Resource report

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Harmonisation of strategies for exploitation of biological sample collections

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Biological samples have been collected or are currently being collected by all cohorts that are part of the Cohort and Longtudinal Studies Enhancement Resources (CLOSER). Most cohorts have also produced DNA banks for use in genetic studies. The genotyping data and data generated from biosamples from cohorts is frequently used in cross cohort analysis. The most common example of cross cohort work utilising data from samples are Genome Wide Association Studies. These have covered a wide range of phenotypes including but not limited to birth weight[1,2], educational attainment[3], cardiac phenotypes[4], lung function[5] and timing of puberty[6]. Data generated from biological samples can also be compared at different timepoints within a cohort to investigate how biomarkers change over time, for example samples from the Avon Longitudinal Study of Parents and Children (ALSPAC) study have been used to investigate how biomarkers of thyroid function mature during childhood[7]. Analysis of DNA samples taken across the life course from longitudinal cohort studies have recently been exploited in numerous epigenetics studies as illustrated by the use of samples from the ALSPAC study to create the widely used Accessible Resource for Integrated Epigenomic Studies (ARIES)[8].

When using data generated from analysis of samples in cross cohort or longitudinal comparison studies sample collection, processing and storage conditions need to be considered. Ideally samples will all have been handled using identical protocols developed when cohort studies were established. This is feasible for a particular clinic sweep as illustrated by the protocols developed for UK Biobank[9]. However, since sample collection from longitudinal cohorts can continue over many decades it is impossible to ensure identical protocols are used throughout the life time of the study. Since the samples collected early in life are often the most valuable for research related to the long term effects of childhood exposures it is essential methods which maximise the use of these valuable existing sample collections are developed. In addition, different cohorts face different challenges when collecting samples, for example some, like ALSPAC, cover a relatively small geographical area and it is feasible for participants to visit a central research clinic to donate samples where as samples from the national cohorts often need to be collected by research nurses or interviewers in participants' homes. Sample collection protocols are always a compromise which maximise the amount of data to be obtained from samples within the financial and practical restraints of a given fieldwork sweep. It is therefore essential that records are kept of how samples were collected, processed and stored and that this information is made available to researchers analysing samples. It will not be feasible to run all assays on all samples as some analytes will degrade over time however a large number of assays will not be affected by storage or processing conditions. Therefore, it is essential that access committees

approving release of samples take this into account and ensure samples are only provided for assays that can generate reliable data when sample history is taken into account.

This review is a summary of the biological samples available for further analysis from CLOSER studies in 2016 and is based on information provided to the workpackage 3 team by the individual studies. In 2016 field work and initial sample analysis was in progress for sweeps of some cohorts so samples from those collections were not yet available for release (eg ALSPAC's 24 year clinic and Generation 2 collections, the first sample collection for the 1970 British Cohort Study and the most recent collection from the 1946 cohort). Details of these new collections are not included in this report. The following tables contain information related to sample collection, processing and storage history which should be taken into account when planning future analysis of the samples and when harmonising data obtained from them. However, the tables do not include details of the number of samples available since this will change as samples are released for analysis. Details of samples from some studies can be found on the UKCRC Tissue Directory (https://www.biobankinguk.org/) but up to date information regarding the number of samples currently available will need to be provided by the individual studies when this is required.

The following tables are in the attached spreadsheet CLOSER_biosamples_review_tables.xlsx.

Table 1 - Samples available from the Hertfordshire cohort
Table 2 - Samples available from the MRC National Survey of Health and Development (1946 birth cohort)
Table 3 - Samples available from the 1958 National Child Development Study
Table 4 - Samples available from Understanding Society: the UK Household Longitudinal Study
Table 5 - Samples available from the ALSPAC Cohort - Mothers' samples
Table 6 - Samples available from the ALSPAC Cohort – original participants' samples
Table 7 - Samples available from the ALSPAC Cohort - Partners' samples (Note this is the Mother's partner)
Table 8 - Samples available from the Southampton Women's Study
Table 9 - Samples available from the Millennium Cohort Study
Table 10 - DNA available from all cohorts
Table 11 – Lymphoblastoid cell lines available from all cohorts

