***Comorbidities and Risk Factors of Dementia***

**Project Acronym or Short Study Title: Comorbidities and Risk Factors of Dementia**

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# Protocol Synopsis

This research project aims to address comorbidities and risk factors for dementia in the Vancouver Island Electronic Health Records (EHR) and to shed light on whether there are common patterns that may be used to highlight individuals who are at greater risk of dementia.

Specifically, the research seeks to summarize individual patient’s service system encounter history, highlight patterns related to the temporal appearance of chronic disease diagnoses, and summarize (at a cohort level) the risks of dementia related to diseases and previous medications.

The research design entails forming a cohort of individuals who have received a dementia diagnosis, evaluating the services used prior to diagnosis and developing models to assess the most common comorbidities associated with dementia and the extent to which risk increases with other chronic conditions and specific medications used.

# Background & Rationale

Current research indicates that as the number of medications an individual is prescribed increases so does the risk of dementia (Lai et al., 2012). This may be due to increased risk due to multiple comorbidities (Bunn et al., 2014) or the medications themselves. Drug induced dementias are estimated to comprise up to 12% of all dementia cases (Moore et al., 1999).

Additionally, there are valuable questions regarding the relationship between cancer and dementia. Shared genetic risk factors for the development of cancer and cognitive decline, coupled with the effect of chemotherapy on these systems, are thought to contribute to cognitive impairment in patients after chemotherapy (Ahles et al., 2007). Common mechanisms such as chronic inflammation, and common risk factors such as diabetes and obesity, have been implicated in the link between cancer and cognitive decline (Ganguli, 2014) but research also shows lower rates of certain types of cancer in patients diagnosed with dementia and vice versa (Ganguli, 2014; these relationships persist despite correcting for reporting artifacts and survival bias).

The relationship between cancer and dementia is complicated (Ganguli, 2015) and although there is substantial evidence surrounding the neurotoxic effect of certain chemotherapy agents (Ganguli, 2015; Heflin et al., 2005), animal studies show other cancer drugs reduce neurodegeneration (some showing neuroprotective effects; Cramer et al., 2012; Ganguli, 2014). For example, in mouse models, the chemotherapy drug bexarotene was effective in clearing amyloid and also in improving cognition (Cramer et al., 2012), raising the possibility of repurposing those agents for use with dementia patients.

# Objectives

* Evaluate and identify comorbidities and chronic diseases that may result in an increased risk of dementia.
* Assess whether there is a common temporal appearance of diseases resulting in dementia.
* Identify rates of dementia within the subgroups of cancer, cancer plus chemotherapy, transplant patients and other chronic diseases.
* Identify types of chemotherapy and whether there are subgroups within this population that are protected from, or at increased risk of, dementia.

# Major Research Hypotheses and Associated Research Questions

This proposal defines a cohort for which a program of research can be investigated examining several questions such as:

1. What are the comorbidities associated with dementia? (Factor analysis; Poblador-Plou et al., 2014; Bunn et al., 2014)
2. After accounting for number of chronic conditions, do the number of medications affect the risk of dementia? (Lai et al., 2012)
3. What are the rates of dementia and rates of dementia after cancer? (consider age at death)
4. What are the rates of dementia after cancer vs rates of dementia after cancer and chemotherapy?
5. Are there different health outcomes associated with type of chemotherapy drug?
6. Does the number of medications being taken affect risk of dementia?
7. What are the rates of drug induced dementia? (and which drugs?)
8. What are the health outcomes after transplants? (recurrence, chronic diseases, dementia).
9. What are the health outcomes after cancer? (recurrence of the same cancer, chronic diseases, dementia).

# Study Approach, Design

## Phase 1 - Descriptive; Describe and explore the cohort to get a feel for the usage and profiles that emerge. Evaluate the rates of dementia within specific subsets (e.g., type of chemotherapy received) and whether they differ or not. As a final step a small subsample (e.g., individuals with dementia diagnosis) will be examined in order to look at the finer details of encounters and service usage related to the temporal appearance of chronic diseases and dementia.

