Introduction
In 2016 the Chief Medical Officer highlighted in her report the importance of risk stratification to target screening/prevention strategies. This is especially relevant to cancers of cardiovascular disease (CVD) where there is a continuing need to reduce morbidity and mortality. Equally important to improving long-term survival of cancer patients is earlier diagnosis.

Risk stratification and early detection has been hampered by the lack of clinically useful biomarkers with those in use discovered at least 30 years ago. However, with advances in technologies to isolate and characterise genomic, proteomic and other biomarkers and increasing use of robust case-control study designs (PROBE - Prospective Specimen Collection Retrospective Blinded Evaluation), the stage is set for discovery of markers, individually and in combination, to detect disease earlier.

The UKCTOCS Longitudinal Women’s Cohort (UKLWC) with longitudinal samples and data preceding disease diagnosis provides a unique resource to move the field forward. Key features of the biorepository in the course of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (2001-date) are:

- **Sample Size**: 202,280 women
- **Representativeness**: Recruited through random invitation from NHS age sex registers in England, Wales and N. Ireland with a 16.3% acceptance rate
- **Consent** for use of samples in secondary ethically approved academic and industry studies
- **Section 251 approval and established linkage to electronic health records** (HES, ONS, cancer registry, NCIN and MINAP)
- **Longitudinal follow up**: Currently median 14 years
- **Large numbers**: Of women diagnosed post recruitment with disease; for e.g. cancer (n>24,000) and other common diseases (e.g. circulatory diseases n>84,000)
- **High quality serum biorepository** (Figure 1)

Objectives
1. To undertake risk prediction and early detection biomarker studies in cancer/cardiovascular disease
2. To evaluate the suitability of the serum samples for multi-omics analysis

Methods
Collaborations were set up using the Data Access process (Figure 2) to undertake nested case control studies in specific cancers and CVD using state-of-the-art technologies.

- Cases were identified using data from multiple sources - cancer registries (NHS Digital & Northern Ireland; National Cancer Intelligence Network - NCIN, Hospital Episode Statistics (England & Wales), death registry (NHS Digital & Northern Ireland) and MINAP (Myocardial Ischaemia National Audit Project), plus self reporting on follow up questionnaires
- Controls were matched to cases using minimum criteria
- Longitudinal sample sets were identified to assess biomarker change over time in the individual
- Where required, details of diagnosis and treatment were obtained through contacting GPs/treating clinicians (breast cancer) or retrieving hospital notes and independent review (ovarian cancer)
- Blinded assay of the biomarker was undertaken in randomly selected cases and controls divided into training and validation sets

Results
The initial study in 2007 was undertaken using the cutting edge proteomics strategy in an ovarian cancer sample set funded by an MRC grant. Since then, 44 collaborations (local, national and international) focusing on discovery/validation of risk and early detection biomarkers have been undertaken, supported by public, charity and industry funding (Tables 1a&b).

The success of initial collaborations led to further exploration of the biomarker by other groups. For example, our longitudinal p53 autoantibody profiling of colorectal cancers with University of Copenhagen (2008-2013) led to evaluation of p53 autoantibody profile in ovarian cancer by the group at MD Anderson (2015-2017), with the same colorectal sample set currently being included in a collaboration “A Novel Microfluidic Platform for Ultrasonic Autoantibody Detection” with Rutgers University, New Jersey, USA.

The initial BRC-funded work in genetics of cardiovascular disease and DNA methylation signatures in cancer (2008-2011) led to (1) further studies on metabolomics in the CVD case control set funded by the British Heart Foundation (BHF) and enabled AH to set up the UCLES (UCL-LSHTM-Edinburgh-Bristol) Consortium and support an application under review for a BHF research excellence award, (2) EU FP7 funding to explore DNA methylation signatures as early detection markers.

Conclusions
The resource has resulted in a number of successful collaborations which have explored a variety of risk/early detection markers/biomarker panels in cancers that contribute most to mortality (high grade serous ovarian cancer, pancreatic cancer, fatal breast cancer). For most, early detection biomarkers performance was improved by use of longitudinal algorithms.

Table 1a: Risk prediction/Early detection biomarker studies undertaken using a case-control design nested within UKLWC - academic collaborations

Table 1b: Risk prediction/Early detection biomarker studies undertaken using a case-control design nested within UKLWC - industry collaborations

Table 1c: Risk prediction/Early detection biomarker studies undertaken using a case-control design nested within UKLWC - all collaborations

https://www.ucl.ac.uk/womens-health/research/womens-cancer/gynaecological-cancer-research-centre/ukctocs-longitudinal-womens-cohort