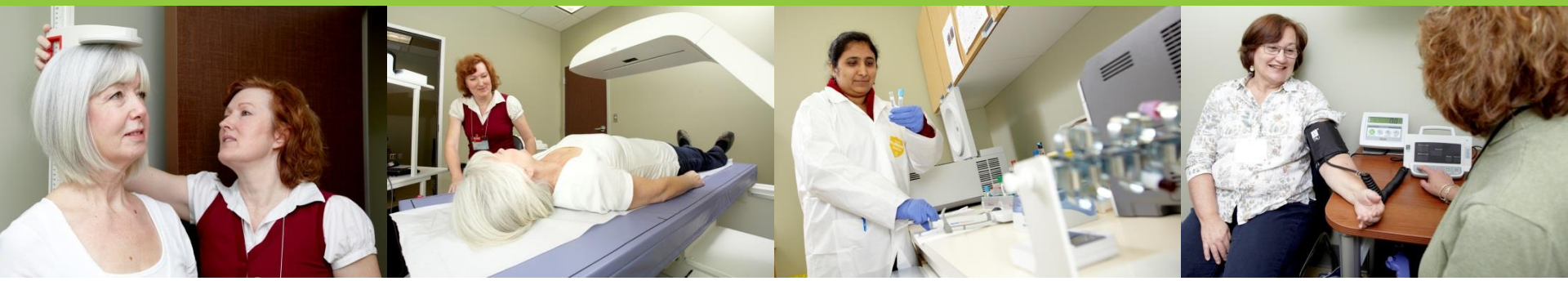




Transforming Everyday Life into Extraordinary Ideas



Canadian Longitudinal Study on Aging: Data for Frailty Research

Lauren Griffith, PhD
Associate Scientific Director, CLSA
Dept. Clinical Epidemiology & Biostatistics
McMaster University

Chris Verschoor, PhD
Research Associate, CLSA
Dept. Pathology and Molecular Medicine
McMaster University

Summer Program in Aging, Toronto Ontario
May 10th, 2016

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Talk Outline

- What is Frailty
- Measuring Frailty
- Data available in the Canadian Longitudinal Study on Aging (CLSA)
  - Alpha-numeric, physical measures → LG
  - Biological samples, biomarkers → CV
- Shameless plug for you to use CLSA Data

What is Frailty?

A

B

Which of these two individuals would you consider frail and why?

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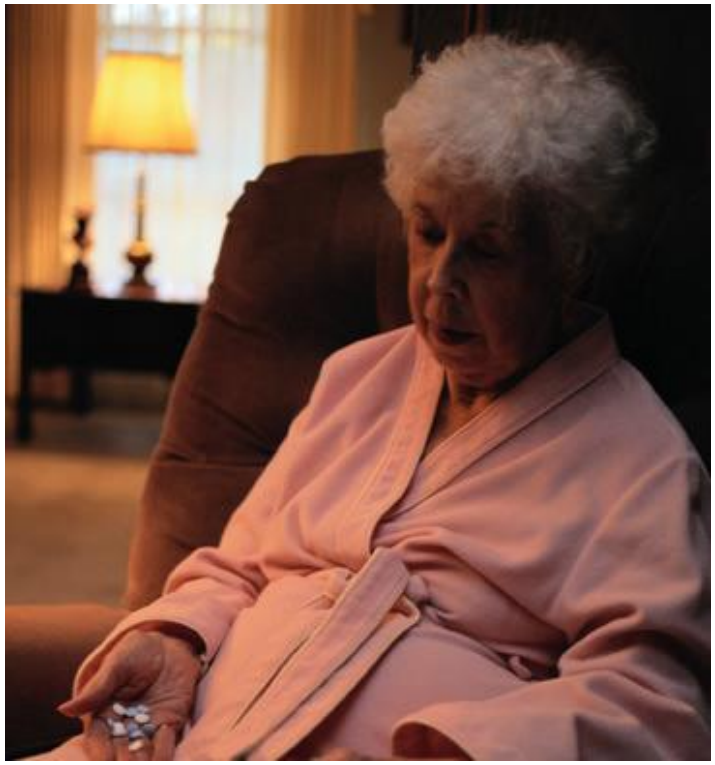
What is Frailty?



A

B

Which of these two individuals would you consider frail and why?

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What is Frailty?

A

B

Which of these two individuals would you consider frail and why?

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What is Frailty?

A

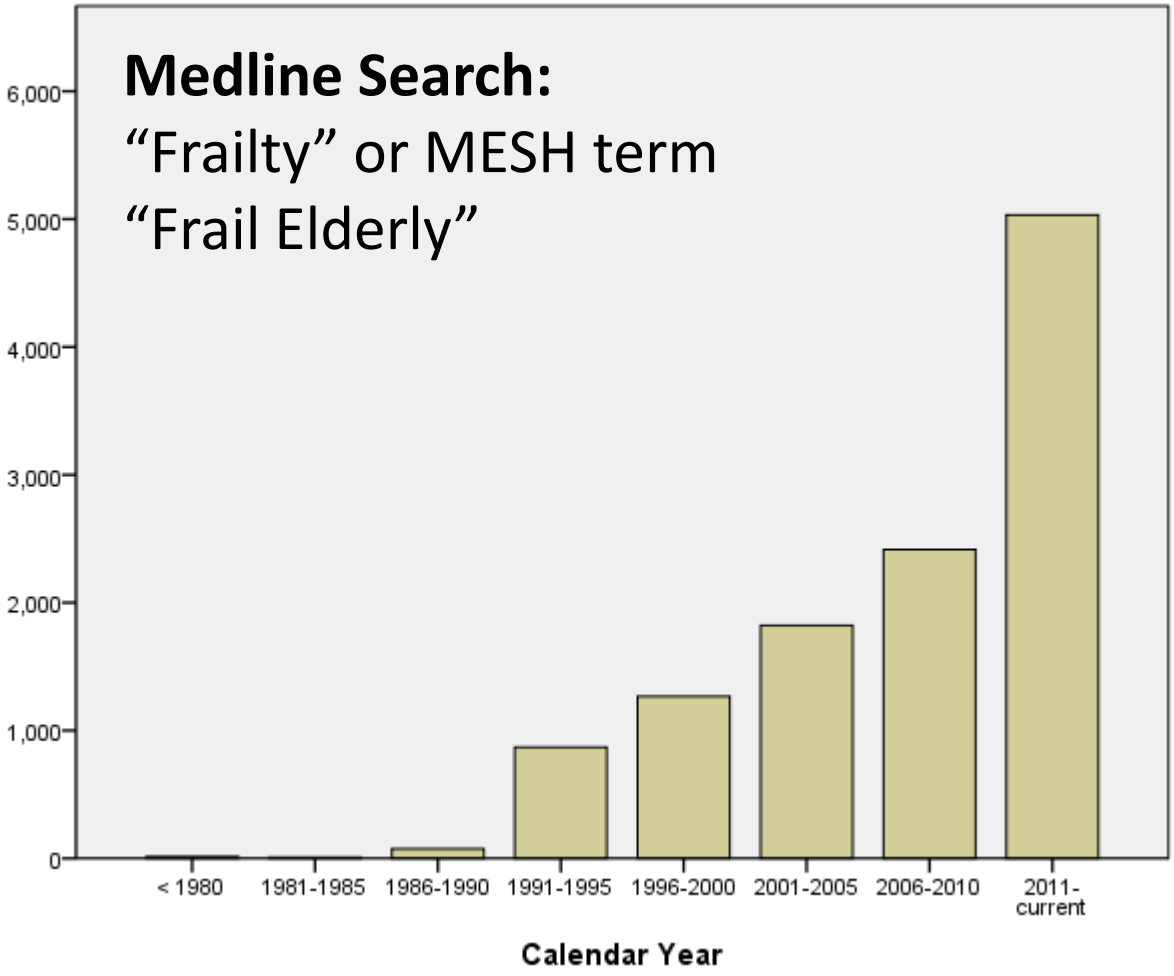
B

Which of these two individuals would you consider frail and why?

