A digital pathway for genetic testing in UK NHS patients with cancer: BRCA-DIRECT randomised study internal pilot

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ABSTRACT

Background Germline genetic testing affords multiple opportunities for women with breast cancer; however, current UK NHS models for delivery of germline genetic testing are clinician-intensive and only a minority of breast cancer cases access testing.

Methods We designed a rapid, digital pathway, supported by a genetics specialist hotline, for delivery of germline testing of BRCA1/BRCA2/PALB2 (BRCA-testing), integrated into routine UK NHS breast cancer care. We piloted the pathway, as part of the larger BRCA-DIRECT study, in 130 unscreened patients with breast cancer and gathered preliminary data from a randomised comparison of delivery of pretest information digitally (fully digital pathway) or via telephone consultation with a genetics professional (partially digital pathway).

Results Uptake of genetic testing was 98.4%, with good satisfaction reported for both the fully and partially digital pathways. Similar outcomes were observed in both arms regarding patient knowledge score and anxiety, with <5% of patients contacting the genetics specialist hotline. All progression criteria established for continuation of the study were met.

Conclusion Pilot data indicate preliminary demonstration of feasibility and acceptability of a fully digital pathway for BRCA-testing and support proceeding to a full powered study for evaluation of non-inferiority of the fully digital pathway, detailed quantitative assessment of outcomes and operational economic analyses.

Trial registration number ISRCTN87845055.

INTRODUCTION

Testing of patients with cancer for high penetrance breast-ovarian cancer susceptibility gene (CSGs) BRCA1, BRCA2 and PALB2 offers three potential benefits. First, identification of a germline pathogenic variant can provide insights into the oncogenesis of their cancer, potentially informing selection of chemotherapeutic agents, including platinum and targeted therapies such as poly-ADP ribose polymerase inhibitors. Second, knowledge of elevated risk of subsequent breast, ovarian and other cancers may direct the patient towards risk-reducing surgery and/or intensive surveillance. Third, cascade testing for the pathogenic variant enables identification of family members who carry it, are at elevated risk of cancer and might benefit.
from medical interventions, as well as providing reassurance for those who do not carry the familial variant.

Historically, variant scanning along the length of a CSG was labour-intensive and thus expensive, typically taking several months in a diagnostic laboratory. Hence, germline genetic testing was largely divorced from acute diagnostic oncology, instead being initiated more typically by those who had successfully completed treatment for a prior cancer diagnosis and unaffected relatives concerned by their family history. With the advent of next-generation sequencing (NGS) technologies, sequencing of CSGs has become relatively cheap, rapid and high-throughput. Furthermore, we have good knowledge of the pathogenicity of variants in well-characterised genes such as BRCA1, BRCA2, MLH1 and MSH2, such that interpretation can be streamlined via automated bioinformatics pipelines, with a low rate of variants of uncertain significance (VUS). Thus, it is increasingly feasible from the laboratory perspective that large-scale, rapid CSG analysis could be offered routinely as part of the diagnostic workup for all patients with relevant cancers. This in principle offers opportunity for patient’s primary surgery to combine treatment of the current cancer with risk reduction for future cancers. For example, bilateral mastectomy rather than localised excision may be performed in a BRCA1-positive woman with newly diagnosed breast cancer.

However, while technological advances have driven massive improvement in laboratory capacity, substantial barriers within the upstream and downstream clinical pathways remain. The traditional model of individualised patient referral to clinical genetics for management of pretest genetic counselling, consenting, sample acquisition and return of results reflects an era in which patient volumes were low and timescales unpressured. To facilitate rapid delivery to larger populations of patients with cancer, there have been attempts to transition germline genetic testing across into mainstream oncology.2–4 For ovarian cancer, of which there are ~7500 cases per year in the UK and a ~15% frequency of germline pathogenic variants of BRCA1/BRCA2,5 6 over the last 5 years there has been relatively successful implementation of universal testing using a variety of ‘mainstreaming’ models.2,7 For breast cancer, the incidence is much higher (~56 000/year)8 while the pick-up rate of pathogenic variants is more modest (~3%–5% in total for BRCA1/BRCA2/PALB2).9–11 Delivery of germline genetic testing by mainstream breast cancer oncological clinicians has been piloted, but success has been more limited. Lack of requisite expertise, high workload, large patient numbers and perceived relevance of germline testing for immediate clinical decision-making have been cited as causes for clinician reluctance.12

Limitations of the precision oncology model in improving outcomes in those diagnosed with advanced cancers has led to renewed focus on improving cancer early detection and prevention. Such interventions are most impactful applied to those at very high priori risk of cancer. However; despite being the earliest, most common and arguably most widely established paradigm of high penetrance cancer susceptibility, recent analyses suggest low ascertainment, with fewer than 3% of BRCA1/BRCA2 heterozygotes across Greater London identified.13

Recent health economic analyses, using UK-specific and other costing parameters, demonstrate testing of BRCA1/BRCA2 genes in unsolicited patients with breast cancer to be cost-effective.14–17 However, the current NHS eligibility criteria exclude >80% of patients with breast cancer from germline genetic testing, a restriction now arguably driven more by capacity and costs of clinical manpower than laboratory assays.18–20 It is paradoxical therefore, that complex evaluation of family history to exclude ineligible patients still occupies a substantial proportion of capacity of expert genetics clinicians of which the system is so short. Furthermore, due to small family size, male transmission, fractured transmission of familial information and variation in penetrance and chance, the current family based criteria fail to catch about half of BRCA heterozygotes.21 22

An additional consequence of this high threshold for NHS germline genetic testing is diversion of ‘ineligible’ patients with breast cancer to private and direct-to-consumer testing. As well as driving inequity, these laboratories function outside of the regulatory standards and informatics systems unifying the UK NHS diagnostic laboratory network, through which we ensure that variant information and classifications are consistent, shared and updated. These parallel systems have ethical implications regarding equity of access to downstream NHS-funded interventions,23–25 and create additional friction regarding NHS evaluation of spurious results for patients who were ineligible for NHS testing.24 25

We and others have hypothesised that integration within NHS diagnostic cancer pathways of simple technology platforms could mitigate the impasse.26–28 Requirement for detailed individualised genetic counselling to inform the decision to undertake a genetic test comes from early models for Huntington disease and prenatal scenarios.29–31 For a cancer patient, a germline genetic test is arguably one component of a suite of tests potentially informing their cancer management, and while there are also important considerations to be made about possible implications of the result for their future and family, the information relating to the test is largely generic. Likewise, operational management of consent, sample transmission and return of results is largely formulaic. However, integration within NHS clinical and laboratory information systems of this digital pathway is critical to ensure (i) full communication of results across clinical organisations, (ii) appropriate expert management of nuanced scenarios such as uncertain variants and BRCA-negative patients with strong/unique family histories and (iii) ongoing VUS review with patient recontact.

Over the last decade, there has been considerable focus in NHS strategy on application of digital solutions to extend and improve access to healthcare, a trend dramatically catalysed by the COVID-19 pandemic. Furthermore, there has been concurrent high priority within NHS England for expanded application of genetic testing for personalised prediction.30 11 We therefore sought to design a digital pathway that was rapid, patient-centred, ‘light-touch’ for clinicians, and integrated into NHS clinical, laboratory and informatics systems, by which genetic testing could be delivered to mainstream patients with cancer at potentially much greater scale. For our exemplar clinical scenario, we applied this pathway to BRCA-testing (BRCA1/BRCA2/PALB2 gene testing) in unselected mainstream patients with breast cancer.

While a digital pathway would be presumed to improve capacity and efficiency, questions remain regarding whether a digital route might adversely impact anxiety, satisfaction and/or understanding of the genetic testing process for patients with cancer. Furthermore, while we presuppose that patients with cancer would value the rapidity, convenience and flexibility of a digital pathway, these trade-offs have not been well explored, in particular for UK NHS patients.28 32 11 As well as evaluating patient responses to the digital pathway, we also leveraged this opportunity to compare by randomisation two approaches to delivery of pretest information. Half the patients underwent the ‘fully digital pathway’ with pretest information
delivered digitally, while half the patients had a pretest telephone consultation with a genetics professional (the ‘partially digital pathway’).

We here present data on development of the BRCA-DIRECT pathway, evaluation of our internal pilot of the BRCA-DIRECT pathway in 130 unselected NHS patients with breast cancer, preliminary data from randomised comparison in this population between digital and telephone consultation delivery of pretest information and assessment of progression criterion established to support continuation of the study to the full recruitment target for well powered analyses of outcomes.

METHODS
We describe materials and methods relating to three constituent activities, namely: (i) development of the BRCA-DIRECT digital pathway, (ii) evaluation of the BRCA-DIRECT digital pathway, (iii) randomised evaluation of delivery pretest information, comparing digital delivery (fully digital pathway) with telephone consultation with a genetics professional (partially digital pathway) as well as (iv) assessment against established progression criteria for continuation of the study (figure 1). For full details, see online supplemental methods.

