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Title: Multi-disciplinary interventions in a Specialist Drug Development Unit to improve family history documentation and onward referral of patients with advanced cancer to Cancer Genetics Services

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Abstract

Background:

Molecular aberrations in cancer may represent therapeutic targets, and, if arising from the germline, 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 multi-disciplinary interventions on family history taking in 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 DDU review clinic

2. “Traffic light” system flagging cancers with heritable component

3. Virtual multi-disciplinary 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 retrospective chart review.

Results: Frequency of family history taking, and referral to CGU, increased with each intervention, particularly, the virtual MDM (40%-v- 85%). Referral rates increased over the study 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 short estimated life expectancy. Multidisciplinary working between CGU and DDU facilitates germline testing of those patients that may otherwise miss the opportunity.

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 inherited predisposition to cancer due to germline variation. Recognition of individuals with germline variants in cancer predisposition genes may not only facilitate personalization 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, cancer at younger than expected age, or individuals with a positive family history of cancers with a shared genetic aetiology. Criteria for 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 in the Royal Marsden represents one of the largest Phase 1 trials unit in Europe, with approximately 600-700 patients assessed each year. Referrals are accepted from anywhere in the UK, 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 co-morbidity.

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 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 Drug Development Unit in our institution are sub-optimal, even for those patients affected at young ages(3). Pedigree drawing in the Cancer Genetics Unit in our institution is undertaken using departmental software, and familial pedigrees are stored separately from individual Electronic Patient Records (EPR). Family history documentation on the hospital 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 focusing 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 involving clinical genetics can also have a positive impact(13). In the absence of availability of clinicians to participate in clinics or 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 DDU to the Cancer Genetics Unit (CGU).

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:

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

Interventions

Intervention 1: Embedding a Genetics Clinician in one clinic per week

For a period of one year, a clinician from the Cancer Genetics Unit attended one clinic in DDU per week. Prior to clinic, patients attending the clinic were discussed in a multi-disciplinary team meeting. Patients that 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.

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, viral or environmental factors rather than germline predisposition (e.g. Cervical cancer, lung cancer), for which the patient was unlikely to be eligible for 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 depending

on their age at diagnosis or family history. DDU clinicians were encouraged to refer patients with cancers in the Red categories irrespective of family history, and patients with cancers in the orange/green categories if there was a positive family history of cancer, or earlier 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 proforma.

Intervention 3: Virtual multidisciplinary review of patient history

As part of pre-clinic preparation, the electronic record of patients attending clinics in DDU were 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 Cancer Genetics Unit. Formal referral by DDU clinicians to the CGU was required before appointments were offered.

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 Cancer Genetics Unit (19 weeks). Given the small patient numbers, formal statistical analysis was not undertaken.

Family history taking and onward referral from DDU to CGU

Referral rates from DDU to CGU were prospectively recorded over the study period. Data was recorded with respect to absolute number of referrals from DDU to CGU, as well as relative number of referrals from DDU as proportion of all referrals to CGU. The electronic patient records 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.

Results

Unselected Patients (n = 100)

Genetic Assessment Prior to referral to DDU

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

Family History Recording and onward referral

Family cancer history was documented in 75 of 100 unselected cases reviewed. Variability across study periods 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 DDU (table 1), and 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 CGU (n=3 (10%)) than those patients discharged back to local oncology services, of whom 7 (10%) and 5 (7%) had been reviewed or were referred to CGU, respectively.

Patients referred to CGU

Patient Demographics

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

Referral Rates

Prior to active interventions, referrals of patients from DDU accounted for 0.36% of referrals to the CGU, with 5 referrals in one year (table 2). Embedding of a clinician from 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 DDU in period 5 (23 in 19 weeks) accounted for 3.81% of total referrals to CGU.

Outcome of Genetic Review

Of ninety-one patients referred to CGU by DDU; 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 mismatch repair deficiency was undertaken prior to germline investigation. The tumours of 28 (33%) patients were assessed by immunohistochemistry to check for mismatch repair deficiency. Forty-four patients (52%) underwent at least one diagnostic germline test; including 10 patients who had testing prior to 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 patients recruited to the Breast and Ovarian Cancer Susceptibility (BOCS) study, 8 to the Colorectal Gene Identification (CORGI) study, one to the Factors associated with Childhood Tumours (FACT), 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.

Germline Variants Identified

Germline variants were identified in four patients in this cohort (supplementary table 4), including two patients tested prior to 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, after presenting to 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 re-interpretation 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.

Discussion

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, 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, and germline genetic testing is rapidly becoming cheaper, and eligibility criteria for genetic testing becoming broader. Guidelines for tumour-based assessment to guide germline diagnostics are also being utilised 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.

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 their family history to hand at the time of their 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 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 DDU, as well as an increase of referral rates to Cancer Genetics. We did not

formally assess the quality of family history documentation. Documentation of family history does not necessarily ensure onward referral of 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 to 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 agent. It is likely therefore that discussing the need for Clinical Genetics assessment may be deferred, or left to the primary treating team.