What is Frailty?

- Geriatricians and health care professionals that work with older adults tend to be able to agree what a person who is frail looks like
- But there is little consensus on how to measure it

Measuring Frailty



Number of Articles

< 1980	14
2011-now	5,033

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What is Frailty?

- The current consensus on the definition of frailty is that “Frailty is a clinical state in which there is an increase in an individual’s vulnerability for developing increased dependency and/or mortality when exposed to a stressor.”

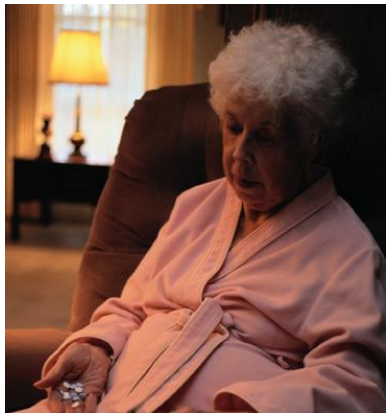
Morley JE, Vellas B, Abellan van Kan G, Anker SD, Bauer JM, Bernabel R et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013. 14(6): 392-7

Measuring Frailty

Phenotype model (Fried)

Five criteria related to labelling a person as frail (Fried et al. J Gerontol 2001;56A:M146-M156)

- Physical Inactivity
- Slow gait speed
- Weakness/low strength
- Exhaustion/Fatigue
- Weight loss



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Measuring Frailty

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- Exhaustion/Fatigue
- Weight loss

Additional components: cognitive impairment, mood (Sourail et al. J Gerontol 2012;67:1197-1204)

Operationalizing Frailty
Example: SHARE Study

• Physical Inactivity	How often do you engage in activities that require a low or moderate level of energy?	<1 to 3 times/ month
• Slow Gait Speed	Because of health problems, do you have difficulty walking 100 m or climbing one flight of stairs without resting?	Yes to either question
• Weakness	Dynamometer (hand drip strength)	Gender and BMI cut-points
• Exhaustion	In the last month have you had too little energy to do things you wanted to do?	Yes
• Weight Loss	What has your appetite been like? and/or Have you been eating less or more?	Diminished desire for food or eating less

Endorsing 3 or more = Frail

Measuring Frailty

Cumulative Deficits (Frailty Index)

- Health status can be represented by the number of health deficits that a person accumulates
- Used 92 variables from CSHA (Mitnitski AB, Rockwood K. Accumulation of Deficits as a Proxy Measure of Aging Scientific World. 2001;1:323-336)

Measuring Frailty

Creating a Cumulative Deficit (Frailty Index)

- Requires at least 30-40 health deficits
  - Related to aging and health status
  - Do not saturate too early
  - Cover a range of systems
- (total number of health deficits in the individual)/ (the total number of health deficits examined)

Measuring Frailty

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY *Inspiring Minds*

Measuring Frailty

- Used CSHA data to compare
  - Frailty Index (based on 70 variables)
  - Clinical Frailty Scale

Calculated ROC curves for predicting 5-year probability death and institutionalization

Rockwood K, et al. A Global Clinical Measure of Fitness and Frailty in Elderly People. CMAJ 2005;173:489-495

Measuring Frailty

Table 3: Receiver operating characteristic (ROC) analyses for adverse outcomes within 70 months

	Area under the ROC curve	
Assessment tool	Death	Entry into an institution
Cumulative Illness Rating Scale	0.58	0.62
Modified Mini-Mental State Examination	0.64	0.69
CSHA rules-based definition of frailty	0.66	0.70
CSHA Function Scale	0.68	0.80
CSHA Frailty Index	0.69	0.72
CSHA Clinical Frailty Scale	0.70	0.75

Note: CSHA = Canadian Study of Health and Aging.

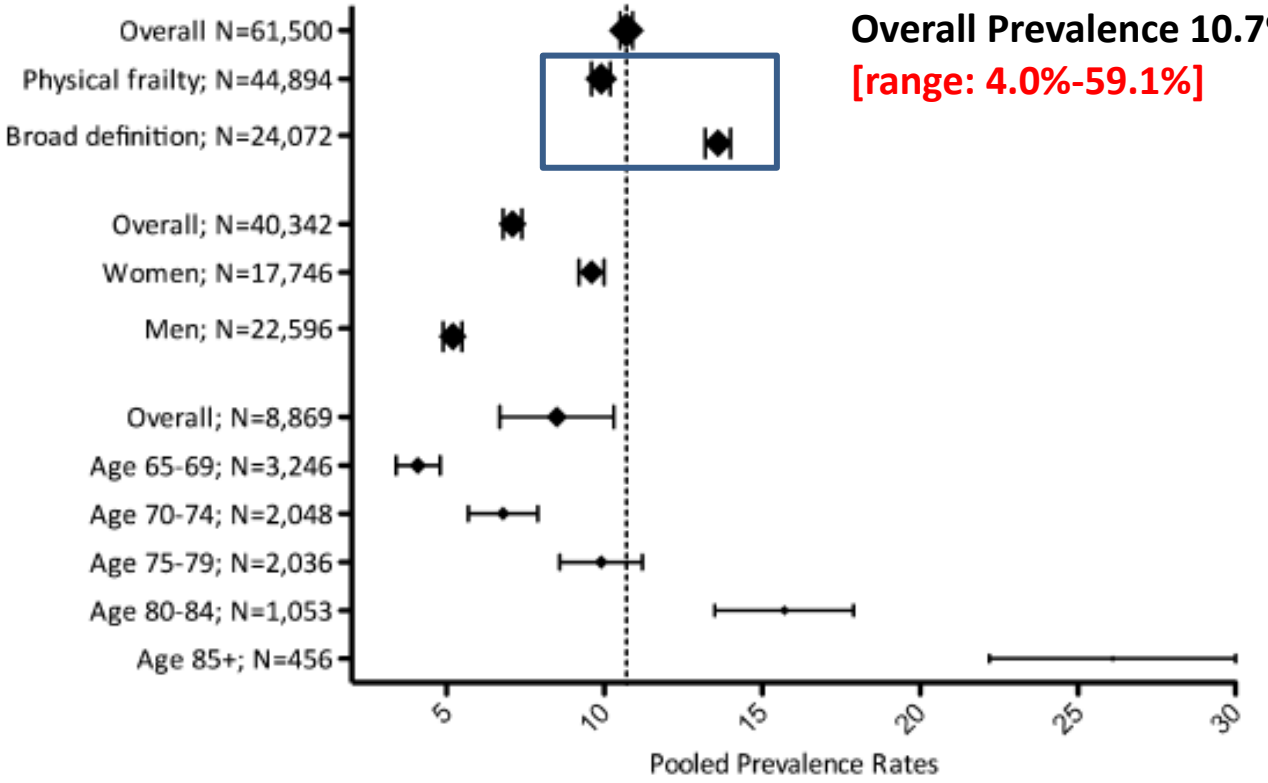
Rockwood K, et al. A Global Clinical Measure of Fitness and Frailty in Elderly People. CMAJ 2005;173:489-495

