Transforming Everyday Life into Extraordinary Ideas
Canadian Longitudinal Study on Aging: Advancing the Science of Population Health and Aging through Interdisciplinary Research

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Population aging

- Due to declining fertility and increasing longevity (demographic transition)
- Unprecedented, accelerating, shifts will be permanent
- Profound implications for human life, including health
Rectangularization of the survival curve
Compression of morbidity

- Morbidity compressed into a short period prior to death
- Represented an important shift in thinking
- Departure from the medical model of aging, which assumed that death always occurred as a result of a disease process, and that older age was a period of inevitable decline

Figure: Mortality According to Age in the Absence of Premature Death
Compression of morbidity

Fries’ paradigm based on the premise that:

• The length of human life is fixed
  AND
• Chronic disease can be postponed

• Predicted that the increase in life expectancy would plateau in the coming decades, particularly life expectancy from age 65 which excludes early life mortality
Distribution of life table deaths

U.S. females
1900
1985
Theoretical

Life expectancy at birth
(U.S. 1900)

Life expectancy at birth
(U.S. 1988)

Range of theoretical estimates for average life-span

Verified longest lived individual as of 1990
Evidence suggests otherwise

- Is average life expectancy approaching an upper limit to life expectancy?
  - The evidence that the average life span is 85 years is unconvincing
  - There is no evidence for further rectangularization of survival curves

- Will age at first infirmity increase?
  - There is no evidence for over-all declines in incidence of morbidity: on the contrary
  - Evidence for actual "(de)compression" of morbidity is ambiguous
Historical increases of life expectancy
Oepen and Vaupel, Science 2002; C Finch adaptation

Phase 1
early urban

Phase 2
sanitation-nutrition

Phase 3?
regeneration
modern medicine
Social Policy Innovation

Life-expectancy in years

1550 1600 1650 1700 1750 1800 1850 1900 1950 2000 2050

England
Norway
New Zealand
Iceland
Netherlands
Sweden
Japan
Demographic Futures

Upward trend in life expectancy continue, cease, or reverse?

+ Effective interventions against age-related diseases
+ Improved environment for ageing
+ Life-cycle deceleration (delayed reproduction)

- Adverse effects of excess nutrition
- Adverse effects of alcohol and drug abuse
- Adverse effects of increasingly sedentary lifestyles
- Life-cycle acceleration (early maturation)
Why aging occurs

Intrinsic

Extrinsic

How aging is caused
# Genes Associated With Avoiding Late-Life Disease in Humans

## Table 4

<table>
<thead>
<tr>
<th>GENE</th>
<th>BIOCHEMICAL FUNCTION</th>
<th>COMMENTS</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE</td>
<td>Lipoprotein metabolism</td>
<td>E2 variant is frequent in centenarians while E4 variant as a risk factor for Alzheimer’s disease is rare in centenarians.</td>
<td>Schachter et al. 1994</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
<td>Plays a role in regulating blood pressure.</td>
<td>Schachter et al. 1994</td>
</tr>
<tr>
<td>PAI1</td>
<td>Plasminogen activator inhibitor 1</td>
<td>Plays a role in blood clotting, thus affecting risk of stroke and heart attack.</td>
<td>Mannucci et al. 1997</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>Histocompatibility locus antigen</td>
<td>DR variant is frequent in centenarians; resists infection and inflammation?</td>
<td>Ivanova et al. 1998</td>
</tr>
<tr>
<td>WRN</td>
<td>Possesses both DNA helicase and exonuclease activity</td>
<td>Gene responsible for Werner’s Syndrome; mutation leads to a variety of aging-related pathologies, e.g., cataracts, cancer, osteoporosis, slow wound healing, etc.</td>
<td>Yu et al. 1996</td>
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<td></td>
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<td>Huang et al. 1998</td>
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<td>Martin and Oshima 2000</td>
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<tr>
<td>B3AR</td>
<td>B-3 adrenergic receptor</td>
<td>Allelic form present affects time of onset of Type 2 diabetes.</td>
<td>Walston et al. 1995</td>
</tr>
<tr>
<td>MTHFR</td>
<td>5-, 10-methylenetetrahydrofolate reductase</td>
<td>Deficiency leads to increased levels of homocysteine and DNA hypomethylation; increases risk of cardiovascular disease and cancer.</td>
<td>Heijmans et al. 2000</td>
</tr>
<tr>
<td>KLOTHO</td>
<td>Membrane protein with $\beta$-glucosidase activity?</td>
<td>Homozygous variant form is underrepresented in elderly individuals.</td>
<td>Arking et al. 2002</td>
</tr>
</tbody>
</table>
Genetic Heritability of Human Lifespan
Cournil & Kirkwood *Trends in Genetics* 2001

**Twin Studies**
- McGue et al (1993) 0.22
- Herskind et al (1996) 0.25
- Ljungquist et al (1998) <0.33

**Traditional Family Studies**
- Philippe (1978) 0-0.24
- Bocquet-Appel & Jakobi (1990) 0.10-0.30
- Mayer (1990) 0.10-0.33
- Gavrilova et al (1998) 0.18-0.58
- Cournil et al (2000) 0.27

Genes account for 25% of what determines disease and longevity
Non-Biological/Medical Determinants of Aging?

