referral to the DDU

Twelve of 100 (12%) unselected patients reviewed had undergone some form of germline genetic testing before their referral to the DDU. Immunohistochemistry to assess mismatch repair (MMR) proficiency was performed on the tumours of an additional 5 patients with Lynch syndrome-associated cancers. Patients with tumours demonstrating MMR deficiency were all appropriately referred to the CGU.

#### 4.1.2. Family history recording and onward referral

Family cancer history was documented in 75 of 100 unselected cases reviewed. Variability in the proportion of patients for whom family history was documented was noted, increasing from 40% cases in period 1 to 85% in period 5 ([Table 1](#)). These patients were heterogeneous in terms of age at diagnosis and time interval between diagnosis and presentation in the DDU ([Table 1](#)) and

Table 1  
Family history documentation, genetics review and investigations in 100 unselected DDU patients over 5 time points.

Intervention	Median age at diagnosis (range), years <	Median length of time between diagnosis and presentation at the DDU (Range), years	Genetic review before referral to the DDU <sup>a</sup>	Mismatch repair immunohistochemistry n (%) <sup>b</sup> <	Number of cases whose family history was documented <sup>c</sup> , n (%) <sup>d</sup> <	Number of cases with suspicious family history of cancer, n (%) <sup>e</sup> <	Number of cases referred on because of family history <sup>f</sup> , n (%) <sup>d</sup> <
None	65 (20–84)	2 (1–13)	2 (10%)	0/7 (0%)	8 (40%)	2 (25%)	0 (0)
Embedded genetics clinician	53 (20–76)	2 (<1–12)	2 (10%)	1/4 (25%)	14 (70%)	6 (43%)	1 (17%)
None	52 (26–84)	3 (<1–20)	1 (5%)	2/5 (40%)	18 (90%)	5 (28%)	1 (20%)
Traffic light system	57 (31–73)	3 (1–10)	3 (15%)	2/7 (29%)	18 (90%)	10 (56%)	2 (20%)
Virtual MDT	59 (23–77)	2 (<1–9)	4 (20%)	0/3 (0%)	17 (85%)	4 (24%)	0 (0%)
Overall	54.5 (20–84)	21 (<1–20)	12 (12%)	5/26 (19%)	75 (75%)	27 (27%)	4 (15%)

DDU, Drug Development Unit; MDT, multidisciplinary team.

<sup>a</sup> Formal review or mainstream genetic testing.

<sup>b</sup> Percentage of Lynch syndrome-associated tumours.

<sup>c</sup> Recorded by clinician in the DDU.

<sup>d</sup> Percentage of cases whose family history was documented by a DDU clinician.

<sup>e</sup> Cases not previously reviewed by genetics or case where there was a change in personal/family history since review.

<sup>f</sup> Percentage of cases with pertinent family history.

cancer type (Supplementary Table 2). Three patients had multiple primary cancers. Those patients allocated to a phase 1 trial (n = 31) were more likely to have had genetic testing (n = 4, 13%) or be referred to the CGU (n = 3 [10%]) than those patients discharged back to local oncology services; of whom, 7 patients (10%) and 5 patients (7%) had been reviewed and were referred to the CGU, respectively.

## 4.2. Patients referred to the CGU

### 4.2.1. Patient demographics

In total, over the 42-month study period, 91 patients were referred from the DDU to CGU; of whom, twelve patients had a personal history of two or more primary cancers (six with two primaries and six with three primaries). The diagnoses of patients referred are outlined in Supplementary Table 3.

### 4.2.2. Referral rates

Before active interventions, referrals of patients from the DDU accounted for 0.36% of referrals to the CGU, with 5 referrals in one year (Table 2). Embedding of a clinician from the CGU in one DDU clinic per week led to a greater than 8-fold increase in referrals from the unit (5 vs 43 per year). The increase in referral rates was not sustained when this intervention stopped (n = 6 referrals in 30 weeks). Introduction of the ‘traffic light’ system led to an increase in referral rates (13 in 22 weeks), and a greater increase in referral rates was noted upon introduction of the virtual patient review by a geneticist, such that referrals from the DDU in period 5 (23 in 19 weeks) accounted for 3.81% of total referrals to the CGU.

