Escarpment Cancer Research Institute

ESCARPMENT CANCER RESEARCH INSTITUTE (ECRI)

A Joint McMaster University/Hamilton Health Sciences Research Institute

5-Year Report (2016-2021)

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Inspiring Research: because every patient matters

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EXECUTIVE SUMMARY

The Escarpment Cancer Research Institute (ECRI) was established in July 2011 as a Joint McMaster University/Hamilton Health Sciences Research Institute. The current document is a summary report of ECRI activities from 2016-2021 prepared for its Governing Board. Although the report follows the template recommended for a Joint University/Hospital Research Institute, it occasionally strays from the template for completeness, ease of understanding and flow.

The goals of the report are to: 1) provide an update of ECRI's progress and accomplishments from 2016-2021 in order to support renewal of the Research Institute for another five-year term, 2) be a resource for the selection of the next Scientific Director, as Dr. Levine is stepping down effective June 2022, and 3) describe future opportunities.

In any dynamic organization, turnover of people is essential for maintaining vitality and renewal. In 2016, there were 17 ECRI core scientists and eight associate members. Since then, seven researchers have retired or departed Hamilton. There are now 24 core scientists in ECRI, including 11 new members (eight of whom are female) in the Institute's young researcher category. In addition, there are 11 associate members. ECRI researchers cover a range of disciplines including medical oncology, radiation oncology, surgical oncology, hematology oncology, nursing, clinical chemistry, biostatistics, psychology, health policy, and computer engineering. Since 2016 there has been the addition of one new endowed chair.

ECRI is an incubator of emerging ideas, a hub for mentorship of young researchers and an interface for collaboration across the University. The clinical trials infrastructure of the Ontario Clinical Oncology Group (OCOG) and the McMaster ICES hub (led by an ECRI scientist) provide fertile ground for the training of young researchers. The Institute has three internationally recognized research programs: the OCOG Trials Group previously led by Dr. Levine and now Dr Wright, Breast Cancer Radiotherapy (RT) Trials led by Dr. Whelan, and Palliative Care led by Dr. Seow. These flagship programs are markers of ECRI's success. ECRI scientists have been very productive as gauged by the standard academic metrics of grants and publications. They have attracted many millions of dollars in research funding and published in high impact journals. The results of ECRI studies have changed patient care, benefiting both patients and the cancer system.

There is no doubt that over the last two years the Covid-19 pandemic has posed a major challenge for research across the country and has been disruptive to ECRI. It is remarkable however, that through this time ECRI has continued to produce high quality research which is a testament to the resilience of the researchers and staff.

Going forward we will continue to give attention to our flagship programs: Clinical Trials, Breast Cancer RT Trials and Palliative Care. We are excited about pursuing new research opportunities in digital health including virtual care and remote monitoring and using artificial intelligence to build a learning health system. Building translational research by establishing strong collaborations with Dr. Sheila Singh, the Director of the new Centre for Discovery in Cancer Research at McMaster University, will be a priority

The future is bright for ECRI. We are excited about the research opportunities, but realistic that there will be challenges as healthcare continues to evolve.

INTRODUCTION

In 2011 the Escarpment Cancer Research Institute (ECRI) was established as a Joint Hamilton Health Sciences (HHS)/McMaster University Research Institute (Appendix I). ECRI is committed to conducting interdisciplinary research that impacts on patient outcomes. It is governed by the host institutions and nested within the McMaster Department of Oncology. Both ECRI and the Department of Oncology are located on the HHS Juravinski Hospital and Cancer Centre (JHCC) campus. The proximal location of both ECRI and the Department of Oncology to the JHCC ensures an integrated approach to cancer care, education, interprofessional practice and research. This unique environment informs the ECRI research plan.

ECRI was established with three foundational research programs: Clinical Trials, Quality Care & Knowledge Translation (KT), and Translational Research. In part, ECRI research was informed by the pressing needs and priorities of the Juravinski Cancer Centre (JCC) and regional cancer program. During its first five years ECRI made substantial progress in meeting its goal of conducting research that impacts on the lives of people affected by cancer. It fostered collaborations with other McMaster research groups in order to build on collective expertise and to pursue interdisciplinary avenues of research. The results of ECRI studies changed patient care, benefiting both patients and the cancer system. By the standard academic metrics of grants and publications, ECRI scientists were very productive. In the second quarter of 2016, a five year report was submitted to the Governing Board (Appendix II) and in September 2016 ECRI was renewed for a five-year term.

The current report has three goals. The first one is to provide an update of ECRI's progress and accomplishments from 2016-2021 in order to support renewal of the Research Institute for another five-year term. The second goal is to be a resource that will guide the selection of the next Scientific Director, as Dr. Levine is stepping down effective June 2022. The final goal is to describe future opportunities based on the foundation that has been built.

PROGRESS OF ECRI SINCE 2016

Second 5-year plan

In 2017, ECRI members worked to create a second 5-year plan for the Institute. The products from these discussions were: 1) a framework for the development of an ECRI research study, 2) clarification of membership requirements, and 3) a rebranding of theme names. As part of the process, Dr. Levine met with each scientist to discuss their research goals, their engagement with ECRI and their research productivity. These activities led to the preparation of an annual research plan for the governing institutions. The research goals and productivity for each individual ECRI member are described in the annual report 2018-2019 that was submitted to ECRI's Governing Board in April 2019 (Appendix III). .

The Changing Environment for Research

Since the early 2000s there have been major changes in the healthcare system in Canada which no doubt, have had an impact on research in academic health science centres, particularly clinical research. These changes are continuing around us, and the health system is evolving. Research needs to evolve to stay in sync. Some of the changes include, but are not limited to:

1. The health system is more patient-centred. Patients are better informed, in part because of the internet and social media.
2. Value-based care is based on the concepts that high quality evidence is paramount, treatments should improve patient outcomes and treatments that are expensive and provide limited benefit should be avoided (1).
3. Patient privacy is very important, and systems need to be in place to ensure protection of privacy.
4. A major challenge is the cost of healthcare which has continued to increase based on the aging population and the cost of technology and drugs. Although funding from governments to support healthcare has increased, it has not kept up with costs. Hence, despite billions of dollars being spent on healthcare, there is a chronic shortfall. This has impacted on the research that ECRI does. For example, in the 1970-90s, the costs of some aspects of doing clinical trials, e.g. imaging and lab work, were passed on to hospitals. This is no longer possible.
5. The regulatory environment for clinical research has become more intense and complex with Health Canada establishing legislation guiding research on drugs, biologics and devices. Although this has increased accountability, it has also resulted in substantially more bureaucracy that has also contributed to the increased cost of conducting trials.
6. Sex/gender and equity have become major issues in society. It is not surprising that they have also entered the research domain. Applicants for CIHR grants need to pass tutorials on sex/gender equity prior to grant submission. There is strong evidence that economically and socially disadvantaged populations have worse health outcomes (2).
7. There are greater clinical demands on clinician researchers making it more difficult for these individuals to have sustainable productive research portfolios, the opportunities for recruiting and funding researchers have been drastically reduced (particularly for non-clinical research candidates), and the dollars to support research and the infrastructure to foster good science are fewer and more competitive to acquire.

The Covid 19 Pandemic

The pandemic has caused a major disruption in research. Clinical trials across Canada shut down and there was little recruitment of new patients to cancer trials. Follow-up for existing trials switched to virtual visits. The discontinuation of patient accrual had an economic impact on OCOG, one of the cornerstones of ECRI. In August 2020, just as the system was starting to recover from the first wave of COVID-19, the second wave struck. Recruitment to trials which had opened, was slowed down. In April 2021, the third wave of COVID-19 arrived. It resulted in ICUs filling up to 100% capacity, and physician and nursing staff being seconded to the ICUs. In August 2021, the fourth wave arrived, and the cycle repeated itself. At the time of submission of this report to our Board, the Omicron variant is resulting in major system disruptions. The

impact of the pandemic on a clinician's ability to conduct clinical research has been affected and is a challenge looking forward.

ECRI FACULTY (2016-2021)

There were 17 scientists when ECRI first began in 2011. In the last five years, there have been a number of retirements from ECRI (Arnold, Bane, Brouwers, Elit, Gulenchyn, Hirte, Julian and Muti). Dr. Brouwers, ECRI's Deputy Director, with expertise in knowledge translation and implementation left Hamilton to take up a new leadership position at the University of Ottawa. . Dr. Sussman became the Chair of the Department of Oncology and had less time to lead research. Since the time of the last report (2016), a number of new young researchers have become ECRI members (Table 1). The ECRI Executive realized that a key factor for the long term sustainability of ECRI, and oncology research per se, was to establish a core of young researchers with drive and passion for research. To this end, a conscious decision was made to identify researchers within the first five years of their university appointment and ensure that they had a senior mentor in ECRI who committed time to working with them on all aspects of their research (grant preparation, writing manuscripts and career guidance). This is a work in progress.

Table 1: ECRI Young Researchers

Researcher	**Department/Division**	**Mentor**	**Theme**
Amaris Balitsky	Hematology Oncology	Levine	Virtual care, CarT cell
Tobias Berg [€]	Hematology Oncology	Sussman, Singh, Bramson	Leukemia, stem cells
Mira Goldberg	Radiation Oncology	Whelan	New radiation technologies
Aly-Khan Lalani	Medical Oncology	Levine, Swaminath	Immunotherapy, gut microbiome
Oren Levine	Medical Oncology	Sussman, Meyer, Levine	End of life care
Hira Mian*	Hematology Oncology	Seow, Sussman, Levine	Multiple myeloma, geriatrics
Ashirbani Saha[α]	Data Science	Levine, Petch, Sussman	Machine learning
Kara Schnarr	Radiation Oncology	Seow, Pond, Whelan	Gynecological cancers
Karen Zhang	Psychiatry (Psychologist)	Levine, Bryant-Lukosius, Sussman	Psychosocial support
Elena Parvez	Surgery	Levine, Whelan	Local therapy breast cancer, equity issues
Elysia Donovan	Radiation Oncology	Swaminath, Whelan	Oligo metastatic disease

[€] Boris Family Chair in Leukemia and Hematopoietic Stem Cell Translational Research
[α] BRIGHT Run Breast Cancer Learning Health System Chair
* HHS Early Career Award

The list of ECRI scientists (not including those in Table 1) are in Table 2. Currently, among the ECRI scientists there are three endowed chairs, one OICR Senior Scientist, one Tier I Canada Research Chair and one Tier 2 Canada Research Chair.

