CLSA Follow-Up 1
Renewal Protocol
Submitted to CIHR June 2014

Aim of the Renewal Application

Prospective population-based studies of aging have established their scientific value for evaluating extrinsic and intrinsic exposures in relation to healthy aging, psychosocial and disease outcomes. The prospective cohort design is advantageous in its ability to measure the occurrence of exposure before the onset of the outcome and to evaluate numerous exposures and outcomes in a single study. However, very few large-scale cohorts have been designed to understand the link between multiple exposures and the *transitions* and *trajectories* of healthy aging. Longitudinal cohorts like the Canadian Longitudinal Study on Aging (CLSA) have the potential to be instrumental in spurring mechanistic and translational research activities. The epidemiologic transition over the last century has resulted in a shift in disease burden from infectious diseases towards morbidity and mortality from chronic diseases. This, coupled with low infant mortality rates, low fertility rates, and increasing life expectancies, has resulted in health and social care debates in Canada and across the developed world that requires good population-based longitudinal data that not only address the needs of the current aged population but also provides ongoing insight into the needs and the requirements of the baby boom cohort.

Since 2010, the CLSA team has achieved major successes in the design and implementation of the CLSA, from building infrastructure to capture, manage, and store data and bio-samples, assembling measurement tools and conducting pilot work to assess the feasibility of numerous aspects of the study to reaching our pre-established recruitment target of 50,000 participants by the spring of 2015. We have met our recruitment and baseline data collection goals for the CLSA Tracking (20,000) and have started the Maintaining Contact Questionnaire (MCQ, the between-wave brief questionnaire) with these participants. At the time of writing, 4,000 participants have completed the MCQ with a retention rate of approximately 95% (4% have refused to continue and 1% have died). We are also meeting our goals for recruiting the 30,000 CLSA Comprehensive participants. As of June 10th, 2014, we have completed recruitment, consent, and baseline face-to-face interviews with 22,000 people, about 20,000 of whom have also completed their Data Collection Site (DCS) visit (i.e., are enrolled). We are on target to recruit and assess the remaining 10,000 participants by the spring of 2015 given our 60% conversion rate from "pre-recruit" (we currently have a bank of 20,000 pre-recruits) to "recruit". We have obtained health card numbers from over 90% of participants along with their written consent to conduct linkage studies using provincial healthcare administrative databases. Of the participants recruited into the CLSA Comprehensive, we have obtained blood and urine samples from about 94%.

The CLSA is a unique resource ideally positioned for novel contributions to the understanding of the processes of aging including factors associated with longevity and the etiology of diseases and disability. With continued follow-up, repeat collection of the baseline data and biospecimens, linkage to administrative health databases, and the addition of collection tools to incorporate new and emerging areas of science, the CLSA is positioned to be the largest and most complete cohort of aging in Canada. Its value as an important resource for cross-province and population comparisons to inform practice and policy will increase over time, providing research opportunities unprecedented in Canada, and internationally.

The mechanics and logistics of conducting the CLSA are considerable and in this regard, the CLSA leadership was also successful in garnering peer-reviewed funding from the Canada Foundation for Innovation in late 2009 ($10.5 million matched by provinces and universities for a total of $26.5 million) to build facilities across Canada to carry out population health research, the CLSA being the first study to use the infrastructure. The establishment of this infrastructure has allowed the CLSA research team to collect high quality data in a standardized and efficient fashion. The development of the infrastructure and the acquisition of the equipment occurred between 2010 and 2011. The current application to CIHR is for operational funds to conduct two CLSA follow-up waves (Follow-up 1: 2015-2018; and Follow-up 2: 2018-2021).

The specific aims of this application based on the requirements of the funding call are:

Application Aim 1: To present the status of the CLSA recruitment and baseline data collection (2010-2015). We provide an overview of the CLSA design, selection, and recruitment status for all 50,000 participants, baseline ethics approvals, development of the study content, data collection tools and measures, the quality management system, and the management of the data and sample platform. We also report on the creation of the national infrastructure to carry out large population-based studies in Canada, of which the CLSA is the primary end user. We provide data on progress to date with respect to recruitment and data collection, and present some preliminary descriptive statistics for the recruited sample.

Application Aim 2: To present the analysis of baseline biological samples for biomarkers to further enhance the CLSA platform (n=30,000). We provide an overview and rationale for the selection of core clinical chemistry biomarkers, genetics and epigenetic biomarkers, methods to carry out analyses of core clinical chemistry biomarkers, genetics and epigenetic markers, and their integration into the core CLSA data platform.

Application Aim 3: To describe the first 3-year follow-up (2015-2018). We provide an overview of the CLSA follow-up, the process for review of baseline measures, rationale for proposed additions and deletions to the baseline measures, ongoing ethics approval, implementation of proxies in the CLSA, further development of the infrastructure to carry out follow-up, and strategies for participant retention.

Application Aim 4: To describe the second 3-year follow-up (2018-2021). We provide an overview of the second CLSA follow-up, processes for the review of the measures used in baseline and the first follow-up, timing for the development of the second set of follow-up measures, and proposed repeat of the analysis of the core biomarkers based on the samples from first follow-up.

Application Aim 5: To describe the core business plan of the CLSA. We provide information concerning the overall CLSA governance structure, management and operational structure, succession planning, partnership framework, and promotional and communication strategies. We also describe how the business plan has been developed to support the use and enhancement of the CLSA platform

INTRODUCTION

Historical Context and Background of the Canadian Longitudinal Study on Aging

The CLSA has advanced beyond the original vision of the Institute of Aging of the Canadian Institutes of Health Research (CIHR) in 2001, to the reality of a federally funded national research platform in 2009. At the outset, CIHR provided $23.5million in implementation and operational funds to assemble the cohort and collect baseline data. A budget shortfall of $3.75 million was raised by the CLSA team (as per the requirement of the funding agreement) from several sources for a budget total of $27.25 million. The CLSA protocol was enhanced through a succession of international peer reviews, a multi-sectoral CIHR-based Steering Committee, a CIHR Ethical, Legal, and Social Issues (ELSI) Advisory committee, as well as CIHR-funded pilot studies conducted by the CLSA research team;[1-7] each being an essential component to assuring the excellence of the science and making the CLSA relevant to multiple sectors. Following international peer review, funding was approved to recruit and follow 50,000 people between the ages of 45 and 85 years every 3 years for the next 20 years. The CLSA research team engaged researchers and policymakers from across Canada to develop a research platform to explore the aging process from cell to society. A hallmark of the CLSA leadership has been inclusivity resulting in the creation of collaborations and partnerships that have been sustained over more than a decade. These collaborations include researchers and policymakers from a wide variety of scientific and policy disciplines and enrich the scientific and methodological aspect of the platform. The large national sample with repeated collection of information on exposures, diseases, psychosocial consequences, and biological specimens over 20 years was viewed by the peer review committee as innovative. The interim telephone contact between each full wave of follow-up was considered essential to minimize loss to follow-up. The collection of additional data as needs are identified over time was also endorsed. The international peer review committee commented that CLSA will contribute to our

understanding of transitions and trajectories within an aging population, and will differ from other longitudinal studies of aging worldwide through the breadth of its scope, the frequency of follow-up, the young minimum age of recruitment into the study, the ethno-cultural diversity of Canada's population, repeated measures of biological sample and the potential to link CLSA data to health administrative data at the provincial level.

Rationale for the Canadian Longitudinal Study on Aging (CLSA)

The CLSA was designed to capture the concept of life pathways and cumulative influences of life events on a range of outcomes.[10,11] The outcomes include healthy aging and transitions into, and out of, critical and sensitive periods related to the aging process (e.g., changes in family structure and changes in work and retirement status, or the diagnosis of a chronic disease).[12-14] Research on the development of life pathways suggests that individual and contextual factors broaden, deepen and become increasingly differentiated over time.[15,16] Age-dependent patterns of changing intrinsic (biological) and extrinsic (environmental) factors are most powerful at times of transitions between life phases.[13,16,17] As individuals move along life pathways, they may modify or adapt their roles, personal ties and/or social relationships to meet the demands of their changing physical, psychological, social and biological environments, and employ novel strategies and/or technologies to respond to these changes. Investigators in many countries now recognize the importance of collecting longitudinal data for understanding aging and informing decision making and this recognition is reflected in studies such as the Health and Retirement Study (HRS),[18] Midlife in the United States (MIDUS),[19] the English Longitudinal Study of Ageing (ELSA),[20] and the Survey of Health, Ageing and Retirement in Europe (SHARE).[21] Nevertheless, these studies are at best moderately powered to examine interactions between intrinsic and extrinsic factors that are associated with health outcomes, have limited multidisciplinarity, and are focused mostly on the aged population.

Recent advances in biosciences (e.g., genetics, epigenetics, and metabolomics), informatics, and population health research have changed the face of health research, presenting new and exciting possibilities for scientific discovery. To maximize the potential of these emerging sciences and to convert it into ground-breaking research and knowledge, novel research platforms to bridge the biosciences with population and public health sciences are needed. This need has led to a call for multidisciplinary, longitudinal studies of aging. Several factors make these more complex studies different from their predecessors. The major difference is the ability to study biological (especially genetics and epigenetics), physical, lifestyle, and psychosocial factors in the same individuals, in combination with large sample sizes, resulting in increased statistical power to address complex interrelationships and to study rare outcomes and events. With the emergence of multi-level analytical techniques, we also have the tools to study the influence of contextual level factors and individual level factors. Thus, in the modern era of longitudinal research, we move beyond merely describing change over time to actually studying the dynamic determinants of change within and between individuals over time. In addition, very few studies of aging have integrated repeated biological sampling as part of their protocol on large number of people to understand the role of changing biomarkers within the same individual over time in order to elucidate the process of aging, and to study how changing biological processes interact with changing physical, economic, and psychosocial environments to produce deleterious or positive health outcomes.

Canadian Context

One of the many pressing policy implications of an aging population in Canada is health and social care affordability.[22] Conservative forecasts suggest that the proportion of seniors in the Canadian population will reach an unprecedented level in the years to come. Nationally, the proportion of the population aged 65 years or more is projected to increase over the next 20 years to approximately 22% of the Canadian population, or almost 10 million Canadians (Figure 1). Total health and social care expenditures in Canada now exceed roughly $300 billion with healthcare alone at approximately $211

billon, the largest expenditure item in provincial budgets. As the baby boom generation approaches and enters into second careers (an emerging phenomenon) or moves toward retirement, the challenges that Canada faces in supporting a diverse and multi-ethnic aging population will intensify. The baby boomers' shifting lifestyle choices make them one of the most compelling demographics to study. A challenge for health and social policymakers is the lack of strong evidence to inform public health, and social policy decision making that is directed toward preventing morbidity and improving the health of Canada's aging population.

Overarching Goals of the CLSA

The overall goal of the CLSA is to provide the most accurate picture of the dynamic process of adult development and healthy aging. Through extensive data collection, we will be in position to investigate the interrelationships among intrinsic and extrinsic factors influencing health from mid-life to older age. In designing a study to examine health transitions and trajectories with the goal of identifying modifiable factors with the potential to inform the development of interventions to improve the health of populations as they age, diverse expertise is needed. The research team includes experts from across Canada in biology, genetics, clinical research, social sciences, economics, psychology, nutrition, kinesiology, health services, biostatistics, epidemiology, and population health (Table of Expertise).

The CLSA is not only a research study but is also a platform designed to support the provision of data and bio-samples, building capacity for high quality research on aging in Canada and elsewhere, that enable researchers to respond to a wide variety of research questions. For example, researchers can apply to access data and/or bio-samples to conduct research to examine the association between sets of variables, identified in physical, psychological, lifestyle and behaviour, and social domains, and the development of disease, disability, and its psychosocial consequences. There are opportunities to examine the relationships among precursors (e.g., epigenetic markers, nutritional status, physical environment), changes in traits (e.g., cognition, inflammatory biomarkers), and the consequences of the changing phenotype on the development or prevention of disease (e.g., dementia or depression), disability (e.g., frailty or physical limitations), and psychosocial outcomes (e.g., emotional distress or social isolation). Here we provide some examples of research questions that could be addressed with CLSA data:

- What are the determinants of changes in biological, physical, psychological, and social function over time and across ages?
- What is the magnitude of the role of genetic and epigenetic factors in the aging process?
- What factors distinguish individuals who experience healthy/successful aging from those who do not?
- Is decline in cognitive functions (memory, executive function, and psychomotor speed) in mid and later life associated with changes in social participation?
- How do changes in mobility impact upon indicators of physical health including falls and other injuries, fear of falls, frailty, disability, and other physical outcomes, adjusting for other factors?
- Are there identifiable patterns of cognitive functioning in midlife that predict the onset of dementia in later life?
- How do work and family transitions intersect with negative/positive changes in social networks and social support and how do these transitions influence overall health?

<u>Aim 1:</u> To present the status of the CLSA recruitment and baseline data collection (2010-2015).

Overview of the CLSA design

The CLSA is a Canada-wide study of 50,000 people between the ages of 45 and 85 years at recruitment. Baseline inclusion criteria are; community dwelling, cognitively unimpaired, and able to speak and understand English or French. Baseline exclusion criteria are; being a resident of a federal First Nations reserve or other First Nations settlements in the provinces; being a full-time member of the Canadian Armed Forces; and not a permanent resident or Canadian citizen. Individuals living in

households and transitional housing arrangements are included at the baseline but individuals living in long-term care institutions (i.e., those providing 24-hour nursing care) are excluded at baseline. CLSA participants who become institutionalized during the course of the follow-up will continue to be followed through either telephone or personal interviews, or interviews with proxies, as feasible. CLSA participants who over the course of the study move (within or between provinces, from a province to a territory, or out of Canada) will also be followed at their new location if feasible. At baseline, all 50,000 participants were asked to provide a core set of information on demographic and lifestyle/behaviour measures, social measures, physical/clinical measures, psychological measures, economic measures, health status measures, and health services use. This core information is collected through 60-minute telephone interviews from 20,000 (CLSA Tracking) (see Appendix 1 for this questionnaire) participants and via 70-minute in-home interviews from 30,000 (CLSA Comprehensive) participants. All 50,000 participants are also asked to provide their health insurance number and to consent to linkage to health claims data in provincial healthcare administrative databases. Participants not willing to provide their health insurance numbers are still eligible to participate.

In addition to the in-home interview, participants who are recruited to the CLSA Comprehensive (30,000) are also asked to visit a CLSA data collection site (DCS) (within 25km to 50km of their home) within 2-3 weeks of the in-home interview to undergo detailed physical assessments and to provide a blood and urine sample, collected as part of the DCS visit. The blood and urine samples are not mandatory but to be enrolled in the Comprehensive participants must complete both the in-home interview and the DCS assessment.

Following the baseline assessments for all 50,000 participants, the data for the core information set is to be collected at 3-year intervals via an in-home interview for the CLSA Comprehensive participants and a telephone interview for the CLSA Tracking participants. The DCS visits for the Comprehensive CLSA will also occur at three-year intervals. Keeping in mind the magnitude of this study and the challenges in retaining our participants, we have implemented a mid-wave, maintaining contact questionnaire (MCQ) for all participants via telephone to collect limited additional data and to document any changes in contact information.

All telephone-administered interviews for the CLSA baseline were conducted from Computer Assisted Telephone Interview (CATI) sites at the University of Victoria, University of Manitoba, Dalhousie University, and Université de Sherbrooke (French interviews). The in-home interviews for the CLSA comprehensive are conducted by CLSA trained interviewers using Computer Assisted Personal Interviews (CAPI). The baseline, in-home, CLSA interview consisted of two parts, informed consent, and administration of the questionnaire, Appendix 1. Interviewers are equipped with a photo identification card bearing the CLSA logo and are required to show this card to participants before entering their homes. Interviewers telephone participants prior to scheduled interviews to confirm the day and time, as well as to ask participants to have their medications ready for when the interviewer arrives.

Here we briefly describe the 2.5 - 3 hour Data Collection Site visit that forms part of the assessment for CLSA comprehensive participants. DCSs were established in 11 cities across Canada: Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montréal, Sherbrooke, Halifax, and St. John’s. Nine of the DCSs are each responsible for 3,000 participants, and DCSs in Vancouver and Surrey share the recruitment of 3,000 participants from the Greater Vancouver corridor, with each being responsible for 1,500. At the DCS, participants undergo a physical assessment and neuropsychological battery. All assessments are administered according to standardized protocols by carefully trained CLSA staff and the order of participant flow through each of the 11 DCSs is identical. Figures 2 & 3 depict the recruitment and data collection flow for the CLSA Comprehensive. Participants are reminded of the DCS visit to confirm their attendance one day prior to the scheduled visit.

Room 1: Upon arrival participants proceed to the reception desk, where a research assistant (RA) verifies their name, and logs them into the system along with the following information: 1) Name; 2) Date of birth; 3) Address; 4) Contact person and contact information; and 5) Consent to contact proxy for participants aged 70 years or over. Participants' check-in times are electronically recorded as they are logged into the system.

Room 2: An RA administers a brief questionnaire to assess potential contraindications to the assessments that are to be performed during the DCS visit (Appendix 1). If a contraindication is found, the information is immediately entered into the system, and when a participant with a contraindication arrives at the data collection room where the contraindicated procedure would be administered, the person staffing the room is alerted by an automated message to forgo the procedure and software automatically blocks the procedure to avoid any operator error.

Room 3 – Participants' waist-hip ratio, weight, and standing height are measured. Other measures in this room include heart rate, blood pressure, ECG, carotid ultrasound, and spirometry.

Room 4 –Participants are scanned using DXA for whole body, hip, and spine for bone density, lean muscle mass and aortic calcification.

Room 5 – In this interview room participants complete the first components of the neuropsychological battery (i.e., event-based Prospective Memory Test, Stroop, Controlled Oral Word Association Test, and Choice Reaction Time), a hearing test, and a questionnaire on social networks, availability of social support, and social participation. (Appendix 1)

Room 6 – Located in the DCS corridor, participants do the 4-metre walk test and the timed get-up-and-go test.

Room 7 – Physical measures continue in this room with standing balance, chair rise, and grip strength. A vision test (preceding grip strength) is also conducted. The vision test includes visual acuity using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart, assessment of intraocular pressure using a tonometer, and a fundus photograph using a retinal camera.

Room 8 – Participants undergo the remainder of the neuropsychological battery (time-based Prospective Memory Test) and answer the disease symptom questionnaire. (Appendix 1)

Room 9– Once all assessments are complete, participants who have agreed to provide blood and urine samples proceed to the biospecimens collection room, where 50 ml of non-fasting blood and a 10ml spot urine are obtained. All samples are processed within 2 hours of sample collection and stored at -80 degree Celsius prior to shipping by cryoshippers to the Biorepository and Bioanalysis Center in Hamilton for long-term storage in liquid nitrogen. Measurement of hematological parameters is time sensitive and the AcT DIFF Hematology Analyzer from Beckman Coulter (Fullerton, CA) is used to provide a complete blood cell count (e.g., red cell, platelet, neutrophil, and monocyte). All biosample test data are automatically transferred to the Laboratory Information Management System (LIMS) and then to the CLSA database.

Room 1 - Participants return to reception for checkout and receive $30 to defray the cost of attending the DCS visit. Participants also receive a computer printout of selected DCS measurement results. The printout includes body mass index, waist-hip ratio, blood pressure, hearing, visual acuity, lung capacity, and bone mineral density.

Pilot Testing of the CLSA Baseline Protocol

In preparing to launch the CLSA, the research team conducted several pilot studies of the instruments and processes used at the baseline. We pre-tested the CATI and CAPI questionnaires. At the Hamilton and Montreal Data Collection Sites we pre-tested the flow of participants, timing and feasibility of each assessment, comprehension of the training material, standard operating procedures, functionality of the software and hardware, and collection, processing, storage, and shipping of blood and urine samples collected at these sites to a central location. The pilot testing resulted in some modifications to our processes and instructional material before the launch of the full baseline CLSA.

Finally, in addition each CATI and DCS was given a run in period to work out local implementation issues before collecting data from actual CLSA participants.

Continued participation in the event of cognitive, physical or sensory impairment

As our participants age, it is inevitable that some will experience cognitive decline to the extent that it affects their ability to complete the CLSA data collection. In addition, mobility impairment and sensory impairment (vision and or hearing) may compromise a participant's ability to provide information as part of the CLSA. We know from the Canadian Study of Health and Aging, for example, that about 17% of the population over the age of 65 has some form of mild cognitive impairment.[24] Balancing the need to prepare for proxy respondents with the feasibility of querying all 50,000 participants to identify proxies, we have chosen the age of 70 as the age at which to initiate inquiry regarding a proxy protocol. There are two main issues to consider; the first is the participant's ability to make decisions concerning continuing participation in the study; the second is the ability to take part in the study itself (i.e., answering questions, comprehending instructions). Thus, all participants aged 70 or over at baseline are asked to complete an additional consent document in which they can indicate their wishes in the event of cognitive decline, or should they become unable to participate on their own for other reasons. The participant is asked to provide the contact information for someone that they would like to take on the role of proxy decision maker and proxy information provider (the same person may fulfill both of these roles), should they wish to continue participating in the CLSA. The proxy decision maker would be responsible for deciding whether the participant remains enrolled in the study while the proxy information provider may be called upon to answer questions on behalf of the participant. The contact information for the proxy decision maker/information provider is entered into a database and subsequently re-confirmed with the participant at each wave of the study. Participants are asked to inform their proxy that they have been named as such, however the proxy is not contacted by the CLSA until the need for a proxy is identified. At each follow-up, we will approach all participants who have reached the age of 70 since the previous contact. It is also recognized that the requirements for a proxy for research purposes may differ by province. While having no intended legal status, the signed document serves as a guide for the participant and a point of departure for discussion with the identified proxy. To date, there are approximately 11,200 participants over the age of 70 and of these 75% have provided signed consent indicating their desire to continue participation with a proxy should the need arise in the future. We did not use any proxies at baseline since cognitive impairment was an exclusion criterion but protocols for the activation of proxies will be implemented at the first follow-up. All proxy protocols have been developed with extensive input from the ELSI Advisory Committee.

In order to retain participants who become unable to participate fully in the CLSA but have expressed a desire to continue, we will come to depend upon proxy respondents. We will develop questionnaires adapted for use with proxies, ensuring that the questions are asked to the proxy about the participant. An interviewer-training module will be added to those already available in the CLSA to guide interviewers on how to ask the questions of proxies. The literature is clear on the fact that the reliability of proxy information varies according to the relationship of the proxy to the index subject (Nelson, et al, 1994[25] remains one of the most cited papers on proxy response) and the specific topic of query. Overall, reliability has been shown to be good for demographic information and cigarette smoking but lower for mediation use, alcohol consumption, and physical activities. In addition it has been shown, not surprisingly, that reliability improves when questions only require a binary response,[26] although this approach naturally reduces the amount of information collected and consequently the statistical power of analyses. An adhoc working group has been formed (C Wolfson, D Hogan, S Kirkland, and H Tuokko) to create proxy versions of the CLSA questionnaires for the various components of the CLSA taking into account evidence from the literature and balancing the need for reliability with the need for, and the feasibility of, obtaining the information. This group will work closely with the ELSI committee.

At the Data Collection sites, the ability of the participant to follow instructions is key to a successful visit. We anticipate that participants who require proxies will also have difficulty at the DCS. We will develop standard operating procedures to consider this. The Clinical Working Group will guide the review of the DCS assessments to determine which could be completed by individuals with cognitive impairment. This may overlap with the planned in-home assessments being designed for those unable to attend the DCS (primarily due to mobility problems). The contraindications questionnaire will also be adapted to include the ability to indicate that some assessments should not be undertaken due to participant impairment (cognitive, physical, or sensory)

Coordinated ethics process

Traditionally, in Canada, large multi-centre studies have had to obtain ethics approval from each collaborating institution separately, leading to heterogeneous information packages and consent forms and in some cases variable methods of recruitment and data collection. This process can slow down the study launch and makes the operational aspects of the study very difficult, cumbersome, and expensive. The CLSA team in collaboration with all associated Research Ethics Boards (REB) across Canada created a coordinated ethics process for the CLSA under the leadership of the McMaster REB. To review the process briefly, the baseline proposal was, and all subsequent amendments are, prepared centrally by the CLSA and submitted to the lead institution REB (McMaster), the documents and the McMaster review is then posted on a secure portal (Canadian Network Portal for Health Intelligence CNPHI), and the collaborating CLSA site REBs are notified and then conduct their own review and post their response on the portal. When all responses are posted, the comments are collated by McMaster REB and forwarded to the CLSA team to address. The CLSA team response is sent via the McMaster REB for final approval and sign off by each of the local REBs. The amendments and renewals are submitted once a year using the same procedure as the full baseline proposal. The annual renewal occurs on May 19/20th of each year, and is signed between the local REB and the local site PI. The advantage of this process is many-fold. It is critical to maintaining the standardized and centralized data collection protocol. It also ensures that the CLSA runs according to the highest ethical standards.

Ethical, Legal, and Social Issues (ELSI)

There is a wide range of ethical, legal, and social issues that arise in a study the magnitude of the CLSA. The CIHR Advisory Committee on Ethical, Legal, and Social Issues (ELSI) for the CLSA is an independent, arm's length group established by CIHR. The committee is comprised of ethicists and bio-ethicists, lawyers, privacy experts and commissioners, and at least one lay member from the community. With support from CIHR's Ethics office, the mandate of the ELSI Advisory Committee has been to: 1) provide independent, critical advice to the CLSA Scientific Management Team on actions and best practices to address ethical, legal and social issues during the first five-year implementation phase of the CLSA; 2) to contribute to the advancement of ELSI knowledge related to the CLSA and similar CIHR-funded, population-based, longitudinal studies, databases and biorepositories; and 3) to disseminate ELSI knowledge to the external community of relevant stakeholders. The Committee proactively addresses potential issues raised by the CLSA via regularly scheduled teleconferences and at one face-to-face meeting annually. A Co-PI (Susan Kirkland) is an ex-officio member of the group and provides liaison to the CLSA. Issues of relevance to the CLSA are put forth in an annual work plan, and are prioritized according to need. To date the ELSI Committee has been instrumental in providing advice on issues directly related to the conduct of the CLSA such as the use of proxies, advance directives for research, and ethical and legal considerations in the management of participants with cognitive decline in a longitudinal study. They have also provided advice on the routine return of individual results to participants, and consideration of where law and ethics stand with respect to individual autonomy in the context of a research platform and participants' rights to access personal information held by the CLSA. The committee has explored the complex nature of withdrawal in the CLSA, with considerations given

to the future use of samples, data, and data linkage, including issues related to data and sample destruction and the default to be instituted when participants have not specified their preferences with respect to withdrawal. The advice of the ELSI Committee has been integral to the development of study documents including participant information packages and consents, and policies such as the privacy policy. As we move forward with the follow-ups we anticipate that the ELSI committee will continue to provide guidance to the CLSA team.

Selection and Recruitment of the CLSA Sample

Three approaches were used for recruitment into the CLSA cohort: a) a subset of participants in the Canadian Community Health Survey – Healthy Aging (CCHS); b) the registries of provincial health care systems; and c) Random Digit Dialling (RDD) of landline telephones. For each sampling approach, there are several steps for enrollment into the CLSA cohort. The first step, "pre-recruitment", takes place when selected people provided their name, contact information, and consent for CLSA researchers to contact them to recruit them into the study. Depending on the sampling frame, a person was designated to be a 'pre-recruit' when s/he indicated that their contact information could be sent to the CLSA. In the second step, those pre-recruits who consented to complete all the required baseline interviews and assessments were considered "recruited". Recruits are only considered to have been "enrolled" in the CLSA once signed consent has been received. Written consent was provided during the in-home interviews for the CLSA comprehensive participants; the CLSA tracking participants provided verbal consent during their 60-minute baseline interview and had to mail their written consent form. We provide additional information on sample recruitment in the section on "Challenges and Risk Mitigation Strategies". (Appendix 2)

Attrition Due to Deaths, Refusals to Continue, Losses to Follow-up

Attrition due to losses to follow-up, deaths, and refusals to continue in the study will be an ongoing important challenge for the CLSA. Information provided by Statistics Canada on the attrition rates for the National Population Health Survey (NPHS) for the period 1994-95 to 2000-2001 provided the basis for an estimate of the proportion of CLSA study participants projected to be lost over 20 years. Using this information along with age-sex specific mortality rates, we estimate that roughly half of the sample will remain at the end of 20 years. While we cannot influence mortality, we will use several strategies to minimize losses to follow-up and to enhance engagement in the CLSA to minimize refusals. For instance, a protocol for tracing "lost" participants at follow-up will include linkages with mortality databases and contact with alternate contacts identified at baseline.

Sample Size Calculations

Estimation of sample size requires information on the specific effect sizes that are desired to be detected and/or the desired precision for parameter estimation. Given the diversity of goals and statistical models that are bound to accompany them, it is virtually impossible to provide global meaningful effect sizes for sample size calculations. In addition, the use of the CLSA as a platform for future (and yet unknown) research questions asked and analyzed by others precludes such calculations. Consequently, one strategy we used was to carry out simulations based on simplified hypothesized evolutions of the cohort experience over time. The prevalence of selected exposures and the incidence of selected outcomes, such as particular chronic diseases, over the period of follow-up, were used as a guide to assess the *adequacy* of the proposed sample size in selected situations. First, the expected number of cases of an outcome was simulated for each 3-year wave of the CLSA based on sex- and age-specific incidence rates and taking into account the aging of the cohort over time.[27] The simulations also accounted for mortality (based on age and sex specific annual mortality rates from Statistics Canada) and attrition due to loss to follow-up (estimated at 0.5% per year based on the attrition rates for the NPHS (1994-95 to 2000-01).[28] For a condition with a high annual incidence rate, such as hypertension (sex- and age-specific incidence rates ranging from 31 to 43 cases/1,000 persons per year),[29] we would expect almost 1,520 cases from a cohort of 20,000 people and 1,860 to 2,580 cases from a cohort of

30,000 people (at the end of baseline data collection). We also investigated power profiles for the CLSA for two types of outcomes: hazard ratios (for incidence studies) and odds ratios (for nested case-control studies) based on an iterative simulation-based approach. Simulations were undertaken to determine the minimum detectable hazard ratio (MDHR) for the comprehensive cohort (n=30,000) and for the minimal detectable odds ratio (MDOR) for the combined cohort (n=50,000). (Appendix 3 & 4)

Development of the Content for the Baseline CLSA

The scientific content for the baseline was developed in collaboration with six working groups to identify biological, clinical, healthcare services, lifestyle, and behaviour, psychological, social measures for inclusion in the CLSA. A methodology working group was also formed to inform the methodological and sampling aspects of the study. These working groups were comprised of experts from genetics, epigenetics, clinical chemistry, biochemistry, dentistry, rehabilitation sciences, demography, sociology, psychology, economics, behavioural sciences, nutrition, epidemiology, nursing, health services, biostatistics and information sciences, as well as several subspecialties of medicine. Under the direction of a theme leader, each working group developed background material, a rationale for proposed content domains, and a list of tools and measurement instruments for possible inclusion in the CLSA. The working groups were encouraged to use the following guidelines to inform study content:

- multidisciplinary issues considered critical to the understanding of the aging process
- questions that would require a longitudinal approach to study
- areas that were felt to serve a niche: i.e., were understudied or were not the subject of other ongoing or planned studies of aging in Canada or elsewhere, or for which Canada or Canadian researchers were well situated to answer.

As a second layer of refinement, feasibility and practical issues were assessed:

- Is there a tool available to measure this issue/question?
- How long it will take to administer.
- What are the psychometric properties of the tool?
- Is the measure responsive (sensitive enough to detect change)?
- Is it relevant across the CLSA age groups?
- Is the tool available in both English and French
- Are there unique resources or equipment required?

A second phase of study content development and refinement was undertaken by the Co-PIs, involving strategies to set priorities for content inclusion, and to reduce the number of measures. Following iterations between the PIs and the Working Groups, the following measures were implemented in the baseline CLSA. In some instances, material originally slated for inclusion in the baseline assessment was judged appropriate to be moved to the Maintaining Contact Questionnaire administered 18 months after the baseline.

Baseline Biological Samples

Blood and urine specimens are being collected from comprehensive participants (30,000). At the time of writing, we have collected blood and urine samples on 20,000/30,000 participants and the remaining samples will be collected as we enrol the remaining 10,000 participants over the next 10 months. Non-fasting blood is being collected in six tube types (no additive, citrate, and heparin, EDTA, ACD, and CPT) to produce nine specimen types (serum, four types of plasma, whole blood, buffy coat, preserved cells, and purified peripheral blood mononuclear cells). The decision to collect non-fasting blood samples does not diminish the value of the CLSA biological sample resource, as these samples will be used for many different assays. For example, non-fasting measures of specific lipids, which are traditionally measured following 8-12 hour fast, have been shown to be highly predictive of cardiovascular disease risk.[30] The measurement of HbA1C does not require fasting.[31] Whole blood dried in microwell plates containing filter paper is being collected for DNA extraction. In addition, we collect

10 ml of spot urine sample from each participant. The urine is then stored in cryo freezers without any additive. All the collection and processing takes place in the purpose built Data Collection Sites (DCS) and biospecimens are processed within two hours of collection and are stored on site at -80 degree Celsius before shipping weekly in cryoshippers at -160 degree Celsius to Hamilton to be stored in liquid nitrogen freezers. A total of 42 0.5-mL aliquots per person are being stored. (Table 1)

Baseline Physical Function and Disease Measures

Physical Function Measures

The depth of information collected about physical function, and the methods for collecting this information differ between the Tracking and Comprehensive CLSA (i.e., telephone vs. face-to-face and physical assessment). Nevertheless, the majority of the measurement domains, and many of the questionnaire-based measures themselves, overlap for the full complement of 50,000 participants permitting common analyses on the full cohort. Table 2 presents the CLSA measures of physical functioning including the modes of measurement between the Tracking and Comprehensive CLSA. Unless otherwise specified, the questionnaire content is collected during the baseline interview.