CONSENT

In addition to the sample collection, processing and storage conditions it is essential that sample analysis is carried out in line with the consent obtained from the participants when they donated samples. A review of the documents used for collection of consent for obtaining biological samples in the CLOSER cohorts has been undertaken. Guidance and practices have evolved over the life time of the cohorts and changed as a result of legislation such as the UK Human Tissue Act (2004). The results of the review are recorded in the following paper which is currently being finalised for publication.

Informed consent in the CLOSER cohorts. Shavanthi Rajatileka, Alix Groom, Andrew Turner, Susan Ring and Madeleine Murtagh

In this paper we will assess the information contained within the consent documents (consent forms and participant information sheets) used during biological sample sweeps by seven of the longitudinal studies included in the CLOSER network in relation to recommendations by the UK's Health Research Authority (HRA) and UK funders. We also report on changes observed in consent documentation following the introduction of the Human Tissue Act 2004.

References

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Table 1 - Samples available from the Hertfordshire cohort

Timepoint	Where taken	Sample Type	Processed		Fasting	Products	Storage
			Within 2 hours	Delayed			
Baseline Hertfordshire 1999-2004	Clinic	Whole blood	Not known		yes and no	plasma	-80 °C
	Clinic	Urine	Not known		n/a	urine	-80 °C
European Study of Osteoarthritis 2011-2012	Not known	Whole blood	Not known			plasma	-80 °C
Hertfordshire Sarcopenia Study 2010-	Clinic	Blood	yes		yes	plasma	-80^{o}C
						DNA	-80^{o}C
	Clinic	overnight urine		X	n/a	urine	-80 °C
	Clinic	Muscle biopsy			n/a	muscle fibres	-80 °C

Table 2 - Samples available from the MRC National Survey of Health and Development (1946 Birth cohort

Timepoint	Where taken (who by if home)	Sample type	Processed		Fasting	Products	Storage
			Within 2 hours	Delayed			
1999	home visit (nurse)	Buccal sample		X	n/a	DNA	-80°C
		Blood EDTA		X	no	DNA	-80°C
						plasma	-80°C
		Blood heparin		X	no	plasma	-80°C
		Blood CPDA		X	no	lymphoblastoid cell lines	cryopreserved - 180°C
2006-2011	Study clinic or home visit (nurse)	Blood heparin		X	yes	plasma	-80°C
		Blood EDTA		X	yes	DNA	-80°C
						plasma	-80°C
		Blood citrate		X	yes	plasma	-80°C
		Blood CPDA		X	yes	lymphoblastoid cell lines	cryopreserved - 180°C
		Blood serum tube		X	yes	serum	-80°C
		Saliva		X		saliva	-80°C
		Urine (overnight)		X		urine	-80°C

Table 3 - Samples available from the 1958 National Child Development Study

Time point	Where taken (who by if home)	Sample Type	Processing time		Fasting	Products	Storage
			Within 2 hours	Delayed			
2002-2004	home visit (nurse)	Blood citrate tube		X	no	Citrated plasma	-80°C
2002-2004	home visit (nurse)	Blood serum tube		X	no	serum	-80°C
2002-2004	home visit (nurse)	Blood EDTA		X	no	DNA	-80°C
						plasma	-80°C
2002-2004	home visit (nurse)	Blood CPDA		X	no	Lymphoblastoid cell line	cryopreserved 180°C
						Peripheral blood Lymphocytes	cryopreserved 180°C
						CPDA plasma	-80°C
2002-2004	home (participant)	Saliva		x	n/a	saliva	-80°C
2002-2004	home (participant)	Saliva		x	n/a	saliva	-80°C

Table 4 - Samples available from Understanding Society: the UK Household Longitudinal Study