Measuring Frailty

Systematic Review on measures of frailty
(Bouillon K et al. BMC Geriatrics 2013;13:64)

- 27 articles describing separate frailty scales (range 1-38)
- range of domains: physical functioning, disability, disease, sensory impairment, cognition, nutrition, mood, and social support

Prevalence of Frailty



Overall Prevalence 10.7%
[range: 4.0%-59.1%]

Figure 1. Prevalence of frailty and 95% CIs

Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. J Am Geriatr Soc 2012;60:1487-1492

Challenges

Bergman et al., Frailty: An Emerging Research and Clinical Paradigm – Issues and Controversies J Gerontol A Biol Med Sci 2007;62:731-737

- Operational definition of frailty should further our understanding between frailty, its biological basis, impairments and longitudinal changes and trajectories in physical function as well as the contribution of social, environmental and behavioural factors
- This requires longitudinal, population-based data with great breadth

→ **CLSA**

CLSA Leads

Lead Principal Investigator
Parminder Raina (McMaster)

Co-principal Investigator
Christina Wolfson (McGill)

Co-principal Investigator
Susan Kirkland (Dalhousie)

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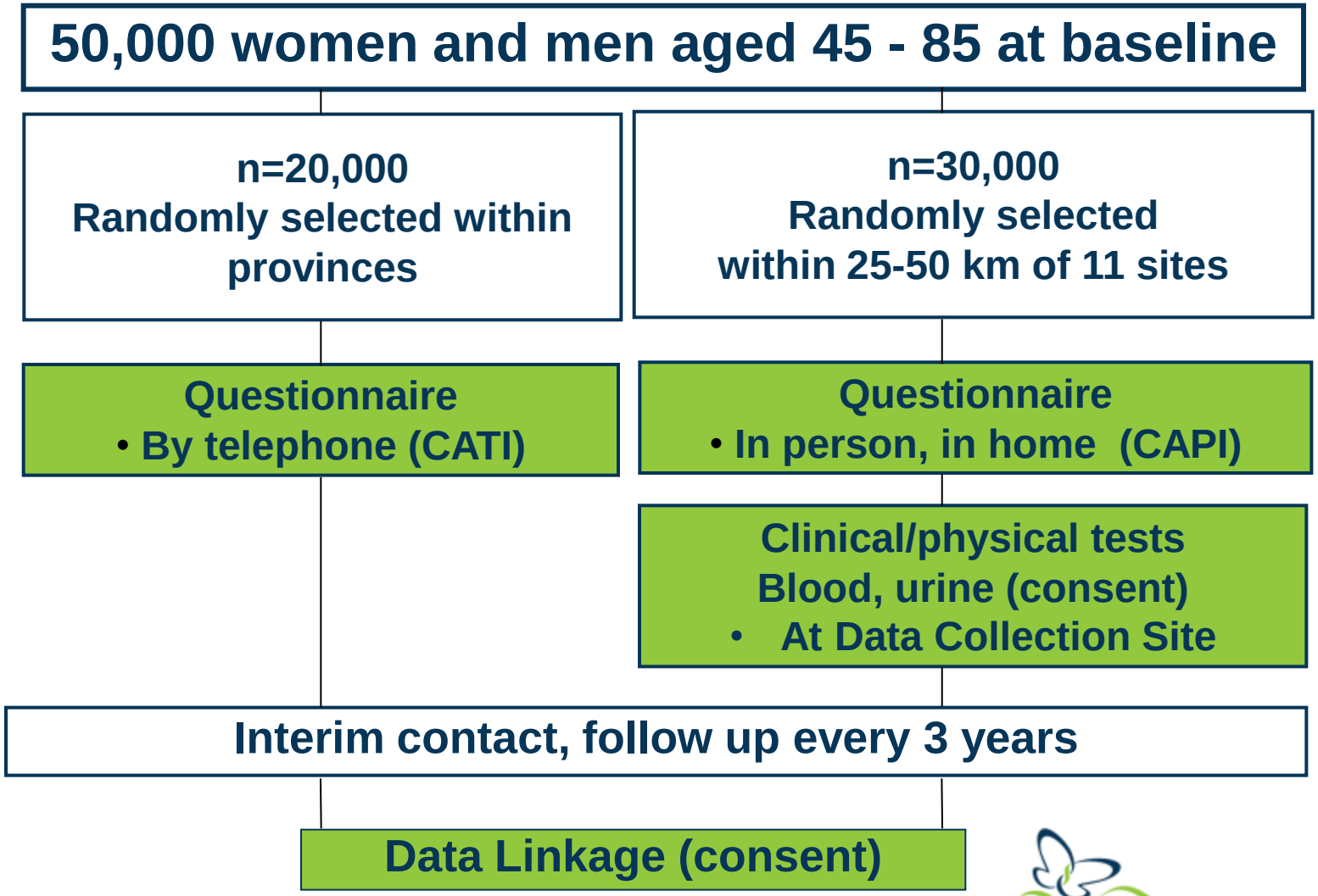
What is the Canadian Longitudinal Study on Aging (CLSA)?

"The Canadian Longitudinal Study on Aging is the largest most comprehensive research platform and infrastructure available for aging research with longitudinal data that will span 20 years from over 50,000 Canadians over the age of 45"