Design of the BRCA-DIRECT digital pathway
A preliminary pathway and materials were designed by the core study team (three clinical geneticists, two genetic counsellors, one oncology/genetics specialist nurse, five psycho-oncological researchers and two research/study coordinators). This was followed by iterative consultations with (a) a broader clinical group (two clinical geneticists, one genetic counsellor, two oncologists and one oncology surgeon) and (b) a group of eight patients, who evaluated (i) materials for the fully digital pathway for testing of germline BRCA1/BRCA2/PALB2 and (ii) core functionality of the BRCA-DIRECT digital platform, as described in box 1.

Pilot of the BRCA-DIRECT digital pathway
We piloted the BRCA-DIRECT (fully and partially digital) pathway in 130 unselected patients with breast cancer recruited from three hospital sites under the Royal Marsden NHS Foundation Trust, London, UK (RMH). See figure 1 for full study pathway and adaptations due to COVID-19.

Eligibility
Patients were eligible if they had a diagnosis of invasive breast cancer or high-grade ductal carcinoma in situ and were above 18 years of age. Inclusion criteria were self-assessed good comprehension of English language, and access to a smartphone and/or email. Exclusions included previous testing for BRCA1, BRCA2 and PALB2.

Study recruitment
Information regarding BRCA-DIRECT was made available in outpatient departments via posters, leaflets and verbally from oncology professionals (specialist nurses and doctors). Those patients expressing interest were provided with a BRCA-DIRECT pack comprising a saliva collection kit, study patient information sheet and consent form and a postal return envelope. On receipt of the study consent form, patients were notified via email and/or SMS and enabled to create an account on the BRCA-DIRECT platform.

Baseline data collection
Demographic data relevant to evaluation of the BRCA-DIRECT pathway (eg, educational status, level of social support, ethnicity) were collected digitally via the BRCA-DIRECT platform, in addition to data core to the BRCA-DIRECT pathway (eg, relevant personal and family history of cancer). Key medical details were confirmed by the study team from the patient medical record, including confirmation of cancer status, status of breast cancer treatment and (planned) surgery date.

Outcomes for evaluation of the BRCA-DIRECT pathway
We evaluated acceptability of the BRCA-DIRECT digital pathway via the following approaches:
1. Patient progression through the BRCA-DIRECT pathway, evaluating percentage uptake of genetic testing, turnaround times for results (time-to-results) and withdrawals.
2. Patient usage of the BRCA-DIRECT telephone hotline calls, assessing volume, timing and content of calls categorised as either (i) genetics specialist or (ii) administrative.
3. Patient satisfaction with the BRCA-DIRECT digital pathway, evaluating using a 15-item study-specific survey, conducted 7 days postreceipt of test result (T2).
4. Healthcare professional (HCP) satisfaction with the BRCA-DIRECT digital pathway compared with standard clinical care pathways via a 10-item study-specific survey.
5. Structured interviews, involving 26 questions completed with 10 patients to capture more detailed feedback on the BRCA-DIRECT pathway.

Randomised evaluation comparing BRCA-DIRECT digital pretest information with standard-of-care pretest one-to-one genetic counselling
Randomisation
Using the on-line Sealed Envelope randomisation list generator, ahead of the study, we randomised study IDs 1:1 to receive pretest information digitally via the BRCA-DIRECT platform (fully digital pathway) or via telephone consultation with a genetics professional (partially digital pathway).34

Outcomes used for comparative evaluation of pretest information
1. Reported satisfaction and perceived convenience with the method in which they received the pretest information were compared using 5-point Likert scales.
2. Knowledge relating to BRCA-testing, assessed at baseline and 7 days after genetic test consent using a questionnaire comprising 14 ‘true’ or ‘false’ statements. Average (mean) overall scores and percentage of correct responses to individual questions were compared between the two arms at the two time points.
3. Patient anxiety, measured at baseline (T0), 7 days after BRCA-test consent (T1) and 7 (T2) and 28 days (T3) after receiving their results, using the Spielberger State-Trait Anxiety Inventory for Adults (STAI).35 The Intolerance of Uncertainty Scale (IUS) was also administered at baseline.36

Study progression criteria
We established five progression criterion to support continuation from the pilot to a full powered study of 1000 patients, evaluating recruitment, retention, questionnaire completion, patient satisfaction with the digital intervention and change in knowledge from T0 to T1 in both the fully and partially digital arms (online supplemental table 1).
RESULTS

Study population characteristics

Recruitment to the BRCA-DIRECT internal pilot took place between 5 July 2021 and 10 October 2021 (97 days). During this time, 146 women with breast cancer expressed positive interest in participating, with 130 (89.0%) returning study consent forms and samples (figure 2; online supplemental figure 3).

Of the 130 women who consented to the study, 52.3% of patients were newly diagnosed and presurgical, 28.5% postsurgical under active treatment and the remainder under follow-up (6.9%) or metastatic (12.3%). Patients ranged from 33 to 87 years of age, with a mean age of 59 years old. See further demographics in table 1.
Evaluation of the BRCA-DIRECT digital pathway

Uptake of BRCA-testing

Five (5/130) women withdrew from the study prior to receiving their pretest information. Of those who received pretest information, 123/125 (98.4%) consented to BRCA-testing; the two who withdrew were from the telephone (partially digital) arm (figure 2, online supplemental figure 3). See online supplemental table 2 for detail on withdrawals.

Hotline usage

The BRCA-DIRECT hotline was used overall by 24.7% of patients. Five ‘genetics specialist’ calls were made by patients (3.8% of all patients), seeking more information about what the results meant for the individual and their family members. Additional calls (63) were ‘administrative’ calls from 31 patients, with the majority relating to timing of results (n=35) and technical aspects of accessing the platform (n=18) (table 2).

Results turnaround

Samples were sequenced for all patients who completed their genetic test consent. Of the 123 results, there were 3 pathogenic variants, 0 likely pathogenic variants, 0 ‘hot’ VUS (5 evidence points) and 120 negative results. The overall median (IQR) time for testing of samples (from genetic-test consent to availability of results) was 27.6 (22.4–33.5) days, with similar turnaround times for patients in the fully digital (26.0 (20.6–33.2) days) and partially digital arms (28.6 (22.6–34.5) days) (online supplemental table 3).

Patient satisfaction with the pathway

Patient-reported satisfaction and perceived convenience for (a) pretest information delivery and (b) delivery of results was overall high with 86% of responses being ≥4 (5=most convenient/satisfied); see figure 3 for comparison between digital and telephone pretest information. Seven per cent of patients reported seeking assistance with accessing the BRCA-DIRECT platform from clinical/study staff (2.0% (2/100)) or friends/family members (5.0% (5/100)), and 13% sought assistance with providing a saliva sample, 12.0% (12/100) from clinical/study staff and 1.0% (1/100) from friends/family members (online supplemental table 4).

Patients accessed the BRCA-DIRECT digital platform by a smartphone alone (45.0%), desktop computer/laptop alone (24.0%), tablet alone (8.0%) or from some combination of devices (23.0%) (online supplemental table 4). Patient interviews revealed that reminder notifications were useful (all scored either 4 or 5, with 5 being very useful and 1 being not useful). Of those who received both SMS and email reminders, there was an equal balance preferring SMS compared with email notifications, with patients noting that SMS notifications acted ‘as a reminder’ and the emails enabled an easy link to complete questionnaires via a computer or laptop.

Healthcare professional satisfaction with the pathway

Eleven HCPs responded to the survey (18.2% clinical nurses; 18.2% consultant breast oncologists; 36.4% consultant breast surgeons; 27.3% other). The majority agreed (to varying extents) that all aspects of the BRCA-DIRECT digital pathway were
Cancer genetics

Figure 2  Consolidated Standards of Reporting Trials flow chart detailing patient progression through the BRCA-DIRECT pilot study, including number of patients included in analysis at each stage, separated by pretest information randomisation allocation following enrolment. Light green: study-specific outcome measures. Dark green: digital pretest information (fully digital arm). Dark blue: telephone pretest information (partially digital arm). Light blue: standard pathway procedures. See online supplemental figure 3 for more detail on patient progression and reasons for withdrawal or exclusions at each stage.

equivalent (or superior) to standard-of-care, with the exception of end-to-end time-to-results (27.3% disagreed, 45.5% agreed, 27.3% neither agreed nor disagreed) (online supplemental table 5). Overall, 72.7% perceived the benefits of the pathway to outweigh the challenges of the pathway (online supplemental table 6) and 80.0% believed that the BRCA-DIRECT pathway is ready to be implemented in the NHS.

Randomised comparison of delivery of pretest information
Sixty patients, out of 125 (48.0%), were randomised to receive digital pretest information (fully digital pathway) and 65/125 (52.0%) were randomised to receive pretest information via telephone consultation with a genetics professional (partially digital pathway) (see figure 2).