Table 2: ECRI Researchers

Name	Discipline	Department	Category
Bryant-Lukosius[μ]	Nursing	School of Nursing	Scientist
Juergens	Medical Oncology	Oncology	Scientist
Kavsak	Clinical Chemistry	Path & Molec Med	Scientist
Levine*	Medical Oncology	Oncology	Scientist
Parpia	Biostatistics	Oncology	Scientist
Pond[#]	Biostatistics	Oncology	Scientist
Seow[α]	Health Services	Oncology	Scientist
Serrano	Surgical Oncology	Surgery	Scientist
Simunovic	Surgical Oncology	Surgery	Scientist
Sussman	Radiation Oncology	Oncology	Scientist
Swaminath	Radiation Oncology	Oncology	Scientist
Whelan[±]	Radiation Oncology	Oncology	Scientist
Wright	Radiation Oncology	Oncology	Scientist
Bramson	Immunology	Path & Molec Med	Associate
Daniel	Biology	Science	Associate
Dayes	Radiation Oncology	Oncology	Associate
Dhesy	Medical Oncology	Oncology	Associate
Ellis	Medical Oncology	Oncology	Associate
Hotte	Medical Oncology	Oncology	Associate
Kazemi	Medical Oncology	Oncology	Associate
McGillian	Virtual Care	School of Nursing	Associate
Meyer	Hematology	Oncology	Associate
Meyers	Medical Oncology	Oncology	Associate
Mukherjee	Medical Oncology	Oncology	Associate
Slaven	Palliative Care	Family Medicine	Associate

* Buffett Taylor Chair in Breast Cancer Research, [μ] Alba DiCenso Chair in Advanced Practice Nursing, # OICR Senior Scientist, α CRC Tier 2 Palliative Care, ± CRC Tier 1 Breast Cancer

ECRI RESEARCH PERFORMANCE (2016-2021)

ECRI's research agenda has been successfully driven by ECRI researchers continuing their own independent research. They work in teams which are often multidisciplinary and focus on clinically relevant problems. During the last five years, ECRI research in three domains has thrived and is internationally recognized: Clinical Trials, Radiotherapy in Breast Cancer and Palliative Care. There is no doubt that they will continue to grow and develop further in future years. These three programs will be described in more detail below. In addition, ECRI is considered a collective which is an incubator of emerging ideas, a hub for mentorship, and an interface for collaboration across the University.

The usual metrics of productivity of a research institute such as ECRI are grants received from peer-review agencies, magnitude of funding received from grants, contracts and industry, and publications.

Research Funding

To report the total amount of funding brought in by ECRI researchers over the last five years was not straight forward. Research funds are held in two institutions which can be considered as "banks", McMaster University and Hamilton Health Sciences (Fund 6 accounts). Revenue from Canadian Institutes of Health Research (CIHR), Canadian Cancer Society Research Institute (CCSRI), Ontario Institute of Cancer Research (OICR), and the US National Institutes of Health (NIH) are typically held at McMaster. Funds from the HHS and JCC Foundations, industry, OICR, and Cancer Care Ontario (Ontario Health) are held at HHS. McMaster University and HHS have different fiscal year-ends and use different accounting methods. Dr Levine had to work with financial personnel from each institution and cross verify data from researcher's CVs to achieve a reliable valid description of ECRI research funding. Based on these considerations the data will be presented separately for each "bank". The ECRI financial data held in HHS accounts is shown in Table 3 and that for McMaster accounts in Table 4.

The total funding held in HHS is $13,777,693 (Table 3). The JCC Foundation has generously granted over $1 million from 2016-2021. This source has often provided seed-funding for studies conducted by young researchers. Over $6 million has been brought in from industry and over $6 million from other sources e.g., CCO, OICR, HHS.

The total amount of funding from 2016-2021 held in McMaster accounts is $52,579,710 (Table 4). Over $25 million comes from peer-review agencies, e.g., CIHR, CCSRI, and NIH. Another $20 million has come other sources e.g., peer-review agencies where an ECRI researcher is a co-investigator, but the principal investigator is not from ECRI.
Thus, the total ECRI funding over the last 5 years is $66,357,403.

Publications

To obtain an accurate tabulation of peer-review publications by ECRI researchers over the last five years was not a straight forward task. We used the same rules as were used in the previous 5-year report; book chapters and abstracts were not included, and a publication was only counted once if there were more than one ECRI researcher as an author. To account for the publications using such rules, would be very challenging by hand. An electronic approach was needed.
Dr. Ashirbani Saha, the data scientist and expert in artificial intelligence who was recently recruited to the Department of Oncology and ECRI, played a lead role in this task and we thank her.

A bibliometric search report (2016-2021) using electronic data bases such as Pub Med. was obtained from the McMaster Library. As some researchers started to work with ECRI mid-way through the aforementioned time period or were missing from the bibliometric search report, their updated CVs were collected. A computer program in MATLAB (Natick, MA, USA) was written to parse the bibliometric report and have a preliminary structured list of all publications (publication list) having at least one author from ECRI. The publication list also indicated if an ECRI researcher is the first author of a publication. Additionally, through another set of computer programs, descriptive statistics was collected for total number of unique publications, total and first-authored publications by an ECRI researcher with year-wise break-up of similar

information. (Note, the CVs were up-dated to at least July 1, 2021. Some were updated to a more recent date e.g., December 2021).

Based on the preliminary publication list and the corresponding statistics, we were able to determine problems such as difference in naming conventions (e. g. Smith, Joe Andrew vs. Smith, J.A.), presence of non-ECRI researchers with similar initials, missing ECRI researchers, and missing publications. We modified the computer program to address different naming conventions and removed non-ECRI researchers and produced a new publication list. We sought CVs and added the missing researchers to ECRI's final list of researchers and their missing publications to the new publication list. For the new members, we screened publications by their time of commencement as an ECRI member and/or affiliation mentioned in the publications. These publications (from CVs) were manually added to the new publication list. The second set of computer programs was used to produce the descriptive statistics on the new publication list. The publication list was also used to generate the final list of all and first-and last-authored publications in a uniform format.

Based on the above considerations, there were a total of 838 ECRI publications during the 2016-2021 period (Table 5). An ECRI researcher was either the first or last author, for 345 publications, respectively (Table 5). The table also presents the number of publications each year. The publication list for first or last-authored papers can be found in Appendix IV. All of the publications for each ECRI researcher are also found in their CV (Appendix V).

Summary

ECRI's productivity as gauged by the metrics of funding and publications is very respectable given the mix of young researchers and experienced investigators and the challenges brought on by the pandemic. Apart from grants and publications, there are other functions that ECRI members play in supporting the research enterprise, e.g., mentoring, presenting at ECRI seminars, membership in REBs, e.g. HIREB (Pond, Parpia) and OCREB (Wright), chairing a grant review panel for internal JCC Foundation awards (Bryant-Lukosius, Dayes), and administration (Juergens, as Head of the JCC Clinical Trials Department, plays a pivotal role in ensuring its success in supporting trials through recruitment and data collection).

Clinical Trials

Ontario Clinical Oncology Group

The ECRI Clinical Trials Research Program continues to be vibrant. The Ontario Clinical Oncology Group (OCOG) is a cornerstone of the Research Institute. OCOG works with networks of investigators provincially, nationally and further afield to design, execute and analyze clinical trials. In some cases, the principal investigators (PIs) are ECRI members. The OCOG Coordination & Method Centre (CMC) is located in the Juravinski Hospital, adjacent to the JCC. OCOG is fortunate to have a team of Faculty biostatisticians who are also methodologists and expert in clinical trials (Pond, Parpia and Julian (retired in 2020)). OCOG trial activity between 2016 and 2021 is shown in Table 6. There is an exciting mix of trials covering: 1) diagnostic imaging, 2) novel radiotherapy regimens, 3) quality of care, and

4) immunotherapy. Examples of OCOG trials are highlighted below to illustrate the variety and impact. In September 2021, Dr. Levine stepped down as Head of OCOG and Dr. Wright assumed the Director position.

Table 6: OCOG Trials 2016-2021

Trial	Funding	Investigators	Intervention	Outcome	N/Target	Status
PET ABC	CCO	Dayes, Eisen, George	bone scan, CT thorax/abdomen vs. PET/CT	Upstage to Stage IV	361/370	Ongoing
PETMUSE	CCO	Sridhar (PMH), Powers Mukherjee	CT thorax, abdomen/pelvis + or - PET	Treatment received	360/370	Ongoing
PROFIT	CIHR	Catton (PMH), Lukka, Julian	50.4 Gy /12 fx over 2.4 weeks vs 78 Gy/ 39 fx over 8 weeks	Biochemical/ clinical failure	1204	J Clin Oncol (3)
LUSTRE	CCSRI	Swaminath, Whelan, Parpia, Wright	SBRT (49 Gy/4fx or 60 Gy/8fx over 8-14 days) vs 60 Gy/15fx over 3 weeks	Local control	232/334	Ongoing
ALMERA	CIHR	Tsakiridis, Pond, Wright, Whelan	Chemo/RT + metformin vs. Chemo/RT	Progression, death	50	JAMA Oncol (5)
ATOM	OICR	Krzyzanowska (PMH), Julian, Grunfeld (Toronto), Levine	Nurse-led remote (telephone) management	Emergency visits, hospitalizations	20 centres	BMJ (6)
CYTOSHRINK	BMS	Lalani, Swaminath, Pond	Ipilimumab/ Nivolumab + or – SBRT to primary kidney lesion (30-40 Gy/5 f) (2:1)	PFS	17/75	Ongoing
ADVANCE	Roche	Meyers, Swaminath, Serrano, Pond	Neoadjuvant atezolizumab + bevacizumab, both q3wks x 4 cycles vs neoadjuvant SBRT 30-40 Gy, 6-8 Gy / day over five days	Hepatic resection	70	Ongoing

For approximately 15 years, OCOG has conducted clinical trials in Ontario to evaluate PET in oncology. This is a special program initially established by the Ontario Ministry of Health and Long-Term Care to generate evidence on the utility of PET for various oncology indications. PET is attractive in oncology because radioactive sugar is avidly taken up by metabolizing cancer cells. The potential for this technology is in staging the cancer, i.e. determining the extent of the cancer which guides treatment. The results of these trials inform policy in Ontario and whether PET is funded for a specific indication. This research program is unique and is the largest of its kind globally. There are two PET trials that are currently ongoing.