- Nutrition
- Lifestyle
- Environment
  - Physical
  - Social
  - Economic
  - Work Place
  - Psychological
- Chance
Intrinsic and Extrinsic Factors

Environmental influences
(e.g., rural, socio-economic, exercise, nutrition)

Chronic diseases
(e.g., diabetes, cancer, dementia, arthritis, cardio)

Inflammation
infections

Health & Social Services Utilization

Time (Longitudinal Study)
The Canadian Longitudinal Study on Aging (CLSA)

A key strategic initiative of CIHR

More than 160 researchers - 26 institutions

Multidisciplinary - biology, genetics, medicine, psychology, sociology, demography, economics, epidemiology, nursing, nutrition, health services, biostatistics, population health
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.
Our Aim

To study aging as a dynamic process and the inter-relationship among intrinsic and extrinsic factors from mid-life to older age.
Innovation - Cell to Society

- Mid life to old age
- Quantitative traits
  - Physical
  - Social
  - Psychological
- Gene-environment interactions
- Disease, disability, psychosocial consequences
- Adaptation
Overall Aims of the CLSA

- The progression of **health** from middle-age to early old age to older old age
- The determinants of **well-being and quality of life**
- Risk Factors (including genetics) of **Chronic diseases**
- **Cognitive functioning** and **mental health**
- **Disability** and the compression of morbidity
- The examination of socioeconomic and health **inequalities** in an aging population
- **Social participation, social relationships and care giving** in an aging population
- **Retirement** and **post retirement** labor market activity
Participant Recruitment

- Vancouver
- Victoria
- Surrey
- Calgary
- Winnipeg
- Hamilton
- Ottawa
- Montreal
- Sherbrooke
- Halifax
- St. John’s
Participants (50,000)

Enrolled

Questionnaire Data (50,000)

Physical Exam and Biological Specimen (30,000)

Active Follow-up (F) Every 3 years
- Questionnaire
- Physical exam
- Biological samples

Maintaining Contact Interview (MC) mid-wave
- Update contact information
- Short Questionnaire

Passive Follow-up Every 3 years
- Health care utilization
- Disease registries
- Mortality databases

Data and Biological Sample Repositories

Researchers
Depth and Breadth of CLSA

**PHYSICAL & COGNITIVE MEASUREMENTS**
- Height & weight
- Waist and hip measurements
- Blood Pressure
- Grip strength, timed up-and-go, chair raise, 4-m walk
- Standing balance
- Vision (retinal imaging, Tonometer & visual acuity)
- Hearing (audiometer)
- Spirometry
- Body composition (DEXA)
- Bone density (DEXA)
- Aortic calcification (DEXA)
- ECG
- Carotid Plaque sweep (ultrasound)
- Carotid intima-media thickness (ultrasound)
- Cognitive assessment (30 min. battery)

**HEALTH INFORMATION**
- Chronic disease symptoms (**disease algorithm**)
- Medication and supplements intake
- Women’s health
- Self-reported health service use
- Oral health
- Preventative health
- Administrative data linkage health services & drugs & other administrative databases

**PSYCHOSOCIAL**
- Social participation
- Social networks and support
- Caregiving and care receiving
- Mood, psychological distress
- PTSD
- Coping, adaptation
- Injuries and consumer products
- Work-to-retirement transitions
- Retirement planning
- Social inequalities
- Mobility-lifespace
- Built environments & Contextual Factors
- Income, Wealth and Assets

**LIFESTYLE & SOCIODEMOGRAPHIC**
- Smoking
- Alcohol consumption
- Physical activity (PASE)
- Nutrition (nutritional risk and food frequency)
- Birth location
- Ethnicity/race/gender
- Marital status
- Education
Data Collection Sites (DCS)

11 ACROSS CANADA

- 5 participants per day (40 weeks)
- 50 mL blood
- Urine sample
- Hematology tests (AcT DIFF, Beckman Coulter)
Bio specimens
42 aliquots per participant
Storage System

Tubes

§ 500-μL V bottom, screw-top tubes (Matrix Tubes, Thermo Fisher Scientific)
§ Open-bottomed boxes for fast scanning
§ Standard 96 well format
§ Potential for ‘pick and place’ robotic retrieval and storage box compression ('defragging')