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

Study Overview



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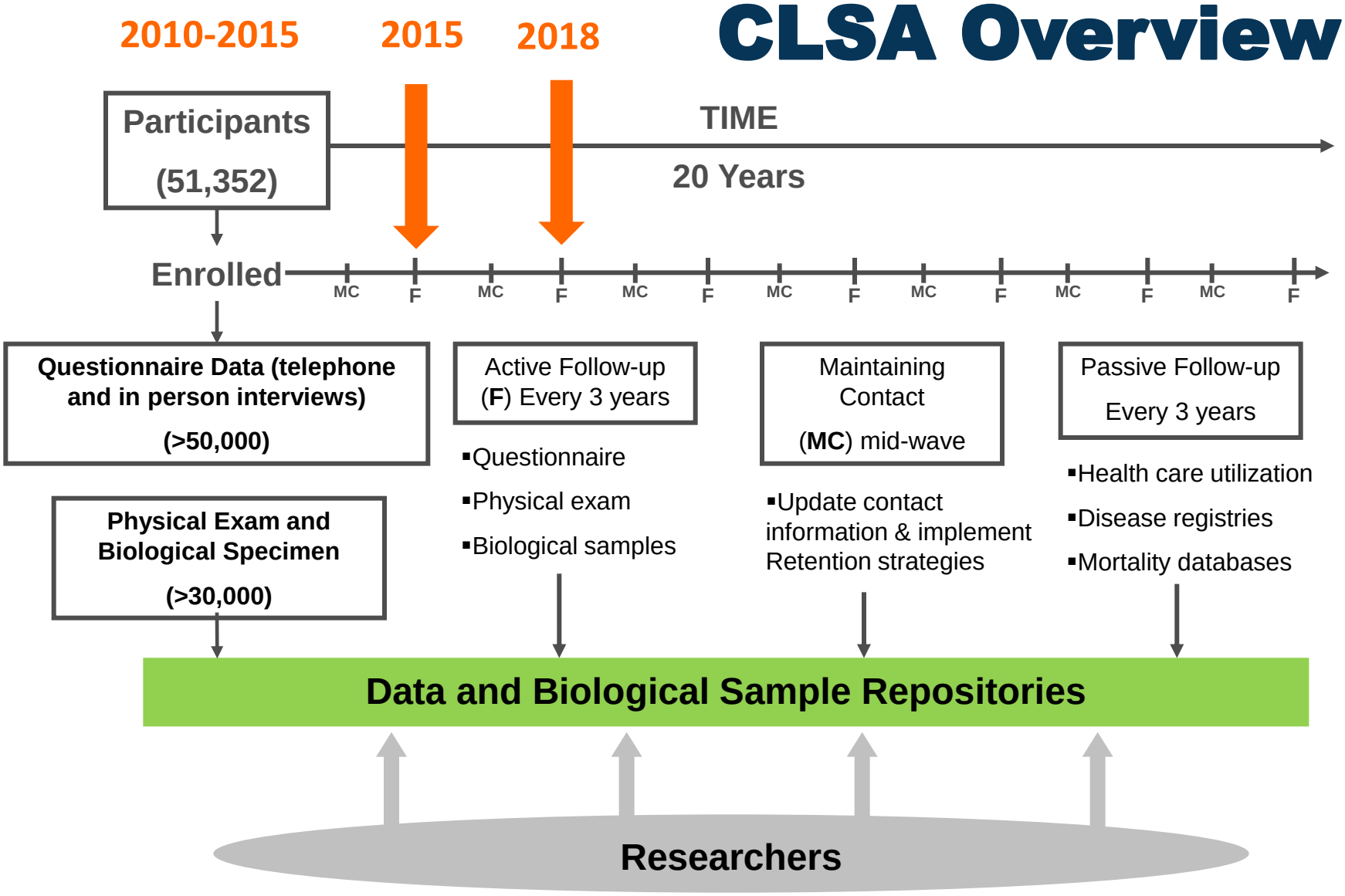
CLSA Overview



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Depth and Breadth of Baseline 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**

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PSYCHOSOCIAL

- Social participation
- Social networks and support
- Caregiving and care receiving
- Mood, psychological distress
- Veteran's Identifier & PTSD
- Coping, adaptation
- Injuries and consumer products
- Work-to-retirement transitions
- Retirement planning
- Social inequalities
- Mobility-life space
- Transportation
- Built environments & Contextual Factors
- Air Pollution
- 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

Recruitment & Data Collection
Telephone Interviews

- Recruitment of 21,241 participants for telephone interviews:
  - ✓ Statistics Canada CCHS on Healthy Aging
  - ✓ Provincial Health Care Registries
  - ✓ Random Digit Dialing
- **Baseline data collection is completed!**
- **Data is now available to researcher community**
- Maintaining contact interviews initiated in 2013 (**completed in early 2016, retention rate 95%**)
- First follow-up began 2015

Recruitment & Data Collection

Home Interviews and Data Collection Site Visits

- Recruitment of 30,097 for Home Interviews and Data Collection Site Visits:
  - ✓ Provincial Health Care Registries
  - ✓ Random Digit Dialing
- Baseline data collection 2012 to 2015: **Data collection completed**
- **Initial Data release for 30,097 April 30, 2016**
- Maintaining Contact Interviews initiated in 2014 (**completed, retention rate 96%**)
- First follow-up began 2015

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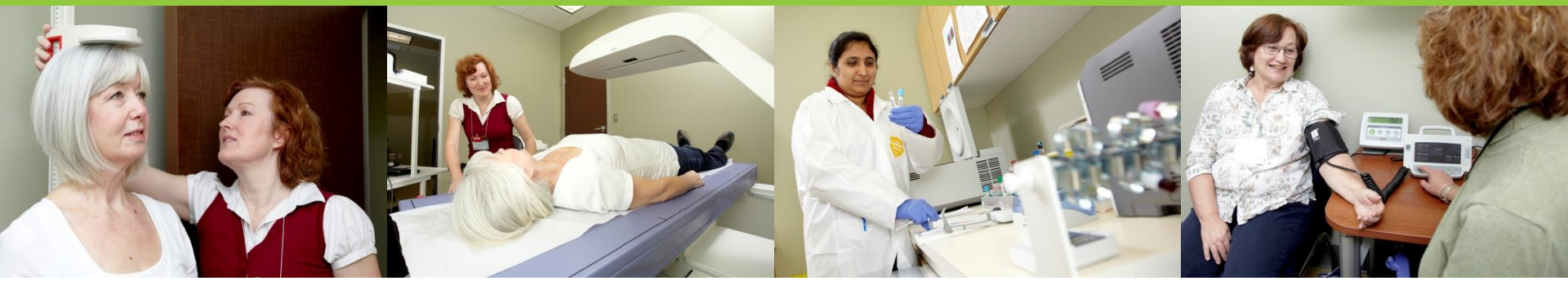


Preliminary analysis conducted by David Kanters (MSc Candidate) using CLSA data (21,242 telephone interviews)

