

A Renal Program Nested in a Larger Population Health Management (PHM) Program

Institute for Clinical Evaluation Science, Kidney, Dialysis, and Transplant Program (ICES KDT)

Setting & Background

Lead Organization & Individuals: ICES KDT

- Dr. Amit Garg, Program Lead
- Dr. Joseph Kim, Co-Program Lead

Key Partners

- Ontario Renal Network (manages and coordinates kidney care in the province of Ontario, Canada)
- Trillium Gift of Life Network (Ontario's organ procurement agency)

Health Care System Structure & Organization: Ontario has a single-payer health care system that provides services to approximately 14 million Ontario residents. Services include:

- Universal access to hospital care and physician services; and
- Drug coverage for people age 65 and over or for special patient populations.

Target Population: Patients with kidney disease (acute kidney injury, chronic kidney disease [CKD], end-stage renal disease [ESRD]) across Ontario, Canada.

Data Sources: ICES contains over 50 large administrative databases with over 25 years of patient data, encompassing much of the publicly funded administrative health services records for the Ontario population eligible for universal health coverage since 1986. Patient data are linked across datasets using unique encoded patient identifiers. Data include:

- Physician billing records;
- Hospital/emergency room encounters;
- Vital status information;
- Drug data;
- Laboratory data; and
- Other data sets.

Data Infrastructure: All ICES data holdings are held in a secure, isolated network at ICES Sunnybrook. At ICES satellite sites (e.g., ICES Western), data from this server are accessed

remotely via secure, dedicated data lines. This architecture and remote data access has been approved by the Information and Privacy Commissioner of Ontario.

Key Dates: ICES was established in 1992, ICES KDT was launched in January 2013.

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Introduction

ICES is an independent, non-profit organization that was established in 1992 at the Sunnybrook Hospital Campus in Toronto, Ontario, Canada. It encompasses a community of research, data, and clinical experts and a secure and accessible array of Ontario's health-related data. It grew out of a need to focus on research. ICES' mission is research excellence to support policy development, better care, and improved health outcomes. It allows for the study of health interventions, health care utilization, and outcomes among the general population as well as unique subgroups. In addition, ICES allows long-term, passive follow-up of patient outcomes that would be extremely costly or not possible through a clinical trial or prospective cohort study.

In 2006, ICES and Ontario's Ministry of Health and Long-Term Care (MOHLTC) proposed to establish ICES satellite sites across Ontario at each of the medical schools. The purpose of these satellite sites is to expand capacity to generate high-quality health research across the province. ICES Western (London, Ontario) was established in 2012 at the London Health Sciences Centre with Dr. Amit Garg as the Site Director.

ICES KDT grew out of an established PHM program. All research conducted at ICES goes through one of the seven research programs. The Kidney, Dialysis, and Transplantation (KDT) program was the sixth program to be established at ICES and the only program that is managed at one of the ICES satellite sites (and outside of ICES Sunnybrook). Dr. Amit Garg is the inaugural Program Lead (Nephrologist at London Health Sciences Centre, London, Ontario and President Elect of the Canadian Society of Nephrology) and Dr. Joseph Kim is the Co-Lead (Nephrologist at the University Health Network, Toronto, Ontario).

Funding: ICES Sunnybrook receives some core funding from the MOHLTC. However, most of the research initiated by investigators, including all research done through ICES satellite sites, is dependent on external grant funding. Major funding sources include the Canadian Institutes of Health Research (CIHR), local funding agencies, and disease-specific organizations such as the Heart and Stroke Foundation, Cancer Care Ontario, and the Kidney Foundation of Canada. Although funding sources in publications and other deliverables are acknowledged, all ICES research remains independent of these funding sources.

Applied Health Research Questions (AHRQ) are research requests from a knowledge user for new evidence to inform policy and program development, which will have a positive influence on the Ontario health care system. These requests can include rapid responses, technical briefs, or full research studies – with the latter requiring a longer timeline to complete and greater

resources. If an AHRQ research request and budget is approved, then the MOHLTC provides the necessary funding to the research institute to complete the knowledge request. ICES is one of the core research institutes that receives AHRQ requests. Based on the content of the request, the appropriate ICES research program is contacted to complete the request.

Methods

Key elements to implementing ICES are listed below.

- Core investigators and staff;
- Key knowledge users;
- Partnerships;
- Common data sources;
- Data quality;
- Study designs; and
- Analytic techniques.

