MSD AstraZeneca

CECOG
Central European Cooperative Oncology Group

A Guide To Genetic Consenting

Module 13:
Future approaches to BRCA testing – investigations into app-based testing

Prof. Clare Turnbull

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Learning objectives

The primary purpose of this learning module is to inform and educate non-genetics HCPs on genetic consenting.

This module will enable HCPs to:

- Be aware of alternative models of genetic consenting
- Understand how genetic testing can guide treatment decisions in cancer

HCP=healthcare professional

BRCA-DIRECT: randomised evaluation in women diagnosed with breast cancer of digitally-delivered pre-test information for BRCA testing

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Speaker communication from Professor Turnbull

Study background[1]

- Laboratory element of genetic testing is (relatively) **cheap** and **high-throughput**
- **Limited capacity** is a consequence of:
  - Laborious workflows for:
    - Pre-test genetic counselling appointments (limited workforce)
    - Return of results
- **Direct-to-consumer tests**
  - Expansion; variable cost
  - Concerns regarding data quality (accuracy of variant calling, variant classification)
  - Results not held within UK laboratory infrastructure
    - Family contact
    - Variant reinterpretation

Proof-of-concept study to examine **feasibility, safety and acceptability** of **digital pathways for the delivery of genetic pre-test information and workflows** within **UK NHS clinical and laboratory infrastructure**[2]

NHS=National Health Service

1. Speaker communication from Professor Turnbull. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022

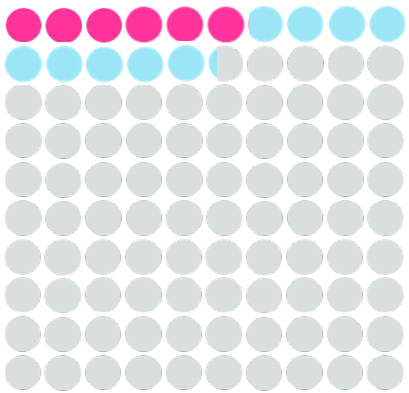
Which patient population / genes?[1,2]
Breast cancer: *BRCA1 / BRCA2*

- Germline genetic testing of **ovarian cancer**: delivery well established
- Germline genetic testing of **colorectal cancer**: pathology (tumour) pathways
- Germline genetic testing of **breast cancer:**
  - <15% eligible via NHS National Testing Directory
  - Therapeutic information
  - Large patient volume (55,920 new diagnoses per year; >900,000 prevalent diagnoses)[3]
- ~6% detection rate for *BRCA1 / BRCA2*[4]

National Testing Directory 2022[2,5,6]

***BRCA1 / BRCA2 / PALB2*: full screen incl. dosage**

- Breast cancer + family history, pathology adjusted Manchester score ≥15 or CanRisk score ≥10%
- Breast cancer (age <40 years, excluding Grade 1), OR
- Breast cancer <45 years and one FDR with BC age <45 years
- Bilateral breast cancer (age <60 years), OR
- TNBC (age <60 years), OR
- Breast cancer, Ashkenazi heritage



Unidentified pathogenic variant carrier
Identified pathogenic variant carrier[4]
Identified variant uncertain significance carrier[7]

BRCA1/2=Breast Cancer Gene 1/2; NHS=National Health Service; PALB2=partner and localiser of BRCA2 gene

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022; 2. Speaker communication from Professor Turnbull; 3. University of York. Available at: [https://www.york.ac.uk/news-and-events/news/2022/research/salt-breast-cancer/]. Accessed July 2022; 4. Toss A, et al. *Cancers*. 2020;12:125; 5. National Genomic Test Directory 2022. https://www.england.nhs.uk/publication/national-genomic-test-directories. Accessed July 2022; 6. National Institute of Clinical Excellence Guidelines. CG164. January 2013. Accessed July 2022; 7. Hikmat Abdel-Razeq, et al. *Front Oncol*. 2022;12.