Patient-reported satisfaction and convenience of delivery of pretest information were similar in both arms. In the fully digital arm, 85.7% of patients scored ≥4 for convenience and 87.8% scored ≥4 for satisfaction, compared with 86.3% and 88.2%, respectively in the telephone arm (figure 3). The amount of information and complexity of information were also considered to be ‘about right’ in the digital arm (89.8% and 91.8%), with figures being similar in the telephone arm (94.1% and 98.0%) (online supplemental table 7).

Following receipt of the pretest information, mean knowledge scores increased from 5.2/14 (SD 3.3) at baseline to 8.6/14 (SD 3.5) (online supplemental tables 8 and 9). The observed trend was similar between the digital (4.7/14 (SD 3.1) and 7.3/14 (SD 3.7)) and telephone arm (5.6/14 (SD 3.4) and 9.9/14 (SD 2.7)), as was the proportion of correct responses to individual questions in both arms (see online supplemental figure 5).

Mean (SD) anxiety scores decreased from the pretest baseline (T0) through to the ‘7 days post results’ time point (T2) in both the digital arm (45.1 (SD 13.6) at T0 and 37.3 (SD 12.9) at T2) and telephone arm (44.0 (SD 13.4) at T0, and 37.5 (SD 13.7) at T2). In both arms, results were similar at 7 days and 28 days postreceipt of results (online supplemental table 10). Baseline trait anxiety scores and IUS were similar in patients between the two arms (online supplemental table 10).

Safety reporting was conducted in line with the study protocol and ethics approvals. No serious adverse events relating to the fully or partially digital pathways were recorded during the BRCA-DIRECT pilot.

Progression criteria
All progression criteria established to support continuation of the study were met or exceeded (online supplemental table 11).

DISCUSSION
We have presented data from our pilot of the BRCA-DIRECT pathway in the first 130 unselected patients with breast cancer from mainstream oncology services in 3 NHS hospitals, of whom half had the fully digital pathway (digital pretest information) and half had the partially digital pathway (telephone
consultation pretest information). Considering the fully digital BRCA-direct pathway: uptake of BRCA-testing was high (60/64, 93.8%, with all withdrawals being prior to pretest information), as were ratings for perceived convenience and satisfaction for how they received pretest information and results (42/49 (87.8%) scoring as 4–5/5). Preliminary data regarding delivery of pretest information showed similar patient knowledge score, anxiety or satisfaction scores for the digital delivery and telephone genetic counselling.

As expected from general internet-access patterns, the BRCA-DIRECT platform was mainly accessed via a smartphone. However, a mixture of devices were used, demonstrating the importance of optimising the digital platform across different devices. Usability of the BRCA-DIRECT digital pathway was demonstrated to be high, with low numbers of patients requiring support, as indicated by both patient feedback (5.0% stated they sought technical support from another person) and analysis of calls placed to the hotline (23.8% of patients made a hotline call for administrative support regarding the platform). Notably, only 3.8% of patients accessed the hotline for expert genetics support, with all of these relating to results rather than pretest information. Similar hotline usage patterns have been reported by Gaba et al.37 in unselected population-based personalised ovarian cancer risk assessment.

The majority of patient hotline calls placed were administrative and related to availability of results (35/68 (55.9%)). The time-to-results (median (IQR) time from receipt of sample (and study consent) to return of results) was 38.4 days (31.3–48.8) and testing turnaround time (time from genetic test consent to results available) was 27.6 days (22.4–33.3), reflecting the communicated turnaround time estimation of 3–4 weeks. However, the upper quartile of testing turnaround times experienced significant delays, reflective of the impact over this period of COVID-19-related supply chain issues for reagents and staffing shortages. Permissive estimates of turnaround time and provision on the digital platform of clear and accurate time-frames for turnaround of results is clearly critical for successful implementation and scaling of a fully digital pathway.

Table 1 BRCA-DIRECT pilot study patient demographics

<table>
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<th>Demographic Groups</th>
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<th>Pretest information allocation</th>
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<td>Digital</td>
<td>23 (35.9)</td>
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</table>

GCSE, General Certificate of Secondary Education; NVQ, National Vocational Qualification.
Five patients, out of 123, either failed to confirm that their results were received digitally or failed to book an appointment following notification of the results being available. Possible explanations included return of results coinciding with in-patient or treatment activity or patient demise. An alert was placed to the respective oncology professional, ensuring diversion to clinician-directed return of results. Such deviations illustrate the importance of integration of the digital pathway within oncology care delivery, ensuring both clinician awareness regarding patient progression with genetic testing and that results have been returned.

### Limitations of study

The randomisation pertained to just delivery of pretest information, not the full pathway. This allowed us to perform a direct comparison of groups between which only delivery of pretest information differed. However, for those in the telephone (partially digital) arm, digital appointment bookings were likely more accessible, rapid and flexible than a standard NHS clinical service. In that regard, a study of randomisation between an NHS standard-of-care pathway versus a BRCA-DIRECT fully digital pathway would be informative; this was not feasible as...
NHS clinical appointments could not be allocated to patients not eligible for NHS testing. HCP feedback indicated areas where the pathway was equivalent (or superior) to standard care, however, number of responses was limited.

Accessibility on account of both digital literacy/access and language was identified by HCPs as one of the main challenges/shortcomings to the BRCA-DIRECT digital pathway. Ability and willingness to access a digital platform was one of the criteria for eligibility. Thus, our randomised comparison only pertained to this restricted subset of patients with breast cancer, although that we explicitly allowed study participation for those using the device/credentials of a trusted nominee. We sought to capture the reasons for patients declining participation in the study, but were limited to only those willing to offer such a response and could not collect detailed demographics on this group.

The eligibility criterion requiring patients to have a good comprehension of English was established to protect the safety and integrity of patients, aiming to ensure comprehension of the digital pretest information and subsequent informed consent to genetic testing, as well as enabling patients to proceed through the digital tasks by responding to notifications. Developing and translating the digital platform, notifications and pretest information was beyond the limitations of this study but should be considered in any broader rollout.

Additionally, it was challenging to ensure that in their feedback, patients were accurately differentiating the core BRCA-DIRECT pathway (saliva sample, core baseline information, digital pretest information, test consent, return of results) from the elements of the process relating to the evaluative study (study consent, extra baseline info, knowledge scores and STAI): from patient interviews and patient-reported method of pretest information/results delivery, there was evidence of the two being conflated.

Future developments

The outcomes of the established progression criteria supported study continuation, with all criteria met or exceeded. Based on the findings and feedback from the semi-qualitative interviews, minor adaptations have been made to the digital pretest information, knowledge survey and patient reminders, largely to improve consistency of language and clarity of instructions. Based on the turnaround times, hotline usage and satisfaction surveys, adaptations to the sample-laboratory pathway have been implemented, with continued attention to the feasibility of returning results sufficiently rapidly to reliably inform surgical decision-making in those proceeding to surgery without neoadjuvant chemotherapy. With these adaptations, we shall progress to the full study of 1000 women, for a highly powered comparison of the therapy. With these adaptations, we shall progress to the full study of 1000 women, for a highly powered comparison of the therapy.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by The Institute of Cancer Research/ Royal Marsden NHS Foundation Trust for Clinical Research. The study received favourable opinion from the London—Chelsea Research Ethics Committee (REC) on 4 January 2021 (REC reference: 20/L01/1200) and full Health Research Authority (HRA) and Health and Care Research Wales (HCRW) approval on 4 January 2021. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data from this study are not publicly available due to inclusion of special category and sensitive data. Data access requests can be made to the corresponding author for consideration.

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A digital pathway for genetic testing in UK NHS cancer patients: BRCA-DIRECT randomised study internal pilot


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Supplementary Methods
BRCA-DIRECT PATHWAY

Patient DNA sampling

Patient saliva samples were collected using Isohelix Genefix (GFX) Saliva DNA/RNA Collection and Stabilization kits. Patients were provided with instructions on how to collect their sample independently in clinic or at home with postal return to minimise aerosol generating procedures during the COVID19 pandemic. A blood sample pathway was also made available for patients already having clinical/routine bloods taken.

Laboratory analysis

Genetic analysis was undertaken at The Centre for Molecular Pathology (Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK) accredited to International Organization for Standardization (ISO) 15189:2012 (UKAS laboratory accreditation: 20653 Medical Single (ukas.com)).

The exonic regions of BRCA1 (ENST00000357654), BRCA2 (ENST00000380152) and PALB2 ((ENST00000261584)) and flanking intronic regions of 20bps were amplified using a bespoke Qiagen Qiaseq targeted DNA panel and sequenced using Illumina technologies via MiSeq/Nextseq platforms. Alignment and calling of small variants and copy number variants was undertaken using a customised pipeline comprising an in-house bioinformatics pipeline validated against a panel of known BRCA1 and BRCA2 variants*. Multiplex Ligation-dependent Probe Amplification (MLPA) (MRC-Holland kit) was performed to evaluate suspected copy number variants (CNVs).