Disease Ascertainment Algorithms

Diagnosis of chronic diseases requires information from multiple sources, including self-report, physical examination, biospecimens, or imaging. Even with this information, diagnostic uncertainty for many conditions often prevails in clinical practice due to the variable nature of disease presentation. This situation is exacerbated in large-scale population studies because non-physicians often do disease ascertainment. To improve assessment of disease in large, population-based studies, researchers have developed disease-specific algorithms.[32,33] In the CLSA Comprehensive, we do not include physician assessments and for this reason, we have developed and validated algorithms for 11 chronic conditions that use several pieces of information to ascertain disease. This information includes responses from the disease symptom questions (asked at the DCS) and details on medication use. Some algorithms also require physical or biological assessments (e.g., HbA1c test for the diabetes algorithm, spirometry for the respiratory diseases). The algorithms are shown in Appendix 5a & 5b: disease algorithms and validation paper).

Baseline Psychological Measures

We used several instruments to measure four domains of psychological aspects of aging at baseline. These include cognition (memory, executive function, and psychomotor speed), mood, psychopathology, and personality traits (openness, conscientiousness, extraversion, agreeableness, and neuroticism) (Table 3).

Baseline Social Measures

We included several social and economic domains to measure social aspects of aging at baseline for both the Tracking and Comprehensive participants. These domains were social networks (including online social networking) and social support, social participation, informal and formal care, transitions in work and retirement, social inequalities and wealth, and matters of place (including migration, transportation and the built environment), Table 4.

Baseline Lifestyle, Behaviour, and Socio-Demographic Measures

Physical activity was included in the MCQ for the Tracking and Comprehensive participants and was quantified using the Physical Activity Scale for the Elderly (PASE) questionnaire.[34-38] Individuals were asked to report leisure time activity, household activity and work-related activity in the past week. The PASE was chosen because it reflects traditional domains of physical activity (e.g., light, moderate, and strenuous sports or recreational activities), as well as types of activities more commonly performed by elderly people (e.g., walking and sitting activities). Nutritional risk was also assessed in the CLSA Tracking Maintaining Contact interview using the abbreviated version of the SCREEN II.[39] Nutritional intake was measured in the CLSA Comprehensive in-home interview using the Short food frequency Diet Questionnaire (SDQ).

The CLSA baseline also included 23 items measuring past and current tobacco consumption and environmental smoke exposure and the amount and type of alcohol consumed (past 12 months/ever). Detailed demographic information was also collected at baseline including sex, age, education, income, ethnicity, language, and religion.

Secondary (Passive) Data Collection

In jurisdictions where permitted, the primary data of all CLSA participants who provided a health insurance numbers and signed consent for linkage will be linked to existing health care administrative databases (e.g., drug plans [for those ≥ 65 years or those who are on social assistance], physician visits, medical service plans, hospitalization, homecare, and mortality). The purpose of these linkages is to collect complementary information on medication use and health services resource utilization, and ascertain diagnoses, deaths, and causes of death.

Creation of the CLSA Infrastructure

To ensure the long-term success of the CLSA, a dedicated infrastructure was required. No such infrastructure was available in Canada. The needed infrastructure had to be broad enough to ensure efficient and sustained study operation and management and include the capacity to collect and link primary data, securely store biological and clinical samples, and securely store large amounts of alphanumeric and radiographic image data. The Government of Canada, through the Canada Foundation for Innovation, funded the needed infrastructure in June 2009. The infrastructure, which is operational, includes the National Coordinating Centre (NCC), the Biorepository and Bioanalysis Centre (BBC), four CATI sites, the Genetics and Epigenetics Centre (GEC), the Statistical Analysis Centre (SAC), and 11 DCS (Figure 4). Each unit is equipped with the specialized equipment needed to capture, store and analyze data. The NCC, BBC, all four CATI sites, GEC, SAC, and 11 DCS are currently functional. The roles of these infrastructure components are described below.

- National Coordinating Centre (NCC): The NCC, at McMaster University, is responsible for the overall management of the CLSA. The NCC manages the recruitment of CLSA participants, leads data collection operations, develops standard operating procedures and protocols, provides staff training, and plays a central role in data management. The NCC also provides overall management of the DCS, CATI sites, SAC, BBC and GEC.
- Computer-Assisted Telephone Interviewing Centre (CATI): The Dalhousie University CATI centre shares responsibility for overseeing the operation of all CATI sites in collaboration with the NCC. CATI sites are responsible for conducting the main-wave interviews for the CLSA Tracking and the MCQ interviews for the CLSA Tracking and Comprehensive.
- Statistical Analysis Centre (SAC): The SAC, at McGill University, is the analytic nexus of the CLSA and works closely with the NCC to provide secure data storage, user management and statistical collaboration to CLSA researchers and other users of the CLSA research data platform. The SAC accesses de-identified data from the NCC server, provides secure data storage, and produces a cleaned, linkable, locked dataset for each cycle of data collection. The SAC also provides quality control checks of collected data on a regular basis.
- Data Collection Sites (DCS): Each DCS, led by a site principal investigator, is responsible for conducting the physical assessments, collecting biospecimens, and administering questionnaire-based assessments for 3,000* participants during each three-year wave of the study. DCS interviewers also make initial recruitment telephone calls to potential Comprehensive participants. (*In British Columbia, the Vancouver and Surrey DCS are responsible for 1,500 participants during each wave.)
- Biorepository and Bioanalysis Centre (BBC): The BBC, located in Hamilton, works closely with the NCC and its responsibilities include sample storage in liquid nitrogen freezers, shipping and receiving cryoshippers weekly from DCSs across Canada, quality assessment of biological sample collection, management of the sample storage and retrieval, management of

the consumables to collect biological samples, support to the sites for collecting and processing samples, biomarker discovery, and analysis.

- Genetics and Epigenetics Centre (GEC): The GEC, located in Vancouver, works closely with the NCC and the BBC. The GEC is closely affiliated with the UBC Brain Research Centre. The GEC is responsible for DNA extraction, epigenetic analyses, and bioinformatics using unbiased microarray-based approaches to measure the genome in subsets of CLSA subjects over time.

Information Technology Architecture and Infrastructure

Given the scope and complexity of the CLSA's data collection activities, information technology experts employed at the NCC and in collaboration with Maelstrom Research in Montreal have developed a novel suite of software infrastructure to manage the collection, storage, and dissemination of the CLSA data. This infrastructure includes four parts: a participant relationship manager (PRM), computer-assisted telephone interviewing (CATI) software, computer-assisted personal interviewing (CAPI) software, and a central data repository (CDR). Each part, implemented as one or more unique web applications, aggregates new and existing open-source software for specific purposes within the study. The details of the CLSA IT infrastructure and its capabilities are described in Appendix 7.

Quality Management System for the CLSA

A quality management system (QMS), implemented and managed through a quality system (QS), was created to cover various aspects of the quality control and quality assurance processes of the CLSA. The complexity of the CLSA and the wide array of data being collected required a QMS to accomplish: 1) standardized approaches to data collection; 2) reduction in errors in data collection; 3) sustainable quality objectives over time; 4) enhancement of the efficiency and effectiveness of study operations; 5) protection of participant privacy; and, 6) satisfaction of stakeholders' need for high-quality, accurate, and valid data. Figure 5 shows the CLSA's QS organizational structure. The centre of the QS is the Senior Management Team (SMT), which liaises with the Operations Committee (OC), Quality Control Committee (QCC), and Statistical Analysis Centre (SAC). Quality assurance (QA) and quality control (QC) policies and procedures are communicated to the CATI sites and DCSs, the BBC, the GEC, and the NCC. Staff are trained, and expected to follow all QA and QC policies and procedures during their day-to-day activities (e.g., collecting data during interviews). The SAC reviews the quality of collected data and with input from QCC, SMT and BBC; the NCC provides feedback to the sites. The NCC also drafts QA and QC procedures related to site operation (e.g., exporting locally collected data to the CLSA's central server) and data collection (e.g., standard operating procedures for conducting DCS tests such as spirometry). The CLSA's Information Technology Team devises and implements all computerized hardware and software systems needed to support the QA and QC processes. The SMT oversees the modification of QA and QC practices as needed, with advice from the QCC, BBC and SAC (see Appendix 8 for more details).

CLSA Quality Assurance and Quality Control Activities

There are 12 components (Figure 6) in the QS to ensure the collection of high quality data and all QA and QC aspects of the CLSA. These components are used routinely by all enabling units and the SMT to ensure that the CLSA operates with the highest level of efficiency and quality. We briefly describe these components below.

Assessments: CLSA data are evaluated monthly for completeness and accuracy. These assessments include identification of missing data, unusually large or small image file sizes, proper application of skip patterns, and verification of interview and DCS visit timings. Additional assessments include reliability and validity testing of instruments (e.g., audiometer) and processes (e.g., neurological test battery scoring). We also perform random checks on DCS and CATI staff to ensure that accurate data are being captured.

Continual Improvement: Each CATI site and DCS undergoes an annual site audit to assess safety and site layout (DCS), operational efficiency, staff adherence to standard operating procedures (SOPs)

(Appendix 9), interviewer techniques, and staff interaction with participants. Each study site also conducts its own performance monitoring through daily observation of staff and quarterly interviews with each staff member. On a monthly basis, five participants per CATI site who completed interviews within the previous four weeks are randomly selected and asked a few questions about the CATI interview (e.g., on-time start, length, friendliness of interviewer). Similar questions are asked of participants at the DCS visit concerning their experience with the in-home interview.

Documents and Records: Staff at the NCC, including a trained librarian and documentalist, are responsible for cataloguing and updating all CLSA documentation, and distributing current versions of documents to study sites. The CLSA has developed a document management system that formalizes the steps required to develop, revise, translate, release, and archive all study documentation. The system includes a process to ensure that all documentation has proper version control. All documents are reviewed annually, and revised as needed, to account for changes in study procedures. As most documents are initially prepared in English, the CLSA's translation team ensures that all participant documents are translated into French, with back translation and subsequent peer review to verify accuracy of the translations.

Information Management: Prior to the release of new or updated CLSA software, the information technology team implements a testing phase to ensure that the software works properly. Data security is promoted through the issuance of unique login names and passwords for each staff member requiring software access. Different security levels exist to manage access to software and data. All physical servers and software maintain audit trails to identify every electronic operation performed by staff. The audit trails localize each operation to the site and staff person performing the operation.

Personnel: To ensure that CLSA personnel (e.g., CATI and in-home interviewers, and DCS staff), perform all data collection activities in a standardized fashion; the CLSA has a rigorous training process. Ongoing training to cover new or revised study procedures is accomplished through regular bi-weekly or monthly video conferences. Re-training of individual staff members is also conducted when a site or staff member is identified as not following one or more SOPs.

Equipment: The calibration and maintenance schedules for DCS equipment are summarized and circulated to all local site coordinators. Local coordinators are responsible for ensuring the equipment is calibrated and maintained according to schedule.

Process Management: The CLSA uses the Canadian Postal system to recruit participants and receive documents from participants. The Participant Management Team (PMT) at the NCC performs regular quality checks on all outgoing mail to ensure the accuracy of the envelope content. The PMT also performs double data entry on all mail (e.g., consent forms, proxy consent to contact forms) received at the NCC.

Stakeholder Focus: The CLSA maintains a toll-free telephone number and online message submission service for participants to ask questions or provide feedback. Participants may communicate with the CLSA in English or French. NCC staff triage all messages from participants and route response requests to the staff member with the appropriate content expertise; response requests that cannot be addressed by staff are forwarded to a member of the SMT for guidance.

Managing Non-conforming Events: The CLSA has developed numerous SOPs to govern responses to non-conforming events (e.g., accidents suffered by staff or participants, equipment malfunctions). Local site coordinators discuss responses to non-conforming events during the regular monthly video conferences. These findings are reported to the local site PI, who consults the site clinician investigator and appropriate action is taken.

Purchasing/Inventory: The CLSA has an inventory and purchasing system to select vendors, generate purchase orders, and negotiate pricing to receive equipment, services, and supplies. The majority of the consumables purchased are distributed centrally by the BBC and NCC. This system ensures that CLSA staff record all batch numbers and that supplies are delivered on time to sites. The

centralized management of the consumables ensures that all the quality features are recorded and managed in a consistent fashion and all sites are using the same vendor.

Facilities and Safety: The CLSA's enabling units are housed on the campuses of local universities or research institutes and each unit is governed by the health/safety requirements of the host institution.

Organization: The CLSA has established an organizational structure to ensure the promotion of high-quality research, codifying our quality processes through extensive SOPs and training documents.

Management of the Data and Sample Platform

It is fundamental to the CLSA to ensure that data are collected efficiently, and stored and transmitted securely. As a multi-site study, the following standard procedures are being implemented to promote high-quality attention to data management at each site.

Data Security: The CLSA is committed to respecting personal privacy, safeguarding the confidentiality of personal information, and ensuring a secure environment for electronic and physical records.
The CLSA meets these commitments by:

1. Establishing clear principles and policies for the protection of personal information, emphasizing high standards of organizational, technical and physical security practices and protocols;
2. Communicating privacy protection policies and practices to staff, affiliates and stakeholders;
3. Restricting access to personal information to members of the CLSA who have authorized access;
4. Submitting research protocols involving use of CLSA data to research ethics boards for review;
5. Ensuring that staff are trained in the principles and practices of personal information protection and requiring annual written commitments, to respect the CLSA's principles, policies and practices in the protection of personal information;
6. Ensuring the consistency of CLSA's policies and practices with national and international standards of privacy protection in health research and legislative requirements.

A manual system and an electronic system of data storage are in use. Data stored in the manual system (locked filing cabinets in access-controlled environments) include correspondence-related materials (e.g., address labels, transportable media, signed informed consent forms, and passwords). Passwords are stored in a separate locked location from other study materials. Data stored on secure servers at the NCC include participant contact information and raw data. For participant contact information, the CLSA adheres to policies and procedures consistent with those described in the CIHR Best Practices for Protecting Privacy in Health Research, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and the Canadian Standards Association Privacy Code.

Secure Data Flow Post-collection

All collected data, accompanied by unique study identification numbers (de-identified data without name or contact information), is transmitted via VPN to the central server at the NCC. The NCC issues a unique study identification number to each participant after initially receiving the name and contact information. Data transfer between local sites and the NCC is governed by the security protocols specified in the data access agreements that have been signed between McMaster University and the universities that host DCS or CATI sites.

Data Transfer and Storage

Databases and electronic files of collected data are transferred from one location to another in a fully encrypted manner using the VPN. All electronic data are housed on a central server located at the NCC and backed up on two different servers, along with a backup at SAC. A complete list of direct identifiers (names, contact information) is stored separately in a master database at the NCC. Only the lead researchers and authorized research staff have the code to link response records to direct identifiers. All study data, whether electronic or paper-based are kept in secure locations that are accessible to authorized personnel only. All computers with access to the VPN employ passwords at both the device and network levels. DCS interviewers are each assigned a laptop for in-home interviews. Laptop hard

drives are password-protected and encrypted to ensure the security of participant data in the event a computer is lost or stolen. All data are backed up as per CLSA protocols. (Appendix 7)

Data and Sample Access

A fundamental principle of the CLSA is to provide the research community with the collected data while protecting the privacy and confidentiality of study participants. To this end, the Statistical Analysis Centre coordinates data access, produces locked datasets for each cycle of data collection, and provides statistical support and analytical expertise for internal CLSA analyses. To ensure data quality, the CLSA data curator (at the SAC) checks the completeness and accuracy of newly collected data on an ongoing basis.

The Data and Sample Access Committee (DSAC) reviews all applications for the use of CLSA data (Appendix 10) and is responsible for monitoring the approved applications for progress as set forth in the timelines submitted as part of the application. Researchers who receive data have a set period to complete their analyses and if analyses are not completed in the period, the applicant must either submit a request for a time extension or relinquish the right to use the data. The DSAC, working with the NCC and the SAC, requires researchers to sign a data sharing agreement, Appendix 10. The biospecimens are depletable resources and thus particular attention is paid to the appropriate use of these samples. The current plan for availability of biospecimens is as follows:

1. 70% of the baseline CLSA biospecimens will be held back for longitudinal research over the 20-year period;
2. 10% of the baseline CLSA biospecimens will be available for release in the five years following the baseline assessment;
3. 20% of the baseline CLSA biospecimens will be available for release at the midpoint of the study follow-up (i.e., at 10 years after the baseline assessment).

Exclusive access to the platform cannot be granted to any applicant. Users are entitled to use the CLSA platform (i.e., data and/or biospecimens) only for the duration and purposes of the approved research as presented in the application. The user is not entitled to publish or otherwise disseminate any CLSA data, any assay data, or any derived variable data at the individual participant level.

Following review of an application from a researcher to the DSAC, the committee will make a recommendation to the SMT for approval or rejection and in all cases provide comments to the applicant which may serve to improve the proposed research, and in the case of rejection will provide reasons for rejection. Figure 7 illustrates the process for data access starting with the potential applicant's review of the materials on the CLSA website (see DataPreview Portal, below) through to the final stage of release of the data to the user. The turnaround times in this figure are approximate given that up until now the DSAC has met on an ad hoc basis following receipt of an application.

While the platform is being developed, the CLSA research team will, from time to time, use the early data and biospecimens for data quality purposes, such as to validate and improve methods of data collection and analysis. Such use is determined and approved by the SMT and does not require approval by the DSAC.

The Data and Sample Access Committee

The DSAC was struck in 2012 and since then has met 4 times. A total of 5 applications were received and reviewed and 3 were approved. Each of the 3 approved users requested alphanumeric data from the 20,000 members of the Tracking CLSA and now that these data are ready for release, the final steps in releasing the data to these users is underway (i.e., verifying ethical approval, requirement for a data access agreement, cost recovery fees, etc.). The ongoing plan is to hold 4 DSAC meetings per year. For 2014 given the timing of the first data release, 3 additional meetings will be scheduled (July, September, and December).

DataPreview Portal

It is essential to the success of the CLSA platform to ensure that the researcher and stakeholder communities are able to obtain information about the CLSA, the data and biospecimens collected, and the details of the process to request access to the platform. Similar to the UK Biorepository Data "Showcase", the CLSA has created the DataPreview portal based on MICA software developed by Maelstrom Research. DataPreview has been designed as a portal to provide a complete resource on the CLSA with special attention to the needs of individuals wishing to access the data and samples. DataPreview contains essential information (i.e., metadata) in a concise format, from the study protocol to data dictionaries and data collection tools used in the CLSA. The inaugural version of the CLSA DataPreview portal allows visitors to view snapshots of information collected by the CLSA from over 20,000 Tracking CLSA participants at baseline. A separate page for each variable includes details on how the information was collected and coded, along with summary statistics. A powerful search engine allows users to filter specific study content of interest to them. As the site develops, targeted study queries will be available with a password (provided upon request).

DataPreview provides a gateway to obtain access to aggregate CLSA data and information about biospecimens. The portal contains a description of the access process and includes all documentation describing the process and the forms needed to apply for, and use, CLSA data and biospecimens. The portal also includes contact information for CLSA staff during all stages of the application process, from application to data release. Frequently Asked Questions are also included. These questions will be updated regularly based on queries sent to the portal from visitors.

Following approval of an access application, and once the administrative components of the data transfer agreement are completed, users are provided with customized data dictionaries and customized data sets tailored to their study request. The DataPreview has been built for the data resulting from the Computer Assisted Telephone interviews and was launched on May 15, 2014. We anticipate that changes and improvements will be needed over the coming months based on usage. In addition, in the next 6 months we will expand the functionality and content of DataPreview to include the data resulting from the in-home interviews, visits to the Data Collection sites and biospecimens.

Preliminary Descriptive Statistics

As noted, the recruitment and baseline data collection for the Tracking CLSA is complete while for the Comprehensive CLSA these processes are ongoing. We have, however, taken this opportunity to present some very preliminary descriptive statistics (age, sex, province, education, income and self-rated health) for the Tracking CLSA along with those for 21,594 (of 30,000) Comprehensive participants recruited and assessed to date. It is important to note that while the data from the Tracking CLSA participants have been cleaned, the data from the Comprehensive CLSA participants are only partially cleaned and appropriate sampling adjustments have not been made to balance all our age, sex, and educations quotas. Therefore, it is important not to over interpret any differences or unexpected findings. The overall descriptive statistics are presented in Table 5, while the age and sex stratification on these variables are presented in Table 6a and 6b for the Tracking CLSA and Table 7a and 7b for the Comprehensive CLSA participants. It is of note that for the Comprehensive CLSA there are no sites in PEI, New Brunswick, or Saskatchewan, but that the overall distribution across provinces is quite similar despite the differences in methods of sampling.

Challenges and Risk mitigation strategies

One of the keys to success for the CLSA has been to try and identify potential challenges in advance and have several alternate strategies available to mitigate risk.

Getting Started on Time: At the time that we initiated recruitment of the Tracking CLSA through collaboration with Statistics Canada our CFI funded telephone interview facilities were not yet ready to recruit and collect data. The establishment of the infrastructure was delayed due to lengthy agreement negotiations with CFI and 10 universities across Canada. However, we had to engage Statistics Canada

as they were ready to implement their CCHS-Healthy Aging Survey and this survey was to be used as a recruitment vehicle for the CLSA Tracking participants. To ensure that we did not miss this opportunity, the lead institution (McMaster) provided bridge funding to establish interim CATI centres to begin recruitment.

Ethics Review Process: Another challenge that would have resulted in a substantial delay in launching the CLSA was the ethics review process in Canadian institutions. In anticipation of this challenge, the CLSA leadership started exploring the possibility of conducting a coordinated REB review process to have a single harmonized consent process as well as accelerate the process of review so that the CLSA could be launched roughly at the same time at all sites. We were successful in establishing this coordinated review not only for the baseline but for the annual amendment process as well.

Targeting low SES Postal Codes: As we approached the midpoint of recruitment for the CLSA Tracking, we found that the proportion of enrollees in the CLSA with low education was below that in the general population, which was itself fairly low. Since the statistical power to examine the effects of such variables on health outcomes increases when there is heterogeneity in the variable, indeed when the numbers with high and low education are roughly equal, we chose to address the imbalance in the CLSA sample. We used 2006 census data to identify areas with high proportions of residents who had relatively low levels of education. The finest level of data available to us was 'dissemination area'. We used these to identify postal codes for the relevant areas, and in the later stages of recruitment, we restricted our sample to these areas. To ensure the cohort had sufficient heterogeneity with respect to education level, we extended the CLSA recruitment for the telephone interview cohort for an additional 3 months. We pilot tested the procedure in Nova Scotia. About 50% of those who replied expressing interest in the study (i.e., were pre-recruited) were of lower education across all age and sex strata. We regarded this as a success, and extended the oversampling to other provinces. Based on the success of the oversampling in the Tracking cohort, the same procedures are being employed to the comprehensive recruitment.

The overall response rates for the CLSA are the product of pre-recruitment rates, recruitment rates and enrollment rates, taking account of eligibility. Our preliminary data indicate that the overall response rate is about 15% and the recruitment rates are lower than expected. However, the recruitment rate (conditional on being pre-recruited) is about 45%. (See details on sampling methods in Appendix 2). In general, the response rates for population studies have declined in Canada and other developed countries. For example, the response rates for other large cohorts in Canada are in the 10 to 15% range as well.[40]

Reallocation of Participants: The original intent in the CLSA Comprehensive was to recruit 3,000 participants at each DCS over a 3-year period. While this has been challenging but doable for the majority of sites, it has not been as easily attainable for some. Some sites were faced with unique and varied challenges (cumbersome institutional personnel hiring policies, high cancellation rates due to urban/rural location, etc), some of which had an impact on the ability to reach the targeted numbers of participant visits over time. Sites in Montreal and Calgary both faced challenges and undertook additional strategies to catch up with recruitment. However, despite many efforts, the Memorial DCS has been unable to successfully employ corrective strategies. Site progress is monitored closely by the NCC and the SMT and when it became evident that the Memorial DCS targets could not be met, the immediate action of reallocation of participants to other sites was implemented to keep the entire cohort on track. (Table 8). The strategy was agreed upon by the Operations Committee.

Non-Return of Consent Forms: For the Tracking CLSA we have been faced with the challenge that some individuals who completed their telephone interview did not return their written consent form even after multiple mail and telephone reminders. Without the signed consent, these individuals cannot be

considered enrolled. The extended recruitment period and oversampling of people with low education helped to replace these individuals.

Summary of Progress to Date for the Implementation of the Baseline CLSA:

During the period of baseline funding, February 1 2010 to April 2015, we:

- Finalized the funding agreement with CIHR (early 2010);
- Developed all questionnaires and identified equipment required for the physical assessment;
- Developed training documentation and Standard Operating Procedures (SOPs), developed video training material and pilot tested all measures (March 2010 to January 2012);
- Finalized the funding agreement with CFI and all participating institutions (September 2009 to January 2011);
- Developed requests for proposals to hire contractors and vendors, evaluated all bids, created a harmonized purchasing policy across all institutions;
- Renovated all dedicated facilities across the country, acquired equipment and tested all the equipment (December 2010 to May 2012);
- Developed CLSA website and promotional video for participants (2013);
- Developed the software and hardware infrastructure to capture and store all CLSA data and biospecimens (September 2010-ongoing);
- Developed REB applications for ethics approval (June 2011 to October 2011);
- Developed agreements to access the sampling frames to recruit CLSA participants (January 2010 to December 2011);
- Started recruitment for the CLSA Tracking in 2011 and finished recruitment and baseline data collection in early 2014;
- Compared the CLSA Tracking characteristics with Statistics Canada's Canadian Community Health Survey on Healthy Aging (CCHS) and 2006 Census data to assess the heterogeneity of the CLSA Tracking (20,000);
- Engaged in recruiting low SES sample to ensure reasonable sample heterogeneity in the CLSA. This extra sampling and data collection was completed in May 2014 for the Tracking cohort;
- Developed data and sample access policies, data and sample access application, IP policy and data transfer agreements between January 2013 and May 2014;
- Developed a data catalogue, data dictionaries, sampling weights, sampling documents and data access agreements for the CLSA Tracking data release (2013 and 2014);
- Cleaned and coded data on the 20,000 Tracking participants;
- Announced the first release of the CLSA Tracking data-- researchers will be able to access these data in summer of 2014. The second release of the data of the complete data set (which will include scored data on cognition) is targeted for the fall of 2014;
- Started recruitment and the data collection for the CLSA Comprehensive in June 2012 at all sites across Canada. Our goal was to recruit and collect data on 10,000 participants from June 2012 to May 2013; 10,000 from June 2013 to May 2014; and 10,000 from June 2014 to May 2015. We have been able to meet all of our milestones for the first two years of our recruitment and data collection. We are on target to finish recruitment of all 30,000;
- We are currently examining the distribution of our CLSA Comprehensive sample against CCHS and Census data to ensure adequate heterogeneity in the sample. The planned release of these data and biospecimens is early 2016.
- Began the telephone Maintaining Contact Questionnaire (MCQ) interview for all 20,000 CLSA Tracking participants in the Fall of 2013 with a plan to be finished in the Fall of 2015; and
- Began the telephone MCQ for the CLSA Comprehensive participants in the Spring of 2014 with a plan to be finished in the Fall of 2016.

Aim 2: Biomarker analysis of the CLSA baseline Biological Samples

This aim responds to the CIHR's request for a proposal to enrich the "CLSA core platform" by analyzing a core set of biological markers from samples collected and stored at baseline.

Specifically, the objective of the proposal is to describe: 1) the rationale and process for the selection of a core set of clinical chemistry biomarkers, genotyping, and epigenetic markers; 2) the analytical techniques used to analyse these markers; and 3) the quality assurance methods for assessing the quality of the sample and method used. For more detailed information on Aim 2 please see Appendix 11 Epigenetics and Appendix 12 Genetics.

Rationale

From a biological perspective, "aging" is generally defined as the gradual deterioration of all biological systems. Such deterioration will occur as a function of chronological age, but the rate is dependent on many factors including genetics, epigenetics, environment, and underlying disease or pathological abnormality.[41] It is also possible that the majority of the biological markers of aging may not be consistent throughout life and those identified in early life may be different from those in late life, suggesting that we can only enhance our understanding of "aging" through longitudinal studies. Very few longitudinal studies of aging, however, have repeatedly measured changing patterns of biomarkers, metabolomics, miRNA, or epigenetic data to elucidate the process of aging, and to study how biological processes interact with the physical and psychosocial environments to produce diseases and/or deleterious health trajectories and outcomes. Conceptually, the events responsible for biological aging (from physiological through molecular) have been debated by proponents of environmental effects (i.e., the "wear and tear" process of aging) and genetic components (i.e., the "programmed" aging). In humans, there have been extensive efforts using replicative senescence of cell; research on centenarians; comparisons of young versus old at the organ, cellular, and molecular levels; and the study of premature aging syndromes (e.g., progeria) to help understand the mechanisms leading to aging.[42-47] Genetic factors that influence longevity are thought to be those that control survival processes such as DNA repair and antioxidant defense, mechanisms that are also implicated in disease processes such as cancer. The role of apoptosis, or cell death, as a mechanism to eliminate damaged cells, the role of cellular senescence in suppressing cell division, and the mechanisms of telomere loss provide complex and interweaving links with aging.[48] Such research implicates the polygenic nature of the human aging process,[44,49,50] arguing for an integrated approach to the identification of the underlying mechanisms that might be responsible for disease and aging processes.

While genetic variation undoubtedly contributes to general aging and certain age-related diseases, which is an important focus of the CLSA, there is substantial variation in the age of onset of, or severity of, disease in individuals with the same genomes.[51] There is also evidence that the incidence of disease varies according to life circumstances, such as living in low socio-economic status conditions (SES), which is not easy to reconcile with a simple genetic model for disease unless genetics is associated with SES. The gene-environment interaction and epigenetics provides an attractive concept for such mediators, as the epigenome has dynamic features that can be altered by both the physical and the social environment, in addition to being strongly affected by lifestyle factors such as nutrition. Therefore, in theory, the epigenome could change during the life course as part of the normal developmental program and in response to a number of life factors. Epigenetic mechanisms that influence gene expression include DNA methylation and/or changes in chromatin structure among others.[52] Epigenetic mechanisms are vital in controlling how genes interact with the environment. An increasing body of persuasive evidence supports a role for epigenetic changes in the etiology of aging and its associated disease sequelae.[53] Several studies comparing groups of young and old individuals reported an age-dependent decrease in either bulk levels of methylated cytosines or gene-specific DNA methylation in human tissues, including peripheral blood leukocytes.[54-56] The general theme of these studies was consistent with the hypothesis of the epigenome acting to mediate between internal and external

environmental signals during the aging process and the genome. However, the common caveat to all these early studies is that they were cross-sectional in design

The ability to correlate chemistry biomarkers, genetic, epigenetic, metabolomics or miRNA measures with a large number of factors such as physical and social life circumstances, and disease outcomes in a large longitudinal study like CLSA will create the most comprehensive and insightful framework for understanding the mechanisms by which various biologic and physiological systems can be altered during aging.[52,53] Further, there are likely numerous biological markers of aging or complex chronic diseases, and thus it is critical that the parallel measurement of DNA methylation, genotyping, biomarkers, metabolites, and miRNA expression patterns in the same sample be done to enable researchers to decipher the functional circuitry between the biological markers such as genome or the epigenome, and the environment and how it impacts the transitions and trajectories as individuals age. For example, having vitamin D measurement in the same group of participants in the CLSA who have also been genotyped provides the opportunity to understand the biological plausibility that vitamin D might be implicated in neurological processing or not. This assertion is based on the fact that the brain has the biosynthetic machinery (25-hydroxylase31 and 1-alpha-hydroxylase32) for synthesis of the active form of vitamin D (1,25-dihydroxyvitamin D), and contains a wide distribution of vitamin D receptors (VDRs) in many cell types (microglia, astrocytes, oligodendrocytes, Schwann cells).[57] Furthermore, age-related diseases develop over a long period of time. Our ability to identify changing biological markers to detect underlying pathological or physiological changes may provide an opportunity to personalize clinical care to prevent diseases and disability. It is also important to note that the separation of biomarkers of disease from biomarkers of aging is a major challenge and therefore our approach to building CLSA core biomarker platform from multiple biological perspectives may allow researchers to differentiate between “healthy” agers and “unhealthy” agers, and understand underlying mechanisms of disease and disability.

CLSA Infrastructure for Biospecimens

The details of the collection of the biological samples are described in Aim 1 of the main proposal. Briefly, there are three major pillars of the CLSA biospecimens collection strategy: 1) **a comprehensive biospecimens collection** with the wide variety of sample types and a large number of aliquots to facilitate the analysis of biological markers currently known for studying aging and future proofing for biomarkers not currently known; 2) **a quality management system** including standard operating procedures to ensure consistency across sites, quality control methods to monitor consistency, as well as training, safety policies and processes to carry out the activities, and allow collection of pre-analytical data to enhance the interpretation of the biological data; and 3) **a biological marker analysis strategy** to maximize the use of each aliquot, and provide results using harmonized and robust methods to preclude bias from batch to batch and over-time.

Approach to the Selection of Core Biological Markers

In recent years, the application of powerful biologic markers of exposure, disease, and disease susceptibility in epidemiological studies has allowed for the investigation of complex pathophysiological mechanisms connecting exposures and outcomes in chronic diseases. Aging encompasses pathophysiological changes on a background of non-pathophysiological processes. Disentangling these overlapping paths to uncover biomarkers of aging necessitates exploration of a compilation of biological markers. Increasing blood creatinine concentration could herald chronic kidney disease and elevated B-type natriuretic peptide (BNP) may lead to the investigation of heart failure, or, these ‘increased’ values may simply reflect the natural biochemical history of aging. One biological marker alone is unlikely to suffice and many biomarkers are yet to be discovered. The dynamic state of aging includes the allostatic load that accumulates from physiological ‘wear and tear’. The ability of the organism to circumvent, respond, and adapt to these damaging events is a function of environmental, genetic and epigenetic constituents. In this section of the proposal, we describe our

overall strategy to identify the set of biological markers to enrich the core CLSA baseline platform. The sections on clinical chemistry, genetics, and epigenetics will provide more details about the rationale for the selection of key core biological markers to be included in the CLSA.