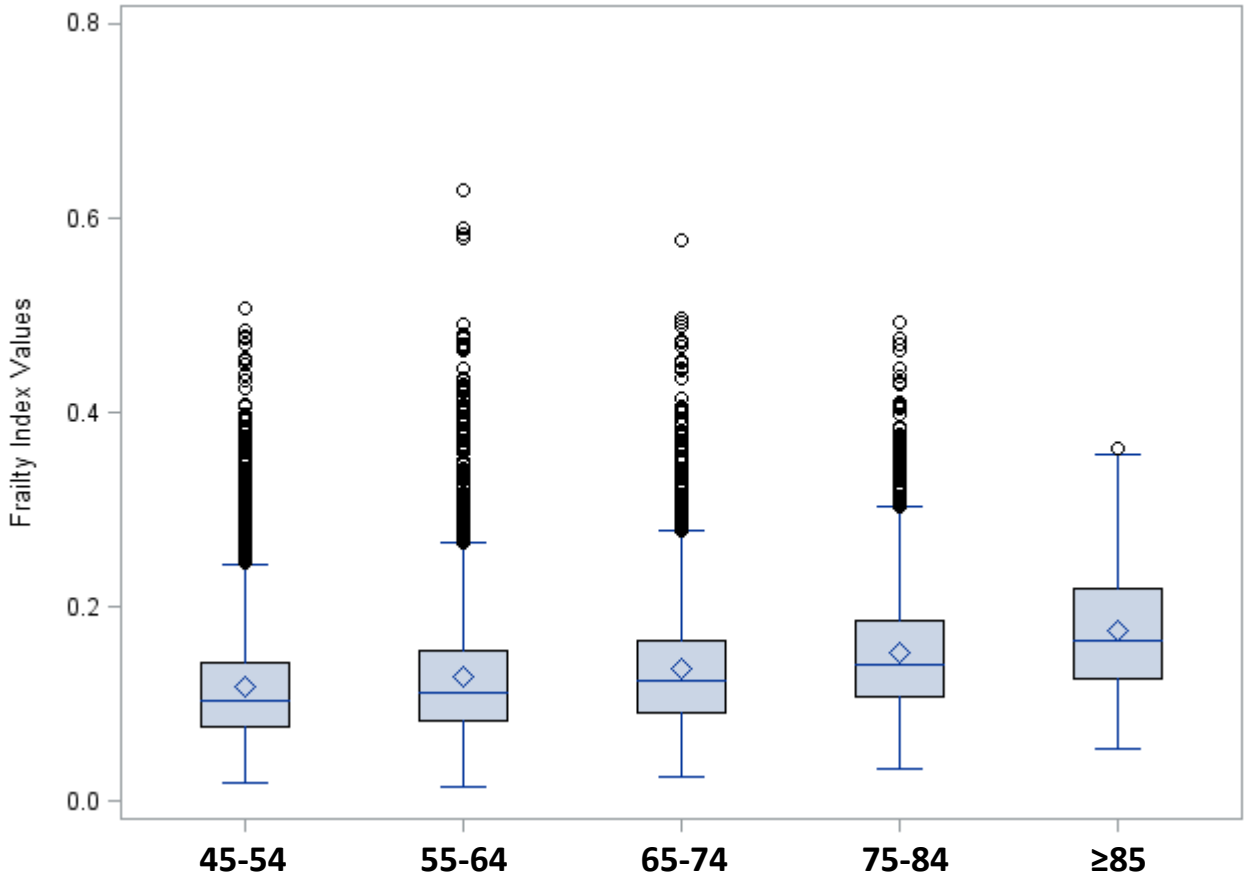
One Project Goal

- Identify frail participants within the CLSA
  - Create a frailty index from health deficits in the CLSA (cumulative deficits)
  - Assess construct validity

Overview of Frailty Index

- All variables transformed to a value from 0 (no deficit) to 1 (maximum deficit)
  - Self-rated Health: Poor (1) Fair (0.75) Good (0.5) Very Good (0.25) Excellent (0)
  - Chronic Conditions: Absent (0), Present (1)
  - Cognitive Test: 1-(score)/(maximum achievable score)
- **90** health deficits included
- Frailty index value is calculated as the proportion of total deficits present

Very Preliminary Analyses



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Very Preliminary Analyses

Pearson Correlation Coefficients and P-Values for Correlates of Frailty								
	Age	**Sex (M)**	**Income**	**Education**	**Fall status**	**Injuries**	**CR Informal**	**CR Formal**
Frailty Index	0.18	-0.11	-0.35	-0.19	0.12	0.11	0.31	0.30
	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

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Biomarkers of Frailty and the CLSA

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What is a Biomarker?

- A BIOlogical MARKER
- Biomarkers definitions working group of the NIH (Clin Pharmacol Ther 2001: 69: 89-95)

"*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*"

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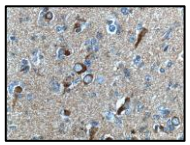
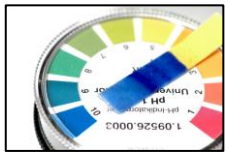
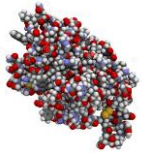
Examples of biomarkers



Amyloid beta
Alzheimer's disease

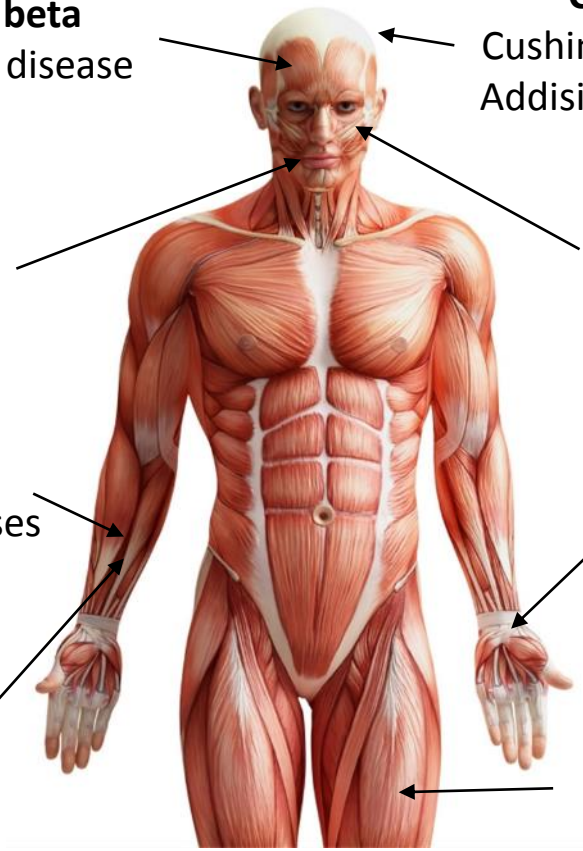


Acidity (pH)
Exam performance
COPD

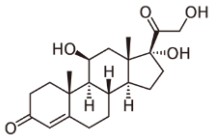


Interleukin 6 (IL-6)
Many age-related diseases

Red blood cells
Anemia
Surgical outcome



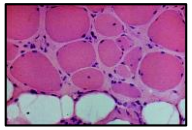
Cortisol
Cushing's disease
Addision's disease



