Known and Unknown Unknowns: Balancing Knowledge Creation and Implementation

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Conflicts of Interest

- Local site Principal Investigator, Canadian Longitudinal Study on Aging
- Principal Investigator, Canadian Consortium of Neurodegeneration in Aging

My Inspiration

"… there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know." – Donald Rumsfeld (February 12, 2002)

Objectives

- Cover different territory than the other three keynotes
  - Challenging inequalities: Critical reflections on the social impacts of aging research (Dr. Thomas Scharf)
  - Special Panel Presentation on Knowledge Translation in Aging
    - Challenges and opportunities in knowledge translation in health care (Dr. Sharon Straus)
    - Dancing in the Dark? Connecting Social Research and Policy (Dr. Janet Fast)

Objectives

- Will deal primarily with biomedical research
  - Do not wish to suggest other areas less important
- Talk about the need for knowledge discovery
  - But balanced with investments in implementation
- Review
  - Big Science (Little and Mid-Sized Science) – is gerontology Big Science?
  - Big Data – what is it? How is it different? What is its potential role in aging research?

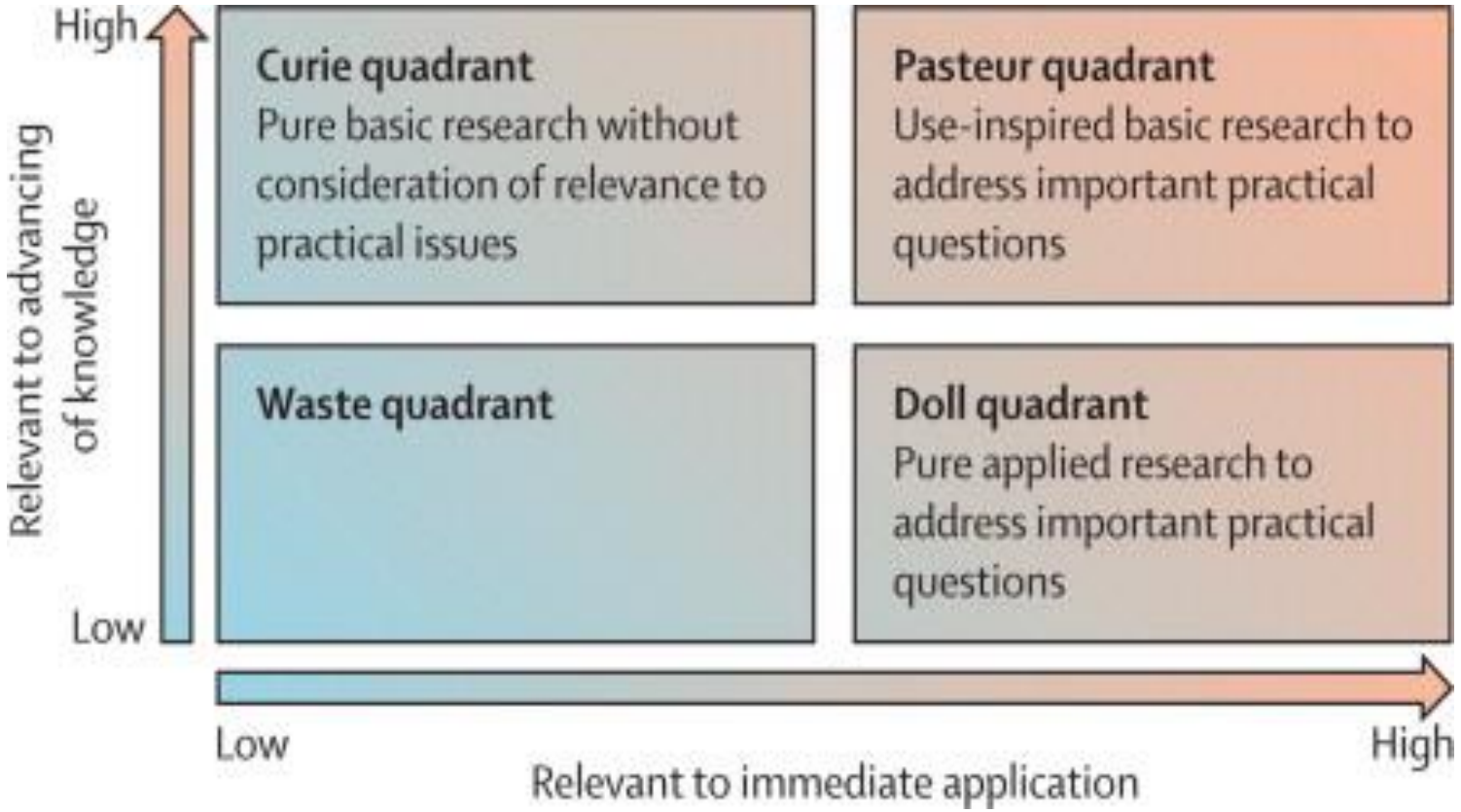


Figure 1. Classification of different categories of research