Impact of ^{18}F-FDG PET-CT versus Conventional Staging in the Management of Patients Presenting with Clinical Stage III Breast Cancer (PETABC): In PETABC, patients who present with locally advanced breast cancer (LABC), i.e. with large, bulky tumour in the breast and/or bulky axillary lymph nodes, are randomly allocated to staging with bone scan and CT thorax and abdomen (usual approach) versus PET scan. The outcome is the detection of metastases and upstaging to Stage IV. If occult metastases are detected, then treatment switches from potentially curative to palliative. The trial opened in April 2016 and 361 of a target 370 patients have been recruited.

Impact of Positron Emission Tomography (PET) Imaging in Muscle-invasive Urothelial Carcinoma of the Bladder Staging (PET MUSE): Standard preoperative imaging in patients with muscle invasive bladder cancer (MIBC) consists of CT scan of the chest, abdomen and pelvis. Treatment of MIBC consists of cystectomy and pelvic lymph node dissection with consideration of perioperative chemotherapy, or external beam radiotherapy for patients that cannot undergo surgery. Better staging would allow more aggressive treatment for those patients who have a high chance of cure and would avoid highly morbid treatments in those patients who have metastases. In the PETMUSE trial, patients with MIBC who have undergone standard CT staging are randomized to PET/CT versus no PET/CT. The primary outcome measure is treatment received, including avoidance of cystectomy, more extensive lymph node dissection or neoadjuvant chemotherapy followed by cystectomy. The trial opened in April 2015 and to date 360 of a target 370 patients have been entered.

A Randomized Trial of a HypoFractionated Radiation Regimen for The Treatment of Localized Prostate Cancer (PROFIT): Over the years OCOG has conducted trials evaluating innovative RT regimens. In PROFIT, 1,204 men with intermediate risk early prostate cancer were randomized to a 2.4 week course of hypofractionated radiotherapy (RT) or a standard 8 weeks of treatment between 2006 and 2011. The trial was funded by CIHR. In 2017, at a median follow-up of 5.7 years, the analysis showed no difference in failure rates and toxicity between treatment groups (3). Based on the results of the PROFIT trial and several other randomized trials, hypofractionated RT as used in PROFIT is recommended for intermediate risk prostate cancer (4).

A Randomized Trial of Medically-Inoperable Stage I Non-Small Cell Lung Cancer (NSCLC) Patients Comparing Stereotactic Body Radiotherapy Versus Conventional Radiotherapy (LUSTRE): External RT is the preferred treatment option in patients with Stage I non-small cell lung cancer (NSCLC) who cannot undergo surgery. Conventional RT for NSCLC is typically given as a prolonged course of treatment over 3-6½ weeks. The JCC is a Canadian leader in a new radiotherapy technique; stereotactic body radiation therapy (SBRT), which can deliver high doses of radiation over a short time precisely to the tumour sparing surrounding normal tissue. In LUSTRE, patients with Stage I NSCLC who are not eligible for surgery are randomized to SBRT over 8-14 days or conventional RT three weeks. The primary outcome measure is local control. Recruitment began in May 2014 at 16 Canadian centres. In December 2019, a decision was made to discontinue recruitment after 232 of a targeted 324 patients had been recruited because of low recruitment. An analysis is planned for January 2022. There are very few trials of SBRT in NSCLC. SBRT is attractive to patients because it is given over a much shorter time

than usual RT. The LUSTRE trial will provide important information on the efficacy and safety of SBRT.

A Phase II Study to Investigate a Combination of Metformin with Chemo-Radiotherapy in Patients with Locally Advanced Non-Small Cell Lung Cancer (ALMERA): Laboratory studies suggest that metformin may increase the effects of radiation and chemotherapy. In addition, observational studies suggest that metformin improved survival in diabetic patients with cancer. In ALMERA, patients with Stage III NSLC were randomized to platinum-based chemotherapy, concurrent with chest radiotherapy (Gy), or the same treatment plus metformin (2000 mg per day) during chemo-radiotherapy and afterwards for up to 12 months. Between 2014 and 2019, 54 patients were randomized (26 in the experimental arm and 28 in the control arm). The addition of metformin to chemo-radiation was associated with worse treatment efficacy and increased toxicity compared to combined modality therapy alone (5).

A Pragmatic Cluster-Randomized Trial of Ambulatory Toxicity Management in Patients Receiving Adjuvant or Neo-adjuvant Chemotherapy for Early-Stage Breast Cancer (ATOM): Women undergoing chemotherapy for breast cancer frequently experience toxicity and go to the emergency department (ED) and sometimes require hospitalization (H). ED visits and H may be preventable with adequate support between clinic visits. In a cluster randomized trial, 20 cancer centres in Ontario were allocated to standardized, nurse-led remote (telephone) management of common toxicities at two time points following each chemotherapy cycle or routine care. Over 2,000 Ontario women commencing adjuvant/neoadjuvant chemotherapy for early-stage breast cancer were enrolled between February 2016 and November 2017. There was no difference in the mean number of ED+H visits/patient between arms. The study was published in the BMJ (6). The telephone-based intervention in ATOM predates the COVID-19 pandemic with its associated rapid switch to telephone-based virtual care. The experience with ATOM encourages us to continue research with virtual care and patient remote automated monitoring (RAM) (7).

Phase II trial of Cytoreductive Stereotactic Hypofractionated Radiotherapy with Combination Ipilimumab and Nivolumab for Metastatic Kidney Cancer (CYTOSHRINK): Standard first line treatment of metastatic renal cell carcinoma (mRCC) now includes immune checkpoint blockade (ICB). In the past cytoreductive nephrectomy (CN) was commonly used in mRCC, but now it has been called into question. We hypothesized that hypofractionated radiation to the primary tumour will enhance the immune response and creating an "abscopal effect" whereby both target and non-target lesions respond to treatment. In the Phase 2 CYTOSHRINK trial, patients with mRCC are randomized to immunotherapy with Ipilimumab/Nivolumab plus SBRT or Ipilimumab/Nivolumab alone. The primary outcome is PFS. To date 17 patients have been recruited to sites in Hamilton, Toronto, London and Australia.

Neoadjuvant Combination of Atezolizumab/Bevacizumab Versus Neoadjuvant Radiation Therapy Prior to Hepatectomy in Hepatocellular Carcinoma with Portal Vein Tumour Thrombus (ADVANCE): Surgical resection is the usual treatment for most patients with solitary hepatocellular carcinoma (HCC). The presence of portal vein tumour thrombus (PVTT) is associated with a poor prognosis, and as a result, patients usually do not undergo surgery. In this trial, two experimental treatments are evaluated as neoadjuvant therapy to improve the surgical resection rate. Patents with HCC and PVTT are randomized to neoadjuvant atezolizumab, an

anti-PDL1 agent, for four cycles, and bevacizumab, an anti-VEGF agent, for four cycles or neoadjuvant SBRT. After completion of neoadjuvant therapy, those patients whose HCC tumour has responded will proceed to hepatic surgery. A maximum of 35 patients per arm will be entered. The arm with the highest resection rate will be selected for further study. The trial has been approved by Health Canada and it is anticipated that the first patient will be enrolled in January 2022.

Radiation Therapy Research in Breast Cancer

For many years, Dr. Whelan, an ECRI scientist who holds a Tier 1 CRC, has led a research program evaluating new radiation therapy regimens for the adjuvant treatment of women following lumpectomy or mastectomy for breast cancer. More recently he has evaluated the use of biomarkers to tailor radiation therapy approaches for early-stage disease. In many instances these trials have been conducted through OCOG, but on two occasions the trials have been conducted through the Canadian Clinical Trials Group at Queens. ECRI is fortunate to have such a distinguished researcher as a member. He is internationally recognized for his research and is one of the top radiation oncology trialists in the world. This program's progress between 2016-2021 is described below and in Table 7.

Table 7: Breast Cancer Radiotherapy Trials

Trial	Funding	Investigators	Intervention	Outcome	N/Target	Status
RAPID	CIHR	Whelan, Olivotto, Julian	38.5 Gy APBI in 10 fx, BID over 5 days vs WBI 42.5 Gy/16 over 21 days	Ipsilateral breast ca recurrence, cosmesis	2135	J Clin Oncol (8), Lancet (9)
LUMINA	CCSRI	Whelan, Bane, Parpia	Luminal A cohort + < 2cm+ > 55 years	Ipsilateral breast ca recurrence	500	Ongoing
MA39	CCTG	Whelan	Node + biomarker low risk randomized to regional RT or no regional RT	Recurrence, survival	500/2140	Ongoing
RHEAL	CCSRI	Whelan, Parpia	Node + randomized to regional Rads, 40 Gy/15 vs. 26 Gy in 5	Lymphedema, recurrence	50/588	Ongoing
OPAR	CBCF	Kim, Whelan	PBI 27.5Gy or 30Gy, both in five daily fractions	Cosmesis	284	Completed
RAPID II	CIHR	Whelan, Parpia	Node -, tumours < 3cm randomized to 26 Gy WBI/5 versus 26 Gy APBI /5	Ipsilateral breast ca recurrence, cosmesis	910	Ongoing
DUCHESS	Genomic Health	Rakovitch, Whelan	Oncotype DX Breast DCIS Score assay	Change in recommendation for RT	217	Breast Cancer Research & Rx (10)
ELISA	CIHR	Rakovitch, Whelan	DCIS Score assay + < 2.5 cm + age >45	Ipsilateral local recurrence	500	Ongoing

8-Year Results of a Multi-Centre Randomized Trial of External Beam Accelerated Partial Breast Versus Whole Breast Irradiation After Breast Conserving Surgery in Women with Ductal Carcinoma in Situ and Node-Negative Breast Cancer (RAPID): RAPID compared large doses of radiation per fraction (38.5 Gy in 10 fractions delivered twice per day over 5–8 days) to only part of the breast called accelerated partial breast irradiation (APBI) and standard whole breast irradiation (WBI) (42.5 Gy in 16 fractions once per day over 21 days) with the goal to improve convenience of treatment. Between 2006 and 2011, 2,135 patients were recruited from 43 sites in Canada and Australia. In 2014, an unplanned interim analysis at 2.5 years median follow-up demonstrated that APBI was associated with increased late radiation morbidity and adverse cosmetic outcome compared to the standard (8). In 2019, at a median follow-up of 8.6 years, the analysis showed that the cumulative rates of breast cancer recurrence were low in both groups and that APBI was non-inferior to WBI in preventing IBTR (9).