Changing criteria for 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 mismatch repair by immunohistochemistry now universally advocated for patients with certain tumour types(23). Furthermore, molecular profiling of tumour DNA using broad multigene panels, whole exome or whole genome sequencing is being increasingly utilised 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 done 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 Clinical

Genetics in some regions are suboptimal, and this may not be feasible. 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(26).

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 that 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 that may benefit from further assessment by the requesting clinician to the CGU is required. Ten out of a total of 44 patients undergoing germline testing in this cohort underwent testing prior to formal review in 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%) 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%) of patients had a personal or familial history suspicious for 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 mismatch repair by immunohistochemistry. 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 (27, 28) and upper urinary tract cancers (29), 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 that may have been too young for pre-symptomatic testing at the time of their parent's diagnosis(30), to discuss risks of second primary cancers and risk-reducing interventions in the setting of prolonged disease-free intervals (31-33), or to facilitate re-interpretation and reclassification of variants if so required(34).

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 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 that 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 DDU, and these results were therefore

not always available at the time of Clinical Genetics assessment or virtual MDT. A Genomic Tumour Advisory Board (GTAB) 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 100000 Genome 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 that should be referred to the CGU that may otherwise would not be considered for referral based on their family history or tumour type. It is our hope that this will become more standard practice as tumour testing becomes more routinely available.

Virtual Review

Introduction of a "virtual" review of the patient with advanced cancer prior to discharge from an oncology service, or, in our case, at the time of presentation to an experimental trials unit, by a genetics professional represents a unique opportunity to capture now-eligible patients that may previously have been denied genetic testing, or that 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 is low, which may reflect missed opportunities, or reticence by clinicians to broach the topic in this vulnerable group (35, 36). The family of patients approaching end of life that are not eligible for genetic testing, or that are unable to consent for genetic testing, may benefit from banking of DNA from their relative to facilitate testing at a later date. This practice is, however, not routinely performed(37). 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, but nor is it reassuring, as an alternative, unidentified, shared aetiology may exist for a

genetically heterogeneous cancer in the family.

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 detail about first- and second-degree relatives, other 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 the 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 CGU actively engaged with the DDU. We speculate that this may be due to several factors including high turnover of junior medical staff but 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.

Conclusion

This study demonstrates a number of positive impacts of increased engagement between 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 CGU. High rates of tumour testing, germline diagnostic testing, DNA storage and recruitment to studies indicate that referrals were appropriate. A number of patients that 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 suggest 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 out-patient clinics; and may be particularly useful in regions where suboptimal staffing levels preclude the physical presence of a Clinical Geneticist at a formal multidisciplinary meeting. 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

The authors have no conflicts of interest to declare.

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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 DDU (Range), years	Genetic Review Prior to referral to DDU[α]	Mismatch Repair Immuno-histochemistry n (%[β])	Number of cases where family history was documented[δ], n (%)	Number of cases with suspicious family history of cancer, n (%[ε])	Number of cases referred on because of family history[ζ], n (%[η])
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%)

α: formal review or mainstream genetic testing
β: percentage of Lynch syndrome-associated tumours
δ: recorded by clinician in DDU
ε: percentage of cases where family history documented by DDU clinician
ζ : cases not previously reviewed by genetics, or case where there was a change in personal/family history since review
η: percentage of cases with pertinent family history

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

Intervention	Time Point	Number of Weeks	Number of total referrals received by CGU	Number of referrals from DDU to GHU (% 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

Table 3: Outcome of Genetic Assessment

Intervention	Number of patients referred from DDU to CGU	Number of patients reviewed in 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[a,b]	3	16[d]	11	18[i]	3[l]	10[n]
None	6	5[a]	0	1[e]	0	5	0	2[o]
Traffic Light System	13	12[a]	0	2[f]	0	6[j]	1[m]	1[p]
Virtual MDT	23	21[c]	0	9[g,h]	3	12[k]	0	5[q]
Intervention	**91**	**85 (93%)**	**3 (4%)**	**28(33%)**	**15 (18%)**	**44 (52%)**	**4 (9%)**	**18**

a: patient died before review (n=3 total)
b: 1 patient failed to attend (1); c: 2 patients failed to attend (2)
d: Tumours: Colon (7), rectal (3), endometrial (1), cholangiocarcinoma (1), ovarian (1), small bowel (1), pancreatic (1), appendiceal (1); **e**: Tumour: Colon (1); **f**: Tumours: Colon (1), rectal (1); **g**: Tumours: Colon (5), Endometrial (4), Rectal (1)
h: One patient had two primaries (colon and endometrial; both assessed by IHC)
i: 6 patients had testing before review (6)
j: 1 patient had testing before review (1)
k: 3 patients had testing before review (3)
l: 1 patient with a *SPINK1* pathogenic variant, 1 patient with pathogenic *BRCA2* variant (known), 1 patient with *RAD51C* VOUS
m: 1 patient with a *TP53* pathogenic variant
n: Breast and Ovarian Cancer Susceptibility Study (BOCS) (5), Factors Associated with Childhood Tumours study (FACT) (1), Colorectal Gene Identification Study (CORGI) (4);
o: BOCS (2); **p**: CORGI (1); **q**: CORGI (3), Personalised Medicine in Prostate Cancer study (2)
CGU: Cancer Genetics Unit, DDU: Drug Development Unit, MDT: Multidisciplinary Team meeting, MMR: Mismatch Repair, IHC: immunohistochemistry

