Transforming Everyday Life
into Extraordinary Ideas

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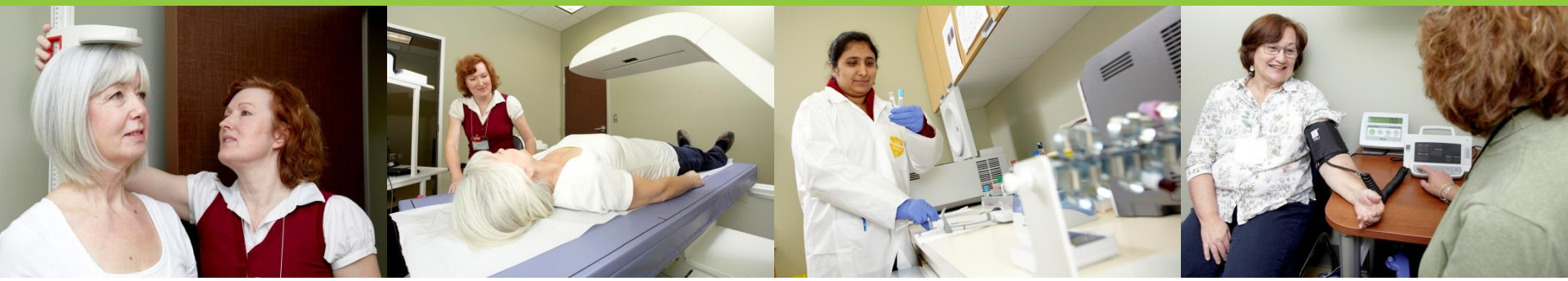
Étude longitudinale canadienne sur le vieillissement



Canadian Longitudinal Study on Aging: Advancing the Science of Population Health and Aging through Interdisciplinary Research

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McMaster University, Hamilton

Vancouver, April 2012

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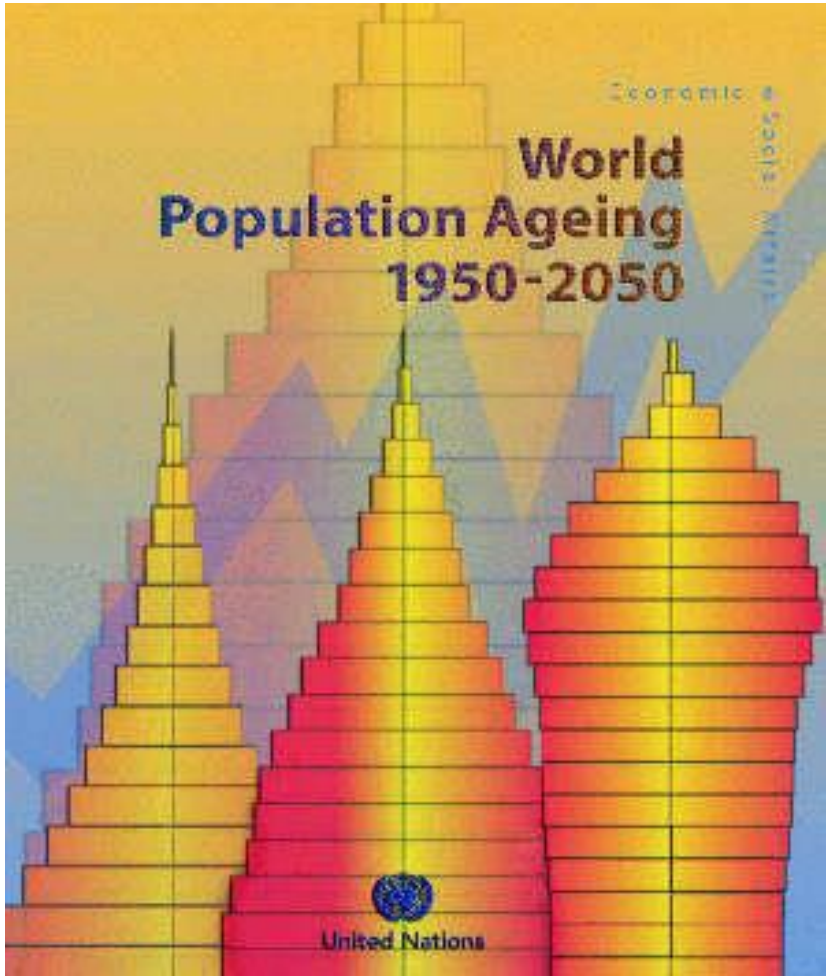
Population aging

- Due to declining fertility and increasing longevity (demographic transition)
- Unprecedented, accelerating, shifts will be permanent
- Profound implications for human life, including health



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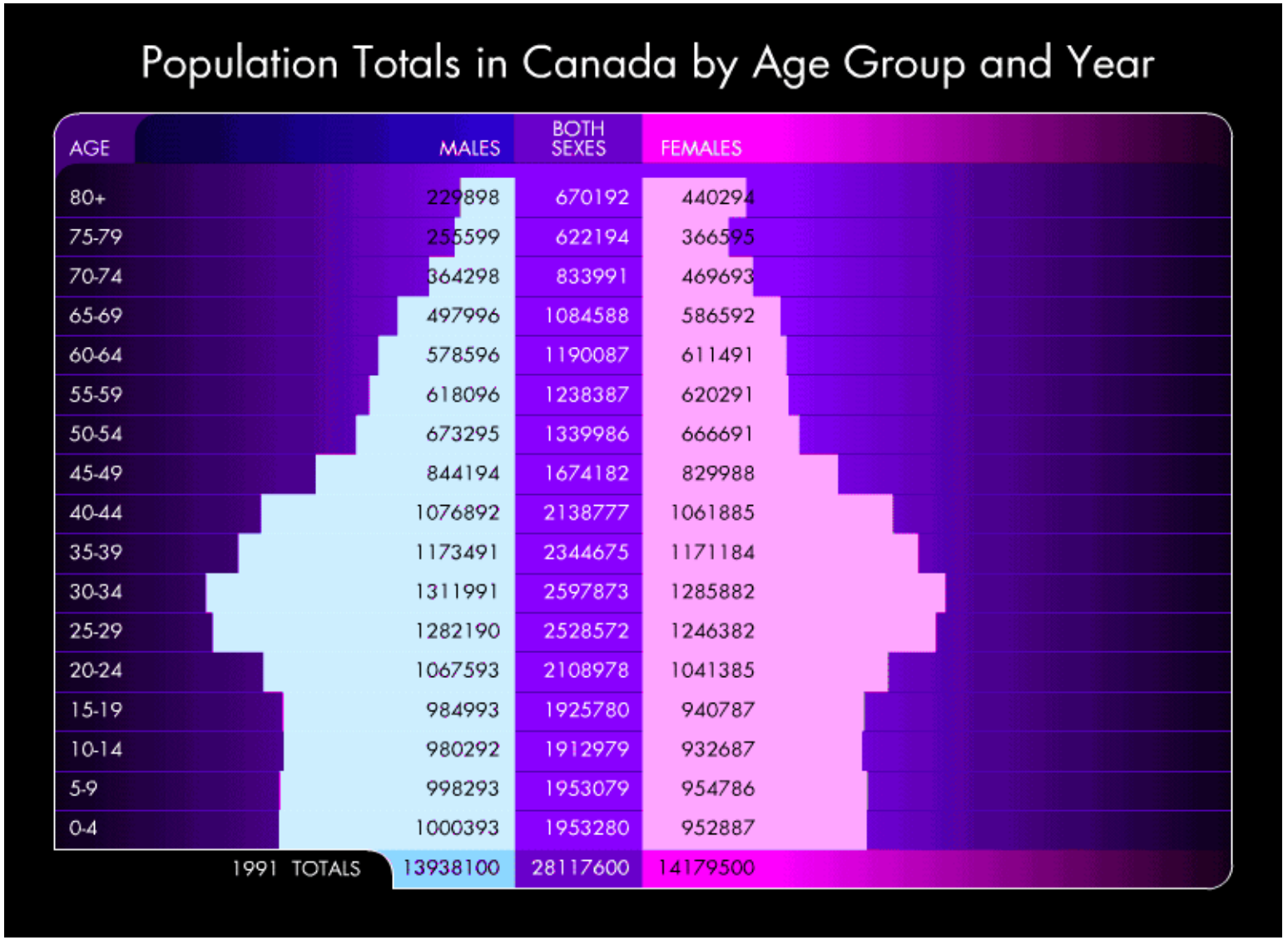
Population Totals in Canada by Age Group and Year



