



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

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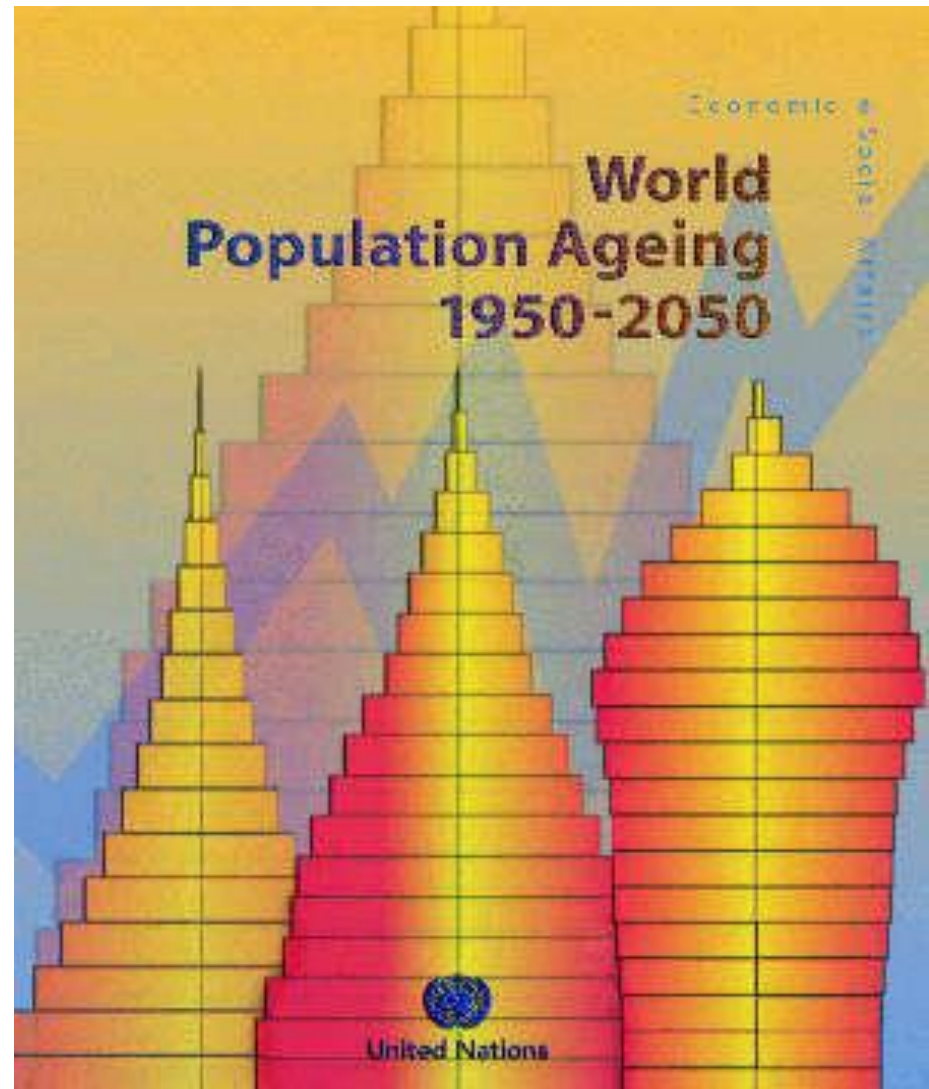
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Population aging

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



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

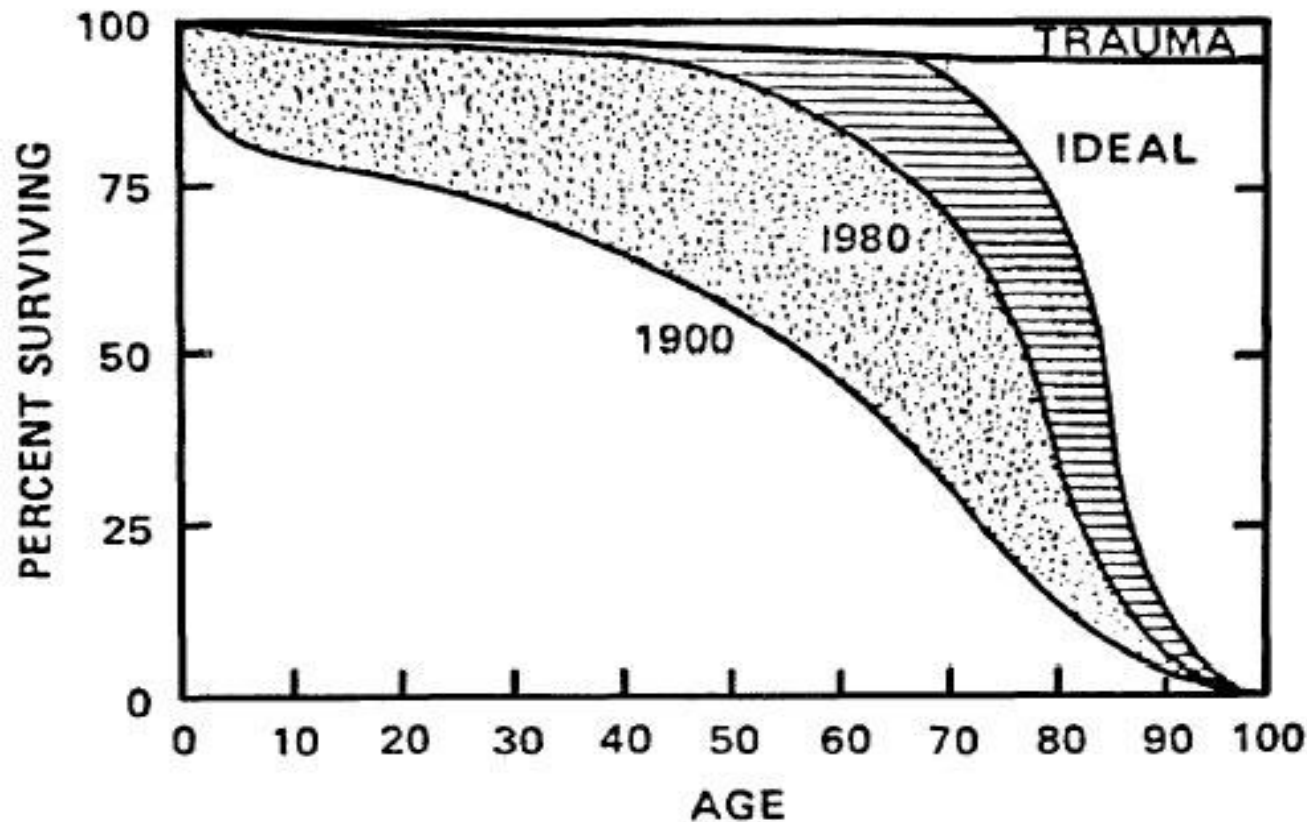
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Rectangularization of the survival curve