Red (refer patient)	Orange (review family history ± discuss with genetics team)	Green (likely somatic in origin/environmental factors - discuss if suspicious family history or younger than expected age of onset)
Breast <45/Triple Negative at any age/bilateral	Breast	Cervical cancer
Colorectal cancer - MMRd any age	Differentiated thyroid cancer	Vaginal/vulval cancer
Adrenocortical carcinoma	MMRp colorectal cancer	Lung cancer
Parathyroid cancer	Brain Tumour	Head and neck cancer
Medullary Thyroid Cancer	Sarcoma	low grade serous/mucinous ovarian cancer
Phaeochromocytoma <40 /FHx	Phaeochromocytoma >40y	haematological malignancies
Paraganglioma at any age	MMRp Endometrial	Testicular cancers
Non mucinous Ovarian cancer at any age	Stromal Ovarian/testicular tumours	Melanoma
Endometrial - MMRd	Malignant peripheral nerve sheath tumour	
MMRd tumour of any type	Schwannoma	
Diffuse Gastric cancer	Any Cancer <40	
Ureteric cancer	Any cancer with suspicious family history	
Retinoblastoma	Multiple Primary cancers	
	Prostate cancer <70	

Supplementary Table 1: "Traffic Light" classification system

Cancer	N
Adrenal	1
Bladder	2*
Brain	3
Breast	11*
Cervix	4
Cholangiocarcinoma	1
Choroid	1
Colon	20
Endometrial	1
GIST	2
Lung	11
mCUP	1
Melanoma	3*
Mesothelioma	3
Oesophageal	6
Oropharyngeal	1
Ovarian	10
Pancreatic	4*
Penis	1
Prostate	6*
Rectal	5*
Renal	1
Sarcoma	2
Thymus	1
Thyroid	1
Vagina	1
Vulva	1
*some cases occurring in patients with multiple primary diagnoses	

Supplementary Table 2: Cancer diagnoses in 100 unselected DDU patients included in audit

Type of Cancer	Number of tumours	Median Age at Diagnosis (Range)
Breast	25[#]	42 (24-78)
Colon	16	45 (20-77)
Ovarian	14	62 (44-75)
Pancreatic	7	57 (49-70)
Sarcoma	7	20 (6-39)
Rectal	6	47 (31-66)
Prostate	5	66 (50-69)
Endometrial	5	64 (51-73)
Melanoma	3*	49 (49)
Adrenocortical	3	50 (49-58)
Brain	2	38 (26-50)
Bladder	2	66 (59-73)
Cholangiocarcinoma	2	54.5 (49-60)
Appendix	1	54
Cervix	1	45
Mesothelioma	1	43
Nasopharyngeal	1	32
Kidney	1	65
Apocrine skin	1	73
Carcinoid	1	67
Small bowel	1	33
Medullary Thyroid	1	53
Wilms	1	3
NHL	1	69
Lung	1	38
Anal	1	69
	110	

*one patient had 2 primary melanoma
[#] one patient had bilateral breast cancer

Supplementary Table 3: Demographics of patients referred to CGU

Diagnosis	**Age at Diagnosis**	**Age at referral to CGU**	**Previous Genetic Testing**	**Known genetic results**	**Action in CGU**	**Gene**	**Variant**	**Variant Classification**
Pancreatic Cancer	49	50	*BRCA1* *BRCA2*	Uninformative	*PRSS1* and *SPINK1* testing	*SPINK1*	c.101A>G, p.(Asn34Ser)	Likely Pathogenic
Astrocytoma	26	35	*Nil*	n/a	*TP53* testing	*TP53*	c.715A>G, p.Asn239Asp	Pathogenic
High Grade Serous Ovarian cancer	44	55	*BRCA1* *BRCA2* *RAD51C* *RAD51D* *BRIP1*	*RAD51C* Variant of Uncertain Significance (patient unaware of result)	Return of result and re-interpretation of variant, recruited to BOCS	*RAD51C*	c.428A>G, p.(Gln143Arg)	Likely Benign (reclassified from Variant of Uncertain Significance)
High Grade Serous Ovarian cancer	47	62	*BRCA1* *BRCA2*	Known pathogenic *BRCA2* variant	Discussion regarding risks to family – cascade testing	*BRCA2*	c.1689G>A, p.Trp563X	Pathogenic
BOCS: Breast and Ovarian Cancer Susceptibility Study								

Supplementary Table 4: Patients in whom germline variants were identified