UK Biobank Biomarker Project

Details of assays and quality control information for the urinary biomarker data

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1.0 Introduction

In order to enhance further the value of the UK Biobank resource to researchers, UK Biobank has embarked on a project to measure a wide range of biochemical markers in biological samples collected at baseline (2006-2010) in all 500,000 participants (and also in the samples provided by 20,000 participants who returned for a "Repeat Assessment" in 2012/ 2013).

The project seeks to measure biomarkers in three matrices – urine, packed red blood cells (PRBC) and serum – using a phased analysis approach.

This document is provided as a companion document to the urinary biomarker data available through the UK Biobank Showcase.

It is intended to provide basic information on:-

- Assay selection & project scope
- Methods and equipment
- Urinary assay performance characteristics
- Quality system and scope of accreditation

2.0 Assay Selection & Project Scope

Overall, 36 biomarkers were selected for assay in all 500,000 participants, full details of which can be found at http://www.ukbiobank.ac.uk/uk-biobank-biomarker-panel/

They were selected for analysis because they represent established risk factors for disease, are established diagnostic measures, or characterise phenotypes not otherwise well assessed.

The project was co-ordinated by the Enhancement Working Group, with input from external experts, where required (listed in Appendix 1 – Expert Advisors).

This document focuses on the urinary biomarkers only.

3.0 Assay Equipment and Information

Table 1 below lists the urine assays conducted together with details of the manufacturer of the assay, the units, principle of measurement and analytical range of the instrument.

Assay	Assay Manufacturer	Analysis Method	Units of Measurement	Manufacturer's Analytical Range
Microalbumin	Randox Bioscience, UK	Immuno-turbidimetric	mg/L	6.7 - 200
Enzymatic Creatinine	Beckman Coulter (UK), Ltd	Enzymatic	µmol/L	88 - 44200
Potassium	Beckman Coulter (UK), Ltd	ISE Ion Selective Electrode	mmol/L	2 - 200
Sodium	Beckman Coulter (UK), Ltd	ISE Ion Selective Electrode	mmol/L	10 - 400

Table 1: Instrumentation and assays

All tests were carried out on a single Beckman Coulter AU5400 clinical chemistry analyser using the manufacturer's reagents and calibrators except urinary microalbumin which used reagents and calibrators sourced from Randox Bioscience, UK.

The Beckman Coulter AU5400 series clinical chemistry analyser (Figure 1) uses a photometric measurement[1] for the determination of creatinine and microalbumin concentration and a potentiometric[2] measurement for the determination of sodium and potassium concentration.

Figure 1: Beckman Coulter AU5400 Series Clinical Chemistry Analyser

3.1 Results Outside of the Reportable Range

Each assay was validated against the manufacturer's performance information. Linearity experiments determined the reportable range. For each assay, the observed reportable range covered the manufacturer's analytical range. The manufacturer's analytical ranges for the four assays are listed in Table 1.

Showcase data only includes valid results (results returned by the instrument that are within the reportable range); where a valid result was not obtained, the result field is left empty and an accompanying entry is made in the result flag field indicating the reason for the null result.

Where the reason for the null result is that the returned value is greater than the top of the analytical range, then the result flag comprises the value of the top of the analytical range preceded by a ">".

Similarly where the reason for the null result is that the returned value is less than the bottom of the analytical range, then result flag comprises the value of the bottom of the analytical range preceded by a "<", as shown in Table 2.

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[1] Photometric measurements make use of a change in optical density of a fluid (from the reagent blank) to determine the concentration of an analyte

[2] Potentiometric measurements (via the Ion-Selective Electrode (ISE) module) make use of the electrical potential generated by ions in a sample passing through a crown ether membrane electrode. A membrane potential is developed according to the Nernst Equation for a specific ion from which the ion concentration can be calculated

Assay	If instrument result is…	Result flag value
Sodium (mmol/L)	Below the bottom of the reportable range	<10
	Above the top of the reportable range	>400
Potassium (mmol/L)	Below the bottom of the reportable range	<2.0
	Above the top of the reportable range	>200
Creatinine (µmol/L)	Below the bottom of the reportable range	<88
	Above the top of the reportable range	>44200[3]
Microalbumin (mg/L)	Below the bottom of the reportable range	<6.7
	Above the top of the reportable range	>200[4]

Table 2: Result Flags

Additional information:

The analysis method for urinary sodium and potassium involves a pre-dilution of sample step, no further dilution is taken.

The analysis method for urinary microalbumin and creatinine assays allows samples with results exceeding the upper analytical limit of the assay to be diluted and re-analysed. Where a sample has been diluted to produce a result in the analytical range the Showcase data will show a validated result that appears to exceed the analytical range.

4.0 Assay Performance Characteristics

As noted above, each assay method was validated or verified against the manufacturers' performance information[5] prior to commencing analysis. In addition, throughout the project detailed quality and method performance protocols were carried out to maintain confidence that the assays were performing to the manufacturers' specification.

One element of the quality protocol was the bracketing of participant samples with Internal Quality Control (IQC) samples of known high and low concentration. IQC samples were run prior to each batch of participant samples (opening bracket) and after each batch (closing bracket)[6]. Participant results were validated into the dataset if both the opening and closing IQC results were within the set control limits for the analytical process.

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3 Refer to additional Information section.

4 As footnote 3.

5 The performance targets used were those provided by the assay reagent supplier; for the creatinine, sodium and potassium assay methods performance targets were provided Beckman Coulter and for the microalbumin assay method performance targets were provided by Randox Bioscience, UK.