Study background: breast cancer use-case

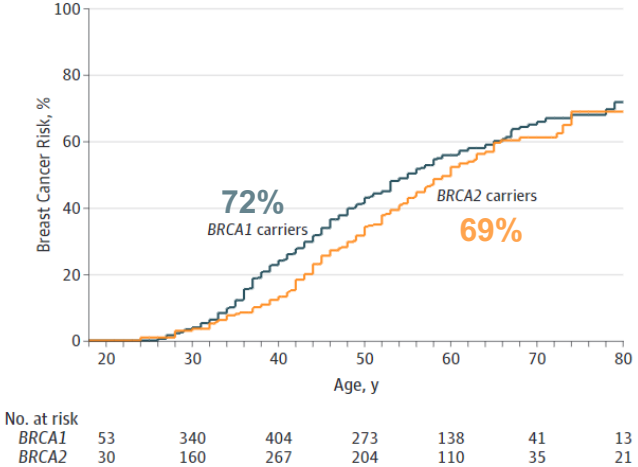
- Recent UK Health Economic analyses have shown that testing for these genes in breast cancer are now **cost-effective**[1,2]
  - £20,000–£30,000 per quality-adjusted life year
- Response to previous **web-based aids** of further knowledge have had positive results
- Surveys of oncology professionals revealed **mainstreaming of genetic testing** was **low in breast cancer** services, owing to:[3,4]
  - Overwhelming patient volume
  - Lack of time during appointments
  - Complex eligibility criteria to navigate
  - Lack of counselling expertise; legal concerns

1. Sun L, et al. *JAMA Oncol* 2019;5:1718–1730; 2. Manchanda R, et al. *J Natl Cancer Inst* 2018;110:714–725; 3. Hallowell N, et al. *Fam Cancer* 2019;18:293–301; 4. Slade I, et al. *Genome Med* 2015;7:18

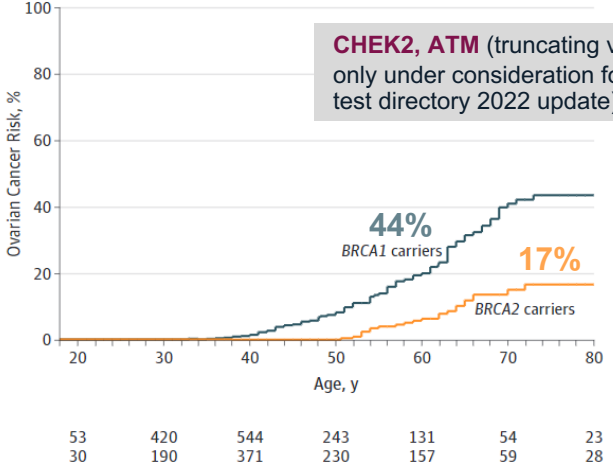
Risk profile of genes included?

Estimated cumulative risks of breast and ovarian cancers in mutation carriers[1,2]

Cumulative risk of **first BC** among *BRCA1* and *BRCA2* mutation carriers



Cumulative risk of **first OC** among *BRCA1* and *BRCA2* mutation carriers



CHEK2, ATM (truncating variants only under consideration for NHS test directory 2022 update)[2]

Cancer risk	The general female population	A woman with a gene fault (pathogenic variant) in:		
		BRCA1	*BRCA2*	*PALB2*
Ovarian cancer Average lifetime risk to age 80	2%[3]	44%[1]	17%[1]	5%[4]
First breast cancer Average lifetime risk to age 80	15%[5]	72%[1]	69%[1]	53%[4]

BC=breast cancer; NHS=National Health Service; OC-ovarian cancer

1. Kuchenbaecker KB et al. JAMA. 2017;317(23):2402–2416; 2; Speaker communication from Professor Turnbull; 3. Cancer Research UK. Ovarian Cancer Risk. Available at: [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/risk-factors]. Accessed July 2022; 4. Yang X et al. J Clin Oncol. 2020;38(7):674-685; 5 Cancer Research UK. Breast Cancer Risk. Available at: [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/risk-factors]. Accessed July 2022

Study Overview

BRCA-DIRECT
Clinically-Integrated Clinician-Lite Rapid Digital
Genetic Susceptibility Biomarker Testing

Primary objective
To evaluate if digital delivery of pre-test information is **non-inferior** to standard practice

Secondary objectives

- To **assess knowledge** about genetic testing for BRCA genes, following delivery of pre-test information
- To **assess anxiety** following delivery of pre-test information and test results

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022.

Study Overview (continued)

BRCA-DIRECT
Clinically-Integrated Clinician-Lite Rapid Digital
Genetic Susceptibility Biomarker Testing

Recruitment
1000 patients from across The Royal Marsden NHS Foundation Trust and Manchester University NHS Foundation Trust

Internal phase

- First 120 women recruited (aim for 60 in each arm)
- After internal phase is complete there will be a pause
- Analyses of data and detailed user feedback (optional telephone interviews; up to 50 interviews)

NHS=National Health Service

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022.