## Phase 2 – Go ahead after data exploration;

## Phase 3 – Develop models; After the data have been explored models that best represent both the data and the questions will be developed.

## Phase 4 - Publications; Each question will be published as a paper in an academic journal and presented at a conference.

1. Design, methodology
2. Cohort is defined as the inclusion of individuals who have:
   1. a dementia diagnosis or encounter.
   2. undergone a
      1. transplant (palette 99)
      2. chemotherapy, or
      3. cancer (palette 76 and 36).
   3. a drug induced dementia or delirium diagnosis

There are an estimated XXXXX individuals who will be included in the cohort.

1. Sample size, power considerations
   1. Sample sizes over 100 would be preferred for mixed effect modeling. (Stan to provide an idea of numbers then update this section)
2. Statistical approach
   1. Descriptive analysis - provide an understanding of the cohort.
   2. Factor analysis of comorbidities in relation to dementia - identify sets of variables with an underlying common factor. This method, in addition to identifying associations between groups of variables, allows the same variable to become part of several factors. Results will be compared to other studies such as Poblador-Plou et al.’s (2014) factor analysis of comorbidities of dementia.
   3. Additional models will be developed after descriptive data has been explored. (Potential models include: mixed effects models, growth mixture models, proportional hazards models)
3. Data elements
   1. RAI Neurological
   2. RAI Summary
   3. DAD diagnosis
   4. Secondary diagnosis (contributor to time in acute care)
   5. Sequence and duration for events (length of stay (regular days and alternate level of care, ALC)
   6. Oncology encounters (palette 76 and 36)
   7. Transplant encounters (palette 99)
   8. Pharmacy data (palette code 81)
   9. Vital statistics
   10. Morgue (palette code 66)
   11. Cause of death
4. Products

The products related to this research include papers and conference presentations related to Section 4 research questions. Recommendations and a report can also be provided to Island Health if any outcomes relevant to service utilization, early disease identification etc. become apparent.

# Data management

All data is housed within the data warehouse within the Island Health Secure Research Environment. Once the cohort is defined a data warehouse staff person (i.e., an Enterprise Data Warehouse Specialist (EDW)) will create a delimited body of data that fit the defined cohort. The data will be de-identified according to Safe Harbor methodology (described below in Section 11). In order to meet the requirements of Safe Harbor de-identification around dates, each date will be expressed in terms of days before/after a date that has been set as Day 0. This method is more conservative than the Safe Harbor requirements, while fully preserving the sequence of events and the duration that separates events. The data will then be exported the data to a portal (i.e., a secure research environment/data disclosure access environment or isolated secure analysis server). Project researchers will be provided with an ID to virtually log into the portal located on the Island Health server.

# Consent, Protection of Privacy

1. Consent - It would not be feasible to request participation consent for such a large set of individuals. The data will be de-identified according to Island Health and Safe Harbor Protocols and adhere to privacy policies as laid out in the TCPS2 to ensure privacy (Article 5.5a of the Tri-council Policy, TCPS2).
2. Protection of privacy - The level of access to the warehoused data afforded to the researcher will be ensured through the use of three sets of controls:
   1. Administrative – agreements between Island Health and all members of the research team will specify activities that will be performed with the research data;
   2. Technical – to prevent unauthorized access to research data; to prevent unauthorized export of person-level data from the data disclosure environment; to prevent unauthorized import of person-level data from external data sources into the data disclosure environment.
   3. Data de-identification – to minimize risk for re-identification in the event of unauthorized access or in the event that researchers engaged in activities proscribed by Data Disclosure and Access Agreements; to enable the body of research data used to generate the models to be deemed to be free from Protected Health Information, or other personal information, in order to enable legislation and policy-compliant data access without consent. See further information on Safe Harbor methodology in Section 11, below.