Variants were classified according to the ACMG-AMP variant classification framework, using the specifications detailed by UK-ACGS (UK Association of Clinical Genomic
Scientists) and CanVIG-UK (Cancer variant interpretation Group UK)\(^1\), \(^2\), \(^3\). As per recommendations of UK-ACGS (UK Association of Clinical Genomic Scientists), the classification was presented using evidence (exponent) points and only variants classified as pathogenic, likely pathogenic or hot variants of uncertain significant (hot VUS) (4/5 evidence points) were included on the laboratory report. \(^3\), \(^2\), \(^4\)

**BRCA-DIRECT Telephone Hotline**

A telephone hotline was available for patients 9am-to-5pm, Monday-to-Friday (excluding public holidays). The hotline was staffed by genetics professionals (genetic counsellor, onco-genetics specialist nurse or clinical geneticist) to support with calls requiring specialist knowledge about genetic testing and/or the results. Research administrators were also available to support with technical or administrative calls only.

Details of the telephone hotline were widely visible within the BRCA-DIRECT digital platform and across study materials available to patients from initial approach about BRCA-DIRECT. All calls to the hotline were logged via the BRCA-DIRECT platform with the following details recorded: date of call, length of call, call handler and free-hand notes.

**BRCA-DIRECT Digital Platform**

The BRCA-DIRECT digital platform consisted of a custom-built database and website housed on isolated, secure servers at the Institute of Cancer Research and integrated with email and SMS messaging systems.

Data security and information governance provisions were incorporated into the design and build of the BRCA-DIRECT platform for handling special category and patient identifiable data and ensuring compliance with relevant governing principles, including General Data Protection Regulation (GDPR).
Independent and moderated user-testing of the platform functionality and content was conducted with clinical genetics specialists, researchers, and patients and the platform optimised for usability and functionality across different devices. The resulting features of the BRCA-DIRECT digital platform are outlined below.

Role-specific administrative access

Administrative functionality of the platform included: (i) adding/amending patient profiles, (ii) management of patient workflow, (iii) tracking patient samples, (iv) logging telephone appointments and hotline calls, (v) management of results, and (vi) generating letters. Administrative user access was specified by role (laboratory user, hospital site-specific clinical user, or genetic counsellor users) to ensure minimal need-to-know access to specific patient data.

Patient user access

Patient user profiles were created by administrative users upon receipt of an expression of interest (EOI) or study consent form, enabling participants to register for a personalised account and receive automated reminders via email and/or SMS to complete tasks within specified conditions.

Patient workflow

The patient workflow was structured into ten steps, which comprised both those elements core to the BRCA-DIRECT pathway (eg collection of critical baseline information, pre-test information, test consent and test results), and elements related to the evaluative study (questionnaires and surveys)(see supplementary figure 2).

Upon login, the patient’s position in the workflow was reflected to them. Following completion of each step, the next step would be presented to the patient via a pop-up
explanation. Progression and access to specific steps was automated based on (i) timing, (ii) confirmed completion of a previous step, or (iii) administrative update.

BRCA-DIRECT digital pre-test information

Digital pre-test information was developed to be of equivalent content and depth to a standard genetic counselling appointment. The materials were developed by the study team and evolved for language, content and presentation via iterative consultation with our clinical and patient user-groups. The final package comprised 21 static screens of written information and schematics. These included 13 core screens covering topics such as genetic inheritance, cancer risk and the process of BRCA-testing and seven screens entitled “more detailed information”, which addressed insurance, options for risk reduction and oncogenesis (Appendix 1).

After viewing all screens, patients were advised to contact the genetic specialist hotline if they required additional support with understanding the information and were required to confirm they had received the pre-test information before proceeding to the digital genetic test consent form.

Digital genetic test consent

The genetic test consent form was designed to reflect directly the contents of the ‘Record of Discussion Regarding Genomic Testing’ used in the UK NHS Genomic Medicine Service, and evolved following consultation with our clinical and patient user-groups.

The digital consent form required participants to mark that they had read and confirmed each statement, followed by typing a digital signature and confirming the date. A confirmatory pop-up notice was required to be acknowledged by the patient upon submission on the form. After confirmation, a PDF copy of the consent form was
made available for the patient to download. A copy was also sent to the patients GP and added to the hospital medical record.

Return of BRCA-test results
Availability of results was communicated to the patient from the BRCA-DIRECT platform via SMS and/or email and, upon login to the platform, the patient received their result either digitally via the BRCA-DIRECT platform or was invited to book a 1:1 telephone consultation with a genetics professional (half-day telephone slots (9am-12pm or 1pm-4pm) available from the following day).

Participants were pre-allocated to receive results digitally (97.5%) or via telephone consultation (2.5%) using the on-line Sealed Envelope™ randomisation list generator.[5] All those with a negative result received their result according to the pre-allocated randomisation. Participants with a reported variant (hot VUS, Likely Pathogenic, Pathogenic), predicted maximum 5% of participants, received their result via telephone consultation, regardless of pre-allocated randomisation.

Formal Communication of BRCA-test results and patient follow-up
A summary letter was automatically generated according to the result of negative (no variants reported), positive (Pathogenic, Likely Pathogenic variant reported) or VUS. The letter was auto-populated with the patients' clinical diagnosis, self-reported family history, test outcomes and accordant clinical recommendations (including screening recommendations predicated on family/personal cancer history for those with negative results) and was sent with the laboratory report to the patient, GP and hospital clinical team. For patients in whom a VUS/Likely Pathogenic/Pathogenic variant is reported, a clinical genetics referral letter was also generated.
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A digital pathway for genetic testing in UK NHS cancer patients: BRCA-DIRECT randomised study internal pilot

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Supplementary Tables and Figures

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Supplementary figure 4: BRCA-DIRECT pathway stages. 1) Pre-test information delivery; 2) decision to proceed with genetic test; 3) testing of sample; 4) results delivery.

Supplementary table 4: Patient reported access and support requirements during involvement with the BRCA-DIRECT digital pathway.

Supplementary table 5: Healthcare professional reported satisfaction with elements of the BRCA-DIRECT digital pathway compared with standard care.

Supplementary table 6: Healthcare professional reported benefits and challenges/short-falls of the BRCA-DIRECT digital pathway.

Supplementary table 7: Patient reported feedback on the content of pre-test information delivered either digitally via the BRCA-DIRECT platform (fully-digital pathway) or via a telephone appointment with a genetics specialist nurse or counsellor (partially-digital pathway).

Supplementary table 8: Average (mean) knowledge scores out of a total of 14 points at baseline (T0) and 7-days post-genetic test consent (T1) in all patients, patients randomised to receive pre-test information digitally only (fully-digital pathway), and patients randomised to receive pre-test information via telephone consultation with a genetics professional only (partially-digital pathway).

Supplementary table 9: Knowledge score questions and number of patients answering individual knowledge questions correctly in the digital and telephone pre-test information arms at baseline (T0) and 7-days post-genetic test consent.

Supplementary figure 5: Knowledge test: Percentage of patients answering individual knowledge questions correctly and the overall average (mean) knowledge score for patients (% correct out of a total of 14) in the digital (green) and telephone (blue) pre-test information arms at baseline (T0) (lighter bars) and 7-days post-genetic test consent (T1) (darker bars).

Supplementary table 10: Mean Intolerance of Uncertainty, ‘trait’ anxiety (State Trait Anxiety Index (STAI) Y2) and ‘state’ anxiety (STAI Y1) scores of all patients and those randomised to receive digital pre-test information or telephone pre-test information only. Mean ‘state’ anxiety scores (STAI Y1) are captured at baseline (T0), 7-days post-genetic test consent (T1), 7-days post-genetic test results (T2), and 28-days post-genetic test results (T3) and exclude patients who completed >5 days after the time point.

Supplementary table 11: Progression criteria outcomes.
**Supplementary figure 1:** Overview of the BRCA-DIRECT digital pathway, encompassing comparison between delivery of pre-test information by digital format (fully digital pathway, green) or telephone appointment with a genetics professional (partially digital pathway, blue).