A Prospective Cohort Study Evaluating Risk of Local Recurrence Following Breast Conserving Surgery and Endocrine Therapy in Low-Risk Luminal A Breast Cancer (LUMINA): The aim is to use biomarkers to identify a group of patients after BCS who can be spared RT because the tumour is at very low risk of recurring. Women with breast cancer belonging to the Luminal A subtype based on positive hormone receptor and low Ki67 score which measures cell proliferation are eligible. Other clinical factors used to define the cohort include negative axillary nodes, age > 55 years, and tumour size < 2 cm. The cohort of 500 patients were enrolled between 2013 and 2017 are being followed. An analysis is to be performed at a median follow-up of five years which will occur at the end of 2021. If LUMINA confirms that women with Luminal A breast cancers are at very low risk of local recurrence, it is conceivable that as many as 25% of patients having BCS can avoid unnecessary RT.

CCTG MA.39 Regional Radiotherapy in Biomarker Low-Risk Node Positive and T3N0 Breast Cancer (TAILOR RT): In a previous CCTG trial (MA.20), led by Dr. Whelan, additional regional radiotherapy (RT) was evaluated in women with node positive breast cancer having undergone lumpectomy and proved to have a significant benefit in terms of disease-free survival and distant recurrence. Regional RT was associated with an increased risk of pneumonitis and lymphedema. Dr. Whelan is PI of the CCTG MA.39 trial which evaluates the need of regional RT in biomarker low risk node positive breast cancer. In this trial, patients with 1-3 positive nodes with estrogen receptor positive tumours and an Oncotype Dx recurrent score < 25 are randomly allocated to regional RT (to supraclavicular, axillary and internal mammary nodes and chest wall after mastectomy) or no regional RT following BCS or mastectomy. It is unclear whether patients with low-risk breast cancer need to receive regional RT. Some women may be getting RT who do not need it and are exposed to the side effects of their treatment without benefit.

Randomized Trial of Hypofractionated Loco-regional Radiotherapy in Breast Cancer and Lymphedema (RHEAL): Regional RT is standard therapy following mastectomy and increasingly being given post-lumpectomy in women with node positive breast cancer. The major concern with regional RT is the occurrence of lymphedema which can be as high as 20%. In the past, women with node positive breast cancer who required radiotherapy to the regional nodes after lumpectomy or mastectomy were treated with 50 Gy in 25 fractions over five weeks. The RHEAL trial compares a current standard approach for local regional therapy (40 Gy in 15 fractions) with a hypofractionated approach (26 Gy in 5 fractions) for regional therapy in

women with node positive breast cancer. The primary outcome is lymphedema. The first patient was enrolled in February 2021, and to date 60 of 588 patients are enrolled.

Accelerated Partial Breast Irradiation Given Once-a-Day (RAPID II): Currently, the majority of women with early-stage breast cancer following BCS are treated with WBI once daily over three weeks. Recently, based on results of a single trial from the UK and the COVID-19 pandemic, radiation oncologists, including those in Canada, have switched to only five days of WBI with larger daily doses of RT. However, there is some data to suggest that 4-5 treatments of WBI are associated with increased chronic toxicity to the breast tissue, e.g. shrinkage, and fibrosis, and worse long term cosmetic results. It is postulated that the worst cosmesis seen in RAPID was related to the twice a day fractionation. In the OPAR Phase II randomized trial, Drs. Kim and Whelan compared two partial breast irradiation regimens given once per day which were shown to be safe and effective. Building on this experience, Drs. Whelan and Parpia were recently funded by CIHR to conduct a trial in women with node negative breast cancer and tumours < 3cm who have undergone BCS comparing 26 Gy WBI/5 fractions and 26 Gy APBI/5 fractions. For the proposed trial, it is hypothesized that PBI will be associated with a non-inferior local recurrence rate but less toxicity and better cosmesis than WBI.

*Evaluation of the Duc*tal *Carcinoma in Situ (DCIS) Score for Decisions on Radiotherapy in Patients with Low/Intermediate Risk DCIS (DUCHESS)*: WBI is commonly given following BCS for women with DCIS to reduce the risk of local recurrence. The DUCHESS cohort study evaluated the use of the biomarker Oncotype DCIS score at the point of care in 217 women with DCIS following BCS. The study showed that physician's prediction of local recurrence following BCS varied widely and that the Oncotype DCIS score appeared to provide more reliable estimates of risk of local recurrence. The use of the score led to less use of RT following BCS and was well accepted by physicians and patients (10). This has led to a new trial called ELISA funded by CIHR, which will prospectively evaluate omission of RT in patients deemed at low risk based on the Oncotype DCIS score and other clinicopathological factors.

Palliative Care

The ECRI palliative care research program continues to strengthen. Palliative care is defined as an approach to care that improves the quality of life for patients facing serious illness and their families. It includes pain and symptom management and relief from psychological spiritual and social issues. Research has shown that despite the benefits of early integration of palliative care, most patients get palliative care very late in the cancer trajectory or not at all. This means many patients are not receiving optimal care and potentially requiring unnecessary hospitalizations and excess healthcare costs at end of life.

ECRI member, Dr. Seow, is an international leader in palliative care research. He holds a CRC Tier II in Palliative Care and Health System Innovation. His program of research focuses on interventions that increase access to palliative care, especially in the home and community, and improve patient and family experience. His research has been used to inform decision makers to change policy, healthcare providers to change clinical practice, and patients and families to change their illness experience. He has collaborated with many ECRI scientists in various research projects (Table 8).

Table 8: Palliative Care Studies 2016-2021

Study	Funding	Investigators	Other McMaster Departments	Outcome	Status
CAPACITI	CIHR	Seow, Pond, O. Levine	Social Work, HEI, Division of Palliative Care, Primary Care	Earlier identification and more access to home-based palliative care	Ongoing
CAPACITI-FN	ISC (Indigenous Services Canada)	Seow	Indigenous Health Learning Lodge	Culturally appropriate community intervention	Ongoing
Communication Training for Serious Illness in Cancer	JCCF	O. Levine		Education modules for communication skills in serious illness	Ongoing
ARCC	CCSRI	Seow, Mian, Schnarr	Gynecology, Surgery	Quality indicators for end-of-life care with patient reported outcome	JCO Oncology Prac (11) Current Oncology (12) PLOS One (13) BMJ Open (14)
PROVIEW	CIHR	Seow, Juergens, Mian, Saha	Biostatistics, Patient Engagement	Patient-family predictive e-tool for survival, function, and symptoms	JAMA Network Open (15) Palliative Medicine (16)
Waiting Room Revolution	JCCF	Seow, Winemaker, Juergens, Ellis, Slaven, Bryant-Lukosius	Division of Palliative Care	Education for patients and families	Ongoing

Increasing Access to Community-Based Palliative Care

Palliative care education: CAPACITI (Community Access to PAlliative Care via Interprofessional Teams Intervention) is an education program for primary care providers. Over three modules (12 webinar sessions), it provides them with tools and practice supports to increase access to home-based palliative care for patients with advanced illness. CAPACITI is being evaluated using a cluster randomized trial. Primary care teams across Canada are recruited and randomized to receive the facilitated training with applied activities (intervention) vs. self-directed access to the educational materials only (control). The outcomes are increased access for patients, earlier initiation palliative care, increased provider knowledge and interprofessional collaboration. The trial is unique in that it moves from clinical symptom education to operationalization of an early palliative care approach, focused on process and behavior change. In 2020, the non-randomized pilot intervention recruited 27 teams (154 providers) from Ontario: the results showed an increase in identification of patients requiring palliative care, improved confidence and team collaboration. Collaborating with Pallium Canada, the RCT cohort began in November 2021, and has recruited 73 team (210 providers) across 10 provinces.

In January 2021, the First Nations (FN) and Inuit Health Branch of Indigenous Services Canada funded Dr. Seow and team to adapt the CAPACITI intervention to FN communities in Ontario.

The aim is for the CAPACITI curriculum to be adapted and co-designed with communities serving Indigenous populations across Ontario. The end result is to develop a culturally-relevant, effective and scalable program to increase access to early palliative care supports in FN communities and ultimately to support FN individuals living with serious illness, like cancer, at home. The project has already recruited 18 FN providers from diverse communities to help co-design the materials starting in 2022.

Communication Training: ECRI member Dr. O. Levine is the HHS site lead for conducting Serious Illness Conversation training at the JCC in 2020. This work has led to his obtaining funding for a project examining virtual strategies for teaching communication skills specific to improve communication around advancing illness, early palliative care and advance care planning in oncology in 2021. The project will develop a curriculum that will be tested in oncology residents and medical and radiation oncologists from various disease-site groups. The goal is to change clinician behavior, improve communication skills and improve patient/family outcomes, such as reduced anxiety. These combined research projects show that palliative care education and clinical skill-development is a robust research program.

Population-based Research: Several ECRI researchers use administrative data to measure and advance palliative care quality indicators. System-level palliative care quality indicators are lacking, which limits system-level targets for improvement. Dr. Seow, along with co-investigators from across the country have validated cancer quality indicators about unnecessary acute care use at the end of life using administrative data to produce national standards (11-14). For instance, one indicator is the percent who received physician visits at home and/or palliative home care services in their last 90 days of life. As a result of this research, these quality indicators have been adopted by Health Quality Ontario and the Canadian Partnership Against Cancer. In Ontario, these indicators are reported quarterly to regional teams as targets for health system improvement and as accountability measures to the MOHLTC since 2018. This program of work has been renewed for additional funding to look at cancer-specific quality indicators such as within lymphoma, colorectal cancer and uterine cancer, working closely with ECRI researchers Mian and Schnarr.