# Data retention

The researchers will work with a copy of data from the Island Health Enterprise Data Warehouse (EDW). The copy is housed within EDW and are subject to BC provincial and Island Health data retention policies, which require that the information be retained indefinitely. The Personal Identifiers are not included in the copy of the data made accessible to researchers and the research data file will be retained for the period of time that complies with Island Health and TCPS2 policies.

# Publication of Results

The completion of this research will include traditional documents submitted for publication and presentations at professional conferences such as The Gerontological Society of America (GSA) as well as lay articles to be submitted to newspapers, magazines and online publications.

# References

Ahles, T. A., & Saykin, A. J. (2007). Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature Reviews Cancer*, *7*(3), 192-201.

Bunn, F., Burn, A. M., Goodman, C., Rait, G., Norton, S., Robinson, L., ... & Brayne, C. (2014). Comorbidity and dementia: a scoping review of the literature. *BMC medicine*, *12*(1), 192.

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# Safe Harbor Identifiers

The following material is copied from Malin (2012) ***Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (***[***https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#safeharborguidance***](https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#safeharborguidance)***) .* For a .pdf version, see** [**https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs\_deid\_guidance.pdf**](https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf)

## Guidance on Satisfying the Safe Harbor Method

In §164.514(b), the Safe Harbor method for de-identification is defined as follows:

(2)(i) The following identifiers of the individual or of relatives, employers, or household members of the individual, are removed:

(A) Names

(B) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census:  
(1) The geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people; and  
(2) The initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000

(C) All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

(D) Telephone numbers, Fax numbers, Email addresses, Internet Protocol (IP) addresses

(L) Vehicle identifiers and serial numbers, including license plate numbers

(M) Device identifiers and serial numbers

(N) Web Universal Resource Locators (URLs)

(G) Social security numbers, Medical record numbers, Account numbers, Health plan beneficiary numbers

(P) Biometric identifiers, including finger and voice prints

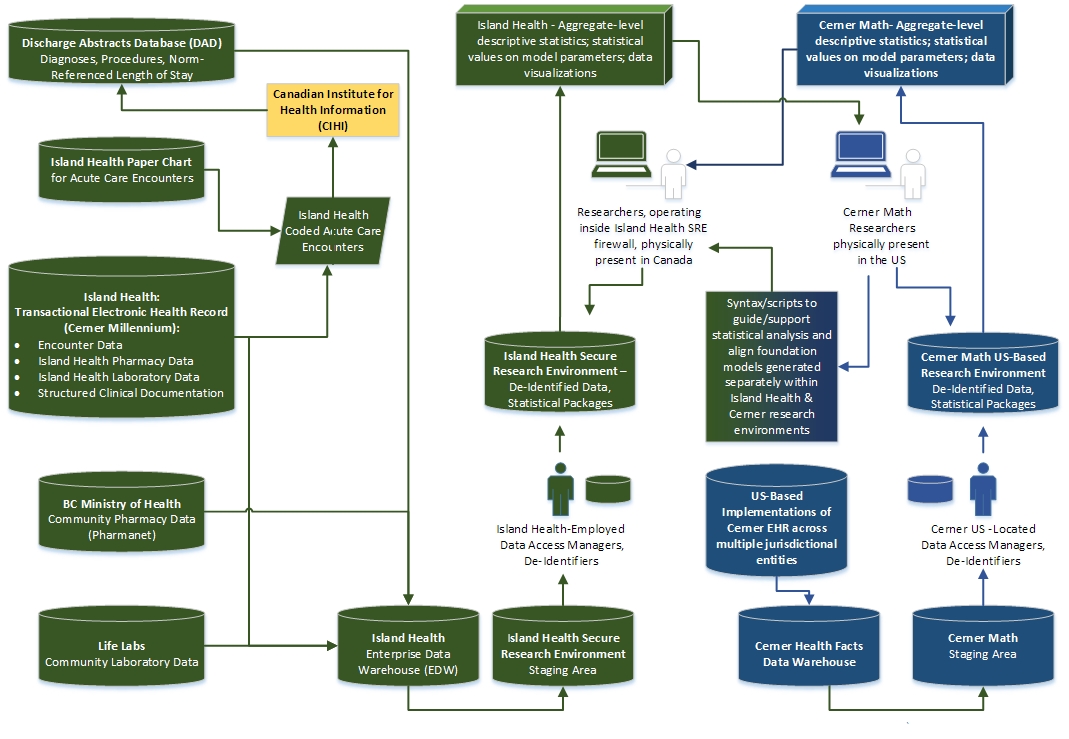
(Q) Full-face photographs and any comparable images

