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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Vancouver, April 2012
Population aging

- Due to declining fertility and increasing longevity (demographic transition)

- Unprecedented, accelerating, shifts will be permanent

- Profound implications for human life, including health
### Population Totals in Canada by Age Group and Year

<table>
<thead>
<tr>
<th>AGE</th>
<th>MALES</th>
<th>BOTH SEXES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>80+</td>
<td>229898</td>
<td>670192</td>
<td>440294</td>
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<tr>
<td>75-79</td>
<td>255599</td>
<td>622194</td>
<td>366595</td>
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<tr>
<td>70-74</td>
<td>364298</td>
<td>833991</td>
<td>469693</td>
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<tr>
<td>65-69</td>
<td>497996</td>
<td>1084588</td>
<td>586592</td>
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<tr>
<td>60-64</td>
<td>578596</td>
<td>1190087</td>
<td>611491</td>
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<tr>
<td>55-59</td>
<td>618096</td>
<td>1238387</td>
<td>620291</td>
</tr>
<tr>
<td>50-54</td>
<td>673295</td>
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<td>666691</td>
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<tr>
<td>45-49</td>
<td>844194</td>
<td>1674182</td>
<td>829988</td>
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<tr>
<td>40-44</td>
<td>1076892</td>
<td>2138777</td>
<td>1061885</td>
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<td>35-39</td>
<td>1173491</td>
<td>2344675</td>
<td>1171184</td>
</tr>
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<td>30-34</td>
<td>1311991</td>
<td>2597873</td>
<td>1285882</td>
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<td>25-29</td>
<td>1282190</td>
<td>2528572</td>
<td>1246382</td>
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<td>20-24</td>
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<td>15-19</td>
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<td>940787</td>
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<td>10-14</td>
<td>980292</td>
<td>1912979</td>
<td>932687</td>
</tr>
<tr>
<td>5-9</td>
<td>998293</td>
<td>1953079</td>
<td>954786</td>
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<tr>
<td>0-4</td>
<td>1000393</td>
<td>1953280</td>
<td>952887</td>
</tr>
</tbody>
</table>

**1991 TOTALS:**
- MALES: 13938100
- BOTH SEXES: 28117600
- FEMALES: 14179500
Rectangularization of the survival curve

FURTHER INCREASE IN LIFE EXPECTANCY

Squaring the survival curve

PERCENT SURVIVING

AGE

1900

1980

TRAUMA

IDEAL

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

Deaths

Age
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&lt;br&gt;Huang et al. 1998&lt;br&gt;Martin and Oshima 2000</td>
</tr>
<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 β-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
Epigenetics

ON/OFF SWITCH (GENE)

GUMMED UP ON/OFF SWITCH (GENE)

30 nm fiber 10 nm fiber

CANNOT

- Me

CANNOT

Me-

GUM

CANNOT

-HAc

GUM

CAN

-DNA AND CHROMOSOME LEVELS
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)

**Genetics**
(e.g., telomeres/oxidative stress, psychological & cognitive abilities, immune functions)

**Aging**

**Health Services Utilization**

**Time (Longitudinal Study)**
Strategic Partners

- Strategic initiative of the Canadian Institutes of Health Research (CIHR)
- Funded by CIHR and the Canada Foundation for Innovation (CFI)
- Provinces and universities across Canada
Our Vision

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.
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
Interdisciplinary Research Agenda

Methods

Policy

Sociology

Psychology

HSR

Biology/genetics

Clinical

Lifestyle
Overall Goals 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**
  - Cardiovascular, Cerebrovascular, Neurological, Respiratory, Vision and Hearing, Diabetes, Renal, Metabolic, Cancer, Osteoarthritis, Osteoporosis, Depression, Musculoskeletal, Cancer
- **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 caregiving** in an aging population
- **Retirement** and **post-retirement** labour market activity
## Depth and Breadth of CLSA

### PHYSICAL & COGNITIVE MEASUREMENTS
- Height & weight
- Waist and hip measurements
- Bioimpedence
- Arterial pressure
- Mean heart rate
- Grip strength, timed up-and-go, chair raise, 4-m walk
- Standing balance
- Vision
- Hearing
- Spirometry
- Bone density
- Aortic calcification
- ECG
- Carotid intima-media thickness
- Cognitive assessment

