Biochemistry – assays underway

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Nested case-control measurements

- Most common approach for biomarker analyses
  - But will result in requests to measure the same biomarker on different subsets at different times
  - Data would be incomparable across the cohort
- Cohort-wide measurement more efficient
- Nested case-control approach may still be suitable for biomarkers that are:
  - Disease-specific
  - Expensive
- UK Biobank will put out 'calls'

Rationale for a centralised biochemical panel for all 500,000 participants

- **Increases the usability** of the resource, by allowing:
  - case-cohort analyses
  - cross-sectional analyses with prevalent disease
  - identification of subsets based on assay values
- **Good quality control** to conduct assays in all participants at the same
- **Cost-effective** to conduct these assays at one time
  - Economies of scale
  - Avoid multiple retrieval costs
- **Efficient management** of depletable samples
- **Rapid** availability of results to researchers

Strategy for inclusion

- **Established risk factors for disease**
  - e.g. lipids for vascular disease; sex hormones for cancer
- **Diagnostic markers**
  - e.g. HbA1c and glucose for diabetes; Rheumatoid Factor for arthritis
- **Characterize phenotypes not otherwise assessed**
  - e.g. biomarkers for renal and liver function

Biomarkers to be measured

Cardiovascular:

- Cholesterol
- Direct LDL-cholesterol
- HDL-Cholesterol
- Triglyceride
- Apolipoprotein A
- Apolipoprotein B
- C-reactive Protein
- Fibrinogen
- D-dimer
- Lipoprotein (a)

Cancer:

- SHBG
- Testosterone
- Oestradiol
- IGF-I

Bone and joint:

- Vitamin D
- Rheumatoid factor
- Alkaline Phosphatase
- Calcium

Liver:

- Albumin
- Direct Bilirubin
- Total Bilirubin
- Gamma glutamyltransferase
- Alanine aminotransferase
- Aspartate aminotransferase

Diabetes:

- HbA1c
- Glucose

Renal:

- Creatinine
- Cystatin C
- Total protein
- Urea
- Phosphate
- Urate
- Creatinine (urine)
- Sodium (urine)
- Potassium (urine)
- Albumin (urine)

Sample selection strategy

- Aim to minimise clustering of samples with similar participant characteristics within a batch
  - to avoid systematic bias in future case-control analyses

- Algorithm that selects samples from different assessment centres to achieve a wide spread of characteristics across each assay batch
  - Keeps the relative proportions of samples from each centre constant
  - maintains high retrieval rate (~1,600 samples/day)

Logistics

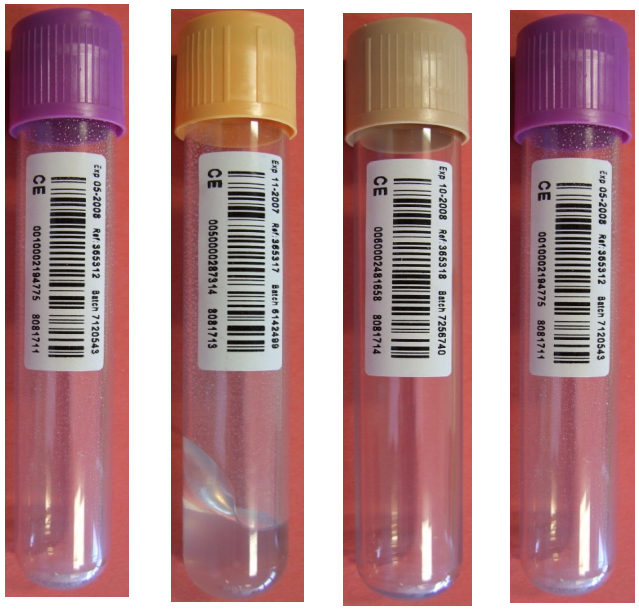
- Dedicated lab at UK Biobank co-ordinating centre
- Preparation phase:
  - Equipment installation
  - Staff recruitment/training
  - Appropriate lab accreditation
  - Method validation

Method Validation and Quality Control

- Validation of assays
  - Validation of methods
  - Validation across multiple instruments
  - Validation of sample type (if atypical)
  - Validation of internal QC regimes and assay performance (i.e. precision and accuracy)
- Stringent internal QC measures to ensure analyte stability and to prevent lab drift
- Use of external QA schemes, where available

Sample throughput

EDTA Plasma | Serum | Urine | Packed RBC

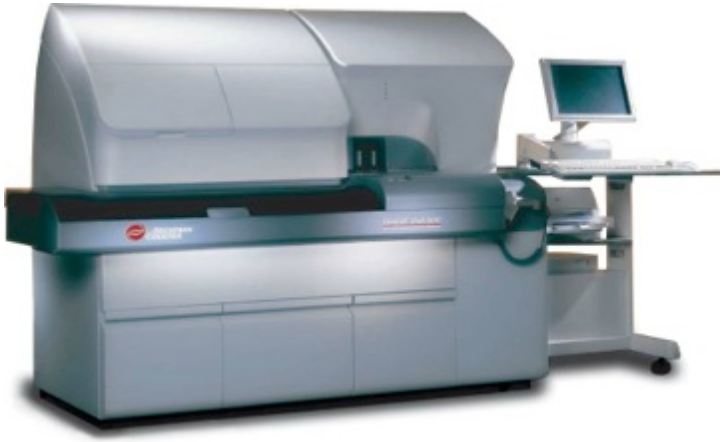


UK Biobank Co-ordinating Centre

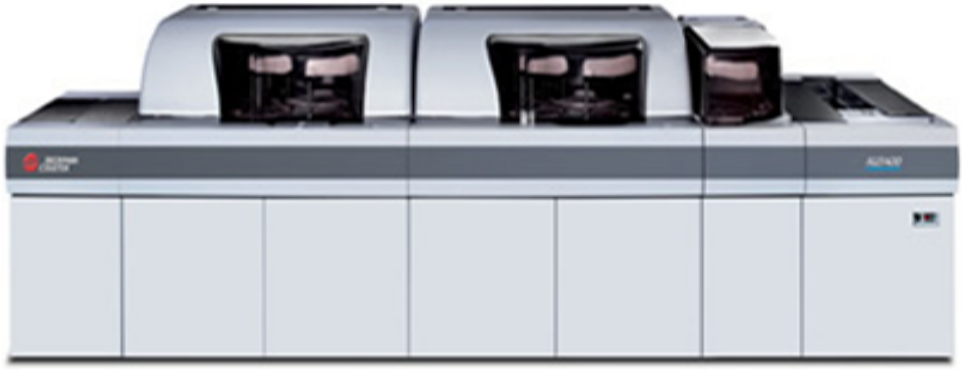
Sample Type	No. Analytes Tested	Sample throughput per day
Urine	4	3,000
Red Blood Cells	1	1,200
Plasma	2	1,600
Serum	29	1,600

Analysis phase

- 17 high-throughput analysers
- Multiple systems – redundancy
- 24/7 operation for most analytes to produce rapid results



Beckman Coulter DxI Immunoassay platform



Beckman Coulter AU5400 clinical chemistry analyser

Timeline

- Phased approach
  - Simplifies the process
  - Single sample type on each analyser at any given time

Sample type	Start date	Duration (end date)
Urine	June 2014	6 months (Dec 2014)
Red blood cells	June 2014	14 months (Sept 2015)
Plasma/serum	Dec 2014	10 months (Oct 2015)

Aim to release data in phases, when available