FURTHER INCREASE IN LIFE EXPECTANCY

Squaring the survival curve



Compression of morbidity

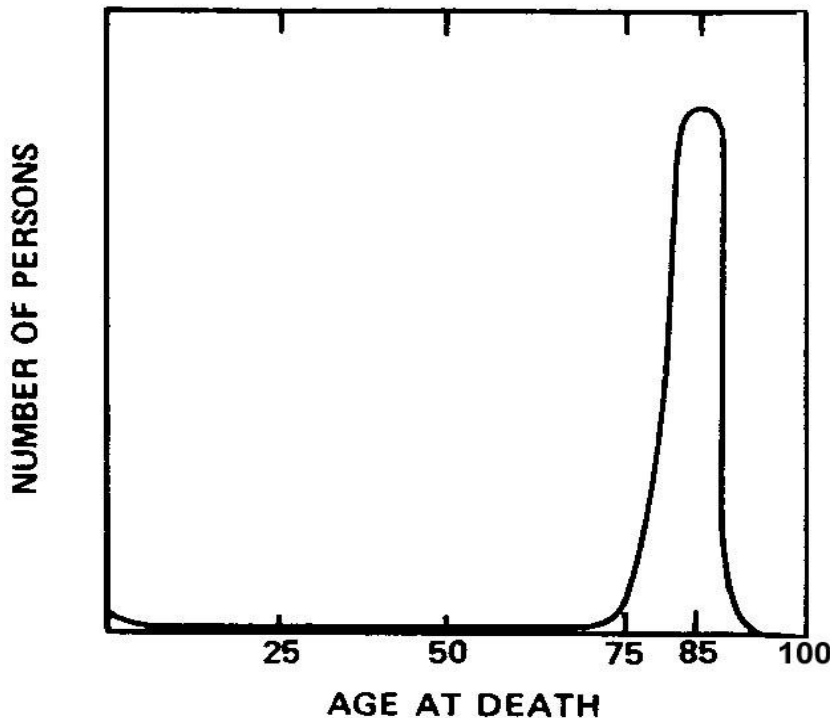


Figure: Mortality According to Age in the Absence of Premature Death

- 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

Compression of morbidity

Fries' paradigm based on the premise that:

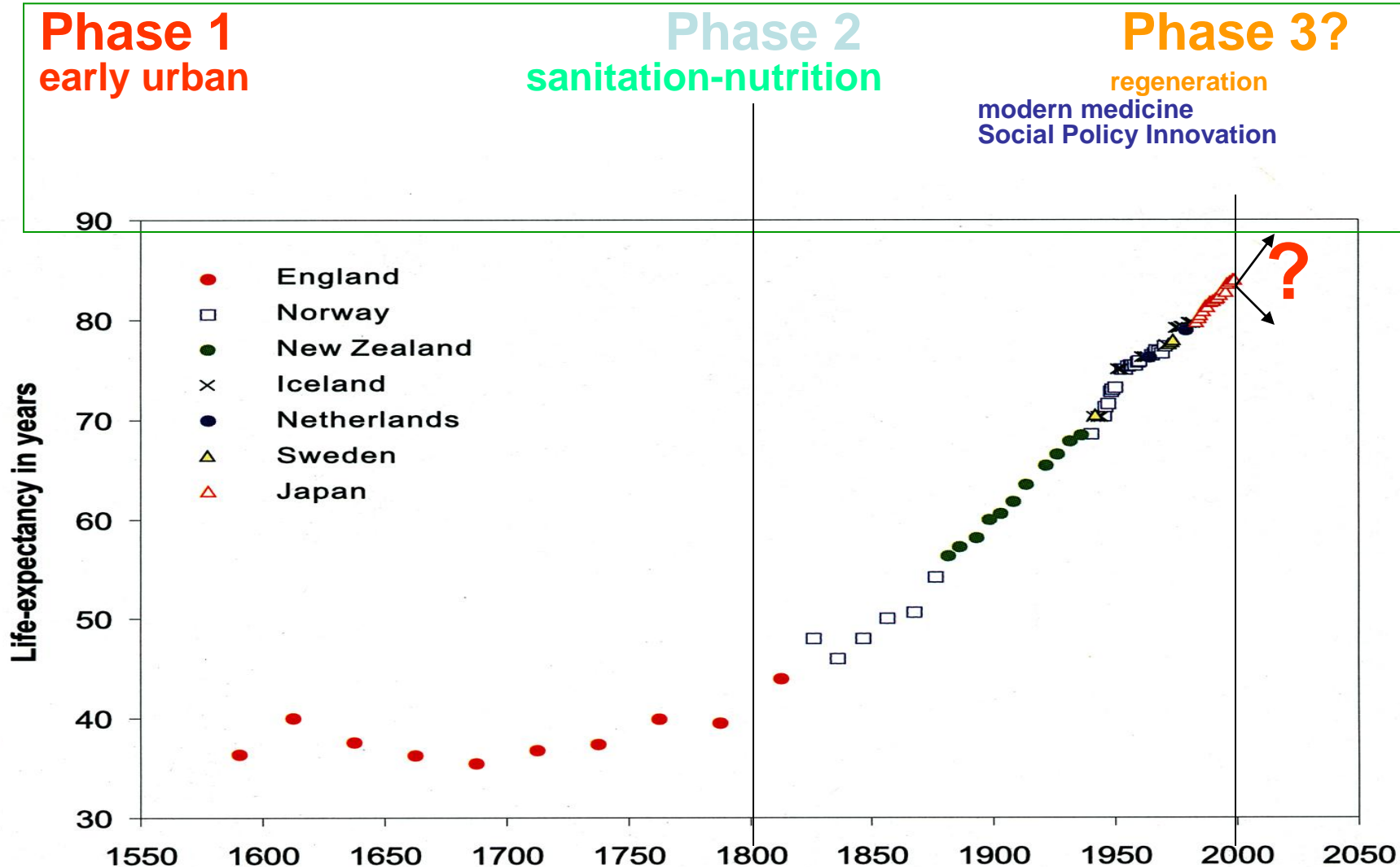
- The length of human life is fixed
AND
- Chronic disease can be postponed
- Predicted that the increase in life expectancy would plateau in the coming decades, particularly life expectancy from age 65 which excludes early life mortality

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

Oeppen and Vaupel, Science 2002; C Finch adaptation



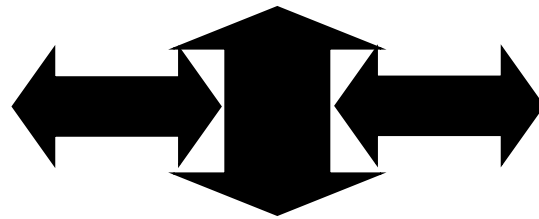
Demographic Futures

- 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