### HEALTH INFORMATION
- Chronic disease symptoms (11 chronic conditions)
- Medication intake & compliance
- 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
- Coping, adaptation
- Work-to-retirement transitions
- Job-demand/effort reward
- Retirement planning
- Social inequalities
- Mobility-lifespace
- Built environments
- Wealth

### LIFESTYLE & SOCIODEMOGRAPHIC
- Smoking
- Alcohol consumption
- Physical activity
- Nutrition
- Birth location
- Ethnicity/race/gender
- Marital status
- Education
- Income
Equipment and Infrastructure Supporting Research on Aging

Computer-Assisted Telephone Interview Centres
Collect health and psychosocial data (located in Halifax and Sherbrooke).

Genetics and Epigenetics Centre
Genotyping, epigenetic analysis, and bioinformatics, (located in Vancouver)

Biological Processing Centre
Bio-banking, biomarker discovery & analysis (located in Hamilton).

National Coordinating Centre
Oversight, project management, data management, communication for overall initiative
(located in Hamilton)

Data Collection Centres
Collection of nutrition, physical, clinical data, & biological specimens.

Statistical Analysis Centre
Assimilation, distribution and analysis of all CLSA data (located in Montreal).
Participants Consent to Participate in CLSA

Potential Participants Sent Study Information

Biological Data
- Blood
- Urine

Participants Provide Questionnaire Data (n=50,000)

Physical/Psychological Data
- Neuropsychological Battery
- Performance Testing
- Anthropometric Measures
- Bone Density, Body Composition
- Aortic Calcification
- ECG
- Carotid Intimal-Medial Thickness
- Pulmonary Function
- Vision and Hearing

n=30,000 Home Interview

n=20,000 Telephone Interview

Stored in Biorepository and Bioanalysis Centre (BBC)

Stored in (NCC/SAC)

Questionnaire Data Processed
Achievements

- Set up of CATI
- Successful DCS set up and pilot studies
- Infrastructure / IT Design
- Coordinated purchasing process
- Software development
- Coordinated REB process
- Partnership MOH/Data Stewards
Participant Recruitment

Comprehensive Tracking
Tracking Cohort Timeline (2009-2015)

- 2009: Initial contact names to NCC
- 2010: Wave 1 - Recruitment & Baseline data collection, 5,000
- 2011: Wave 1 - Recruit remaining sample, Baseline interview all 20,000
- 2012: MC* Interviews
- 2013: Wave 2 interviews

* MC= Maintaining Contact
Comprehensive Cohort Timeline (2009-2015)

2010

2011

2012

2013

2014

2015

2016

1st phase recruitment + baseline data collection - 1,000/DCS

2nd phase recruitment + baseline data collection 1,000/DCS

3rd phase recruitment + baseline data collection 1,000/DCS

REB Process

1st phase MC interviews 1,000/DCS

2nd phase MC interviews 1,000/DCS

3rd phase MC interviews 1,000/DCS

*MC = Maintaining Contact

Contact
Launch of the CLSA

- First selection of 20,000 started in late 2008 in collaboration with Statistics Canada CCHS Healthy Aging module (Tracking cohort)
  - Approximately 12,500 have agreed to release their names to CLSA (5,000 have been recruited)
- Remaining 15,000 for Tracking cohort are currently being recruited; to be completed late 2012
  - Provincial Client Registries or Random Digit Dialing
- Recruitment for remaining 30,000 started in early 2012 (Comprehensive cohort); to be completed early 2015
  - Provincial Client Registries or Random Digit Dialing
Diabetes Algorithm

Self-report of physician diagnosed Diabetes

No

Taking medication

No

FPG 6.1-6.9

IFG*

FPG <6.1

No DM

Yes

FPG ≥7

Definite DM

FPG 6.1-6.9

Probable DM

Taking medication

Yes

No

FPG <6.1

No

*If self-report is removed, then this box = ‘possible diabetes’
Example

Physical Function

Mobility
**Mobility**
«activity & participation» *

**Examples of precursors**

*Individual (or intrinsic)*
- Chronic diseases (eg 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
Mobility

Mobility as a precursor:

Is mobility in mid- and later life associated with physical, psychological and social functioning? Specifically:

- How do changes in mobility impact upon indicators of psychological health including, depression, psychological distress, satisfaction with life, adjusting for other factors?
Mobility

Mobility as a mediator:

How does mobility in mid- and later life mediate relationships between determinants of health and health outcomes? Specifically:

• How does compromised mobility mediate the relationship between income and health?
Mobility

Mobility as an outcome:

How do physical, psychological, and social functioning in mid- and later life relate to changes in mobility? Specifically:

- What is the relationship between inflammatory biomarkers (e.g., IL-6, C reactive protein, albumin), hormonal biomarkers (e.g., IGF-1, T3, T4), metabolic (e.g., fasting glucose, cholesterol) or immunological markers (TNFα), oxidative stress (e.g., vitamin E and C), vitamin D, and (Epi) genetic markers (e.g., IGF-I and Apo-E) and changes in mobility and how is this relationship modified by SES?

- What is the relationship between neighbourhood deprivation and incident mobility disability in aging population?
Data Collection Sites (DCS)

11 ACROSS CANADA

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

Matrix boxes
§ Pre-charged vapor shippers (-160ºC)
§ 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
  - Maximum time from collection to storage is 2 h
  - Storage at $-160^\circ$C
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)
- LIMS (LabWare)
- CryoMORE, (Air Liquide) safety monitoring system
Biorepository and Bioanalysis Centre (BBC)

Biorepository

- Installation May 2012
- LIMS implementation April
- Hiring BBC coordinator

[Image of a group of people and laboratory equipment]
CLSA by the numbers

- 50,000 participants
- 20 years to complete the study
- 57,487 Lines of code making up Sabretooth, Beartooth and Mastodon (software)
- Up to 140,000 Telephone interviews
- Up to 210,000 Home interviews
- Up to 210,000 Visits to data collection sites
- Up to 8,820,000 biospecimen aliquots
- Up to 300,000 Follow-up calls
- Up to 129 million Questions asked during telephone interviews
- Up to 219 million Data points collected during CLSA home interviews and visits to data collection sites
- Up to 348 million Anticipated number of data points that will form the CLSA research platform
CLSA Governance Structure
Canadian Investment

$50M Canadian investment in national platform

- $23.5M CIHR for 5 Years (86% of the required funding)
  - Expectation is to identify non-CIHR partners (in kind or $$)

- $10M CFI for 5 Years (infrastructure)

- $10M Provinces for 5 Years (infrastructure)

- $6.5M Universities and other partners
CLSA Partners

- PHAC Neurological Diseases
- PHAC Injury
- Veterans Affairs
- Statistics Canada
- Ontario Ministry of Health and Long-Term Care
- Provinces
- Universities
- Large number of in-kind contributions from vendors and suppliers
COLLABORATE AND INNOVATE

INFRASTRUCTURE
- State-of-the-art facilities: bio-repository and bio-analysis laboratories, fully equipped data collection facilities and call centres across Canada, statistical analysis centre, genetics and epigenetics centre
- Novel open-source software for conducting multicentre research
- Novel hardware design and architecture
- Secure data management systems to preserve participant confidentiality
- Collaboration and harmonization with other national and international cohorts

RESEARCH
- Progression and management of disease and disability
- Risk factor identification
- Co-morbidity
- Psychosocial aspects of health
- Genetic and epigenetic aspects of disease and disability
- Biospecimen and preservation research
- Biomarker discovery for early detection and management of disease
- Research platform for auxiliary studies
- Trajectories of healthy aging
- Quality of life

OUTPUTS
- Healthcare utilization patterns
- Evidence to inform health and public policy
- Personalized medicine to improve outcomes
- Development of interventions and programs
- Development of services and products
- Research capacity
- Advanced science of aging
- Improved health of Canadians
Discussion Points

- Value of the CLSA platform
- Data access and IP policies
- Opportunities for collaboration for the core data collection CLSA
- Opportunities for analyses of the data and biological samples
- Opportunities for using CLSA facilities for non-CLSA research
- Opportunities for sub-studies
<table>
<thead>
<tr>
<th><strong>Lead PI</strong></th>
<th>Parminder Raina <em>(McMaster)</em></th>
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<tr>
<td><strong>CO-PI</strong></td>
<td>Christina Wolfson <em>(McGill)</em> and Susan Kirkland <em>(Dalhousie)</em></td>
</tr>
<tr>
<td><strong>Key Senior Co-Investigators</strong></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>
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**Scientific Working Group**

See our website – www.clsa-elcv.ca
raina@mcmaster.ca

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

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