### 4.2.3. Outcome of genetics review

Of ninety-one patients referred to the CGU by DDU clinicians, 85 (93%) patients were reviewed by a member of the Clinical Genetics team (Table 3). Three patients failed to attend (3%), and an additional three patients passed away before their appointment. Each patient reviewed in the CGU had a thorough assessment of family history to determine eligibility for germline diagnostic testing. For patients affected by tumours associated with Lynch syndrome, immunohistochemical analysis of tumour for MMR deficiency was undertaken to determine if germline MMR gene testing was indicated. The tumours of 28 (33%) patients were assessed by immunohistochemistry (IHC) to check for MMR deficiency. Forty-four patients (52%) underwent at least one diagnostic germline test, including 10 patients who had testing before review in the CGU. Of those reviewed, three (4%) patients declined germline testing. Germline variants were identified in four patients (9% of those tested). Eighteen patients were recruited to germline genetic sequencing research studies over the study period, including 7

Table 2  
Changes in rates of referral from the DDU to CGU over time.

Intervention	Time point	Number of weeks	Number of total referrals received by the CGU	Number of referrals from the DDU to CGU (% of total referrals)	Estimated number of referrals per annum
None	06/07/2015–03/07/2016	52	1392	5 (0.36%)	5
Embedded genetics clinician	04/07/2016–09/07/2017	53	1649	44 (2.67%)	43
None	10/07/2017–04/02/2018	30	941	6 (0.64%)	10
Traffic light system	05/02/2018–08/07/2018	22	703	13 (1.85%)	31
Virtual MDT	09/07/2018–20/11/2018	19	604	23 (3.81%)	63

DDU, Drug Development Unit; CGU, Cancer Genetics Unit; MDT, multidisciplinary team.

patients recruited to the Breast and Ovarian Cancer Susceptibility study, 8 to the Colorectal Gene Identification study, one to the Factors Associated with Childhood Tumours study and 2 to the Precision Medicine in Prostate Cancer study. Fifteen patients agreed to store a sample of their DNA, to facilitate genetic testing at a later date. All patients reviewed were provided with advice regarding their future cancer risk and the risks to their blood relatives. Recommendations for surveillance were also provided, based on family history and/or germline test result if applicable.

#### 4.2.4. Germline variants identified

Germline variants were identified in four patients in this cohort (Supplementary Table 4), including two patients tested before referral to the CGU, both having undergone germline testing via mainstream pathway, following a diagnosis of high-grade serous ovarian cancers in their 40s. One of these patients was found to have a pathogenic *BRCA2* variant and referred to the CGU at the age of 62 years, after presenting to the DDU, to facilitate completion of cascade testing in her children, who had reached adulthood since her diagnosis. The other patient was found to have a variant of uncertain significance in *RAD51C* but was unaware of her result. She was referred to the CGU for further discussion, and reinterpretation of the variant was performed, facilitating reclassification to likely benign. Another patient with early onset pancreatic cancer required further testing of *PRSS1* and *SPINK1* in light of a family history of acute pancreatitis, following an uninformative *BRCA1/BRCA2* genetic test. Another patient was found to have a pathogenic variant in *TP53*, after presenting with multiple primary cancers at young ages.

Two patients were referred to the CGU following detection of variants with high minor allele frequency as part of tumour testing, both of which were confirmed as somatic variants following germline testing.

## 5. Discussion

### 5.1. Recognition of cancer predisposition

Cancer predisposition syndromes are under-recognised and under-diagnosed. Recognition of an inherited

cancer predisposition syndrome as a cause of a patient's cancer may be useful in therapeutic decision-making, to inform surgical approach or chemotherapeutic strategy or to rationalise use of targeted therapies. Furthermore, identification of an inherited predisposition provides the opportunity to identify at-risk relatives and intervene with risk-reducing strategies at a pre-symptomatic stage. Genetic testing of individuals with a significant a priori risk of carrying a highly penetrant genetic variant is cost-effective; germline genetic testing is rapidly becoming cheaper, and eligibility criteria for genetic testing are becoming broader. Guidelines for tumour-based assessment to guide germline diagnostics are also being used more widely. Over time, individuals with cancer may become eligible for germline genetic testing because of changes in their family history or as a consequence of changes to regional or national guidelines.