Iain Chalmers, Michael B Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A Metin Gülmezoglu, David W Howells, John P A Ioannidis, Sandy Oliver

How to increase value and reduce waste when research priorities are set

Lancet Volume 383, Issue 9912, 2014, 156–165

http://dx.doi.org/10.1016/S0140-6736(13)62229-1

Explain Quadrants

- Pure basic research (advance knowledge)
  - Marie Curie
- Pure applied research (increase immediate applicability of research in practice and policy)
  - Richard Doll – identifying smoking as cause of lung cancer
- Use-inspired basic research (advance both)
  - Louis Pasteur – basic work motivated to solve problems caused by infections (animals and men)
- Waste (projects that contribute nothing or very little to either)

Reducing Waste

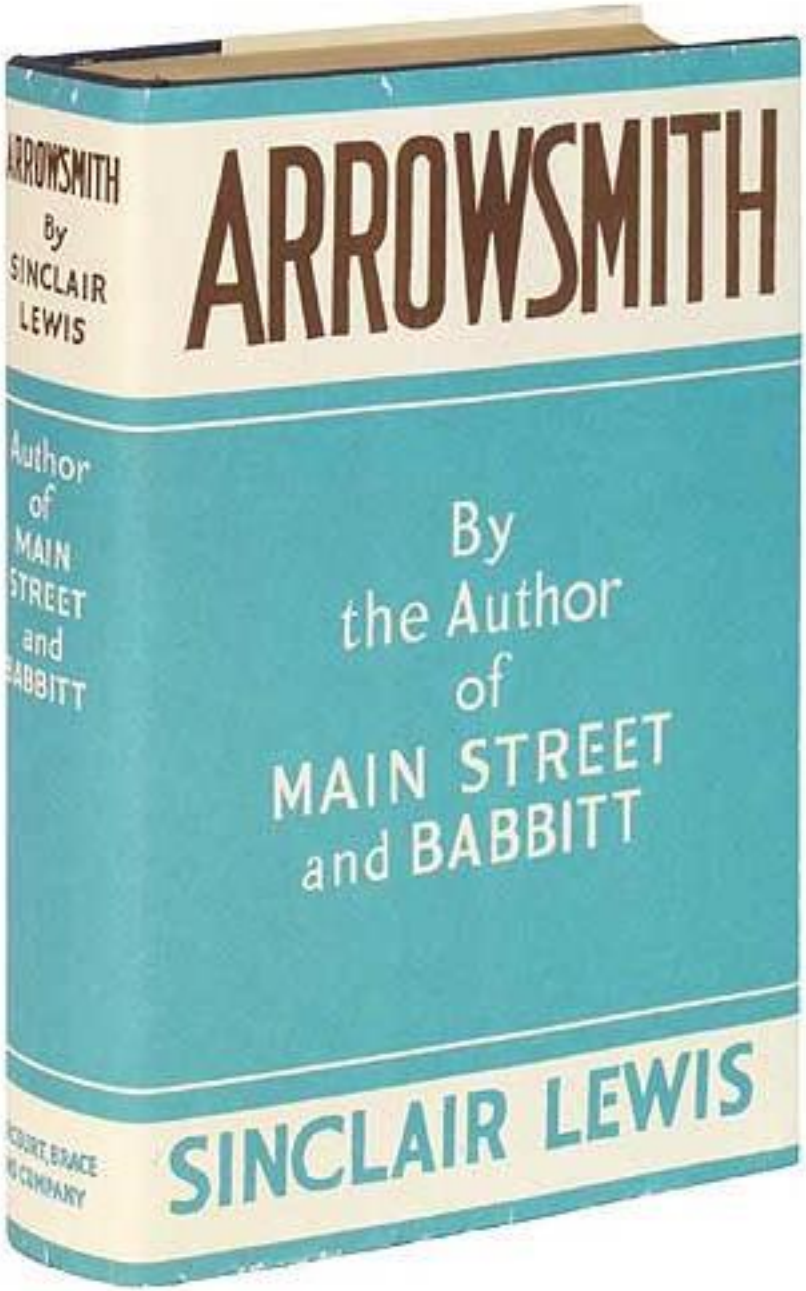
- Waste is not novel research that doesn't show positive results
  - Not everything works out (high risk game) + we learn from failures – we need to take chances
  - But, what is funded by external bodies must be transparent, ethical, reasonable, and reported
- Avoidable waste
  - Need to improve yield from basic research
  - How funders make decisions should be transparent – must take into account potential users of research
  - Always perform a systematic review of available evidence before embarking on a research study
  - Need to track what work is in progress – Lancet 2014, 383: 156-65