Improving Patient and Family Experience

Predictive tools using patient-reported outcomes: Early integration of palliative care with active cancer treatment can improve quality of life, symptom control and survival. Dr. Seow, working with other ECRI scientists (Juergens and others), developed an online tool, called PROVIEW, to support early integration of palliative care supports. Specifically designed for patients and families. It uses information they have access to (such as their cancer type, stage and symptoms today) to predict the likelihood to have high symptom burden or decreased function in the next six months. The tool can also predict survival. (www.individualizedhealth.ca/proview-tool) (15,16). PROVIEW provides changing survival and symptom predictions as the disease progresses over time, which aims to support discussions about integrating palliative care alongside disease-modifying therapies. Furthermore, cancer-specific adaptations for PROVIEW have been proposed in the disease sites of multiple myeloma (Mian) and breast cancer (Saha). Cancer-specific PROVIEW tools will provide more accurate and relevant information to patients by incorporating biomarkers, immunology treatment, etc. The tools will be tested by clinicians

and patients at the JCC and other cancer centres for impact to patient decision-making and outcomes.

Education for patient-family empowerment: As part of an education initiative, ECRI scientists Seow, Slaven, Bryant-Lukosius, Ellis and Juergens worked together to recruit lung cancer patients and their caregivers to discuss the acceptability of information about early palliative care interventions. The qualitative interviews revealed the need for supports, but a barrier to language and terminology of palliative care. The results reinforced learnings from interviews conducted by palliative care clinician, Dr. Winemaker, with her patients dying at home. Drs. Seow and Winemaker took their learnings and developed a healthcare podcast targeted at patients and families to enable them to discuss a palliative care approach earlier in the trajectory, without having to label the approach palliative care (17). The podcast, called the Waiting Room Revolution (www.waitingroomrevolution.com) interviews clinicians, palliative care experts, policymakers, healthcare providers, patients and families. It has interviewed ECRI members: M. Levine (breast cancer), Juergens (Lung Cancer Canada), Mian (Myeloma Canada), as well as developing new collaborations nationally and internationally, such as with Palliative Care Australia, Dying Matters UK and Stanford Centre for Palliative Care in the US. It has been ranked in the top 2.5% of global podcasts, as rated by ListenNotes.com, and reached 30,000 listeners in its first six months of launching.

UNIQUE FUNCTIONS OF ECRI

Incubator of New Ideas

ECRI is an incubator of new emerging ideas. It applies its expertise in research methodology, builds on the collective research experience, and reaches out to contacts to help researchers identify and formulate the right question to address a clinical problem, to design the appropriate study for that question, and then execute the study. The ECRI seminars serve as a vehicle for researchers to present their ideas and receive feedback. We will discuss three examples of research that are in the incubator category. Survivorship has been in the research menu of ECRI since before 2016. It is an example of a research area that started off in the incubator phase and has been evolving slowly but steadily; it is not yet considered a program of research. Digital Health, including Virtual Care and Remote Access Learning (RAM) and Building a Breast Cancer Learning Health System (LHS), are relatively recent exciting additions to the research agenda and offer much promise for the future.

Survivorship: Models of care in survivorship and survivorship outcomes remain two major theme areas of Dr. Sussman's research. While he did step down as provincial survivorship lead in 2017 when he took on the role of Chair of the Department of Oncology, he has maintained the role of senior advisor to the OH CCO survivorship program. In 2019, he was the senior author on a provincial policy document that provided a framework for models of follow-up care, including a specific focus on transition to primary care when appropriate. He continues to work with colleagues at the provincial cancer agency to develop risk stratification models to inform follow-up and in 2020 received a grant from ARCC (Applied Research in Cancer Control) to model risk profiles of breast, colorectal and prostate cancer survivors. This study, involving a cohort of over 100,000 cancer survivors will identify the demographic, treatment and symptom factors associated with care transitions that can be considered in designing and testing risk stratification

approaches to cancer survivorship follow-up. These findings will inform the development of an intervention to more systematically identify survivors who should be considered for transition to primary care.

To complement this work Dr. Sussman was successful in obtaining a subgrant from within the CIHR CANIMPACT (2021) to conduct a local descriptive study of over 2,500 transitioned cancer survivors at the JHCC to identify factors associated with transition and return to oncology after transition. This study also includes a qualitative component using a series of focus groups with oncologists, family physicians and patients to understand their perspectives on risk stratification and explore the feasibility of a more systematic approach to identifying candidates for transition to primary care.

While the COVID-19 pandemic caused an abrupt and significant interruption in many research activities. The need for evidence to inform the development and implementation of virtual care approaches became a significant priority for cancer care systems. In response to this need, Dr. Sussman co-led the development and conduct of a rapid systematic review of virtual care in cancer this year that is being used by OH-CCO to develop virtual care guidance for implementation of virtual care platforms into the future .

Over the next two years, Dr. Sussman plans to work with Dr. Saha, a data scientist who recently was recruited as the BRIGHT Run Chair, to model risk profiles in breast cancer survivors using existing curated datasets. This work will inform the development of an intervention designed to provide real time notification to clinicians of the optimal approach to follow-up care within their survivor populations. The resulting work is expected to improve the quality, efficacy and effectiveness of survivorship care for all survivors.

Surgical Oncology: Dr. Simunovic is a surgical oncologist with expertise in colorectal cancer. He was the first general surgeon to be a member of ECRI. The goal of his research is to improve the outcomes of patients with colorectal cancer undergoing surgery by focusing on the processes of surgical care. His research blends the methods of classic health services research, use of administrative data and clinical trials with quality improvement. His studies have evaluated factors that could improve the quality of surgery and thus improve patient outcome, e.g. surgical margins, the importance of a multidisciplinary tumour board and safety.

Dr. Serrano is a surgical oncologist with expertise in hepatobiliary cancers. The overall goal of his research plan is to improve the long-term outcomes of patients with hepatobiliary cancers undergoing surgery by identifying new therapeutic regimens that can work in parallel with surgery, to decrease recurrence and improve survival. He is currently finetuning his skills in clinical research methods by pursuing a PhD in clinical epidemiology in the Department of Health Research Methods, Evidence and Impact at McMaster University. He has performed a series of clinical trials and accompanying exploratory studies, aimed at improving accrual to clinical trials in patients undergoing cancer surgery. Dr. Serrano has demonstrated strength as a collaborative surgical member of ECRI in multidisciplinary research. He is working with Drs. Meyers (medical oncologist) and Swaminath (radiation oncologist) in the ADVANCE trial in patients with hepatocellular carcinoma (HCC) and portal vein thrombosis. In this trial novel

neoadjuvant approaches, immune check point inhibitors and SBRT are being studied as neoadjuvant therapy in HCC.

Dr. Parvez is an ECRI Young Researcher who recently joined the Department of Surgery. She is a breast cancer surgical oncologist. During her fellowship at the Jewish General Hospital in Montreal she successfully applied for and received a CIHR grant for a trial to evaluate the omission of radiation therapy following a complete response to neoadjuvant chemotherapy in patients with breast cancer. She recently commenced research examining the association between immigration status and breast cancer survival and quality of care outcomes using provincial administrative data. In addition, she will conduct a qualitative study examining the experience of immigrant women with breast cancer with particular focus on perceived bias.

Virtual Care (VC) and Remote Access Monitoring (RAM): Virtual care allows healthcare providers to remotely interact (tablet, telephone) with patients. The COVID 19 pandemic caused a rapid switch to virtual care in the JCC, mostly through the telephone. At one point, approximately, 70% of visits to the JCC were virtual. Prior to the onset of the pandemic, researchers at HHS Hamilton General and PHRI, Drs. McGillian and Devereux, started pioneering research in virtual care and RAM in patients who had undergone cardiac surgery or general surgery. RAM technology remotely captures patients' biophysical data (e.g. blood pressure, weight) and transmits these data to clinicians so that they can intervene, as needed (18). As part of the RAM intervention, they added an Android tablet which facilitates two-way daily communication between the patient and clinicians.

Cancer patients have complex needs, which are often not met. Virtual care could potentially play a role in addressing gaps in care. Dr. Levine has begun a collaboration with Drs. McGillion and Devereaux. The first study involves SMArTVIEW technology in patients with non-small lung cancer (NSCLC). The study is an adaptation of the perioperative SMArTVIEW model and is supported by a grant from Roche. NSCLC patients are often elderly and are treated with chemotherapy with or without radiation. They experience side effects of treatment and symptoms from the cancer. In contrast to peri-operative patients, NSCLC patients do not improve over time; rather, their condition deteriorates. They have many needs and often visit the ED or are hospitalized (19). Phase I (user testing), which involves training participants (patients and nurses) on how to use the Phillips system started in December 2021. In Phase II, a prospective pilot trial will be conducted where advanced NSLC patients will use the SMArTVIEW system while undergoing therapy. Outcomes will include compliance with VC-RAM and ED visits. Dr .Amaris Balitsky, a ECRI Young Researcher, has taken a lead role in this project. A multicentre RCT comparing this intervention to usual care is planned for the future. Trials will then be expanded to other high risk cancer patient groups, e.g. hematology transplant patients and breast cancer patients receiving chemotherapy. Finally, we plan to conduct studies of RAM and virtual care for patients in the survivorship phase. For each area, we will follow the same steps: user testing, pilot cohort study and multicentre RCTs in Canada.

VC-RAM is a high priority area for HHS. The new collaboration for VC-RAM research in cardiac surgery, peri-operative care and oncology is exciting. There are two recent developments which will help foster the collaboration. The research requires centralized operational infrastructure to allow the conduct of multiple VC-RAM studies, simultaneously,

with centralized oversight of populations being monitored. Based on these considerations, Drs. McGillion, Devereaux and Levine applied to CFI for funding ($ 2 million) to construct a VC-RAM command centre which will be located on the fourth floor of the JCC. The application was successful, and construction will be starting soon. Recently, the trio received funding ($1 million annually for 10 years) for the VICTOR project which will support the VC-RAM research.