BRCA-DIRECT Genetics Specialist Telephone Hotline Available

- **FULLY DIGITAL**
  - Digital Pre-Test Information
  - Pre-test counselling
  - Genetic Test Consent
  - NHS Diagnostic Test

- **PARTIALLY DIGITAL**
  - Express of interest
  - Study consent
  - Personal and Family History Questionnaire
  - Telephone Appointment with Genetics Professional

- **BRCA-DIRECT Geneareal Specialist Telephone Hotline Available**
  - Negative results delivered digitally
  - VUS/Positive
  - Clinical Genetics Referral
  - VUS/Positive Returned Via Telephone Appointment with Genetics Professional

- **Baseline questionnaires (T0)**
- **7 days post genetic test consent questionnaires (T1)**
- **7 and 28 days post results questionnaires (T2, T3)**

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Supplementary figure 2: An overview of the BRCA-DIRECT digital platform patient (blue) and administrative (orange) functionality with supportive images from the online webpages.
### Supplementary table 1: BRCA-DIRECT pilot study progression criteria

<table>
<thead>
<tr>
<th>Progression Criterion</th>
<th>Recruitment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruitment rate</strong></td>
<td>Recruitment rate during the pilot is &gt;90% of what is required to meet the full study target (1000 patients recruited across two hospital trusts equivalent in case load).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression Criterion</th>
<th>Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retention</strong></td>
<td>Retention is &gt;75% at final follow-up.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression Criterion</th>
<th>Questionnaire completion compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt;80% of patients complete surveys within a window of 7 days of the expected deadline.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression Criterion</th>
<th>Satisfaction with the digital intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A satisfaction score of ≥3 in at least 80% of patients for questions 9a (How satisfied were you with the way you received your pre-test information?) and 9b (How satisfied were you with the way you received your results?) of the Patient Satisfaction Survey (PSS).</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression Criterion</th>
<th>Change in knowledge following pre-test information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average (mean) knowledge questionnaire score at T1 at least as high as the average at T0 in both arms.</strong></td>
<td></td>
</tr>
</tbody>
</table>

Enrolment

Expressed interest in participating (n=146)

- Excluded (n=16)
  - Ineligible (n=1)
  - Declined to participate (active)(n=4)
  - No consent returned within 8 weeks (passive)(n=11)

Consented to the study (n=130)

Allocated to Digital pre-test information (n=64)

- Received pre-test information (n=60)
- Consented to genetic testing (n=60)
- Completed 7-day post-consent questionnaires (n=60)
  - Excluded (completed outside of window)(n=4)

Genetic Test Results

- Positive (n=1)
  - Returned digitally (n=54)
  - Returned via telephone (n=1)

- Negative (n=59)
  - Returned digitally (n=54)
  - Returned via telephone (n=1)

7-day post-results questionnaire completed (n=55)
  - Excluded (completed outside of window)(n=5)

PSS completed (n=49)

Allocation

Allocated to Telephone pre-test information (n=60)

- Received pre-test information (n=65)
- Consented to genetic testing (n=63)
- Completed 7-day post-consent questionnaires (n=63)
  - Excluded (completed outside of window)(n=2)

Genetic Test Results

- Positive (n=2)
  - Returned digitally (n=58)
  - Returned via telephone (n=2)

7-day post-results questionnaire completed (n=58)
  - Excluded (completed outside of window)(n=5)

PSS completed (n=51)

Follow up

Lost to follow up (Results returned outside of study) (n=5)

- Digital (n=4)
- Telephone (n=1)

Lost to follow up

- Digital (n=1)
- Telephone (n=4)

Withdrawals

n=5 (Digital=4; Telephone=1)

Expressed interest in participating
**Supplementary table 2: Details of patient withdrawal following study consent**

<table>
<thead>
<tr>
<th>Withdrawal characteristics</th>
<th>All  (n)</th>
<th>Digital (n)</th>
<th>Telephone (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total withdrawals*</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Stage of withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to creating a BRCA-DIRECT account</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Before receiving pre-test information</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>After receiving pre-test information,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to genetic test consent</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Failed to receive results**</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Follow up (7/28-day follow up questionnaires)</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Type of withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active withdrawal (patient contacted study)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Passive withdrawal (&gt;6 weeks, no activity)</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Reason for withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too many digital steps to complete</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>A lot going on, not the right time for study participation/genetic testing</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Failure to progress, reason unknown</td>
<td>16</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

**5/123 patients failed to confirm that they had received their results after viewing digitally. Possible explanations for non-receipt via the BRCA-DIRECT pathway included return of results coinciding with in-patient or treatment activity or patient decease. An alert was placed to the respective oncology professional, to ensure clinician-directed return of results.**
Supplementary table 3: Median number of days taken to progress through the BRCA-DIRECT pathway from point of study consent to delivery of results (time-to-results), separated by study stage (1-4) and pre-test information allocation arm (digital or telephone appointment). See supplementary figure 4 for an overview of pathway stages.

<table>
<thead>
<tr>
<th>Stage</th>
<th>All</th>
<th>Pre-test information allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median Days (IQR)</td>
</tr>
<tr>
<td>Pre-test information</td>
<td>125</td>
<td>8.4 (5.5 - 12.6)</td>
</tr>
<tr>
<td>delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decision to proceed</td>
<td>123</td>
<td>0.0 (0.0 - 0.0)</td>
</tr>
<tr>
<td>with genetic test*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testing of sample**</td>
<td>123</td>
<td>27.6 (22.4 - 33.5)</td>
</tr>
<tr>
<td>Results delivery</td>
<td>118</td>
<td>0.0 (0.0 - 1.4)</td>
</tr>
<tr>
<td>Time-to-results</td>
<td>118</td>
<td>38.4 (31.3 - 48.8)</td>
</tr>
</tbody>
</table>

* Genetic test consent forms were available to complete digitally immediately after patients had either a) viewed all of the digital screens or b) the patient record had been updated following the telephone appointment.

**Sequencing of the sample was initiated at a minimum of 1 day post genetic test consent to allow time for patients to change their mind.

Supplementary figure 4: BRCA-DIRECT pathway stages. 1) Pre-test information delivery; 2) decision to proceed with genetic test; 3) testing of sample; 4) results delivery.
**Supplementary table 4:** Patient reported access and support requirements during involvement with the BRCA-DIRECT digital pathway.

<table>
<thead>
<tr>
<th>Area of support/access</th>
<th>Responses</th>
<th>All</th>
<th>Pre-test information allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Digital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>n%</td>
</tr>
<tr>
<td><strong>Devices used to access BRCA-DIRECT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smartphone only</td>
<td>45</td>
<td>45.0%</td>
<td>49.0%</td>
</tr>
<tr>
<td>Desktop Computer/Laptop only</td>
<td>24</td>
<td>24.0%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Desktop Computer/Laptop, Tablet and Smartphone</td>
<td>1</td>
<td>1.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Desktop Computer/Laptop and Tablet and Smartphone</td>
<td>14</td>
<td>14.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Tablet and Smartphone</td>
<td>7</td>
<td>7.0%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Desktop Computer/Laptop and Tablet</td>
<td>1</td>
<td>1.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Tablet only</td>
<td>8</td>
<td>8.0%</td>
<td>12.2%</td>
</tr>
<tr>
<td><strong>Assistance required with providing sample</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes: Clinical</td>
<td>12</td>
<td>12.0%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Yes: friend or family member</td>
<td>1</td>
<td>1.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>No</td>
<td>87</td>
<td>87.0%</td>
<td>79.6%</td>
</tr>
<tr>
<td><strong>Technical assistance required to access/use the BRCA-DIRECT platform</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes: Clinical</td>
<td>2</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Yes: Friend or family member</td>
<td>5</td>
<td>5.0%</td>
<td>6.1%</td>
</tr>
<tr>
<td>No</td>
<td>93</td>
<td>93.0%</td>
<td>91.8%</td>
</tr>
<tr>
<td><strong>Made a call to the hotline (patient reported)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>8%</td>
<td>8.2%</td>
</tr>
<tr>
<td>No</td>
<td>92</td>
<td>92%</td>
<td>91.8%</td>
</tr>
</tbody>
</table>

**Supplementary table 5:** Healthcare professional reported satisfaction with elements of the BRCA-DIRECT digital pathway compared with standard care

<table>
<thead>
<tr>
<th>I have found the following aspects of the BRCA-DIRECT digital pathway to be equivalent (or superior) to standard care:</th>
<th>Disagree (%)</th>
<th>Neither Agree nor Disagree (%)</th>
<th>Agree (%)</th>
<th>Responses (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosample collection (ie saliva)</td>
<td>0.0%</td>
<td>36.4%</td>
<td>63.6%</td>
<td>11</td>
</tr>
<tr>
<td>Delivery of standardised pre-test information (ie digital)</td>
<td>0.0%</td>
<td>45.5%</td>
<td>54.5%</td>
<td>11</td>
</tr>
<tr>
<td>Patient access to individualised specialist advice (ie genetics specialist telephone hotline)</td>
<td>0.0%</td>
<td>36.4%</td>
<td>63.6%</td>
<td>11</td>
</tr>
<tr>
<td>Test uptake</td>
<td>0.0%</td>
<td>9.1%</td>
<td>90.9%</td>
<td>11</td>
</tr>
<tr>
<td>End-to-end time-to-results</td>
<td>27.3%</td>
<td>27.3%</td>
<td>45.5%</td>
<td>11</td>
</tr>
<tr>
<td>Communication of test results to patients</td>
<td>9.1%</td>
<td>18.2%</td>
<td>72.7%</td>
<td>11</td>
</tr>
<tr>
<td>Communication of test results to clinicians</td>
<td>27.3%</td>
<td>0.0%</td>
<td>72.7%</td>
<td>11</td>
</tr>
<tr>
<td>Psychological effect on patients</td>
<td>18.2%</td>
<td>18.2%</td>
<td>63.6%</td>
<td>11</td>
</tr>
<tr>
<td>Use of healthcare professional time</td>
<td>27.3%</td>
<td>0.0%</td>
<td>72.7%</td>
<td>11</td>
</tr>
<tr>
<td>Communication of patient status/updates</td>
<td>18.2%</td>
<td>9.1%</td>
<td>72.7%</td>
<td>11</td>
</tr>
</tbody>
</table>
**Supplementary table 6**: Healthcare professional reported benefits and challenges/short-falls of the BRCA-DIRECT digital pathway