### 5.2. Assessment of family history

Taking a thorough three-generation family history is a fundamental requirement of a genetics assessment, to inform accurate risk estimation and guide genetic testing. However, acquisition of such information is laborious, and the patient may not have accurate information regarding his/her family history to provide at the time of his/her routine oncology appointment. Furthermore, family histories are dynamic, and assessment of a patient's family history of cancer should not be considered a 'one-off' exercise. Previous studies have shown that omitting discussions about family history or genetic testing, or failure to recognise the relevance of the recorded family history, may be a barrier to referral of patients to genetic services [14–19]. Misconceptions regarding ability to perform testing in unaffected family members or on tumour samples posthumously or lack of awareness of changing eligibility criteria for genetic testing may also represent barriers to referral [14]. This study demonstrated an improvement in attempts to record family history of new patients presenting to the DDU, as well as an increase of referral rates to the CGU. We did not formally assess the quality of family history documentation. Documentation of family history does not necessarily ensure onward referral of

Table 3  
Outcome of genetic assessment.

Intervention	Number of patients referred from the DDU to CGU	Number of patients reviewed in the CGU	Number of patients choosing not to have germline assessment	Number of tumour tests (MMR IHC)	DNA storage	Number of germline diagnostic tests	Number of variants identified	Recruitment to research studies
None	5	5	0	0	1	3	0	0
Embedded genetics clinician	44	42 <sup>a,b</sup>	3	16 <sup>d</sup>	11	18 <sup>i</sup>	3 <sup>l</sup>	10 <sup>n</sup>
None	6	5 <sup>a</sup>	0	1 <sup>e</sup>	0	5	0	2 <sup>o</sup>
Traffic light system	13	12 <sup>a</sup>	0	2 <sup>f</sup>	0	6 <sup>j</sup>	1 <sup>m</sup>	1 <sup>p</sup>
Virtual MDT	23	21 <sup>c</sup>	0	9 <sup>g,h</sup>	3	12 <sup>k</sup>	0	5 <sup>q</sup>
Intervention	91	85 (93%)	3 (4%)	28 (33%)	15 (18%)	44 (52%)	4 (9%)	18

CGU, Cancer Genetics Unit; DDU, Drug Development Unit; MDT, multidisciplinary team; MMR, mismatch repair; IHC, immunohistochemistry.

<sup>a</sup> Patient died before review (n = 3 total).

<sup>b</sup> One patient failed to attend [1].

<sup>c</sup> Two patients failed to attend [2].

<sup>d</sup> Tumours: colon [7], rectal [3], endometrial [1], cholangiocarcinoma [1], ovarian [1], small bowel [1], pancreatic [1] and appendiceal [1].

<sup>e</sup> Tumour: colon [1].

<sup>f</sup> Tumours: colon [1] and rectal [1].

<sup>g</sup> Tumours: colon [5], endometrial [4], rectal [1].

<sup>h</sup> One patient had two primaries (colon and endometrial; both assessed by IHC).

<sup>i</sup> Six patients had testing before review [6].

<sup>j</sup> One patient had testing before review [1].

<sup>k</sup> Three patients had testing before review [3].

<sup>l</sup> One patient with a *SPINK1* pathogenic variant, 1 patient with pathogenic *BRCA2* variant (known) and 1 patient with *RAD51C* variant of uncertain significance (VOUS).

<sup>m</sup> One patient with a *TP53* pathogenic variant.

<sup>n</sup> Breast and Ovarian Cancer Susceptibility (BOCS) study [5], Factors Associated with Childhood Tumours (FACT) study [1], Colorectal Gene Identification (CORGI) study [4].

<sup>o</sup> BOCS [2].

<sup>p</sup> CORGI [1].

<sup>q</sup> CORGI [3], Personalised Medicine in Prostate Cancer study [2].

patients with likely inherited cancer predisposition syndromes [20], as exhibited in this study during periods 3 and 4, when family history documentation by DDU clinicians improved compared with the period when CGU clinicians were embedded in DDU clinics, but onward referrals to CGU decreased. Potential contributing factors for this may include the assumption that patients with positive family histories and a long personal cancer history have previously been, or would be, referred for genetic counselling and testing by another of their many health care providers, analogous to a bystander effect. It is also important to acknowledge that family history is only one part of the clinical assessment, the main focus of which is to assess the performance status and suitability of a patient for inclusion in an experimental clinical trial and to provide information about trials and experimental agents. It is likely therefore that discussing the need for clinical genetics assessment may be deferred or left to the primary treating team.