Building a Learning Health System: Information is key to the delivery of quality cancer care in our rapidly changing healthcare system. Frontline physicians need reliable and timely information on treatments that they administer daily, and the associated impact on patient outcomes such as tumour shrinkage, symptoms, side effects and quality of life. This information was recognized by the Institute of Medicine (IoM) when they described the Learning Healthcare System (LHS); a continuous cycle or feedback loop in which scientific evidence informs clinical practice, while data gathered from clinical practice and administrative sources inform care and scientific investigation (20). In reality, the latter part of the loop is missing, and clinicians do not have timely information to know whether their patients have optimal clinical outcomes. Existing methods of capturing patient experience and outcome data (e.g. administrative databases, chart reviews) have limitations. In addition, those who oversee the cancer system have difficulty knowing whether practice is consistent with the most up-to-date treatment guidelines, and how care compares between regions. Finally, in a time of limited resources, such information is important to system planners.

In recent years there has been much enthusiasm for the electronic health record (EHR), which collects patients' electronically stored health information in a digital format. The EHR is a treasure trove of health information and is a rich natural resource that can be tapped. Although some progress has been made, the potential value of EHRs has yet to be fully realized. EHRs could provide insights into real world patient experiences and outcomes but are difficult to tap into for their data.

In 2016, HHS and IBM Canada formed a strategic alliance. Dr. Levine saw an opportunity to investigate whether artificial intelligence (AI) could be used to extract data on a breast cancer patient's treatment and clinical course. In a pilot project using IBM Watson technology, Dr. Levine and colleagues demonstrated that the clinical course of patients with Stage III breast cancer could be characterized (21). Unstructured data from the EHR was interrogated using natural language processing (NLP), a type of AI. The following information was captured: tumour characteristics, stage at presentation, treatments received and outcomes (e.g. recurrence, death, toxicity and QOL) up to two years from diagnosis. These combined elements were used to describe the patient's journey. Although the results of the study were preliminary, they demonstrated that the hospital had the necessary data to build a view of the patient journey and that it was possible to extract, read and combine this data in a way that helped unlock the potential value and derive insights for clinical decision-making. This project was funded by Roche Canada ($600,000).

The results of the pilot study provided poof of principle. The next step was to scale up the patient population to a large cohort of patients with all stages of breast cancer. Dr. Levine

teamed up with Dr. Jeremy Petch from HHS CREATE and Pentavere, a company that specializes in NLP. A platform which includes a cohort of 3,000 breast cancer patients seen at the JCC between 2015 and 2017 has been created. NLP will be applied to the patient notes, imaging reports and pathology reports to extract the information on the clinical course of the patients' disease. Currently the validation phase of the study is occurring. A very unique feature of the work is that every new breast cancer patient presenting to the JCC will automatically be enrolled in the cohort. The project is funded by Roche Canada ($400,000).

The focus on the EHR as a source of patient outcome data is a key step in the evolution of DH. Once the platform is established, there will be the opportunity for the new BRIGHT Run Breast Cancer Learning Health System Chair, Dr. Saha, to interrogate the data using machine learning to discover insights into prognosis and care.

Hub for Mentorship of Young Researchers

Many of the clinical oncologists recruited to the McMaster Department of Oncology and HHS in oncology specialties have undergone research training following completion of their clinical training. Although many aspire to have a successful research career as an independent investigator, most do not succeed. The first five years after completion of a research fellowship are critical formative years in the development as a clinician investigator. Mentorship, a critical mass of like-minded researchers, and protected time are important factors for research success.

ECRI plays an important role in the development of young researchers by providing them with a nurturing environment for continued research development. Currently, ECRI has 11 individuals in the category of Young Researcher (see Table I). ECRI senior researchers provide mentorship, i.e. they help the young researcher define the right scientific question and write grants and papers. ECRI provides the young researcher with infrastructure. For example, they have access to OCOG biostatisticians and clinical trialists who are faculty within the Department of Oncology and research assistants. Similarly, the health services research scientists provide infrastructure through the ICES McMaster Hub and Supportive Cancer Care Research Unit. The development of young researchers follows two models. In the first, the researcher is on track to develop an independent research program. They are already working on several projects which are related. They are serving an apprenticeship with one of the senior ECRI scientists. Such individuals are on a trajectory to become independent clinical investigators. The second model is where the clinician researcher has completed a research fellowship but is not developing an independent program of research. They may have a burning question to address. In this situation ECRI can provide the "space" and environment to develop a research protocol, seek funding and carry out the study. ECRI members come together as a team to help the young researcher address their research question.

ECRI Young Investigators

Dr. O. Levine: Enabling Person-Centred Communication around End-of-Life Care in Oncology

Oren Levine is an Assistant Professor in the Department of Oncology and a medical oncologist with clinical expertise in gastrointestinal malignancies and breast cancer. The clinical/health system problems his research addresses are: 1) communication training for person-centred care

for patients and families with advanced cancer diagnoses, 2) evaluating electronic learning in oncology, and 3) early integration of a palliative approach to care in oncology for patients with advanced cancer.

His initial studies were related to code status communication training in postgraduate oncology programs. He conducted a national survey among medical oncology and radiation oncology residents. The results showed that residents often found themselves in urgent situations leading code status discussions with patients and families but had received little formal teaching or evaluation in this area. Residents indicated a desire for more training in this skill. Accordingly, Dr. Levine developed an intervention to enhance residents' communication skills on code status. The intervention was based on a novel conceptual framework called PULSES, which is a six-step approach to code status discussion (Prognosis, Underlying values, Long-term outcomes of resuscitation, Short-term outcomes of resuscitation, Educated recommendation and Summarize and document). He then conducted a multicentre randomized trial evaluating the effect of a workshop teaching the PULSES framework. The results showed that PULSES training improved performance among oncology residents for code status discussions in simulated patient encounters. When surveyed, participants recommended the PULSES training to other oncology residents, and many reported applying the PULSES framework in their clinical work.

Dr. Levine is the clinical lead for implementation of the Serious Illness Care Program (SICP) at the JCC. SICP is a multicomponent communication intervention that aims to build capacity among oncology healthcare providers to have more frequent, earlier and more person-centred conversations about goals of care with patients facing life-limiting illness. Dr. Levine is conducting a number of scholarly projects from the SIC implementation at JCC: 1) validation of virtual SICP training, 2) a qualitative project exploring optimal trigger criteria for SIC through interviews with SICP-trained clinicians, and 3) evaluation of quality of written documentation of goals of care in the medical record. This work is supported by an education grant for SICP implementation work from the JCC Foundation.

Dr. Levine's work in code status communication through PULSES and goals of care through SICP come together in the RESTORED study (Remote Education Strategies Teaching Oncology Residents skills for End-of-life Discussions). This study is supported by a grant from the McMaster FHS Education Scholarship Fund. Cancer is a devastating illness and difficult conversations are commonplace in oncology practice. Oncology residents express a desire for more training in difficult conversations. Currently, communication training is limited, and educational resources are variable. There is a need for a more comprehensive communication curriculum addressing key topics including breaking bad news, goals of care discussion, transitioning away from active cancer treatment and code status. Dr. Levine is conducting a study that is addressing this need. He is developing a curriculum for critical conversations in oncology using electronic learning modules (ELMs) and virtual standardized patient (SP) encounters. Their feasibility will be tested and then evaluated in a randomized trial.

Dr. Aly-Khan Lalani: Translational Research in Genitourinary Malignancy

Dr. Lalani is an Assistant Professor in the Department of Oncology and a medical oncologist with clinical expertise in genitourinary malignancies. His passion is translational research related to novel therapies in kidney cancer.

He is principal investigator of a randomized trial called, "Cytoreductive Stereotactic Hypofractionated Radiotherapy with Combination Ipilimumab/Nivolumab for Metastatic Kidney Cancer (CYTOSHRINK): a Randomized Phase II Study". Along with a team of ECRI investigators (Swaminath, Hotte, Pond) and OCOG, he designed the trial and obtained an investigator-initiated grant from Bristol Myers Squibb to conduct the multicentre trial. Patients with metastatic renal cell carcinoma (mRCC) are usually treated with immunotherapy consisting of ipilimumab plus nivolumab (I/N). Both agents are check point inhibitors. In the past, cytoreductive surgery was done for patients with mRCC. Based on the results of recent research this is no longer the case. Stereotactic body radiotherapy (SBRT) delivers large doses of radiation to a very small, focused area, thereby minimizing radiation exposure of normal surrounding tissues; thereby limiting toxicity. The JCC is a Canadian leader in SBRT. In the CYTOSRHRINK Randomized Phase II Trial, patients with mRCC receive either SBRT to the cancer plus I/N or I/N alone. The primary outcome is progression-free survival. The SBRT may play a key role in not only providing a convenient cytoreductive effect on the primary kidney lesion but may also create an additional abscopal effect that could lead to enhanced off-target immunotherapeutic response. The trial commenced in March 2020 and 17 patients have been enrolled. Four centres in Ontario and one in Australia are currently participating. The target sample size is 78.

The CYTOSHRINK randomized design provides an exciting framework to evaluate potential biomarkers that can predict response to immune therapy. Dr. Lalani designed a companion correlative biomarker study where biomarker collection is embedded in the trial design. Blood and stool samples are collected at baseline and on trial therapy. Changes in circulating blood biomarkers, e.g. including cytokines, germline and circulating free DNA, and peripheral blood mononuclear cells and the gut microbiome will be assessed and contextualized with baseline tumour tissue samples using nano string technology. Drs. Lalani, Bramson and team have secured a grant from BioCanRx – which is a Network of Excellence funded by the Government of Canada to support the correlative study.

Dr. Lalani is very interested in the gut microbiome and its role in the host response to immune checkpoint blockade for mRCC. The microbiome is the genetic material of all the microbes (bacteria, fungi, protozoa and viruses) and their environment that reside within the human body. The microbiome is essential for human development, immunity and nutrition. Recently, the composition of gut microbiota has been shown to influence the anti-cancer response to immunotherapy. Bacteria lining the gut play a role in immune cell function, mucosal barrier function, inflammation and cellular metabolism – both locally and systemically. Dr. Lalani established a partnership with Dr. Surette from the Farncombe Family Digestive Health Research Institute at McMaster University, which has optimized state-of-the-art RNA-based and metagenomic sequencing techniques required for microbiome characterization. In a pilot study, serial stool samples are being collected from patients with mRCC who are receiving

immunotherapy with check point inhibitors. Samples are sent to Dr. Surette's lab and will be processed for microbiome analysis using the 16S ribosomal RNA-based technique platform. These microbial signatures will be contextualized with clinical outcomes using bioinformatics. The overall aim of the pilot feasibility study is to develop a greater understanding of the mechanisms of interplay between the host microbiome and anti-tumour immune response in mRCC patients. Dr. Lalani secured funding to support this study in part through a JCC Foundation Grant.