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For the Clinician</strong></td>
<td></td>
</tr>
<tr>
<td>Greater access to testing</td>
<td>Lack of information regarding patient progression</td>
</tr>
<tr>
<td>Reduced clinical time</td>
<td>Treatment delays: as a result of laboratory turnaround times</td>
</tr>
<tr>
<td>Faster turnaround of results</td>
<td>Treatment delays: due to failure of patient to progress or lack of understanding digital process</td>
</tr>
<tr>
<td>Simpler pathway/process</td>
<td>Difficult to ensure patient comprehension of the genetic testing information</td>
</tr>
<tr>
<td><strong>For the Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Non-invasive procedure</td>
<td>Digital literacy/access to digital pathway</td>
</tr>
<tr>
<td>Faster turnaround time</td>
<td>Treatment delays: as a result of laboratory turnaround times</td>
</tr>
<tr>
<td>More empowered</td>
<td>Treatment delays: as a result of patient requirement to actively proceed with the pathway.</td>
</tr>
<tr>
<td>Simpler pathway</td>
<td>Additional test/process to engage with during active treatment or difficult time.</td>
</tr>
<tr>
<td>Greater involvement of family and sharing of information</td>
<td>Eligibility/language barriers</td>
</tr>
<tr>
<td>Greater access to testing</td>
<td></td>
</tr>
</tbody>
</table>

**Supplementary table 7**: Patient reported feedback on the content of pre-test information delivered either digitally via the BRCA-DIRECT platform (fully-digital pathway) or via a telephone appointment with a genetics specialist nurse or counsellor (partially-digital pathway).

<table>
<thead>
<tr>
<th>Pre-test information feedback</th>
<th>All</th>
<th>Digital</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td><strong>Amount of information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too much</td>
<td>6</td>
<td>6.0%</td>
<td>4</td>
</tr>
<tr>
<td>Too little</td>
<td>2</td>
<td>2.0%</td>
<td>1</td>
</tr>
<tr>
<td>About right</td>
<td>92</td>
<td>92.0%</td>
<td>44</td>
</tr>
<tr>
<td><strong>Information content</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Too complicated</td>
<td>5</td>
<td>5.0%</td>
<td>4</td>
</tr>
<tr>
<td>Too simple</td>
<td>0</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>About right</td>
<td>95</td>
<td>95.0%</td>
<td>45</td>
</tr>
</tbody>
</table>
**Supplementary table 8:** Average (mean) knowledge scores out of a total of 14 points at baseline (T0) and 7-days post-genetic test consent (T1) in all patients, patients randomised to receive pre-test information digitally only (fully-digital pathway), and patients randomised to receive pre-test information via telephone consultation with a genetics professional only (partially-digital pathway).

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline (T0)</th>
<th>7 days post-genetic test consent (T1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean score</td>
</tr>
<tr>
<td>All patients</td>
<td>128</td>
<td>5.2</td>
</tr>
<tr>
<td>Digital Only</td>
<td>63</td>
<td>4.7</td>
</tr>
<tr>
<td>Telephone Only</td>
<td>65</td>
<td>5.6</td>
</tr>
</tbody>
</table>
**Supplementary table 9:** Knowledge score questions and number of patients answering individual knowledge questions correctly in the digital and telephone pre-test information arms at baseline (T0) and 7-days post-genetic test consent.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Digital T0</th>
<th>Digital T1</th>
<th>Telephone T0</th>
<th>Telephone T1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients at time point</strong></td>
<td>63</td>
<td>56</td>
<td>65</td>
<td>58</td>
</tr>
<tr>
<td><strong>Questions</strong></td>
<td><strong>Number of patients answering correctly, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I can only inherit gene faults (pathogenic variants) in a BRCA gene from my mother</td>
<td>23 (36.5%)</td>
<td>30 (53.6%)</td>
<td>26 (40.0%)</td>
<td>47 (81.0%)</td>
</tr>
<tr>
<td>If my mother has a gene fault (pathogenic variant) in a BRCA gene, I will definitely inherit it</td>
<td>29 (46.0%)</td>
<td>37 (66.1%)</td>
<td>38 (58.5%)</td>
<td>54 (93.1%)</td>
</tr>
<tr>
<td>If a woman has a gene fault (pathogenic variant) in a BRCA gene, her daughter is more likely to have inherited the gene fault (pathogenic variant) if the daughter looks more like her mother than her father.</td>
<td>30 (47.6%)</td>
<td>34 (60.7%)</td>
<td>35 (53.8%)</td>
<td>50 (86.2%)</td>
</tr>
<tr>
<td>All women with a BRCA gene fault (pathogenic variant) will develop breast cancer</td>
<td>30 (47.6%)</td>
<td>45 (80.4%)</td>
<td>40 (61.5%)</td>
<td>54 (93.1%)</td>
</tr>
<tr>
<td>About 30 in every 100 women (30%) who develop breast cancer have a gene fault (pathogenic variant) in BRCA1/BRCA2/PALB2</td>
<td>3 (4.8%)</td>
<td>6 (10.7%)</td>
<td>9 (13.8%)</td>
<td>25 (43.1%)</td>
</tr>
<tr>
<td>A woman with breast cancer and a gene fault (pathogenic variant) in BRCA1/BRCA2/PALB2 has a significantly increased risk compared to the general female population of developing the following cancers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Another breast cancer</td>
<td>36 (57.1%)</td>
<td>43 (76.8%)</td>
<td>43 (66.2%)</td>
<td>52 (89.7%)</td>
</tr>
<tr>
<td>Cervical cancer (cancer of the cervix)</td>
<td>9 (14.3%)</td>
<td>15 (26.8%)</td>
<td>8 (12.3%)</td>
<td>17 (29.3%)</td>
</tr>
<tr>
<td>Ovarian cancer (cancer of the ovaries)</td>
<td>21 (33.3%)</td>
<td>33 (58.9%)</td>
<td>33 (50.8%)</td>
<td>47 (81.0%)</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>13 (20.6%)</td>
<td>19 (33.9%)</td>
<td>18 (27.7%)</td>
<td>24 (41.4%)</td>
</tr>
<tr>
<td>If my BRCA-test shows I have a gene fault (pathogenic variant), my relatives can be tested to see if they carry the gene fault (pathogenic variant)</td>
<td>42 (66.7%)</td>
<td>44 (78.6%)</td>
<td>48 (73.8%)</td>
<td>56 (96.6%)</td>
</tr>
<tr>
<td>If my BRCA-test shows a VUS (variant of uncertain significance), my relatives will routinely be tested to see if they carry the VUS</td>
<td>7 (11.1%)</td>
<td>22 (39.3%)</td>
<td>6 (9.2%)</td>
<td>35 (60.3%)</td>
</tr>
<tr>
<td>Female family members found to carry a BRCA gene fault (pathogenic variant) may be offered surgery to reduce their risk of developing cancer</td>
<td>31 (49.2%)</td>
<td>32 (57.1%)</td>
<td>39 (60.0%)</td>
<td>46 (79.3%)</td>
</tr>
<tr>
<td>A woman with breast cancer and a gene fault (pathogenic variant) in her BRCA genes can’t get life insurance cover</td>
<td>17 (27.0%)</td>
<td>27 (48.2%)</td>
<td>18 (27.7%)</td>
<td>43 (74.1%)</td>
</tr>
<tr>
<td>If any relatives without cancer take a BRCA-test and the result shows they have a gene fault (pathogenic variant), they must declare their result if they wish to get life insurance</td>
<td>6 (9.5%)</td>
<td>20 (35.7%)</td>
<td>6 (9.2%)</td>
<td>21 (36.2%)</td>
</tr>
</tbody>
</table>
Supplementary figure 5: Knowledge test: Percentage of patients answering individual knowledge questions correctly and the overall average (mean) knowledge score for patients (% correct out of a total of 14) in the digital (green) and telephone (blue) pre-test information arms at baseline (T0) (lighter bars) and 7-days post-genetic test consent (T1) (darker bars).

