Biomarkers of Frailty: A Collaboration between CLSA, CFN, Metabolon & MIRA

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Canadian Frailty Network
September, 2019, Toronto, ON
What is the Canadian Longitudinal Study on Aging (CLSA)?

A research platform – Infrastructure to enable state-of-the-art, interdisciplinary population-based research and evidenced-based decision-making that will lead to better health and quality of life for Canadians.
Participants aged 45 to 85 at baseline (51,338)

Active follow-up every 3 years

CLSA Research Platform

50,000 women and men aged 45 - 85 at baseline

Target: 20,000
Actual: 21,241
Randomly selected within provinces

Target: 30,000
Actual: 30,097
Randomly selected within 25-50 km of 11 sites

Questionnaire
• By telephone (CATI)

Questionnaire
• In person, in home (CAPI)

Clinical/physical tests
Blood, urine
• @ Data Collection Site

2010 - 2015  2015  2018
Baseline & Follow-up 1 Questionnaires
Tracking & Comprehensive

Socio-Demographic
- Age
- Sex
- Country of birth
- Ethnicity
- Culture
- Language
- Veteran Identifiers
- Education
- Province of residence
- Urban / Rural
- Religion
- Marital status
- Sexual orientation
- Income
- Wealth
- Home Ownership
- Gender identity
- Vital status

Lifestyle & Behaviour
- Smoking
- Alcohol Use
- Nutritional Risk
- Physical Activities
- Dietary Supplement Use

Current Data Availability: [www.clsa-elcv.ca/data-availability](http://www.clsa-elcv.ca/data-availability)
Baseline & Follow-up 1 Questionnaires
Tracking & Comprehensive

- Self-Reported Chronic Conditions & Disease Symptoms:
  - Diabetes
  - Stroke/Cerebrovascular
  - Traumatic Brain Injury
  - Hypo & Hyperthyroidism
  - Hypertension
  - Ischemic Heart Disease
  - Osteoarthritis of the Hand
  - Osteoarthritis of the Hip
  - Osteoarthritis of the Knee
  - Musculoskeletal
  - Osteoporosis
  - Neurological
  - Neuropsychiatric
  - Asthma
  - COPD
  - Gastrointestinal
  - Cancer
  - Epilepsy

Baseline only
- General Health
- Women’s Health
- Vision
- Hearing
- Oral Health
- ADL/IADL
- Pain and Discomfort
- Health Care Utilization
- Injuries
- Falls
- Falls due to Consumer Products
- Preventative Health Behaviours
- Hearing Handicap Inventory for the Elderly
- Unmet Health Care Needs

Follow-up 1 only

Physical Health

Current Data Availability: www.clsa-elcv.ca/data-availability
Baseline & Follow-up 1 Questionnaires
Tracking & Comprehensive

Psychological Health
- Depression
- General mental health (self-reported)
- Satisfaction with Life
- Post-traumatic Stress Disorder
- Cognitive Battery:
  - Rey I/Rey II
  - Animal Fluency Test
  - Mental Alternation Test
  - Meta Memory
  - Subjective Cognitive Decline
- Loneliness Scale
- Childhood Maltreatment Elder Abuse

Labour Force
- Retirement Status
- Pre-Retirement Labour Force Participation
- Pre-Retirement Labour Force Participation – open text
- Labour Force
- Labour Force – open text question
- Retirement Planning*
  - Work Limitations Questionnaire

Social Health
- Social Networks
- Social Support – Availability
- Social Participation
- Care Receiving 1/ Formal Care
- Care Receiving 2/ Informal Care
- Care Giving
- Social Inequality
- Online Social Networking
- Transportation, Mobility, Migration
- Built Environments
- Social Cohesion

*Abbreviated in Comprehensive

Current Data Availability: www.clsa-elcv.ca/data-availability

Baseline only
Follow-up 1 only
Baseline & Follow-up 1 Questionnaires
Tracking & Comprehensive

Comprehensive Only
• Short Diet Questionnaire
• Disease Algorithms & Disease Symptoms
• Medications
• Sleep & Snoring
• Life Space Index
• Psychological Distress
• Personality Traits