AGE	MALES	BOTH SEXES	FEMALES
80+	229898	670192	440294
75-79	255599	622194	366595
70-74	364298	833991	469693
65-69	497996	1084588	586592
60-64	578596	1190087	611491
55-59	618096	1238387	620291
50-54	673295	1339986	666691
45-49	844194	1674182	829988
40-44	1076892	2138777	1061885
35-39	1173491	2344675	1171184
30-34	1311991	2597873	1285882
25-29	1282190	2528572	1246382
20-24	1067593	2108978	1041385
15-19	984993	1925780	940787
10-14	980292	1912979	932687
5-9	998293	1953079	954786
0-4	1000393	1953280	952887
1991 TOTALS	13938100	28117600	14179500

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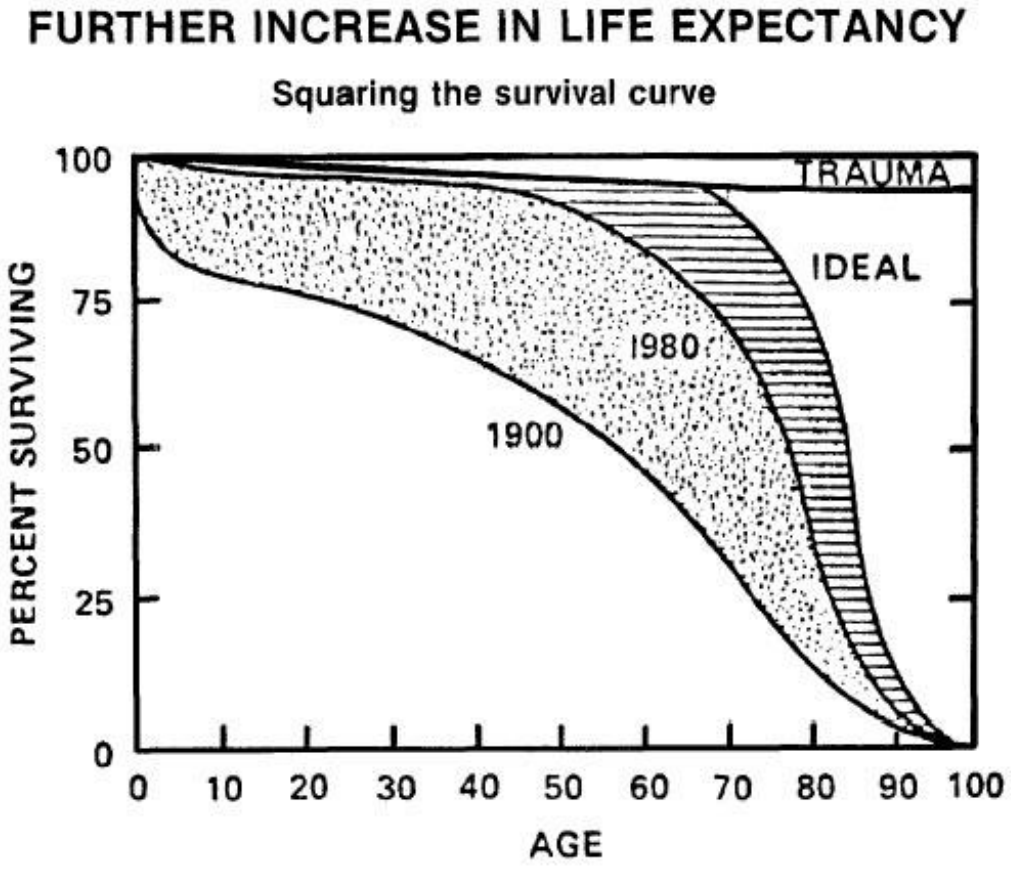
Rectangularization of the survival curve



JAMES F. FRIES, M.D., THE NEW ENGLAND JOURNAL OF MEDICINE, JULY 17, 1980.

Compression of morbidity

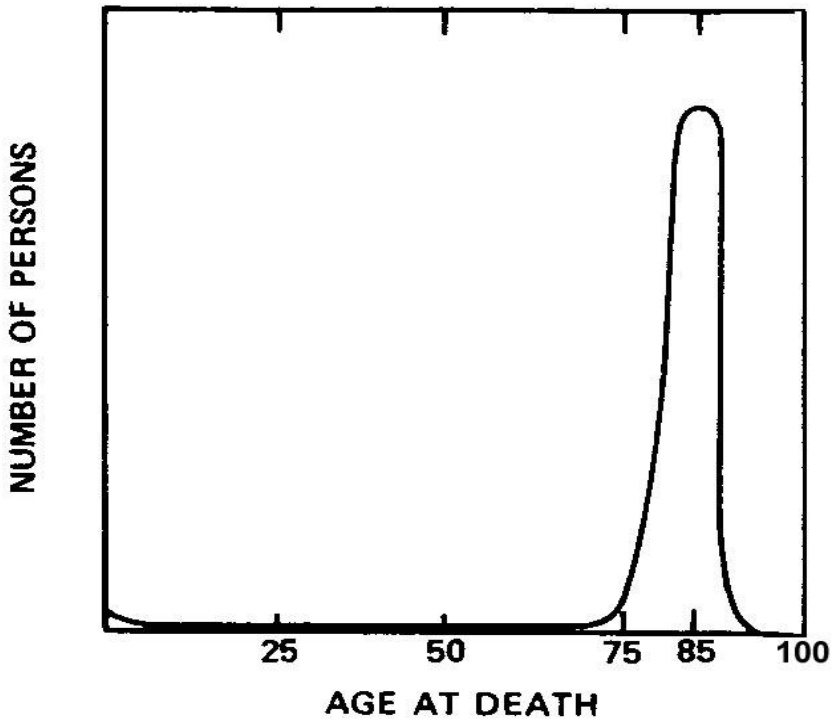


Figure: Mortality According to Age in the Absense of Premature Death

- 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

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Compression of morbidity

Fries' paradigm based on the premise that:

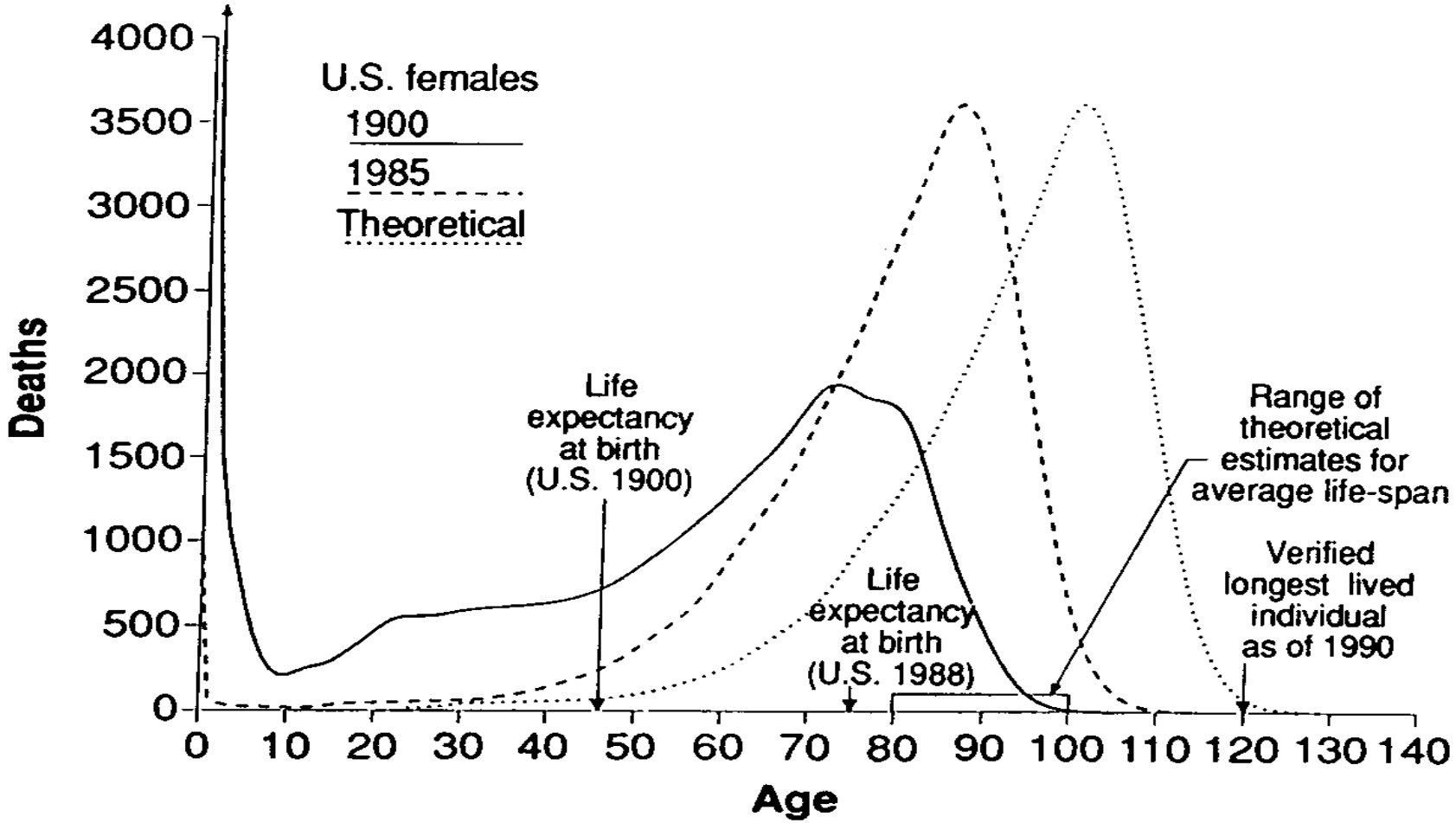
- The length of human life is fixed

  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



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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

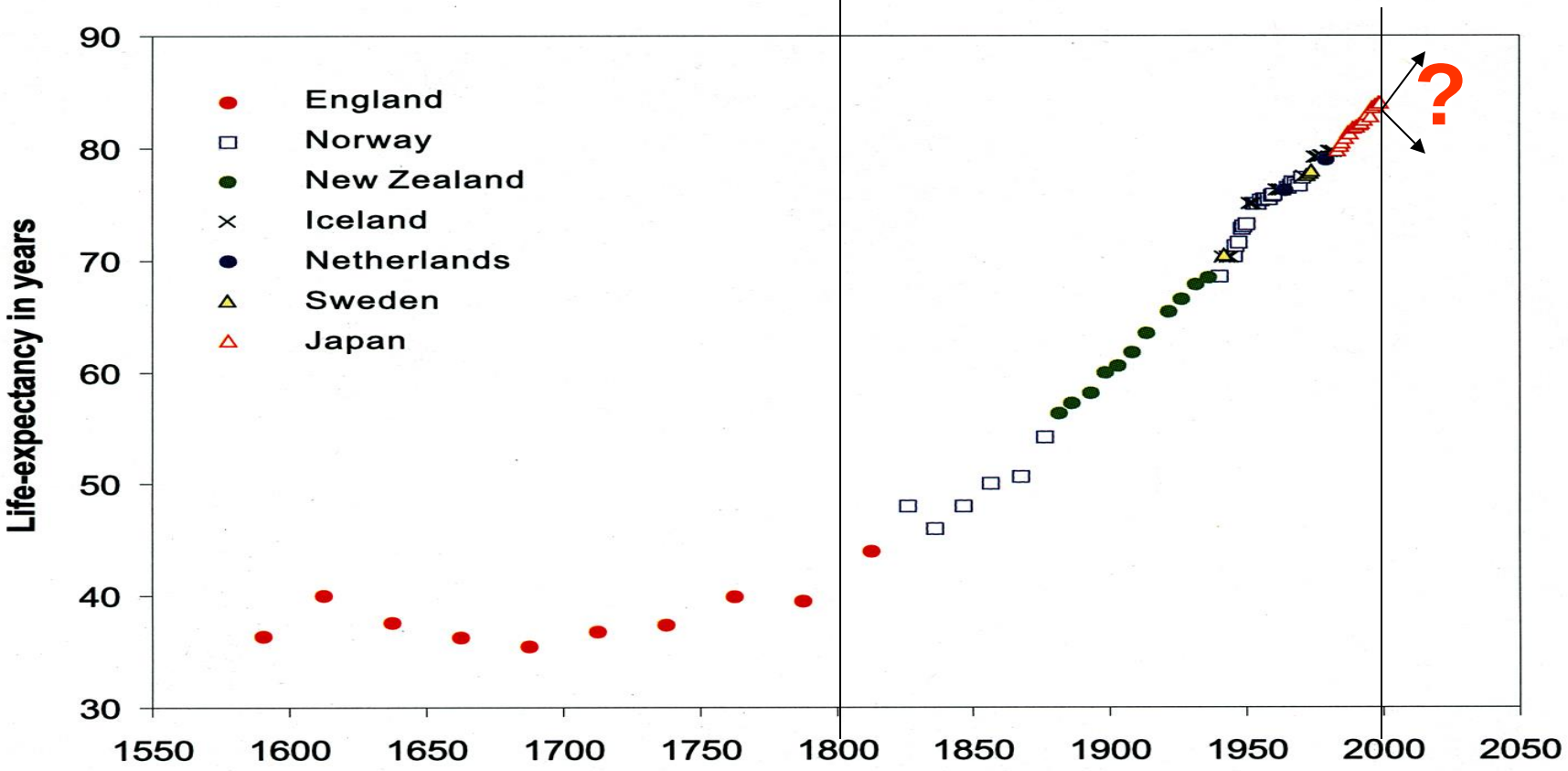
Historical increases of life expectancy

Oepen and Vaupel, Science 2002; C Finch adaptation

Phase 1
early urban

Phase 2
sanitation-nutrition

Phase 3?
regeneration
modern medicine
Social Policy Innovation



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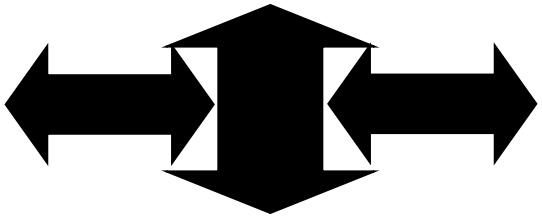
Demographic Futures

- 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

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Genes Associated With Avoiding Late-Life Disease in Humans

Table 4

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

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

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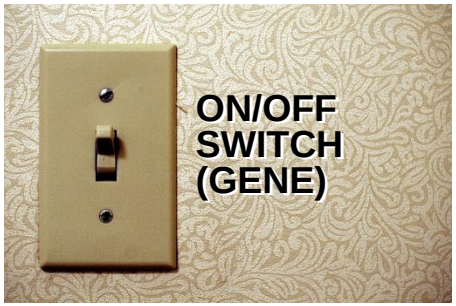
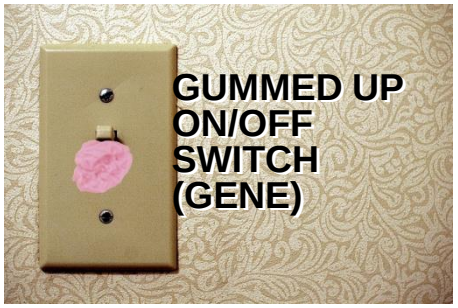
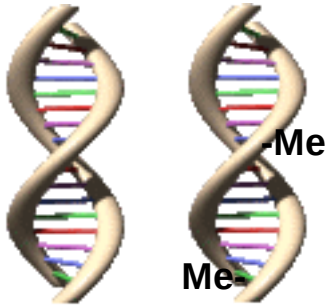
Epigenetics





CANNOT



CAN

GUM

GUM

30 nm fiber 10 nm fiber

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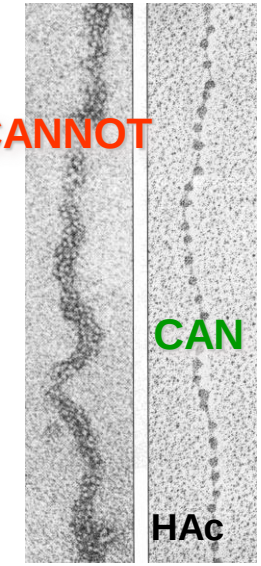

DNA AND CHROMOSOME LEVELS

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Non-Biological/Medical Determinants of Aging?

