APPENDIX II: 2016 5-Year Report

ESCARPMENT CANCER RESEARCH INSTITUTE (ECRI)

A Joint McMaster University/Hamilton Health Sciences Research Institute

Five-Year Report

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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. ECRI represented the culmination of many years of discussion, planning and the collective commitment of its founding partners: the Department of Oncology in the Faculty of Health Sciences (FHS) at McMaster University, Hamilton Health Sciences (HHS) and the Juravinski Cancer Centre (JCC). The current document is a five year summary report of ECRI activities since its inception and its plans for the future. The report is written in response to a request from FHS Dean J. Kelton and HHS President R. MacIsaac and is required for the review of the Scientific Director, Dr. M. Levine, in consideration of reappointment for a second term. The document follows the template recommended for a summary report of a Joint University-Hospital Research Institutes provided by its governing organizations, although it occasionally strays from the template for completeness, ease of understanding and flow.

The report contains a description of ECRI's activities during the period 2011-2015; the plans for the next five year term, including a transformative vision to maximize ECRI's potential, and a presentation of ECRI's organizational structure and financial model.

There are currently 17 core scientists in ECRI covering a range of disciplines including medical oncology, radiation oncology, surgical oncology, gynecology oncology, pathology, nursing, clinical pathology, biostatistics, psychology, health policy and epidemiology. Among the ECRI scientists there are two endowed chairs, three OICR Clinician Scientists, one CIHR Investigator and one Tier I Canada Research Chair. ECRI's research is informed by the pressing needs and priorities of the JCC and regional cancer program. In order to strengthen the linkages between ECRI and the clinical cancer program and ECRI and basic scientists at McMaster, eight Associate Members were appointed.

ECRI was established with three foundational research programs: Clinical Trials, Quality Care & Knowledge Translation (KT) and Translational Research. ECRI has made substantial progress in meeting its goal of conducting research that impacts on the lives of people affected by cancer. Researchers have benefitted from the consolidation and co-location of their activity and purpose within the new research institute. In addition, ECRI has fostered collaboration with other McMaster cancer research groups in order to build on collective expertise and to pursue interdisciplinary avenues of research. By the standard academic metrics of grants and publications, ECRI scientists have been very productive. They have attracted many millions of dollars in research funding and published in high impact journals. Furthermore, the results of ECRI studies have changed patient care, benefiting both patients and the cancer system.

Having achieved this initial level of development, ECRI sought external input to help consider ways that the institute might extend its potential for greater impact. Thus, an external review was conducted by Dr. Simon Sutcliffe, one of the eminent cancer leaders in Canada, in May 2015. He commended ECRI for having been very successful in a challenging environment and stated that by all standard academic measures, ECRI and its members had been productive and impactful. Most importantly, he provided advice and strategy on how ECRI could move forward in the next five years to realize its full potential by embracing a problem-based approach

to prioritized cancer challenges through the use of fluid, interdisciplinary teams, led by ECRI researchers, but including collaborators across multiple disciplinary domains. Practically, this would require shifting away from crafting research projects solely along the traditional themes of clinical trials, health services research and translational research to more of a problem-based approach that optimizes the intellectual capital and innovation of ECRI members and their collaborators to solve cancer problems.

This concept resonated with the ECRI leadership and was embraced by the scientists. To realize this vision ECRI has developed the concept of a Strategic Research Collaboration. Four Strategic Research Collaborations have been identified; two (Survivorship, Palliative Care) are already well established in terms of active research and designated leadership. The other two (Application & Evaluation of Precision Medicine, Uncertainty) are at an earlier idea and proof of concept stage of development. The identification and activity associated with Strategic Research Collaborations are intended to be fluid and to change over time. Individual ECRI scientists will continue with their own portfolios of research in order to ensure that an exciting successful research enterprise provides the environment and foundation to not only fuel the Strategic Research Collaborations but also continues to reflect the strength and interests of individual researchers. ECRI research will continue to be informed by the pressing needs and priorities of the JCC and regional cancer program. The "LHIN as a Lab" will continue to be a concept that helps drive this commitment.

After four years, ECRI is established and has gained traction. ECRI is ambitious and is keen to do more. The ECRI tagline, "Inspiring Research: because every patient matters" will continue to be the guiding philosophy for ECRI.