Tracking Only
• Self-reported Height
• Self-reported Weight
• Functional Status
• Dietary Supplement Use
• Medication Use

Current Data Availability: www.clsa-elcv.ca/data-availability
**Physical Assessments**

**Comprehensive Only**

- Measured Height/Weight
- Body Mass Index
- Hip & Waist Circumference
- Blood pressure & Pulse Rate
- Body Composition
- Timed Get Up and Go
- Standing balance
- 4-metre walk
- Chair rise
- Grip strength
- Visual Acuity
- Fundus Scans (Diabetic Retinopathy & micro vessel disease)
- Tonometry
- Hearing
- Spirometry
- Carotid Intima Media Thickness
- Carotid Pulse Wave Velocity
- ECG, Aortic Calcification
- Bone Density by DXA
- Body Composition by DXA

**Psychological Measures**

- Full Cognitive Battery*
  - Miami Prospective Memory Test (event- & time-based)
  - Stroop – Victoria Version
  - Controlled Oral Word Association Test
  - Choice Reaction Time
  - Meta Memory
  - Subjective Cognitive decline

*Includes Rey, Mental Alternation & Animal Fluency Tests. Meta Memory, Subjective Cognitive Decline

**Biospecimens**

- Blood
  - Serum
  - Plasma
  - Buffy Coat
  - Whole blood
  - Cells
  - DNA
  - PBMC
- Urine
  - Random

**Current Data Availability:** [www.clsa-elcv.ca/data-availability](http://www.clsa-elcv.ca/data-availability)
Upcoming Follow-up 1 Releases

- Cognition
- Alphanumeric physical assessment data:
  - Spirometry
  - Hearing
  - Visual acuity, Tonometry, Fundus Scans
  - Electrocardiogram
  - Carotid-intima Media Thickness
- Hematology

Available Fall 2019
Upcoming Releases

- Chemistry FU-1
- Epigenetics (Baseline)
- Metabolomics (Baseline)
- Medications Baseline & FU-1

Anticipated 2019-2020
Follow-up 2
New Data

- Positive Mental Health
- Generalized Anxiety Disorder
- Digit Triplet Test for Hearing
- Sitting Height measurement
- Weight Perception
- Resiliency
- Intimate Partner Violence
- Post-traumatic Stress Disorder (re-introduced)

Data collection launched Summer 2018
Ends 2021

Follow-up 2
New Data
CLSA Biomarkers for Frailty Research
THE JOURNAL OF FRAILTY & AGING

PROCEEDINGS OF THE CANADIAN FRAILTY NETWORK WORKSHOP: IDENTIFYING BIOMARKERS OF FRAILTY TO SUPPORT FRAILTY RISK ASSESSMENT, DIAGNOSIS AND PROGNOSIS.

TORONTO, JANUARY 15, 2018


FOR THE CANADIAN FRAILTY NETWORK
Principles to Guide Future CFN biomarker initiatives

1) Biomarkers should reflect a pathophysiological pathway or mechanism that is fundamental to frailty onset, development/progression and severity. Conceptually there may be two categories of biomarkers:
   • i) Biomarkers that are linked with frailty but are not causal to the pathophysiology of frailty. These would not be actionable.
   • ii) Biomarkers that are a component of the pathophysiology of frailty and have a causal role. These would be actionable such that the modulation of the biomarker could directly affect the onset or severity of frailty and/or progression of frailty.

2) The utility of biomarkers can be classified into two different types:
   • i) Biomarkers to increase the utility of (or support) existing clinical frailty measures (e.g., FI).
   • ii) Biomarkers to be used independently of clinical frailty measures.

3) Biomarkers should be able to be embedded in clinical assessments and tools, but more research on how to best achieve this is needed. Concomitant use of both a clinical frailty assessment instrument and biomarkers is likely to be the optimal method to bring about personalized frailty assessment and individualized care plans.

4) Biomarkers chosen for a clinical tool should be evaluated on their ability to accomplish the ultimate clinical purpose. For instance, biomarkers used for diagnosis may be different from those used for risk assessment, which may differ from those used for prognosis.

