

PROTECT-C: Population-Based Germline Testing for Early Detection and Prevention of Cancer

Amanda Dibden¹, Caitlin Fierheller¹, Jacqueline Sia¹, Subhasheene Ganesan¹, Grace Norman¹, Rosie Corbie¹, Dona Chakraborty¹, Hamda Mohammed¹, Priyanka Deshmukh¹, Jingsong Zhao¹, Yuxiao Sun¹, Laura White¹, Tia Whenham¹, Eamonn Sheridan², Alison Kraus², Usha Menon³, Ian Tomlinson⁴, Caroline Presho⁵, Kevin Monahan⁶, Veerle Coupe⁷, Nick West⁸, Clare Turnbull⁹, Beth Torr⁹, Helene Schlecht¹⁰, George Burghel¹⁰, Andrew Wallace¹⁰, Antonis Antoniou¹¹, Judith Hayward^{13,14}, Imran Rafi^{13,14}, Samantha Quaife¹, Jo Waller¹, Rhian Gabe¹, Rosa Legood¹⁵, Gareth Evans¹⁶, Stephen Duffy¹, Adam Brentnall¹ and Ranjit Manchanda¹ on behalf of the PROTECT-C study team and collaborators.

¹Wolfson Institute of Population Health, Queen Mary University of London, UK; ²Leeds Institute for Molecular Medicine, St James's Hospital, UK; ³MRC Clinical Trials Unit, Institute of Clinical Trials & Methodology, University College London, UK; ⁴Edinburgh Cancer Research Centre, UK; ⁵BRCA Umbrella, UK; ⁶St Mark's Hospital and Imperial College London, UK; ⁷Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands; ⁸Department of Pathology, University of Leeds, UK; ⁹Institute of Cancer Research, London, UK; ¹⁰Genomic Diagnostics Laboratory, Manchester Centre for Genomic Medicine, UK; ¹¹University of Cambridge, UK; ¹²Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds Teaching Hospitals NHS trust, UK; ¹³Royal College of General Practitioners, London, UK; ¹⁴Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, UK; ¹⁵Centre for Genomic Medicine, Division of Evolution and Genomic Science, University of Manchester, MAHSC, UK

Introduction

- Pathogenic variants (PVs) in several cancer susceptibility genes (CSGs) increase the risk of developing breast, ovarian, endometrial and colorectal cancers - many are potentially preventable
- Effective preventive options include risk-reducing surgery, medical prevention, screening and lifestyle changes
- Genetic testing is currently only offered to women identified as high-risk using clinical/family-history based criteria via specialised genetics clinics
- Thresholds for testing are high: 50-80% of PV-carriers do not meet the current testing criteria and are missed

Objectives

PRIMARY OBJECTIVE: to evaluate the impact of population-based genetic testing on identification of pathogenic/likely pathogenic variants in high and moderate penetrance CSGs compared with family-history genetic testing

Secondary objectives:

- Cost-effectiveness
- Impact of return of variants of uncertain significance
- Experience with using & usability of the PROTECT-C App
- Experiences of participants with undergoing genetic testing
- Uptake of cascade testing
- Satisfaction and regret with population-based testing
- Impact of genetic testing on quality of life and psychosocial wellbeing
- Uptake of risk management options in CSG specific PV-carriers & women at moderate/high risk of breast & ovarian cancers

Eligibility

Inclusion criteria:

- Protect-C will recruit **5,000** women, trans men and non-binary people with female reproductive organs who are ≥18 years

Exclusion criteria:

- Individuals who have:
 - Undergone genetic testing for one or more of the following CSGs: *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D*, *BRIP1*, *MLH1*, *MSH2*, *MSH6*
 - One or more first- or second-degree relatives with a PV in any of above CSGs; or
 - Inability to provide informed consent

Study Design

- PROTECT-C is a **completely digital** prospective cohort study evaluating population-based genetic testing using a **Direct-to-Participant (DTP) approach**
- Participants are recruited via **self-referral** and **invitations** sent through NHS Digitrials
- Saliva samples will be collected via **post**
- Recruitment, genetic testing consent process, and return of results will be undertaken via a **bespoke digital app platform**
- Participants will be supported by a dedicated helpline, email or virtual appointment with a specially trained counsellor

Opening soon!