Microwell Plates

§ 3-section GenPlates (Genvault) with FTA paper
§ Standard 96 well format
§ Dried overnight in GenVault FastDryer and sealed with an adhesive foil cover
Shipping

Matrix boxes
§ Pre-charged vapor shippers (-160°C)
§ Weekly shipments to BBC (overnight courier)
§ Equipped with data loggers

GenPlates
§ Envelopes with dessicant
Quality

*Standard protocols to minimize process variation*

**Supplies**
§ Received by the BBC and packaged for monthly shipments to the DCS
§ Barcode labels for supplies generated at BBC
§ Lot numbers and expiry dates tracked centrally

**Biospecimens**
§ Scanned at each stage of processing and handling to provide a detailed history of the biospecimen
§ Characteristics of samples documented
§ Sample integrity maximized
  o Maximum time from collection to storage is 2 h
  o Storage at -160°C
CLSA Infrastructure

- National Coordinating Centre (McMaster)
- Biorepository and Bioanalysis Centre (McMaster)
- IT Infrastructure (McMaster)
- Statistical Analysis Centre (McGill)
- Genetics and Epigenetics Centre (UBC)
- 4 Computer-Assisted Telephone Interview Sites
  - Victoria, Winnipeg, Sherbrooke and Halifax
- 11 Data Collection Sites
  - Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton/Toronto, Ottawa, Montreal, Sherbrooke, Halifax and St. John’s
**Biorepository and Bioanalysis Centre (BBC)**

**Biorepository**
- Installation May 2012
- LIMS implementation April
- Hiring BBC coordinator
Biorepository and Bioanalysis Centre (BBC)

Biorepository

- 31 nitrogen tanks (5 million aliquots)
- Autofilled from a bulk nitrogen tank
- Cryocarts
- Personal Archive, dry storage at room temperature (humidity controlled)
- LI MS (LabWare)
- CryoMORE, (Air Liquide) safety monitoring system
CLSA collaborated with Statistics Canada to develop Sampling Strategy

- **Target population**: People aged 45-85 living in private occupied dwellings in the ten provinces

- **Excluded**:
  - Residents of the three territories
  - Persons living on Indian reserves or Crown lands
  - Persons living in institutions
  - Full-time members of the Canadian Forces
  - Residents of some remote regions
Sampling

- Choose representative sample of eligible Canadians
  - 20K Tracking cohort; 30K Comprehensive cohort
  - Specified numbers in age-sex groups by province
- Options for methods of selection:
  - Statistics Canada
  - Using provincial health registries
  - Random digit dialing
- In Alberta and maybe BC, it appears we cannot use registries
Tracking Cohort of the CLSA (n=20,000)
Baseline Recruitment and Data Collection

- First selection of 20,000 started in late 2011
  - Completed 60 minute questionnaire by telephone on about 12,000 individuals
  - Plan to complete tracking by the end of January 2013
- Mid 2013 we will begin our maintaining contact interviews (30 minute telephone interview)
  - Minimize loss to follow-up
  - Collect additional data
Comprehensive Cohort of the CLSA (n=30,000)
Implementation Plan for the Comprehensive Cohort (n=30,000)

- Cohort of 30,000 persons to be recruited within 25 to 50 km radius of 11 data collection sites (DCS)
  - Victoria (3000), Vancouver (1500), Burnaby (1500), Calgary (3000), Winnipeg (3000), Hamilton (3000), Ottawa (3000), Montreal (3000), Sherbrooke (3000), Halifax (3000), St. John’s (3000)
Comprehensive Cohort
Rolling Recruitment

❖ First batch of 1000 people to be recruited/site (mid-2012 to mid-2013)
  ❖ Maintaining contact by phone (end of 2013 - end 2014)

❖ Second batch of 1000 people to be recruited/site (mid-2013 to mid-2014)
  ❖ Maintaining contact: (end of 2014-end of 2015)

❖ Third batch of 1000 people to be recruited/site (mid-2014 to mid 2015)
  ❖ Maintaining contact: (end of 2015-end of 2016)
What is required to create a Centralized Platform like CLSA?

- Good Governance
- Coordinated ongoing ethics approval process
- Transparent Data and Sample Access Policies
- Transparent Data Ownership and IP Policies
- Integrated IT infrastructure
Data and Sample Access

• Data and Sample Access is Open
  • All researchers have access to data
    • No special access to the “creators” of the platform
    • Individual level data versus aggregate data
    • Genetic versus Health (Depression) versus Social data

• Ethical and Legal Considerations
  • How the data are used and what purpose?
  • Public sector versus Private sector access to data
CLSA Partners

- Public Health Agency of Canada
- Veterans Affairs Canada
- Statistics Canada
- Ontario Ministry of Health and Long-Term Care
- Provinces
- Universities
- Large number of in-kind contributions from vendors and suppliers
Use of the CLSA Platform: Examples
Exercise
Diet
Social and intellectual enrichment
Drugs

Carotidal atherosclerosis
Endothelial cells insult
Comorbidity

Hypercholesterolemia
Hypertension
Diabetes
Hormones
Infection

Dyslipidemia
Genetics and lifestyle (ApoE, obesity, smoking, social and environmental stressors, etc.)