Core Investigators and Staff

ICES KDT is comprised of 16 core investigators, most of whom are nephrologists who care for patients with kidney disease. Many also have master's or PhD degrees in epidemiology and biostatistics. Investigators require substantial understanding of the ICES data holdings and research processes before they can lead their own projects. Once this is demonstrated through success in grants and publications using ICES data, investigators can apply to become ICES Scientists. Nine of the 16 core investigators are also ICES Scientists.

The core support staff consists of a lead analyst (Post-Doc in biostatistics), lead research coordinator (PhD in training in epidemiology), program administrator, as well as a growing team of other epidemiologists, biostatisticians, and research assistants. Some staff have specialized interests in content areas (e.g., transplant, stroke, hemorrhage) and methodological areas (e.g., health geography, cluster randomized trials, economics).

Key Knowledge Users

There are two key knowledge users who are involved in producing novel information to help inform CKD-related programs and policies.

- 1) The Ontario Renal Network (ORN) provides overall leadership and strategic direction to effectively organize and manage the delivery of kidney services in Ontario. Over the last six years, ORN and ICES KDT have been working together to produce novel information to help inform strategic kidney priorities in the province. A three-year research plan to complete priority objectives relevant to the ORN (e.g., palliative care, home dialysis, time from ESRD to transplant) has recently been developed.
- 2) The Trillium Gift of Life Network is a not-for-profit agency of the government of Ontario. Trillium plans, promotes, coordinates, and supports organ and tissue donation and transplantation across Ontario. Its mission is to save and enhance the lives of Ontarians through the gift of organ and tissue donation and transplantation. Trillium and ICES KDT have worked together for the past six years and have demonstrated a large impact, particularly in the area of deceased organ donation registration.

Other Partnerships

Last year, ICES KDT received an information request from the Métis Nation of Ontario to investigate kidney disease prevalence and outcomes among this unique group of individuals (previously only pan-Aboriginal estimates of kidney disease prevalence in the province had been completed). ICES KDT is also interested in working with the Chiefs of Ontario to study kidney disease prevalence and outcomes among First Nation individuals.

ICES KDT is exploring new provincial, national, and international partnerships. They are currently working with Australian investigators to explore rates and outcomes of cancer screening among patients with CKD in Ontario.

Common Data Sources

ICES contains over 50 databases on health care encounters, demographics, population/geography, disease-specific registries, and many others. ICES KDT uses some of these databases more frequently than others.

Frequently Used Databases and Data Holdings

Database	Description	Details
<i>Administrative Health Care Databases</i>		
Discharge Abstract Database (Canadian Institutes for Health Information)	Hospital discharge abstracts for acute, chronic and rehabilitative care (1988 onward)	Diagnoses, procedures, comorbidities, length of stay.
National Ambulatory Care Reporting System (Canadian Institutes for Health Information)	Emergency department visits (2002 and onwards); same day surgeries (1991 onward)	Reasons for visit, triage level, interventions, mode of arrival.
Ontario Drug Benefits Database (Ontario Ministry of Health and Long-term Care)	Claims for prescribed drugs covered by the Ontario Drug Formulary for adults aged 65+ and those receiving social assistance (1990 onward)	Drug ID number, drug quantity, prescription date, cost.
Ontario Health Insurance Plan (Ontario Ministry of Health and Long-term Care)	Reimbursement claims made by fee-for-service physicians and community-based labs (1991 onward)	Service provided, diagnosis codes, physician specialty.
<i>Other Administrative Databases and Macros</i>		
Registered Persons Database (Ontario Ministry of Health and Long-term Care)	Basic demographic information on anyone who has received an Ontario health card (1990 onward)	Date of birth, date of death, sex, geographic information.
Costing Macro	Calculates health care costs over a specified time period (2002 onward)	Cost of health care utilization.
<i>Laboratory and Kidney-Specific Linked Cohorts/Registries</i>		
Canadian Organ Replacement Registry (Canadian Institutes for Health Information)	Characteristics, treatments, and outcomes of vital organ transplantation and renal dialysis activities in Canada (1998 onward)	Dialysis modality and transplant organ, laboratory values.
Dialysis Measurement, Analysis and Reporting System	Prospective cohort study of new dialysis patients across seven dialysis programs in Ontario (2008 onward)	Dialysis modality, comorbidity, dialysis access, outcomes.