Balance

- Knowledge discovery must be balanced with knowledge translation
- Alberta Innovates – Health Solutions *Knowledge Translation Strategic Plan*
  - Priorities of end-users influence the research agenda
  - Develop the capacities of end-users to participate in the research processes
  - Develop the capacities of the research community to design and execute health research that considers and incorporates application considerations
  - Support knowledge syntheses
  - Support the creation of networks

Alberta Dementia Strategy

- Recommendations about research and innovation
  - Priorities of people living with dementia and practitioners will influence the research agenda
  - Proposal to develop the capacities of end-users to participate in the research processes
  - Intend to develop the capacities of the research community to design & execute health research that considers and incorporates application considerations
- Recognize need to support
  - Discovery research, and
  - Fostering innovation & implementation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Little & Mid-Sized Science

- Won 1926 Pulitzer Prize
  - Martin Arrowsmith and his journey from a small Midwest US town to the upper levels of research; ends with him pursuing independent research in the backwoods of Vermont
- Romantic view of individual researchers free to work alone on problems of their own choosing
- Since the post-WWII era most work in a variety of organizations (collective process)
- Nobel Prize allows the awarding of only three individuals in any one topic per year

Big Science

- "… occurs when society deems an area of research important enough to throw money and resources at it" - Scientific American October 2015, p. 35
- Large-scale instruments & facilities, supported by funding from government or international agencies, where research is conducted by teams of scientists and technicians (big budgets, teams/staff, machines, and/or laboratories)
- Manhattan Project ($23-27 billion)

Big Science

- Recommended reading
  - Alvin Weinberg: Impact of Large-Scale Science on the United States. Science 1961, 134: 161-64.
- Big Science afflicted by the triple diseases of "journalitis, moneyitis, administratitis"
- Here to stay but –
  - "We must make Big Science flourish without … allowing it to trample Little Science – that is, we must nurture small-scale excellence as carefully as we lavish gifts on large-scale spectaculars."

Definitions of Big Science

- Quantitative (numbers)
  - Money, manpower, and/or time: "… large-scale research and development programs costing hundreds of millions, even billions, and lasting a decade or more" - Lambright, 1998: 260
- Qualitative (there are a number of ways it might be considered "big")
  - Geographic (e.g., *science cities*), economic (cost), multidisciplinary, multinational - Galison, 1992: 2
- Comparative

Big Science in the Life Sciences

- Human Genome Project ($4.7 billion over 13 years) – sequencing the entire human genetic code
  - Work decentralized among a number of research sites rather than concentrated in a single one
  - Goal was the production of the sequence of the human genome
  - Project supported in part by private firms hoping to use the genome to develop new pharmaceuticals and other medical products
  - *Initial sequencing and analysis of the human genome* (Nature 2001, 412: 565) had 2883 authors (who gets the Nobel?)