5) Different care settings are likely to require different biomarkers due to variation in prevalence of both frailty and biomarkers in different populations.

6) Any candidate biomarker should be validated in different populations, care settings and environments.

7) An ideal frailty biomarker would be able to measure the effectiveness of an intervention.

8) Practical considerations related to ease of measurement (i.e., special instruments and/or expertise required) and ease of securing biological samples (e.g., tissue biopsy vs blood sample collection) should be considered when selecting frailty biomarkers.
CLSA biospecimens

Legend:
- Citrate
- Serum
- Heparin
- EDTA
- ACD
- CPT
- Urine

0.5 mL Matrix tube with 2D barcode

Hematology tests performed at the DCS

First Centrifugation

Second Centrifugation

Serum

Plasma

Buffy Coat

Addition of DMSO

Centrifugation and Cell Washing

Resuspension in PBS

Platelet poor plasma

Plasma

Whole Blood

Cells

Mononucleocytes

Urine

GenPlate
## Core Biomarkers in the CLSA

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<tr>
<th>Category</th>
<th>N</th>
<th>Biomarkers</th>
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<td>- Alanine aminotransferase (ALT)</td>
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<td>- C-reactive protein (CRP)</td>
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<td>- Creatinine</td>
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<td>- Cholesterol</td>
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<td>- Free T4</td>
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<td>- eGFR</td>
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<td>- TNF-Alpha (n=10,000) (FU-1)</td>
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<td>- ~1,300 metabolites</td>
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<td><strong>GENETICS</strong></td>
<td>26,871*</td>
<td>- Genotypes (Affymetrix Axiom array, 794k SNPs)</td>
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<td>- Imputation (Haplotype Reference Consortium release 1.1, 39.2M SNPs)</td>
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<td>- Platelets</td>
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Metabolon’s HD4 Global Metabolomics Profiling
Screens >5000 Named and >7000 Unnamed Biochemicals And Reports
Back All Detected

Metabolite Coverage
The DiscoveryHD4 platform provides the industry’s broadest class coverage from a single sample.

### Amino Acid Metabolism
- Amino Acid catabolism
- Bioactive intermediates & toxic amines
- Glutathione metabolism
- Inflammatory mediators
- Microbiome metabolism
- Polyamines/ornithine metabolism
- Urea Cycle

### Cofactor & Vitamin Metabolism
- Ascorbate metabolism
- CoA metabolism
- FAD metabolism
- Folate metabolism
- NAD/NADP metabolism
- PLP metabolism
- SAM metabolism
- Many other cofactors and vitamins (tocopherol, B12, Biotin)

### Nucleotide Metabolism
- Degradation of nucleotides
- Deoxyribonucleotides
- DNA damage
- FAD metabolism
- Modified nucleotides
- Nucleotide Coenzymes
- Purine and pyrimidine de novo synthesis
- Purine and pyrimidine salvage synthesis
- Ribose metabolism

### Microbiome Metabolism
- Z+ bile acids
- Aromatic amino acids
- Energy
- Choline/carnitine
- Xenobiotics
- Fatty acids/short chain medium chain
- Vitamins
- Polyamines

### Carbohydrate Metabolism
- Gluconeogenesis
- Glucose metabolism
- Glycogen metabolism
- Glycolysis/pathways
- Metabolism of other carbon sources
- Metabolism of sugars (fructose, galactose)
- Polyol metabolism
- Pyruvate metabolism

### Energy Metabolism
- Acyl-carnitines
- Beta-oxidation
- Creatine metabolism
- FAD metabolism
- Glycolysis
- Mitochondrial function
- Pentose phosphate pathway

### Lipid Metabolism
- Bile acids
- Bioactive lipids
- Cholesterol
- Fatty acids
- Sphingolipids
- Inflammatory mediators
- Lyso phosphatidylcholines
- Sterols
- Oxidized lipids (COX, LOX)

### Novel Metabolites
- Novel drug metabolites
- Novel xenobiotics
- Novel microbiota metabolites
- Novel by-products of non-canonical host metabolism

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Around 1,000 metabolites across diverse classes can be measured* from 100 μL of plasma/serum, 50-100 mg of tissue, or a 50-100 μL cell pellet with approximately 5% CVs.