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	Histocompatibility 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-methylenetetrahydrofolate 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

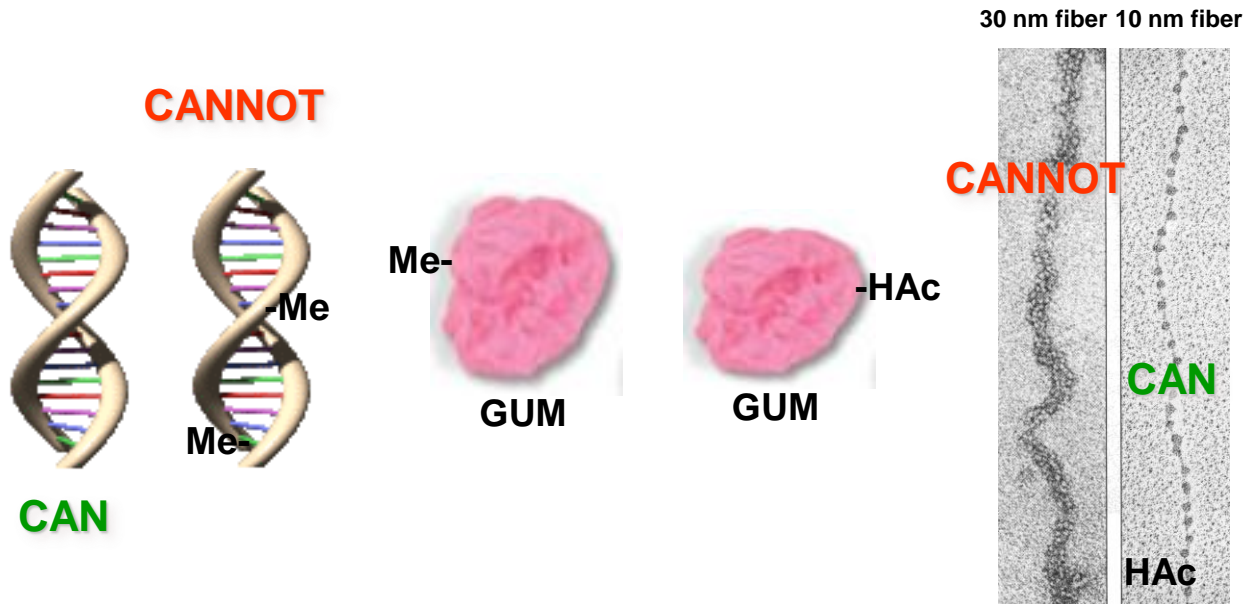
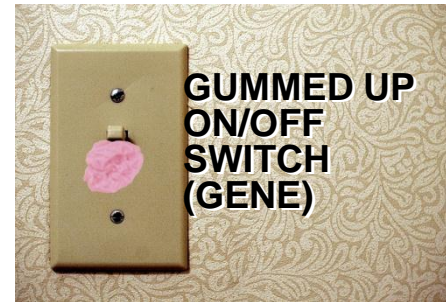
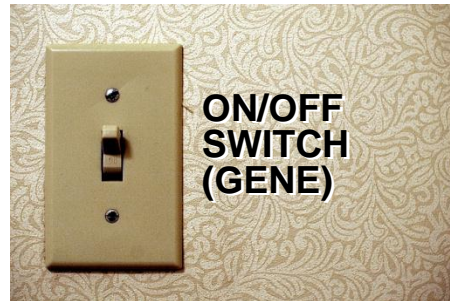
▪ Philippe (1978)	0-0.24
▪ Bocquet-Appel & Jakobi (1990)	0.10-0.30
▪ Mayer (1990)	0.10-0.33
▪ Gavrilova et al (1998)	0.18-0.58
▪ Cournil et al (2000)	0.27