- Nutrition
- Lifestyle
- Environment
  - Physical
  - Social
  - Economic
  - Work Place
  - Psychological
- Chance

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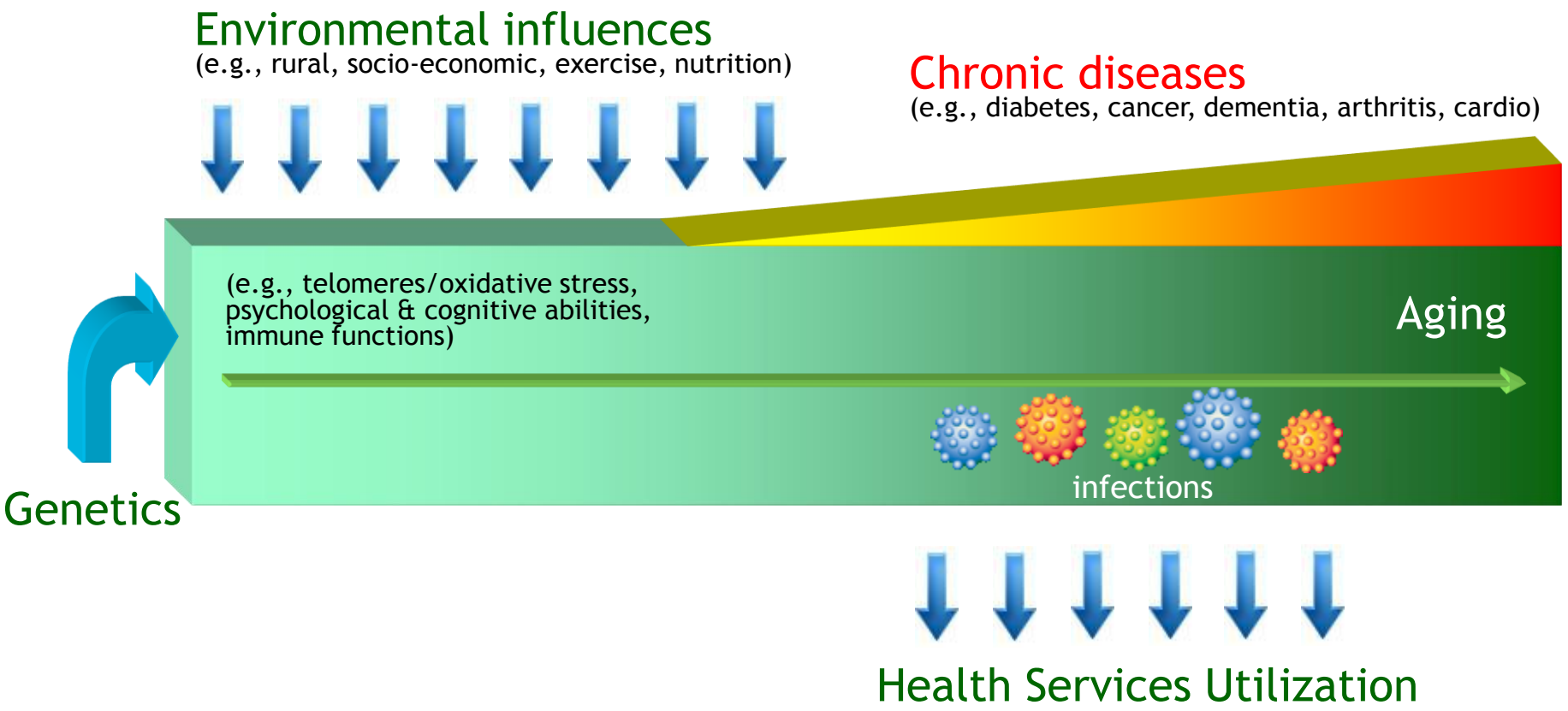
Intrinsic and Extrinsic Factors



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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

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

INNOVATION.CA
FONDATION CANADIENNE POUR L'INNOVATION
CANADA FOUNDATION FOR INNOVATION

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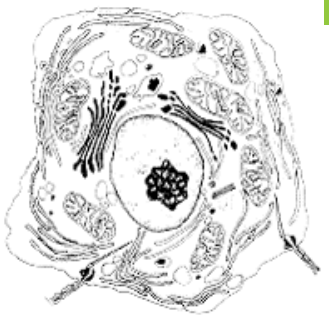
Our Vision

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.

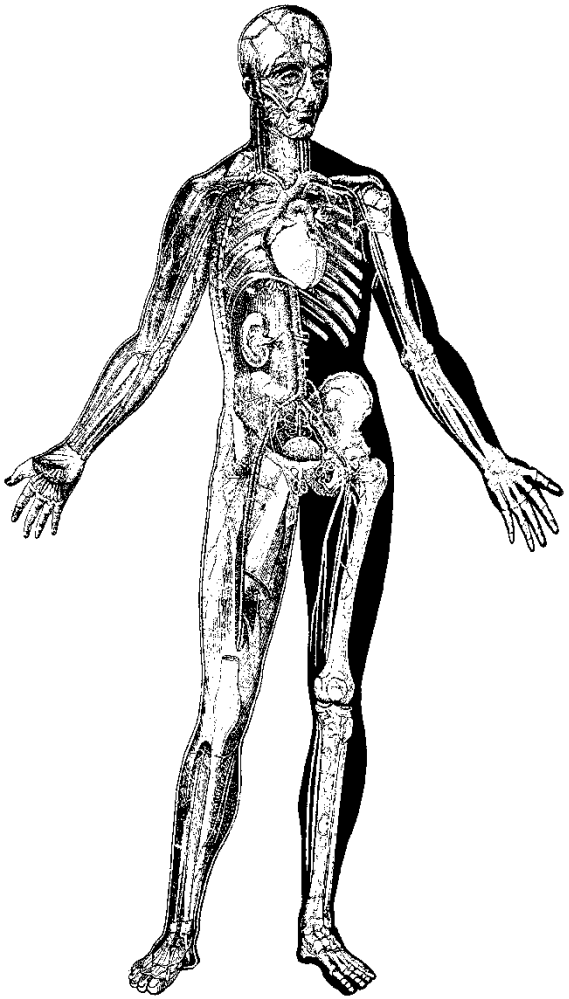
Our Aim

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



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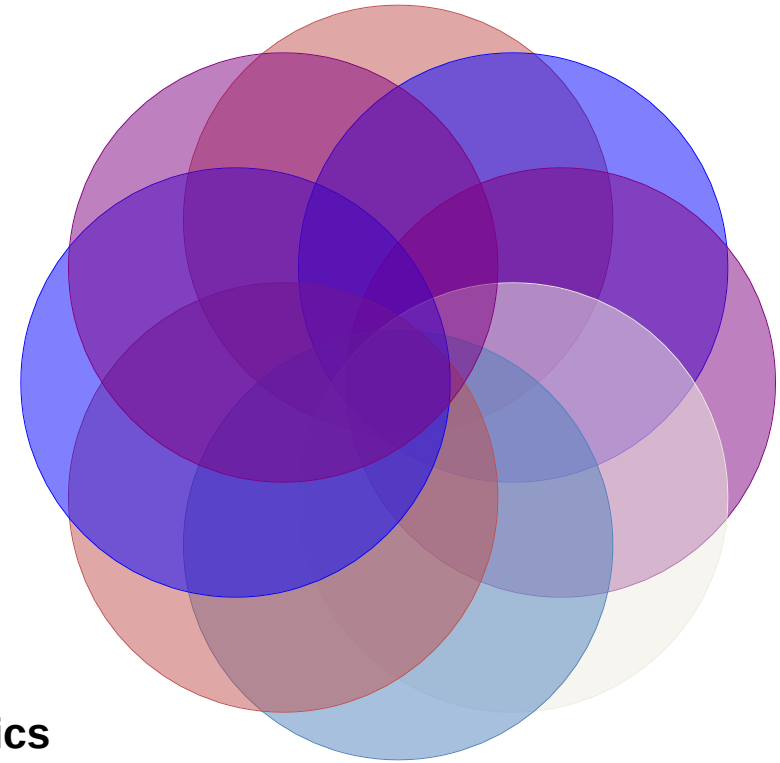
Interdisciplinary Research Agenda



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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

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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