Dr Hira Mian: Multiple Myeloma: Optimization of Care

Dr. Mian is a hematologist with expertise in the treatment of malignant disorders of the blood. Her major research interest is in multiple myeloma (MM) which is a cancer of plasma cells. It is a disease of older patients with a median age of 70 years at diagnosis. The median overall survival of MM patients ranges between 5-10 years, although there is substantial variation depending upon disease and patient specific factors. As MM is considered "incurable", the goal of treatment is to control the cancer while maintaining good quality of life throughout the disease course.

Although there has been tremendous progress in MM treatment including the availability of many novel therapies, recent data shows that as many as 50-75% of "real-world" patients are ineligible for MM clinical trials based upon narrow inclusion criteria. Dr. Mian's research program is called "Multiple Myeloma-Optimizing Care of Patients (MM-OPT)". The aims are to optimize and improve outcomes among MM patients in the setting of usual clinical practice. She plans to achieve this objective with a two-pronged attack. First, by identifying variations in presentation, symptoms, outcomes and treatment among different subgroups of patients with MM. Second, by optimizing risk stratification based upon frailty assessment and testing strategies to address any identified gaps in care.

Dr. Mian uses administrative databases to study outcomes of MM patients. In one of her first studies, she used ICES population-based data to conduct a longitudinal study to examine symptom trajectory and to determine factors associated with symptom burden in the first year following diagnosis among transplant-ineligible adults with MM receiving treatment between 2007-2018 in Ontario. The study was funded by the JCC Foundation. One year following diagnosis there continued to be a substantial burden of symptoms, with over 25% of the cohort reporting moderate/severe levels of each of the following symptoms: tiredness, impaired well-being, pain, drowsiness and loss of appetite. Additionally, whereas physical symptoms such as pain improved over time, psychosocial symptoms of anxiety/depression showed minimal improvement with generally flat scores. Furthermore, there was a difference in treatment patterns and outcomes in older patients. This stimulated her research interest in geriatric oncology. She is currently leading a multicentre prospective study evaluating the changes that occur in frailty over time among MM patients during treatment. Dr. Mian hopes that with better risk stratification, additional strategies/interventions can be devised for optimizing outcomes among this group.

Furthermore, based upon previous administrative database work conducted by Dr. Mian, she hypothesized that a possible reason for poorer outcomes in older patients with MM was poor

compliance with taking anti-MM medications. To this end she designed and is conducting a randomized trial evaluating a comprehensive strategy to improve compliance with oral chemotherapy in MM. The trial is supported by a grant from the HHS New Investigator Fund.

She submitted a project grant to CIHR in March 2021. This is an accomplishment given that she is a junior investigator and the relatively short time she has been a member of Faculty. The proposal to CIHR is about a unique population of patients with hematologic malignancies; those with non-curable malignancies such as MM. Their clinical course is typically protracted with variation in the symptom burden, but the disease is ultimately fatal. Treatment decision-making can be challenging given the different illness trajectories. The underlying premise of her research is that providing patients and their families with accurate information on both survival and disease-related quality of life (QOL) during the illness trajectory will improve patient/physician shared decision-making leading to improved utilization of palliative care. Her co-applicant in the project is Dr. Seow. She currently has an early career award from HHS which allows for protected time and additional resources to further build her research program.

Dr. Amaris Balitsky: Virtual care and Remote Monitoring

Dr. Balitsky joined the Department of Oncology as a faculty member in July 2021 after having completed a research fellowship in ECRI. She is a hematologist with methodology training in the HRM. She conducts health services research and is currently refining her research focus. She is conducting a cohort study in patients undergoing CAR-T cell therapy at the JH. Patients are having blood collected for biomarkers and completion of QOL questionnaires and PROs. She is playing a leading role in the introduction of virtual care and remote monitoring in the JCC. Virtual care has not only affected patients, but it has had an impact on physicians too. Dr Balitsky has developed an instrument to measure physician outcomes with virtual care, e.g. satisfaction. This is relevant because when various virtual care interventions are evaluated in clinical trials, it will be important to measure both patient and physician centered outcomes.

Dr Tobias Berg: Translational Research in Acute Leukemia

In 2019, Dr Berg was appointed the inaugural Boris Family Chair for Leukemia and Hematopoietic Stem Cell Research. He is developing a leukemia and stem cell research program with a focus on translational research. Dr. Berg has faced two challenges within the first year of his appointment. The first, was the decision by the University to dissolve the Stem Cell and Cancer Research Institute, where his lab was to be situated. The second challenge arises from the current pandemic and the sudden ramp down of laboratory activity in March 2020. Despite these challenges, Dr. Berg has made significant advances in the establishment of his research program: developing infrastructure, training programs and research collaborations that have put him on a solid course for success. He is Head of the HHS McMaster Research Cancer Stem Cell Bank, a unique biobank that is longitudinally collecting viable cell samples from patients with AML and other hematological malignancies for functional studies in collaborating laboratories within the university. The current focus of his research is on identifying determinants of treatment response in Acute Myeloid Leukemia (AML). AML is the most common form of acute leukemia in adult patients and at the same time an important oncological model disease where many important paradigms in the treatment of cancer have originally been identified. In

his laboratory, he is implementing Minimal Residual Disease (MRD) detection techniques using both multi-parameter flow cytometry as well as molecular diagnostics. One target that Dr. Berg is working on in this context is the histone-methyl transferase LSD1 that has previously been identified as a promising target in AML. Dr. Berg has been successful in obtaining infrastructure funding from the Canadian Foundation for Innovation (John R. Evans Leaders Fund), and the Ontario Research Fund. He recently received an OICR Clinical Translation Pathway Award.

Dr Ashirbani Saha

Dr Saha is a data scientist with expertise in artificial intelligence (AI) and machine learning. She has a PHD in computer engineering and she is the inaugural McMaster BRIGHT Run Breast Cancer Learning Health System Chair. Her research will impact local breast-cancer screening, diagnosis, treatment and outcomes. She will open the door to applying AI, one of the most exciting new frontiers in cancer research, into ECRI research. She will use AI to analyze information in ways aimed at helping breast cancer patients. Ashirbani will be part of a multidisciplinary team of researchers. She will bring us new ideas and will stimulate other researchers to think even more broadly and boldly.

COLLABORATIONS

Within Hamilton

McMaster

There are linkages developing in translational research between ECRI clinicians and basic scientists at McMaster. Dr. Lalani is conducting the CYTOSHRINK trial in patients with renal cell cancer. They are receiving immunotherapy with PDL1 inhibitors. Blood samples are sent to the Bramson laboratory in the Immunology Research Centre for biomarker analysis. In addition, stool samples are sent to the Surette Laboratory for microbiome analysis.

Dr. Seow is the Director of the ICES-McMaster site. In the past five years he has used ICES databases to advance his programs of research around community-based palliative care, opioid use and cancer-related pain, patient-reported outcomes in cancer patients, and predictive machine learning tools for cancer. Moreover, he has worked with several Department of Oncology faculty to publish research in cardio-oncology (Kavsak), multiple myeloma (Mian), uterine cancer and imaging (Schnarr), thoracic radiotherapy (Swaminath), and cancer survivorship (Sussman). He has also been involved in several cancer-related graduate student projects using ICES data, including on sarcoma (Bozzo, MHS), colorectal cancer surgery (Bogach, MHS), social determinants and uterine cancer outcomes (Helpman, MPH), machine learning and cancer outcomes (Cygu, PhD), survivorship (Cerasuolo, PhD), and adolescent and young adult cancer (Rae, PhD).

Currently, the ICES-McMaster site supports 14 ICES scientists affiliated with McMaster, 52 additional investigators and 25 students/trainees. It has 117 active projects from across the University.

Hamilton Health Sciences

There are linkages established between ECRI and the Population Health Research Institute (PHRI). This started with a collaboration between Drs. Dhesy, Leung and Kavsak in cardio-oncology. Biomarker studies for cardiac damage were studied in breast cancer patients receiving anthracycline chemotherapy and Herceptin. This study was led by Dr. Dhesy. Subsequently, a pilot study was conducted in breast cancer patients receiving Herceptin to prevent reduction in left ventricular ejection fraction. Drs. Devereaux and McGillion from PHRI are collaborating with Dr. Levine in the area of VC and RAM. They applied for and received a John R. Evans Leadership fund grant from CFI to create infrastructure for a command centre. They have also received $10 million ($1 million per year) in operational funds from the HHS Research Institute Foundation for the VICTOR Program to conduct studies in virtual care and RAM.

A collaboration has been established between ECRI and CREATE. CREATE is the centre for data science and digital health at HHS. CREATE is a hub of innovation in HHS and is lead by Dr. Petch. This group is staffed with experts in AI, data sciences and software engineering. CREATE will help clinicians produce information technology solutions that can raise the quality of patient care and improve medial outcomes.

Regional Thromboembolism Program

Over the years Jim Julian and Sameer Parpia established a strong research collaboration with Dr. Clive Kearon and the regional thromboembolism program. They conducted a series of trials evaluating d-Dimer. The most recent one was published in the New England Journal of Medicine (22).

<u>Outside of Hamilton</u>

ECRI has linkages with organizations outside of Hamilton. The Canadian Cancer Clinical Trials Group (CTG) is an academic trials group that coordinates cancer clinical trials across Canada. ECRI investigators have chaired CTG committees, e.g. Whelan (breast cancer), Juergens (lung cancer), Wright (Data Safety Monitoring Committee) and Drs. Parpia and Julian have been members of the DSMC.