Human Brain

- Human Brain Project (EU) - $1+ billion over 10 years
  - Big data integration and analysis
  - Computational modeling
- BRAIN Initiative (US) - to ramp up to a total of $5 billion by 2025
  - Tools to enable a brain census and for recording/ modulating brain circuit activity linked to behavior
  - Multilevel brain activity
  - New computational models and theory

Canadian Consortium on Neurodegeneration in Aging

CCNA CCNV

Canadian Consortium on Neurodegeneration in Aging

Consortium Canadien en neurodégénérescence associée au Vieillissement

Canadian Consortium on Neurodegeneration in Aging

- Signature Initiative of the CIHR established in 2014 by the organization with other funding partners
- National program spanning all aspects of dementia research (molecular to health care systems) that is designed to accelerate progress towards a better understanding of these conditions, their prevention & management in order to enhance the quality of life of those living with dementia (including caregivers) & the quality of services offered to them
- Platform for international collaboration
- Unique elements
  - Impact of gender & sex
  - Cohorts of 1600 intensely studied individuals

Canadian Consortium on Neurodegeneration in Aging

- 48 principal applicants (19 junior researchers)
  - 5 from Alberta
  - 20 Ontario, 14 from Québec, 4 BC, 2 from Saskatchewan, 3 from Nova Scotia
- 336 total researchers (moving target – about 360)
  - 30 from Alberta
  - 134 Ontario, 91 Québec, 33 BC, 15 Saskatchewan, 7 Manitoba, 10 Nova Scotia, 5 New Brunswick, & 11 International Collaborators

Canadian Consortium on Neurodegeneration in Aging

- Complex organization – aim is to be a model of distributed innovation under a central funding & administrative umbrella that encourages collaboration
  - 3 themes
  - 20 teams
  - 8 platforms
  - 4 cross-cutting programs

Big Science and Gerontology

- Historically hasn't been the focus
  - Gerontology "not a titan of Big Science [p. 8] … senescence 'secondary' problem for most disciplines and professions [p. 11]" - Achenbaum: Crossing Frontiers (1995)
  - "… two hurdles frustrated Butler's efforts to realize his dream that NIA … would invest in old age in a manner commensurate with … societal aging … gerontology remained peripheral to Big Science & vested interests in the policy area … (and an) emerging power elite who wanted to cut the size of Big Government [p. 113]" – Achenbaum: Robert N. Butler, MD (2013)
- Practitioners & the field, though, have contributed to and benefited from Big Science in other areas

Canadian Longitudinal Study on Aging

- Strategic Initiative of the CIHR
  - Funding from CIHR, CFI, several provincial governments, and other partners
- Overview: National long-term study that will follow approximately 50,000 men and women 45 to 85 years of age at enrollment for 20+ years
  - Information will be collected on the evolution over time of their biological, physical, psychological, social, and lifestyle characteristics in order to better understand how, individually and in combination, these factors impact both the maintenance of health and the development of diseases and disability as people age

Canadian Longitudinal Study on Aging

- Two components (*tracking* and *comprehensive*)
  - Tracking (approximately 20,000): data collected through computer assisted telephone interviews
  - Comprehensive (approximately 30,000): undergo an in-home interview + visit to CLSA Data Collection Site (DCS) where additional data (including physical assessments) & biological specimens will be collected
  - Participants in the tracking component can be from anywhere within the 10 Canadian provinces while those recruited into the comprehensive one must live within a 25-50 km radius of their local DCS

Canadian Longitudinal Study on Aging

Scientific Management Team - PIs

Lead Principal Investigator
Parminder Raina (McMaster)

Co-principal Investigator
Christina Wolfson (McGill)

Co-principal Investigator
Susan Kirkland (Dalhousie)

CLSA Team

- In addition to the three Principal Investigators
  - 11 Local Site Principal Investigators
  - 160+ researchers in 26 post-secondary institutions
  - 120+ operational staff
  - Approximately 51,352 Participants Enrolled