### 5.3. Changing criteria for germline genetic testing

Criteria for genetic testing include not just family history-focused criteria, but increasingly pathology- or patient-focused factors [21,22], and assessment of MMR by IHC is now universally advocated for patients with certain tumour types [23]. Furthermore, molecular profiling of tumour DNA using broad multigene panels or whole exome or whole genome sequencing is being increasingly used to aid in therapeutic decision-making. This gives rise to the possibility of inadvertently identifying a germline variant during tumour testing [24], which may have implications not just for treatment and trial allocation but also for the wider family. Most patients undergoing this type of testing are interested in receiving secondary germline results [25]. Ideally, assessment of the tumour and of the germline should be carried out complementarily.

In our institution, it was possible to undertake a multidisciplinary assessment to determine eligibility for germline genetic testing. As well as facilitating identification of patients in need of germline assessment; this also facilitated triage of cases in real time. However, staffing levels in the Clinical Genetics services in some regions are suboptimal, and active participation by a member of the Clinical Genetics team in an MDT may not be feasible in every centre. In institutions where genetics professionals are not available to actively participate in such an assessment, other health professionals can be trained to recognise and refer such patients. Aids such as the ‘traffic light’ list used in this study may be helpful in such situations. Access to rapid germline genetic testing can also be facilitated through mainstreaming pathways [22].

### 5.4. Assessment in the CGU

The mainstreaming cancer genetics programme has been in practice for a number of years in our institution [22]. Patients found to carry likely pathogenic/pathogenic variants or variants of uncertain significance in *BRCA1* or *BRCA2* tested via this mainstreaming pathway are automatically offered an appointment in the CGU. Patients who have undergone uninformative genetic testing in the mainstream context may also benefit from formal clinical genetics review, to facilitate a more thorough review of the family history and facilitate further testing for rare, syndromic causes of cancer predisposition. In our institution, appointments are not automatically generated for patients with uninformative results, and therefore, recognition and onward referral of patients who may benefit from further assessment by the requesting clinician to the CGU is required. Ten of a total of 44 patients undergoing germline testing in this cohort underwent testing before formal review in the CGU. Patients with previous negative genetic tests were offered further testing or recruitment to research studies as appropriate, depending on personal and family history and availability of further NHS-funded genetic tests. Of patients undergoing further testing or undergoing testing for the first time ( $n = 34$ ), two (5.8%) of them were found to carry pathogenic highly penetrant variants in cancer predisposition genes.

An additional three (4%) patients were offered, but declined, germline assessment. A further fifteen (18%) patients had a personal or familial history suspicious of an underlying genetic predisposition, for which NHS-funded testing was not available at the time of their review or for which the genetic aetiology has not yet been elucidated. DNA from these patients was stored to facilitate testing at a later date.

Germline testing is not the only way of assessing whether cancer is due to an underlying genetic predisposition. A third of patients referred underwent tumour-based assessment of MMR by IHC. This is now recommended universally for colorectal tumours, but was not always routinely performed historically. There is increasing evidence to support universal MMR IHC of endometrial [26,27] and upper urinary tract cancers [28], but at the current time, this is not routinely undertaken and is typically only undertaken at the request of genetics professionals.

As we have shown in this study, certain patients with *known* germline genetic variants and a long cancer history may also benefit from re-referral to a genetics unit, for example, to facilitate recruitment to new research studies, to support disclosure and enable cascade testing in offspring who may have been too young for pre-symptomatic testing at the time of their parent’s diagnosis [29], to discuss risks of second primary cancers and risk-reducing interventions in the setting of prolonged

disease-free intervals [30–32] or to facilitate reinterpretation and reclassification of variants if so required [33].

### 5.5. Tumour DNA testing

There is an apparently low rate of referral of individuals to discuss results of tumour testing. As a significant proportion of patients referred to the DDU have already undergone relevant germline assessment, some of the variants identified on tumour DNA sequencing are expected, as we have previously shown [3]. Furthermore, only those patients who are being considered for clinical trials based on their performance status and availability of potentially suitable trials are offered tumour testing; while consideration of germline genetics assessment was unrestricted. Therefore, not all patients referred to the CGU had undergone tumour-based assessment. Furthermore, tumour-based genetic testing is usually performed after clinical review in the DDU, and these results were therefore not always available at the time of clinical genetics assessment or virtual MDT meeting. A Genomic Tumour Advisory Board has been recently established in our institution, in collaboration with other institutions in our region, to interpret and advise on management of results arising from the 100,000 Genomes Project. Clinical and research teams within the hospitals are also encouraged to submit cases from other research studies to this board to discuss relevant or challenging results and to identify patients who should be referred to the CGU, that otherwise may not have been considered for referral based on their family history or tumour type. It is our hope that this will become a more standard practice as tumour-based genetic testing becomes more routinely available.