At the outset of study planning in 2009, the members of the Biology Working Group (BWG) under the direction of the Drs. Balion (Clinical Chemist), Kobor (Epigenetics) established a process for the collection of the wide variety of the biological sample to be collected in the CLSA and stored for future analyses. This process included searching literature, conducting feasibility studies[7] and consulting researchers and clinicians across the country. This process resulted in a list of biological markers that might be of interest to the research community and guided the sample collection protocol for the CLSA (Table 9). For the purposes of the current proposal, we reconstituted our BWG to identify the core set of biological markers to be included in the CLSA platform. Figure 8 describes our conceptual approach that highlights the intersection between biological sample aliquot, method, and biological marker. Briefly, we wanted to ensure that core biological markers should be supported by the literature and from longitudinal studies, where possible, in order to be considered for this proposal, and that the biological markers showed association with age related diseases or the aging process. Second, we wanted to make sure that we use stored aliquots in the most efficient fashion to ensure that the minimal amount is used to avoid refreezing of the sample. The selection of an analytical platform was also critical to ensure the comparability of results over time. Finally, given the fixed budget for these analyses, we wanted to make sure that there was good balance between the costs of the test and its scientific value from a longitudinal perspective and that the resulting data will allow us to; 1) assess long-term variability of a given biological marker; 2) contribute in the refinement of the CLSA diseases ascertainment algorithms; 3) conduct etiological research; and 4) use biological markers to identify participants for future sub-studies within CLSA.

Based on the principals identified in Figure 8, the BWG was further divided into sub-groups, as described in the Figure 8 (Biology Working Group Biomarker Teams). Once the first list of the biological markers was generated along with the rationale, we engaged our clinical working groups and other key other researchers to review the proposed list of biological markers to ensure their clinical as well as research utility. Based on these discussions and consultations, the final list of core biological markers was generated and is justified below in each of the sections on clinical chemistry, genetic and epigenetics

Clinical chemistry biomarkers

Clinical chemistry biomarkers are fundamental tests performed within a clinical laboratory diagnose disease, to monitor disease progression or response to therapy, and to screen for the presence of underlying disease in an apparently healthy individual. The test menu is broad and extensive as it encompasses all biomarkers currently used for diagnosis or screening of diseases from those that appear at birth to pathologies that arise throughout life until death. The vast majority of these many hundreds of tests are performed on blood and urine. The components measured within these specimens include proteins, enzymes, hormones, lipids, carbohydrates, metals, electrolytes, vitamins, and metabolites. It is common to find these biomarkers in many epidemiological and clinical studies. They do not include biomarkers within the domains of hematology (CLSA already measures Complete Blood Counts, [white blood cell, lymphocytes, monocytes, granulocytes, red blood cell, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, red blood cell distribution width, platelets, mean platelet volume]), infectious disease, microbiology, toxicology and genetics. For the purposes of this proposal, we reviewed several longitudinal studies of aging that had evaluated biomarkers and determined which biomarkers were the most important for the CLSA platform. It is interesting to note that many of these longitudinal studies only measured these biomarkers at one point in time. World-wide, 26 longitudinal studies[18-21,58-81] were identified that included collection of biospecimens and measurement of biomarkers (Table 10). Few studies provided a rationale describing

how biomarkers were selected. Seventy-eight individual tests were identified and the frequency of their use is shown in Table 11. The most frequently measured biomarkers were lipids (high-density lipoprotein, cholesterol, low-density lipoprotein, triglycerides), hemoglobin A1C (HbA1c), glucose, c-reactive protein (CRP), biomarkers of cardiovascular disease, diabetes, and inflammation. The other biomarkers are additional biomarkers of these pathologies as well as those used in the detection of renal function, bone health, liver disease, endocrine function, nutrition, and anemia.

We further reviewed the biomarkers identified in these studies to determine whether these were associated with either mechanisms related to the aging process, disease of aging, or both. A recent literature review conducted by Engelfriet, et al., (2013) identified over one hundred biomarkers and were categorized as biomarkers of biologic processes, disease or both.[41] (Table 12) Based on these reviews and consultation, we selected a subset of biomarkers that were restricted to tests performed within clinical chemistry laboratories and that were linked to disease process and/or underlying processes of aging. (Table 12)

As one of the long-term objectives of the CLSA is to quantify the changing nature of biomarkers as people age, we also used data from a systematic review of geriatric reference intervals.[82] Briefly, this review captured all studies from 1989 to 2013 that provided reference intervals for clinical chemistry tests done in blood for individuals' $\geq$ 65 years of age. There were 62 included studies that presented reference intervals for 93 different chemistry tests. This review identified biomarkers that showed a difference in reference intervals between young and old age groups. Figure 9 illustrates those analytes that had data from two or more studies with respect to increases, decreases, or no change with age. However, variations in selection of the reference population (number of individuals, exclusion criteria, ages) and statistical methods for the calculation of reference intervals makes it difficult to assess whether there is truly a significant change in these analytes with age or not.

We selected a core set of biomarkers that not only full fill our pre-established selection criteria (Figure 8) but also cover several of the physiological systems that are important to studies of the aging population. The proposed panel of clinical biomarkers for the core CLSA includes albumin, creatinine, c-reactive protein, ferritin, hemoglobin A1C, lipids, thyroid stimulating hormone, freeT4 and vitamin D, and are further justified below.

We also excluded some of the biomarkers that are measured in many other studies of aging but are not relevant to the Canadian population. For example, Canadians are replete in folate following fortification of flour of this vitamin in 2001and therefore it is not desirable to measure folate in a population-based cohort like CLSA.[83]

Albumin (ALB)

A decrease in albumin levels is a significantly important clinical laboratory finding, although increased levels can be found and are mostly linked to dehydration. Decreased albumin concentration can be caused by decreased synthesis in the liver due to liver disease (e.g., liver cirrhosis), malnutrition and malabsorption, protein loss through kidneys, skin and intestines during nephrotic syndrome, burns and enteropathies, hemodilution and acute disease state. Albumin has been shown to play an important role in oral health, as shown in a recent six year follow-up Japanese study, demonstrating a relationship between hypoalbuminemia and high risk of tooth root caries.[84] Serum albumin levels are also an important biomarker of general health status in the elderly, and is associated with the risk for death.[84,85] Hypoalbuminemia is also postulated to be a biomarker of inflammation, whereby a drop in serum albumin in the first 6 months was associated with increasing all-cause and cardiovascular death risks in the subsequent 18 months, while a rise in serum albumin was a predictor of better survival independent of baseline serum albumin in maintenance hemodialysis patients.[86] The International Association of Gerontology/International Academy of Nutrition and Aging (IAG/IANA) Task Force (2004) indicates that in older hospitalized patients, albumin levels may be a better indicator of prognosis than nutritional status.

Alanine Aminotransferase (ALT)

Alanine aminotransferase (ALT) is present in the hepatocyte cytoplasm and hepatotoxins such as alcohols, medications, drugs, and viral infection can damage hepatocytes resulting in ALT leakage from the cells into the circulatory system. ALT is a reliable biomarker of liver function and is clinically used as an indicator of wide range of liver conditions including hepatitis, cirrhosis, fatty liver disease, alcoholic liver disease, and liver cancer. Between 2005 and 2013, a nearly 30% increase in liver-related deaths was observed in the Canadian population.[87] This number is expected to continue increasing, especially in the older members of the population, due to the chronic nature of these disorders.

Creatinine (CREA)

Creatinine is a waste product and its measurement in serum is the most commonly used test for kidney function. It is excreted in urine by glomerular filtration, (small amounts are secreted by the proximal tubule, but little to no reabsorption occurs). Creatinine clearance is a measure for creatinine elimination from the body by kidneys and estimates the glomerular filtration rate (eGFR). At higher plasma concentrations, more urine creatinine is secreted causing overestimation of GFR.[88] It is recommended that eGFR be reported routinely in clinical laboratories and for this purpose the Modification of Diet in Renal Disease (MDRD) equation is used. While there are otherbio markers of kidney function, such as urea and cystatin C, creatinine is the test of choice because of its cost-effectiveness.[88] Elevated serum creatinine concentrations are strongly associated with older age, along with diabetes and treatment for hypertension.[89] Although the decline of GFR was previously regarded as a normal part of aging, even in people without kidney disease, it is now considered to be an independent predictor of adverse outcomes (cardiovascular disease and death) in the elderly. Longitudinal studies among community-dwelling adults have shown age-related decline in renal function of approximately 0.75 mL/min per year after age 40. The prevalence of moderate renal impairment (creatinine clearance < 30 mL/min) among elderly Ontario long-term care residents is 10% for men (65-100+ years) and 24 % for women (65-100+ years).[90]

C-reactive Protein (CRP)

C-reactive protein (CRP) is an innate immune response biomarker of inflammation, synthesized primarily by the liver, and by the smooth muscle cells of the coronary artery in response to pro-inflammatory cytokines.[91,92] CRP blood levels can rise, within 10 hours, to 1,000 times the reference value, and usually take ten to twelve days to decline to baseline levels after an inflammatory event.[93] Under normal physiological conditions, healthy individuals have serum CRP concentrations below 1 μg/mL. While the absolute CRP level is influenced by smoking, body mass index[93] and seasons,[94] detection of smaller serum elevations of CRP using high sensitivity assays (hsCRP) can be used to predict risk of future coronary events in otherwise healthy individuals, with moderate Framingham cardiovascular risk scores,[95,96] or in people with acute or stable coronary syndromes.[97] The prognostic value of hsCRP as a marker of cardiovascular risk has been recognized by The American Heart Association, AHA, the Centers for Disease Control and Prevention, CDC,[98] and The National Academy of Clinical Biochemistry's, NACB.[99] Healthy elderly individuals display increased levels of inflammatory biomarkers.[100] In the aging population, chronic elevation of hsCRP has also been associated with conditions beyond vascular inflammation, including obesity,[101] type II diabetes,[102] cancer,[103] chronic kidney disease[104] and a general physical decline.[105]

Ferritin (FERR)

Ferritin, a 450-kDa protein present in every cell type, can incorporate up to 4500 iron atoms in a non-toxic but bioavailable form.[106] Serum ferritin is a reliable indicator of the body's iron stores[107] and is a better measure of anemia than iron. In healthy individuals, ferritin concentration positively correlates with age and body mass index.[108] Very low values are found in individuals suffering from iron deficiency anemia. Conversely, values are elevated in subjects with iron-overload disease and hemochromatosis.[109] Ferritin is also an acute phase reactant and acts as a biomarker of acute and chronic

inflammation.[110] The aging process is associated with a subclinical chronic inflammation and associated increase in ferritin levels independent of iron status.[111-113] However, evidence from the NHANES III shows that, after the third decade of life, ferritin serum levels remain stable in healthy men and decline around 70 years of age and older. Conversely, ferritin levels in women are relatively low until menopause and then slightly increase later in life.[114]

Hemoglobin A1C (HbA1C)

A1C levels are used to define the percentage of glycated hemoglobin.[115] Its formation is irreversible and its concentration depends on the lifespan of erythrocytes (≈ 120 days) and glucose level in the blood. Its value is free of the wide diurnal fluctuations that occur with food ingestion, exercise, stress, and medication.[116] Following the guidelines from the International Expert Committee, endorsed by the American Diabetes Association,[117] A1C can be used as an alternative biomarker to glucose for the diagnosis of type 2 diabetes (T2DM), and to guide therapy.[118] In many longitudinal studies, A1C is used as a biomarker of metabolic control for micro- and macro-vascular complications from T2DM.[119] In subjects without diabetes, A1C correlates directly with cardiovascular disease,[120,121] chronic kidney disease[122] and mortality.[123] In addition, increased levels of A1C correlate inversely with vitamin D ($25(OH)D_3$) concentration, hence suggesting a protective role for vitamin D in T2DM development.[124] In the elderly non-diabetic population, data from longitudinal and cross-sectional studies have shown that A1C levels rise with age[125] and might be associated with increased risk of cognitive decline.[126-128] In the CLSA, A1C measurement is also included as one of the decision points to identify individuals with or without T2DM.

Lipid Panel (CHOL, HDL, TRIG, calculated non HDL and LDL)

Measurement of a lipid profile typically includes total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides. Based on the results from the Framingham Heart Study, measurement of the basic lipid profile provides an estimate of whether an individual is prone to a 10-year risk of cardiovascular disease.[129] Originally, this risk estimate was derived from a calculation of age, total cholesterol, HDL, smoking, diabetes, and systolic blood pressure, and was later adapted with modifiers such as family history of cardiovascular disease and ethnic background.[130,131] In addition, the Canadian guidelines have embraced more recent studies which have shown that measurement of non-HDL cholesterol, which is the difference between total cholesterol and HDL, correlates more strongly with cardiovascular disease events as compared to LDL.[130] However, more studies are needed regarding the consequences of elevated non-HDL in the aging population.

Thyroid Stimulating Hormone (TSH) and Free Thyroxine (FT4)

Thyroid-stimulating hormone (TSH) is produced by the pituitary gland and stimulates the production and release of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland. Approximately 90% of the thyroid hormones consist of T4 and only about 0.1% of this pool is made up of non-protein bound free T4, which is the biologically active form.[132] T4 and T3 are responsible for controlling metabolism where excessive production (hyperthyroidism) leads to increased heart rate, anxiety, weight loss, difficulty sleeping, tremors, and puffiness around the eyes. Insufficient production (hypothyroidism) of thyroid hormones lead to weight gain, dry skin, cold intolerance, irregular menstruation, and fatigue. Hypothyroidism is 5-8 times more common in women than men and the prevalence may depend on dietary and environmental factors that affect iodine intake.[133] On the other hand, prevalence of hyperthyroidism ranges from 0.5% to 3% in individuals older than 60 years of age.[133] TSH and free T4 measurements are also included as one of the decision points to identify individuals with or without thyroid disorders.

Vitamin D

Vitamin D (25(OH)D) is a steroid hormone usually associated with calcium and phosphate homeostasis, bone mineralization, and general health. Elderly individuals, 70 years and older, produce

roughly 25% less vitamin D than a younger person with comparable sun exposure time.[134] There is, well established link between vitamin D deficiency and risk of osteoporosis and falls.[135] However, new evidence suggests that low serum levels of this biomarker may represent a risk factor for other age-related diseases, such as cardiovascular disease[136] and type 2 diabetes.[137] Low levels of vitamin D has also been linked to a higher risk of developing certain types of cancers.[138] There is also some evidence that vitamin D may be involved in neuroplasticity through its neuroprotective effects.[139] Indeed, the brain has biosynthetic machinery for vitamin D synthesis and contains a wide distribution of vitamin D receptors (VDR),[140,141] and the prevalence of low vitamin D is especially high among the elderly.[142] The magnitude of deficiency varies by country and factors including solar radiation (latitude and season), outdoor activity, skin pigmentation, diet, and cultural behaviour (e.g., clothing, sunscreen). Establishing a causal link between a deficiency in vitamin D and cognitive function or dementia pathology would irrefutably have major public health implications. A recent systematic review[143] suggested that lower vitamin D concentrations might be associated with poorer cognitive function and a higher risk of Alzheimer's disease. However, robust large longitudinal studies or randomized clinical trials of vitamin D supplementation are needed to determine the significance of this association.

METHODS

Core chemistry biomarkers will be measured on all the people who provided blood in the CLSA (estimated number based on 94% consent rate would be 28,200 participants) to obtain a better understanding of the biochemical process of aging as they pertain to various clinical conditions as described above and in (Table 13). It is anticipated that measurement of these 14 (12 measured and 2 calculated) biomarkers will provide valuable insight into outcome prediction or indicate valuable associations with chronic diseases and the aging process. Each biomarker will be measured on high-throughput instruments used for routine clinical work at Calgary Laboratory Services. Table 13 summarizes the specimen requirements, the analytical measurement and clinical reportable range, lower limit of detection, assay imprecision, assay interferences due to icterus, hemolysis, and lipemia, and the principle of the measurement method. Measurement of all biomarkers will use one-serum aliquots while HbA1c will use one aliquot of whole blood. The analytical measurement range indicates the dynamic readings for the instrument without modification to the specimen such as dilution, concentrations, or other pre-treatments. The reportable range indicates the range of analyte values that are clinically significant and what is reported following specimen modifications such as dilutions, concentrations, and pre-treatments. Likewise, the lower limit of detection indicates the lower limit of the clinical reportable range. Assay imprecision represents the closeness of agreement or reproducibility between independent results under controlled conditions of the clinical laboratory. The values for imprecision are expressed as the variation (coefficient of variation) around a central value (mean) of quality control material and were determined from the average performance for the respective analytes over one year at Calgary Laboratory Services. The main interferences with measurement for chemistry analyzers are associated with hemolysis, icterus, and lipemia, due to hemoglobin, bilirubin, and triglycerides, respectively. These substances absorb light at various wavelengths used for spectrophotometric determinations of many chemistry analyzers and can significantly interfere with measurements at certain thresholds as described in Table 13. In addition, all analytes measured on the Roche Diagnostics instruments can have automated quantitative serum indices reported for additional quality control regarding potential interferences. Gross hemolysis, icterus, or lipemia are determined visually for 25-hydroxyvitamin D. All samples will be shipped to Calgary Laboratory Services by cryoshippers and in-transit temperature data will be downloaded from the data logger. Upon receipt, samples will be stored at -80^{o}C until analysis. Storage temperature is recorded on a daily basis. Samples will be thawed at room temperature, aliquotted into secondary containers, and accessioned and labelled with barcodes. All the analyses will be completed between 2015 and 2018.

Quality and Harmonization of Biomarker Results

Consistency in the measurement of biomarkers is vital to obtain results that can be interpreted without bias over time. It is also imperative to ensure the biospecimens for which these biomarkers will be measured are of highest quality. Lack of quality leads to inaccurate and non-reproducible results, which compromises data interpretation and reduces the value of the study. To mitigate risk of the dataset, appropriate control procedures are necessary. We have in place a comprehensive system to capture pre-analytical variables that could affect tests results. Tables 14 and 15 illustrate the data that is collected. These data allow the retrieval of high-quality samples that are appropriate for the proposed analysis (e.g., biomarkers that are affected by gross hemolysis would not be retrieved). The availability of the pre-analytical data also allows for investigating the suspicious result, especially if these results are returned to the participants because of their abnormal value (e.g., vacutainer tube lot numbers, temperature issues, and processing delays).

Internal quality control (QC) material using both manufacturer (Roche) and third party (Bio-Rad) is analyzed for all levels on routine and standby cassettes on the c701. On the e602 modules, all three levels of QC are analyzed on the current reagent packs with one level run on the standby reagent packs. QC is analyzed and checked at the beginning of the day so all troubleshooting can be done before samples begin processing. QC is analyzed for all levels on routine reagent bottle sets every 3 hours for the c701 and every 24 hours for the e602 modules. QC is analyzed after loading new reagent, maintenance, calibration, or troubleshooting. External quality control will be monitored using proficiency testing surveys from the College of American Pathologists (CAP). These surveys involve three challenges per annum and report results based on peer groups organized by method and reagent type. The report includes the mean, standard deviation, coefficient of variation, median, low, and high value, and final count of reported results that were not excluded as outliers. Failure to achieve a satisfactory overall testing event performance for two consecutive testing events or two out of three consecutive testing events is considered unsuccessful performance.

Genetic Markers

The objective of this section of the proposal is to genome-wide genotype CLSA participants in order to identify common, low frequency, and rare genetic variants imparting susceptibility to aging-related disease and traits.

Rationale

Most aging-related diseases are moderately heritable, which suggests that variation in DNA base pairs (referred to as single nucleotide polymorphisms, or SNPs) is partially responsible for disease etiology. The identification of susceptibility SNPs is attractive since they are generally free of confounding, not prone to reverse causation and can identify proteins and pathways related to disease etiology using humans, rather than model organisms. Since 2007, ~13,000 susceptibility variants have been identified for a host of human traits and disease and most of these have been widely replicated and surpass stringent p-value thresholds. This technology-driven advance has been enabled through genome-wide genotyping, which simultaneously tests association of most known common genetic variation with a disease or trait.

CLSA represents a unique opportunity for Canadians to lead large-scale genomics initiatives since the dense phenotyping, follow-up and sample size of CLSA is rivaled by few cohorts in the world. Recent advances in genotyping technology have made such large-scale genotyping affordable and imputation strategies (which enable the estimation of unobserved genotypes through haplotype blocks) have recently facilitated the assessment of low frequency and rare genetic variants (those with a minor allele frequency [MAF] <5 and <1%, respectively) in large populations. Some of these rare variants may impart a larger risk for disease and on traits, in contrast to the typically small effects of common variants, and therefore may be more helpful in directly identifying causal proteins and pathways. We

hypothesize that common, low frequency and rare genetic variants may describe susceptibility to aging-related diseases and traits.

Method

We will randomly select 10,000 participants from the 28,200 participants who gave blood samples in CLSA for genotyping. DNA is currently stored in buffy coat and will be extracted using standard protocols. We will use the Affymetrix UKBiorepository array, which assays 820,967 SNPs, ~ 111,000 of which are exomic coding variants and the rest are representative common variants from the entire genome. It provides highly cost-efficient capture of SNPs with a MAF ≥1% and includes genetic variants which will allow us to capture genetic variation across different ancestries in the CLSA sample. Using these SNPs as a scaffold, we will impute unobserved genotypes using a highly reliable method we have recently developed[144,145] down to a MAF of 0.1% in samples of European ancestry (which comprise >90% of the CLSA sample). After standard quality control procedures, all genotypes will be made available for release to CLSA researchers following CLSA's data release policy. We will then encourage investigators to lead and participate in international genome-wide association studies (GWAS) consortia to identify and replicate associations with traits and diseases, thereby identify proteins and pathways relevant to ageing. We anticipate to genome-wide genotype the remaining 10k samples from CLSA in the next follow-up phase.

Through collaboration with other Canadian cohorts, we have achieved unprecedented cost efficiencies allowing the purchase of genotyping chips for $48 USD per sample.

Genome-wide genotyping and novel imputation methods will enable the CLSA to lead new international initiatives to identify common, low frequency, and rare genetic determinants of ageing-related disease and therefore provide insight into the biologic determinants of these diseases in humans.

Epigenetic Markers

Epigenetics is rapidly emerging as an attractive process relevant to human health and disease, an important role has emerged for epigenetics at the interface between the environment and the genome. In context of aging, it is of particular interest that while DNA methylation is a very stable epigenetic mark, it is also dynamic across the lifetime. Specifically, numerous environmental influences have been associated with variation in DNA methylation.[146-148] These include nutritional factors, exposure to environmental pollutants, and social environment. It is this plasticity that underlies much of the potential contribution of DNA methylation to multifactorial diseases and complex phenotypes, and CLSA is an ideal platform for such research. Integrating developmental and environmental forces shaping the epigenome, one attractive model is that age-related changes in DNA methylation likely reflect the accumulated exposures of the epigenome to a wide range of internal and external factors. At the extreme, these changes contribute to cancer development as best exemplified by the age-dependent hyper-methylation of promoters of tumour suppressor genes.[149] However, it is likely that epigenetics has a much broader and more nuanced implication for aging. Consistent with this, there already is evidence suggesting that epigenetic modifications are associated with important aspects of successful aging, including psychological and cognitive abilities, as well as proper functioning of the immune system.[150-152] The recent development of quantitative methods for high-throughput measurements of DNA methylation has enabled detailed ascertainment of the role of this key epigenetic mark during aging. The resulting identification of age-dependent differentially methylated regions (aDMRs) in different tissues strongly suggests that epigenetics needs to be considered an integral part of molecular aging research. Importantly, aDMRs are, in some cases, precise enough that age can be predicted from as few as three CpGs.[153] This has led to the intriguing proposal that DNA methylation serves as an "epigenetic clock". We propose to identify, test, and validate a core set of CpGs that will become part of the core CLSA platform. The inclusion of these key CpGs will make CLSA the largest epigenetic biomarker study in the world. The identification of these CpGs at baseline and in future waves of the CLSA will allow us to explore its relationship with a multitude of health outcomes including mortality, function, and disease.

For example, it is postulated that epigenetic and chronological age might be highly correlated for normally aging subjects, but that subjects whose epigenetic age is much higher or lower, as a function of their prior life experiences, than their chronological age might experience different health trajectories later in life. The CLSA epigenetic platform would be ideal to tackle such emerging research questions.

DNA methylation sites associated with aging

To identify the preliminary list of age-associated CpG sites to be used in our model, we examined the literature to find reliable publications that examined age and DNA methylation in blood. We found six of these studies and examined the overlap of these sites across these six studies (Table 16).[153-158] Recent research has emphasized the importance of correcting for cell type in these studies, as many sites of DNA methylation are associated with subtypes of white blood cells, the compositions of which change with age.[147,159] Thus to reduce the likelihood that our sites are associated with age due to being associated with cell type, we required that all our sites of interest be identified in at least one of the two studies in our list which included an analysis of cell type composition (Studies 4 and 5 in Table 16).

The approach described here differs from epigenome-wide association studies (EWAS) that assess DNA methylation genome-wide. A targeted analysis such as this, when performed on known markers of aging and with a concrete plan for model creation, tuning, and validation, is much more cost-effective than an EWAS study, though the volume of information created is less. We are confident that our targeted analysis will give an accurate measurement of epigenetic age, which could inform participant selection for future EWAS studies on a subset of the CLSA participants.

Measurement of DNA methylation marks

Isolation of DNA from PBMCs is extremely reliable, and we anticipate no problems in acquiring enough DNA from the stored samples. Blood aliquots for the CLSA consist of a minimum of 500,000 cells, twice the minimum number required for DNA methylation analysis. To control for batch effects over time for both pyrosequencing and Sequenom, we will include controls with known DNA methylation levels in both the training phase as well as the experimental phase. Raw DNA methylation values will be corrected for inter-individual differences in blood cell composition using the complete blood count that was obtained for each sample in conjunction with our regression method before being used in our statistical model to predict epigenetic age.

Practically, the assays to examine DNA methylation at these sites are taking advantage of bisulfite treatment of genomic DNA, which selectively modifies cytosine residues that are not methylated to thymidine, while leaving methylated cytosines intact. Thus, this approach converts epigenetic information to sequence-based information. We will use Sequenom EpiTyper along with pyrosequencing for highly quantitative assessment of CpG methylation at single nucleotide resolution over DNA stretches of approximately 200 base pairs surrounding the epigenetic clock CpGs. Both technologies begin with PCR amplification of the bisulfite treated DNA around the CpG of interest. For pyrosequencing, primer extension, and real-time monitoring of the incorporated base at the CpG site give representative DNA methylation levels sequence the resulting PCR product. For Sequenom EpiTyper, the PCR product is fragmented into segments containing a single CpG each and measured on a finely calibrated mass spectrometer. The mass difference between the bisulfite modified un-methylated cytosine and unmodified methylated cytosine give percent methylation. The selection of method for each assay depends highly on the genomic context of each, particularly in terms of surrounding CpGs – areas with very high levels of CpGs tend to be assayed best using pyrosequencing, while areas with slightly lower CpG density can be assayed with either platform. Both pyrosequencing and Sequenom EpiTyper are fully functional as part of the CFI funded Genetics and Epigenetics Centre of the CLSA. We will select 5,000 individuals from the CLSA genetics component described above that will reflect the age sex distributions of the CLSA Comprehensive sample to carry out the proposed epigenetic study. From these 5,000, we will randomly select 1,000 participants to conduct epigenetic analysis to assess our model of epigenetic age. In this training set, chronological age will be regressed on the CpGs using a

penalized regression model, which will transform methylation at the 15 indicator CpGs to a measurement of "epigenetic age". To test the predictive value of the epigenetic clock on the training set, three accuracy measures will be tested: Pearson correlation coefficient, median 'error', and 'average age acceleration'.[156] These measurements will assist with tuning the model to fit the training set samples. Next, we will validate this prediction on a further 4,000 CLSA participants. Finally, we will re-apply the tuned and verified model to the 5,000 CLSA participants together and generate measurements of "epigenetic age" for each participant from the residuals of linear regression which will be included in the core CLSA databases for future research.

There are a number of possible applications of an epigenetic biomarker to the CLSA data. Many independent studies have established that using measurements of DNA methylation at specific sites can accurately predict chronological age, but little is known about how these sites can predict future health related outcomes. Thus one possible application would be comparing the health (for example as defined by levels of functional dependency) trajectories of epigenetically old and epigenetically young participants, to determine whether the known age biomarkers are also associated with health, and whether they can be used to predict future health in the subsequent waves of the CLSA.

Ethics and Genetic and Epigenetic Ethical Legal Society Issues (GELS) for the Aim 2

Ethics approval will be sought for the biomarker proposal from McMaster and all the participating institutions as per CLSA coordinated process described in aim1. In addition, we will develop protocols to address all the GELS related issues for the Aim 2 by seeking advice from the CLSA ELSI committee.

Data Storage and Management

All the data will be stored on secure CLSA servers. The access to biomarker data will be governed by the CLSA DSAC policy, Appendix 10.

Timelines

Our proposed timelines for all the activities with aim 2 are from 2015 to 2018. This timeline allows us to generate biomarker data within a reasonable period to further enhance the utility and value of the CLSA platform for researchers and partners.

Aim 3: To describe the first 3-year follow-up (2015-2018).

As noted in earlier sections, the major waves of CLSA data collection occur every 3 years with a brief contact with participants (i.e., Maintaining Contact) in between these major waves. During the period April 1 2015 to March 31 2021, data collection will consist of the ongoing assessment of study participants. The 3-year period will include the following:

- First follow-up for the 20,000 CLSA Tracking participants June 2015 – May 2018
- First follow-up for the 30,000 CLSA Comprehensive participants June 2015 – May 2018
- The second telephone administered maintaining contact interview will begin in this 3-year period for all 50,000 participants Dec 2016 – Nov 2019

Review of Study Measures

In preparing for the first follow-up of the cohort the research team has undertaken an in-depth evaluation of the measures collected at baseline to ensure that essential measures remain and problematic measures are replaced or improved and that the science of the platform is enhanced to keep pace with changing ideas and priorities of the research community. Balancing these components is challenging in a study with specific aims to examine trajectories of aging, as trajectories, by definition, suggest that the same information (ideally by repeating the same measure) be collected over time to create these trajectories. We describe below some the strategies that we have used to meet these challenges. From a governance perspective, it is important to note that final decisions regarding changes (additions, deletions, and modifications) to the study content have been implemented by the three PIs following input on data quality from the SAC team and recommendations on content from the CLSA Working Groups.

A face-to-face meeting of Working Group leaders and key CLSA investigators took place at McMaster University in September 2013 at which time a plan was put in place whereby each of the content area working groups was asked to review the information collected as part of the CLSA baseline with a view to identifying changes required for the next wave of data collection, recognizing that participant burden could not change substantially. Each working group was provided with a full set of baseline materials and tasked to:

1. Review baseline questions and assessments;
2. Make recommendations concerning measures/questions/assessments to be repeated, removed or changed for the first follow-up (along with rationale);
3. Make recommendations concerning measures/questions/assessments to be added to the first follow-up (along with rationale)

Each Co-PI was assigned responsibility for two Working Groups and served as a resource person throughout this process. The first recommendations were received by the SMT in December 2013 and since that time, there has been an iterative process leading up to the final recommendations. As needed, the data curator was able to provide empirical evidence relating to the "performance" of measures as requested by the Working Groups. Recommendations concerning the removal of items were primarily conditions that do not change over time, such as language first learned at home in childhood, place of birth. The more difficult challenge was to settle on the inclusion of new material, where discussion with respect to the rationale was much more extensive.

New measures added to study content

New study content and measures, justified based on the scientific literature, were proposed by all WGs. The complete list of revisions, additions, and deletions is contained in Appendixes 6 & 13. Here we summarize the key new areas and the justification for each as provided by the WGs.

Clinical Working Group (CWG)

Child maltreatment: Childhood maltreatment (CM) is a significant risk factor for the development of negative mental and physical health outcomes.[160] Individuals who experience CM are at greater risk for depression, post-traumatic stress disorder, anxiety disorders, alcohol and drug dependence,[161-163] as well as a number of chronic conditions, including cardiovascular disease, gastrointestinal and metabolic disorders, neurological and musculoskeletal and respiratory problems.[160,161] Converging scientific evidence suggests that early adverse experiences, such as CM, become 'biologically embedded' into multiple systems, altering brain function, neuroendocrine responses to stress and immune system function.[164,165] These findings suggest that the root of many adult diseases may originate in early childhood during sensitive periods of development where biological systems are most susceptible to adverse environmental conditions. Although prevalence varies worldwide, it well recognized that CM is alarmingly common. A recently published report based upon the 2012 Canadian Community Health Survey reported that the prevalence of any of 3 types of child abuse was 32.1%, with physical abuse being most common (26.1%), followed by sexual abuse (10.1%) and exposure to intimate partner violence (7.9%). Women were more likely than men to have experienced sexual abuse (as children) and exposure to intimate partner violence. Men were more likely than women to have experienced physical child abuse and any other child abuse. All three types of child abuse were associated with all types of interview-diagnosed mental disorders, self- reported mental conditions, and suicidal ideation and suicide attempts even after adjustment for sociodemographic variables. We propose to include questions concerning the occurrence of CM along with four questions assessing childhood emotional abuse, neglect, and exposure to emotional intimate partner violence in the CLSA. The inclusion of questions in CLSA exploring childhood maltreatment, presents an unparalleled opportunity to assess the associations of childhood abuse with a large number of biological, sociological, medical, economic and other factors. The proposed questionnaire has been used in many studies of child maltreatment in Canada and by Statistics Canada, and has been validated.[166,167]

Elder Abuse: Abuse and neglect of older people is a worldwide phenomenon, but accurate prevalence is hard to determine, for many reasons including variable definitions, reluctance to admit abuse, and in the absence of a gold standard, inadequate detection instruments. A recent systematic review concluded that 6% of older people had been abused within the previous month.[168] Nearly one quarter of older persons had been subjected to psychological abuse, and 10% of long term care staff admitted to committing physical abuse against residents.[168]The best Canadian prevalence estimates were obtained by telephone interviews with over 2,000 individuals over age 65, in which 4% reported that they had been victims of abuse.[169] In population-based studies, the questionnaire most frequently used to determine prevalence is the Conflict Tactics Scale (CTS) a 39 item instrument covering a wide range of items.[170] A number of shorter instruments have been developed for screening and case finding, mostly in clinical practice. Without a gold standard however, their psychometric properties have been hard to determine. The Elder Abuse Suspicion Index (EASI)[171] is a 6-item instrument (available in English and French) which has been has been developed and validated for clinical practice. However, recently the feasibility of use of a 5-item self-administered version has been published.[172] While not originally intended for use in population-based studies the CLSA has chosen to include this measure in the first follow-up as part of the face-to-face interview.