Intraocular pressure
Glaucoma

Swelling (edema)
Arthritis
Diabetes

Adhesion molecules
Myositis and myopathy



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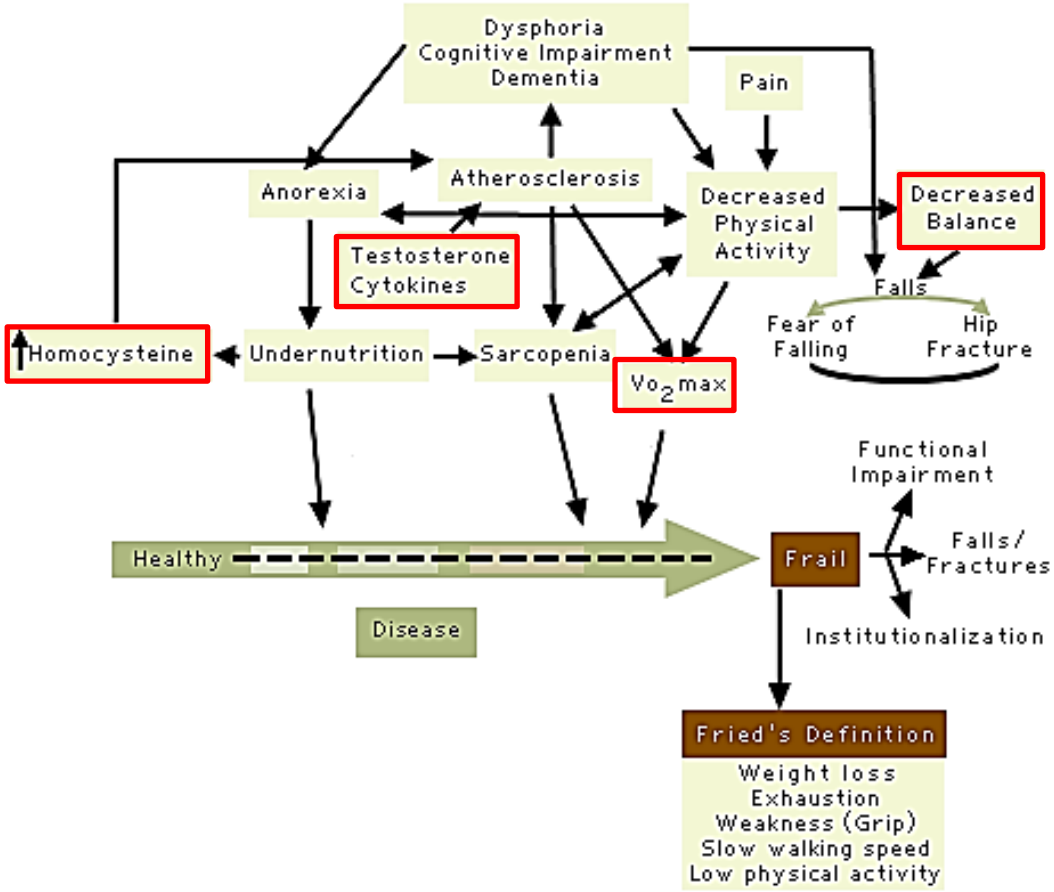
How biomarkers are related to frailty

Some examples….

- Albumin
- CRP
- IL-6
- VO_2 max
- Adiponectin
- oxLDL
- Grip strength
- Balance



http://www.thedoctorwillseeyounow.com/content/aging/art2070.html

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… specific examples

- Exhaustion [**muscle oxygenation**]
  - Direct: Red blood cell phenotype or concentration
  - Indirect: iron, ferritin, vitamin B12, folate, {inflammation}

- Strength (speed, grip) **[muscle growth/loss]**
  - Direct: muscle fibre size
  - Indirect: insulin, glucose, Hb1ac, testosterone, IGF-1, {inflammation}

- Cognition **[neurodegeneration]**
  - Direct: protein (Aβ, α-synuclein) accumulation, cerebral infarcts or atrophy
  - Indirect: IGF-1, lipids and cholesterol, APOE (DNA), {inflammation}

Studies relating blood biomarkers to frailty

- Collerton et al., 2012. Mech Age Devel. PMID: 22663935
  - Newcastle 85+ (n=845), Fried and Rockwood
  - TNF/IL-6 secretion, CRP, albumin, WBCs, neutrophils
- Saum et al., 2015: Gerontology. PMID: 25924722
  - ESTHER (n=2518), Fried
  - D-ROM, thiol (TTL), CRP
- Gale et al., 2013: Age. PMID: 23543263
  - ELSA (n=2146), Fried
  - CRP, fibrinogen

- Lippi et al., 2015: Clin Chem Lab Med. PMID: 25993734
  - Coming soon…. FRAILOMIC (n=up to 75,000!)
  - mtDNA, CRP, MMP9, miRNA… more than 50

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One step further…

Four great studies from Dalhousie

- Howlett et al., 2014; BMC Med. PMID:25288274
- Rockwood et al., 2015; JAMDA. PMID: 25952475
- Mitnitski et al., 2015; BMC Med. PMID: 26166298
- Blodgett et al., 2016; Age Ageing. PMID: 27076524

- Define a **laboratory index (FI-Lab)** using 23 biomarkers, including albumin, calcium, folate, vitamin B12, glucose, urea, blood pressure.
- **FI-Lab** associated with clinical frailty index as well as mortality and risk of adverse outcomes (institutionalization, hospitalization, general health, etc.)

What is the point?

- Why measure biomarkers when we have frailty criteria and indices?

1) Biomarkers can predict pre-clinical frailty
2) Easier to measure many biomarkers in a standardized and objective manner.

Back to the CLSA…

Biomarkers we are currently measuring

PHYSICAL & COGNITIVE

- 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
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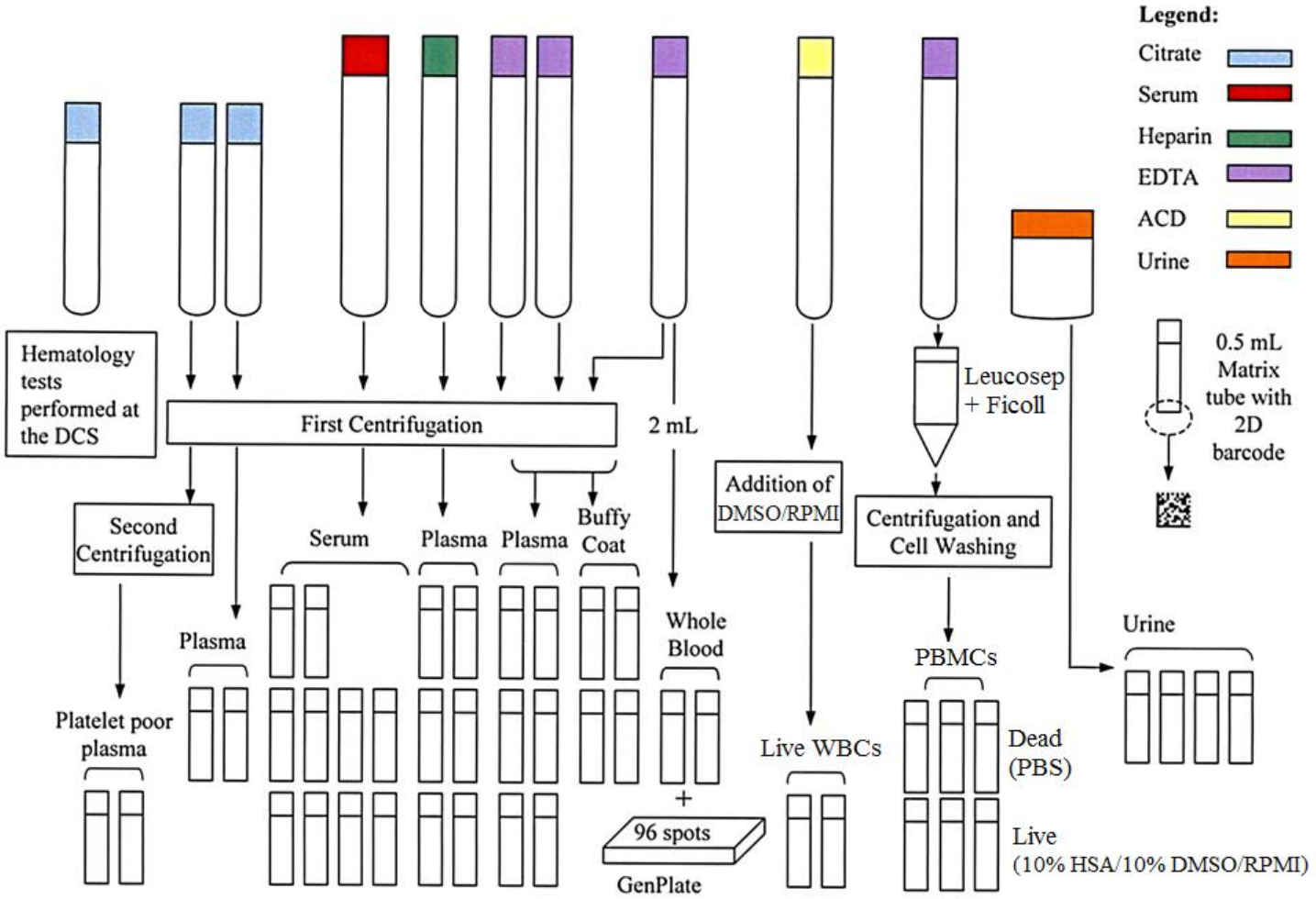
- Cognitive assessment (30 min. battery)