Scan here for more information

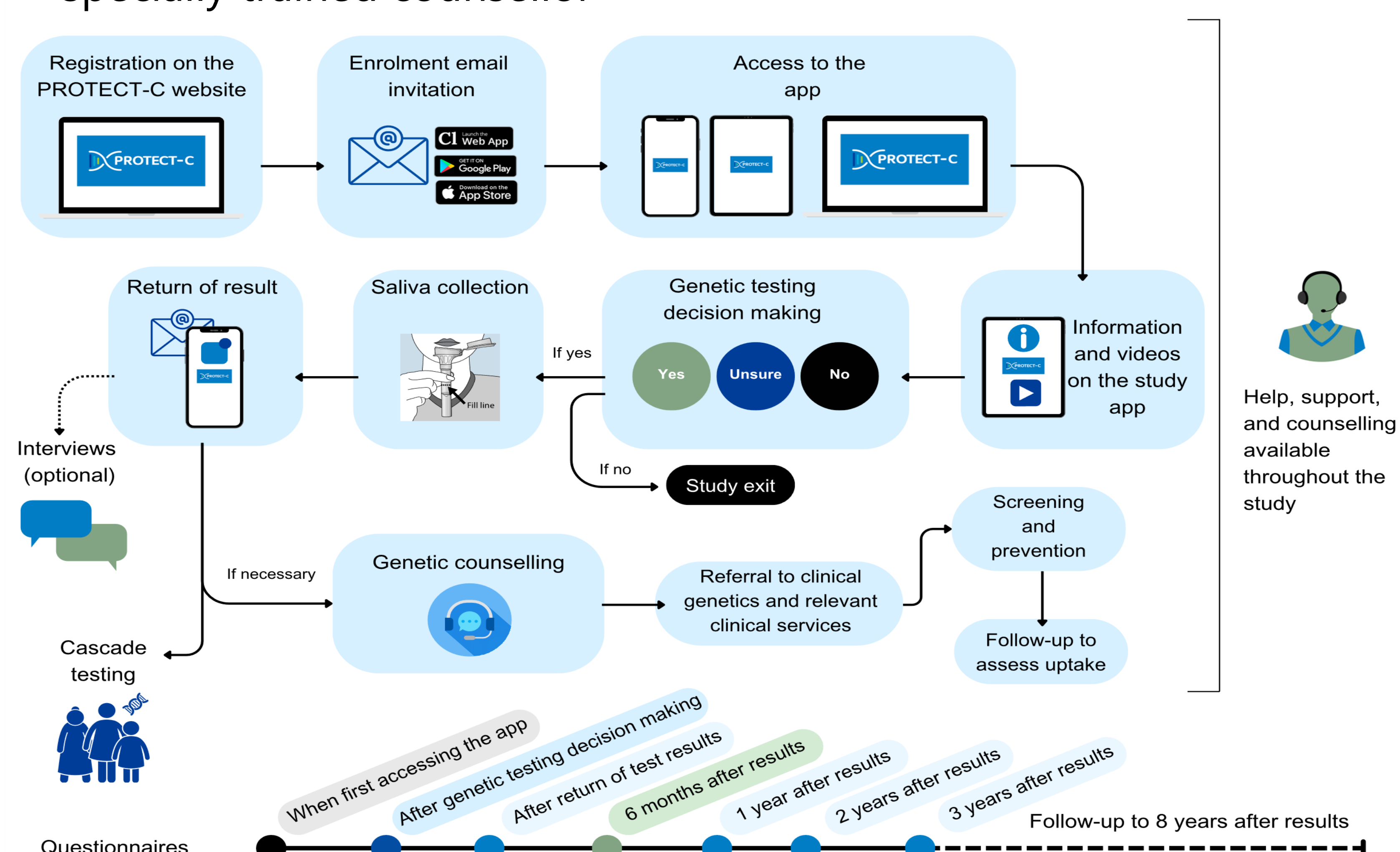


Figure 1: Participant journey flow chart

Analysis, Results and Conclusions

- Recruitment is expected to **open in early 2026** and is anticipated to take **18-24 months**
- Analysis** of the primary objective will be undertaken after the final participant has undergone genetic testing and received a valid result
- The **end of the study** will be 24 months after receipt of the last (Year 8) follow-up questionnaire from the final participant
- PROTECT-C will **address knowledge gaps** including the uptake and acceptability, psychosocial outcomes and cost-effectiveness of DTP population-based testing

Funding and Ethics

PROTECT-C is funded by Yorkshire Cancer Research. IRAS ID: 328404