Q1. I can only inherit pathogenic faults in a BRCA gene from my mother (A: False)
Q2. If my mother has a pathogenic fault in a BRCA gene, I will definitely inherit it (A: False)
Q3. If a woman has a pathogenic fault in a BRCA gene, her daughter is more likely to have inherited the pathogenic variant if the daughter looks more like her mother than her father (A: False)
Q4. All women with BRCA gene pathogenic faults will develop breast cancer (A: False)
Q5. About thirty in every hundred women (30%) who develop breast cancer have a pathogenic fault in BRCA1/BRCA2/PALB2 (A: False)
Q6. A woman with breast cancer and a pathogenic fault in BRCA1/BRCA2/PALB2 has a significantly increased risk compared to the general female population of developing the following cancers:
   - Another breast cancer (A: True)
   - Cervical cancer (cancer of the cervix) (A: False)
   - Ovarian cancer (cancer of the ovaries) (A: True)
   - Kidney cancer (A: False)
Q7. If my test for BRCA genes shows I have a pathogenic fault, my relatives can be tested to see if they carry the pathogenic fault (A: True)
Q8. If my BRCA gene test shows a VUS (variant of uncertain significance), my relatives will routinely be tested to see if they carry the VUS. (A: False)
Q9. Female family members found to carry a BRCA gene pathogenic fault may be offered surgery to reduce their risk of developing cancer (A: True)
Q10. A woman with breast cancer and a pathogenic fault in her BRCA genes can't get life insurance cover (A: False)
Q11. If any of her relatives unaffected with cancer take a BRCA gene test and the result shows they have a pathogenic fault, they must declare their BRCA gene status if they wish to get life insurance (A: False)

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**Supplementary table 10:** Mean Intolerance of Uncertainty, ‘trait’ anxiety (State Trait Anxiety Index (STAI) Y2) and ‘state’ anxiety (STAI Y1) scores of all patients and those randomised to receive digital pre-test information or telephone pre-test information only. Mean ‘state’ anxiety scores (STAI Y1) are captured at baseline (T0), 7-days post-genetic test consent (T1), 7-days post-genetic test results (T2), and 28-days post-genetic test results (T3) and exclude patients who completed >5 days after the time point.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Intolerance of Uncertainty</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Trait</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>All</td>
<td>27.7</td>
<td>39.6</td>
</tr>
<tr>
<td></td>
<td>9.6</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td>Digital</td>
<td>27.2</td>
<td>39.5</td>
</tr>
<tr>
<td></td>
<td>9.7</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Telephone</td>
<td>28.2</td>
<td>39.7</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>65</td>
</tr>
</tbody>
</table>

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**Supplementary table 11: Progression criteria outcomes.**

<table>
<thead>
<tr>
<th>Progression Criterion</th>
<th>Evaluation</th>
<th>Criterion met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Recruitment rate during the pilot is &gt;90% of what is required to meet the full study target (1000 patients recruited across two hospital trusts equivalent in case load).</td>
<td>A recruitment rate of 1.3 per day was observed over the study pilot recruitment period. To meet the recruitment target of 1000 patients, a recruitment rate of 2.7 would be required in the full study (870 patients recruited with 326 days). With the addition of another NHS hospital trust, expected to recruit at equal or greater rate (based on case load), recruitment rate can be predicted to equal 2.6 per day (96.3% of the required rate).</td>
<td>Progression criterion met.</td>
</tr>
<tr>
<td>2 Retention is &gt;75% at final follow-up.</td>
<td>Retention at final follow up (T3) = 84.6% (110/130 patients).</td>
<td>Progression criterion met.</td>
</tr>
<tr>
<td>3 &gt;80% of patients complete surveys within a window of 7 days of the expected deadline.</td>
<td>Patient completion of outcome measures within a window of 7-days: T1 = 95.1%; T2 = 91.2%; T3 = 90.9%</td>
<td>Progression criterion met.</td>
</tr>
<tr>
<td>4 A satisfaction score of ≥3 in at least 80% of patients for questions 9a (How satisfied were you with the way you received your pre-test information?) and 9b (How satisfied were you with the way you received your results?) of the Patient Satisfaction Survey (PSS).</td>
<td>Patient-reported satisfaction of ≥3 with method of receiving: Pre-test information = 98.0% Results = 95.0%</td>
<td>Progression criterion met.</td>
</tr>
<tr>
<td>5 Average (mean) knowledge questionnaire score at T1 at least as high as the average at T0 in both arms.</td>
<td>Overall, mean knowledge scores increased from 5.2/14 (SD 3.3) at T0 to 8.8/14 (SD 3.5) at T1. Digital arm: T0 = 4.7/14 (SD 3.1) and T1 = 7.3/14 (SD 3.7) Telephone arm: T0 = 5.6/14 (SD 3.4) and T1 = 9.9/14 (SD 2.7)</td>
<td>Progression criterion met.</td>
</tr>
</tbody>
</table>
Genetics and Cancer Risk

Some people are at greater risk of cancer than others. This can be because of genetic factors inherited from their parents.

Usually this is due to inheriting from both parents a greater than average dose of thousands of minor genetic factors. However, sometimes there can be a fault in a particular gene inherited from one parent that causes a large increase in the risk of cancer.

This gene fault is called a 'pathogenic variant' and the gene in which it is found is called a 'cancer susceptibility gene'.

If you have been born with a gene fault (pathogenic variant) in a cancer susceptibility gene, it does not mean that you will definitely develop cancer, but it makes it more likely than someone who was not born with the gene fault (pathogenic variant).

Inherited Cancer Risk

These genes are 'cancer susceptibility genes' as they play an important role in controlling cell growth.

If the gene contains a fault (a pathogenic variant), the gene doesn't function properly. This can mean that cells may grow and divide in an uncontrolled fashion leading to cancer.

Three cancer susceptibility genes are strongly associated with an increased risk of developing breast cancer. They are called BRCA1, BRCA2, PALB2, and are often known as the 'BRCA genes'.

Inherited Cancer Risk (continued)

An average woman in the general population has a 12% risk of developing breast cancer by the age of 80.

A woman with a gene fault (pathogenic variant) in BRCA1 or BRCA2 has approximately a 70% risk of developing breast cancer by the age of 80.

A woman with a gene fault (pathogenic variant) in PALB2 has approximately a 30% risk of developing breast cancer by the age of 80.

Inherited Cancer Risk (continued)

Compared to women who do not have a gene fault (pathogenic variant), a woman with a gene fault (pathogenic variant) in one of her BRCA genes, who goes on to develop breast cancer also has:

- a higher risk of developing another breast cancer in the same or opposite breast.
- a higher risk of developing cancer of the ovaries (or fallopian tubes) - especially for BRCA1.
- a small increase in risk of pancreatic cancer - BRCA2 and PALB2 only

BRCA2 is also associated with a modest increase in risk for men of developing prostate cancer. BRCA2 and PALB2 increase the risk of male breast cancer but it is still uncommon.

Inherited Cancer Risk (continued)

Cancer Risk

<table>
<thead>
<tr>
<th>Cancer Risk</th>
<th>The general population</th>
<th>A woman with a gene fault (pathogenic variant) in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Cancer</td>
<td>1.5%</td>
<td>BRCA1: 44%, BRCA2: 5%, PALB2: 5%</td>
</tr>
<tr>
<td>Average lifetime risk to age 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>1.2%</td>
<td>BRCA1: 2%, BRCA2: 2.5%, PALB2: 2.5%</td>
</tr>
<tr>
<td>Average lifetime risk to age 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Breast Cancer</td>
<td>12%</td>
<td>BRCA1: 70%, BRCA2: 50%</td>
</tr>
<tr>
<td>Average lifetime risk to age 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A second Breast Cancer after the first one</td>
<td>5%</td>
<td>BRCA1: 18%, Not well known</td>
</tr>
<tr>
<td>In next 20 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Testing your BRCA genes

A 'BRCA test' looks at the DNA in your cells. A sample of your saliva or blood is sent to the laboratory where it is removed from the cells. The part of this DNA which contains your BRCA genes is examined to see if it contains genetic changes inherited from your parents.

There are three possible test results:

- Negative: no gene faults (pathogenic variants) were found in your BRCA genes.
- Variant of Uncertain Significance (VUS): in 1 out of 1000 tests (1%) we look at VUS. A VUS result means that we currently don’t know if the gene change is harmless or if it increases your risk of developing cancer. Overall, most VUSs are likely to be harmless.
- Positive: a gene fault (pathogenic variant) has been identified. Inherited cancer risk was found in your genes. 3 out of 100 women with breast cancer (3%) will be found to have a gene fault (pathogenic variant) in their BRCA genes.

After receiving your test result, you will be sent a full report and detailed letter. A copy of this letter will be sent to your GP and your cancer clinicians.

It is standard NHS practice to store DNA samples used for genetic testing. Your DNA may be used for ‘quality control’ including for testing of your other family members. Your test data will be stored securely as part of your NHS clinical record.

Why have a BRCA-test?

The reasons for having a BRCA-test are to get more information about:

- **Why you developed cancer**
- **Whether or not you are at high risk of developing a new breast cancer**
- **Whether or not your family members (both male and female) are at high risk of developing breast and other cancers associated with these genes**

When you develop breast cancer:

- **Which drugs and surgery are best for treating your breast cancer**

Receiving a test result that is a VUS

A variant of uncertain significance (VUS) is a genetic change that we are unable to clearly interpret. This means that we cannot say categorically whether this gene change is pathogenic (harmful) or harmless. The majority of changes found in genes are harmless and therefore most of these VUSs are likely to be harmless. Around 2 out of 100 BRCA tests (2%) will return a VUS result.