Cohort group	Timepoint	Where taken	Sample type	Processed		Fasting	Products	Storage
				Within 2 hours	Delayed			
Adults	2010-2012	Home (nurse)	Blood serum tube		yes	no	serum	-80°C
Adults	2010-2012	Home (nurse)	Blood citrate tube		yes	no	plasma	-80°C
Adults	2010-2012	Home (nurse)	Blood EDTA		yes	no	plasma	-80°C
							DNA	-80°C

Table 5 - Samples available from the ALSPAC Cohort - Mothers' samples

Cohort Group	Timepoint	Where taken (who by if home)	Sample type	Processed		Fasting	Products	Storage
				Within 2 hours	Delayed			
mother	antenatal (1990-1992)	NHS clinic	Blood (acid washed)		X	no	whole blood	4°C
		NHS clinic	Blood EDTA		X	no	plasma	-20°C
							white cells (for DNA)	-20°C
							red blood cells	-20°C
		NHS clinic	Blood serum tube		X	no	serum	-20°C
		NHS clinic	Blood heparin tube		X	no	plasma	-80°C
							white cells (for DNA)	-80°C
							red blood cells	-20°C
		NHS clinic	Urine		X	no	urine	-20°C
	1993	Home (participant)	Hair	n/a	n/a	n/a	hair	Room temp
		Home (participant)	Nails	n/a	n/a	n/a	nails	Room temp
	2004-2008	ALSPAC clinic	Blood (CPDA)	x		no	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood heparin tube	X		no	plasma	-80°C
	FOM1 - 2008-2011	ALSPAC clinic	Blood flouride tube	X		yes	plama	-80°C
			Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)	x		yes	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood EDTA tube	X		yes	white cells (for DNA)	-80°C
							plasma	-80°C
	FOM2 - 2011-2013	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)	x		yes	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood EDTA tube	X		yes	white cells (for DNA)	-80°C
							plasma	-80°C
	FOM3 - 2013-2014	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)	x		yes	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood EDTA tube	X		yes	white cells (for DNA)	-80°C
							plasma	-80°C
	FOM4 - 2014-2015	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)	x		yes	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood EDTA tube	X		yes	white cells (for DNA)	-80°C
							plasma	-80°C

Table 6 - Samples available from the ALSPAC Cohort - Original participants' samples