### 5.6. Virtual review

Introduction of a ‘virtual’ review of the patient with advanced cancer before discharge from an oncology service, or, in our case, at the time of presentation to an experimental trial unit, by a genetics professional represents a unique opportunity to capture now-eligible patients who may previously have been denied genetic testing or who were never referred for genetic assessment [13]. Patients with advanced cancer nearing the end of their life should be given the opportunity to avail of genetic testing should they choose to do so, as this may provide crucial information for their blood relatives. However, awareness and uptake of genetic testing in this cohort of patients are low, which may reflect missed opportunities or reticence by clinicians to broach the topic in this vulnerable group [34,35]. The family of patients approaching the end of life who are not eligible for genetic testing, or who are unable to consent for genetic testing, may benefit from banking of DNA from their relatives to facilitate testing at a later date. This

practice is, however, not routinely performed [36]. Genetic testing in a family is best undertaken in the affected individual, as the likelihood of identifying a causative germline variant is higher than in the unaffected relative; and specific variant testing can then be rolled out to unaffected family members. Where no living affected family member exists, germline testing of unaffected relatives may not be informative, as failure to identify a genetic variant does not exclude the possibility of such a variant in the affected individual, nor is it reassuring, as an alternative, unidentified, shared aetiology may exist for a genetically heterogeneous cancer in the family.

## 6. Limitations and further research

We did not formally audit the quality of family history taking in this study. Significant variability was noted in this regard, with some clinicians recording significant details about first- and second-degree relatives, others restricting their comments to first-degree relatives and others commenting only on the family history of the presenting cancer of the proband. In recording an apparently negative family history of cancer, some clinicians recorded ‘nil of note’ or ‘nil relevant’, comments which may be subjective and biased by the clinician’s recognition of cancers of different types with shared genetic aetiology.

In this study, we did not explore other factors that may modify referral rates, such as changes in trial portfolios leading to change in patient demographics. Virtual review of patients at the time of their initial presentation has disadvantages, in that this review is dependent on the patient’s personal history and family history available for review, which may be incomplete or unconfirmed.

This approach also increases the workload for the CGU without formal remuneration. We note that the impact of the early interventions was not sustained during the periods where no staff member from the CGU actively engaged with the DDU. We speculate that this may be due to several factors, including high turnover of junior medical staff, but we did not explore this formally. An audit is also required to determine if all patients flagged for referral by the virtual review process were appropriately referred by DDU clinicians to the CGU or to their local clinical genetics service by their treating team.

## 7. Conclusion

This study demonstrates a number of positive impacts of increased engagement between the DDU and CGU, particularly of virtual review of patients by a member of the CGU team. The study demonstrates improved recording of family history by DDU clinicians and increased referral of patients to the CGU. High rates of

tumour testing, germline diagnostic testing, DNA storage and recruitment to studies indicate that referrals were appropriate. A number of patients who had previously been reviewed by genetics professionals at an earlier point in their treatment required further testing when reviewed in our clinic, reflecting the rapid evolution of germline testing criteria and technology. A low ‘failure to attend’ rate suggests genetic counselling and testing is acceptable in this cohort of patients. Similar interventions could be recapitulated in other settings, such as palliative care or in transitional clinics for survivors of paediatric cancers, or at the time of discharge from routine oncology clinics. In this study, the intervention with the greatest impact has been the ‘virtual’ MDT. This ‘virtual’ approach facilitates patient review by clinical genetics professionals without increasing pressure on outpatient clinics and may be particularly useful in regions where suboptimal staffing levels preclude the physical presence of a clinical geneticist at a formal MDM. In the ‘genomic era’, where germline and somatic variation will be considered routinely in planning treatment, it is increasingly important that patients have access to both types of genetic testing.

#### Conflict of interest statement

None declared.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2019.04.009>.