Genes account for 25% of what determines disease and longevity



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EPIGENETICS



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

Environmental influences

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



Chronic diseases

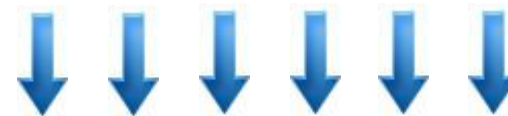
(e.g., diabetes, cancer, dementia, arthritis, cardio)

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

Aging



infections



Health Services Utilization



Genetics

Time (Longitudinal Study)



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The Canadian Longitudinal Study on Aging (CLSA)

- ▶ A key strategic initiative of CIHR
 - ▶ The Canadian Longitudinal Study on Aging
- ▶ More than 160 researchers - 26 institutions
- ▶ Multidisciplinary - biology, genetics, medicine, psychology, sociology, demography, economics, epidemiology, nursing, nutrition, health services, biostatistics, population health



CLSA- The Concept

The Vision

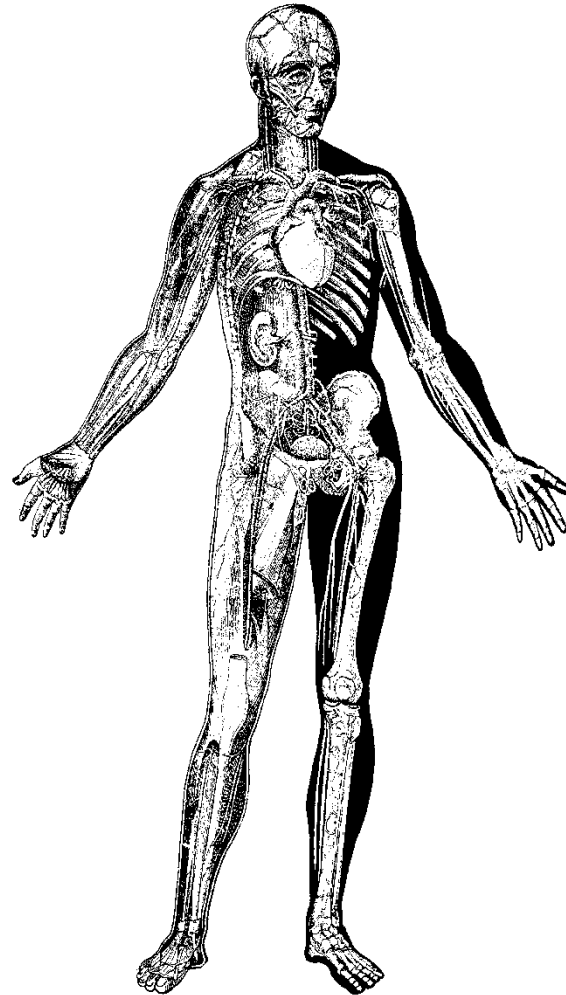
A research platform - - infrastructure to enable state-of-the-art interdisciplinary population based *research* and *evidenced-based* decision making.

The 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

CLSA Architecture



Interdisciplinary team of 50,000 (at 11 sites)

Questionnaires, Clinical, Biological, Physical

Follow-up over 20 years

Every 3 years age 45-85



Sampling and Subject Selection

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

CLSA – CCHS Healthy Aging

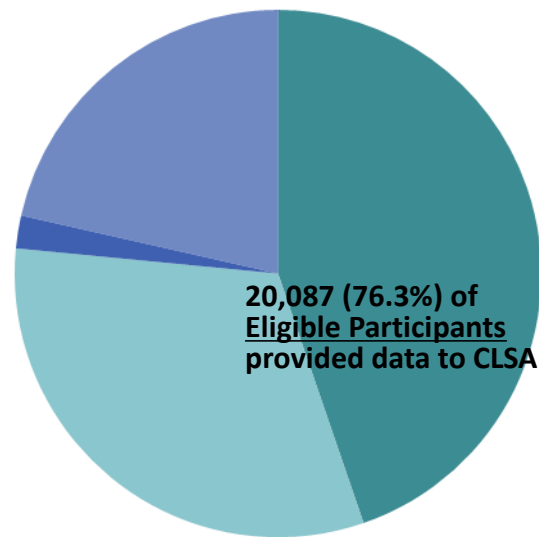
Multi-stage sampling

- Sampling frame 2006 Census
- Selection
 - Clusters based on Census dissemination area blocks
 - Dwellings within cluster
 - Person within dwelling
- Response Rate
 - Household-level 80.8%
 - Person-level 92.1%
 - Overall 74.4%