(R) Any other unique identifying number, characteristic, or code, except as permitted by paragraph (c) of this section; and

(K) Certificate/license numbers

(ii) The covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information

# Sample data flow diagram

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**Table I.** Creation of Analysis-Ready De-Identified Research Data Set in Island Health Data Disclosure Environment

|  |  |  |
| --- | --- | --- |
| **Step** | **Activity** | **Parties Involved** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **IH DW Staff** | **IH Dir ACR** | **HI Res** | **UVIC Res** | **Cerner Res** | **O’sight Group** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | EDW attaches fully anonymized identifier to information coming into the data warehouse from Island Health source data systems and removes Direct Identifiers. EDW retains the key to enable re-identification of data but never discloses to Researchers. Research data are drawn from this larger body of anonymized data in the EDW. | Perf |  |  |  |  |  |
| 2 | Supply EDW team with detailed data requirements for research, reflecting research questions, proposed analyses and data requirements as delineated in research protocol. |  | Perf | Perf | Perf | Perf |  |
| 3 | Generate SQL queries to create a delimited body of data elements that are required to address the research questions & carry out research modeling activities. | Perf | C/A | C/A | C/A | C/A |  |
| 4 | Validate that SQL queries have correctly translated documented data requirements with holdings in the EDW. | Perf | Perf | Perf | Perf | Perf |  |
| 5 | Execute SQL queries to create a copy of required data elements in a secure database inside the Island Health firewall. | Perf |  |  |  |  |  |
| 6 | Replace anonymized EDW identifier with a fully anonymized study-specific ID. EDW retains the key to enable linking of research data with other contents in the EDW. | Perf |  |  |  |  |  |
| 7 | Bring BC provincial PharmaNet data into Island Health DDE as per protocol detailed in Table II | See Table II (Linking Island Health Data with Externally-Supplied Pharmacy and Lab Data Inside the Island Health Data Disclosure Environment) | | | | | |
| 8 | Bring BC community Lab data into Island Health DDE as per protocol detailed in Table II. |
| 9 | Employing meta-data associated with research data elements, partition research data into two sub-sets, using the following scheme:   * 1. Indirect Identifiers (Quasi-Identifiers)   2. Attribute Values that could conceivably be linked to Unique Identifiers via the intermediary of actual knowledge that is either held by members of the Research Team or could be acquired by members of the research team. |  | Perf | Perf | Perf | Perf |  |
| 10 | Apply random transformation to dates in the body of Research Information in the DDE in such a way that sequence and duration are preserved at an individual case level. The protocol routinely employed by the Cerner Math group will be followed by the Island Health parties performing these activities | Perf | C/A | C/A | C/A | C/A |  |
| 11 | Employ Statistical Disclosure Control (SDC) methods to evaluate risks for Re-Identification:   1. Risks associated with Indirect Identifiers 2. Risks associated with subset of Attribute Values that have been deemed to hold some potential to function as Indirect Identifiers. | Perf | Perf | C/A | C/A | C/A | C/A |
| 12 | Apply transformations to the body of Research Information research data file to address quantified risks for Re-Identification. Options include Perturbative and Non-Perturbative changes, with Non-Perturbative changes regarded as the preferred option | Perf | Perf | C/A | C/A | C/A |  |
| 13 | Generate document detailing: (a) all of the transformations that have been applied to the research data in order to achieve acceptable levels of risk for Re-Identification, and (b) all of the analyses conducted to quantify risk for Re-Identification | Perf | Perf | C/A | C/A | C/A | C/A |
| 14 | Circulate documentation of results to the Smart Antibiogram project Analytics Oversight Group to adjudicate on whether an adequate level of residual risk for Re-Identification has met island Health and Cerner Math standards. Minutes generated by the Island Health Director, Applied Clinical Research.  If the data are not approved for disclosure to Researchers – GOTO Step 12.  If the data are approved for disclosure to Researchers – GOTO Step 15. |  | Perf |  |  |  | Adj/ App |
| 15 | Authorize Island Health Information Management/Information Technology to activate accounts for Cerner Math Researchers. This enables these Researchers to interact with the Smart Antibiogram Research Information through a VPN tunnel into the DDE in the Island Health firewall |  | Perf |  |  |  |  |
| 16 | Island Health Data Warehouse Staff add Researchers to the authorization groups associated with contents and locations of the Smart Antibiogram data) | Perf |  |  |  |  |  |