6 The batch size maximum was set at 300 samples; typically IQC brackets were run every 100 samples

Table 3 provides information on assay performance, summarising the Coefficients of Variation[7] (CVs) derived from the IQC data for each assay over the period of the project.

Biomarker	IQC level	IQC material in the range[8]	CV (%)	Comment
Sodium	Low	74-77 mmol/L	0.99	3 IQC lots used
	High	166-173 mmol/L	0.82	4 IQC lots used
Potassium	Low	29-30 mmol/L	1.10	3 IQC lots used
	High	79-84 mmol/L	1.18	4 IQC lots used
Microalbumin	Low	21-27 mg/L	2.08	3 IQC lots used; 7 reagent lots used; 8 combinations
	High	51-67 mg/L	1.85	3 IQC lots used; 7 reagent lots used; 9 combinations
Creatinine	Low	6645-7320 µmol/L	2.09	3 IQC lots used; 10 reagent lots used; 11 combinations
	High	16890-17665 µmol/L	2.10	4 IQC lots used; 10 reagent lots used, 12 combinations

Table 3 – Assay performance of urine methods

Additional information:

Each assay was registered on the WEQAS General Urine Chemistry EQA scheme and assay performance externally verified via the results returned from participation in this scheme.

A sample selection algorithm was implemented to ensure no bias or drift was introduced to the assay as a consequence of the order of sample analysis.

5.0 ISO 17025 Quality Accreditation

The Biomarker Project was run under a strict quality regime. All assays were conducted under systems designed for and consistent with the internationally recognised standard for testing and calibration laboratories - ISO17025.

During the project the UK Biobank laboratories were successfully externally audited against the ISO17025 standard. From the 17th December 2015, the UK Biobank laboratories have accreditation to ISO17025 as a testing laboratory. The urine methods supporting the biomarker project for sodium, potassium and creatinine and microalbumin appear on the scope of accreditation (UKAS accreditation reference: 8975).

[7] Coefficient of variation is a standardized measure of dispersion of a frequency distribution; it is defined as the ratio of the standard deviation to the mean and is widely used to express the precision and repeatability of an assay. A low CV indicates a well-controlled assay

[8] For each assay, a number of IQC lots were used; the table presents the range of lot means

Appendix 1 – Expert Advisors

The tables below list (in alphabetical order) the members of the UK Biobank Enhancements Working Group which initiated the project, the Design Phase Expert Group who led on the selection of markers and assays, and the Biomarker Expert Working Group who guided and advised the project during its operational phase.

The UK Biobank project team would like to acknowledge the support and express thanks to all those who contributed their time and expertise to this project.

UK Biobank Enhancements Working Group

Individuals Name	Organisation
Chair: Prof Paul Elliott	Imperial College, London
Associate Prof Naomi Allen	University of Oxford/UK Biobank
Dr Rachael Almond	UK Biobank
Prof Sir Rory Collins	University of Oxford/UK Biobank
Prof Frank Kelly	Kings College London
Dr Tim Peakman	UK Biobank
Prof Naveed Sattar	University of Glasgow
Prof Augustin Scalbert	International Agency for Research on Cancer, Lyon
Dr Simon Sheard	UK Biobank
Dr Ioanna Tzoulaki	Imperial College, London
Prof Anthony Whetton	University of Manchester

Previous members: Prof Mark Caulfield (London); Prof John Gallacher (Oxford); Prof Alan Silman (Oxford); Prof Nick Wareham (Cambridge).

Biomarker Expert Working Group

Individuals Name	Organisation
Associate Prof Naomi Allen	University of Oxford/UK Biobank
Dr Rachael Almond	UK Biobank
Mrs Karen Chung	University of Oxford
Mr Richard Chung	University of Oxford
Mr Daniel Fry	UK Biobank
Mr Mark Gordon	UK Biobank
Dr Michael Hill	University of Oxford
Dr Gareth McClean	University of Oxford
Mr Stewart Moffat	UK Biobank
Dr Simon Sheard	UK Biobank
Mrs Jane Wintour	University of Oxford

Design Phase Expert Working Group

Individuals Name	Organisation
Prof Jane Armitage	University of Oxford
Prof Peter Burney	Imperial College, London
Dr Karen Canfell	University of Sydney, Australia
Prof Robert Clarke	University of Oxford
Prof John Danesh	University of Cambridge
Prof Paul Foster	Moorfields Eye Hospital, London
Dr Silvia Franceschi	International Agency for Research on Cancer (IARC), Lyon, France
Dr Marc Gunter	Imperial College, London (now IARC)
Prof Ian Hall	University of Nottingham
Dr Anna Hansell	Imperial College, London
Prof Nick Harvey	MRC Life-course Epidemiology Unit, University of Southampton
Dr Michael Hill	University of Oxford
Prof Debbie Jarvis	Imperial College, London
Prof Tim Key	University of Oxford
Prof Michael Kidd	Flinders University, Adelaide, Australia
Prof Dave Leon	London School of Hygiene & Tropical Medicine, London
Prof Gordon Lowe	University of Glasgow
Dr Teri Manolio	National Institute of Health, Bethesda, USA
Prof Stephen MacMahon	George Institute, University of Sydney/University of Oxford
Prof Naveed Sattar	University of Glasgow
Prof Liam Smeeth	London School of Hygiene & Tropical Medicine, London
Prof David Strachan	St George's Hospital, London
Prof Martin Tobin	University of Leicester
Prof Paolo Vineis	Imperial College, London
Prof Cyrus Cooper	MRC Life-course Epidemiology Unit, University of Southampton