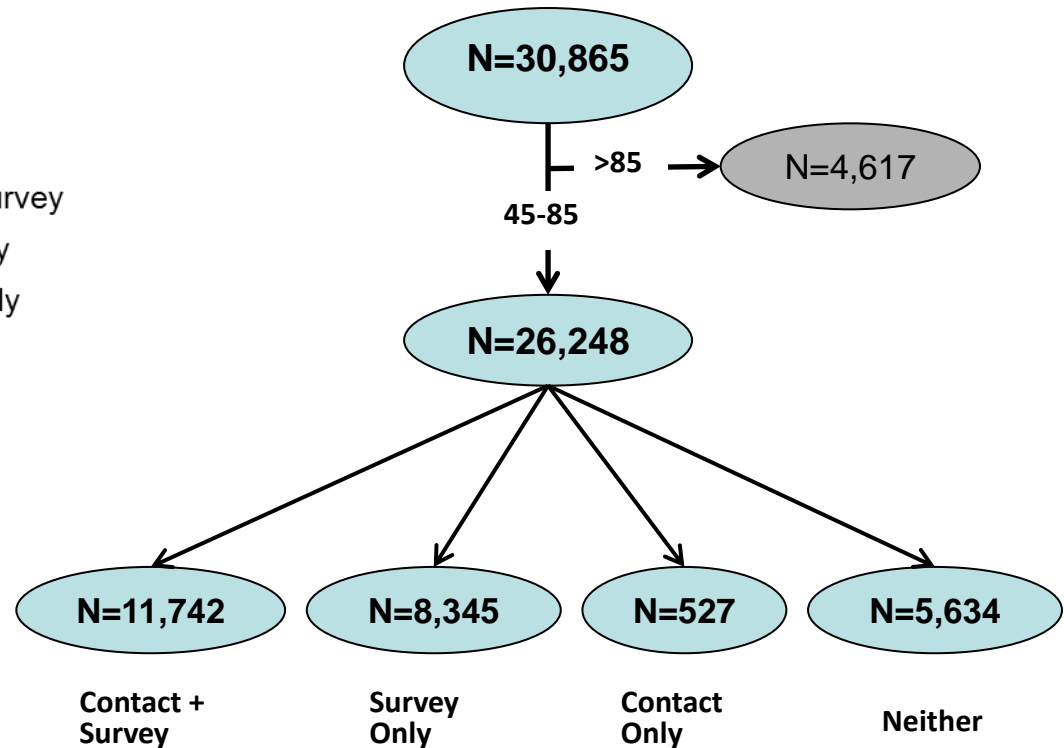
CLSA – CCHS Healthy Aging

Participants were asked to share:

- Their contact information with the CLSA (for recruitment)
- Their survey responses with the CLSA (for analysis)



- Contact+Survey
- Survey Only
- Contact Only
- Neither



Aims of 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:
 - Using provincial health registries
 - Random digit dialing
- In Alberta and Quebec, we could not use registries

Example of requirement by province

Tracking cohort

Alberta

	45-54		55-64		65-74		75-85		Total
	M	F	M	F	M	F	M	F	
# Required	306	306	306	306	204	204	204	204	2,040
# Providing Contact Info	121	128	153	193	108	138	74	107	1,022
# Anticipated through CCHS	28	35	56	82	53	64	33	25	376
# Additional Participants	278	271	250	224	151	140	171	179	1,664
# Need to Sample*	X	X	X	X	X	X	X	X	X

*** This will depend on the recruitment rate per number sampled**



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RDD approach

- Randomly sample numbers as far as possible in specified area codes and with next 3 digits in relevant area
- Identify eligible people at that number
- Randomly choose one person
- Recruit willing participants

Issues in using RDD

- Identifying numbers in specified area
- Having up-to-date list of numbers
- Ability to compute sample weights
- Presence of landlines and/or cellphones
- Eligibility within household – changes over time
- Method of initial contact
- Households without phones
- Numbers may be businesses, out of order, etc.
- People away from home (snowbirds, etc.)

Cell phones and landlines

- Statistics Canada survey December 2010
- Supplement to Labour Force Survey
- Households using cellphones exclusively:
 - Overall: 13%
 - Age 18-34 50%
 - Over 35 8%
 - Over 55 4%
- Increasing over time
- Landlines reach nearly all our eligibles

‘Cold calling’ vs prior contact/letters

- Time and expense of mailing letters (only possible when we have name and address)
- May increase willingness to talk to interviewers (call display)
- Perhaps try both initially and then move to using one

Contacting subjects

- On average, anticipate making many calls to recruit a single person
 - Up to 7-10 calls to obtain response
 - Leave message?
 - Willingness to participate
- Working on assumption of 20% 'recruitment rate' for health registry data (15% in 75-85 age group)
- Exclude households without a phone

Some questions

- Should we try both cold calling and prior contact?
- Is it OK to exclude households without a phone?
- Should we leave a message after n calls fail to contact anyone at the number?
- Should we exclude cell phones?