Eligibility criteria

Inclusion criteria[1]

- **>18 years** of age
- Diagnosis of invasive breast cancer or high-grade ductal carcinoma in situ
- Good **comprehension** of the **English** language
- Access to a smartphone or email, plus **internet access**

Exclusion criteria[1]

Previous genetic testing (*BRCA1*, *BRCA2*)

Other criteria[2]

Patients **can be recruited** during the following stages in their treatment:

- New patient, pre-surgical
- New patient, pre-surgical, neoadjuvant chemotherapy
- New patient, post-surgical, adjuvant chemoradiotherapy
- Patient under follow-up, disease-free, maintenance treatment only
- Metastatic

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022; 2. Speaker communication from Professor Turnbull

Outcomes

Primary[1]

Uptake of genetic testing

Test offer-to-results time

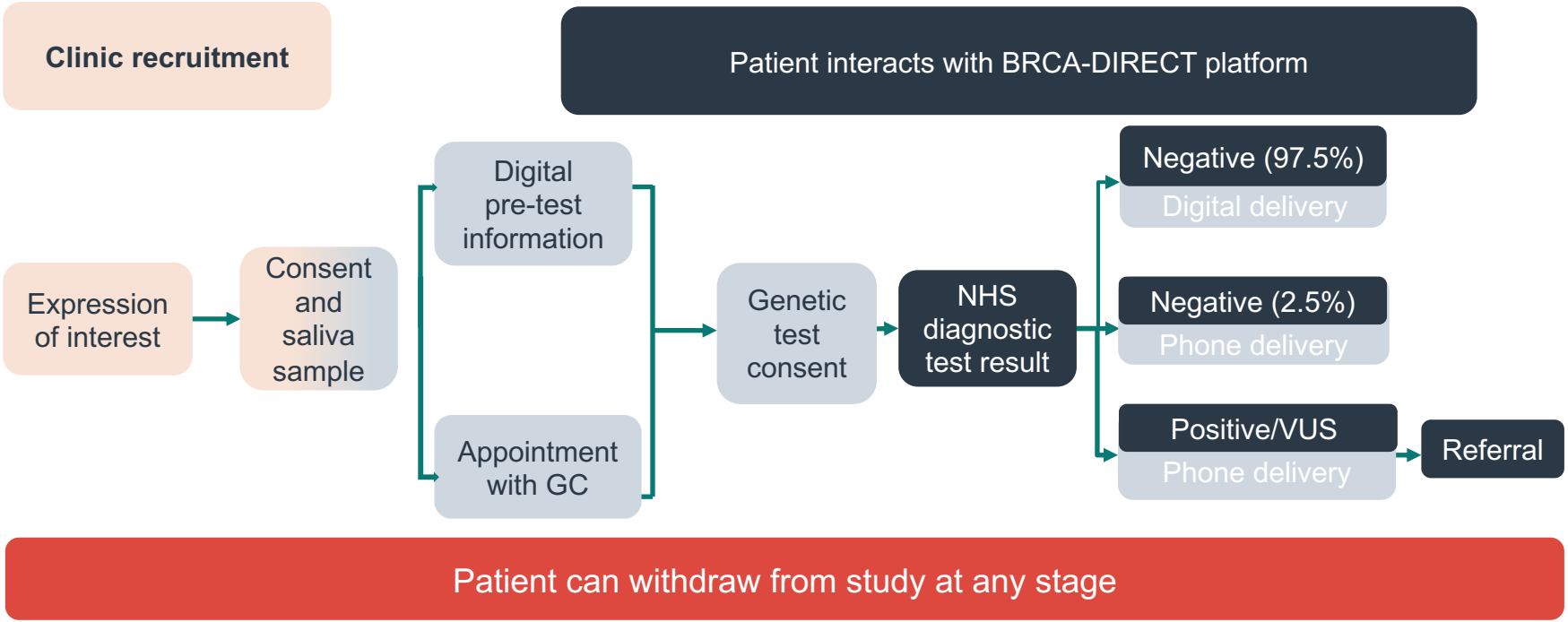
Helpline usage

Questionnaires[2]	Outcome	Timepoint
Intolerance of Uncertainty	Anxiety around genetic testing	Baseline
State-Trait Anxiety Inventory (STAI)	Anxiety around genetic testing	Baseline, 7 days after genetic test consent, 7 days after results, 28 days after results
Knowledge Questionnaire	Knowledge of genetic testing for BRCA genes	Baseline, 7 days after genetic test consent
Participant Survey	Satisfaction with process	7 days after results
Healthcare Professional Survey	Satisfaction with process	At end of pilot phase, and end of study