CLSA Infrastructure

- Eleven Data Collection Sites (2 Vancouver)
- National Coordinating Centre (McMaster)
- Biorepository and Bioanalysis Centre (McMaster)
- Statistical Analysis Centre (McGill)
- Genetics and Epigenetics Centre (UBC)
- Four Computer-Assisted Telephone Interview Centres

CLSA DataPreview Portal

- CLSA data and biological samples are available to approved Canadian and international public sector researchers, with no preferential or exclusive access for any individual
- Navigate around the site to find information about the application process and requirements for data and sample access
- Begin by reading *Frequently Asked Questions*
- https://datapreview.clsa-elcv.ca/

Big or “Biggish” Science? CCNA and CCNA Funding

- CLSA
  - Over $50 million to establish infrastructure & perform baseline assessments
  - $41.6 million for next 5 years
- CCNA
  - $21.6 million CIHR
  - $10.6 million partners ($4 million from the Alzheimer Society of Canada)

Big Data

- Amount of information growing rapidly
- The term “big data” initially coined in fields like astronomy and genomics
- No rigorous definition
  - Initially meant the quantity of data had grown so large that it would be greater than the memory of a personal computer, what might be sent as an email attachment, or what could fit on a few CDs
  - Doesn’t solely refer to the size of complex datasets – it encompasses all aspects of working with them from acquisition to analysis – Naturejobs Blog, October 13,2015