Epilepsy: In Canada, very little is known about the incidence or prevalence of epilepsy. The national point prevalence, was estimated to be between 5.2 and 5.6 per 1,000, based upon analyses of the 3rd cycle of the National Population Health Survey and the first cycle of the Canadian Community Health Survey, both of which relied upon a single self-report question.[173] At baseline, the CLSA relied upon a similar single questionnaire item. A recent prospective population-based study demonstrated that the sensitivity of a single self-report questions is only 76.2%.[174] Over the past two years we developed the Canadian Longitudinal Study on Aging – Epilepsy Algorithm (CLSA-EA) and conducted a validation study within the CLSA to estimate the diagnostic accuracy of the CLSA-EA. We administered the CLSA-EA to a consecutive sample of 201 CLSA Comprehensive participants as well as a consecutive sample of 41 individuals from an epilepsy-enriched general neurology clinic. Of the 112 English and 130 French-speaking participants, 34 had a lifetime history of epilepsy. The estimated sensitivity and specificity of the CLSA-EA was 97.1% and 60.6% respectively for the lifetime prevalence of epilepsy; 90.9% and 73.2% for the point prevalence of active epilepsy. In addition, using an *a priori* modified CLSA-EA (i.e., using a more inclusive definition of "probable epilepsy") sensitivities and specificities for the lifetime prevalence of epilepsy were 97.1% and 98.1% and for point prevalence of active epilepsy were 100% and 98.6%. The CLSA-EA will be added to the follow-up for all 50,000 participants. Included on an ongoing basis, it will permit estimation of the incidence of active epilepsy in Canada.

Hearing: The addition of a *functional* measure of hearing is an important addition to the assessment of hearing and communication in the CLSA. The standard test of hearing acuity is pure-tone audiometry, which is already being conducted in the CLSA Comprehensive. Pure-tone thresholds provide information about whether sound is audible and there is a strong relationship between pure-tone thresholds and the ability to recognize words in ideal quiet conditions. However, the most devastating hearing-related problem of older adults is difficulty understanding speech in the noisy situations often encountered in everyday life. Speech understanding in noise is not well predicted by pure-tone thresholds. Speech understanding involves supra-threshold processing of the spectral and temporal properties of speech and the noises that interfere with it. A test of speech-in-noise is a useful addition so that this important *functional* ability can be directly measured. A suitable, very short instrument is the "Digits in Noise" test.[175] This validated test is available in English and French, and takes approximately 2 minutes to administer. The "Hearing Handicap Inventory for the Elderly-Short"[176] is a measure of the psychosocial effects of hearing (loss) on a person. It is a 10-item questionnaire that has been widely used

and with well documented test properties and will be used in the Comprehensive CLSA face-to-face interview.

Arterial Stiffness: Currently in the CLSA, we are using GE Vivid I carotid ultrasound at a frame rate of 20, to capture images for cIMT and plaque sweep. The GE Vivid I has the capability to capture images at high frame rates (HFR). High frame rates can provide more images per second, giving images an enhanced temporal resolution. Of interest to this proposal and for CLSA follow-up, high frame rate image acquisition can be used to measure static elasticity in tissues,[177] providing an alternative to traditional measures of arterial stiffness that were not previously possible in the CLSA.[178] Temporal resolution is an integral component of vascular motion imaging. For the study of carotid intima-media thickness (cIMT), cineloops of ultrasound images were taken at baseline and will be repeated in the follow-up, with the most clear, end-diastolic image chosen as the representative measurement of the endothelial and arterial muscular layer. Many factors come into play when optimizing the image of the arterial wall, since these measurements are in millimeters. A high frame rate will allow multiple images to capture cIMT in a short window of time. High frame rate imaging can help reduce the amount of time needed to keep the cIMT present while still capturing enough images for analysis. With an increase in resolution and ease of imaging, having a high frame rate mode will dramatically increase the quality of images for quality assessment of cIMT in the CLSA Comprehensive. A clinically significant use of high frame rate ultrasound imaging is the emerging measure of tissue-strain imaging.[179] An increase in arterial stiffness is correlated with impaired longitudinal wall motion.[180] With tissue-strain imaging, the longitudinal wall motion of a carotid artery can be assessed. As one of the markers of arterial health, arterial stiffness evaluation is in need of a non-invasive, easily repeatable method. Research and studies with tissue-strain imaging with high frame rates can explore this new option. Incorporation of high frame rate imaging is very simple and is easily applied to the existing CLSA standard operating procedures (SOP). With high frame rates, both cIMT and images for arterial stiffness can be easily collected at once and there is no additional time or participant burden. The addition and usage of high frame rate ultrasound imaging in the CLSA provides many benefits in terms of data collection, temporal resolution and image quality will benefit greatly. Concerning research, further analysis can be conducted on the same set of data, which will greatly advance our knowledge and tools to study arterial health. The use of high frame rate at follow-up does not affect the longitudinal harmonization of the baseline cIMT measure with the follow-up measures of the cIMT.

Decedents in the CLSA: Based on the age distribution of our cohort and annual mortality rate data from Statistics Canada[181] we anticipate that approximately 1,117 males and 921 females will die by the first follow-up and an additional 1,283 males and 1,101 females by the second follow-up. Prior to the first follow-up of the CLSA, we will link the CLSA data with mortality data available from Statistics Canada. The vital statistics include the underlying, immediate and antecedent causes of death are coded according to the ICD-10 codes. The linkage will be done using health card number and deterministic algorithms using surname, sex, and date of birth of participants. We estimate at least a 90% linkage rate.[182] However, death certificates, while useful, contain limited information about the time and cause of death and data gleaned from death certification are not sufficient to understand important issues about residential transitions (e.g., moving into long-term care or a hospice) or health care utilization in the period prior to death.[183] Thus the CWG is developing a decedent questionnaire to complement the information that will be obtained through vital statistics linkage. This questionnaire will be administered to a close relative or friend of study participants who have died since their baseline interview. In taking on this task, the CWG considered several domains of information that have been included in decedent questionnaires and were asked to focus on domains with clinical- and policy-relevance and areas that were understudied, while balancing participant burden. The CLSA decedent questionnaire will elicit information about the date and cause of death (to complement or supplement information from vital statistics), the trajectory of functional decline,[184] residential transitions,[185,186] and health care

utilization[187,188] in the 3 months prior to death. In addition information will be sought on the quality of dying and death.[189] Many of the domains and questions were adapted from the Decedent questionnaire used in the Canadian Study on Health and Aging,[190] and the English Longitudinal Study on Aging (ELSA).[20] Many of the previous studies did not measure the domain of quality of dying and death. This module was adapted from the Quality of Dying and Death Questionnaire.[191] An additional question was developed to assess the trajectory of death based on the work by Lunney.[184] This question will help assess the course of disability at the end of life.[192]

Social Working Group (SWG)

Workability: Surprisingly little is known about how older workers adapt to their changing circumstances. Perceived work ability is the ability of a worker to perform his/her job, taking into account the specific work demands, individual health conditions and mental resources.[193] Of interest is the relationship between the capacities of the older worker, the nature of work demands, and specific injury and health issues. Work ability is comprised of a complex of interactions involving health, the physical, psychological, and social prerequisites of functioning, and personal and environmental factors. The largest, ongoing study of the influence of ageing on work ability in workers 45 and over,[193] indicates that work content, work organization and work environment are significant factors associated with declines in work capacity and higher rates of retirement due to workplace injury**.** Although individual differences in functional capacity increase with age, older workers are generally more vulnerable to stress due to physical demands (e.g., poor work postures)[194] and are less tolerant of night work.[195] Likewise, scientific evidence suggests a relationship between psychosocial work factors and physiological and psychological alterations that may increase the likelihood of developing physical and mental health issues. However, little attention has been given to the relationship between psychosocial work factors and the risk of adverse health outcomes, especially for the aging workers.

Swaen, et al.,[196] found that risk factors for an occupational injury included both individual factors (age, sex, education fatigue need for recovery and smoking) and psychosocial work characteristics (high job demands, emotional demands, and conflicts with supervisors and or colleagues). Research into how the older worker adapts to his or her work-environment to avoid a first-time injury and how the workforce accommodates the aging worker is limited. An understanding of the processes by which an older worker successfully adapts to the post-injury environment or chooses to leave the workforce or retire involves several multi-disciplinary and multi-dimensional aspects. The CLSA affords the opportunity to address several gaps in the literature important for the development of programmatic and policy interventions. We will include a measure of workability to address an emerging area of research as to how older workers are accommodated in workplaces, the effect of changing physical, psychological, and social functioning on work and vice versa. In the follow-up of the Comprehensive CLSA, we will administer The Work Limitation Questionnaire (WLQ) to assess the participant's ability to work as a function of their physical or mental disabilities. The WLQ is a reliable and valid measure and is available in both English and French.[197-199]

Psychology Working Group (PWG)

Subjective cognitive decline: Complaints about memory are extremely common in middle aged and older people. While these complaints can occur in the setting of demonstrable cognitive disorders such as mild cognitive impairment (MCI) or a dementia, they are also common in individuals without an overt cognitive disorder. The significance of memory complaints in cognitively normal people has been the subject of debate for many years. While some consider such complaints as harbingers of MCI and eventually dementia others believe that they do not portend future cognitive decline.[200] More recently, in the Rotterdam population-based study of 7983 people over age 55, the presence of subjective memory complaints conferred an increased risk of dementia (HR approximately 1.5) after a mean follow-up of 9 years.[201] In a study of 543 Chinese men and women over age 65, the presence of subjective cognitive complaints did not predict a faster cognitive decline or development of dementia over 3 years.[202] The

CLSA is an ideal vehicle to explore the natural history, risk factors and conditions associated with subjective cognitive decline. The Multifactorial Memory Questionnaire (MMQ) assesses the self-report of cognitive ability in everyday life. This reliable and valid measure examines subjective cognitive complaints to capture pre-clinical signs of cognitive impairment.[203] The MMQ has been validated in both English and French[204] and for ages, 40-91 so would be relevant for the full CLSA cohort. We will also add (on the recommendation of the CWG) two questions to capture the perceived change in memory and if this perceived memory, change worries participants.

Lifestyle Working Group (LWG)

Transportation: Mobility is key for physical and mental health, independence, and quality of life of older adults. n North America, driving is the most common form of transportation used by adults, including those aged 65 and over,[205] even though driving frequency decreases after retirement.[206] Yet, numerous studies have shown that those aged 65 years and over have a high crash rate per miles driven relative to middle-aged adults[207] and the decision to stop driving altogether may sometimes be associated with many negative consequences, such as limited independence and mobility,[208] and decreased life satisfaction, isolation, and loneliness.[209] Kostyniuk and Shope (2003)[205] found that many older adults did not use alternative forms of transportation because they were not aware of the options available to them, or due to high costs, inconvenience, and general distaste. In an examination of participants in an older driver education program,[210] the majority of older adults (60%) reported that they were willing to consider the possibility of changing their driving behavior. A minority of respondents felt that changing driving was not possible for them due to the demands of their lifestyle and a few participants felt that no person should be denied the right to drive. Little is known about the transportation patterns of Canadians. Questions were designed to provide information about exposure to the most common forms of transportation available in most communities and how easy it is for needs to be met using available transportation. These questions have been formulated to add to the existing questions included in the baseline questionnaire by members of the Clinical, Social, Lifestyle and Psychology working groups with additional input from members of the CANDRIVE project (a national project on driving and older adults), and in consultation with policymakers from provincial and federal ministries of transport. The CANDRIVE team has validated the proposed questionnaire in both English and French.

Health Services Working Group (HSWG).

Health care use: Given the prominence of health care expenditures in the public policy discourse, it is essential participants' health care use be assessed in the CLSA. Health care use can be measured via linkage to administrative health care records and/or via self-report. Administrative health care records provide a comprehensive assessment of health care use and have been extensively used in Canada for research and to inform policy (e.g., Roos, Menec & Currie, 2004[211]). However, accessing data, particularly from several provinces is a complex and lengthy process[3] and challenges exist to harmonize available data across provincial health care systems. Self-report health care measures are routinely included in population health studies (e.g., Canadian Community Health Survey). Although the limitations of self-reported health care use measures have been highlighted in the literature, with self-reports tending to underestimate actual health care use,[212-215] such measures nevertheless allow policy-relevant analyses on factors related to health care use, as well as changes in health care use over time. In addition to existing health care use questions in the CLSA, we propose to include questions pertaining to the unmet healthcare needs and preventative health care. For example, 12% of Canadians who identified a need for mental health care indicated that their needs were not being met.[216]

Preventive health behaviours: Preventative health care, such as influenza vaccination, is a key aspect of the health care system and a way to enhance population health and reduce health care use. Recommendations as to which services are effective, for whom (e.g., age groups) and how frequently they should be repeated change over time as new evidence of effectiveness becomes available. Recently,

the U.S. Preventive Services Task Force recommended a range of preventive health care services based on best current evidence, along with recommendations for administration.[217] The use of the following services are being proposed to be assessed in the CLSA follow-ups and include blood pressure checks; blood test for cholesterol; test for diabetes; colorectal screening; cervical cancer screening; mammograms; influenza vaccination, pneumococcal vaccination. Questions relating to these measures are available in English and French.

Biology Working Group (BWG)

There are no proposed additions to the collection of new types of biological samples in the follow-up. However, we will stop collecting whole blood in multi-well plates (GenPlates) embedded with filter paper to preserve whole blood DNA. This particular collection of the whole blood was designed to be collected only at the baseline. The removal of this collection type will allow us to reallocate 1 ml of whole blood to increase from two aliquots to three aliquots for EDTA whole blood and ACD tube respectively (Table 17).

Developing Training Materials and Standard Operating Procedures

To meet the needs of the follow-up protocol, we will update our existing training materials and standard operating procedures. For the new measures, we will develop new training material and standard operating procedures. All modifications will be rigorously pilot tested to ensure the logic and the comprehension of all training and procedural materials. As per our baseline methodology, we will train all our staff before the active data collection for the follow-up starts in the spring of 2015.

Review of Questionnaire format

In addition to the review of questionnaire quality as well as revisions, additions, and deletions to content, all questionnaires will be reviewed and revised to reflect the appropriate time period of observation. This involves determining the appropriate period of response taking into account the three-year interval since the last interview. For example, some questions previously asked in an ever/never format may be adapted to cover the time period since the last interview. In instances where the questions have only been validated over a specific time point, such as “in the last week” an assessment of the most appropriate interval will be undertaken, based on the research behind the question, as determined by the Working Groups. This will then involve programming changes to the interviewer scripts prior to the start of data collection.

Pilot testing of the Follow-up Questionnaires and Protocols:

Much of the questionnaire content will be very similar (and in some cases identical) to the baseline questionnaires but the format will be modified to make it relevant for the follow-up data collection, and the addition of new measures makes it imperative that questionnaire and the protocol be pilot tested before the follow-up launch in the Spring of 2015.

*Contacting CLSA participants for Follow-up 1***:** While this application concerns the first and second CLSA follow-up, it is relevant that there will be an overlap in timing of the conduct of the first MCQ (funded from the first 5 years of funding) with the first follow-up phase of the CLSA. Specifically, the MCQ data collection for the CLSA Tracking began in early 2014 and is projected to finish in the fall of 2015. In addition, the MCQ for the CLSA Comprehensive participants began in May 2014 and is projected to finish by the fall of 2016. Both MCQs overlap with the launch of the first follow-up.

In spring 2015, we will begin the first follow-up for the CLSA Tracking participants with a projected completion in early 2017. We will begin the first follow-up for the CLSA Comprehensive participants in the summer of 2015 with a project completion by April 2018. The follow-up phase will involve utilizing processes (scripts, software, SOPs, etc.) that were developed at baseline and will require some modifications. In preparation for participant contact for follow-up assessments, all participants will receive a letter reminding them that we will be contacting them by phone in the near future to schedule

an appointment either for the telephone interview or for the in-home interview (and subsequent DCS visit).

Data Collection Procedures: The four CLSA Computer Assisted Telephone Sites will once again take on the task of re-contacting CLSA Tracking participants. For the CLSA Comprehensive participants, the local DCS in-home interviewers will contact participants to begin their participation in the first follow-up. At this 3-year point following baseline our CLSA participants will range in age from 48 to 88 and at the older end of the age range it is likely that circumstances may have changed for some participants, and they will not be able to participate as easily as they did at baseline. Specifically, participants may have physically moved to a new location; they may have moved into an institution or care home; they may have developed (or have worsening) visual and/or hearing impairment and/or cognitive impairment and/or mobility challenges. In the time leading up to the beginning of our follow-up we are putting in place strategies aimed at identifying (based on baseline data) those participants who appear to be most at risk of developing (or having worsening) of conditions that may hamper their ability to participate. In addition, we will be developing accompanying protocols to guide the interviewers in the event that any of these conditions arise. These strategies will enable individuals to continue to participate in the CLSA if they wish to do so.

Accommodating change in location of participants: In the CLSA we have chosen to try to follow participants move during the course of the study. For the CLSA Tracking participants, the challenge will be to obtain the new contact information but the data collection procedures can remain the same, indeed for the most part a move to any location can theoretically be accommodated by the CLSA given this mode of data collection. For the CLSA Comprehensive, however, the challenge is greater. If the participant has moved out of range of all of 11 Data Collection Sites, then we will complete the data collection using computer assisted telephone interviews. This will consist of questionnaire data asked not only in the in-home interview but also will include questionnaires that are currently administered at the DCS (e.g., detailed disease symptom questionnaire). CLSA Comprehensive participants who moved into area covered by another DCS, then they will be re-assigned to the DCS and undergo follow-ups as usual. We anticipate that this will be a rare occurrence given the geography of Canada.

When a CLSA participant moves into an institution, we will also attempt to continue to follow them. While each situation may differ depending on the type of institution and the health of the individual, the process for conducting a telephone interview will remain relatively unchanged (provided the person has access to a phone), but the process for conducting an in-home interview and DCS visit will have to be modified.

Accommodating mobility challenges for CLSA Comprehensive participants: At future waves of data collection following the baseline assessment, some participants may become unable to travel to their local DCS and the CLSA will adapt to be able to collect at least a minimum dataset. We have already had CLSA participants who are visually handicapped complete DCS visits. When provision of transportation will not suffice (e.g., participant has a health condition precluding travel), then in-home data collection will be employed. We will cross-train in-home interviews to be able to carry out the minimum data set assessment in the home. The DCS-based questionnaires will be adapted to the in-home environment using CAPI software installed on laptops. The physical measures that are possible to conduct at the in-home assessment and have been endorsed by the Clinical Working Group include grip strength, height, weight, blood pressure, lung function, standing balance, visual acuity, and body composition.

Accommodating cognitive challenges

Protocol for Identifying a Proxy: As indicated previously, the participant consent for a proxy completed at baseline for those 70 and over allows participants to indicate how they would like to participate in the CLSA in the future, in the event of cognitive decline or if they are unable to provide their own responses for other reasons. If they indicate that they would like to continue participating in

the CLSA, they are asked to provide the name and contact information of a person who can make decisions on their behalf (i.e., a proxy decision maker) and a person who could answer questions on their behalf (i.e., a proxy information provider). This has been described more fully in Aim 1.

Cognitive decline and the use of proxies

The process of identifying the presence of cognitive decline sufficient to affect a participant's ability to participate and initiating the use of proxies in a longitudinal study is complex, and there is little guidance in the literature on the practical aspects of implementing such protocols. The CLSA has invested considerable resources into how to address these issues, with extensive input from the ELSI Committee, the expert subgroup of the Psychology Working Group, and the REBs. Acknowledging that this is work in progress, and that these protocols will require continued refinement, we present here the issues, challenges, and proposed solutions.

Protocol for Identifying Potential Cognitive Impairment: One of the primary reasons for being unable to participate in subsequent data collection is likely to be a decline in cognitive abilities. Identifying individuals at highest risk of cognitive decline during the course of the CLSA would allow us to detect those participants for whom we may need to contact a proxy decision maker and/or for whom we may need to collect data fully or in part through a proxy information provider. The exploration and development of an identification strategy is currently underway, utilizing the data collected at the CLSA baseline. We have three sets of information available to us that may be put to use in determining cognitive risk. The first is self-reported information about whether the person has been told by a doctor that they have memory problems. The second set of information is the participant's performance on tests of cognitive function administered to both the CLSA Tracking and CLSA Comprehensive participants (i.e., immediate and delayed recall - Rey Auditory Verbal Learning Test, Memory Alternation Test, and Animal Naming), adjusted for age, sex, and education. These neuropsychological tests have been validated and a population-based cutpoint (a t-score of less than 34) was found to be associated with a range of health outcomes in the Canadian Community Health Survey—Healthy Aging, among the same age group as the CLSA.[218] The last set of information that is useful is the extent of "don't know" and/or missing answers an individual has in the baseline questionnaire. These sets of information are currently being examined, individually and in combination, by an expert subgroup of the Psychology Working Group to determine their usefulness in predicting those in need of a proxy at follow-up.

Protocol for initiating a proxy: Following identification of a participant at risk of cognitive impairment at the first follow-up the interviewer will be prompted to ask the participant a subjective memory question, as recommended by the CWG. The participant's response will determine the course of action. If the response is consistent with the presence of cognitive challenges, the interviewer will suggest that the participant may wish to engage their proxy. If the response is not consistent with the presence of cognitive challenges, the participant will be asked if they are comfortable answering the questions on their own. If they state that they are and want to continue, the interview will continue. If the participant agrees that the proxy should continue the interview, then the interview will be discretely terminated. In the event that a participant who is under 70 years of age is flagged via this process or a person over 70 who has not previously provided a proxy information provider or proxy decision maker is flagged, then the participant will be asked if they wish to identify an individual or individuals to fill those roles. We will provide specific training to the CLSA interviewers to be best able to manage these potentially difficult situations sensitively.

Protocol for Proxy Consent: Contact with the individual identified by the participant to act as their proxy is not initiated until it has been established that a proxy is required. First, the proxy will be contacted by mail by the CLSA. The package will include a cover letter, an information package that includes information on the CLSA and the role of a proxy decision maker and information provider, a copy of the participants' signed consent to identify a proxy, and a blank consent form for the proxy to

sign. Following the mail-out, the individual will be called by a CLSA staff member to follow-up, to go over the materials, and answer any questions that the proxy may have. Once signed consent is received, the interview process will continue with the proxy, using the proxy adapted questionnaire.

Ongoing Consent: Given that there are no major changes in the purpose or scope of the study that would require signed re-consent, ongoing consent will be verbally affirmed at the outset of the follow-up interview, following a brief exchange about the study to ensure that the participant understands what is being asked of them. At this time, the participant's contact information is verified, and any outstanding health insurance card numbers are obtained prior to the start of the interview. Participants who have turned 70 since baseline will be asked to complete the participant consent for a proxy.

Participant Withdrawal

In developing the withdrawal protocol, the ELSI Advisory Committee considered this issue, and the procedures were endorsed by the ELSI Committee and approved by the REBs. The guiding principle is that all participants have the right to withdraw from the CLSA at any point, in person, by phone, email, or mail. However, in order to accommodate the different study requirements of the CLSA Tracking and CLSA Comprehensive and the needs of a research platform, withdrawal options are available to participants. All participants who request to withdraw from the study are informed that the CLSA will no longer contact them in the future, but that their previously collected information (and biospecimenss for CLSA Comprehensive participants) will continue to be used for research purposes. They are given the option of allowing (or refusing) ongoing linkage using their health insurance number (HIN). If it is impossible to review the withdrawal options directly with the participant, the default option for withdrawal is that in addition to no further direct contact and no further linkage using their HIN, the link between any identifiable information (i.e., name and contact information) and de-identified study data (and samples) will be permanently destroyed. This means that it will never be possible to re-link their information, and consequently not possible for a withdrawn participant to be reinstated later. Once the withdrawal option is determined, a letter of confirmation of withdrawal is sent to the participant.

At baseline, as noted, in order to be considered enrolled, a participant must have provided signed consent and completed the baseline assessment. For the CLSA Tracking participants, this is the telephone interview; for the CLSA Comprehensive participants this is the in-home interview and the DCS visit. Technically, a participant cannot withdraw until they have been enrolled, and thus, the Maintaining Contact interview is the first point of contact *initiated by the CLSA* at which withdrawal may be initiated (it can also be initiated by the participant at any point beyond baseline). At the time of writing, 4% of 4,000 CLSA Tracking participants withdrew when contacted to complete the MCQ.

Losses to follow-up

A protocol for tracing study participants who are not located at follow-up will cover linkages with mortality databases and contact with alternate contacts identified at baseline. At each follow-up, some CLSA participants will have died, and we will make every effort to avoid upsetting family members with uninformed calls. The Clinical Working Group has developed a decedent questionnaire that will be used to obtain information in the time leading up to death from a close family member.

Ongoing Coordinated Ethics Review

The ethics amendments for 2013-2014 were recently submitted and are under review by the McMaster REB, in preparation for posting on the portal for the local REBs to access. During the period of the first follow-up, we will continue to work with the McMaster REB to streamline the coordinated ethics process, and ensure that the local REBs remain committed to the process. We will work closely to support the University of Calgary REB, to bring Calgary into the coordinated process. It has been our experience that many REBs across Canada are under-resourced, and while the portal is an efficient solution for the CLSA, the volume of material to review that the CLSA produces has put a strain on the limited resources at some REBs. Indeed not all REBs have moved to electronic submissions requiring a paper copy of the documents (sometimes as many as 900 pages). As the study progresses and the

majority of scripts and data collection instruments have been reviewed by the REBs, it is expected that the volume of materials submitted to the REBs will decrease. This, combined with increased familiarity of the study over time will likely reduce the REB burden. The McMaster REB, in particular the chair, has been pivotal in our ability to continue with the process as a large part of the burden falls upon the McMaster REB. Despite these challenges, we are confident that the coordinated process for CLSA is a far better solution than placing the responsibility in the hands of the local site PIs for separate submissions.

Ethical, Legal, and Social Issues (ELSI):

The CLSA continues to benefit from the critical advice of the ELSI Advisory Committee. Of key prominence is the continued development and implementation of protocols dealing with participant cognitive decline and the use of proxies. Going forward, we anticipate the need for continued ELSI guidance and advice, allowing us to proactively address a number of ethical, legal, and social issues. For example, the biobanking, long term storage and future use of biospecimens including DNA in conjunction with the collection of a wide array of phenotypic information on such a large scale is a relatively new phenomenon and the CLSA stands to benefit from the ELSI Committee's consideration of best practices for their governance and use. Similarly, engagement in collaborative initiatives with other large cohorts and platforms, while clearly beneficial from a scientific perspective, can pose challenges in building alliances without violating pre-established principles with respect to participant privacy and confidentiality. The opportunity to seek and receive expert advice from the ELSI Committee on such substantial issues for the CLSA cannot be underestimated. These issues are relevant to all large-scale studies exploring the gene-environment interactions, and the CLSA, along with the ELSI committee, are poised to provide international leadership in this regard.

Quality Management System (QMS)

The QMS developed at baseline will be the framework for ensuring quality control and quality assurance during the follow-up. The CLSA QMS is a flexible framework that can evolve to accommodate components of the study being added or deleted. During this period, it is expected that emphasis will be placed on assessing the impact of adaptions and accommodations to data collection procedures, such as the comparability of data collected via different methods. Ongoing procedures such as the monitoring and feedback loops established for quality reports, updating of SOPs, and equipment maintenance and calibration will continue. In person, training sessions will be conducted for coordinators, interviewers, and DCS staff. We have also developed training videos for our staff to use to improve their skills. In addition, NCC is continuously engaged in training staff at all sites using videoconferences. The CLSA Operations Manager will also continue the annual site visits to assess the quality control and quality assurance aspects of the data collection.

Strategies for Participant Retention

Participant retention is of paramount importance as we move beyond baseline. Several approaches will be used to enhance retention, many of which are described elsewhere in this proposal. Here we reiterate the primary retention strategies to enhance ongoing study participation.

Study design strategies: The MCQ interviews were developed with the specific intention of improving retention by maintaining direct contact with participants in between follow-ups. This strategy was used successfully in the Canadian Study of Health and Aging in between base line and the first follow-up. The purpose of the MCQ is to maintain awareness of the CLSA and its importance to participants; to validate key contact information; and to initiate tracing mechanisms within a short window of time for those participants we are unable to re contact at the MCQ. Once a participant is identified as unable to be reached for follow-up, the first line of action is to call the person they identified as their alternate contact person at baseline and/or their proxy decision maker. Names are also crosschecked against available mortality databases. The use of computer-based search strategies and directories will also be employed.

Personnel strategies: A critical factor for retention is the establishment and maintenance of trust by participants in the study and its investigators. Since the launch of the CLSA, we have worked hard to integrate these strategies into the fabric of the CLSA. Every interaction with a participant is instrumental in building that trust. Front line staff are critical to participant retention, and are the "face of the CLSA" to participants. CLSA interviewers are supported by the DCS and CATI Managers, as well as the local Principal Investigators. Staff training is developed and overseen by the NCC. Training occurs nationally in person and by teleconference, and is extended and reinforced by training provided locally by the DCS/CATI manager. Biweekly meetings take place via videoconference between the NCC Operations staff and the DCS/CATI managers (with participation from one of the PIs). In this way, issues are dealt with as they arise, and solutions are conveyed to the entire team, resulting in well trained staff with the tools for high quality participant interactions. Many local sites hold biweekly or monthly team meetings not only to review activities but also to share experiences.

Accommodation strategies: Strategies to allow flexible participation over time as people age and face situations that have the potential to positively affect ongoing participation. At the first follow-up, we are developing accommodations for participants who experience cognitive impairment and sensory impairment. We are also developing accommodations for participants who cannot come to the DCS for mobility or transportation reasons, as well as due to a transition to an institution such as a nursing home. Other accommodations will be handled as they arise based on need.

- Accommodation for cognitive decline: The identification of a proxy decision maker and/or a proxy information provider as participants turn 70, as well as a record of the participant's wishes regarding future participation in the event of cognitive decline increases the likelihood of ongoing participation in the event of cognitive decline. This is important not only to decrease attrition, but because cognitive decline is an important outcome with a trajectory that is poorly understood.
- Accommodation for hearing impairment: With time, CLSA participants may develop hearing loss to the point that telephone interviews using standard equipment are no longer possible, or create such a level of frustration for the participant that they withdraw from the study. At the first follow-up interviewers will be instructed to record when a participant experiences difficulty with hearing in an interview over the phone. In instances where a hearing impairment is recorded, further telephone contact is made in consultation with the CATI supervisor. Interviewer pitch and tone is extremely important for those with hearing loss, therefore a simple strategy is to ensure that an interviewer with a strong and deep voice is the selected interviewer. Our current CATI uses Voice Over Internet Protocol (VOIP), which at times are harder to hear as compared to standard landlines. Thus, another option is to conduct the interview using a landline. Ongoing technological and infrastructure modifications and improvements, such as the use of the highest quality headsets and sound baffling techniques, will be explored and implemented as they become available.
- Accommodation for being unable to attend a DCS visit: As participants age, mobility limitations, and/or lack of transportation may become an increasing challenge, and impact attendance at the DCS. A protocol is under development for the conduct of a number of physical measures to be done in the home. This will allow us to retain many participants who would otherwise be forced to drop out. Given that interviewers currently visit participants in their homes as part of each data collection wave, the addition of physical measures in the home is expected to be well received by participants.
- Accommodation for transition to an institution: Similar accommodations for a home visit will be made when participants move to an institution such as an assisted care facility or a nursing home. An additional element will often involve contact with the institutional administrator to obtain permission as required.

Communications strategies: CLSA communication strategies include: regular updates to participants to provide feedback and general study findings; a user-friendly website with information on the study written in a style that is accessible to the lay public; media coverage of the study to publicize the importance of CLSA for Canadians; public outreach and community engagement events, such as open houses and Café Scientifique events. CLSA participants are also given information for direct contact with the CLSA via mail, email, or phone in order to answer questions or provide input. Another strategy under consideration is to identify 'CLSA Champions' who consent to sharing their personal story about participation in the CLSA newsletter or on the CLSA website. As part of the MCQ we collect information on the type of communication tools (e.g., email, websites, social media, etc.) used by participants. We will use this information to tailor our ongoing communication strategies to participants. The return of test results to CLSA Comprehensive participants at the DCS is also a feature of the CLSA that, though not specifically intended to boost retention, has the effect of engaging people and retaining them over time. As repeat follow-up visits occur, people will be increasingly interested in being able to compare their own results over time. We are exploring the possibility of creating a secure on-line profile for individuals to access as they wish.

Approaches that other studies have utilized and may be considered for the CLSA include merchandise with the CLSA logo (e.g., reminder magnets, pens and stationary), birthday cards, and holiday season greetings in December each year, and the use of a CLSA membership card detailing the number of years of participation in the study as follows: bronze [0-5 years], silver [6-10 years], gold [11-15 years], platinum [16-20 years].

Management of Follow-up Data and Samples

The CLSA follow-up will continue to build upon the principles of data and sample management defined at the baseline of the study. An important priority in the CLSA would be start producing longitudinal data files that can be used by researchers to answer specific research questions. In addition, the CLSA will continued to be committed to respecting personal privacy, safeguarding the confidentiality of personal information in our custody, and ensuring a secure environment for electronic and physical records containing personal information as outlined in the Aim 1 of this proposal. All electronic data are stored at the NCC with adequate back-up systems and transmitted using secure VPN as outlined in Aim 1. A copy of the de-identified data and its back up is also stored at the SAC as per protocol. All computers with access to the VPN employ passwords at both the device and network levels. All laptop hard drives are password-protected and encrypted to ensure the security of participant data in the event a computer is lost or stolen.

Data and Sample Access

The details of Data and Sample Access are provided in Aim 1. As we move to the first follow-up, the activities related to access and samples will increase as more data and the bio-samples become available for access by researchers. Depending upon the number of access requests received we will consider either increasing the size of the DSAC or increasing the number of meetings per year. Presently the DataPreview is only available to view summary information from the baseline CLSA Tracking but over time will expand to incorporate the meta data for all aspects of the CLSA Comprehensive. We will also develop a facility for approved users to access the data set directly from DataPreview upon receipt of a unique password.