Cohort Group	Timepoint	Where taken (who by if home)	Sample type	Processed		Fasting	Products	Storage
				Within 2 hours	Delayed			
all children	Birth	NHS	Placenta		x	n/a	whole placenta	room temp in formalin
							wax blocks	room temp
							slides	room temp
			umbilical cord		x	n/a	cord slice	-20 °C
			cord blood - heparin		x	n/a	plasma	freeze dried
					x	n/a	plasma	-20°C/-80°C
					x	n/a	blood spot	-20 °C
					x	n/a	red blood cells	-80°C
					x	n/a	white cells (for DNA)	-80°C
			serum		x	n/a	serum	-20 °C
	6 to 8 months	Home (parent)	Hair	n/a	n/a	n/a	hair	Room temp
		Home (parent)	Nail	n/a	n/a	n/a	nails	Room temp
Children in Focus Group	18 months	ALSPAC clinic	Blood EDTA			no	red blood cells	-80°C
	31 months	ALSPAC clinic	Blood EDTA			no	plasma	-80°C
	43 months	ALSPAC clinic	Blood EDTA			no	white cells (for DNA)	-80°C
							whole blood EDTA	-80°C
							plasma	-80°C
	61 months	ALSPAC clinic	Blood EDTA			no	white cells (for DNA)	-80°C
							red blood cells	-80°C
							plasma	-80°C
			Blood - serum tube			no	serum	-80°C
all children	3 years	Home (parent)	Hair	n/a	n/a	n/a	hair	Room temp
		Home (parent)	Nail	n/a	n/a	n/a	nails	Room temp
	4 years	Home (parent)	Hair	n/a	n/a	n/a	hair	Room temp
		Home (parent)	Nail	n/a	n/a	n/a	nails	Room temp
	5 to 7 years	Home (parent)	milk teeth	n/a	n/a	n	teeth	-20°C
	7 Years (Focus @7)	ALSPAC clinic	Blood serum tube		x	no	serum	-80°C
			Blood EDTA tube		x	no	white cells (for DNA)	-80°C
							red blood cells	-80°C
							blood spot	room temp
							plasma	-80°C
Children in Focus Group	7-8 years	Home (parent)	urine		x	no	urine	-20°C
		ALSPAC clinic	Blood - heparin	x		yes	plasma	-80°C
				x		post glucose	plasma	-80°C
All children	Focus @9 (9.5years)	ALSPAC clinic	Blood heparin tube	X		no	plasma	-80°C
			Blood (CPDA)	x		no	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
	10 years	Home (parent)	urine		x	no	urine	-20 °C
		ALSPAC clinic	mouthswab	x		no	saliva	-20 °C
	Focus @11 (11.5years)	ALSPAC clinic	Blood heparin tube	X		no	plasma	-80°C
			Blood (CPDA)		x	no	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			mouthswab	x		no	saliva	-20 °C
	Teen Focus 1 (12.5 years)	ALSPAC clinic	Saliva	X		no	saliva	-20 °C
	Teen Focus 2 (13 years	ALSPAC clinic	Blood heparin tube	X		no	plasma	-80°C
			Blood (CPDA)		x	no	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
	Teen Focus 3 (15 years)	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)		x	yes	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood EDTA tube	x		yes	plasma	-80°C
							white cells (for DNA)	-80°C
			Blood flouride tube	x		yes	plasma	-80°C
			urine	x		no	urine	-20°C/-80°C
			Hair	n/a	n/a	n/a	hair	room temp
	Teen Focus 4 (17 years)	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)		x	yes	Lymphoblastoid cell line	cryopreserved -180°C
							Peripheral blood Lymphocytes	cryopreserved -180°C
							blood spot	Room temp
			Blood EDTA tube	x		yes	plasma	-80°C
							white cells (for DNA)	-80°C
			Blood flouride tube	x		yes	plasma	-80°C
			urine	x		no	urine	-20°C/-80°C
			Hair	n/a	n/a	n/a	hair	room temp

Table 7 - Samples available from the ALSPAC Cohort - Partners' samples

Note partner is the Mother's current partner at the time samples were collected

Cohort Group	Timepoint	Where taken (who by if home)	Sample type	Processed		Fasting	Products	Storage
				Within 2 hours	Delayed			
Partners	Dec-93	Home (participant)	Hair	n/a	n/a	n/a	hair	Room temp
	Dec-93	Home (participant)	Nail	n/a	n/a	n/a	nails	Room temp
	2004-2008	ALSPAC clinic	Blood (CPDA)	x		no	Lymphoblastoid cell line	cryopreserved 180°C
							Peripheral blood Lymphocytes	cryopreserved 180°C
							blood spot	Room temp
			Blood heparin tube	X		no	plasma	-80°C
	2010	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)	x		yes	Lymphoblastoid cell line	cryopreserved 180°C
							Peripheral blood Lymphocytes	cryopreserved 180°C
							blood spot	Room temp
			Blood EDTA tube	X		yes	white cells (for DNA)	-80°C
							plasma	-80°C
	Focus on Fathers - 2011-2013	ALSPAC clinic	Blood heparin tube	X		yes	plasma	-80°C
			Blood (CPDA)	x		yes	Lymphoblastoid cell line	cryopreserved 180°C
							Peripheral blood Lymphocytes	cryopreserved 180°C
							blood spot	Room temp
			Blood EDTA tube	X		yes	white cells (for DNA)	-80°C
							plasma	-80°C
			Urine		X	n/a	urine	-80°C