**Table 2.** Linking Island Health Data with Externally-Supplied Pharmacy and Lab Data inside the Island Health Data Disclosure Environment

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Step** | **Activity** |  | **Parties Involved** | | | | | |
| **IH DW Staff** | **IH Dir ACR** | **IH Res** | **MoH** | **Com’ty**  **Labs** | **Cerner Res** | **O’sight Group** |
| 1 | Island Health creates the REB-approved study population and a list of anonymized Study ID’s associated with that population. | Perf |  |  |  |  |  |  |
| 2 | Island Health creates temporary anonymized Study ID’s that map onto the Island Health Study ID’s used inside the Smart Antibiogram data holding. | Perf |  |  |  |  |  |  |
| 3 | Island Health maps temporary Study ID’s onto PHN’s. | Perf |  |  |  |  |  |  |
| 4 | Island Health provides MoH or holder of Community Lab data with a linkage file consisting of a list of temporary Study ID’s and PHNs. | Perf |  |  | Perf |  | Perf |  |
| 5 | MoH or holder of Community Lab data attaches Pharmacy/Lab data to PHN’s and then substitutes temporary Study ID’s for PHN’s, deleting the PHN’s from the files to be returned to Island Health. |  |  |  | Perf | Perf | Perf |  |
| 6 | MoH or holder of Community Lab data sends Island Health data warehouse staff the requested, REB-approved data, with temporary Study ID’s associated with the Records. A Secure File Transfer protocol approved by all parties involved in the disclosure is employed. |  |  |  | Perf | Perf |  |  |
| 7 | Island Health attaches MoH or holder of Community Lab data to Smart Antibiogram study population using the Island Health key that links temporary Study ID’s to the Study ID’s employed in Smart Antibiogram data holding. | Perf |  |  |  |  |  |  |
| 8 | Island Health notifies MoH or holder of Community Lab data that the linkage has been completed. | Perf |  |  |  |  | Perf |  |
| 9 | MoH or holder of the Community Lab data destroys the linkage key that associates temporary Study ID’s with PHN’s. |  |  |  | Perf | Perf | C/A |  |
| 10 | MoH or holder of the Community Lab data notifies Island Health that the linkage keys have been destroyed | Perf |  |  | Perf | Perf |  |  |
| 11 | Island Health data warehouse retains a copy of the linkage key for the data retention period associated with the research. This key is never disclosed to Researchers. | Perf |  |  |  |  |  |  |
| 12 | Review, sign-off on implementation of the protocol followed to bring MoH or holder of Community Lab data into the Island Health Smart Antibiogram data holding. |  | Perf | C/A | C/A | C/A | C/A | Perf |