Challenges and Risk mitigation strategies

Participant retention: As noted, attrition and losses to follow-up pose a challenge to any longitudinal cohort on aging. Mitigation of risk involves the implementation of mechanisms that support high quality participant engagement in an ongoing manner. In addition to the MCQ interview, we will continue to explore opportunities to engage with participants. Contrary to our initial expectations, the majority of participants value the opportunity to stay actively connected to the study over and above their commitment to participate in the data collection. As is explored in the Communications section an

increasing number of participants seek to stay connected electronically via use of the website, twitter, You Tube, and email. Local events on health and aging that have been sponsored by the CLSA have also been attended by and received positively by CLSA participants. Increased visibility of the study over the next funding period, through mechanisms such as public events, media publicity, and partnerships with advocacy groups such as CARP not only serves to reinforce the importance of the study, but also instills a sense of pride in the participants themselves.

Use of the data by the research community: The CLSA will only fully realize its potential when the larger research community actively utilizes it. During the first follow-up the first release of both the Tracking and Comprehensive data and samples will occur. Despite being cross-sectional, the depth and breadth of the information available will be of a magnitude unprecedented in Canada to date. Key strategies to increase awareness among the research community include an active presence at national and international conferences such as the Canadian Association of Gerontology (CAG) and the Geriatrics Society of America (GSA); the engagement of graduate students and postdoctoral fellows and the implementation of CLSA webinars that address methodological and substantive uses of the data. Details of the release will be prominent on the CLSA website; DataPreview will provide researchers with the information and tools they need to make a data access request. However, key funding initiatives are required in order to maximize the use of the data. We will work with key funding bodies, including CIHR, to solicit strategic funding calls that support the use of CLSA data.

Aim 4: To describe the second 3-year follow-up (2018-2021).

As we begin to prepare for the second 3-year follow-up, we will have learned many important lessons during the first follow-up. We will know what worked well and what did not at the first follow-up and will modify and adapt processes considering these lessons. During the second follow-up we will, maintain, the CLSA principles employed at baseline that have served the CLSA well. We will strategize to develop new content, conduct pilot studies, support the coordinated ethics process, and to address the growing challenge of cognitive impairment, mobility impairment, and sensory impairment and proxy respondents. We will have experience with linkage to databases and the implementation of decedent questionnaires and will have worked out successful tracing strategies. We will fine-tune our in-home physical assessments as the cohort ages and more participants are unable to travel to their local DCS. The following activities will occur during the second follow-up 2018-2021.

- Second follow-up for the CLSA Tracking participants April 2018 - March 2020
- Second follow-up for the CLSA Comprehensive participants June 2018 - May 2021
- Third telephone administered maintaining contact interview for 50,000 participants will begin in this 3-year period (November 2019) and projected to end in May 2023
- Repeat analysis of biological samples collected during the first follow-up. These analyses will be done between 2018 and 2021.

It should be noted that this period of data collection exceeds the five-year funding window, however we have included the full three-year period for the second follow-up for clarity.

While it is not possible at the present time to specify the exact nature of the changes to be implemented in the second follow-up, the majority of structures and processes in place for the planning and implementation of the first follow-up will be utilized in an ongoing fashion. New science and novel study elements will continue to be explored. Additional elements proposed for the core will require the initiation of sub-studies to pilot the content and procedures prior to implementation. Consideration will also be given to modifications and adaptations that will not only create efficiencies, but will enhance the quality of the platform. For example, new technologies are likely to be available to enhance data collection, especially with respect to software and hardware, biospecimens processing and storage protocols. Data collection protocols and associated SOPs, training and quality systems will be adapted to reflect changes made.

Timing for the development of a more detailed plan for the second follow-up wave will coincide with the proposed interim review by the CIHR, which we anticipate to be scheduled for midway through the upcoming funding period. The interim review panel established by the CIHR will evaluate the second follow-up protocol. The primary role of the working groups during the second follow-up will to evaluate new scientific evidence and incorporate new scientific elements into the CLSA as feasible; and to develop pilot sub-studies and/or validation studies to test the performance of new measures. As we engage in new science, it is anticipated that we will also bring in new expertise to the working groups and perhaps modify the slate of working groups to reflect ongoing needs. We expect the replenishment of working group members to occur over time and this has been planned by including a mix of post-doctoral fellows, junior, mid-career, and senior researchers in each of the working groups.

Over the period spanning the second follow-up, we anticipate losses to the cohort of 8 to 10% at the main follow-up and 4 to 5% at the MCQ since last follow-up because of deaths, withdrawals, and losses to follow-up. These figures are based on our current experience with the baseline MCQ and the experience of other cohorts like NPHS in Canada.[28] Similar to first follow-up, retention strategies will be employed to keep the withdrawals and losses to a minimum. Ongoing monitoring will be in place to assess projected versus actual attrition over time and the impact on event numbers for key outcomes. Patterns and reasons for attrition of participants will also be assessed, as attrition for systematic reasons may result in subsequent data collection phases becoming increasingly based on nonrandom samples. In the event that the numbers deviate substantially from initial projections or demonstrate evidence of excessive bias, the methodological working group will consider statistical strategies for managing addressing bias and strategies for maintaining study numbers, including consideration of the replenishment of losses, or the introduction of a panel design. Recommendations to alter the study design will be assessed by the SMT and the International Scientific Advisory Committee, and will be presented for approval at the CIHR interim review of the study. Attrition will also have an impact on site budgets and staffing, and will likely result in procedural changes to reflect the decreased number of study participants under observation. For example, it may mean reduced hours of operation and a greater reliance on part time staff. It is conceivable, though, that increasing disability amongst some participants may result in longer DCS visits and longer in-home interviews to maximize data collection (as long as these are acceptable to participants). Ongoing monitoring of methodological and procedural aspects of the study will allow for timely intervention as required.

Adaptations, Accommodations

As CLSA participants age (by the second follow-up participants will be in the age range 51 to 91 years), strategies for accommodations will continue to evolve and protocols for an increasing number of scenarios requiring accommodations will be developed. A key accommodation that will be implemented for DCS participants is the possibility to be followed by phone and we will investigate other modalities to maintain contact and communicate with participants. This would allow for migration beyond the study site, and could be used, for example, with participants who are bedridden. It is anticipated that over time, new technologies will be developed, and new modes of data collection will be feasible, acceptable, and cost effective. For example, the administration of questionnaires over the telephone using an interactive voice response system is currently being explored. Additional approaches such as the use of self-administered questionnaires over the web, on portable hand-held devices, or via touch screen monitors may be fruitful avenues to pursue over time. In each case, this would have to be researched and pilot tested prior to implementation.

Ethics

We anticipate that the coordinated ethics process will continue and that all sites will be participating fully. Annual amendments will reflect any changes made to the study content, procedures, and participant interactions such as scripts and communications materials. The introduction of new science into the CLSA will require the consideration of re-consent. The re-consent process will be vetted with

the ELSI Advisory Committee and institutional REBs. In the event that substantial changes are made to the data being collected or the method of collection, study participants will be asked to provide signed re-consent.

Ethical, legal, and social issues

To date the ELSI Committee has been instrumental in providing advice on issues directly related to the conduct of the CLSA. Going forward continued guidance and advice will be needed as the cohort ages and as the platform is used by more researchers and linkage with administrative and other databases is part of the study design.

Biomarkers

Biomarker analysis similar to that proposed in Aim 2 will be repeated to create a unique resource that allows researchers to understand how biomarkers change as people age and how they are related to health and the trajectories of healthy aging. Specifically, we anticipate that the currently proposed clinical chemistry and epigenetic biomarkers in Aim 2 will be repeated over time, and this phase of the biomarker study will use samples from follow-up two. For genotyping, we propose to complete additional 10,000 participants from baseline sample collection to increase the genotyping sample size to 20,000. These large numbers will allow us to examine potential gene-gene and gene-environment interactions for common diseases. However, the final protocol for the analysis of the follow-up one sample will go through same level of process as outlined in the Aim 2.

Aim 5 - Governance, Management Structure, and Business Model

The governance and management structure envisioned and laid out at the CLSA implementation required a carefully crafted plan to ensure scientific excellence, and the long-term sustainability of the project. The CLSA governance structure is designed to provide robust management flexible enough for modification and growth over time and facile management of scientific and succession strategies, accommodating future extensions of the project and the incorporation of additional funders and stakeholders.The management structure (see Appendix 14) is integrated within the governance framework to ensure that the scientific vision of the CLSA is achieved. The science of the CLSA and its supporting infrastructure is administered though the Scientific Management Team (SMT), the Operations Committee (OC), and the Data and Sample Access Committee (DSAC).

The SMT is the principal CLSA governing body and is supported in its work by the CLSA Advisory Council (AC) and the International Scientific Advisory Board (ISAB). The sub-committees of the OC include a Knowledge Translation and Communication Committee (KTCC) and a Training and Research Capacity Committee (TRCC). External oversight for the CLSA is provided by the CIHR. The CIHR Advisory Committee on Ethical, Legal, and Social Issues (ELSI) provides guidance and critical advice to the CLSA on Ethical, Legal, and Social Issues. The explicit and transparent governance structure with external oversight has been viewed as an important facilitator for the CLSA team to access provincial health care databases for sampling purposes and in the future as we begin to link data with healthcare administrative databases. The CLSA governance structure is shown in Appendix 15. The working groups, while not part of the governance structure, play an important role in the creation of the scientific content of the CLSA and are ambassadors for promoting the CLSA in the scientific and policy communities.

As the CLSA platform matures, strategies for the dissemination of data, biospecimenss, and research results and a business model must be in place to meet the needs of end users (e.g., the public, health service providers, managers, researchers, policymakers, and private sector stakeholders). The operational leadership for partnership and business development is executed through the CLSA National Manager.

The knowledge translation and communication aspects of the CLSA also play a critical role in the retention of CLSA participants. From our pilot work, we know that participants want to hear about study results and how their personal investment is resulting in scientific evidence that may help people in

Canada and elsewhere. It is essential that communities involved in the development of public policy for the aging population are supported in the interpretation and use of research results. The KTCC is the primary body responsible for initiating and facilitating knowledge translation and communications activities that support the objectives of the CLSA.

Lead PI, Dr. Parminder Raina (McMaster University), and two co-PIs, Drs. Christina Wolfson (McGill University) and Susan Kirkland (Dalhousie University), direct the CLSA team. The CLSA team includes researchers who lead the CLSA enabling units (Data Collection Sites, Computer Assisted Telephone Interview Sites, Statistical Analysis Centre, Genetics and Epigenetics Centre and Biorepository and Bioanalysis Centre) and/or are members of the working groups or support CLSA activities as collaborators (Table of Expertise). In a 20-year study succession, planning is vital and the TRCC plays an important role in this domain. The TRCC provides advice to the SMT on education, research capacity, and mentorship activities that support the objectives of the CLSA and will set the stage for succession planning

Positioning the CLSA to Address New Opportunities and Embrace New Scientific Collaborations

The CLSA core research team is a dynamic and highly productive group of national and international leaders in the field of aging who all have ongoing collaborations with national and international research teams and these collaborations will be further enhance the positioning of the CLSA platform. The lead and co-principal investigators have nurtured strategic collaborations and associations with national and international researchers These collaborations will achieve three major objectives: 1) the exchange of techniques, skills and expertise relevant to the study of aging in Canada; 2) enrichment of the CLSA platform, the enhancement and advancement of opportunities for scientific gains to be made, particularly with respect to areas which require multiple cohorts from many countries to conduct comparative analysis or require large sample size to the study of gene-environment interactions; and 3) the sharing of the design, conduct, content or study measures with major studies in anticipation of harmonizing information to allow for international comparisons. For example at national level, the CLSA leadership has been actively engaged with the research community to enrich the CLSA platform by identifying core CLSA sub-studies that could be funded from external sources.. Our process to identify key sub-studies will include suggestions from the research community in between major waves. These topics will be discussed with members of the working groups, the International Scientific Advisory Board, and specific input will be gathered from experts in each of the identified areas. In addition, we will consult with ELSI committee to ensure that there are no ethical legal and societal implications of the proposed sub-study. This process is implemented to ensure that the participants are not unduly burdened by the sub-studies and that the CLSA is able to accommodate these studies without compromising the core data collection. However, we will also consider sub-studies that enrich the CLSA platform not through the collection of primary data but by linkage to existing data or registries. We have used this process for the first follow-up for a proposed core sub-study that will collect new brain imaging data on a sub-set of CLSA participants to advance our fundamental knowledge regarding the neural basis of successful cognitive aging. CLSA investigators Drs. Liu-Ambrose and Smith formed a team with researchers outside the CLSA network to design a project called CLSA-BRAIN, which was recently submitted to the CIHR open competition. If funded, it will be implemented at the first follow-up of the CLSA.

The CLSA leadership has also been actively engaged in developing partnerships with national and international collaborators to increase the visibility of the CLSA. A major advantage of these collaborations is that if successful, they bring to the CLSA resources to analyse data and/or enrich the CLSA core with additional data or biomarkers. For example, the vision of the Canadian Consortium on Neurodegeneration in Aging (CCNA) is to create research teams to conduct transformative research to advance understanding of the biology, natural history, clinical presentation and management of Alzheimer’ s disease (AD) and other neurodegenerative disease (NDD). This will be achieved through

the organization of shared clinical and neuropsychological assessment tools, neuropathology protocols, imagining protocols, database, and clinical trials design across the country. The leadership of the CCNA and CLSA worked together at the CCNA application stage to review areas of communality across the two projects. The CCNA has now been funded and we have created a CLSA-CCNA liaison committee with a mandate to identify key intersections between the CCNA and CLSA and explore possible avenues of collaboration. Work is ongoing to harmonize the cognitive measures used in the CLSA with those proposed by CCNA. The CCNA leads are also discussing the use of the CLSA BBC as a central storage venue for the bio-samples collected on their clinical cohort.

One of the priorities of the CLSA leadership is to create opportunities through collaboration to further enrich the core CLSA platform, and one such collaboration with Health Canada has resulted in developing a database using CLSA participant postal codes to determine their exposure to ambient air pollution data. The air pollution data from NASA satellite data and fixed sentinel air monitoring systems across Canada will be used to create this database. The project is funded by Health Canada through an internal grant competition to Dr. Robert Dales. These data will be geocoded and will become part of the CLSA core data set at baseline and the aim is to transform this project to include longitudinal data to be linked to the CLSA primary database. Other similar collaborations are established for the first follow-up with PHAC for child maltreatment and elder abuse and with the Ontario Ministry of Transportation for aging and changes in driving behaviour

In the past two years, six applications have been submitted to the CLSA Data and Sample Access Committee. 5 of the 6 have been reviewed and 3 of 5 were approved. The 6th application was recently submitted and will be reviewed by the DSAC at their upcoming meeting in July 2014. Table 18 lists the applications submitted to DSAC to date. In addition, the CLSA leadership have written 8 letters of support to accompany applications for operating grants; planning grants; and Letters of Intent for Team grants. The areas of research include epigenetics, HIV in older age; the built environment and aging; exposure to ambient air pollution and neurological health; and cognition. While some of these applications are still under review, others have been funded and are included in Table 19.

The CLSA team has been active in forming international partnerships to explore the harmonization of the CLSA data with international cohorts to position CLSA as an international player and use collaborations to further enrich the scientific and infrastructure value of the CLSA. For example, we have been involved in several European Union grant applications to pursue cross-national collaborations. Recently three letters of Intent submitted to Horizon 2020 were approved by the EU to move to the second stage of full proposal submission. The CLSA is a major contributor in each of these LOIs for its depth and breadth of data to address many research questions that were being pursued by the research teams. For example, one team proposes to use CLSA biological resources along with clinical data to develop and validate diagnostic tools for the prognosis of healthy ageing (BIO-AGE: PI: O. Rooyackers, Co-Is: L. Good, P. Raina, et al.). The second team is proposing to study multi-morbidity and ageing through harmonization of several cohorts including EPIC and CLSA (PATH-AGE: PI: I. Romieu Co-Is P. Raina, et al.). The third project concerns healthy aging in European and Canadian Cities (EURBANAGE) and will explore environmental, behavioural, psychosocial and biological pathways of aging in an urban context. (PI: F. van Lenthe Co-Is P. Raina, et al.).

Succession Planning for SMT, DCS Leads, and Working Group Leads

The three co-PIs along with the majority of the key co-investigators have been part of the CLSA team since early in 2002. This is major achievement in research, where many teams falter in the face of funding issues and scientific differences. That being said, the leadership team who took on the task of developing and launching the CLSA is itself “aging” and succession planning is essential to the long-term sustainability of the CLSA. Succession planning for the local site investigators at the Data Collection Sites is assured through the recruitment of co-leads at all enabling units. The leadership team has also been working with their local institutions seeking opportunities to identify researchers who

could be the future leaders of the CLSA. For example, at McMaster University, the CLSA lead institution, the lead PI in collaboration with the Chair of the Department of Clinical Epidemiology and Biostatistics has begun a process of identifying individuals who could potentially be mentored to take on a leadership role in the CLSA and eventually be selected by the CLSA SMT to become the lead Principal Investigator. The selection of this individual will also require agreement from the CLSA Operations Committee. While the CLSA lead PI could theoretically be located at another institution, since McMaster is the lead institution for the CLSA and houses not only the BBC but also the National Coordinating Centre the amount of organization and setup that would be required for another institution to take on the lead makes this unlikely to be feasible and indeed potentially damaging to the timelines of the CLSA.

We have also created a training and capacity-building plan to help ensure the long-term sustainability of the CLSA. For example, the TRCC has identified the need for: 1) Raising awareness of the potential opportunities that the CLSA provides for trainees, emerging and established researchers; 2) Informing institutional programs in aging and health about the potential opportunities for research and training within the CLSA; 3) Creating mentorship mechanisms to create future leaders of the CLSA; 4) Promoting skills training and career building relevant to cross-disciplinary, longitudinal research; 5) Developing training activities and tools; and 6) Seeking, and advocating for, funding mechanisms to support a CLSA training and research capacity building initiative (Appendix 16)

Feasibility of the Renewal Plan

With the experience of the implementation of the CLSA and the establishment of processes, we are confident we can meet the goals laid out in this renewal application. The infrastructure is complete and functioning well and the operational aspects are now firmly in place. The coordinated REB process and the ELSI committee have been very active to anticipate potential ethical issues and have provided advice on how to deal with them. For the content of the first follow-up, the working groups have collaborated to identify and discuss new content to ensure that all interest areas are represented. The addition of the biomarker analysis significantly enhances the value of the platform. Further, when the first follow-up commences the data and sample access process will be finely tuned to aid in the further development of research collaborations and partnerships. Data stewards have been engaged from the start of the CLSA and have been reengaged to start discussions with the provinces and this will become important for linking to health care registries, an appealing feature for many partners and users of the CLSA data. We will continue to develop these relationships to facilitate this work.

An important challenge facing all researchers in Canada and beyond is the increasing costs of research because of the increases in salary fringe benefits at some institutions. The CLSA is anticipating such challenges in the future and is developing strategies to manage them. There are also a number of new activities in addition to the follow-up assessments that will require resources, such as data and biospecimens release and associated operational costs. Strategies to manage these are being implemented. For example additional resources are now provided in the SAC and BBC budgets, these costs will be in part covered by access fees and in part are covered from other areas in the budget where the needs are reduced or eliminated (e.g., recruitment) as well as from partnership funding if feasible.

Data collected as part of the platform often require additional analyses and standardization prior to being available for dissemination. One example is the scoring of the cognitive tests. The cognitive test responses of all 50,000 participants are on audio recordings that need to be scored centrally. The CLSA also stores significant complex images, such as Dual Energy X-ray Absorptiometry images, medial intima thickness of the carotid artery and retinal images. These need to be standardized and converted using specialized software or software developed in house prior to release. Importantly, for genetic and epigenetic analysis, DNA is collected but not extracted. The CLSA is also ensuring that along with data and biospecimens release, extracted DNA is available. While these costs were not initially built into the CLSA platform, we anticipate that we will be able to manage these costs within the proposed budget.

The Sustainability of the CLSA Platform

The CLSA leadership has actively formed partnerships and collaborations to ensure the short and long-term sustainability of the platform. Partners have demonstrated strong interest through significant contributions to the operations of the CLSA platform for the implementation phase (Table 20). Most partnerships to date are around the use of alphanumeric data. We anticipate increased interested in our BBC facilities and the infrastructure and design of this facility. With the expertise of the BBC Director and staff, we plan to provide consulting services on biospecimens collection, processing and management of the samples as has already been demonstrated with the CCNA, Other discussions are underway with potential partners that hope to learn from and in some cases emulate the state of the art Bio Bank facility and IT infrastructure management of the CLSA

These partnerships not only enhance the CLSA scientific capabilities but also provide additional funding for the CLSA. The CLSA has developed costing models for these partnerships based on recovery of direct (materials) and indirect (personnel, equipment, other costs such as maintenance, electricity, insurance etc.) costs plus as a percentage overhead cost to cover operational expenses of the CLSA. This also includes a fee structure that is different between academic and for-profit use. The costing models used for the various partnerships are currently based on models such as described by Gonzales-Sanchez, et al. (2013)[219] and De Sousa, et al. (2009).[220]

The CLSA is developing a costing model for the Bio Bank for a range of services, including biospecimens collection and processing, shipping, receipt, storage, retrieval and distribution of biospecimens. These fees will be based on the same principles. The SAC is also developing a Business Plan to expand its activities to include a statistical consultation service for the CLSA team and for approved users of the data and/or samples from the platform. The aim of the CLSA costing model is to ensure that fees for data and sample access and other services such as IT infrastructure, statistical consultation BBC-related services will generate resources that will not only recover costs but also contribute substantially to support the operations of the CLSA.

From a sustainability point of view our partnership development has been successful in the implementation phase but also for the first follow-up (Table 21), and based on our current established partnerships for the first follow-up, we have already been able to raise approx. $7,000,000 in both in-kind and in cash contributions towards expected match by the CIHR.

Innovative partnerships and collaborations

Other than exploring partnerships with individual entities, the CLSA has also worked with umbrella organizations including the Health Charities Coalition of Canada (HCCC), Neurological Health Charities Canada (NHCC), Canada's Research-Based Pharmaceutical Companies (Rx&D) and others to approach multiple parties simultaneously. The model is that members of such organizations contribute to the CLSA data collection and through membership in the consortium; the contributions for each individual member are lower. Each member can be allocated a research area that is relevant to them exclusively. The foundation has been laid for such models and will be further explored once data are available. The CLSA has also laid the foundation for discussions with health charities, to design funding opportunities to use the CLSA platform.

Partnerships that provide funding to the platform in cash and in-kind are invaluable, but the CLSA also continues to seek and develop partnerships with organizations that can aid in the awareness and promotion of the CLSA as is outlined in Table 21 and in the support letters.

The CLSA is unique due to its infrastructure funded by the Canada Foundation for Innovation. We are actively exploring how our infrastructure can be of benefit to other researchers and organizations. Several academic collaborations are in place using the CLSA infrastructure at our data collection sites and preliminary discussions have been held with other researchers and private industry for using the CLSA BBC infrastructure for biospecimens storage. The infrastructure aspect of the CLSA that has received the most attention is our Data management and IT infrastructure. The CLSA has received

several requests from other researchers and research platforms to learn about the CLSA data management set up as well as looking for IT and data management services. As the CLSA moves into the first follow-up, we envision the development of a software and services suite for large cohorts and research programs that the CLSA can benefit from.

As described in Aim 2, the Biology Working Group together with the Director of the BBC (Dr. Cynthia Balion) and the PIs have prepared a biomarker analysis proposal. Under the leadership of Dr. Balion, the CLSA has also achieved a significant partnership with Calgary Laboratory Services (CLS). Through the partnership that has provided over $1,600,000 cash in-kind contributions, the core biomarker analysis on all 30,000 participants from baseline will be completed before the end of the first follow-up. CLS is a major player in clinical chemistry in Canada and worldwide and their scientific team will be of great value to the CLSA.

Challenges and Risks

Developing partnerships has to be balanced with feasibility within the CLSA. Cash contributors to the CLSA are most often interested in the collection of new data on the CLSA participants. In some instances, the additional data collection fits well within the CLSA framework but in other cases, it may not. These are delicate discussions as the CLSA expounds on the potential of the platform and ensuring the integrity of the CLSA platform. Other aspects to consider are those partnerships that may be provocative (e.g., insurance companies). Further, new research opportunities presented by partners that require the addition of content to the platform or by sub studies on a subset of participants will need to be carefully evaluated to ensure that they fit within the CLSA mandate, will not overburden CLSA participants, and are feasible with resources and budgets available. Another issue is that funds may be made available for a one-time addition of content but not guaranteed for longitudinal reassessment. To ensure consistency in the approach to the inclusion of significant new components of data/sample collection in the CLSA, we have chosen a strategy that all proposals (e.g., addition of buccal swabs, brain imaging on a subset of CLSA participants) must not only be reviewed and approved by the PIs but must also be implemented (if approved and funded) as part of the CLSA data collection and not managed, for instance, at individual sites. In this way, we can ensure not only the rigour of the data collection but also maintain the confidentiality and security of participant information.

As the CLSA has carefully designed its data access policies and procedures, collaborating with large initiatives such as CCNA is not straightforward and our early work in this domain highlighted several challenges including those related to sharing data and/or biospecimens with initiatives using differing data access policies and procedures and with different needs. The CLSA is working on overcoming such challenges through collaborations and in this instance has formed a CLSA-CCNA liaison committee

Currently all initiatives for partnerships are reviewed by, and moved forwarded in collaboration with, the leadership team whereby the Advisory Council takes on the role of evaluating partnership priorities and/or reviewing proposed new partnerships to support the leadership team (SMT) with decisions of balancing the benefit to the CLSA platform with the required additional work and impact on the platform itself.

Overall, the challenge in partnership development for the CLSA is to balance the need for funds for the sustainability and enhancement of the CLSA with the overall vision of the CLSA and the principles that underpin the privileged relationship. With our governance and management structures as well as policies and procedures in place, the CLSA has successfully achieved this balance to date.

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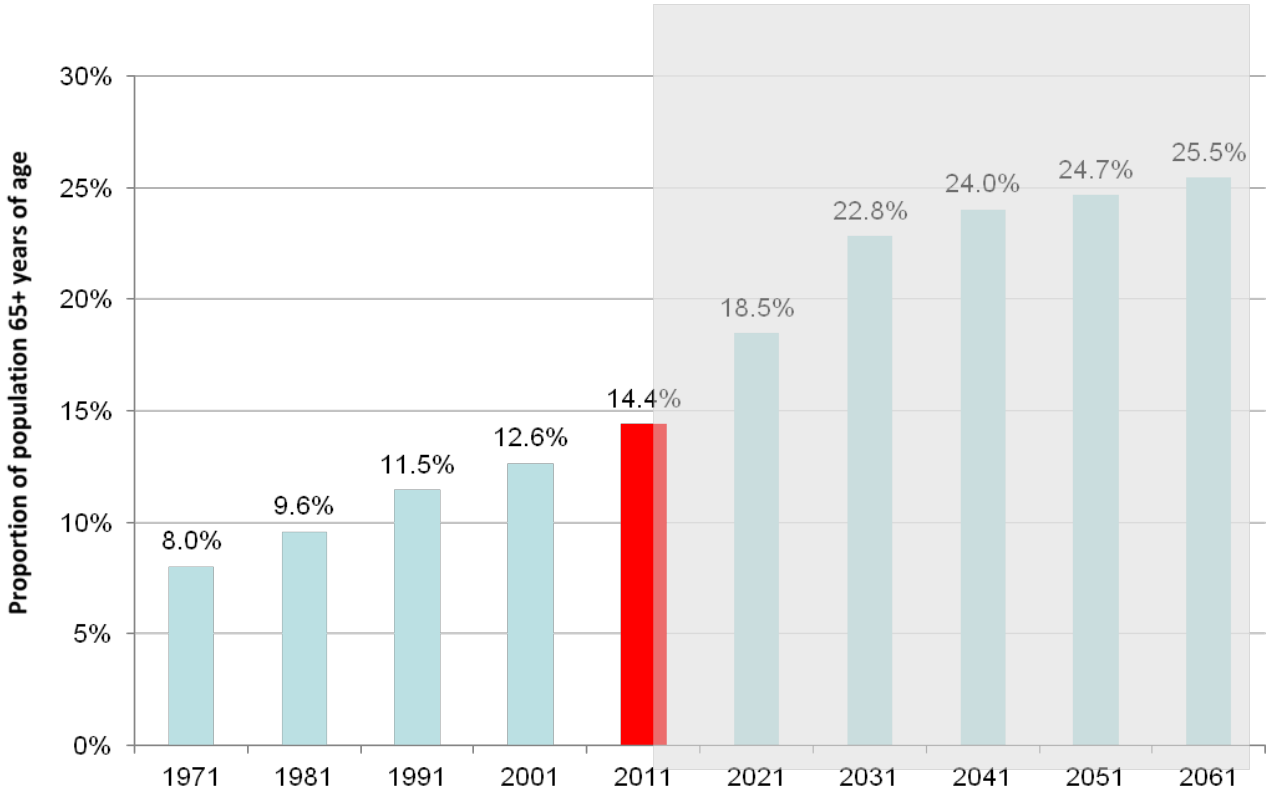
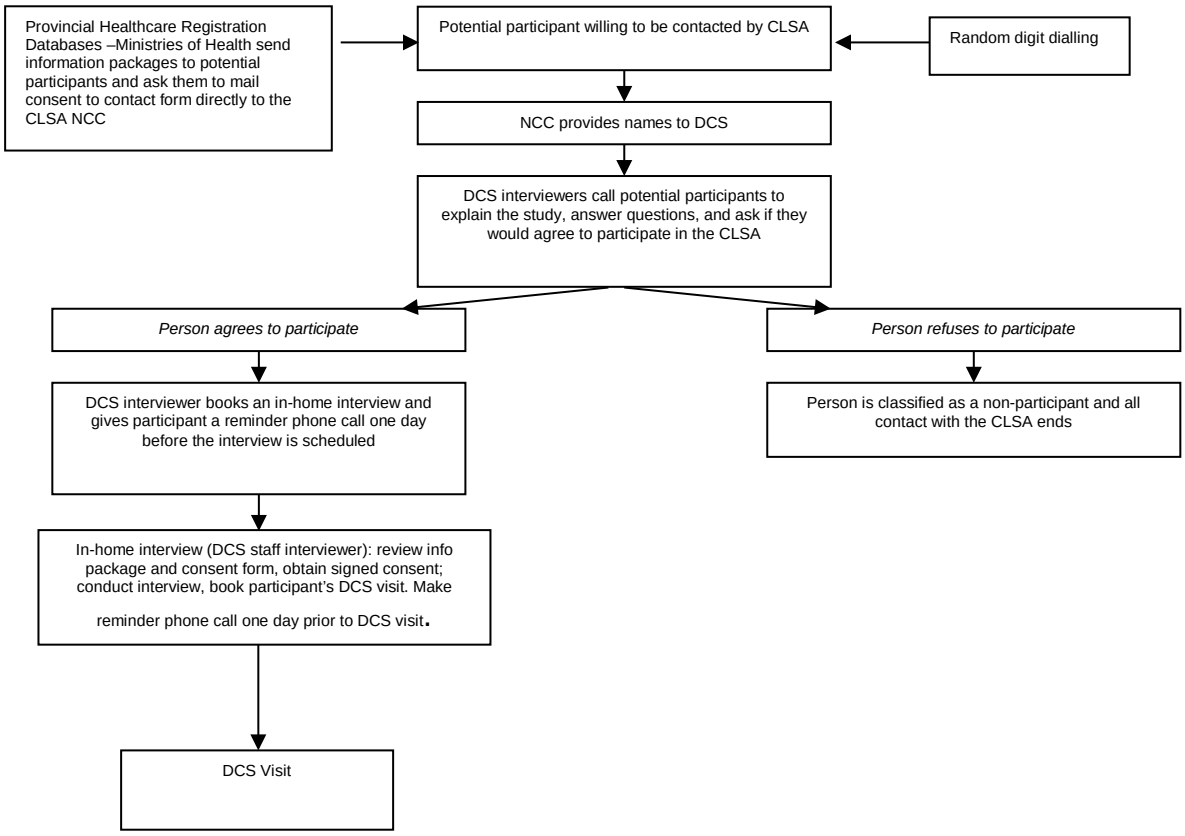
Figure 1: Population Aging

Population aging
65+ representing a larger proportion of population and growing



Source: Census 1971-2011 (projected estimates). Demography Division, Statistics Canada.