Trillium Gift of Life Database	All Ontario living organ donors, deceased organ donors and transplant recipients (1992 onward)	Organ type, transplant date, transplant specific variables for donors and recipients.
Gamma-Dynacare	Outpatient laboratory values for all GD locations in Ontario (>59 million tests in 2012; 2002 onward)	Outpatient laboratory values (e.g., serum creatinine, urine protein, sodium, potassium).
Cerner Data stream (London Health Sciences Centre)	Laboratory values from an electronic medical record operating in 12 hospitals in Southwestern Ontario (>2 million tests; 2000 onward)	Outpatient, inpatient and emergency room laboratory values.
Ontario Renal Reporting System (ORN)	Monthly survey data of specific dialysis indicators (2010 – 2014)	Dialysis status, dialysis modality, access type, laboratory results.
Ontario Laboratory Information System (eHealth Ontario)	<i>To be linked in the Fall/ Winter of 2015.</i> Will include data for all outpatient laboratory and ~75% of all hospital-based tests in Ontario	Outpatient, inpatient and emergency room laboratory values.

For the complete list of ICES data sources, visit the [ICES Data Dictionary](#).

Data Quality

There is very low missing data in the administrative databases. For example, the Registered Persons Database has complete data for date of birth, sex, and date of death, where only 3% of individuals have missing data for urban/ rural status. Furthermore, all-cause mortality has a sensitivity of 94% and a positive predictive value of 100%.

In order to guide the development of studies and ensure consistency in the definitions of baseline characteristics, exclusion criteria, and outcomes, ICES KDT has developed a large set of administrative codes—the KDT Variable Library—that covers over 80 diagnoses and procedures.

ICES KDT has also used the linked laboratory values to perform validation studies for some of the common conditions studied (e.g., acute kidney injury, CKD, hyponatremia). See suggested reference [Fleet, 2013](#). These diagnosis codes generally have lower sensitivity but high positive predictive value. ICES KDT has performed other validation studies using chart reviews to ensure validity of certain conditions such as living kidney donors and ventricular arrhythmia. For all other variables in the KDT Variable Library, efforts are made to ensure face validity through consultation with clinical experts.

Study Designs

The ICES data holdings allow flexibility in study designs, as well as the population of interest. For example, many studies are population-based, focusing on more specific cohorts such as the elderly (especially for drug studies where researchers are limited by the data) or dialysis/transplant groups. The most common study designs are retrospective cohort studies or nested-case control studies (the latter primarily used for rare outcomes in order to match cases to a select number of controls).

ICES KDT is also leveraging the ICES databases to perform more unique studies such as long-term follow-up of prospective cohort studies or clinical trials. By seeking consent to ICES data

linkage and obtaining their Ontario Health Insurance Plan (OHIP) numbers when recruiting patients for these studies, these patients can then be linked to the ICES data holdings. This allows for the passive tracking of these patients over time to see if they develop any long-term, adverse events. This is much cheaper than actively following patients over the years and it is less likely patients will be lost over the follow-up period.

Another research project focuses on cluster randomized trials leveraging the ICES data holdings, with a focus on cluster-level interventions across the 82 Ontario dialysis facilities (~7500 patients) and using the ICES data holdings to assess outcomes for patients attending these facilities. ICES KDT is currently initiating the first cluster trial to test if lowering the dialysis fluid temperature can prevent heart attacks and strokes in dialysis patients, as well as assessing other important patient outcomes.

Analytic Techniques

Propensity scores: A common bias in observational studies is confounding, where the association between the exposure and outcome of interest may be affected by a third variable. To try to account for confounding in studies, ICES KDT often uses propensity score methods. A propensity score is calculated for each study participant based on a set of baseline characteristics (generally over 100 characteristics in studies) to determine their probability of experiencing the exposure. This propensity score can then be used to either match participants with similar scores, provide a weight to the statistical model, or included as a covariate in a multivariable model (similar to the conventional way of controlling for confounding). Some resources for propensity scores are suggested at the end of this document ([Austin 2007](#) & [Austin 2011](#)).

Comorbidity indices: ICES has access to different types of comorbidity indices that can be used to summarize an individual's health status in studies. This is useful for descriptive purposes, as well as accounting for comorbidity and health status in analyses. ICES is currently working on a methods study to determine the ideal comorbidity score to use for patients with kidney disease. Two common indices used in studies are:

- **Charlson Comorbidity Scores:** includes 17 health conditions that predict death, with assigned weights based on the magnitude of the association with death. Only accounts for conditions that are diagnoses when a patient is hospitalized. Therefore, does not discriminate well between participants who are fairly healthy.
- **John Hopkin's Aggregated Diagnostic Groups:** categorizes patients into 1 of 32 (non-mutually exclusive) groups with similar patterns of comorbidity on the basis of condition duration, condition severity, diagnostic certainty, etiology, and specialty care involvement (e.g., medical, surgical). Based on conditions that occur in all hospital settings (inpatient, emergency room, and same day surgery).