VISION, MISSION, CORE VALUES AND FOUNDING THEMES OF ECRI

When ECRI was established it declared statements of vision, mission and core values:

- *Vision*: ECRI will be the national leader of innovative and sustainable solutions that will put research into action for the benefit of people affected by cancer.
- *Mission*: ECRI is dedicated to improving the lives of people affected by cancer. The ECRI research strategy includes clinical advancements, system innovations and knowledge translation.
- *Core values*: Evidence-based, multi-disciplinary, burning passion to succeed, committed to community and international in reach.

ECRI FACULTY

There were 16 founding scientists in ECRI in 2011 and shortly thereafter, a 17th scientist joined (Table 1). The choice of scientists was based on a number of factors including: time available for research, track record and training. Membership definitions and role expectations were more formally developed as ECRI matured. Currently, among the ECRI scientists there are two endowed chairs, three OICR Clinician Scientists, one CIHR Investigator and one Tier I Canada Research Chair. There was a deliberate strategy to include non-clinician faculty who represented other disciplines and areas of excellence, as an important strategy to achieving the ECRI mission.

Table 1: ECRI Scientists

Member		Discipline	Primary Affiliation
Andrew	Arnold	Medical Oncology	Oncology
Anita	Bane	Pathology	Oncology
Melissa	Brouwers	Psychology	Oncology
Denise	Bryant-Lukosius	Nursing	Nursing
Laurie	Elit	Gynecologic Oncology	Obstetrics & Gynecology
Hal	Hirte	Medical Oncology	Oncology
Sebastien	Hotte	Medical Oncology	Oncology
Rosalyn	Juergens	Medical Oncology	Oncology
Jim	Julian	Biostatistics	Oncology
Pete	Kavsak	Clinical Pathology	Pathology & Molecular Medicine
Mark	Levine	Medical Oncology	Oncology
Paola	Muti	Epidemiology	Oncology
Gregory	Pond	Biostatistics	Oncology
Hsien	Seow	Health Policy	Oncology
Marko	Simunovic	Surgical Oncology	Surgery
Jonathan	Sussman	Radiation Oncology	Oncology
Tim	Whelan	Radiation Oncology	Oncology

One of the unique features of ECRI is that it is embedded within a tertiary academic regional cancer centre. The value of this linkage between the research program and the JCC clinical cancer program enabled ECRI to align its research activities and establish sustainable collaborations with the JCC clinical community. For example, in 2013 the leadership of the

clinical program identified palliative care and survivorship as strategic priorities – two areas of established strength within ECRI. In order to strengthen bridges between the clinical and research programs a number of Associate Members were appointed (Table 2). The idea was that they could bring their clinical experiences to ECRI and partner with its scientists in developing a research agenda. This would be one way of ensuring that ECRI would focus on issues that are relevant to patients and clinicians in the cancer centre and the surrounding community. A similar process was taken with the translational research portfolio. Here the appointment of a non-clinician, Jonathan Bramson, PhD, was sought in order to enable collaboration between ECRI clinician scientists and basic scientists in the McMaster Immunology Research Centre to focus on an important and promising area of cancer research.

Table 2: Associate Members

Member		Discipline	Primary Affiliation
Jonathan	Bramson	Immunology	Pathology & Molecular Medicine
Ian	Dayes	Radiation Oncology	Oncology
Bindi	Dhesy	Medical Oncology	Oncology
Peter	Ellis	Medical Oncology	Oncology
Karen	Gulenchyn	Nuclear Medicine	Medicine
Som	Mukherjee	Medical Oncology	Oncology
Anand	Swaminath	Radiation Oncology	Oncology
Jim	Wright	Radiation Oncology	Oncology

RESEARCH PERFORMANCE (2011-2015)

There were three foundational research themes: Clinical Trials, Quality Care & Knowledge Translation (KT) and Translational Research. These were established based on the interests, expertise and logical groupings of the ECRI scientists in 2011. The focus of ECRI is on the application end of the research trajectory that spans discovery through validation to application research. Collaboration is sought and fostered where required, while still within the application domain. The focus remains the immediacy of impact on patient care.

Clinical Trials:

The clinical trials program is vibrant. The Ontario Clinical Oncology Group (OCOG) continues to design and execute a spectrum of trials, from first in human to large multicentre Phase III trials. In some cases the principal investigators (PI) are ECRI members or associate members. A team composed of a clinical epidemiologist (Levine or Whelan), a biostatistician (Julian or Pond) and a PI are responsible for leading each OCOG trial. Sometimes an ECRI scientist is the PI of a trial coordinated by another academic trials group, e.g. the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).