#### References

- [1] Taylor A, Brady AF, Frayling IM, Hanson H, Tischkowitz M, Turnbull C, et al. Consensus for genes to be included on cancer panel tests offered by UK genetics services: guidelines of the UK Cancer Genetics Group. *J Med Genet* 2018;55(6):372–7.
- [2] National Human Genome Research Institute. The cost of sequencing a human genome. 2016. Available from: <https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/>.
- [3] McVeigh TP, Sundar R, Diamantis N, Kaye SB, Banerji U, Lopez JS, et al. The role of genomic profiling in adolescents and young adults (AYAs) with advanced cancer participating in phase I clinical trials. *Eur J Cancer* 2018;95:20–9.
- [4] Acton RT, Burst NM, Casebeer L, Ferguson SM, Greene P, Laird BL, et al. Knowledge, attitudes, and behaviors of Alabama’s primary care physicians regarding cancer genetics. *Acad Med J Assoc Am Med Coll* 2000;75(8):850–2.
- [5] Flynn BS, Wood ME, Ashikaga T, Stockdale A, Dana GS, Naud S. Primary care physicians’ use of family history for cancer risk assessment. *BMC Fam Pract* 2010;11:45.
- [6] Schroy 3rd PC, Barrison AF, Ling BS, Wilson S, Geller AC. Family history and colorectal cancer screening: a survey of physician knowledge and practice patterns. *Am J Gastroenterol* 2002;97(4):1031–6.
- [7] Wilkins-Haug L, Erickson K, Hill L, Power M, Holzman GB, Schulkin J. Obstetrician-gynecologists’ opinions and attitudes on the role of genetics in women’s health. *J Wom Health Gend Base Med* 2000;9(8):873–9.
- [8] Wood ME, Kadlubek P, Pham TH, Wollins DS, Lu KH, Weitzel JN, et al. Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American society of clinical oncology quality oncology practice initiative. *J Clin Oncol* 2014;32(8):824–9.
- [9] Kentwell M, Dow E, Antill Y, Wrede CD, McNally O, Higgs E, et al. Mainstreaming cancer genetics: a model integrating germline BRCA testing into routine ovarian cancer clinics. *Gynecol Oncol* 2017;145(1):130–6.
- [10] Kishan AU, Gomez CL, Dawson NA, Dvorak R, Foster NM, Hoyt A, et al. Increasing appropriate BRCA1/2 mutation testing: the role of family history documentation and genetic counseling in a multidisciplinary clinic. *Ann Surg Oncol* 2016;23(Suppl 5):634–41.
- [11] Pederson HJ, Hussain N, Noss R, Yanda C, O’Rourke C, Eng C, et al. Impact of an embedded genetic counselor on breast cancer treatment. *Breast Canc Res Treat* 2018;169(1):43–6.
- [12] Senter L, O’Malley DM, Backes FJ, Copeland LJ, Fowler JM, Salani R, et al. Genetic consultation embedded in a gynecologic oncology clinic improves compliance with guideline-based care. *Gynecol Oncol* 2017;147(1):110–4.
- [13] Wiggins J, George A, Kemp Z. Genetic testing for breast cancer survivors (abstract) presented at American Society of Human Genetics meeting 2018. 2018.
- [14] Delikurt T, Williamson GR, Anastasiadou V, Skirton H. A systematic review of factors that act as barriers to patient referral to genetic services. *Eur J Hum Genet EJHG* 2015;23(6):739–45.
- [15] Grover S, Stoffel EM, Bussone L, Tschoeigl E, Syngal S. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2004;2(9):813–9.
- [16] Lanceley A, Eagle Z, Ogden G, Gessler S, Razvi K, Ledermann JA, et al. Family history and women with ovarian cancer: is it asked and does it matter?: an observational study. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc* 2012;22(2):254–9.
- [17] Sweet KM, Bradley TL, Westman JA. Identification and referral of families at high risk for cancer susceptibility. *J Clin Oncol Off J Am Soc Clin Oncol* 2002;20(2):528–37.
- [18] Anderson B, McLosky J, Wasilevich E, Lyon-Callo S, Duquette D, Copeland G. Barriers and facilitators for utilization of genetic counseling and risk assessment services in young female breast cancer survivors. *J Cancer Epidemiol* 2012;2012:298745.
- [19] Vogel RI, Niendorf K, Lee H, Petzel S, Lee HY, Geller MA. A qualitative study of barriers to genetic counseling and potential for mobile technology education among women with ovarian cancer. *Hered Cancer Clin Pract* 2018;16:13.
- [20] Iredale R, Jones L, Gray J, Deaville J. The edge effect’: an exploratory study of some factors affecting referrals to cancer genetic services in rural Wales. *Health Place* 2005;11(3):197–204.
- [21] George A. UK BRCA mutation testing in patients with ovarian cancer. *Br J Canc* 2015;113(Suppl 1):S17–21.
- [22] George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci Rep* 2016;6:29506.
- [23] Aildredge JK, Eskander RN. EZH2 inhibition in ARID1A mutated clear cell and endometrioid ovarian and endometrioid endometrial cancers. *Gynecol Oncol Res Pract* 2017;4:17.
- [24] Catenacci DV, Amico AL, Nielsen SM, Geynisman DM, Rambo B, Carey GB, et al. Tumor genome analysis includes germline genome: are we ready for surprises? *Int J Cancer* 2015;136(7):1559–67.
- [25] Hamilton JG, Shuk E, Genoff MC, Rodriguez VM, Hay JL, Offit K, et al. Interest and attitudes of patients with advanced