Results

Funding: ICES KDT has received over \$2M in peer-reviewed grant funding from 15 different grant proposals, including funding from the CIHR, Kidney Foundation of Canada, Heart and Stroke Foundation of Canada, Physicians' Services Incorporated Foundation, and Academic Medical Organization of Southwestern Ontario. Although many of these grants are project-specific funding, one is a large five-year CIHR grant to support our core KDT staff (\$802,023

from 2012 – 2017). ICES KDT also received some support from a local agency to complete a series of projects with knowledge users.

The ORN is directly providing funding to work on priority projects over the next three years. In addition, ICES KDT has received \$100K from 2014 – 2015 in AHRQ funding to support new information requests from our knowledge users.

To ensure sustainability of the program, ICES KDT is applying for new funding opportunities including a MOHLTC-supported competition called the Health System Research Funding Program Awards. If successful, ICES KDT would receive \$500K per year over the next three years.

Publications and Reports: Since 2011, the team has published 65 manuscripts in peer-reviewed journals, with studies featuring in NEJM, JAMA and BMJ, as well as top kidney journals (J Am Soc Neph and Kidney Int). Almost half of these manuscripts have featured trainees as first author (32/65).

ICES KDT has completed seven reports for knowledge users (4 for ORN, 2 for Trillium and 1 for the Métis Nation of Ontario).

Impact on Patient Health and Health Care

1. Risk of Kidney Injury from two Commonly Prescribed Drugs in the Elderly ([Gandhi, 2013](#))

ICES KDT published a study in JAMA that showed a drug interaction between calcium channel blockers and clarithromycin (a common antibiotic used mostly to treat respiratory infections). Elderly individuals taking a calcium channel blocker and co-prescribed clarithromycin compared to another similar antibiotic were at greater risk for acute kidney injury. This information was well-received and was recognized by health care providers across the province, including a pharmacist in Elliot Lake and a registered nurse in London. The latter individual recognized that an elderly patient with an upper respiratory infection was also taking a calcium channel blocker. She discussed the results of this study with the physician who then changed the antibiotic prescription from clarithromycin to azithromycin. Pharmaceutical companies also took notice of these results. One of the manufacturers of clarithromycin, Abbot, reported to Health Canada how many cases of acute kidney injury found in our study occurred while on Biaxin (their brand of clarithromycin). Therefore, 297 cases of acute kidney injury from this drug interaction were reported to Health Canada as a result of the paper.

2. Pregnancy Outcomes of Living Kidney Donors ([Garg, 2014](#))

A 2004 international consensus conference claimed “donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies.” An ICES KDT study found that gestational hypertension or preeclampsia was more likely to occur in living kidney donors than in matched non-donors with similar indicators of baseline health (11% vs. 5% ($p=0.01$)). There was no significant difference in other important maternal or fetal outcomes, and many women had uncomplicated pregnancies after donation. This research garnered significant attention from the public, with 55 media hits in the first few months and it was featured on the website, UpToDate® (read by over 1 million physicians across 174 countries). This work has also been recognized as the “Research Contribution of the Year Award” within ICES KDT’s broader research institution. These results now inform discussions with young women prior to donation, redefine their care in pregnancy, and will feature in new international guidelines.

3. **Building Support for Organ and Tissue Donation in Ontario** ([Li, 2014](#))

Currently more than 1,500 Ontarians are on a wait list for an organ transplant and unfortunately, every three days one patient dies while waiting. In response, Trillium is encouraging more Ontarians to register their consent to donate organs and tissue after death at BeADonor.ca. At present, only 26% of Ontarians are registered. Trillium hopes to double this number (to align with many American states where >50% of citizens are registered). One of the common unfounded myths about organ donation is that physicians will not try as hard to save your life if you registered for organ and tissue donation. In collaboration with Trillium, ICES KDT wanted to dispel this myth by showing that many physicians are registered for organ and tissue donation in Ontario (and by registering they show their confidence in Ontario's organ donation system). ICES KDT found that among approximately 15,000 physicians in Ontario, 43% registered their consent to be an organ donor, far exceeding 26% of the general population who registered. The premise of the study was to de-bunk a popular myth and to assure the public that doctors do everything possible to save lives — regardless of a person's decision to donate. Following the publication of this study on July 16 2014, Trillium reported an increase in the number of registrations on that particular day through BeADonor.ca (250 compared to the 50 registrations on a typical day).