Figure 2: CLSA Comprehensive: Process for Contacting Potential CLSA Participants



clsa élcv
Canadian Longitudinal Study on Aging
Étude longitudinale canadienne sur le vieillissement

Figure 3: The Participant Flow through the DCS

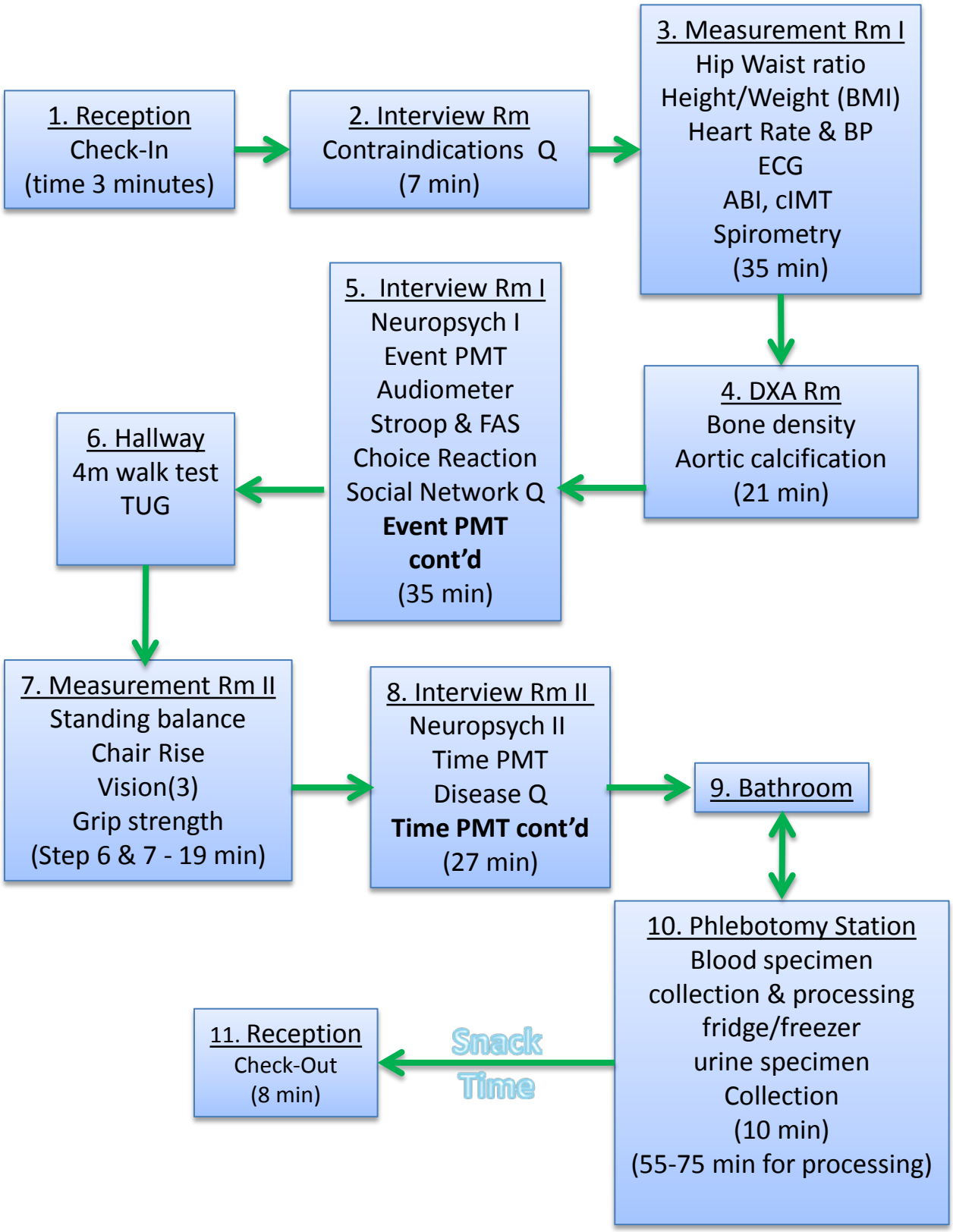


Figure 4: Infrastructure Supporting Research on Aging

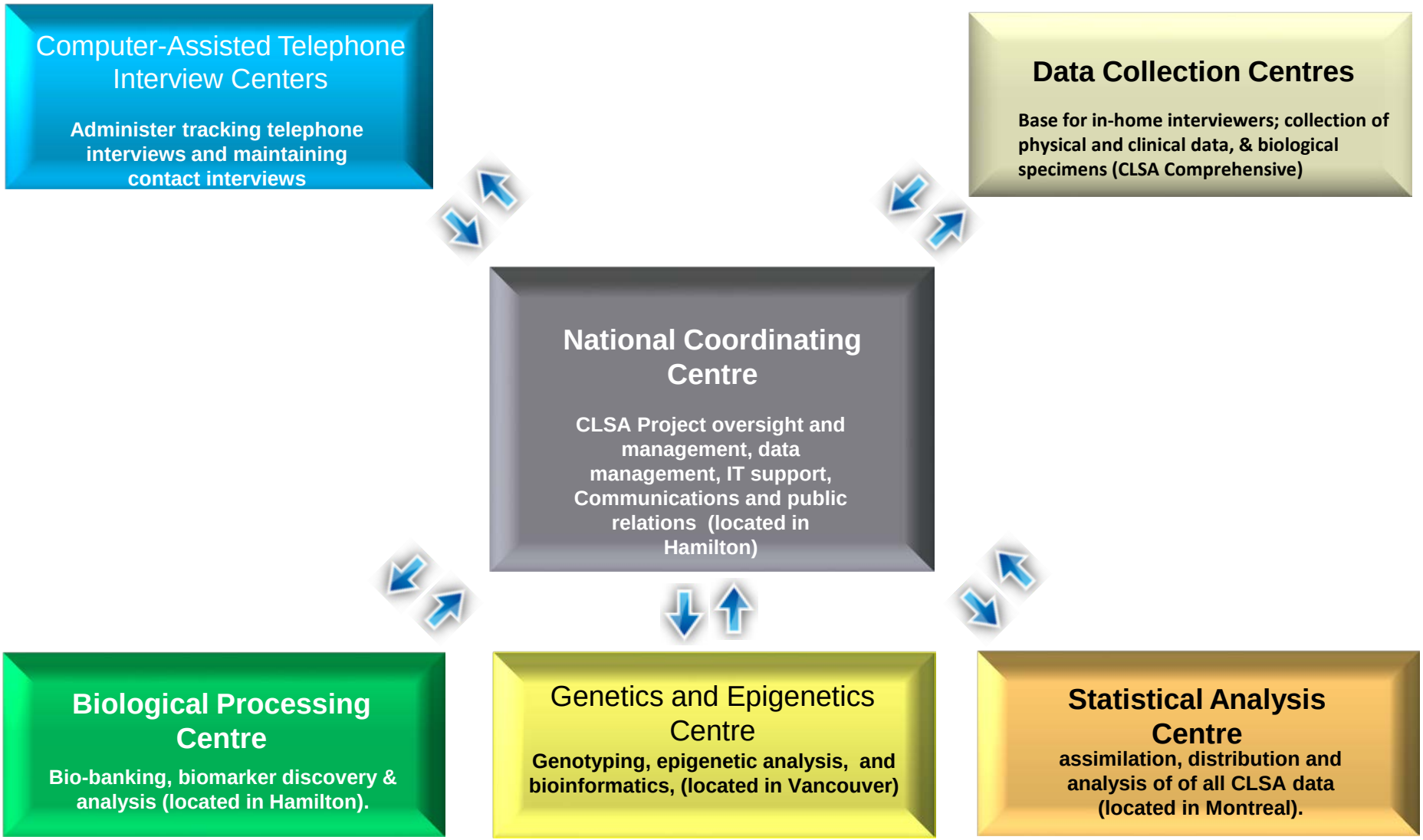


Figure 5: CLSA Quality System Organizational Structure

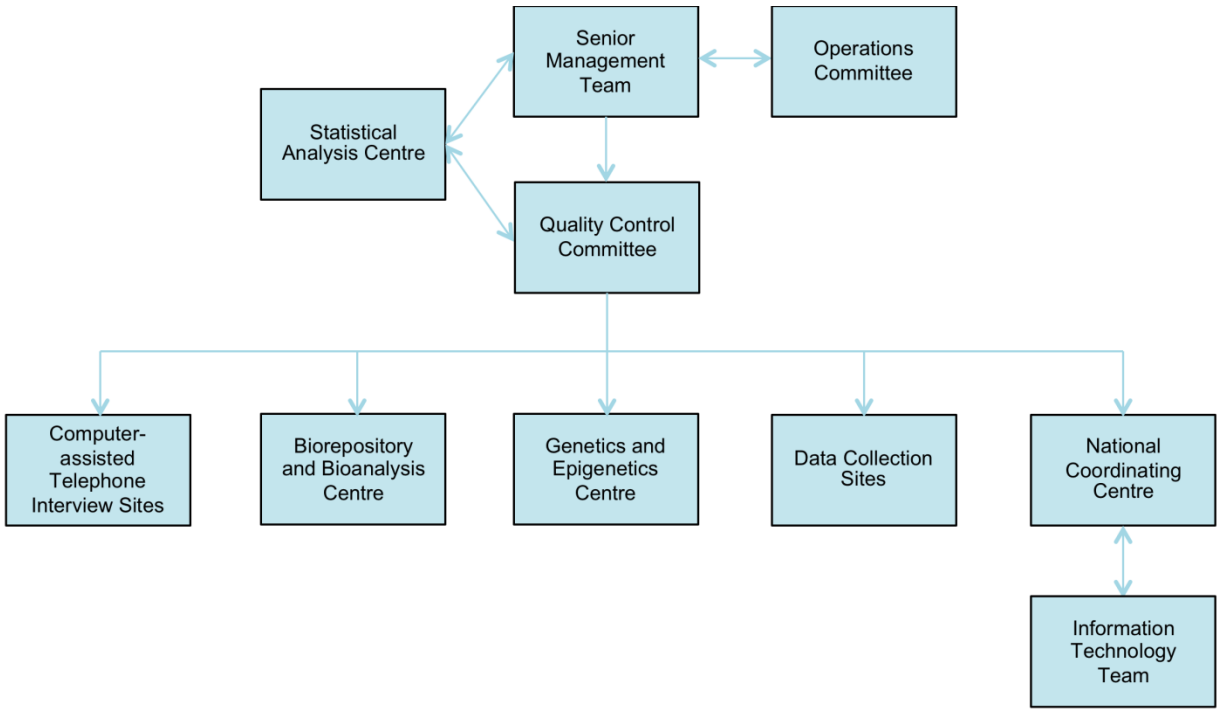


Figure 6 CLSA Quality System

Figure 7 : Process for data access

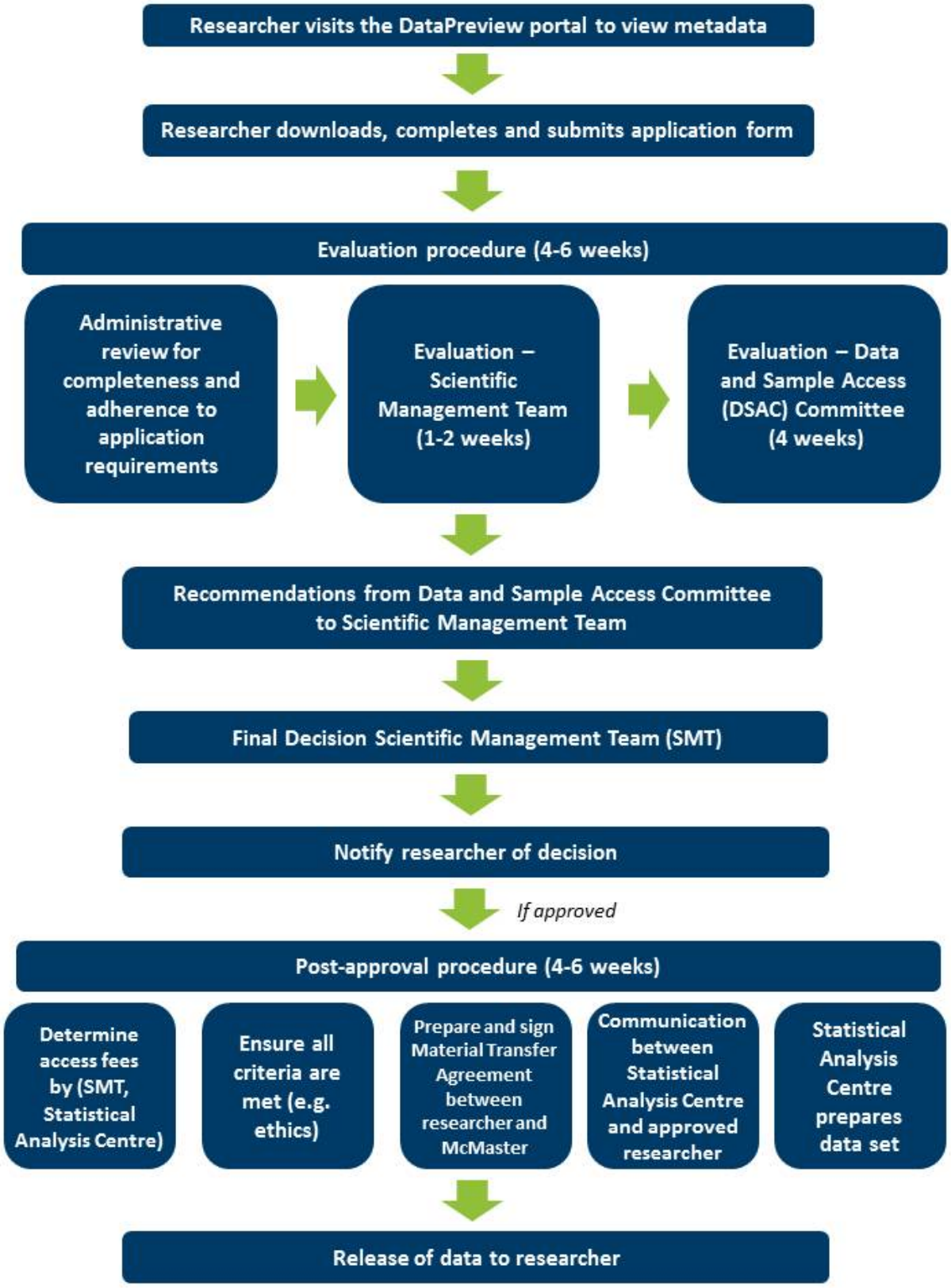
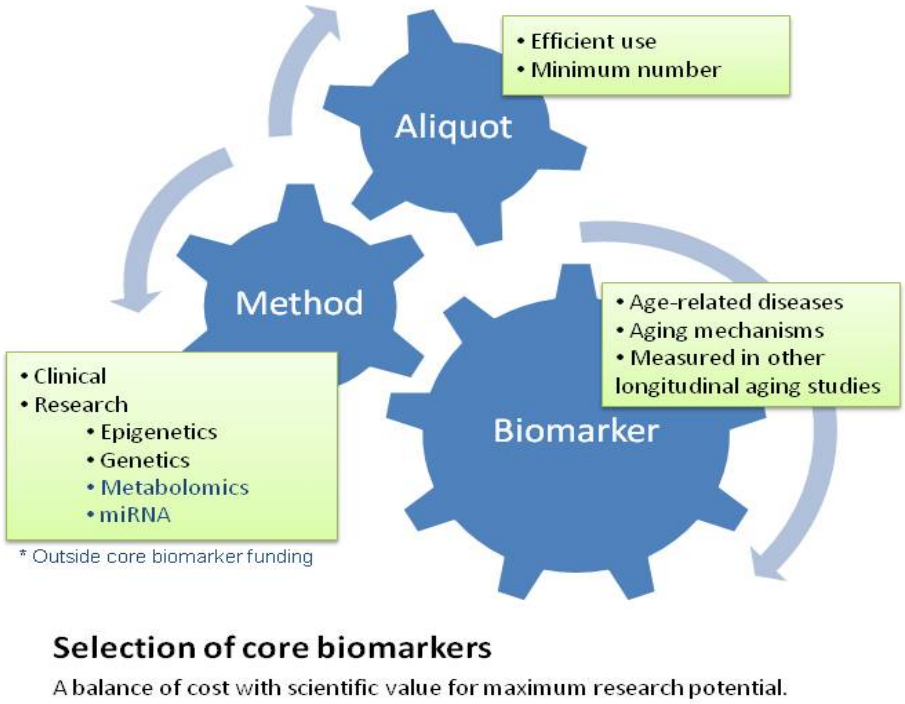


Figure 8: Conceptual Approach to the Selection of Core Biomarkers



Biology Working Group Biomarker Teams

The Biology Working Group was subdivided into teams of clinical chemistry (Drs. Balion, Chin, Sadrzadeh), genetics (Drs. Richard, Lathrop and Patterson) and epigenetics, mRNA and metabolomics (Drs. Kobor, Muti, and Ayotte) and charged with the development of the list of biological markers to be considered for analyses. Other members of the BWG were consulted regularly for their expertise in formulating the final set of core biomarkers for the CLSA include Drs. Jane Rylett and Helene Girouard.

Figure 9: Age trends in biochemical analytes

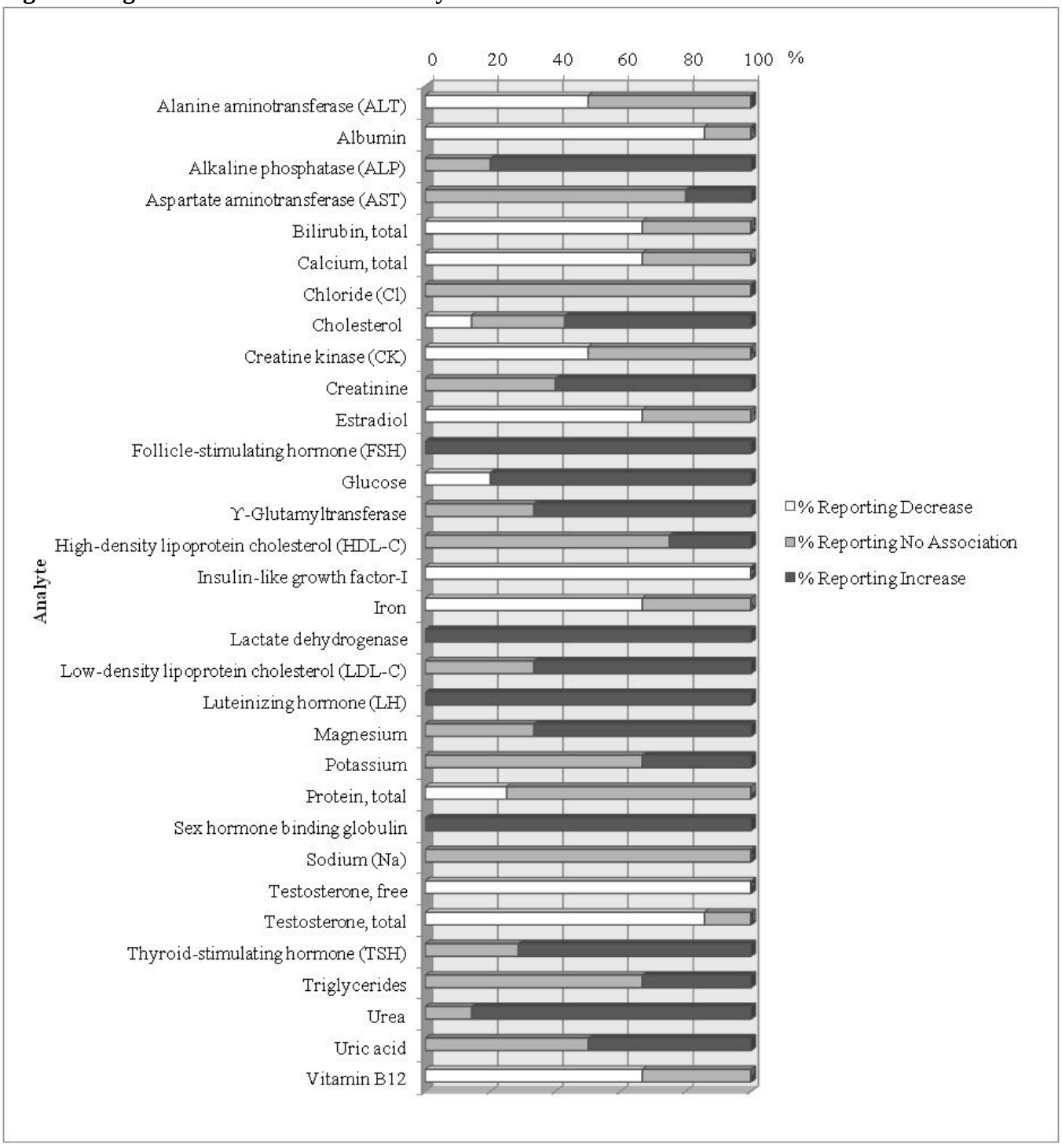


Table 1: Biological Samples Collected at Baseline

Type	Volume (mL)	Number	Total volume (mL)	Number of aliquots
1. Citrate				
3.2% buffered sodium citrate solution, 0.109 M				
Plasma	2.7	1	2.7	2
Plasma, platelet poor	2.7	1	2.7	2
2. Serum				
Spray coated silicone and micronized silica particles				
Serum	10	1	10	8
3. Heparin				
Lithium heparin, 90 USP				
Plasma	6	1	6	6
4. EDTA				
Spray coated K_2 EDTA, 10.8 mg				
Plasma	3	1	3	0[1]
Plasma	6	3	18	6
Buffy coat			(2)	4
Whole blood			(1)	2
Whole blood			(1)	(96)[2]
5. ACD				
Trisodium citrate, 13.2g/L; citric acid, 4.8 g/L; and dextrose 14.7 g/L, 0.4 mL				
Whole blood	3	1	3	2
6. CPT				
Sodium citrate 0.45 mL 0.1 M and Ficoll™ medium				
Mononuclear cells	8	1	8	6
Urine collection container				
Urine	60	1	2	4

Tubes are listed according to the order they will be drawn

[1] Baseline hematology tests performed at the DCS. No aliquots are stored.

[2] Collected only at first collection. Aliquots (10 μL) are stored in GenPlate microwells.

Table 2: CLSA Physical Function Measures at Baseline

Measure	CLSA Baseline	
	Comprehensive Face-to-Face (n=30,000)	Telephone Interview (n=20,000)
Lean Muscle Mass and Body Composition	PE	
Waist and Hip Circumference	PE	
Blood Pressure	PE	
Bone Density	PE	
Aortic Calcification	PE	
Lung Function	PE	
Electrocardiogram (ECG)	PE	
Heart Rate	PE	
Carotid Intima-media Thickness	PE	
Vision	PE and Q	Q
Hearing	PE and Q	Q
Weight and Height	PE	Q
Functional Status	PE	Q
Functional Performance (grip strength, time up & go, Balance, gait)	PE	
Basic Activities of Daily Living	Q	Q
Instrumental Activities of Daily Living	Q	Q
General Health	Q	Q
Life Space Index	Q	
Women's Health	Q	Q
Chronic Conditions	Q[1]	Q
Health Care Utilization	Q[3]	Q[3]
Medication Use	Q[2]	Q[3]
Dietary Supplement Use	Q[2,3]	Q[3]
Oral Health	Q[3]	Q[3]
Injury and Falls	Q	Q
Pain and Discomfort	Q[3]	Q[3]
Sleep	Q	

Q: measured by questionnaire (either telephone or face-to-face administration: 60 to 70 minutes)
PE: measure by physical examination at the data collection site
[1]The CLSA Comprehensive contains additional questions about chronic disease symptoms
[2]DIN information is recorded directly from prescription medications in the CLSA Comprehensive
[3]Measure included in Maintaining Contact Questionnaire only (Telephone administered 30 minutes long)

Table 3: CLSA Psychological Measures at CLSA Baseline

Measure	CLSA Baseline	
	Comprehensive (face-to-face) (n=30,000)	**Telephone Interview (n=20,000)**
Neuropsychological Exam		
Memory		
Rey Auditory Verbal Learning Test	Q	Q
Executive Function		
Mental Alternation Test	Q	Q
Prospective Memory Test	Q	
Stroop Neuropsychological Screening Test	Q	
Controlled Oral Word Association Test	Q	
Animal Naming	Q	Q
Psychomotor Speed		
Simple and Choice Reaction Times	T	
Mood and Psychopathology		
Depression	Q	Q
Life Satisfaction	Q	Q
Posttraumatic Stress disorder	Q	Q
Psychopathology	Q[1]	
Personality Traits	Q[1]	Q[1]

Q: measured by questionnaire (either telephone or face-to-face [comprehensive] administration).
T: measured using a performance test involving an interactive computer touch screen.
[1]: measure included in MCQ only.

Table 4: CLSA Social Measures at CLSA Baseline

Measure	CLSA Baseline	
	Comprehensive face-to-face (n=30,000)	Telephone Interview (n=20,000)
Social Networks	Q	Q
Online Social Networking	Q[1]	Q[1]
Social Support Availability	Q	Q
Social Participation	Q	Q
Care Receiving 1/ Formal Care	Q	Q
Care Receiving 2/ Informal Care	Q	Q
Care Giving	Q	Q
Retirement Status	Q[2]	Q
Pre-Retirement Labour Force Participation	Q[2]	Q
Labour Force	Q[2]	Q
Retirement Planning	Q[2]	Q
Social Inequality	Q[1]	Q[1]
Wealth	Q[1]	Q[1]
Transportation, Mobility, Migration	Q[1]	Q[1]
Built Environments	Q[1]	Q[1]

Q: measured by questionnaire (either telephone or face-to-face administration)
[1]Measure included in Maintaining Contact Questionnaire only
[2]The CLSA Comprehensive will include an abbreviated module

Table 5 – Overall Descriptive Statistics

Variable (category)	**All (n=42522)**		**Tracking (n=20928)**		**Comprehensive (n=21594)**	
	Count	**%**	**Count**	**%**	**Count**	**%**
Province						
Alberta	4067	9.6	2077	9.9	1990	9.2
British Columbia	7047	16.6	2577	12.3	4470	20.7
Manitoba	3550	8.4	1445	6.9	2105	9.7
New Brunswick	1232	2.9	1230	5.9	N/A	N/A
Newfoundland and Labrador	3043	7.2	1329	6.4	1714	7.9
Nova Scotia	3730	8.8	1551	7.4	2179	10.1
Ontario	9295	21.9	4672	22.4	4623	21.4
Prince Edward Island	1111	2.6	1110	5.3	N/A	N/A
Quebec	8058	19.0	3549	17.0	4509	20.9
Saskatchewan	1355	3.2	1355	6.5	N/A	N/A
Age (years)						
45-54	11300	26.6	5774	27.6	5526	25.6
55-64	13369	31.5	6485	31.0	6884	32.0
65-74	9804	23.1	4556	21.8	5248	24.4
75+	8001	18.8	4113	19.7	3888	18.0
Sex						
Male	20137	47.4	10228	48.9	9909	46.0
Female	22336	52.6	10700	51.1	11636	54.0
Education highest degree*						
Grade 8 or lower	878	2.1	524	2.5	354	1.6
Grade 9-10	1393	3.3	873	4.2	520	2.4
Grade 11-13	886	2.1	533	2.6	353	1.6
Secondary school	4930	11.6	2827	13.6	2103	9.8
Some post-secondary	2956	7.0	1589	7.6	1367	6.3
Trade certificate or diploma	4849	11.4	2541	12.2	2308	10.7
Community college, CEGEP	7623	18.0	3904	18.7	3719	17.3
University certificate	1823	4.3	851	4.1	972	4.5
Bachelor's degree	9045	21.3	4193	20.1	4852	22.5
University degree above bachelor	7041	16.6	2841	13.6	4200	19.5
Other postsecondary	965	2.3	168	0.8	797	3.7
Self-rated general health						
Excellent	8287	19.5	3942	18.9	4345	20.2
Very good	16773	39.5	8032	38.4	8741	40.6
Good	12497	29.5	6153	29.4	6344	29.5
Fair	3884	9.2	2171	10.4	1713	8.0
Poor	991	2.3	609	2.9	382	1.8
Total household income ($/yr)						
<20,000	2453	6.2	1315	6.7	1138	5.7
20,000-49,999	10384	26.2	5732	29.3	4652	23.3
50,000-99,000	14238	36.0	7135	36.4	7103	35.5
100,000-149,999	7091	17.9	3187	16.3	3904	19.5
>150,000	5418	13.7	2218	11.3	3200	16.0

Table 6a – Tracking Participants Only (Stratified by Sex)

Variable (category), stratified by sex	**Male (n=10228)**		**Female (n=10700)**	
	Count	**%**	**Count**	**%**
Province				
Alberta	1003	9.8	1074	10.1
British Columbia	1232	12.1	1345	12.6
Manitoba	702	6.9	743	7.0
New Brunswick	617	6.0	613	5.7
Newfoundland and Labrador	652	6.4	677	6.3
Nova Scotia	777	7.6	774	7.2
Ontario	2264	22.2	2408	22.5
Prince Edward Island	549	5.4	561	5.3
Quebec	1759	17.2	1790	16.8
Saskatchewan	656	6.4	699	6.5
Age (years)				
45-54	2777	27.2	2997	28.0
55-64	3147	30.8	3338	31.2
65-74	2251	22.0	2305	21.5
75+	2053	20.1	2060	19.3
Education highest degree				
Grade 8 or lower	286	2.8	238	2.2
Grade 9-10	428	4.2	445	4.2
Grade 11-13	250	2.5	283	2.7
Secondary school	1289	12.7	1538	14.4
Some post-secondary	765	7.5	824	7.7
Trade certificate or diploma	1611	15.8	930	8.7
Community college, CEGEP	1348	13.2	2556	24.0
University certificate	382	3.8	469	4.4
Bachelor’s degree	2062	20.2	2131	20.0
University degree above bachelor	1689	16.6	1152	10.8
Other postsecondary	74	0.7	94	0.9
Self-rated general health				
Excellent	1880	18.4	2062	19.3
Very good	3849	37.7	4183	39.1
Good	3128	30.6	3025	28.3
Fair	1074	10.5	1097	10.3
Poor	285	2.8	324	3.0
Total household income ($/yr)				
<20,000	456	4.7	859	8.8
20,000-49,999	2480	25.3	3252	33.2
50,000-99,999	3806	38.9	3329	34.0
100,000-149,999	1743	17.8	1444	14.7
>150,000	1302	13.3	916	9.3

Table 6b –Tracking Participants Only (Stratified by Age)

Variable (category), by age	**45-54 (n=5774)**		**55-64 (n=6485)**		**65-74 (n=4556)**		**75- (n=3888)**	
	Count	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Province								
Alberta	585	10.1	662	10.2	433	9.5	397	9.7
British Columbia	696	12.1	829	12.8	547	12.0	505	12.3
Manitoba	406	7.0	440	6.8	302	6.6	297	7.2
New Brunswick	337	5.8	373	5.8	274	6.0	246	6.0
Newfoundland & Labrador	374	6.5	396	6.1	296	6.5	263	6.4
Nova Scotia	420	7.3	481	7.4	354	7.8	296	7.2
Ontario	1267	22.0	1442	22.3	1030	22.7	933	22.7
Prince Edward Island	290	5.0	306	4.7	262	5.8	252	6.1
Quebec	1032	17.9	1115	17.2	750	16.5	652	15.9
Saskatchewan	362	6.3	432	6.7	298	6.6	263	6.4
Sex								
Male	2777	48.1	3147	48.5	2251	49.4	2053	49.9
Female	2997	51.9	3338	51.5	2305	50.6	2060	50.1
Education highest degree								
Grade 8 or lower	41	0.7	86	1.3	135	3.0	262	6.4
Grade 9-10	130	2.3	168	2.6	232	5.1	343	8.4
Grade 11-13	88	1.5	161	2.5	115	2.5	169	4.1
Secondary school	699	12.1	946	14.6	650	14.3	532	13.0
Some post-secondary	380	6.6	516	8.0	331	7.3	362	8.9
Trade certificate or diploma	706	12.3	784	12.1	580	12.8	471	11.5
Community college, CEGEP	1346	23.4	1248	19.3	727	16.0	583	14.3
University certificate	214	3.7	248	3.8	202	4.4	187	4.6
Bachelor’s degree	1379	23.9	1389	21.5	797	17.5	628	15.4
University above bachelor	739	12.8	864	13.4	732	16.1	506	12.4
Other postsecondary	40	0.7	48	0.7	42	0.9	38	0.9
Self-rated general health								
Excellent	1207	20.9	1196	18.5	848	18.6	691	16.8
Very good	2252	39.0	2519	38.9	1806	39.7	1455	35.5
Good	1662	28.8	1866	28.8	1320	29.0	1305	31.8
Fair	500	8.7	683	10.5	467	10.3	521	12.7
Poor	152	2.6	216	3.3	109	2.4	132	3.2
Total household inc ($/yr)								
<20,000	240	4.3	368	6.0	334	7.9	373	10.1
20,000-49,999	769	13.8	1522	24.8	1679	39.9	1762	47.8
50,000-99,999	1862	33.5	2462	40.2	1654	39.3	1157	31.4
100,000-149,999	1489	26.8	1066	17.4	361	8.6	271	7.3
>150,000	1199	21.6	712	11.6	182	4.3	125	3.4

Table 7a: Comprehensive Participants Only (Stratified by Sex)

Variable (category), stratified by Sex	**Male (n=9909)**		**Female (n=11636)**	
	Count	**%**	**Count**	**%**
Province				
Alberta	825	8.3	1157	9.9
British Columbia	2058	20.8	2406	20.7
Manitoba	936	9.4	1160	10.0
New Brunswick	N/A	N/A	N/A	N/A
Newfoundland and Labrador	733	7.4	978	8.4
Nova Scotia	966	9.7	1205	10.4
Ontario	2211	22.3	2404	20.7
Prince Edward Island	N/A	N/A	N/A	N/A
Quebec	2179	22.0	2323	20.0
Saskatchewan	0	0.0	0	0.0
Age (years)				
45-54	2357	23.8	3169	27.2
55-64	3193	32.2	3691	31.7
65-74	2476	25.0	2772	23.8
75+	1883	19.0	2004	17.2
Education highest degree*				
Grade 8 or lower	150	1.5	204	1.8
Grade 9-10	220	2.2	300	2.6
Grade 11-13	167	1.7	186	1.6
Secondary school	869	8.8	1234	10.6
Some post-secondary	619	6.3	748	6.4
Trade certificate or diploma	1229	12.4	1079	9.3
Community college, CEGEP	1268	12.8	2451	21.1
University certificate	391	4.0	581	5.0
Bachelor’s degree	2254	22.8	2598	22.4
University degree above bachelor	2343	23.7	1857	16.0
Other postsecondary	372	3.8	376	3.2
Self-rated general health				
Excellent	1943	19.6	2402	20.7
Very good	3900	39.4	4841	41.6
Good	3053	30.8	3291	28.3
Fair	820	8.3	893	7.7
Poor	182	1.8	200	1.7
Total household income ($/yr)				
<20,000	386	4.1	752	7.1
20,000-49,999	1769	18.9	2883	27.2
50,000-99,999	3443	36.7	3660	34.5
100,000-149,999	2036	21.7	1868	17.6
>150,000	1747	18.6	1453	13.7

Table 7b: Comprehensive Participants Only (Stratified by Age)