MOLECULAR AND CELLULAR

- Albumin (ALB)
- Alanine Aminotransferase (ALT)
- Creatinine (CREA)
- C-reactive Protein (CRP)
- Ferritin (FERR)
- Hemoglobin A1C (HbA1C)
- Lipid Panel (CHOL, HDL, TRIG, calculated non HDL and LDL)
- Thyroid Stimulating Hormone (TSH) and Free, Thyroxine (FT4)
- Vitamin D
- Hematology (Hemoglobin, monocytes, lymphocytes, granulocytes, platelets)

CLSA biospecimens



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The CLSA Biorepository

GenPlate storage vaults

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The CLSA Laboratory

Flow Cytometry

Tissue culture facilities

Automated liquid handler

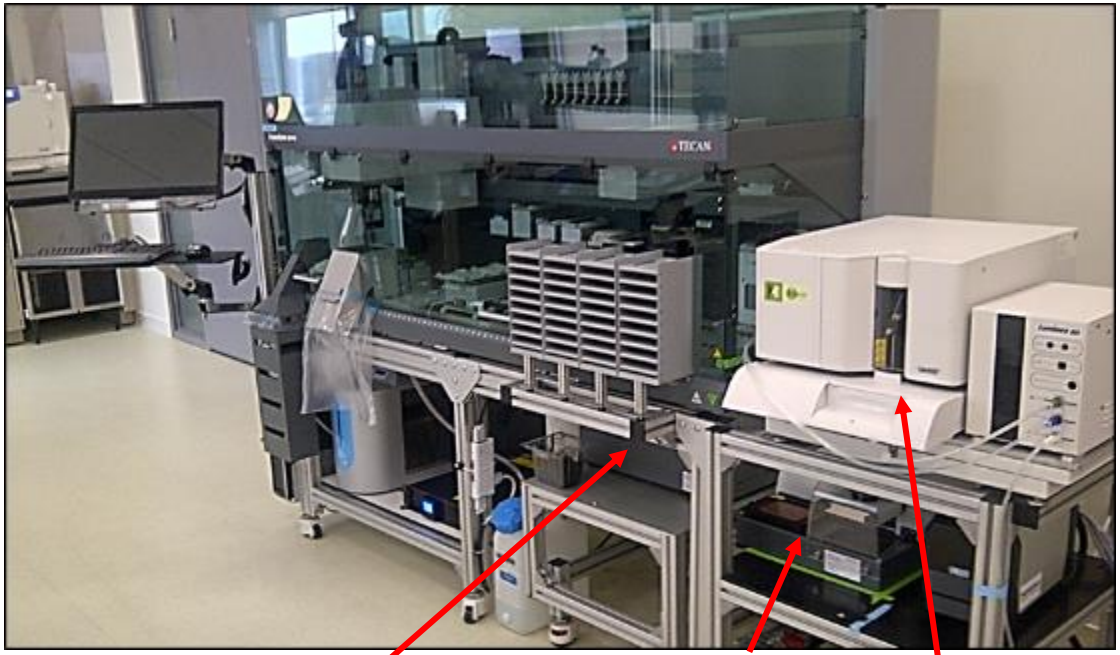

Plate reader/
spectrophotometer

Plate washer

Luminex 200

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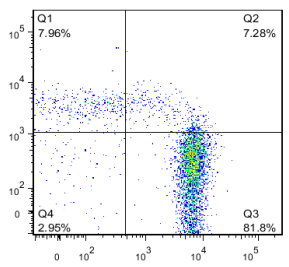
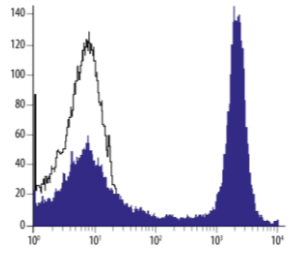
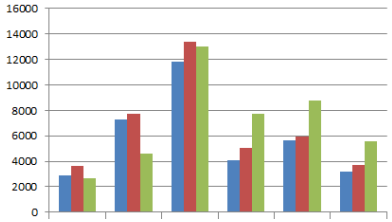
What can we do?

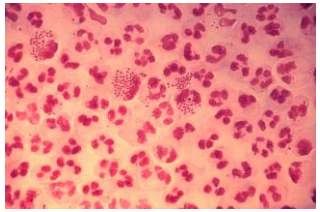
- Prepare assays for flow cytometry
- High-sensitivity multiplexed ELISAs
- Fluorescent, chemiluminescent, absorbance assays





- Cell proportions and counts
- Protein expression
- Cell function (proliferation, phagocytosis, oxidative burst)





- Live cell work
- Bioassays
- Cellular differentiation
- Validation using cell models

Anything! (well, almost anything)

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Accessing CLSA data

Data and Biospecimen Access

- **Fundamental tenets:**
  - The rights, privacy and consent of *participants* must be protected and respected at all times
  - The confidentiality and security of *data and biospecimens* must be safeguarded at all times
  - CLSA data and biospecimens are resources that will be used optimally to support research to benefit all Canadians
  - No preferential or exclusive access

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Who can apply?

- Researchers affiliated with a public-sector research organization
- International researchers may apply for alphanumeric data
- Sharing of biological specimens with international researchers is being considered
- Graduate students and postdoctoral fellows based at Canadian institutions

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What data are available?