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 Data bases

PSYCHOSOCIAL

- Social participation
- Social networks and support
- Care giving 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

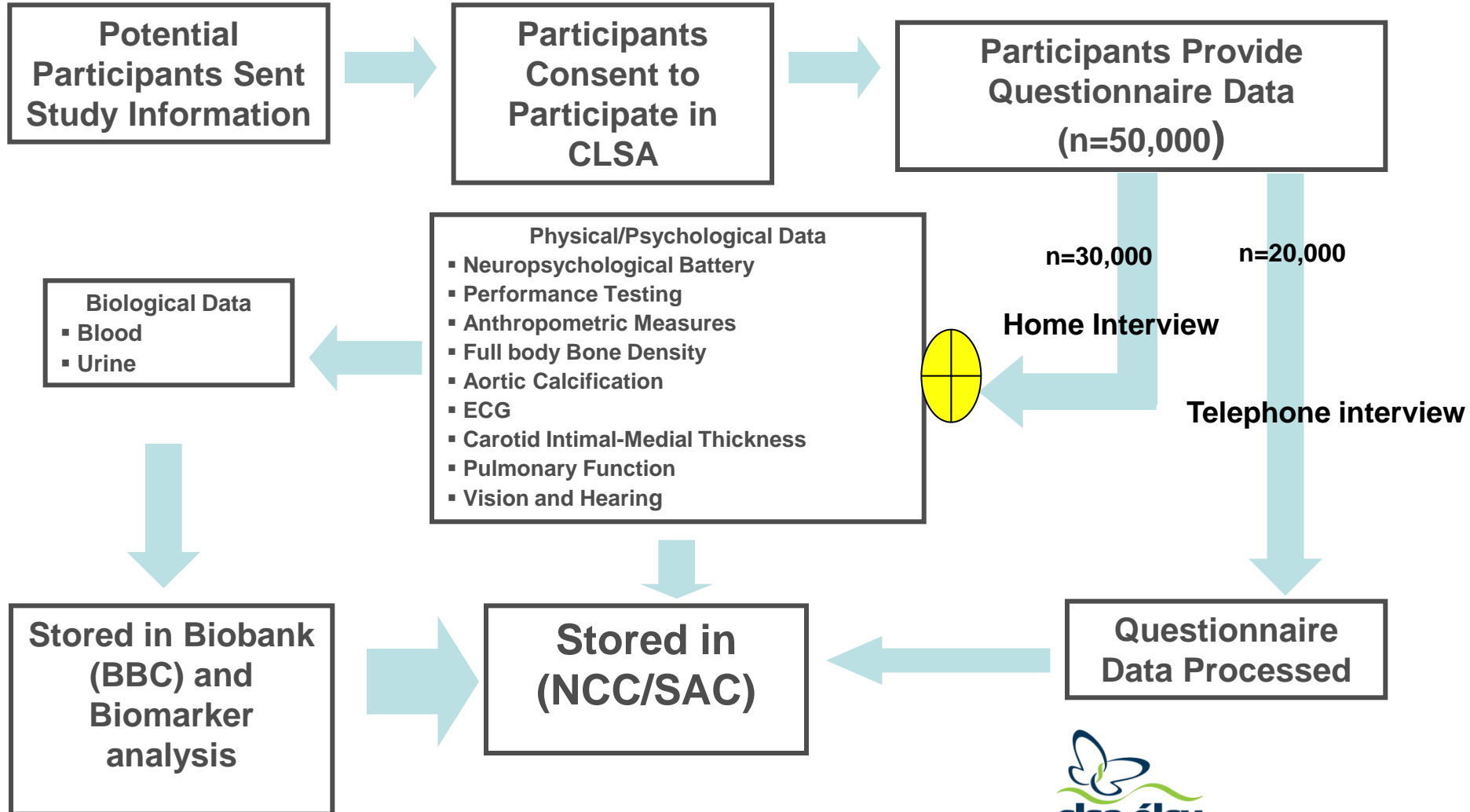
LIFESTYLE & SOCIODEMOGRAPHIC

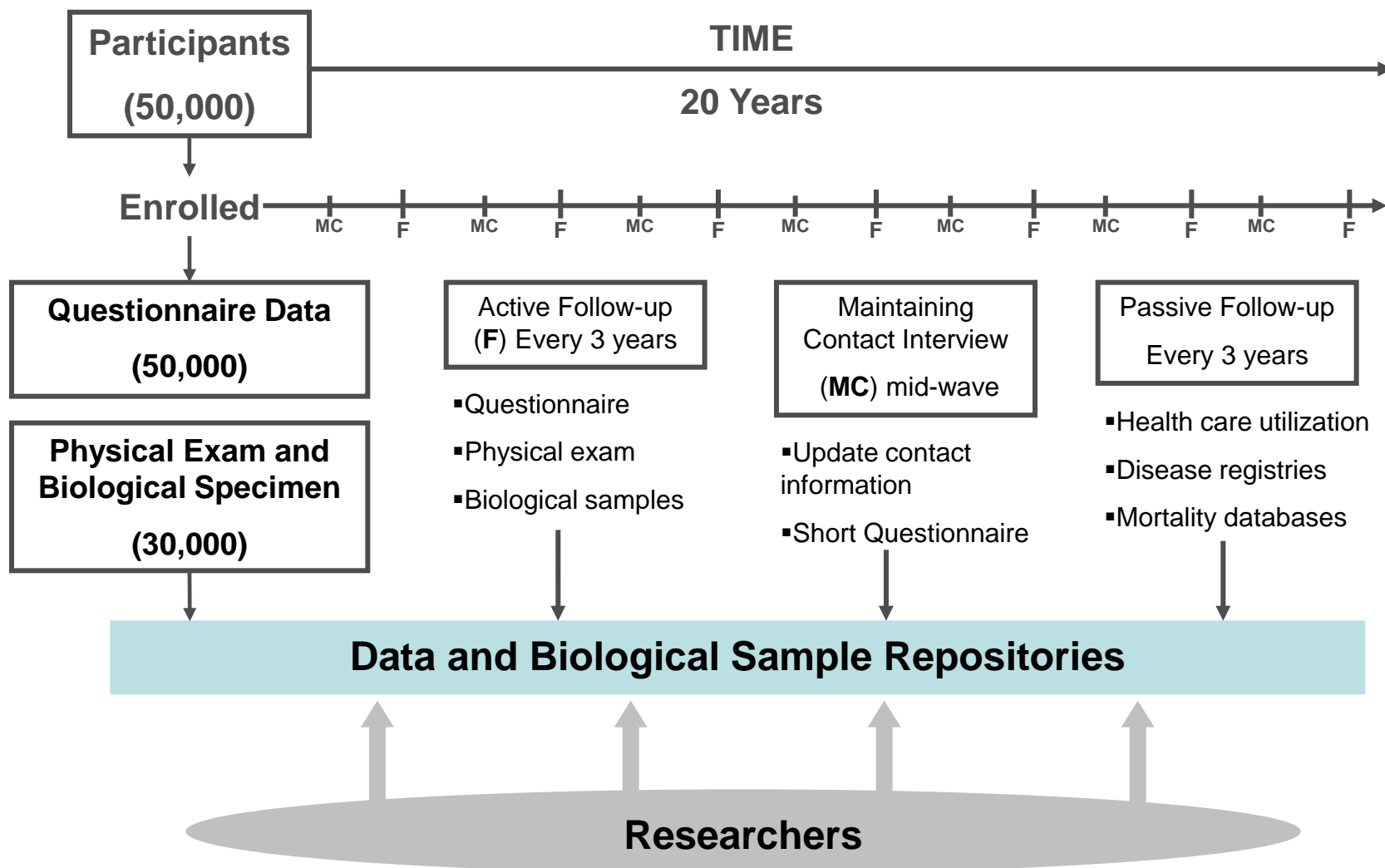
- Smoking
- Alcohol consumption
- Physical activity
- Nutrition
- Birth location
- Ethnicity/Race/Gender
- Marital status
- Education
- Income



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Data Collection Overview





Biological Samples

BIOCHEMICAL & HEMATOLOGICAL ANALYSIS (50 ml Blood; Urine)