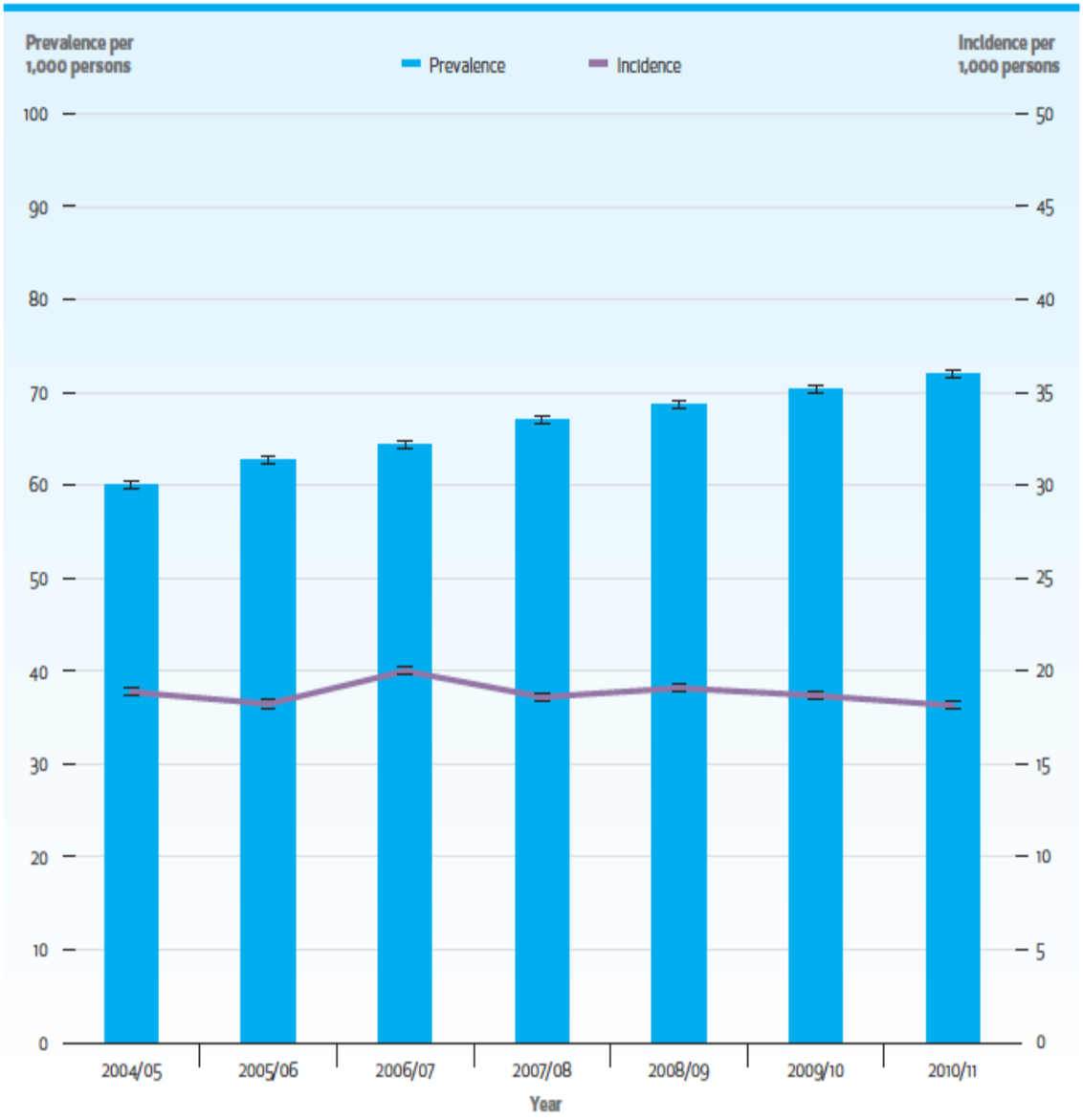
Administrative Data

- Algorithms using ICD-9/ ICD-10 codes (hospitalization, physician claims) +/- use of specific drugs to define presence of a condition
  - Potential uses: epidemiology, monitoring, comparing, projecting & assessing burden (utilization, cost)
- Dementia
  - Hospitalization record OR 3 physician claim records at least 30 days apart in a 2-year period OR prescription claim (cholinesterase inhibitors, memantine)
  - Sensitivity 79.3%, specificity 99.1% - unpublished

EXHIBIT 6.2B Age- and sex-adjusted* prevalence and incidence of dementia (including Alzheimer's disease) per 1,000 persons aged 66 years and older, in Ontario, 2004/05 to 2010/11

Key Findings

- The total number of Ontarians aged 66 years and older with dementia increased from 85,277 in 2004/05 to 126,939 in 2010/11.
- The age- and sex-adjusted prevalence of dementia per 1,000 persons aged 66 years and older increased from 60.1 in 2004/05 to 72.0 in 2010/11.
- The number of Ontarians aged 66 years and older with newly identified dementia was 24,766 in 2004/05 and 28,651 in 2010/11.
- The age- and sex-adjusted incidence of dementia per 1,000 persons aged 66 years and older decreased slightly from 18.9 in 2004/05 to 18.1 in 2010/11.