(vascular) Aging

Peripheral inflammation

Chemokines dysregulation
AGES
ROS and N₂ reactive species
MMPs

T-cells / macrophages recruitment

Cognitive decline

Toxicity and Apoptosis
Vascular dysfunction
Stroke
NT dysfunction

Immunedysfunction

AGING

Hypertension
Dyslipidemia
Genetics and lifestyle (ApoE, obesity, smoking, social and environmental stressors, etc.)

(vascular) Aging

Comorbidity

Peripheralinflammation

Ciganski et al. (2015) ~10% of the Canadian population over 65 years of age is currently living with dementia. Given the demographic and epidemiological trends, the number of cases are expected to rise in the coming decades, where 1 in 7 Canadian men and 1 in 5 Canadian women are expected to develop dementia or other dementias. In the United States, more than 300,000 American adults were diagnosed with Alzheimer’s disease in 2020, an increase from 200,000 in 2019. In 2022, the US Alzheimer’s Association estimated that the direct and indirect costs of Alzheimer’s disease exceeded $305 billion in the United States and will grow to $1.2 trillion in 2050.

It is estimated that 90% of older women and 50% of older men have symptoms of cognitive decline that may precede the development of dementia. Ciganski et al. (2015) 10% of the Canadian population over 65 years of age is currently living with dementia. Given the demographic and epidemiological trends, the number of cases are expected to rise in the coming decades, where 1 in 7 Canadian men and 1 in 5 Canadian women are expected to develop dementia or other dementias. In the United States, more than 300,000 American adults were diagnosed with Alzheimer’s disease in 2020, an increase from 200,000 in 2019. In 2022, the US Alzheimer’s Association estimated that the direct and indirect costs of Alzheimer’s disease exceeded $305 billion in the United States and will grow to $1.2 trillion in 2050.

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## Mobility
«activity & participation» *

### Examples of precursors

**Individual (or intrinsic)**
- Chronic diseases (e.g., osteoarthritis)
- Neuropsychological conditions
- Cognition/Perceived health
- Medication use/Pain/Dizziness
- Poor vision
- Fear of falling/
- Obesity/Nutrition/weight loss/appetite
- Physical activity/fitness/strength
- Functional performance (measured & reported)
- Alcohol use
- Biomarkers (inflammation, hormonal, metabolism, genetics, epigenetics)
- Personality

**Contextual (or extrinsic or environmental)**
- Social participation
- Transportation resources
- Community/neighbourhood characteristics
- Social network/support

### Examples of consequences

**Diseases**
- Osteoporosis, sarcopenia

**Physical Health**
- Injuries/Frailty/Disability
- Poor nutrition status

**Psychological Health**
- Psychological distress
- Quality of life
- Loneliness
- Unmet needs

**Social Health**
- Social participation/engagement/capital
- Work Transitions
- Unmet needs
- Institutionalization
# CLSA CORE TEAM

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<tr>
<th>Role</th>
<th>Members</th>
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<tr>
<td>Lead PI</td>
<td>Parminder Raina <em>(McMaster)</em></td>
</tr>
<tr>
<td>CO-PI</td>
<td>Christina Wolfson <em>(McGill)</em> and Susan Kirkland <em>(Dalhousie)</em></td>
</tr>
<tr>
<td>Key Senior Co-Investigators</td>
<td>Gerry Mugford <em>(Memorial)</em>, Helene Payette <em>(Sherbrooke)</em>, Ron Postuma <em>(McGill)</em>, Larry Chambers and Vanessa Taler <em>(Ottawa)</em>, Harry Shannon, Cynthia Balion, Christopher Patterson, Lauren Griffith and Mark Oremus <em>(McMaster)</em>, Mary Thompson and Chang Bo <em>(Waterloo)</em>, Margaret Penning, Holly Tuokko, <em>(Victoria)</em>, Verena Menec <em>(Manitoba)</em>, David Hogan <em>(Calgary)</em>, Max Cynader, Michael Hayden and Michael Kobor <em>(UBC)</em> and Andrew Wister <em>(SFU)</em></td>
</tr>
<tr>
<td>Scientific Working Group</td>
<td>See our website – <a href="http://www.clsa-elcv.ca">www.clsa-elcv.ca</a></td>
</tr>
</tbody>
</table>
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www.clsa-elcv.ca