STAI=state-trait anxiety inventory

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022; 2. Speaker communication from Professor Turnbull

Patient flowchart

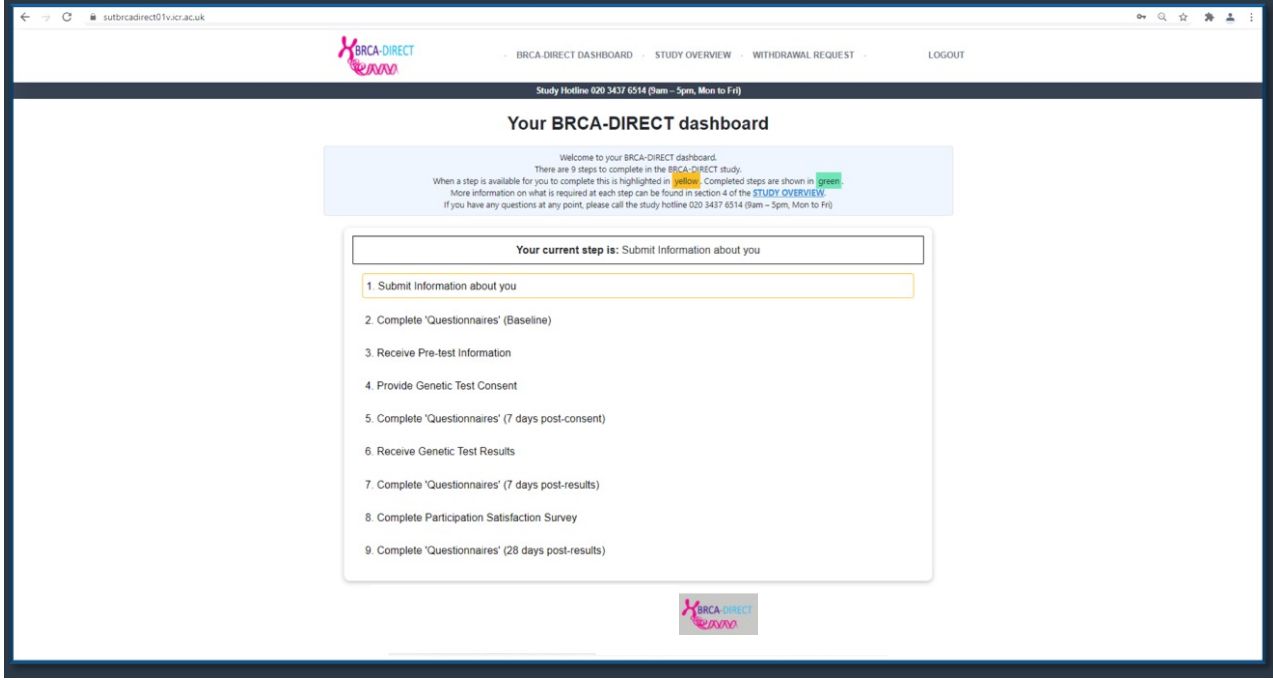


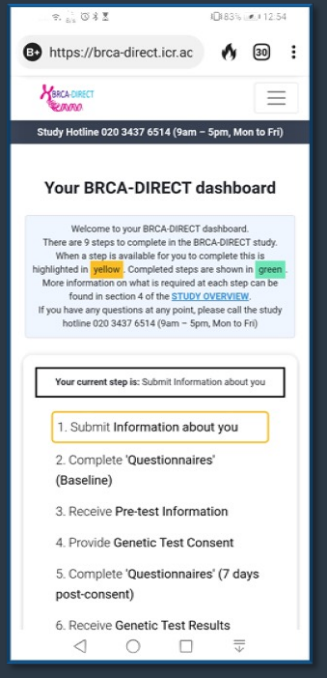
GC=genetic counsellor; NHS=National Health Service; VUS=variant of uncertain significance

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04842799. Accessed July 2022.

BRCA-DIRECT platform (patient view)

The BRCA-DIRECT platform (shown below) can be accessed via most devices that can connect to the internet, including laptops, tablets and smartphones





Website under development

Pre-test information

Genetics and cancer risk

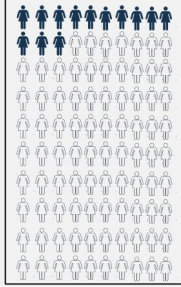
- Some people are at greater risk of cancer than others. This can be because of genetic factors inherited from their parents
- Usually this is due to inheriting from both parents a gr genetic factors. However, sometimes there can be a f parent that causes a large increase in the risk of canc
- This **gene fault** is called a **"pathogenic variant"** and **"cancer susceptibility gene"**
- If you have been born with a gene fault (pathogenic v not mean that you will definitely develop cancer, but it not born with the gene fault (pathogenic variant)

Inherited cancer risk

Unaffected | Pathogenic variant carrier | Breast cancer

First Breast Cancer Risk

An average woman in the general population has an approximately 13% risk of developing breast cancer by the age of 80[1].