**If your test result shows we have found a VUS:**

- We will continue your care as if you had received a negative test result.
- We do not test your family for the VUS. Instead, we manage you and your relatives based on the pattern of breast cancer in the family.
- We may contact you in the future if we receive new information telling us more definitely that your VUS is harmless or is pathogenic (harmful).

Receiving a test result that is negative

Approximately 95 out of 100 (95%) women with breast cancer will receive a negative result from their BRCA test.

A negative test result means:

- It is highly unlikely that your BRCA genes played a part in the development of your breast cancer.
- Your risk of developing another new breast cancer is the same as other women your age who have a similar first breast cancer and family history.
- It is unlikely that your close family members are at particularly high risk of breast cancer, unless you have a significant family history of breast cancer.

What if your test result is positive (gene fault (pathogenic variant) found)?

3 out of 100 (3%) women with breast cancer will receive a positive result from their BRCA test.

**Finding a gene fault (pathogenic variant) in one of your BRCA genes means that:**

- This gene fault is likely to have played a part in the development of your breast cancer.
- The best drugs to treat your current/recent breast cancer may be different to those used for other breast cancers.
- You are at increased risk of developing another breast cancer in the same or opposite breast. This may influence the options for breast surgery for treating your breast cancer.
- You may be at increased risk of developing ovarian cancer and other cancers.
- Other members of your family may also carry the same gene fault (pathogenic variant) and be at increased risk of developing cancer.

What will happen next if your result is positive?

You will have a telephone consultation with a Genetic Counsellor from the BRCA-DIRECT study to answer any questions you may have.

You will be offered an appointment at your local Clinical Genetics service. Here you can discuss your cancer risk in more detail and the options available to you. They will also advise you about contacting your relatives to offer them genetic testing.

Your cancer clinicians will talk with you about options for surgery and/or drugs to treat your breast cancer.

What are the reasons for not having a BRCA-test?

- Some women find the information about their breast cancer, and the treatment choices that need to be made, overwhelming. These women may prefer not to have a BRCA-test at this time.
- Other women are concerned about the implications of a genetic test on their health insurance policy. Screens 15 and 16 provide more information about this.
Additional Information

The following screens contain detailed information on the following:

- Genetic tests and insurance
- Risk reduction
- More about genetics (cancer risk and inheritance)

If you do not understand the information you have already read or have additional questions, please contact the Genetic Counselling helpline on +44(0) 8456 789 012 (Mon – Fri, 9am – 5pm, Monday to Friday).

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### Genetic tests and Insurance

**Insurers routinely request details on your own diagnoses and your family history of disease, and this may influence the terms or premiums. The insurance industry differentiates between a diagnostic genetic test and a predictive genetic test.**

#### Diagnostic genetic test

This is when you have a genetic test following a diagnosis of a condition (e.g. a BRCA test following a diagnosis of breast cancer).

The Association of British Insurers (ABI) states that diagnostic genetic tests can form part of routine medical information when applying for a new policy, and therefore need not be included in your information. In practice, any new applications for life, critical illness and income protection insurance will be strongly influenced by your recent diagnosis of breast cancer. It is unlikely that terms or premiums will be significantly influenced by information regarding detection of a BRCA gene fault (pathogenic variant).

#### Predictive genetic test

This is when you have a genetic test for a condition that runs in your family but you currently have no signs of disease (e.g. a daughter unaffected with cancer having a test to look for a BRCA1 gene fault (pathogenic variant) that was found in her mother with breast cancer).

- A Code of Practice has been developed between the Government and the ABI, which restricts insurers from demanding or using the results of predictive genetic tests.
- If (for example) you are found to carry a BRCA1 gene fault (pathogenic variant) and your sister, unaffected with cancer, takes a predictive test to see if she carries the BRCA1 gene fault (pathogenic variant) found in you, the insurer cannot ask you or your sister about her having the predictive test or about the test result.
- In some cases, it may be in the interests of an unaffected person to declare a negative (normal) result if there is a strong family history of relevant cancers.

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### What can be done about reducing the risk of developing a new cancer for those found to carry a BRCA gene fault (pathogenic variant)?

**New Breast Cancer**

The risk of developing a new breast cancer can be reduced by having an operation to remove one or both healthy breasts. This is called risk-reducing mastectomy. Various types of breast reconstruction are available following risk-reducing mastectomy.

**Women with a new diagnosis of breast cancer and a BRCA gene fault (pathogenic variant)** may choose to have bilateral mastectomy as the operation for removal of their original cancer. Female relatives without cancer carrying the BRCA gene fault (pathogenic variant) may also be offered risk-reducing mastectomy.

Another option is to have very regular scans and/or mammograms with the intention of picking up any new breast cancers at an early stage.

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### What can be done about reducing the risk of developing a new cancer for those found to carry a BRCA gene fault (pathogenic variant)?

**Ovarian Cancer**: can be aggressive with poor outcomes. Women over the age of 40 may be offered an operation to remove their ovaries and Fallopian tubes (tubes which carry eggs to the womb). This is often done as keyhole surgery, where the surgeon only needs to make a tiny cut to remove the ovaries and fallopian tubes.

**Prostate Cancer**: men may be offered screening using a combination of blood tests, scans and removal of samples (biopsies) from the prostate to help detect prostate cancer at an early stage.

**Pancreatic Cancer**: pancreatic screening involves scans or tests using an internal camera; it could be offered to certain carriers of a BRCA gene pathogenic variant, especially if there is pancreatic cancer in the family.

If you are found to carry a BRCA gene fault (pathogenic variant) in the BRCA-DIRECT study, you will be referred to clinical genetics where you can discuss your option and options available to you in more detail.
All cells in our body contain two identical sets of a blueprint called DNA. DNA looks like a long string and contains sequences of code called genes. Genes are responsible for physical characteristics such as eye colour but they also perform other important functions. We inherit one set of DNA from our mother and one from our father, so our genes come in pairs.

When a cell divides, its DNA is copied into the new cells. Genetic changes can arise by chance as the DNA is being copied. Build-up of genetic changes is a normal process that happens over time in all our cells. Some genetic changes can switch on ‘cancerous’ behaviour in the cells, where there is loss of control over how the cells divide, grow and spread. Environmental factors, such as UV light and tobacco smoke will increase the rate of genetic changes.

If you have been born with a gene fault (pathogenic variant) in a cancer susceptibility gene, this means that fewer additional genetic changes will be required for your cells to switch to the cancerous behaviour. Therefore, if you have an inherited gene fault (pathogenic variant), it does not mean that you will definitely develop cancer but it makes it more likely than for someone who was not born with the gene fault (pathogenic variant).

More about genetics: Genetics and Cancer risk

More about genetics: How are genetic changes inherited?

We each have 2 copies of each gene (one inherited from our mother and one inherited from our father). Each parent only provides one set of their genes to each child. The inheritance of gene changes in most cancer susceptibility genes, including BRCA1, BRCA2 and PALB2, is autosomal dominant. So if you carry a gene fault (pathogenic variant) in BRCA1/BRCA2 or PALB2, you would have inherited it from either your mother or your father. If you carry a gene fault (pathogenic variant), each time you have a child, there is a 50% chance you will pass on the gene fault (pathogenic variant) to the child and a 50% chance that you will not.

This does not mean half your children will inherit the gene fault (pathogenic variant). It may be that all of them or none of them inherit the gene fault (pathogenic variant) (like flipping heads on a coin). If your child has not inherited the gene fault (pathogenic variant), it has ‘stopped there’ and cannot be passed on to their children.

Genetic traits are inherited independently of each other. Therefore just because a child has inherited the same hair or eye colour as their mother and looks like her, they still have just a 50% chance of having inherited the gene fault (pathogenic variant) she carries.

Where to find more information

If you still have questions about genetic testing or require further information, please contact the BRCA-DIRECT Genetic Counselling hotline on +44 20 3437 6514 (9am – 5pm, Monday to Friday).

External Sources of Information

A number of charities and NHS organisations have provided information on genetic testing for breast cancer and BRCA gene testing. We have provided some links below for further information – please note, these are generic resources and some information provided may not be relevant to you or the BRCA-DIRECT study.

- NHS Website
  https://www.nhs.uk/conditions/predictive-genetic-tests-cancer/
- Royal Marsden NHS Foundation Trust: Beginners Guide to BRCA1 and BRCA2
- Royal Marsden NHS Foundation Trust: Genetic testing and insurance
- Breast Cancer Now
  https://breastcancernow.org/information-support/have-i-got-breast-cancer/am-i-risk/breast-cancer-in-families/genetic-testing
- Macmillan
- Prevent Breast Cancer
  https://preventbreastcancer.org.uk

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