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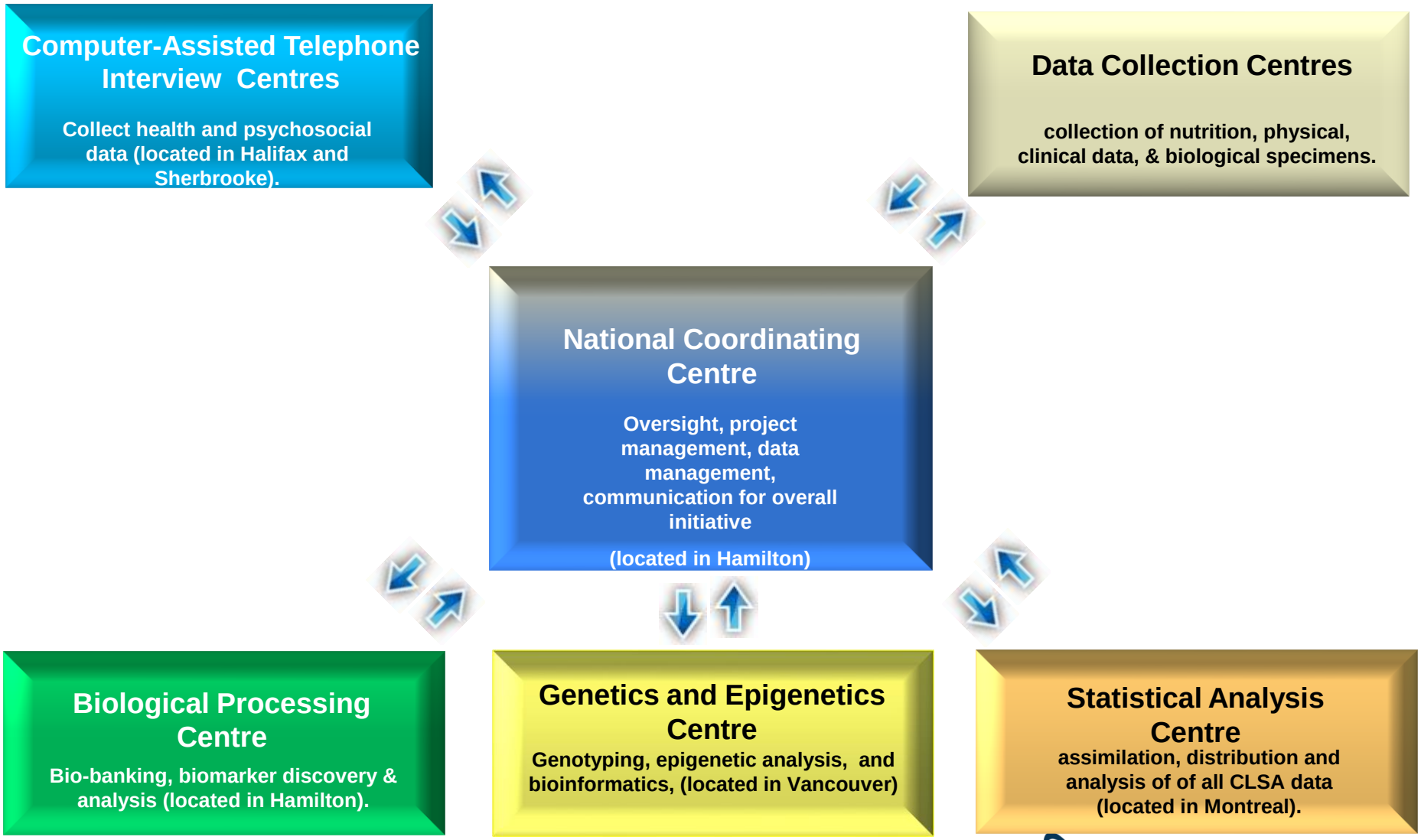
Equipment and Infrastructure Supporting Research on Aging



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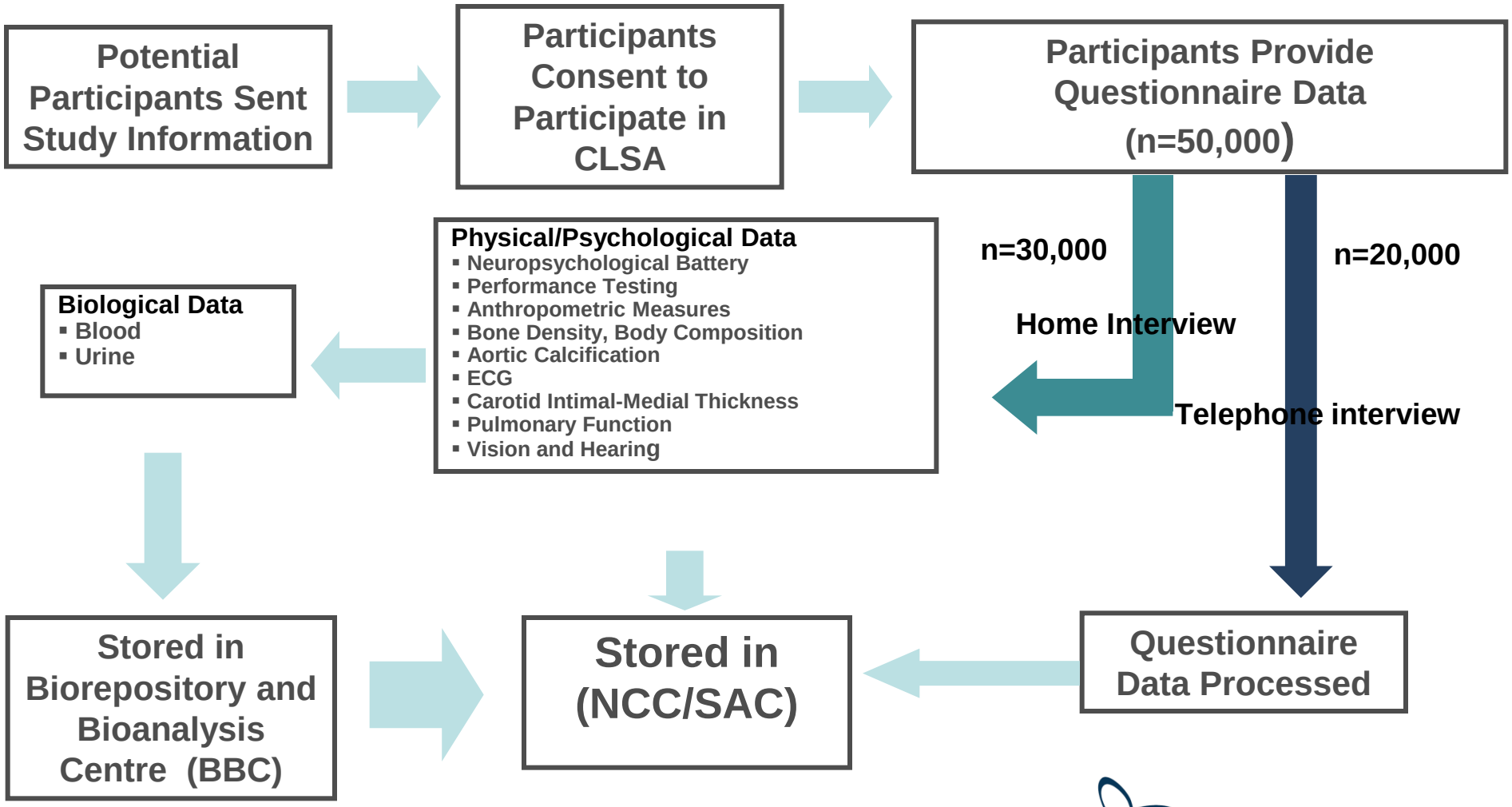
CLSA Data Collection



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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