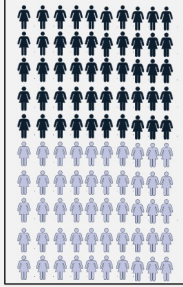


13 out of 100 women will have developed breast cancer by the age of 80.

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[2,3].

70 out of 100 women will have developed breast cancer by the age of 80.

A woman with a gene fault (pathogenic variant) in *PALB2* has approximately a **50% risk** of developing breast cancer by the age of 80[4].



50 out of 100 women will have developed breast cancer by the age of 80.

SOP for standard-of-care arm to ensure equivalent delivery of content

SOP=standard operating procedure

Speaker communication from Professor Turnbull

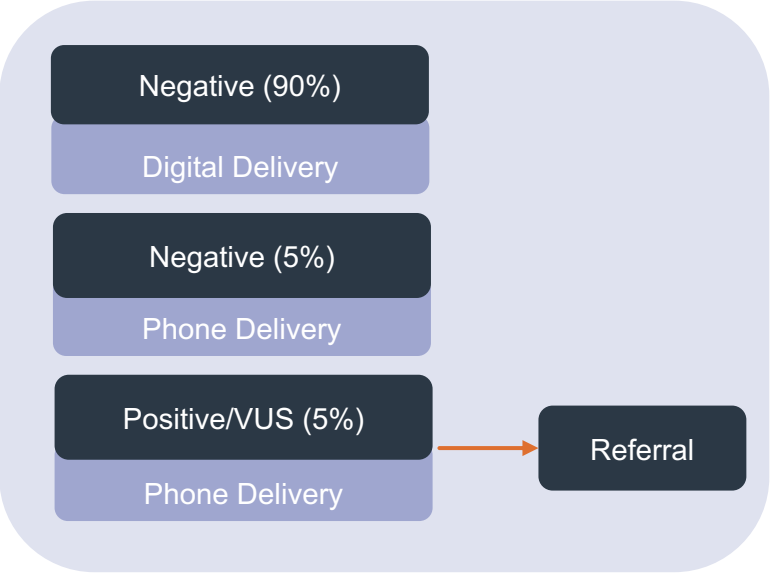
BRCA genetic test: results returned

Negative test result

- 95% will receive their results on the platform
- 5% will book an appointment

Positive test result

- Includes PV or hot VUS
- Book an appointment
- Post-results, automatically generated, personalised letter plus lab report sent to:
    - Patient, GP, oncology team
- Genetics referral



GP=general practitioner; PV=pathogenic variant; VUS=variant of uncertain significance

Speaker communication from Professor Turnbull

Pilot data analysis (60,120)

Good rate of test uptake

- 90-95% test uptake for those who sign for genetic test consent
- Dropout rate confounded by research study protocol

Workflow

- 8 days of return of postal saliva and study consent
- 29 days from test consent to results

Genetic test results

72 results
- 3 pathogenic variants
- 0 hot VUS

Sample type

- Home saliva sample type versus deposit of saliva (COVID-19)
- Blood pathway discontinued

Hotline usage

- Check timing of test results
- Register on platform

Knowledge Questionnaire

- Interesting pattern of knowledge retention for both arms (digital non-inferior)
- Do we give patients too much information?
  - Context of concurrent cancer diagnosis
  - 97% will be negative
- Additional studies

VUS=variant of uncertain significance

Turnbull C, unpublished data 2021.

Summary

From pilot data, BRCA-DIRECT digital pathway appears to be feasible, acceptable and non-inferior

- Evaluative study is more complex than core BRCA-testing workflow
- Pathway / workflow has required lots of ‘tweaks’ (especially COVID-19-related); individualised to NHS location
- Digital platform is external to NHS firewall
- Complexity regarding data protection and workflows for lab reports (sensitive data)

- **Genetics counselling (pre-test knowledge)**
- Reproduced level of knowledge delivered in conventional genetics consultation
- Detailed, many statistics / numbers
- What do patients want (acute diagnosis vs further down the treatment pathway)?
- Provision of graded information
- Opportunity for additional evaluation

Turnbull C, personal opinion.