- **Data from 51,000+ participants will be available to the research community this spring including:**
  - Questionnaire data from all 51,000+ participants
  - Comprehensive physical assessment data and hematological biomarkers from 30,000+ participants who visited data collection sites

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Data Released in 2014

60-minute Telephone Interviews

(21,241 participants)

Questionnaire:

- Age & Sex
- Socio-Demographic Characteristics
- Home Ownership
- Education
- Veteran Identifiers
- Height & Weight
- Smoking & Alcohol Use
- General Health
- Women's Health
- Vision
- Hearing
- Instrumental Activities of Daily Living
- Basic Activities of Daily Living
- Chronic Conditions
- Functional Status
- Cognition (released in 2015)
- Depression
- Satisfaction with Life
- Post-traumatic Stress Disorder
- Social Networks
- Social Support – Availability
- Social Participation
- Care Receiving – Formal & Informal
- Caregiving
- Injuries
- Falls and Consumer Products (e.g. assistive devices)
- Retirement Status
- Retirement Planning
- Pre-Retirement Labour Force Participation
- Labour Force
- Income

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Spring 2016 Data Release

In-Home Face-to-Face Interviews

(30,000+ participants)

Questionnaire:

- Age & Sex
- Socio-Demographic Characteristics
- Home Ownership
- Education
- Veteran Identifiers
- Smoking & Alcohol Use
- Nutrition: Short Diet Questionnaire
- General Health
- Women's Health
- Vision
- Hearing
- Basic Activities of Daily Living
- Instrumental Activities of Daily Living
- Life Space Index
- Sleep
- Satisfaction with Life
- Post-traumatic Stress Disorder
- Care Receiving – Formal & Informal
- Caregiving
- Injuries
- Falls and Consumer Products (e.g. assistive devices)
- Retirement Status
- Pre-Retirement Labour Force Participation
- Labour Force
- Retirement Planning
- Income

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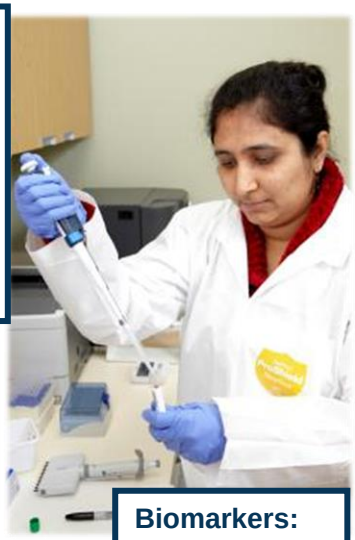
Spring 2016 Data Release

Data Collection Site Visits
(30,000+ participants)

Physical Assessments:

- Height
- Weight
- Waist-Hip Ratio
- Blood Pressure
- ECG
- Spirometry
- Hearing
- 4m Walk
- Timed Up and Go
- Standing Balance
- Chair Rise
- Visual Acuity
- Tonometry
- Grip Strength



Biomarkers:

- Hematology

Questionnaire:

- Social Networks
- Social Support – Availability
- Social Participation
- Disease Symptoms
- Contraindications

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Spring 2016 Data Release

Hematology
(30,000+ participants)

- White blood cells
- Lymphocytes (absolute and relative number)
- Monocytes (absolute and relative number)
- Granulocytes (absolute and relative number)
- Red blood cells
- Hemoglobin
- Hematocrit
- Mean corpuscular volume
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Red blood cell distribution width
- Platelets
- Mean platelet volume

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Spring 2016 Data Release

30-minute Telephone Interviews (51,000+ participants)

Questionnaire:

- Falls
- Pain and Discomfort
- Oral Health
- Snoring
- Parkinsonism
- Health Care Utilization
- Medication Use
- Dietary Supplement Use
- Nutritional Risk
- Physical Activities
- Psychological Distress
- Personality Traits
- Social Inequality
- Online Social Networking
- Transportation, Mobility, Migration
- Built Environments
- Wealth

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Preparing an application

- Consult the Data and Sample Access Policy and Guiding Principles
- Review the pertinent sections of the CLSA protocol and the CLSA questionnaires
- Visit the DataPreview Portal to search datasets
- Complete the Data and/or Biospecimen Request Application
- Identifiable information will not be shared (e.g. six-digit postal codes, names, contact information)
- Queries should be sent to access@clsa-elcv.ca
- Queries related to biospecimens should be sent to bbc@clsa-elcv.ca

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DataPreview Portal

- Gateway to access for data and biospecimens
- Variable search mechanism providing simple descriptive statistics for selected variables
- Currently available for alphanumeric data only
- https://datapreview.clsa-elcv.ca/

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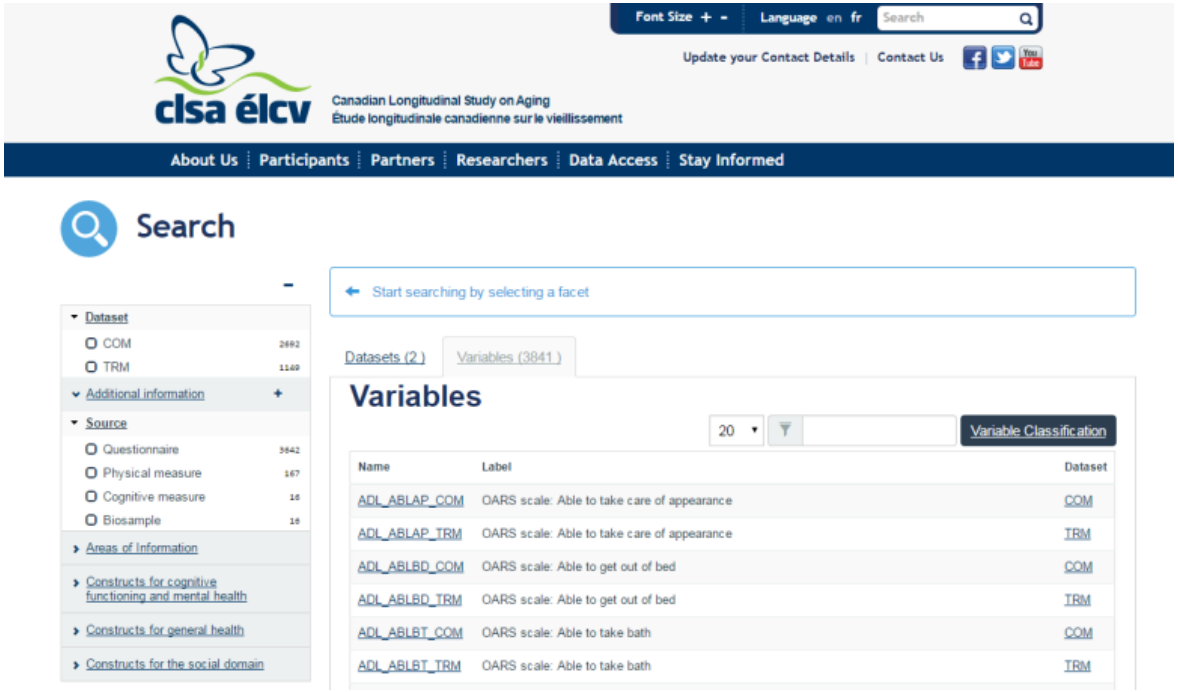
DataPreview Portal



https://datapreview.clsa-elcv.ca/

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Review & Data Access Process

- **Review**: Administrative → Data and Sample Access Committee → Scientific Management Team
- **Approval:** Preparation of CLSA Access Agreement, verification of ethics approval
- **Release:** Raw data provided to approved investigator , cost recovery
- **Enhance:** Return of derived variables to CLSA dataset as appropriate
- Questions? access@clsa-elcv.ca

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Applying for Data Access

- **Application fees**
  - Partial cost-recovery model
  - $3,000 for a straightforward alphanumeric dataset for any number of participants
  - Additional fees applied for requests that require more complex customization
  - **No cost** for graduate students who use these data for their Master's or PhD theses
  - **One free** dataset for postdoctoral fellows

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Questions?

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

Contact:

Lauren Griffith (Associate Scientific Director)

griffith@mcmaster.ca

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

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