- cancer with regard to secondary germline findings from tumor genomic profiling. *J Oncol Pract* 2017;13(7):e590–601.
- [26] Orbegoso Aguilar CM, Vroobel K, Attygalle A, Lalondrelle S, Taylor A, Nobbenhuis M, et al. MMR deficiency(d) in an unselected cohort of endometrial cancer (EC) patients, the Royal Marsden experience (abstract), presented at ESMO Asia 2018. 2018.
- [27] Watkins JC, Yang EJ, Muto MG, Feltmate CM, Berkowitz RS, Horowitz NS, et al. Universal screening for mismatch-repair deficiency in endometrial cancers to identify patients with Lynch syndrome and lynch-like syndrome. *Int J Gynecol Pathol Off J Int Soc Gynecol Pathol* 2017;36(2):115–27.
- [28] Ju JY, Mills AM, Mahadevan MS, Fan J, Culp SH, Thomas MH, et al. Universal Lynch syndrome screening should be performed in all upper tract urothelial carcinomas. *Am J Surg Pathol* 2018; 42(11):1549–55.
- [29] Bradbury AR, Patrick-Miller L, Egleston BL, Olopade OI, Daly MB, Moore CW, et al. When parents disclose BRCA1/2 test results: their communication and perceptions of offspring response. *Cancer* 2012;118(13):3417–25.
- [30] Kotsopoulos J, Narod SA. Prophylactic mastectomy for BRCA mutation carriers after ovarian cancer treatment: is it beneficial? *Expert Rev Anticancer Ther* 2018;18(3):199–200.
- [31] McGee J, Giannakeas V, Karlan B, Lubinski J, Gronwald J, Rosen B, et al. Risk of breast cancer after a diagnosis of ovarian cancer in BRCA mutation carriers: is preventive mastectomy warranted? *Gynecol Oncol* 2017;145(2):346–51.
- [32] Speight B, Tischkowitz M. When to consider risk-reducing mastectomy in BRCA1/BRCA2 mutation carriers with advanced stage ovarian cancer: a case study illustrating the genetic counseling challenges. *J Genet Couns* 2017;26(6):1173–8.
- [33] Vears DF, Niemiec E, Howard HC, Borry P. Analysis of VUS reporting, variant reinterpretation and recontact policies in clinical genomic sequencing consent forms. *Eur J Hum Genet EJHG* 2018;26(12):1743–51.
- [34] Daniels MS, Burzawa JK, Brandt AC, Schmeler KM, Lu KH. A clinical perspective on genetic counseling and testing during end of life care for women with recurrent progressive ovarian cancer: opportunities and challenges. *Fam Cancer* 2011;10(2):193–7.
- [35] Quillin JM, Bodurtha JN, Siminoff LA, Smith TJ. Exploring hereditary cancer among dying cancer patients—a cross-sectional study of hereditary risk and perceived awareness of DNA testing and banking. *J Genet Couns* 2010;19(5):497–525.
- [36] Quillin JM, Bodurtha JN, Siminoff LA, Smith TJ. Physicians' current practices and opportunities for DNA banking of dying patients with cancer. *J Oncol Pract* 2011;7(3):183–7.