Next Steps

Next steps include data sharing across Canada and replicating research studies in other provinces with similar data capabilities such as Alberta, Saskatchewan, and Manitoba. There has also been discussion about international data sharing opportunities with the CKD Prognosis Consortium.

Challenges & Solutions

Funding: Funding is always a potential barrier, given continued growth and dependence on funding to sustain the program. ICES is applying for a health system research fund grant and other peer-reviewed grants to ensure financial sustainability.

Data Storage: Ever increasing data requires more space to store the data as well as data processing limits. This past year, ICES transitioned their UNIX-based SAS 9.3 Display Manager environment to a newer SAS 9.4 Grid environment that uses a combination of Windows and Linux servers. This new system, Research Analytic Environment (RAE), provides users with a more user-friendly Windows interface of SAS Enterprise Guide. On the backend, there is a SAS Grid that is balancing the load across five SAS Workspace servers running Redhat Enterprise Linux. SAS Metadata helps to control access to the ICES Repository, which contains over 3TB of data. The RAE currently supports a user base of 250 scientists, epidemiologists, data analysts, and students. This new data platform will provide a solution to this problem for now.

Privacy: Ensuring privacy and security of the ICES data holdings is a huge responsibility. Privacy officers for each of the ICES sites enforce that all employees and scientists follow the ICES privacy procedures and policies. Regular privacy audits help to ensure there are policies in place to protect the data. Some of these policies include: Access to ICES Data, Destruction of ICES Data, Protection of ICES Data, Linking ICES Data, Privacy Impact Assessment, and Student Projects using ICES Data. For example, the Access to ICES Data Policy describes the different levels of access to the data. Administrative data covenants are the only individuals

allowed to access data with direct personal identifiers. Analysts are allowed access to coded data (with personal identifiers removed), and students have further data access restrictions including data without birthdates and postal codes. Another policy, the Privacy Impact Assessment Policy, describes the review and permissions required when initiating a new project to identify and prevent any privacy risks.

Facilitators

Unique Identifiers: Around the inception of ICES, the Ontario Health Care System switched to assigning OHIP numbers to all eligible Ontario residents (13.7 million people in 2014). OHIP numbers are used to track health care encounters. Individuals receive drug coverage through the Ontario Drug Benefits program if they are over the age of 65, residing in a long-term care facility, have high drug costs relative to their income, are enrolled in the Home Care program, or are receiving social assistance. This health care system is the foundation to ICES' ability to collect health care information for all Ontario citizens, including drug data for the elderly.

Linkage at Various Levels: Unique identifiers allow linkage across various levels and allow new datasets to be easily incorporated into the existing data holdings.

- **Patients.** Based on patients' OHIP numbers, a unique, encrypted identifier known as the ICES key number is created in order to link individuals across databases to assess many different types of health encounters and vital statistics such as death, and to allow follow-up of the patients over time.
- **Clinicians.** Each practicing physician in Ontario is assigned an encrypted physician identifier to associate health care services and prescribing to physicians, as well as to obtain demographic, specialty, and training information for physicians.
- **Facility.** Facility identifiers allow institutions such as hospitals and dialysis facilities to be identified, allowing for reporting at the facility-level.
- **Population-level.** Postal codes and local health integration networks provide information on geography and population-level variables such as income quintile and rural status.

ICES Privacy and Protection of Data: One of the most challenging aspects of being responsible for this rich data source is the ability to respect patients' privacy and ensure the security of the data holdings and personal health information. Since 2005, ICES has been assigned a special designation under Ontario law, where personal health information can be legally disclosed without requiring patient consent for the purposes of analysis, evaluation, and compiling statistical information about the health care system. Only organizations that can demonstrate rigorous privacy practices are eligible and compliance is audited by the Ontario Privacy Commissioner every three years. ICES has established strict privacy policies that are required to maintain ICES's special designation and consequently the ability to access the data holdings. This privacy designation allows ICES to efficiently conduct analysis and compile statistics for the management and effectiveness of the health care system.

Additional Resources Available Upon Request

For additional resources or publications of kidney disease studies using ICES data.
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