* The metabolites detected from the above classes can vary based on the type of sample and the abundance levels in those samples.
About 200 molecules are derived from bacterial metabolism

**Short chain FA:**
- valerate
- Isovalerate
- Methylpropionate

**Lipids:**
- Lyso-PC, lyso-PE
- Monacylglycerol
- cholesterol

**Phenylpropanoids**
- phenyllactate
- phenylacetate
- 3-(4-hydroxyphenyl)propionate
- 3-(4-hydroxyphenyl)propiolate
- 3-(4-hydroxyphenyl)propionate
- 3-phénylpropionate
- phenol sulfone
- 4-hydroxy-3-carboxylic acid
- indoleacetate
- indole-3-carboxylic acid
- n-acetyltryptophan
- indolepropionate
- skatol
- indoleacetylglutamine

**Energy metabolism**
- lactate
- formate, succinate
- glucose
- urea
- creatine
- creatinine
- ketoisovalerate

**Aromatic amino acid metabolism**
- cadaverine
- putrescine
- spermidine
- spermine

**Polyamine metabolism**
- riboflavin
- pyridoxine
- folate

**Energy metabolism**
- trimethylamine-n-oxide
- betaine
- dimethylglycine

**Bile acid metabolism**
- 2nd bile acids:
  - cholate
  - dehydrocholate
  - ursodeoxycholate
  - deoxycholate
  - glycodeoxycholate
  - ketodeoxycholate
  - glycolithocholate sulfate
  - taurocholate
  - taurocholate sulfate
  - lithocholate
  - dikelithocholate
  - ketolithocholate
  - hydroxycholate
  - glycocholenate sulfate
  - taurochenate sulfate
  - glycochololate
  - taurocholate

**Xenobiotic metabolism**
- hippurate
- 2-hydroxyhippurate
- 3-hydroxyhippurate
- 4-hydroxyhippurate
- 3-hydroxybenzoate
- 4-hydroxybenzoate
- 3,4-dihydroxybenzoate
- 2,4,6-trihydroxybenzoate
- p-hydroxybenzaldehyde
- methyl-4-hydroxybenzoate
- 3-(2-hydroxyphenyl)propionate
- vitexin
- daidzein
- genistein

- Exclusively or mainly contributed by bacteria metabolism
- Contributed by both mammalian cells and bacteria
The Metabolome

The metabolome is tightly connected with other “omes.” The metabolome interacts and reflects the activity of the genome, transcriptome, and proteome.

The end result of all biological & environmental interactions is the definitive way to fully understand the phenotype.
NEW OMICS TECHNOLOGIES IN THE CLSA

• Proteomics (O-LINK Multi-Plex Platform)
  • Inflammation panel (1500 CLSA Participants)
    • Available in Fall of 2020

• Whole Genome Sequencing on 500 CLSA participants over two time periods (Pilot)
  • Genetic Instability (Fall of 2020)

• Whole Exome Sequencing discussions in progress
Applying for Data Access

- **Magnolia**, a new web-based data access application system
- User account requests: access@clsae-lcv.ca
- 2-3 working days to receive login information
Applicants advised to plan on receiving data six months after submission deadline
Data Access Fees

• **Partial Cost Recovery Model**
  • **Alphanumeric data**
    • CAD $3,000 for researchers based in Canada
    • CAD $5,000 for researchers based at institutions outside of Canada
  • **Graduate students** using data solely for thesis research & **Postdoctoral fellows** using data solely for the postdoctoral project are eligible for a **fee waiver (once as postdoc)**
  • Trainees must be enrolled at a Canadian institution or be supported by Canadian funds if working outside Canada

• **Images & Complex data**
  • Additional fees of CAD $1,000 apply for access to image files, raw data and datasets that require more complex customization
Contact:
Data inquiries: access@clsa-elcv.ca
General inquiries: info@clsa-elcv.ca

CLSA is funded by the Government of Canada through CIHR and CFI, and provincial governments and universities

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