ECRI has a relationship with OICR. Greg Pond was appointed a Senior Investigator by OICR based on his varied contributions, including being the co-lead of the Biostatistics Training Initiative from 2016-2021, which had as its mission to help train the next generation of biostatistical researchers working in oncology within the province of Ontario. He is also a member of the executive committee for the Window Of Opportunity (WOO) program and provides formal and informal guidance on selected research studies conducted through the Translational Research program, and training sessions through the OICR Rising Stars Network. Dr. Wright has participated on the Ontario Cancer Research Ethics Board. Dr. Juergens is a member of the Canadian Clinical Trials Network.

OCOG is collaborating with the Washington University School of Medicine in St Louis, Missouri to evaluate image-guided, endovascular therapy (EVT) in patients with deep vein

thrombosis. OCOG is the Data Coordinating Centre for two large US multicentre trials. The trials are funded by the NIH. In the ATTRACT trial (Julian, Kearon) patients with acute proximal DVT received catheter-mediated or device-mediated intra-thrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting. The aim was to prevent post-thrombotic syndrome. In the second trial, called C-TRACT (Parpia), imaging-guided iliac vein stent placement is being studied in patients with established disabling iliac-obstructive post thrombotic syndrome. To date, 126 patients have been enrolled.

ORGANIZATION

The organizational structure of ECRI is described in detail in the 2016 ECRI Renewal Document (Appendix II). ECRI's model of operation is collaborative, and its organizational infrastructure is relatively limited. The Scientific Director, Operational Director, and ECRI Executive meet monthly to discuss strategy and operations as related to ECRI research. Because of the upheaval due to the pandemic, a Scientific Advisory Committee has not met.

FINANCES

ECRI has significant in-kind support from its host organizations. Hamilton Health Sciences provides the space for ECRI. The Institute has its base on the JHCC campus. ECRI's walls are "virtual" with the Scientific Director and Director of Operations having offices on the first floor G Wing and fourth floor JCC, respectively. Scientists having offices on the first floor G Wing, fourth floor JCC, third floor JCC, and the Juravinski Hospital. ECRI does not have a formal "headquarters" space.

Salaries of core and associate ECRI members are provided through a number of funding mechanisms primarily managed by the department of the faculty members' primary university appointment. McMaster provide two CRCs and three endowed chairs. Both the FHS and HHS contribute to a portion of the Scientific Director's base salary.

ECRI has no direct operating funds. The ECRI Director of Operation's is also Director, Cancer Research and Clinical Trials JCC and Director of Administration, Department of Oncology McMaster University. She is retiring in January 2022. The new Director Administration for McMaster's Department of Oncology will have ECRI within their portfolio of responsibilities. ECRI does not have dedicated infrastructure staff. This has been identified as a gap in terms of being able to support annual activities, ensure internal and external reporting, provide active maintenance of the website, and other support features that help sustain the day-to-day life of any organization. Research staff are supported by individual researchers through research grants.

SUMMARY AND LOOKING TO THE FUTURE

This document describes ECRI's performance over the last five years (2016-2021). The pandemic has had a significant impact on research at McMaster, HHS and globally for the past two years. For example, laboratories (both wet and dry labs) were closed, and staff worked from home. Recruitment of patients to clinical trials was discontinued and their follow-up was switched virtually. Funding to sustain the research infrastructure became an issue. These changes were unprecedented and ECRI was forced to cut back its research activities. What is remarkable however, is that throughout this time ECRI has continued to produce high quality research which is a testament to the resilience of the researchers and staff.

When ECRI was established, it declared its vision (putting research into action for the benefit of people affected by cancer), mission (improving the lives of people affected by cancer) and core values (evidence-based, multidisciplinary, burning passion to succeed, committed to community and international in reach). These statements have not changed and provide the inspiration for ECRI's work. ECRI has made substantial progress in meeting its goal of conducting research that impacts on the lives of people affected by cancer. In addition, by the standard academic metrics of grants and publications, ECRI scientists have been very productive. The results of ECRI studies have changed patient care, benefiting both patients and the cancer system.

Looking forward, ECRI has a number of assets that support its continuity and sustainability. These include:

- a mix of seasoned senior investigators who give generously of their time to mentor young people
- committed young researchers with new ideas and who are passionate to succeed as clinician investigators
- OCOG provides trials infrastructure, including expertise in biostatistics
- the McMaster ICES Hub provides infrastructure to conduct population health research
- the JCC Clinical Trials Department provides centralized trial activation and management for investigator-initiated trials

Dr. Jack Hirsh, one of McMaster's most successful researchers, stated that the elements for success in research are: *mentorship, a critical mass of like-minded investigators and hard work with a burning passion to succeed.* We are encouraged that ECRI fulfills these criteria. This augurs well for the future, but it is important to stay vigilant.

For success to be sustained, ECRI will stay the course. A joint hospital/university research institute should have internationally recognized research programs as a marker of its success. ECRI has three such research programs, each with outstanding leadership. The research from these programs has generated new knowledge and has improved patient care well beyond local boundaries. They are the OCOG Trials Group previously led by Dr. Levine and now Dr Wright, Breast Cancer Radiotherapy Trials led by Dr. Whelan, and Palliative Care led by Dr. Seow. These flagship programs stand as testaments to ECRI's success. Going forward, our intention is to continue to build these three flagship programs. New areas of research in virtual care and digital health are also expected to increase.

The functionality of ECRI and its success is built on several guiding principles: 1) being an incubator of new ideas, 2) existing as a mentorship hub for young investigators, and 3) building on collaborations, both internal and external. These guiding principles are anticipated to continue to support the strength of ECRI.

ECRI has been purposeful in seeking out young people with a passion for research and mentoring them. To continue ECRI's vitality and for it to be sustained, new blood must be brought into the enterprise. Since 2016, 11 new young investigators have joined ECRI. Within McMaster, ECRI is unique as it has a very close relationship with the McMaster Department of Oncology. Most of the ECRI junior investigators, but not all, hold their primary academic appointments in the Department of Oncology. This relationship between ECRI and the Department of Oncology is seen as mutually beneficial. It is anticipated that ECRI will also continue to be a place for young researchers from other departments interested in multidisciplinary research collaborations related to ECRI thematic areas of focus. ECRI is at an important juncture in terms of its development as a research institute. It is 10 years old, and it is experiencing a number of significant changes, both internal and external.

From an internal perspective, Dr. Levine, ECRI's first (and only) Scientific Director is stepping down from the position in June 2022. It was his dream and doggedness that led to the establishment of ECRI. In the coming months, a new scientific Director needs to be selected. Currently, ECRI has a very strong and talented Executive: Drs. Whelan, Seow, Sussman and Pond. It is the feeling of the current Scientific Director that any one of these individuals have the research and leadership skills to assume the role of Scientific Director of ECRI. Ms. Snider, the Director of ECRI Operations, is retiring at the end of January 2022 and her administrative role will be taken up by the new Director of Operations for the Department of Oncology. Dr. Meyer, HHS VP Oncology and Palliative Care and Associate member of ECRI, is retired at the end of November 2021. It will be important for Dr. Meyer's successor to continue to work closely with the ECRI Scientific Director in supporting research that will impact on the lives of cancer patients in our region. ECRI researchers have access to support services provided by the respective Offices of Research for FHS or HHS, depending which institution holds the funding for a project, and this will continue.

From an external perspective, ECRI is predominately a clinical research institute, focusing on clinical trials and health services research. It was built with the notion of having clinician researchers working with expert non-clinician researchers, e.g. biostatisticians, health service researchers, basic scientists and recently a data scientist with a background in engineering. This multidisciplinary collaboration has worked well. However, there is no doubt that it is threatened by the changes in the healthcare system and the ever-increasing clinical load on ECRI clinicians with less and less infrastructure support. The time spent on clinical activities is encroaching on research time. In terms of value added, ECRI serves as an advocate for protection of the clinician investigators to have time for research. This challenge needs to be urgently addressed.

ECRI's research projects are supported by funding from grants and industry. ECRI has been very frugal in funding for its operations. To move forward in the current environment, we need investment for infrastructure to support young researchers. This could take the form of negotiating for additional protected time for research for these young researchers, but it is of

concern that this strategy will not be successful given the existential threat of clinical need. Funding to support research assistants who can aid young clinically burdened clinicians in carrying out their research is a promising approach. Finally, support for research fellows is integral to a successful strategy. While the current Scientific Director has been able due to his multiple roles, to find ways to support ECRI to date, the new Scientific Director is going to need resources to support collaboration, communication and ongoing development of the Institute. The governing body should be encouraged to explore this as part of the leadership transition plan.

The themes of Clinical Trials and Health Services Research in Palliative Care continue to sustain momentum. We are encouraged by the recent appointments and work of Drs. Berg and Lalani who are infusing excitement into the Translational Research theme. Dr. Berg's research group is forming a link between the research activities ongoing on McMaster campus and the stem cell and cellular therapy group and the adult hematology group at the HHS Juravinski Hospital. Dr. Lalani has successfully added correlative studies to his CYTOSHRINK trial and is collaborating with basic scientists on campus. These two initiatives are a very good start for rebuilding a stronger translational research presence in ECRI. The time is here to foster this type of research. Establishing strong collaborations with Dr. Sheila Singh, who was recently appointed as the Director of the new Centre for Discovery in Cancer Research at McMaster University, will be a priority. It is recognized that investment in ECRI will likely be needed to facilitate this important emerging collaboration. Finally, ECRI is poised to contribute to the exciting innovative research in digital health being fostered at HHS. Collaborations in digital health that have been established need to grow and additional clinician researchers should be encouraged to embrace this opportunity.

A decade ago ECRI put down roots in the cancer program at HHS and McMaster. We are proud of what has been accomplished over the past 10 years. ECRI's focus is on important clinical challenges; the result of its research directly benefits patients and their families. It is a resilient enterprise as it has maintained its mission and stayed the course despite the existential threats and challenges of the pandemic. The future is bright for ECRI. We are excited about the research opportunities, but realistic that there will be challenges as healthcare continues to evolve. When ECRI started we coined the tag line (slogan), "Inspiring research, because every patient matters". As ECRI moves into its second decade, these words will continue to spur us on.

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APPENDICES

I: Original proposal for Escarpment Cancer Research Institute (2011)
II: 5-Year Report 2011-2016
III: Annual report 2018-2019
IV: First or last-authored Publications
V: CVs