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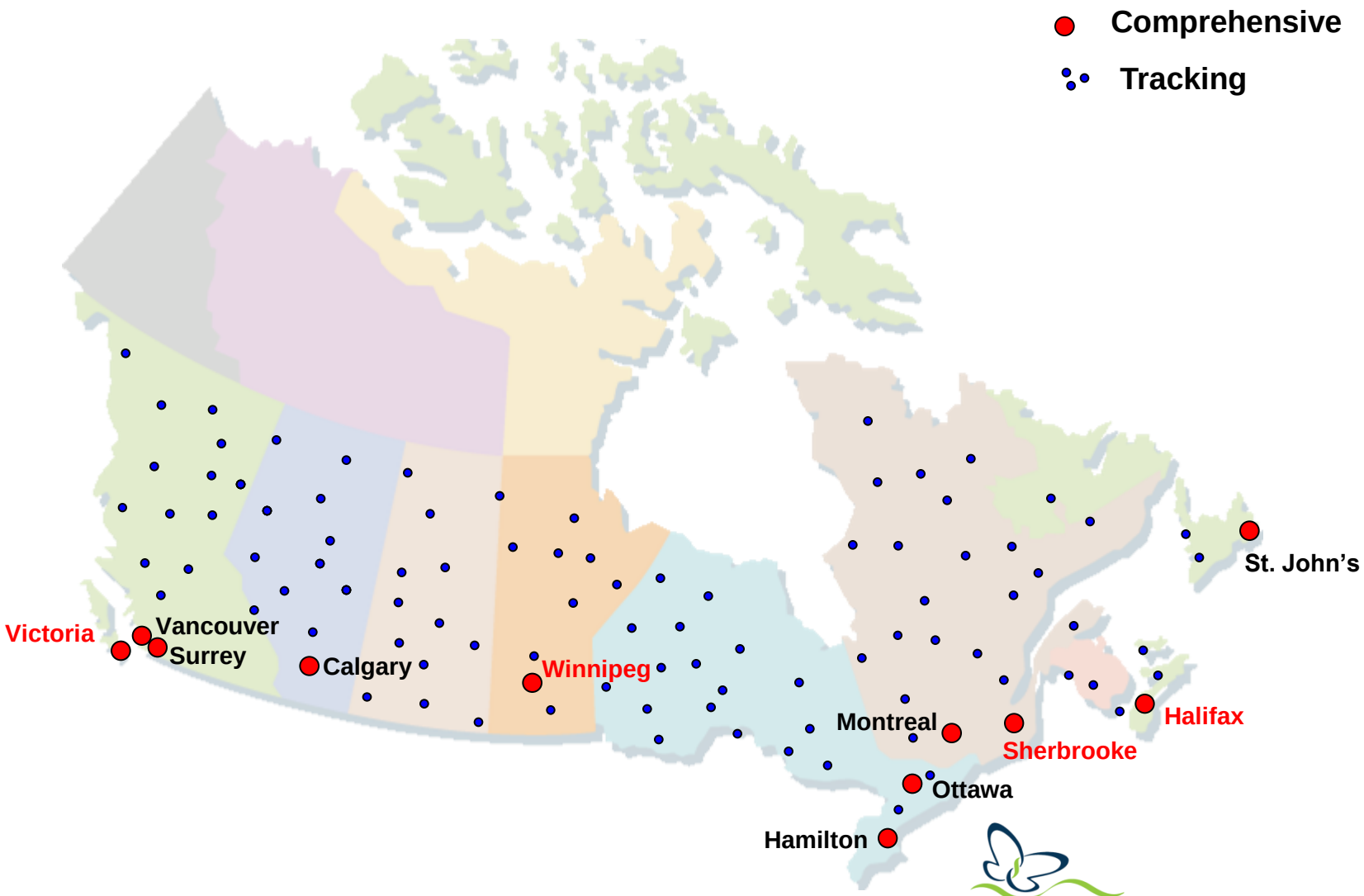
Participant Recruitment



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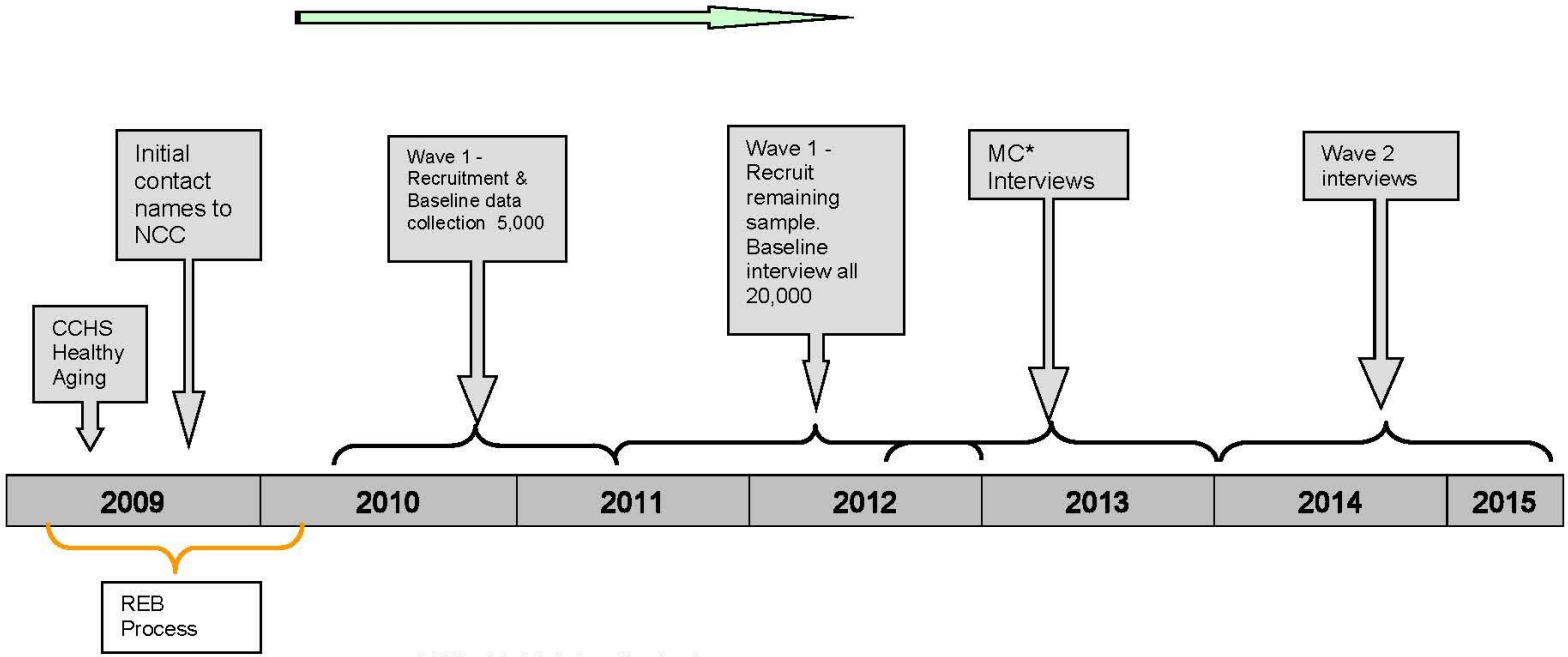
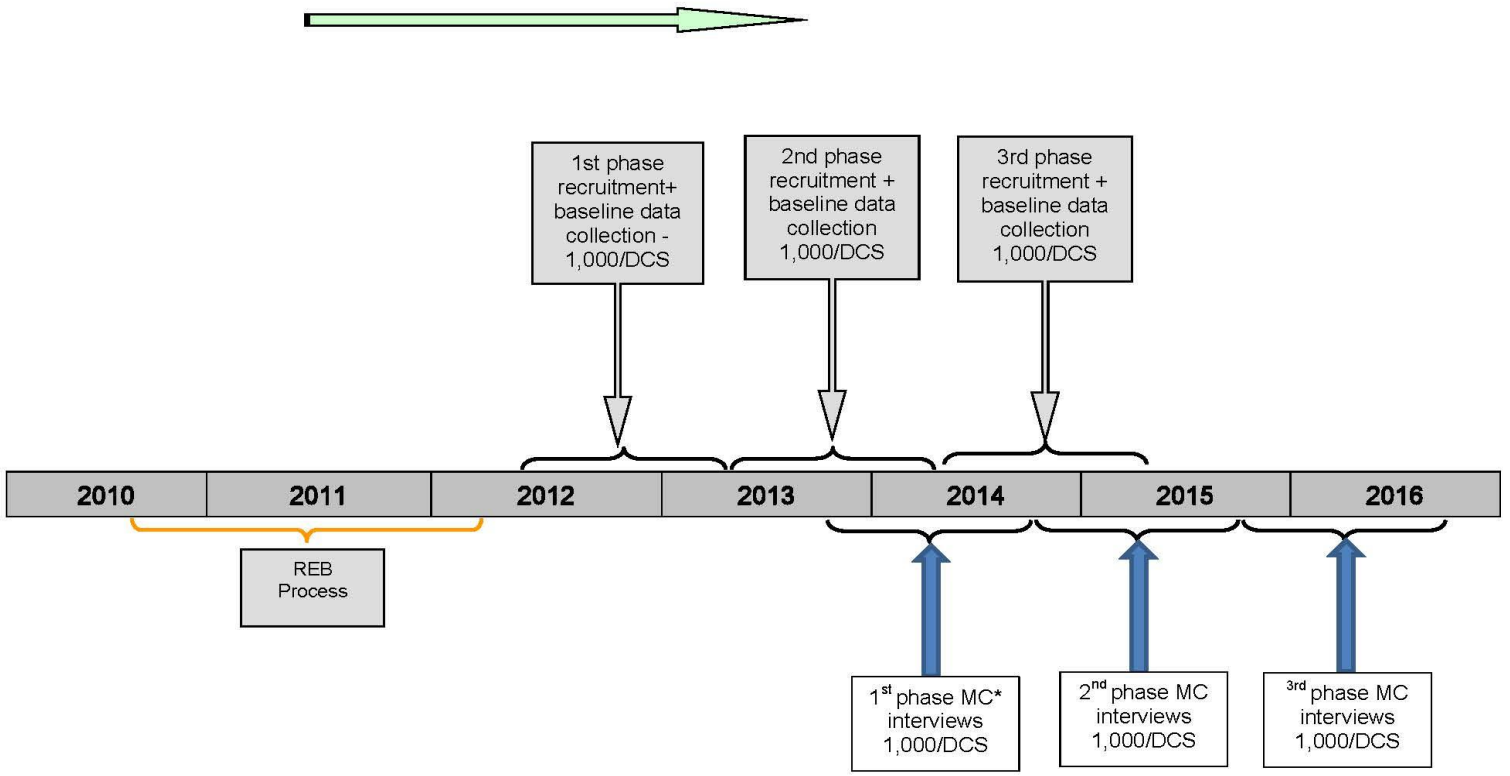
Tracking Cohort Timeline (2009-2015)