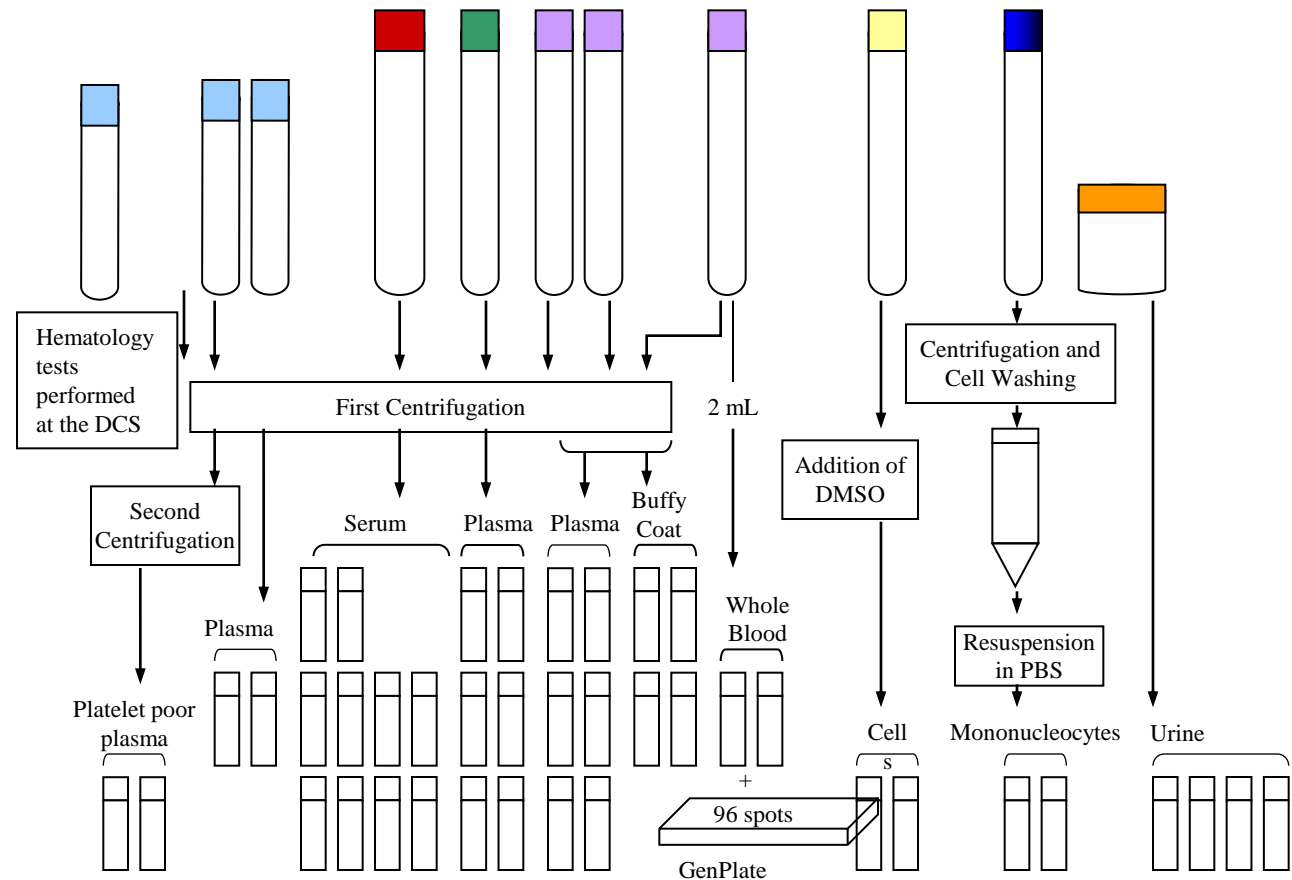
General Hematology

- Basophils
- Eosinophils
- Neutrophils
- Lymphocytes
- Monocytes
- White blood count
- Red blood cells
- Hemoglobin
- Platelets

Lipid Profile

- HDL-cholesterol
- LDL-cholesterol
- Tryglycerides
- Glucose
- Fasting blood sugar

Genetic and Epigenetic Markers



Biospecimen Science

- The study of the molecular integrity of biospecimens
 - How pre-analytical handling affects analytic results
- Based on the desire to have high-quality well-annotated clinical samples to facilitate biomarker discovery and validation

Chaos in the Brickyard

Bernard Forscher Science 1963;142:339



Sources of Variation

Pre-analytical	Analytical	Post-analytical
<ul style="list-style-type: none">▪ Patient state▪ Biological variation▪ Patient preparation▪ Collection▪ Processing▪ Storage	<ul style="list-style-type: none">▪ Method type▪ Calibration▪ Lot number▪ Traceability▪ Interferences	<ul style="list-style-type: none">▪ Transmission of the test result▪ Data analysis▪ Reference intervals, decision limits, algorithms (multi-marker panels)

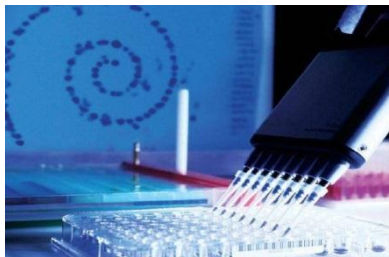
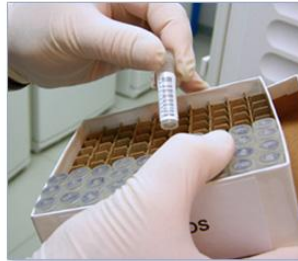
Biospecimen

Uncertainty of measurement

Interpretation



Pre-analytical Variation (Bias)



Time



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Sample Quality is Imperative

- Lack of quality leads to false positives and false negatives, inaccuracy and non-reproducibility
 - Erodes public confidence
 - Wastes time and money
 - Impedes clinical development

High-quality data depends on high-quality analysis and high-quality specimens

Biospecimen Challenges

- Evidence-based best practices and standard operating procedures (SOP)
 - Reduction of process variation to yield unbiased samples
- Quality indicators/molecular markers and metrics for stored samples
- Certification of personnel and accreditation of biobanks
- Reporting criteria for biospecimens
 - Documentation/publication

Example Study Question

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 (TNF α), 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?

Where are we now?



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CLSA Recruitment

Tracking Cohort

- Recruitment via CCHS complete
- Recruitment ongoing in all provinces through Ministry of Health (MoH) and/or Random Digit Dialing (RDD)
- Completion of all 20,000 baseline interviews by Spring 2013
- As of today:
 - 15,728 completed 60 minute baseline interview

Comprehensive Cohort

- Recruiting ongoing in all provinces through MoH and/or RDD
- Goal: complete first 8,000-10,000 baseline DCS visits by July 2013.
- As of today:
 - 5,029 in home interviews and 3,806 DCS visits completed (recruited)



Milestones for 2013

- Complete recruitment for Tracking Cohort – 20,000
- Recruit first 8,000-10,000 participants for Comprehensive Cohort
- Initiate Maintaining Contact for Tracking Cohort
- Data curation, derived variables and data cleaning
- Data access process, portal developed and tested
- Baseline tracking data released (early 2014)
- Planning and development for Wave 2

Upcoming areas of interest and development for the CLSA

- Core biomarker analysis
 - Imaging studies linking vascular imaging and the brain
 - Implementation of neurological conditions initiative
 - Selected possible enhancements to data collection
 - Environmental exposures
 - Life course, adaptation
 - Medication compliance
 - Contextual data
 - Linkages and data harmonization

**What would you like to see
added to the CLSA?**

**Other Ideas for Research
Questions?**



Funded by the Government of Canada through the CIHR and CFI, and by Provincial Governments



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