Variable (category), by age	**45-54 (n=5526)**		**55-64 (n=6884)**		**65-74 (n=5248)**		**75- (n=3888)**	
	Count	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Province								
Alberta	512	9.3	653	9.5	513	9.8	304	7.8
British Columbia	1021	18.5	1366	19.8	1150	21.9	927	23.8
Manitoba	494	8.9	734	10.7	506	9.6	363	9.3
New Brunswick	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Newfoundland & Labrador	467	8.5	621	9.0	450	8.6	173	4.4
Nova Scotia	480	8.7	677	9.8	586	11.2	428	11.0
Ontario	1228	22.2	1437	20.9	1044	19.9	906	23.3
Prince Edward Island	0	0.0	0	0.0	1	0.0	0	0.0
Quebec	1323	23.9	1394	20.3	998	19.0	787	20.2
Saskatchewan	0	0.0	0	0.0	0	0.0	0.0	0.0
Sex								
Male	2357	42.7	3193	46.4	2476	47.2	1883	48.4
Female	3169	57.3	3691	53.6	2772	52.8	2004	51.6
Education highest degree*								
Grade 8 or lower	17	0.3	46	0.7	107	2.0	184	4.8
Grade 9-10	57	1.0	98	1.4	146	2.8	219	5.7
Grade 11-13	51	0.9	92	1.3	95	1.8	115	3.0
Secondary school	437	7.9	648	9.4	547	10.5	471	12.2
Some post- secondary	267	4.8	478	7.0	340	6.5	282	7.3
Trade certificate or diploma	585	10.6	752	10.9	549	10.5	422	10.9
Community college, CEGEP	1167	21.1	1249	18.2	790	15.1	513	13.3
University certificate	211	3.8	273	4.0	282	5.4	206	5.3
Bachelor’s degree	1477	26.7	1674	24.3	1080	20.6	621.0	16.1
University above bachelor	1082	19.6	1341	19.5	1098	21.0	679	17.6
Other postsecondary	172	3.1	226	3.3	199	3.8	152	3.9
Self-rated general health								
Excellent	1131	20.5	1420	20.6	1142	21.8	652	16.8
Very good	2283	41.3	2828	41.1	2124	40.5	1506	38.8
Good	1591	28.8	1977	28.7	1522	29.0	1254	32.3
Fair	433	7.8	520	7.6	365	7.0	395	10.2
Poor	87	1.6	133	1.9	89	1.7	73	1.9
Total household inc ($/yr)								
<20,000	206	3.9	322	5.0	316	6.6	294	8.6
20,000-49,999	596	11.3	1187	18.3	1518	31.5	1351	39.7
50,000-99,999	1553	29.4	2336	36.0	1956	40.6	1258	36.9
100,000-149,999	1428	27.0	1432	22.1	686	14.2	358	10.5
>150,000	1505	28.5	1208	18.6	341	7.1	146	4.3

Table 8: Projected completion of DCS visits and re-distribution of participants from Memorial to remaining 10 DCS

		Projected completes	projected completes	projected completes		Option 1: 800 participants to redistribute to DCS sites	Option 2: 800 participants to redistribute to DCS sites
DCS site:	**Current site goal/wk**	**Mar, 2015**	**April, 2015**	**May, 2015**			
McMaster	23	3001	3093	3185		125	100
McGill	29	2879	2995	3111		100	100
Simon Fraser		1499	1499	1499		-	-
Memorial	18	2091	2163	2235		-	-
Ottawa	25	2975	3075	3175		100	100
Sherbrooke	21	2995	3079	3163		125	100
Dalhousie	26	2972	3072	3172		125	100
Calgary	30	2857	2977	3097		-	-
Victoria	28	2950	3062	3174		100	100
Manitoba	25	2867	2967	3067		-	100
British Columbia	26	1464	1568	1672		125	100
Total		**28624**	**29624**	**30624**		**800**	**800**
Difference		-1376	-376	624			

Table 9: List of potential biomarkers identified through consultation with researchers

Test Name	Sample Type	Sample Volume (mL)	Complexity
Aggrecan condroitin sulfate 846 epitope	S	1.0	R
Aggrecan condroitin sulfate 846 epitope	S	1.0	R
Albumin	Ph	0.3	C
Angiotensin-converting-enzyme, genotype	Pe	1.0	S
Atrial natriuretic peptide (ANP)	Pe	2.0	R
Apolipoprotein E (apoE), genotype	Pe	1.0	S
B-type natriuretic peptide (BNP)	Pe	0.3	S
Calcium, total	Ph	0.3	C
Carotenoids	Ph	2.0	R
Complete blood count (CBC)1	Pe	0.5	C
Chlamydia pneumoniae serology	S	2.0	C
Cholesterol2	S		C
Collagen type II cleavage (C2C)	S	1.0	R
Collagen type II cleavage (C2C)	U	1.0	R
Collagen type I and II cleavage (C1-2C)	S	1.0	R
Collagen type I and II cleavage (C1-2C)	U	1.0	R
C-reactive protein (CRP)	S	0.3	C
Creatinine	Ph	0.3	C
Creatinine	U	0.3	C
Cytochrome P450, genotype	Pe	1.0	S
Cytomegalovirus (CMV) antibodies	S	2.0	C
D-dimer	Pc	0.5	C
Dehydroepiandrosterone sulfate (DHEA-S)	S	1.0	C
Eicosapentanoic acid (EPA)	S	1.5	R
Estradiol	S	0.5	C
Ferritin	S	1.0	C
Fibrinogen	Pc	0.5	C
Fibrinopeptide A3	O	1.0	R
Folate (RBC)4	We	1.0	C
Follicle Stimulating Hormone (FSH)	S	0.5	C
Glucose	Ph	0.3	C
Glucose	Ph	0.3	C
Helicobacter pylori serology	Ph	1.0	C
Hemoglobin A1c (HbA1c)5	We	0.5	C
High Density Lipoprotein (HDL)2	S	0.3	C
Homocysteine	Pe	0.3	C
Herpes simplex virus 1 (HSV-1) serology	S	0.5	C
Insulin-like growth factor 1 (IGF-1)	Ph	1.0	C
Insulin	Ph	0.3	C
Insulin	Ph	0.3	C
Interleukin-6 (IL-6)	S	0.6	R
Iron binding capacity (TIBC)	S	0.5	C
Leptin	Ph	0.3	R

Test Name	Sample Type	Sample Volume (mL)	Complexity
Low density lipoprotein (LDL)2	S		C
Lutenizing hormone (LH)	Ph	0.5	C
Lipoprotein (a)	Pe	0.3	C
Microalbumin/creatinine ratio	U	2.0	C
Plasminogen activator inhibitor (PAI-1)	Pc	0.5	C
Platelet activity	Pc	4.0	S
Platelet aggregation	Pc	4.0	S
Procollagen type II C-propeptide (CPII)	S	1.0	R
Progesterone	Ph	0.5	C
Prolactin	Ph	0.5	C
Protein	U		C
Protein, total	Ph	0.3	C
Prothrombin fragment 1+2	Pc	0.5	R
Selenium6	Pn	1.0	S
Serum amyloid A	S	0.1	R
Soluble CD40 ligand	S	0.5	R
Triiodothyronine, total (TT3)	S	0.5	C
Thyroxine, free (FT4)	S	0.5	C
Testosterone, free	S	0.5	C
Testosterone, total	S	0.5	C
Tissue-plasminogen activator	Pc	0.5	S
Triglycerides2	S		C
Thyroid stimulating hormone (TSH)	S	0.5	C
Vitamin A (retinol)	S	0.5	S
Vitamin B12 (cobalamin)	S	1.0	S
Vitamin C (ascorbic acid)	Ph	2.0	S
Vitamin D (25OH)	S	1.0	S
Vitamin E (alpha-tocopherol)	S	2.0	S
von Willebrand factor antigen	Pc	0.5	S
Zinc	Pn	2.0	S

Sample Types to be Stored

S - Serum
Ph - Plasma, heparin
Pe - Plasma, EDTA
Pc - Plasma, citrate
We - Whole blood, EDTA
B - Buffy coat
Bt- Buffy Coat with Trizol
U - Urine (no preservative)

Additional Sample types to be processed for Genetics/Epigentics

Whole Blood, Acid Citrate
Dextrose+Dimethyl Sulfoxide
Peripheral Blood Mononuclear Cells

Sample Volume

Individual sample volume requirement

Complexity

C - Common test performed in a large laboratory
S - Special test, performed in few laboratories
R - Rare/research test

Table 10: Biomarkers measured at baseline in longitudinal studies on aging.

STUDY NAME	Acronym	Age	ACTH
A Longitudinal Platform for Population Studies in Aging	**INDEPTH**	≥ 50	
Brazilian Longitudinal Study of Heath, Ageing and Wellbeing	**ELSI-BRASIL**	≥ 50	
Canadian Study of Health and Aging	**CSHA**	≥ 65	
Cardiovascular Health Study (sample)	**CHS**	≥ 65	
The China Health and Retirement Longitudinal Study	**CHARLS**	≥ 45	
English Longitudinal Study on Aging	**ELSA**	≥ 50	
Later Life Resilience Study (women from a previous longitudinal study)	**LLRS°**	61-91	
Longitudinal Aging Study Amsterdam	**LASA**	55-85	
MacArthur Study of Successful Aging	**MacArthur°**	70-79	
Mexican Health and Aging Study	**MHAS**	≥ 50	
The National Social Life, Health and Aging Project 2011 (sample)	**NSHAP**	57-85	
National Survey of Midlife Development in the US (sub-sample)	**MIDUS II**	35-86	
Normative Aging Study (sample of initially healthy men)	**Normative °**	21-80	
Rotterdam Study	**Rotterdam °**	≥ 55	
Social Environment and Biomarkers of Aging Study in Taiwan	**SEBAS**	≥ 54[1]	
Study on Global Ageing and Adult Health	**SAGE**	≥ 50[2]	
Survey of Health, Ageing and Retirement in Europe	**SHARE**	≥ 50	
Swedish Adoption Twin Study of Aging	**SATSA**	see[3]	
The Health and Retirement Study	**HRS**	≥ 50	
The Health, Aging, and Body Composition Study	**Health ABC**	70-79	
The Irish Longitudinal Study on Aging	**TILDA**	≥ 50	
The Italian Longitudinal Study on Aging	**ILSA**	65-84	
The Longitudinal Aging Study in India	**LASI**	≥ 45	
UK Biobank	**UK Biobank**	40-69	
Whitehall II Study	**Whitehall II°**	35-55, 58-78	☐
Women's Health and Aging Studies	**WHAS**	≥ 65	
COUNT			**1**

Acronym	ADPN	ALB	ALK	ALT	AO	APOA1	APOB	AST	AVP	BDNF	BIL	Ca
INDEPTH	☐											
ELSI -BRASIL												
CSHA												
CHS		☐										
CHARLS												
ELSA												
LLRS												
LASA		☐										☐
MacArthur		☐	☐	☐	☐			☐			☐	☐
MHAS												
NSHAP												
MIDUS II												
Normative		☐						☐				☐
Rotterdam												
SEBAS		☐									☐	
SAGE						☐*						
SHARE										☐*		
SATSA						☐	☐					
HRS									☐			
Health ABC												
TILDA												
ILSA				☐				☐				
LASI												
UK Biobank		☐	☐	☐		☐	☐	☐				☐
Whitehall II												
WHAS					☐							
COUNT	**1**	**6**	**2**	**3**	**2**	**3**	**2**	**4**	**1**	**1**	**2**	**4**

Acronym	CBC	CHOL	Cl	CORT	CREAT	CRP	CYS-C	D-dimer	DHEA-S	DPD	E-SEL
INDEPTH		☐				☐					
ELSI -BRASIL		☐				☐					
CSHA	☐										
CHS	☐										
CHARLS	☐	☐				☐	☐				
ELSA		☐				☐			☐		
LLRS									☐		
LASA		☐		☐	☐	☐				☐	
MacArthur	☐	☐	☐		☐	☐			☐		
MHAS		☐				☐					
NSHAP					☐	☐					
MIDUS II		☐				☐			☐		☐
Normative	☐										
Rotterdam		☐			☐						
SEBAS	☐	☐			☐				☐		
SAGE						☐					
SHARE		☐				☐					
SATSA		☐			☐						
HRS		☐				☐	☐				
Health ABC						☐					
TILDA		☐									
ILSA		☐			☐						
LASI		☐				☐					
UK Biobank		☐			☐	☐	☐	☐			
Whitehall II				☐		☐					
WHAS											
COUNT	**6**	**17**	**1**	**2**	**8**	**16**	**3**	**1**	**5**	**1**	**1**

Acronym	EBV Ab	E2	FVII	FVIII	FER	FIB	FOL	FRUC	FSH	GGT	GLB	Glucose
INDEPTH												☐
ELSI -BRASIL												
CSHA							☐					☐
CHS												☐
CHARLS												
ELSA					☐	☐						☐
LLRS												
LASA		☐						☐	☐			☐
MacArthur						☐	☐				☐	☐
MHAS												☐
NSHAP	☐											
MIDUS II						☐						
Normative							☐					☐
Rotterdam												☐
SEBAS												☐
SAGE	☐											
SHARE												
SATSA										☐		
HRS												
Health ABC												
TILDA												
ILSA			☐	☐		☐						☐
LASI	☐											☐
UK Biobank		☐				☐						☐
Whitehall II						☐						☐
WHAS												☐
COUNT	**3**	**2**	**1**	**1**	**1**	**6**	**3**	**1**	**1**	**1**	**1**	**15**

Acronym	Hb	HbA1c	HCYS	HDL	HIV	HTC	ICAM	IgE	IGF-1	IL-6	Insulin	Iron
INDEPTH		☐		☐	☐					☐	☐	
ELSI -BRASIL		☐										
CSHA												
CHS				☐							☐	
CHARLS	☐	☐		☐								
ELSA	☐	☐		☐				☐	☐			
LLRS		☐		☐								
LASA	☐		☐	☐		☐			☐	☐		☐
MacArthur		☐	☐	☐		☐				☐		☐
MHAS	☐	☐		☐								
NSHAP	☐	☐										
MIDUS II		☐					☐			☐		
Normative				☐							☐	
Rotterdam				☐								
SEBAS	☐	☐	☐	☐					☐	☐		☐
SAGE	☐	☐		☐*	☐					☐*		
SHARE		☐								☐*		
SATSA				☐								
HRS		☐		☐								
Health ABC										☐		
TILDA		☐		☐								
ILSA	☐	☐		☐		☐					☐	
LASI				☐								
UK Biobank		☐		☐								
Whitehall II		☐		☐					☐	☐	☐	
WHAS												
COUNT	**8**	**17**	**3**	**19**	**2**	**3**	**1**	**1**	**4**	**9**	**5**	**3**

Acronym	K	LDH	LDL	LH	LPA	MCP-1	MMA	Na	OCL	PAI-1	Pb	PHOS
INDEPTH			☐			☐						
ELSI -BRASIL												
CSHA												
CHS			☐									
CHARLS			☐									
ELSA												
LLRS												
LASA			☐	☐			☐		☐			
MacArthur	☐	☐	☐					☐				☐
MHAS												
NSHAP												
MIDUS II												
Normative			☐								☐	
Rotterdam			☐									
SEBAS	☐							☐				
SAGE												
SHARE												
SATSA	☐		☐					☐				
HRS												
Health ABC										☐		
TILDA			☐									
ILSA	☐							☐				
LASI												
UK Biobank			☐		☐							☐
Whitehall II			☐									
WHAS												
COUNT	**4**	**1**	**11**	**1**	**1**	**1**	**1**	**4**	**1**	**1**	**1**	**2**

Acronym	Plat	PTH	RBC	RF	s-VCAM	SAP	SHBG	TEST	TNFa	TP	TRIG	TSH
INDEPTH					☐				☐		☐	
ELSI -BRASIL												
CSHA												
CHS											☐	
CHARLS											☐	
ELSA											☐	
LLRS												
LASA		☐				☐	☐	☐			☐	☐
MacArthur	☐		☐							☐	☐	
MHAS												☐
NSHAP												
MIDUS II												
Normative											☐	
Rotterdam											☐	
SEBAS											☐	
SAGE											☐	
SHARE									☐*			
SATSA											☐	
HRS												
Health ABC									☐			
TILDA											☐	
ILSA	☐		☐								☐	☐
LASI												
UK Biobank				☐			☐	☐		☐	☐	
Whitehall II											☐	
WHAS												
COUNT	**2**	**1**	**2**	**1**	**1**	**1**	**2**	**2**	**3**	**2**	**15**	**3**

Acronym	T3	T4	FT4	UA	Urea	VDRL	VITB[4]	VITD	VITK	VWF	WBC
INDEPTH										☐	
ELSI -BRASIL											
CSHA						☐	☐				
CHS											
CHARLS											
ELSA								☐**			☐
LLRS											
LASA	☐	☐					☐	☐	☐		
MacArthur				☐			☐				☐
MHAS								☐			
NSHAP											
MIDUS II											
Normative							☐				
Rotterdam											
SEBAS											☐
SAGE											
SHARE								☐*			
SATSA											
HRS											
Health ABC											
TILDA											
ILSA	☐	☐	☐	☐							☐
LASI											
UK Biobank					☐			☐			
Whitehall II											
WHAS											
COUNT	**2**	**2**	**1**	**2**	**1**	**1**	**4**	**5**	**1**	**1**	**4**

Legend
(°) Acronym assigned for the purpose of this table.
(*) to be done/planned; (**) at 6 months only
([1]): In 2006 a younger cohort aged 53 - 60 was added; ([2]): SAGE includes respondents 55 years and older with a smaller, comparative cohort of adults aged 18-49 years; ([3]): All pairs of twins from the Swedish Twin Registry who said that they were separated before the age of 10 and raised apart and twins that were raised together and were matched by gender, date, and county of birth; ([4]): Vitamin B12 for LASA. Not clearly indicated which vitamin B for the other studies.

ACTH: Adrenocorticotropic hormone; **ADPN**: Adiponectin; **ALB**: Albumin; **ALK**: Alkaline phosphatase; **ALT**: Alanine aminotransferase; **AO**: Antioxidants; **APOA1**: Apolipoprotein A1; **APOB**: Apolipoprotein B; **AST**: Aspartate aminotransferase; **AVP**: Vasopressin; **BDNF**: Brain derived neurotrophic factor; **BIL**: Bilirubin; **Ca**: Calcium; **CBC**: Cell blood count; **CHOL**: Cholesterol; **Cl**: Chloride; **CORT**: Cortisol; **CREAT**: Creatinine; **CRP**: C-reactive protein; **CYS-C**: Cystatin C; **D-Dimer**: D-Dimer; **DHEAS**: Dehidroepiandrosterone sulfate; **DPD**: Deoxypyridinoline; **E-SEL**: E-Selectin; **EBV-Ab**: Epstein-Barr virus antibodies; **E2**: Estradiol; **FVII**: Factor VII; **FVIII**: Factor VIII; **FER**: Ferritin; **FIB**: Fibrinogen; **FOL**: Folate; **FRUC**: Fructosamine; **FSH**: Follicle-stimulating hormone; **GGT**: Gamma-glutamyl transpeptidase; **GLB**: Globulin; **Glucose**: Glucose; **Hb**: Hemoglobin; **HbA1c**: Glycated hemoglobin; **HCYS**: Homocysteine; **HDL**: High density lipoprotein; **HIV**: Human immunodeficiency virus; **HTC**: Hematocrit; **ICAM**: Intercellular adhesion molecule; **IgE**: Immunoglobulin E; **IGF-1**: Insulin-like growth factor 1; **IL-6**: Interleukin 6; **Insulin**: Insulin; **Iron**: Iron; **K**: Potassium; **LDH**: Lactate dehydrogenase; **LDL**: Low density lipoprotein; **LH**: Luteinizing hormone; **LPA**: Lipoprotein A; **MCP-1**:Monocyte chemoattractant protein-1; **MMA**: Methylmalonic acid; **Na**: Sodium; **OCL**: Osteocalcin; **PAI-1**: Plasminogen activator inhibitor-1; **Pb**: Lead**; PHOS**: Phospate; **Plat**: Platelets; **PTH**: Parathyroid hormone; **RBC**: Red blood cells; **RF**: Rheumatoid factor; **s-VCAM**: Soluble vascular cell adhesion molecule-1; **SAP**: Serum amyloid P component; **SHBG**: Sex hormone-binding globulin; **TEST**: Testosterone; **TNFa**: Tumor necrosis factor alpha; **TP**: Total proteins; **TRIG**: Triglycerides; **TSH**: Thyroid-stimulating hormone; **T3**: Triiodothyronine; **T4**: Thyroxine; **FT4**: Free thyroxine; **UA**: Uric acid; **Urea**: Urea; **VDRL**: Venereal disease research laboratory test; **VITB**: Vitamin B; **VITD**: Vitamin D; **VITK**: Vitamin K; **VWF**: Von Willebrand factor; **WBC**: White blood cells

Table 11: Biomarker test use frequency

Biomarker	N	Biomarker	N	Biomarker	N
High density lipoprotein	19	Albumin	6	Vitamin B	4
Glycated hemoglobin	17	Dehydroepiandrosterone S	5	Alanine aminotransferase	3
Cholesterol	17	Insulin	5	Apolipoprotein A1	3
C-reactive protein	16	Vitamin D	5	Cystatin C	3
Glucose	15	Aspartate aminotransferase	4	Folate	3
Triglycerides	15	Calcium	4	Homocysteine	3
Low density lipoprotein	11	Insulin-like growth factor 1	4	Iron	3
Interleukin-6	9	Potassium	4	Tumor necrosis factor alpha	3
Creatinine	8	Sodium	4	Thyroid-stimulating hormone	3

Note: Only biomarkers that appeared in three or more studies have been listed in this table

Table 12: Biomarker groupings as defined by Engelfriet

Aging process or mechanisms of aging
Aging cells and tissue remodelling
Caveolin-1
Endothelial progenitor cells; blood stream cells
Extracellular matrix remodelling; MMP-9, tissue inhibitor MMP-9, galectin-3
Telomerases
Leukocyte telomere length
Telemerase RNA component; telomerase reverse transcriptase
DNA repair
8-hydroxydeoxyguanosine
Circulation anti-DNA antibodies
Growth, energy, hemostasis, and reproductive function
Growth hormone (GH)
Insulin like growth factor (IGF-1)
HbA1c
Pentosidine
Receptor for advanced glycation end products
Lutenizing hormone (LH)
Follicle stimulating hormone (FSH)
Dehydroepiandrosterone (DHEA)
Triiodothyronine (T3)
Cortisol
Leptin
Adiponectin
Proteins and protein metabolism
Serum amyloid protein (SAA)
Nicotinamide phosphribosyltransferase (visfatin)
Carbonyls, Michael adducts
Eotaxin
Serum N-glycan profile
Lipids and lipid metabolism
Free fatty acids
HDL
LDL
VLDL
Cholesterol
Triglycerides
Isoprostanes
Lipid peroxidation products; malondialdehyde, 4-OH-2-nonenal
Wear and tear, oxygen metabolism
Oxidized LDL

Aging process or mechanisms of aging
Glutathione Glutatione reductase Glutathione peroxidise Thioredoxin reductase-1 Superoxide dismutase Nitric oxide Vitamin A Vitamin E Vitamin D Hypoxia-inducible factor 1
Inflammation Interleukin-6 Tumor necrosis factor (TNF) C-reactive protein (CRP) Pentraxin-3 Cathepsin S
Age-related disease
Oxygen transport Hematocrit Mean cell volume Reticulocytes
Hemoglobin Erythropoetin Ferritin Iron
Blood coagulation D-dimers
Plasmin-antiplasmin
Thrombocyte function (increased platelet activity)
Fibrinogen
Factor VII
Factor VIII
Factor IX
Factor XIII
Von Willebrand factor
Antithrombin III
Protein S
Protein C
Thrombin generation test
Immune system Cell counts: T cell and T cell subclasses CD3+, CD4+, CD8+

Age-related disease – cont'd
B cells (CD19+) Monocytes (CD14+, CD16+) Naïve T cell status (CD28+, CD95-) and proportions containing T-cell receptor excision circles Response against pathogens (CMV antibodies or cellular immunity against influenza virus) Dendritic cells Complement system Immunoglobulins Autoantibodies Phagocytosis
Cardiovascular system
Collagen turnover: carboxyterminal peptide of procollagen type I, carbocy terminal telopeptide of collagen type I, aminoterminal procollagen type III
Natriuretic peptides
Troponin
Endothelin
Elastin
Lung Surfactant D Apelin PaO2
Kidney GFR Creatinine Urea Neutrophil gelatinase-associated lipocalin Cystatin C Fibroblast growth factor 23 1,25-dihydroxy cholecalciferol Parathyroid hormone
Bone and joint *Collagen:*
N-telopeptide cross-links of type 1 collagen C-telopeptide cross-links of type 1 collagen Procollagen type 1 N-terminal propeptide C-terminal propeptide *Bone matrix turnover:* Bone specific alkaline phosphatase Osteoclast derived tartrate-resistant acid phosphatise form 5b

Age-related disease – cont'd
Osteocalcin
Liver
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transferase (GGT)
Albumin
Muscle
Irisin
Brain and nervous system
ß-amyloid

Table 13 Clinical Chemistry Methods

Name	Specimen Type[1]	Sample Vol (µL)	Measuring Range	Reportable Range	LLD	CV[2]	Interferences (µmol/L)			Test Principle	Instrument
							Bilirubin	Hb	Lipemia[3]		
ALB	S P-heparin P-EDTA	2	2-100 g/L	2-99 g/L	2 g/L	2.4% at 25.0 g/L 1.6% at 43.5 g/L	1026	621	NSI if LI < 1000	At the reaction pH, bromcresol purple (BCP) reacts with albumin causing colour change that is measured spectrophotometrically.	Roche Diagnostics Cobas 8000 series c701
ALT	S P-heparin P-EDTA	10	0.08-11.7 µkat/L	4-3000 U/L	0.08 µkat/L	4.9% at 25 U/L 0.9% at 180 U/L	1026	124	NSI if LI < 150	ALT catalyzes transamination reaction between alanine and 2-oxoglutarate producing pyruvate and L-glutamate. In a second reaction, catalyzed by lactate dehydrogenase (LDH), pyruvate is reduced by NADH yielding NAD^+. The rate of NADH oxidation, determined by the decrease in absorbance, is directly proportional to the catalytic ALT activity.	Roche Diagnostics Cobas 8000 series c701
CRP	S P-heparin P-EDTA	6	0.1-20 mg/L	0.1-276.0 mg/L	0.1 mg/L	5.5% at 1.1 mg/L 3.3% at 5.8 mg/L	1030	621	NSI if LI < 500	The assay is based on a latex-enhanced turbidimetric immunoassay method. When an antigen-antibody reaction occurs between CRP in a sample and anti-CRP antibody which has been coated with latex particles, agglutination results. This agglutination is detected as an absorbance change (552 nm).	Roche Diagnostics Cobas 8000 series e602
CHOL	S P-heparin P-EDTA	2	0.1-20.7 mmol/L	0.10-99.99 mmol/L	0.1 mmol/L	1.9% at 2.71 mmol/L 1.2% at 7.52 mmol/L	C-BIL: 274 U-BIL: 239	435	NSI if LI < 2000	Cholesterol esters are hydrolyzed by the action of cholesterol esterase producing free cholesterol and fatty acids. Cholesterol is then oxidized by the action of cholesterol oxidase producing cholest-4-en-3-one and H_2O_2. In the third reaction, catalyzed by peroxidase, H_2O_2 reacts with phenol and 4-aminophenazone yielding a red quinone-imine dye. The increase in absorbance and colour intensity of the dye are directly proportional to cholesterol concentration.	Roche Diagnostics Cobas 8000 series c701

Name	Specimen Type[1]	Sample Vol (µL)	Measuring Range	Reportable Range	LLD	CV[2]	Interferences (µmol/L)			Test Principle	Instrument
							Bilirubin	Hb	Lipemia[3]		
CREA	S P-heparin P-EDTA	2	5-2700 µmol/L	5-6000 mmol/L	5 µmol/L	2.3% at 54 mmol/L 1.5% at 179 mmol/L	C-BIL: 257 U-BIL: 342	497	NSI if LI < 2000	The test principle is based on conversion of creatinine in three consecutive reactions to final products glycine, formaldehyde and H_2O_2, catalyzed by creatininase, creatinase and sarcosine oxidase, respectively. Peroxidase catalyzes the reaction of H_2O_2 with 4-aminophenazone and 2,4,6-triiodo-3-hydroxybenzoic acid producing quinone imine chromogen, whose colour intensity is proportional to creatinine concentration.	Roche Diagnostics Cobas 8000 series c701
FERR	S P-heparin P-EDTA P-citrate	10	0.500-2000 µg/L	1-100000 mg/L	0.5 µg/L	3.3% at 38 mg/L 3.0% at 175 mg/L 3.5% at 389 mg/L	> 1112	> 3100	> 37620	In this assay a monoclonal ferritin-specific antibody labelled with ruthenium complex and a biotinylated monoclonal ferritin-specific antibody react with ferritin to form a sandwich complex. Streptavidin-coated microparticles are added and this complex becomes bound to the solid phase. Ferritin is then measured using electrochemiluminiscence technique.	Roche Diagnostics Cobas 8000 series e602
FT4	S P-heparin P-EDTA	15	0.3-100 pmol/L	0.3-100.0 pmol/L	0.3 pmol/L	2.6% at 14.2 pmol/L 3.0% at 34.6 pmol/L 4.8% at 73.4 pmol/L	> 701	> 621	> 22800	In this assay a specific anti-FT4 antibody labelled with ruthenium complex reacts with FT4. After addition of biotinylated T4 and streptavidin-coated microparticles, the still-free binding sites of the labelled antibody become occupied, with formation of an antibody-hapten complex. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin. FT4 is measured using electrochemiluminiscence technique.	Roche Diagnostics Cobas 8000 series e602

Name	Specimen Type[1]	Sample Vol (µL)	Measuring Range	Reportable Range	LLD	CV[2]	Interferences (µmol/L)			Test Principle	Instrument
							Bilirubin	Hb	Lipemia[3]		
HBA1C	WB P-heparin P-EDTA P-KF/EDTA	6	4.3-24.8 % (0.3-3.4 g/dL)	3.0-20.0%	2.9% (0.1 g/dL)	2.9% at 5.3% 1.9% at 9.7% 1.6% at 14.7%	1000	n/a	9120	HbA1c is analyzed in hemolyzed whole blood by turbidimetric inhibition immunoassay (TINIA). It reacts with anti-HbA1c antibodies with the formation of antigen-antibody complexes, which are soluble because HbA1c molecules have only one site for anti-HbA1c antibodies recognition. In order to obtain insoluble complexes for turbidimetric measurement, polyhaptens are further added to react with excess anti-HbA1c antibodies.	Roche Diagnostics Cobas Integra 800CTS
HDL	S P-heparin P-EDTA P-citrate	2.5	0.08-3.12 mmol/L	0.10-6.20 mmol/L	0.08 mmol/L	2.5% at 0.78 mmol/L 2.1% at 1.52 mmol/L	C-BIL 513 U-BIL: 1026	745	> 13700	In the presence of magnesium ions, dextran sulfate selectively forms water-soluble complexes with LDL, VLDL, and chylomicrons which are resistant to polyetylene glycol-modified cholesterol esterase and cholesterol oxidase. The two enzymes catalyze conversion of HDL cholesterol esters into Δ^4-cholestenone and H_2O_2. H_2O_2 reacts 4-amino-antipyrine and HSDA to form a purple-blue dye, with the colour intensity being directly proportional to cholesterol concentration.	Roche Diagnostics Cobas 8000 series c701
TSH	S P-heparin P-EDTA P-citrate P-KF P-oxalate	50	0.005-100 µIU/mL	0.01-1000.00 mIU/mL	0.005 µIU/mL	1.5% at 0.83 mIU/mL 1.6% at 6.12 mIU/mL 2.3% at 34.99 mIU/mL	> 701	> 621	> 17100	In this assay a monoclonal anti-TSH antibody labelled with ruthenium complex and a biotinylated monoclonal anti-TSH antibody react with TSH to form a sandwich complex. Straptavidin-coated microparticles are added and this compex becomes bound to the solid phase. TSH is then measured using electrochemiluminiscence technique.	Roche Diagnostics Cobas 8000 series e602

Name	Specimen Type[1]	Sample Vol (µL)	Measuring Range	Reportable Range	LLD	CV[2]	Interferences (µmol/L)			Test Principle	Instrument
							Bilirubin	Hb	Lipemia[3]		
TRIG	S P-heparin P-EDTA	2	0.1-10.0 mmol/L	0.1-60.0 mmol/L	0.1 mmol/L	1.5% at 1.08 mmol/L 1.3% at 2.46 mmol/L	C-BIL: 171 U-BIL: 599	434	> 33900 can produce normal results	Lipoprotein lipase cleaves trigycerides to form fatty acids and glycerol, which is then phosphorylated and oxidized by the action of glycerol kinase and glycerol phosphate oxidase. H_2O_2 is produced and reacts with 4-aminophenazone and 4-chlorophenol under the catalytic action of peroxidase forming a red dye. The colour intensity is directly proportional to triglyceride concentration.	Roche Diagnostics Cobas 8000 series c701
VITD	S	25	10.0-375.0 nmol/L	10.0-375.0 nmol/L	10 nmol/L	8.1% at 43.9 nmol/L 7.6% at 62.1 nmol/L 7.3% at 80.5 nmol/L	124.2	684.8	6714.6	Direct competitive chemiluminescence immunoassay. During the first incubation, Vitamin D is dissociated from its binding protein and binds to the specific antibody on the solid phase. Then, the tracer, (vitamin D linked to an isoluminol derivative) is added. After a second incubation, the unbound material is removed with a wash cycle. Vitamin D is measured using chemiluminescence. The light signal is inversely proportional to the concentration of vitamin D.	DiaSorin Liaison XL

LEGEND:

A1c, hemoglobin A1c; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase, AST, aspartate aminotransferase; C-BIL, conjugated bilirubin; CHOL, cholesterol; CRP, C-reactive protein; CREA, creatinine; CV, coefficient of variation; FT4, free thyroxine; Hb, hemoglobin; HDL, high density lipoproteins; LI, lipemia index; LLD, lower limit of detection; NADH, nicotinomide adenine dinucleotide (reduced); NSI, no significant interference ; P-EDTA, plasma with EDTA; P-heparin, plasma with Li-heparin; P-KF, plasma with potassium fluoride; S, serum; TRIG, triglycerides; TSH, thyrotropin or thyroid stimulating hormone; U-BIL, unconjugated bilirubin; VITD, vitamin D (25-hydroxy cholecalciferol); WB, whole blood

[1] Multiple sample types are possible for some analytes. We will use serum for all analytes except for HbA1c where whole blood is needed. All serum analyses will be performed using one 500 µL aliquot. One 500 µL aliquot will be used for HBA1C testing.