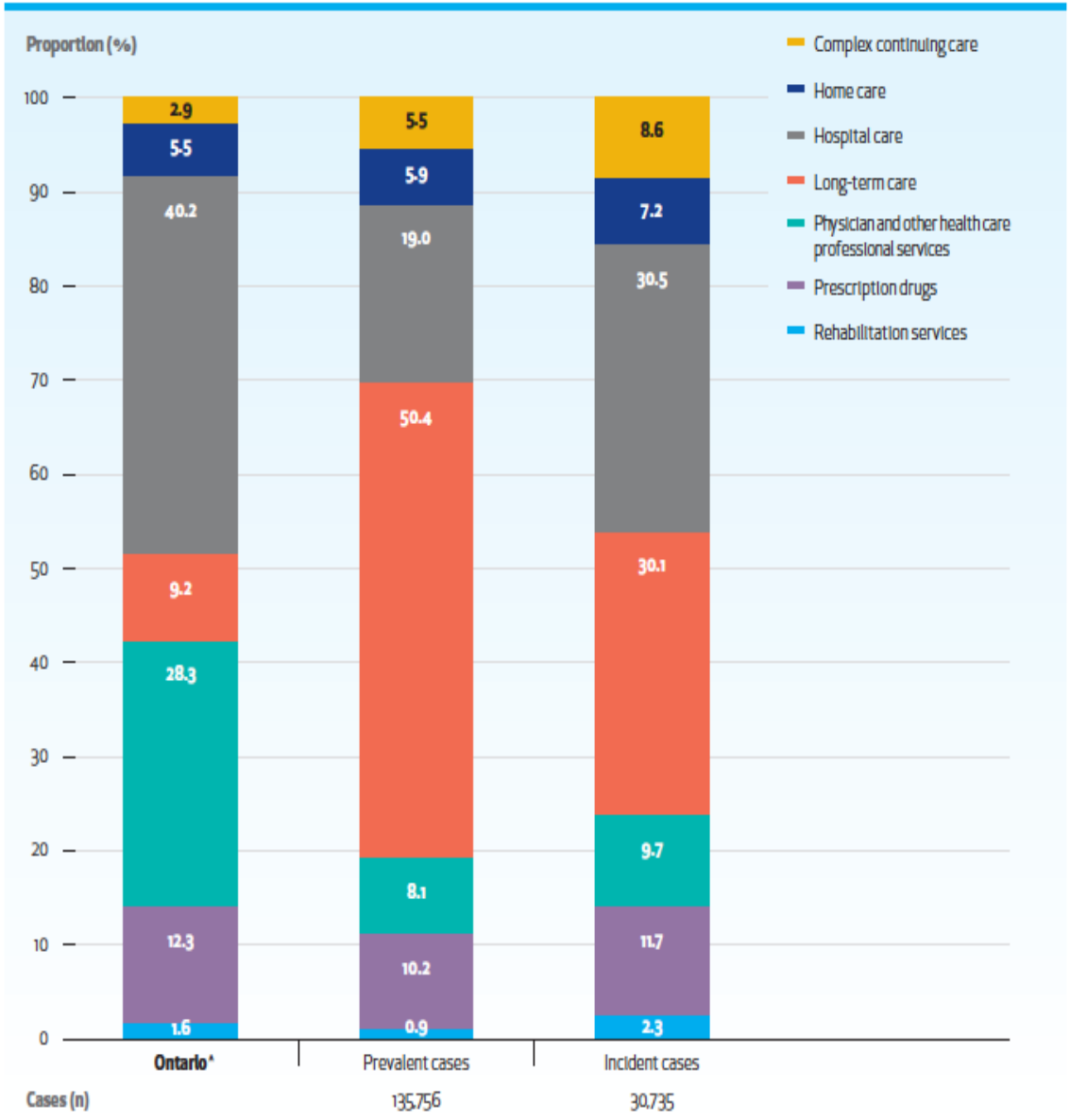
Note: In general, the estimates of prevalence and incidence based on health administrative data should be viewed conservatively. Consult Exhibit 2.1 for the evidence grade for the algorithm used to identify cases for this brain disorder.

Ng R, Maxwell CJ, Yates EA, Nylen K, Antflick J, Jetté N, Bronskill SE. *Brain Disorders in Ontario: Prevalence, Incidence and Costs from Health Administrative Data. Toronto, ON: Institute for Clinical Evaluative Sciences; 2015.*

EXHIBIT 6.6A Proportion of costs* associated with one year† of health system use in Ontario and for prevalent and incident cases with dementia (including Alzheimer's disease), by type of health care service

Key Findings

- Among prevalent cases with dementia, the majority of the costs associated with health system use were attributable to long-term care (50.4%), hospital care (19.0%) and prescription drugs (10.2%).
- Among incident cases with dementia, the majority of the costs associated with health system use were attributable to hospital care (30.5%), long-term care (30.1%) and prescription drugs (11.7%).



Dementia in Alberta

- Population Estimates of Dementia in Alberta (PEDA), Health Analytics Branch of Alberta Health
  - Similar process to that used in Ontario
- Incidence (65+)
  - 14.82/1000 (Ontario 18.1/1000)
- Prevalence (65+)
  - 67.6/1000 (Ontario 72.0/1000)
- Absolute number
  - 2013/14 – 39,304
  - 2042/43 – 225,000

Frailty Index

- Proportion of age-related health deficits (symptoms, signs, disabilities, diseases, lab abnormalities) accumulated over time
  - At least 30-40 (unstable estimates with small numbers)
  - Variable criteria: associated with health status; prevalence generally increases with age (although some age-related adverse conditions can decrease due to survivor effects); must not saturate too early (e.g., presbyopia is nearly universal by age 55); the group of deficits must cover a range of systems; and, if done serially on the same persons should remain constant - BMC Geriatrics 2008, 8:24