Comprehensive Cohort Timeline (2009-2015)

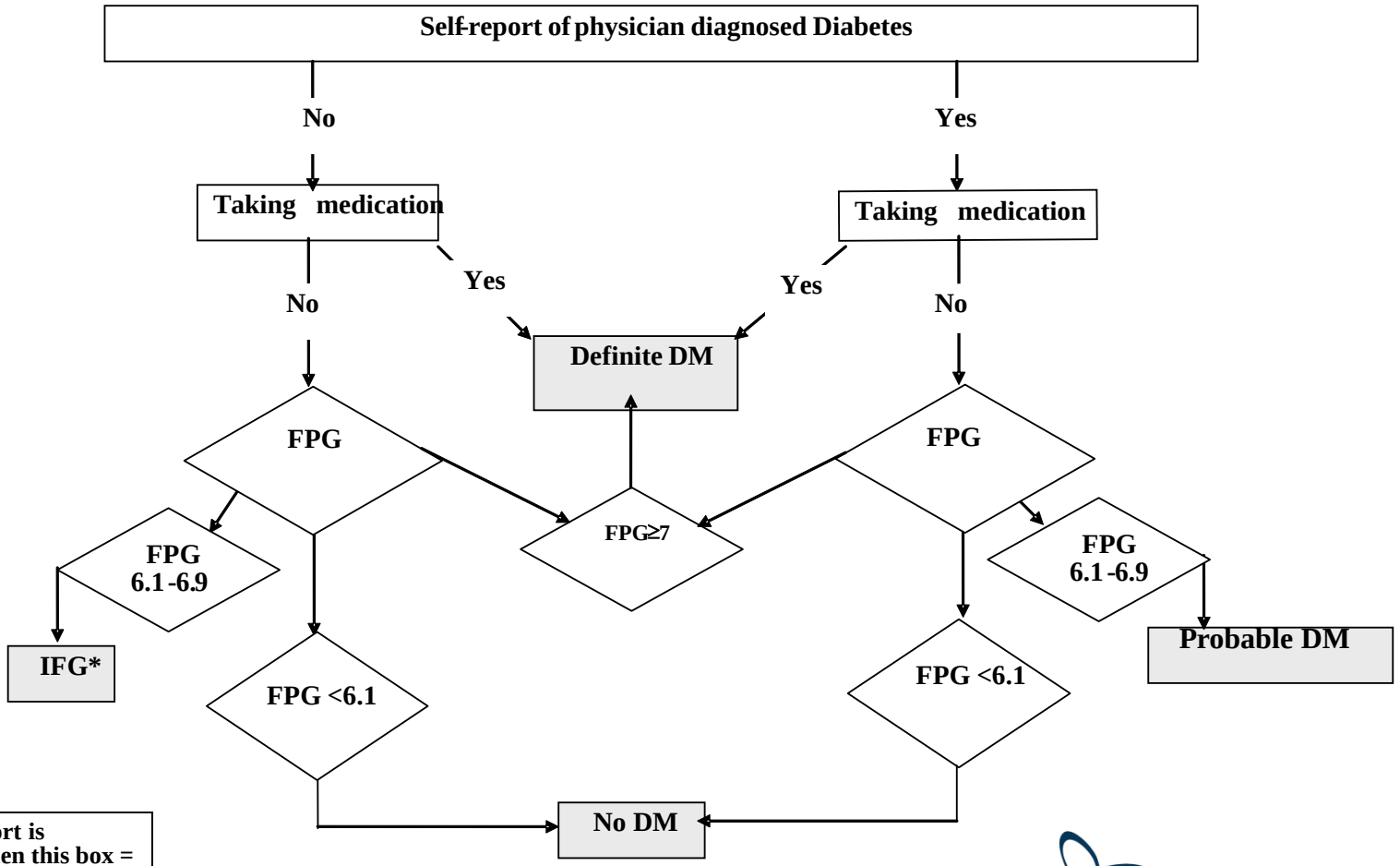


*MC = Maintaining Contact

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



*If self-report is removed, then this box = 'possible diabetes'

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Example

Physical Function

Mobility

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Mobility

*«activity & participation» **

Examples of precursors

Individual (or ìntrinsic)

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 partcipation
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

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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:

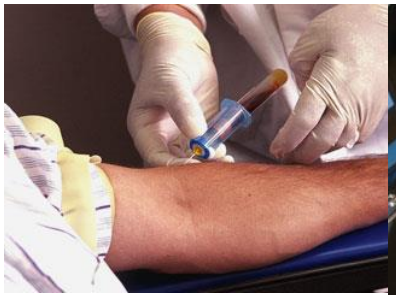
- What is the relationship between inflammatory biomarkers (e.g., IL-6, C reactive protein, albumin), hormonal biomarkers (e.g., IGF-1, T3, T4), metabolic (e.g., fasting glucose, cholesterol) or immunological markers (TNFα), oxidative stress (e.g. vitamin E and C), vitamin D, and (Epi) genetic markers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

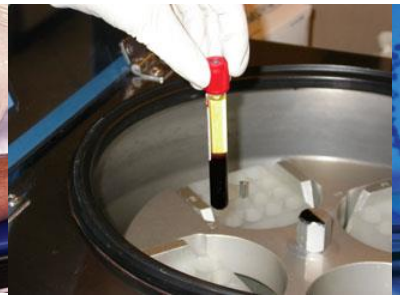
- What is the relationship between neighbourhood deprivation and incident mobility disability in aging population?

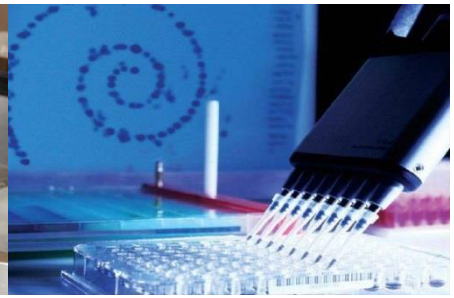
Data Collection Sites (DCS)

11 ACROSS CANADA

- 5 participants per day (40 weeks)
- 50 mL blood
- Urine sample
- Hematology tests (AcT DIFF, Beckman Coulter)







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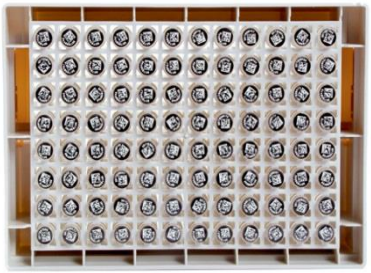
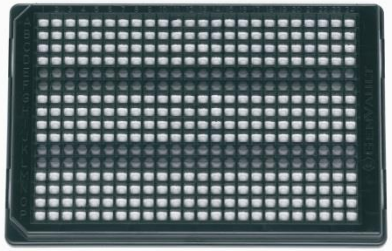
Storage System