[2] Values from current performance at Calgary Laboratory Services (CLS).

[3] Values expressed in µmol/L unless indicated by the lipemia index (LI) which is a measure of turbidity and has no units.

Table 14: Pre-analytical information recorded during biospecimens collection and processing in the CLSA Data Collection Sites - A

VARIABLE	LEVEL	CAPTURED INFORMATION	COMMENTS
Consumables			
	BBC	Lot Number Expiry dates	Centralized distribution from BBC to DCS
Quality Controls (*)			
	DCS	Normal control High control	• Run daily prior processing. New lots every 3 months
	BBC	Summary report	• Received once a month
Sample processing			
		Time stamps	
	DCS (**)	Blood collection Urine collection Start/stop shaker Start/stop centrifuge Start/stop fast dryer In/out freezer In cryoshipper	All samples are processed within 2 hours from withdrawal time
Sample final storage			
		Time stamps	
	BBC	Out from cryoshipper In the tank In the Genvault	• Plasma, serum and urine • Genplates
Temperature			
	DCS (**)	BCP room Fridge Freezer	Samples are stored at -80C (plasma, serum and urine) or RT (Genplate) for a week in each DCS and then shipped o/n to BBC
	BBC	Cryoshippers Tanks	Sensors located on the cryoshipper's lid allow to check for potential temperature fluctuations during shipping time
(*) Quality controls for Beckman Coulter Hematology Analyzer (**) BBC via LIMS			
BBC: Biorepository and Bioanalysis Centre; DCS: Data Collection Site/s; BCP: Biospecimen Collection and Processing room; RT: Room Temperature; LIMS: Laboratory Information Management System			

Table 15: Pre-analytical information recorded during biospecimens collection and processing in the CLSA Data Collection Sites - B

SAMPLE WITHDRAWAL AND COLLECTION			
Blood	Participant	Sample declined	Change of mind
			Feeling unwell
		Sample postponed	Change of mind
			Feeling unwell
	Technician	Arm switch	
		Vein ruptured/collapsed/slow blood flow	
		Incomplete fill	
		No consumables available	
Urine	Participant	Sample declined	Change of mind
			Personal reasons
			Cannot void
			Feeling unwell
		Sample postponed	Personal reasons
			Cannot void
			Feeling unwell
	Technician	Specimen compromised	
		Consumables unavailable	
SAMPLE PROCESSING			
Blood	Sample issue	Clotted	
		Spilled	
		Lost	
	Instrument issue	Broken tube	
		Coulter QC or Coulter malfunction	
		Tubes shaker	
		Pipette/s	
		Centrifuge	
		No sample separation	
	Non-instrument issue	Incomplete fill	
		Not able to aliquot	
		No consumables available	
Urine	Sample issue	Accidental spill	
		Lost sample	
		Not able to aliquot	
		Unidentified sample	
Genplate	Plate issue	Bottom foil detached	
		Plate dropped	
	Technical issue	Pipette malfunction	
		No consumables	
SAMPLE ALIQUOTING			
Blood and Urine	Technical issue	Insufficient sample	
		Insufficient volume	

(An option ‘Other’ was given per each category for open field answers)

Table 16: CpG sites associated with age in 6 studies of DNA methylation and aging. Sites are listed with their nearest gene, distance to that gene's TSS, the class of CpG island, the chromosome, and which of the six studies the sites were found in.

Site	Gene	Distance to TSS	Island class	CHR	Island region	Direction of change	Study					
							1	2	3	4	5	6
cg00059225	GLRA1	40	HC	5	Island	+	y	y	y	y	n	n
cg01820374	LAG3	403	LC	12	N_Shore	−	y	y	n	y	y	n
cg02844545	GCM2	55	HC	6	Island	+	y	y	y	y	n	n
cg06291867	HTR7	509	HC	10	Island	+	y	y	y	y	y	n
cg06493994	SCGN	174	HC	6	Island	+	n	y	y	y	y	y
cg07621046	C10orf82	117	IC	10	Island	+	y	y	y	y	n	n
cg09809672	EDARADD	3	LC	1	N_Shore	−	y	n	n	y	y	y
cg14456683	ZIC1	-170	HC	3	Island	+	y	y	y	y	n	n
cg17861230	PDE4C	309	HC	19	Island	+	y	y	y	y	n	n
cg18815943	FOXE3	571	HC	1	Island	+	n	y	y	n	y	n
cg21296230	GREM1	332	HC	15	Island	+	y	n	y	y	y	y
cg21801378	BRUNOL6	918	HC	15	Island	+	y	y	y	y	y	n
cg22736354	NHLRC1	132	HC	6	Island	+	n	y	y	y	n	y
cg27320127	KCNK12	-926	HC	2	Island	+	y	y	y	y	n	n
cg27553955	KCNG3	911	HC	2	Island	+	y	y	n	y	n	n

1: Bocklandt
2: Bell
3: Horvath
4: Weidner
5: Florath
6: Hannum

Table 17: Types of Biological Samples Collected at 1st Follow-up

Type	Volume (mL)	Number	Total volume (mL)	Number of aliquots
1. Citrate				
3.2% buffered sodium citrate solution, 0.109 M				
Plasma	2.7	1	2.7	2
Plasma, platelet poor	2.7	1	2.7	2
2. Serum				
Spray coated silicone and micronized silica particles				
Serum	10	1	10	8
3. Heparin				
Lithium heparin, 90 USP				
Plasma	6	1	6	6
4. EDTA				
Spray coated K_2 EDTA, 10.8 mg				
Plasma	3	1	3	0[1]
Plasma	6	3	18	6
Buffy coat			(2)	4
Whole blood			(1.5)	3
5. ACD				
Trisodium citrate, 13.2g/L; citric acid, 4.8 g/L; and dextrose 14.7 g/L, 0.4 mL				
Whole blood	3	1	3.5	3
6. CPT				
Sodium citrate 0.45 mL 0.1 M and Ficoll™ medium				
Mononuclear cells	8	1	8	6
Urine collection container				
Urine	60	1	2	4

Tubes are listed according to the order they will be drawn

[1] Follow-up hematology tests performed at the DCS. No aliquots are stored.

THE STUDY TEAM BIOS

A Collaborative Approach

The multidisciplinarity of the CLSA allows for and requires rich collaborations and capacity building both across and between multidisciplinary researchers, practitioners, and policy makers. The CLSA collaboration began with a 2001 symposium — From Cell to Society — in Aylmer, Quebec, where over 100 researchers from 50 institutions across Canada agreed on the need for a new generation of longitudinal studies to support a research program in aging.

The CLSA lead scientific team brings together a diversity of expertise, including genetics, biochemistry, immunology, clinical, geriatrics and gerontology, sociology, psychology, nursing, pharmacy, biology, rehabilitation, epidemiology, computer science, medical anthropology, population health, nutrition, economics, and biostatistics. All of the team members have published their research findings in leading scientific journals, held national and international peer-reviewed grants, and have had considerable experience in translating their findings into policies.

Host Institution

The host institution, McMaster University, views its commitment to the project as an important ongoing initiative. McMaster University has the ability and infrastructure to carry out large clinical and population based studies of the magnitude of CLSA. The Department of Clinical Epidemiology and Biostatistics (CE&B) is a multi-disciplinary department located within McMaster's Faculty of Health Sciences. CE&B's strengths are in clinical research, health services research, health social sciences, health economics, health policy research, and health information science. The academic mission of CE&B is to advance knowledge in evaluative sciences related to health and health care through interdisciplinary research and to facilitate the transfer of research information, with the goal of effecting improvements in health in the communities served. CE&B is internationally acclaimed for the quality and impact of its health research and is regarded as the 'birthplace' of evidence-based medicine. The CE&B will support the financial and human resource needs of the CLSA. The senior management of McMaster University has committed to providing space for the CLSA and will continue to work closely with Dr. Raina to ensure the success of the CLSA.

Lead Investigative Team

The CLSA team is directed by lead principal investigator, Dr. Parminder Raina of McMaster University, and two co-principal investigators, Drs. Christina Wolfson of McGill University and Susan Kirkland of Dalhousie University

Dr. Parminder Raina is a Professor in the Department of Clinical Epidemiology and Biostatistics at McMaster University. He specializes in the epidemiology of aging with emphasis on developing the interdisciplinary field of geroscience to understand the processes of aging from cell to society. He has expertise in epidemiologic modeling, systematic review methodology, injury and knowledge transfer. He holds a Canada Research Chair in Geroscience and the Raymond and Margaret Labarge Chair in Research and Knowledge Application for Optimal Aging. He received the Ontario Premier's Research Excellence award on research in aging to train and mentor new researchers from 2004-2009. He received The Sun Life Research Fellow, and a Teaching Excellence Award for Professors, Clinical Epidemiology and Biostatistics, McMaster University. Dr. Raina is the lead principal investigator of the Canadian Longitudinal Study on Aging (one of the largest and comprehensive studies of aging in the world). He was the Director of the internationally recognized McMaster Evidence-based Practice Center which was funded by the U.S based Agency for Healthcare Research and Quality and is the current Director of the CIHR funded McMaster Evidence Synthesis and Review Centre. Dr. Raina is one of the

founding members of the Ontario Research Coalition of Aging Institutes/Centers funded by the Ontario Ministry of Health and Long-term Care.

Dr. Raina has served on several national and international committees such as WHO-EVIPNet in Asia, Ontario Minister's Advisory Group on Alzheimer Disease and Related Dementias Research, Surveillance Committee of Public Health Agency of Canada and Panel for the Public Dialogue on Privacy and Health Research in Canada. He currently serves on the Advisory Committee for National Elder Abuse Research Project funded by Human Resource Social Development Canada and the National Initiative for the Care of the Elderly (NICE). He is also a member of the External Scientific and Ethics Advisory Board of Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES) and EU funded project SiforAGE.

He is the lead principal investigator of the CLSA and the CLSA-CFI. He will be responsible for the global oversight of the project and will direct the National Coordinating Centre. He is also co-lead for the Hamilton DCS and co-director of the CLSA Biobank along with Dr. Balion. Dr. Raina is also involved in leading the harmonization of the CLSA with national and international cohorts; and leading the development of the IP and commercialization policy for the CLSA. In collaboration with CIHR, he leads the development of communication and partnership strategy for the CLSA. Dr. Raina chairs the Scientific Management Committee of the CLSA.

Dr. Christina Wolfson is a Professor in the Department of Epidemiology and Biostatistics and Occupational Health and in the Department of Medicine at McGill University. She is the Director of the Neuroepidemiology Research Unit at the Research Institute of the McGill University Health Centre and an Associate Member in the Department of Neurology and Neurosurgery, the Department of Mathematics and Statistics and the Division of Geriatric Medicine at McGill University. Dr. Wolfson received her BSc in Mathematics and MSc in Mathematical Statistics from the Department of Mathematics and Statistics, and PhD in Epidemiology and Biostatistics from the Department of Epidemiology & Biostatistics at McGill University and is a Fellow of the American College of Epidemiology. A neuroepidemiologist, her program of research includes the epidemiology of neurodegenerative disorders, notably multiple sclerosis, Parkinson’s disease, and epilepsy with a particular interest in the identification of neurological conditions in population based studies.

She has been a CLSA Co-Principal Investigator since the inception of the CLSA and plays a major role in all ongoing activities of the CLSA both operational and scientific. She is the Director of the Statistical Analysis Centre, the Chair of the Data and Sample Access Committee and the local Principal Investigator for the Montreal CLSA Data Collection Site. Within the CLSA she leads both the Neurological Conditions Initiative and the Veterans’ Health Initiative.

Dr. Susan Kirkland is a Professor in the Departments of Community Health & Epidemiology and Medicine, Dalhousie University Halifax, Nova Scotia. She is the Associate Director (Population Studies) of the Geriatric Medicine Research Unit at Dalhousie, Affiliate Scientist at the QEII Health Sciences Centre, and Director of the Atlantic Interdisciplinary Research Network. She is trained as an epidemiologist, with expertise in aging, chronic disease epidemiology, health services utilization, and women’s health. Her research relates to the epidemiological examination of health outcomes that are prevalent in older populations, including cardiovascular disease (CVD) and osteoporosis, hepatitis C and cognitive impairment, and the exploration of underlying determinants of health, particularly the interplay between gender and the genetic, social, cultural and economic determinants of health. She is an investigator on numerous population based epidemiologic studies including the Canadian Multicentre Osteoporosis Study (CaMos), the Nova Scotia Health Survey and the Canadian Community Health

Survey Follow Up Studies, and she has been a member of the Canadian Health Measures Survey Expert Advisory Committee since its inception. She is currently leading studies in the areas of healthy aging, HIV and aging, frailty, physical activity and obesity, and technologies to support aging in place. She is also a member of the board of the Canadian Society for Epidemiology and Biostatistics, and the Northwood Group of Companies, a non-profit continuing care organization serving residents of Nova Scotia.

Dr. Kirkland has been involved in the CLSA since its inception, and has co-led with Drs. Raina and Wolfson the development of the study design, content, measures, governance structure, and implementations plans. She brings to the team a wealth of knowledge not only in epidemiologic methods relevant to longitudinal studies, but substantive expertise in chronic disease epidemiology, especially as it relates to osteoporosis, cardiovascular disease, and obesity in vulnerable populations. Dr. Kirkland leads the Halifax DCS and is the director of the CLSA CATI network. She is the CLSA ex officio representative on the CIHR Ethical Legal and Social Issues Committee that is advisory to the CLSA. She is responsible for the annual REB ethics submissions and the development of protocols that address ethical, legal and social issues. Dr. Kirkland also co-chairs the Training and Research Capacity Committee of the CLSA.

Co-investigator Team

The CLSA has an extensive team of co-investigators with diversity of expertise. The Table of Expertise includes the full list of CLSA co-investigators, their affiliation, and their role in the CLSA. The following section includes short biographical sketches for each of the DCS, CATI site, enabling units, and working group leads and the Biomarker Team.

University of Ottawa

Dr. Vanessa Taler is an Associate Professor in the School of Psychology at the University of Ottawa and a Scientist at the Bruyère Research Institute. Her research interests focus on cognitive function in healthy aging, mild cognitive impairment, and dementia, with a particular emphasis on language, memory, and executive function. Current projects, funded by the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research, and the Alzheimer Society of Canada, focus on the impact of bilingualism on language processing and cognitive decline; she uses behavioural and electrophysiological measures to explore these questions. A particular interest is in accurate diagnosis of cognitive impairment in bilingual populations.

McMaster University

Dr. Christopher Patterson is a professor in the Division of Geriatric Medicine, Department of Medicine at McMaster University. He is a specialist in Internal and Geriatric Medicine and received additional training in research methodology and clinical epidemiology. He served on the Canadian Task Force on the Periodic Health Examination (now the Canadian Task Force for Preventive Health Care) from 1987 until 2005 producing evidence based guidelines for preventive health manoeuvres in primary care. After the publication of guidelines for screening for cognitive impairment and participation in a number of multi-centre randomized controlled trials for dementing disorders, he served as Co-chair with Dr. Serge Gauthier for the Canadian Consensus Conference on Dementia in 1998. He was a member of the steering committees of the 2nd and 3rd Canadian Consensus Conferences on Dementia, and Co-chaired the Conference again in 2012. Guidelines for the assessment and management of dementing disorders have been produced based upon the best available evidence. He has served on editorial boards of the CPS and Canadian Journal on Aging. He was a member of the Institute of Aging Advisory board

(2006-10). He is the chair of the Clinical Working Group of the Canadian Longitudinal Study of Aging, and serves as a medical advisor to the CLSA.

Dr. Harry Shannon trained in the United Kingdom in mathematics and statistics. He is a professor in the Department of Clinical Epidemiology & Biostatistics at McMaster University where he has been a faculty member since 1977. He also holds an appointment in public health sciences at the University of Toronto. He is a past president of the Canadian Association for Research on Work and Health (CARWH), and has published extensively in this field. He holds a CIHR grant to explore optimal methods of sampling participants for surveys in difficult settings. Dr, Shannon is Chair of the CLSA Methodology Working Group.

Dr. Cynthia Balion is an associate professor in the Department of Pathology and Molecular Medicine at McMaster University, clinical biochemist for the Hamilton Regional Laboratory Medicine Program (HRLMP), co-investigator with the Canadian Longitudinal Study on Aging (CLSA) and director of the CLSA Biorepository and Bioanalysis Centre (BBC). She conducts research in the fields of point of care, evidence-based laboratory medicine, geriatric clinical biochemistry, and blood-based biomarkers of dementia

Université de Sherbrooke

Dr. Hélène Payette is Professor in the Department of Community Health Sciences, Faculty of Medicine and Health Sciences at the Université de Sherbrooke, and senior researcher at the Research Centre on Aging of the Health and Social Services Center - University Institute of Geriatric Studies of Sherbrooke. She specializes in nutrition, epidemiology and aging. Her research interests include healthy eating and its determinants, body composition and functional capacities in the aging individual as well as screening for nutritional risks and evaluation of nutritional interventions in the community-dwelling frail elderly. She was awarded the Betty Havens award in longitudinal research by the Canadian Society of Gerontology (2013). Dr Payette is the principal investigator for the "Québec Longitudinal Study on Nutrition as a Determinant of Successful Aging" (NuAge) (CIHR) where longstanding and current dietary habits and body composition are examined in relation to changes in physical and cognitive status, functional autonomy and social functioning. She currently coordinates the Québec Consortium for Longitudinal Study of Aging funded by the FRQ-S. She is the local site investigator for the Sherbrooke CLSA Data Collection Site and the Sherbrooke CLSA CATI Site and is the Chair of the CLSA Nutrition and Lifestyle Working Group.

Memorial University

Dr. Gerry Mugford is an Associate Professor in the disciplines of medicine and psychiatry at Memorial University, St. John's, Newfoundland. He is Director of the Clinical Epidemiology Graduate Medicine program and is also a psychotherapist and certified Medical and Analytical Hypnotherapist. Dr. Mugford is a founding member of Atlantic Canada HIV Education (ACHIVE) [CME initiatives to support Atlantic Canada health professionals who provide care to PHAs]. He is a founding member of Atlantic Interdisciplinary Research Network for Social and Behavioural Issues in HIV and HCV (AIRN) [an interdisciplinary group with a mandate to build research capacity for both HIV and HCV in Atlantic Canada]. He is a Mentor with the National Canadian Research Training Program in Hepatitis C (NCRTP-Hep-C). He is a member of the Ministerial Advisory Council on HIV, HCV and BBSTIs. His current research initiatives includes HIV/HPV genotypes and associated risk for cervical, anal and oropharyngeal cancers and aging related health conditions. He has published in the areas of Psychological Dysfunction, HIV/AIDS and Arthritis. He currently supervises 12 graduate students (MSc and PHD) working with diverse heath issues. He is active on a number of health related local and

national committees. He has received funding from CIHR, PHAC, RDC, CFI, Health Canada, FoM, etc. He is the local principal investigator for the Newfoundland and Labrador CLSA Data Collection Site.

University of Manitoba

Dr. Verena Menec is a Professor in the Department of Community Health Sciences, Faculty of Medicine at the University of Manitoba. She received a doctorate in social psychology from the University of Manitoba. Dr. Menec served as the Director of the Centre on Aging for nine years (from 2004-20014) and has served on numerous advisory committees, including the Canadian Institutes of Health Research (CIHR) Institute of Aging's Advisory Board from 2005 to 2011. She currently holds a Canada Research Chair in Healthy Aging. Her main research interests lie in the areas of healthy aging, age-friendly communities, and health care utilization among older adults, particularly at the end of life. She is the local site investigator for the Manitoba CLSA Data Collection Site and the Manitoba CLSA CATI Site.

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University of Calgary

Dr. David Hogan is a Professor in the Departments of Clinical Neurosciences, Community Health Sciences, and Medicine at the University of Calgary. He is a specialist in geriatric medicine. From 1984 till 1990 he was a member of the Faculty of Medicine, Dalhousie University. In 1990 he moved to the University of Calgary where he founded the Division of Geriatric Medicine, Department of Medicine and served as its Head for its initial 10 years. Dr Hogan was the inaugural and still holds the Brenda Strafford Foundation Chair in Geriatric Medicine at the University of Calgary (this was the first Chair in geriatric medicine established in Canada). He has served as Chair of the Royal College of Physicians and Surgeons of Canada (RCPSC) Specialty Committee in Geriatric Medicine, Chief Examiner in Geriatric Medicine for the RCPSC, and President of the Canadian Geriatrics Society. Currently he is on the Research Executive Committee of the Canadian Consortium on Neurodegeneration in Aging. Dr. Hogan has authored over 500 publications including approximately 230 peer-reviewed papers. He is the local site investigator for the Calgary CLSA Data Collection Site and a member of the Clinical Working Group.

University of British Columbia

Dr. Max Cynader is Director of the Brain Research Centre, and the Djavad Mowafaghian Centre for Brain Health at Vancouver Coastal Health and The University of British Columbia (UBC). In addition, he holds the Canada Research Chair in Brain Development at UBC and is Professor of Ophthalmology. He is also a Fellow of The Canadian Academy for Health Sciences, a Fellow of The Royal Society of Canada, a Member of the Order of British Columbia (OBC), a Member of the Order of Canada (CM), inducted to the Canadian Medical Hall of Fame, and a Principal Investigator in two of Canada's Networks of Excellence (Stroke and NeuroDevNet). He is the author of over 230 articles published in scientific journals and is the holder of several patents. Dr. Cynader has made important contributions to technology development, and to the commercialization of research results. He is one of the scientific founders of *NeuroVir*, a Vancouver-based biotechnology company which has developed gene therapy products to treat brain diseases. He is also the co-founder of *Wavemakers Research*, a software company which has developed new and proprietary noise reducing technology. Dr. Cynader will be the lead for the Vancouver DCS.

Dr. Michael S. Kobor is an Associate Professor in the Department of Medical Genetics at UBC, and a Senior Scientist at the Centre for Molecular Medicine and Therapeutics, a gene research centre under UBC's Faculty of Medicine and located at the Child and Family Research Institute (CFRI). In addition,

Dr. Kobor holds the Canada Research Chair in Social Epigenetics and serves as the Director of the Program on Social Epigenetics at the Human Early Learning Partnership (HELP) in UBC's School of Population and Public Health. Dr. Kobor's research program at UBC is focused on illuminating the developmental origins of health and disease across the human lifespan. Building upon deep expertise in gene regulation and epigenetics developed over the course of his career, Dr. Kobor is combining fundamental discovery research in model organisms with translational research in human populations. His research is expanding to include a rapidly growing interdisciplinary research thrust on human population epigenetics tackled in close partnership with researchers from child development, psychology, psychiatry, and epidemiology. These studies aim to decipher the mechanisms by which environmental exposures and life experiences can "get under the skin" to regulate the activity of genes and contribute to human physiology and behaviour during the life course of an individual. Dr. Kobor is a Senior Fellow of the Canadian Institute for Advanced Research (CIFAR) Child and Brain Development Program, a Mowafaghian Junior Scholar, and an Investigator with NeuroDevNet NCE and AllerGen NCE Inc. He also serves on the Management Committee of the BC Clinical Genomics Network and is the co-Director of the Genetics and Epigenetics Centre within the Canadian Longitudinal Study of Aging (CLSA), a national cohort for which he also chairs the Training and Research Capacity Committee.

Simon Fraser University

Dr. Andrew Wister is Chair and Professor, Department of Gerontology, and an internationally recognized expert on aging research, issues, policies, and training. Dr. Wister is currently the lead on the SFU Data Collection Site, part of the Canadian Longitudinal Study of Aging (CLSA), as well as the Chair of the CLSA Operations Committee. He is also collaborating on the 5 year SFU Community Trust Fund Endowment (CTEF) LivWell grant entitled "Using a Systems Analytic Approach to Living with Chronic Diseases." He has conducted extensive research covering: population aging and population health with a focus on baby boomer health dynamics; health promotion and evaluation; healthy lifestyle interventions; chronic illness, multiple morbidity and aging; self-care, self-help & mutual aid; and living environment transitions. His most recent authored books include Baby Boomer Health Dynamics: How Are We Aging? (2005) published by University of Toronto Press, and Aging as a Social Process: Canadian Perspectives, 6th Edition (2014) published by Oxford University Press (A. Wister & B. McPherson). Dr. Wister has extensive experience in the collection and analyses of health and social data among older adults and baby boomers, and will contribute expertise in all phases of the CLSA.

University of Victoria

Dr. Debra Sheets received her doctorate in gerontology and public policy from the University of Southern California. She is a board certified as a gerontological nurse and as a nurse educator.

- Elected fellow of the Gerontological Society of America as well as the Association for Gerontology in Higher Education (AGHE);
- Member of Sigma Theta Tau (nursing honor society);
- Former president of Sigma Phi Omega (SPO), the gerontological honor society.

Dr. Sheets has 20 years of clinical nursing experience and Chair the School of Nursing's Undergraduate Curriculum Committee. I also serve on the Undergraduate Program committee, Graduate Nursing Committee, and Nursing Education Subcommittee. She was elected to represent the HSD faculty for the Senate and serve on the Senate Appeals Committee and the Senate Committee on Learning and Teaching at the University of Victoria. She and Dr Lynne Young are local site co-investigators for the University of Victoria CLSA Data Collection Site and CATI Site.

Dr. Lynne Young is a Professor in the School of Nursing in the faculty of Human and Social Development at the University of Victoria and Centre on Aging. She received a doctorate in nursing from the University of British Columbia and completed post-doctoral research at the University of Washington School of Nursing. Her post-doctoral research involved completing an analysis of two large data bases informed by a qualitative study and implemented using a participatory approach. Dr Young's main research interests lie in the areas of women's health and cardiovascular care. She and Dr Debra Sheets are local site co-investigators for the University of Victoria CLSA Data Collection Site and CATI Site.

Dr. Holly Tuokko is a Professor in the Centre on Aging and the Department of Psychology at the University of Victoria. She held a CIHR Senior Investigator award from the Institute of Aging, CIHR (2002-2007) for research in mental health and aging. The current focus of her research is the evolution of cognitive disorders in older adults, the impact these disorders have on functional competencies and how attitudes affect behavior. A major goal of her work is to understand the mediational role attitudes play in the relations between the capabilities of the person and the adaptive behaviors in which they engage. She has published many articles in the field, and serves on the editorial boards of numerous international journals and review boards for various granting agencies and has authored textbooks in the field of geriatric neuropsychological assessment. Dr. Tuokko is the lead of the CLSA Psychology Working Group.

Biomarker Study Team

Dr. Cynthia Balion is an associate professor in the Department of Pathology and Molecular Medicine at McMaster University, clinical biochemist for the Hamilton Regional Laboratory Medicine Program (HRLMP), co-investigator with the Canadian Longitudinal Study on Aging (CLSA) and director of the CLSA Biorepository and Bioanalysis Centre (BBC). She conducts research in the fields of point of care, evidence-based laboratory medicine, geriatric clinical biochemistry, and blood-based biomarkers of dementia

Dr. Michael S. Kobor is an Associate Professor in the Department of Medical Genetics at UBC, and a Senior Scientist at the Centre for Molecular Medicine and Therapeutics, a gene research centre under UBC's Faculty of Medicine and located at the Child and Family Research Institute (CFRI). In addition, Dr. Kobor holds the Canada Research Chair in Social Epigenetics and serves as the Director of the Program on Social Epigenetics at the Human Early Learning Partnership (HELP) in UBC's School of Population and Public Health. Dr. Kobor's research program at UBC is focused on illuminating the developmental origins of health and disease across the human lifespan. Building upon deep expertise in gene regulation and epigenetics developed over the course of his career, Dr. Kobor is combining fundamental discovery research in model organisms with translational research in human populations. His research is expanding to include a rapidly growing interdisciplinary research thrust on human population epigenetics tackled in close partnership with researchers from child development, psychology, psychiatry, and epidemiology. These studies aim to decipher the mechanisms by which environmental exposures and life experiences can "get under the skin" to regulate the activity of genes and contribute to human physiology and behaviour during the life course of an individual. Dr. Kobor is a Senior Fellow of the Canadian Institute for Advanced Research (CIFAR) Child and Brain Development Program, a Mowafaghian Junior Scholar, and an Investigator with NeuroDevNet NCE and AllerGen NCE Inc. He also serves on the Management Committee of the BC Clinical Genomics Network and is the co-Director of the Genetics and Epigenetics Centre within the Canadian Longitudinal Study of Aging (CLSA), a national cohort for which he also chairs the Training and Research Capacity Committee.

Dr. Andrew Paterson is a Senior Scientist in the Program in Genetics and Genome Biology at The Hospital for Sick Children Research Institute in Toronto. He is an Associate Director of The Center for Applied Genomics, a Canadian Genome Center also at The Hospital for Sick Children, and also an Professor in the Epidemiology and Biostatistics Divisions at the Dalla Lana School of Public Health and Institute of Medical Sciences at the University of Toronto. From 2002-12 he held the Canada Research Chair in genetics of complex diseases.

His scientific interests concentrate on the genetics of human diseases. Specifically, he is the lead investigator on large study to investigate the genetic determinants of risk for long-term complications of type 1 diabetes, including retinopathy and nephropathy. He has also worked on a number of other traits, including bleeding disorders, autistic traits, polycystic kidney disease, inflammatory bowel disease, as well as measures of eye sight, heart rate, breast density and blood pressure.

Dr. Paterson has published over 180 papers in various scientific journals. He has presented his research nationally and internationally at numerous conferences and universities.

Dr. Mark Lathrop is a renowned Canadian genomics pioneer Mark Lathrop has been most recently the scientific director of the Centre National de Genotypage (CNG) and of the Fondation Jean Dausset

Centre d'Étude du Polymorphism Humain (CEPH) in Paris, two of the major centres for largescale biological research established by the French government. The principal goal of these centres is to apply genomics and other large-scale methodologies to understanding human disease.

Born in 1950 in Alberta, Prof. Lathrop completed his Bachelor of Science and Master's degrees at the University of Alberta before obtaining his PhD at the University of Washington (Seattle) in biomathematics. He then moved to France, where he was one of the founders of the CEPH, which pioneered international collaboration on the human genome in the 1980s and 1990s.

In 1993, Prof. Lathrop moved to the University of Oxford, where he was at the Wellcome Trust Centre for Human Genetics, an institute created to apply genomic approaches to understanding the molecular basis of human disease. He also co-founded the biotechnology company Oxagen while at the University of Oxford.

Dr. Helene Girouard completed her PhD in cardiovascular physiology in 2002 at the Université de Montreal under the supervision of Dr J. de Champlain, a specialist in the field of hypertension. She then pursued with two fellowships both on the study of cerebrovascular regulation: one at the Weill Medical College of Cornell University with Dr C. Iadecola and a second one at the University of Vermont with Dr Mark T. Nelson. She is now associate professor at the department of pharmacology at the Université de Montréal and the director of the laboratory of neurovascular pharmacology.
The research interests of Dr Girouard are the study of the mechanisms underlying cerebrovascular regulation in health and diseases especialy in the context of vascular dementia. The main objective of her research is to find therapeutical targets to protect the brain in vascular diseases. To reach this objective, she is using various techniques from molecular biology to brain imaging in mice and humans. She published mostly in the field of hypertension and cerebrovascular regulation.

Dr. Paola Muti is a cancer epidemiologist who hold the Mittal-Arcelor-Dofasco Chair in Experimental Cancer Therapeutics at the McMaster University, Hamilton, Ontario. Over the past twenty years, much of Dr. Muti's research has focused on epidemiological methods, particularly on the use of biomarkers in population-based studies and cancer epidemiology. She has investigated methodological questions related to the application of biomarkers in epidemiology of chronic diseases, conducted transitional studies and explored sources of variation in biomarkers. She has received national and international recognition for her work on biomarkers and biological specimen banks. Currently, her major research area is cancer genomics-translational research with a focus on cancer risk assessment and prevention.

Dr. Jane Rylett is a molecular neurobiologist and Alzheimer's disease researcher recognized for contributions in the field of cholinergic neurobiology. She is Professor and Chair, Department of Physiology and Pharmacology, Western University, and Scientist, Molecular Medicine Group, Robarts Research Institute. She received the PhD in Pharmacology, followed by postdoctoral training in neuropharmacology at University of London (England) and neurochemistry at Max-Planck-Institute for Biophysical Chemistry (Germany). She was recruited to a faculty position at Western University as Rubinoff Scholar in Geriatrics.

Her laboratory studies regulation of cholinergic neuron function, and how neurochemical communication is altered in aging and disease. Her research has been funded by agencies including CIHR, Alzheimer Society Canada, Alzheimer's Association [USA], and Ontario Mental Health Foundation. She is leader of the Primary Prevention Theme of Canadian Consortium on Neurodegeneration in Aging. She has received numerous research awards, including Beaubien Award from Alzheimer Society Canada and AltaPharm Senior Scientist Award from Pharmacological Society Canada. Dr. Rylett was appointed Chair of the Institute Advisory Board for CIHR Institute of Aging,

served on Board of Directors of Alzheimer Society Ontario and Alzheimer Society Canada, and as Secretary of Pharmacological Society Canada. She was awarded the Queen Elizabeth II Golden Jubilee Medal by the Governor General Canada for volunteer work and community activities in Alzheimer's disease and the elderly. In 2013, she was appointed Distinguished University Professor at Western University and elected Fellow of Canadian Academy of Health Sciences.

Dr. Pierre Ayotte is Faculty at Direction Toxicologie humaine, Institut national de santé publique du Québec. His area of expertise is Environmental risk factors in breast cancer, Development and validation of biological indicators in environmental epidemiology, Highlighting of the hormonal properties of environmental contaminants

Dr. Hossein Sadrzadeh serves as a Chief of Clinical Biochemistry of Calgary Laboratory Services. Professor of Pathology and Laboratory Medicine University of Calgary; Chief of Clinical Biochemistry Section.

Dr. Alex Chin is a Clinical Assistant Professor, Department of Pathology & Laboratory Medicine and Clinical Chemist, Diagnostic & Scientific Centre, Calgary Laboratory Services