InterRAI Instruments

- Example that used data collected in the Alberta Continuing Care Epidemiological Studies (ACCES)
  - Items from Resident Assessment Instrument for Assisted Living – 43 & 80 item (specific components listed in paper) frailty indices
  - Residents with more severe levels of frailty were more likely to die, be hospitalized, & require admission to long-term care
  - Frail (> 0.3) vs. robust (< 0.2) 1-yr. risk ratios – death 2.69, hospitalization 1.28, and LTC 3.30 - BMC Geriatrics 2012, 12:56

Big Data

- Preceding examples used big datasets but the inquiry of them was pre-determined (diagnostic algorithm, frailty index)
- Traditionally in research we've done hypothesis-driven experiments
  - Research without a hypothesis called "fishing expeditions"
  - Focus on causality
- Large complex databases + powerful computational approaches ➔ data-driven discovery and decision-making
  - "Let the data speak"
  - Correlation and predictive analytics

Big Dataset - Genomic Data

- Science – 17 biobanks hold or plan to hold genomic data on 75,000+ people – Science September 2015
  - 23andME - > 1,000,000
    - Analyze DNA from saliva ($99)
    - About 2000 litres of saliva collected
  - ANCESTRY.COM - > 1,000,000
    - Collaborating with the Google-funded biotech company Calico to look for longevity genes
  - HUMAN LONGEVITY, INC. – 1,000,000 planned
    - Looking for aging-related genes

Big Dataset - Electronic Medical Record (EMR)

- Historically the healthcare industry has generated large amounts of data (record keeping, compliance & regulatory requirements, patient care)
  - Most data is stored in hard copy form
  - Current trend is toward rapid digitization of these data
- Massive quantities of accessible data could support a wide range of medical/ healthcare functions and offer research opportunities (e.g., discovering associations, patterns and trends)
  - Canadian Primary Care Sentinel Surveillance Network (CPCSSN) – in general Canada is lagging on EMRs

Binary Combination:
Biological sample (genetic analysis) plus EMR (health information)

- Precision Medicine Initiative (PMI) Cohort Program (initial budget request of $130 million; recruit at least a million people)
  - Methods: blood sample, undergo examination, agree to share their electronic health record, mobile devices (sleep & physical activity), +/- fecal samples (microbiome - microorganisms inhabiting the human body have an important influence on health and disease)
  - Goal: Tailor medical care to individuals – look at the interplay between health and your DNA

Potential of Combining Health & Non-Health Databases

- First became aware from a journal review I did
  - New quinine prescriptions & Internet searches for leg cramps roughly doubled between the winter lows and summer highs – CMAJ January 26, 2015, doi: 10.1503/cmaj.140497
- Internet searches as a signal of drug-drug interactions and the spread of influenza
- *FICO Medication Adherence Score* based on publicly available data (e.g., home ownership, job status) +/- claims data able to predict future medication adherence (like a credit rating, it can be compiled without a person's knowledge or permission)

Future

- Balance shifting between
  - Supporting individuals ➔ teams (especially those that do interdisplinary science)
  - Funding of projects ➔ programs
- Need to prioritize research funds wisely in an inclusive manner in order to maximize value, avoid waste, and strike appropriate balances
- Growing opportunities in the use of big data but challenges as well
  - Beware of the Big Hype
  - Concerns about the accuracy at an individual level
  - Signals need to be further evaluated & confirmed
  - Consent, privacy, & confidentiality

Future

- "Why biomedical superstars are signing on with Google" – Nature 2015, 526: 484-85
  - Firms like Google are creating well-resourced teams that bring together health expertise with equivalent proficiency in engineering (hardware & software) & data analytics
  - Goals are to create novel miniaturized electronic devices or mobile apps that collect ever more health data (often of a continuous nature) on an individual that can be analyze (often in combination with other data) to ultimately allow the prevention (by utilizing known modifiable predictive associations) or better management (through timely feedback & tailoring treatment) of various conditions

Thank You for Your Attention