Tubes

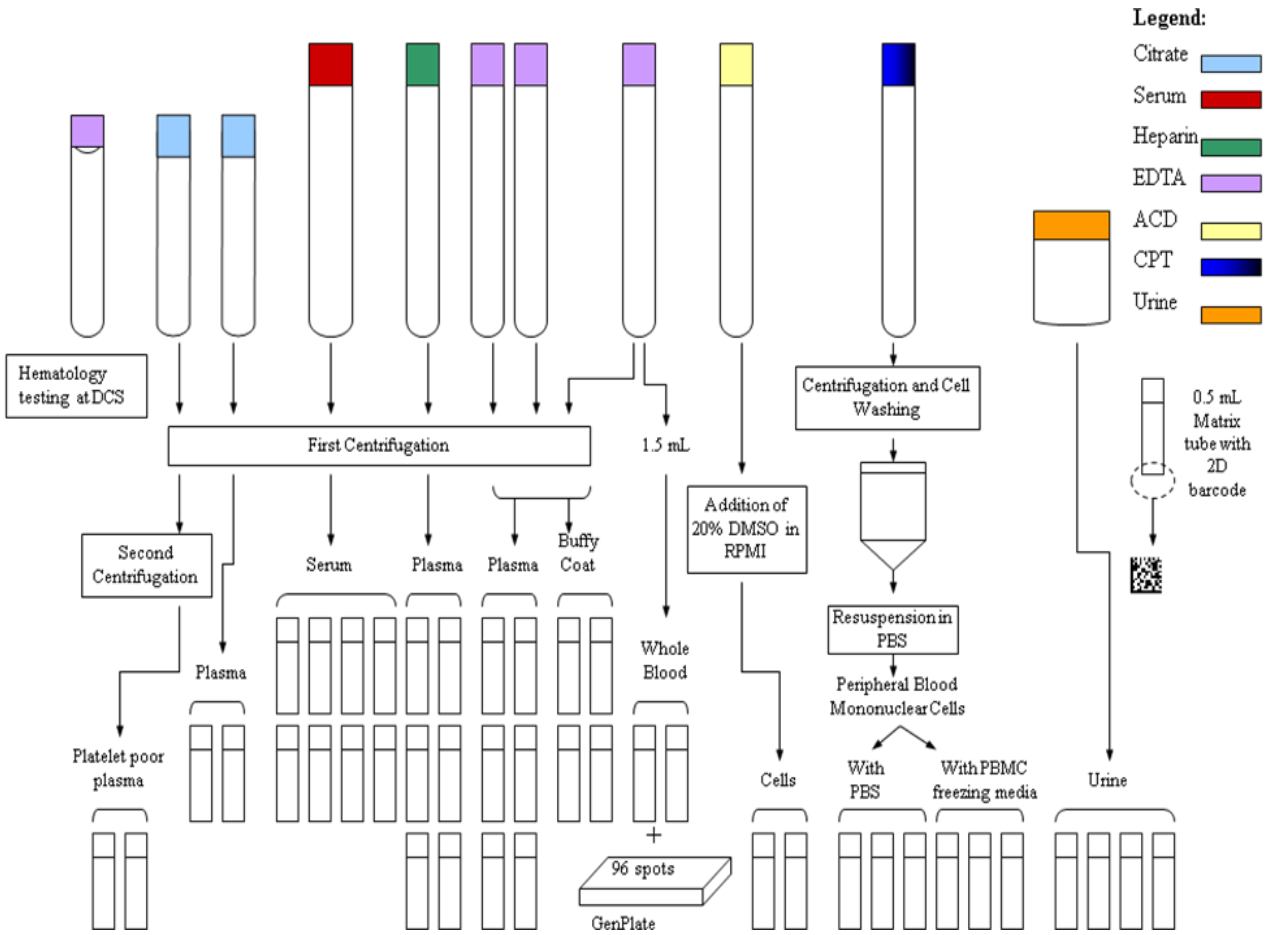
- 500-µL V bottom, screw- top tubes (Matrix Tubes, Thermo Fisher Scientific)
- Open-bottomed boxes for fast scanning
- Standard 96 well format
- Potential for 'pick and place' robotic retrieval and storage box compression ('defragging')

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



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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^{0}C

Biorepository and Bioanalysis Centre (BBC)

HAMILTON

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

ASKION C-line®
work bench

FUTURE

Biorepository and Bioanalysis Centre (BBC)

Biorepository

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

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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

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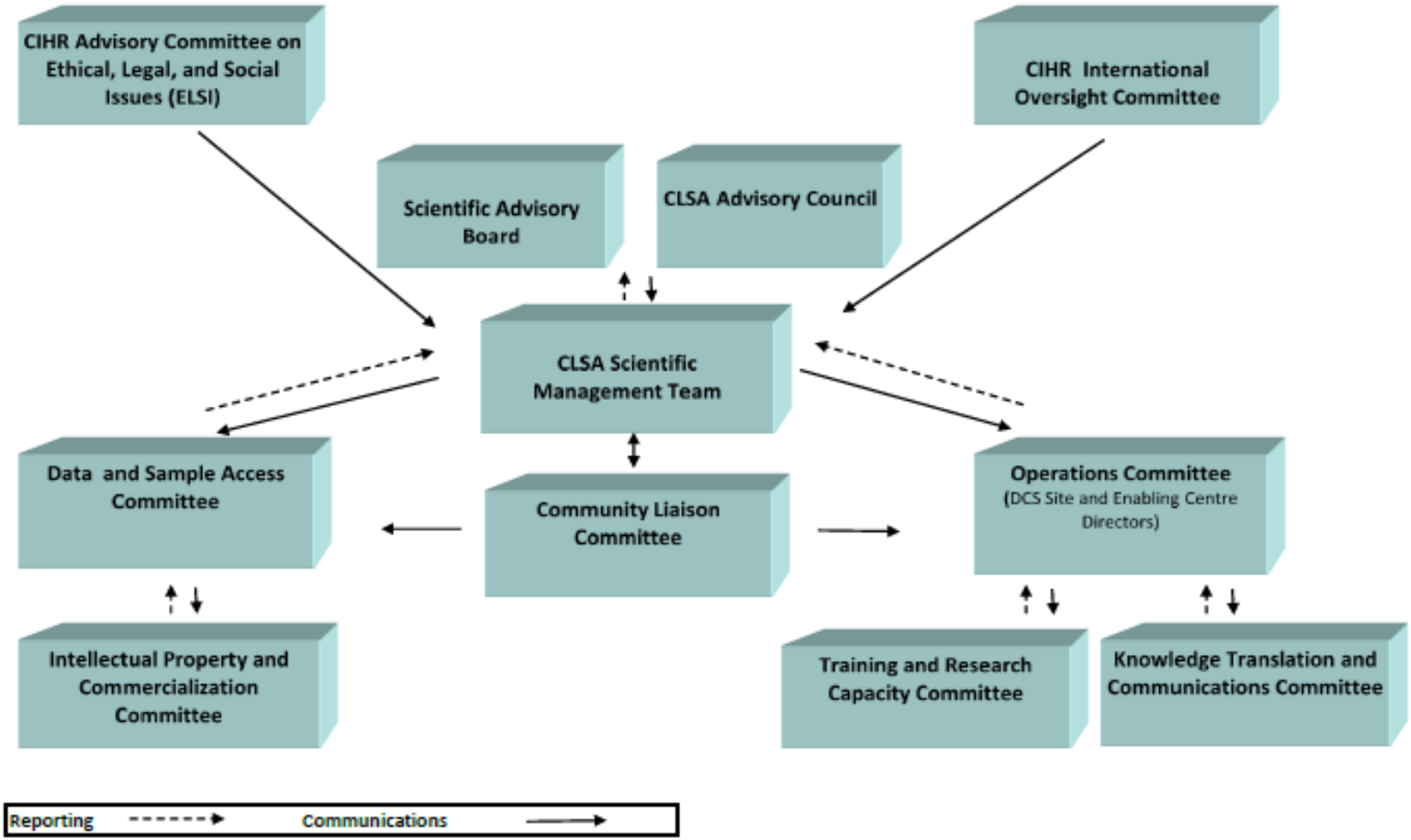
CLSA Governance Structure



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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)
- $6.5 M Universities and other partners

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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

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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

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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

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CLSA CORE TEAM

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

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CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

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