Table 8 - Samples available from the Southampton Women's Study

Cohort Group	Timepoint	Where taken (who by if home)	Sample type	Processed		Fasting	Products	Storage
				Within 2 hours	Delayed			
Mother	Pre-pregnancy 1998-2003	Home visit, GP or clinic	EDTA Blood		x		plasma	-80°C
			Blood		x		DNA	-80°C
			Urine		x	n/a	urine	-80°C
		Home visit	Mouthwash		x	n/a	DNA	-20°C/-80°C
	Early pregnancy (11 weeks) 1998-2007	Maternity clinic	EDTA Blood		x		plasma	-80°C
	Late pregnancy (34 weeks) 1998-2007	Maternity clinic	EDTA Blood		x		plasma	-80°C
child	Birth 1999-2007	Maternity hospital	Cord blood samples (EDTA)		x		plasma	-80°C
		Maternity hospital	Cord and placental cores		x		extracts	-80°C
	ongoing		Buccal swabs				DNA	
Fathers	1999-2005 (19 weeks)	Maternity hospital	mouthwash		X		DNA	-80°C
			EDTA Blood		x		DNA	-80°C
Maternal grandparents	1999-2005	Postal samples	mouthwash		X		DNA	-80°C

Table 9 - Samples available from the Millennium Cohort Study

cohort group	Time point	Where taken	Sample Type	Processed	Fasting	Products	Storage
Child	from age 7	home (participant)	Milk teeth	not known	n/a	teeth	not known
Child	age 14 (2015)	home (interviewer)	Saliva for DNA extraction (Oragene kit)	saliva in Oragene kits stored at room temperature until DNA extracted	n/a	DNA	-80°C
Parents	2015				n/a	DNA	-80°C

Table 10 - DNA available from all cohorts

Cohort	Participant Group if applicable	Source sample type	Timepoint	Storage
Hertfordshire		Blood	2010 onwards	-80°C
NSHD		Blood	1999	-80°C
		Buccal	1999	-80°C
		Blood	2006-2011	-80°C
NCDS		Blood	2002-2004	-80°C
		Lymphoblastoid cell line	2002-2004	-80°C
Understanding Society	Adults	Blood	2010-2012	-80°C
ALSPAC	Mothers	Blood	antenatal	-80°C
		blood	2004-2015	-80°C
		Lymphoblastoid cell line	2004-2015	-80°C
		saliva(1)	various	-80°C
	Children(2)	cord blood	birth	-80°C
		blood	age 7	-80°C
		blood	age 15-17yrs	-80°C
		blood	age 24 yrs	-80°C
		Lymphoblastoid cell line	majority from blood taken at age 9, smaller numbers from later time points	-80°C
		saliva(1)	various	-80°C
	Partners	blood	2004- 2013	-80°C
		Lymphoblastoid cell line	2004- 2013	-80°C
		saliva(1)	various	-80°C
Southampton Womens Study	Mothers	Blood	Pre-pregnancy 1998-2003	-80°C
		Mouthwash		-80°C
	Fathers	Blood	1999-2005	-80°C
		Mouthwash		-80°C
	child	Buccal swabs	ongoing	-80°C
	maternal grandparents	Mouthwash	1999-2005	-80°C
Millennium cohort	children	saliva	age 14 (2015)	-80°C
	parents	saliva	2015	-80°C

(1) - from participants who did not provide a blood sample only

(2) -timepoints where DNA is available from all blood samples collected from a whole cohort visit, sub samples are available from other time poir

Table 11 - Lymphoblastoid cell lines available from all cohorts

Cohort	Participant Group if applicable	Source sample type	Timepoint	Storage
NSHD		peripheral blood lymphocytes	1999	cryopreserved -180°C
	participants who did not give a cell line sample in 1999	peripheral blood lymphocytes	2006-2011	cryopreserved -180°C
NCDS		peripheral blood lymphocytes	2004-2005	cryopreserved -180°C
ALSPAC	Mothers	peripheral blood lymphocytes	2004-2015	cryopreserved -180°C
	Children	peripheral blood lymphocytes	majority from blood taken at age 9, smaller numbers from later time points	cryopreserved -180°C
	Partners	peripheral blood lymphocytes	2004 - 2013	cryopreserved -180°C