Some trials are completed and have changed practice or policy. Some trials are ongoing, while others have long follow-up in order to address important quality of life and long term effects important to patients. Examples of OCOG trials that have informed clinical practice and directly impacted government policy (e.g. PET imaging and biomarker tests) are described.

Positron Emission Tomography (PET) in Oncology:

Over a decade ago, the Ontario Ministry of Health and Long Term Care (MOHLTC) approached OCOG to establish a research program to evaluate PET. This imaging technique is attractive in oncology because of the preferential uptake of radiolabelled glucose by cancer cells compared to non-cancer cells. However, it is very expensive. OCOG worked with the Cancer Care Ontario (CCO) Disease Site Groups to develop and then conduct seven unique trials in breast cancer, non-small cell lung cancer (NSCLC), head & neck cancer, metastatic colorectal cancer to the liver, suspected recurrent cancer and locally advanced cancer of the cervix (1). OCOG's PET evaluation program is the largest of its kind in the world. The results of these studies have informed health policy, specifically whether the test is funded and used in Ontario. The PET trials have been funded by the MOHLTC and CCO. Only the three most recent trials which occurred during the first four years of ECRI are considered.

Hepatic colorectal cancer metastases (Moulton, Gallinger, Julian and Levine): Colorectal cancer patients with liver metastases undergo hepatic resection with curative intent. However, unidentified occult metastases at the time of surgery can render the operation non-curative. It was hypothesized that PET-CT could help avoid non-curative surgery by identifying patients with occult metastases. In the PETCAM multicentre trial, 404 patients with metastatic colorectal cancer to the liver who were being considered for hepatic surgery were randomized to PET-CT or not (PIs, Drs. S. Gallinger and C.A. Moulton, UHN, Toronto). Only 2.7% of the PET-CT patients avoided futile liver surgery and no difference was detected in survival between arms. The results were presented at the American Society of Clinical Oncology (ASCO) and published in the *Journal of the American Medical Association* (2). Based on the PETCAM result PET-CT is not funded in Ontario for this indication.

Recurrent Cancer (Yu, Julian and Levine): Sometimes the diagnosis of recurrent cancer in patients with a previous malignancy can be challenging. Despite conventional imaging, the diagnosis of recurrence is unclear and the patient faces the prospect of an invasive biopsy. The PETREC trial was a prospective cohort study that assessed the clinical utility of PET-CT in the diagnosis of clinically suspected recurrence of cancer (PI, Dr. J. Yu, Internal Medicine, McMaster). Of the 99 subjects who underwent PET-CT, planned management changed after the scan in half of the patients with recurrent cancer being confirmed in 70%. The results were presented at ASCO and published in the *British Journal of Cancer* (3). Based on the study results, PET-CT is funded in Ontario for this indication.

Locally advanced cancer of the cervix (Elit, Fyles, Pond and Levine): Women with locally advanced cervical cancer are usually treated with concurrent chemotherapy and radiation therapy with curative intent. Pre-treatment staging is important to define the extent of disease and guide therapy. In PET LACE , 171 patients with locally advanced cervical cancer were randomized to usual staging with CT abdomen and pelvis or to CT abdomen and pelvis plus PET-CT at four sites in Ontario (PIs, Drs. A. Fyles, radiation oncologist, PMH and L. Elit, gynecology oncologist, JCC). We undertook the study to test whether PET-CT would identify more patients with distant metastases who would become candidates for palliative treatment and whether PET-CT would identify more patients with para-aortic nodes who would receive more extensive para-aortic

radiation. Neither hypothesis was supported. The results were presented at ASCO in June 2015 and to the Provincial PET Steering Committee at CCO in October 2015.

Oncotype Dx Test:

The Oncotype Dx test based on 21 genes provides a relapse score (RS) on the risk of recurrence in women with lymph node negative estrogen receptor positive breast cancer. If the RS is low, chemotherapy is not needed. The test was widely used in the US and there was pressure for it to be adopted in Canada. The challenge is that it is an expensive test ($4,000 US) and only performed by one laboratory in California.

The MOHLTC approached OCOG to conduct a cohort study evaluating the test in Ontario to see how it influenced decision-making and treatments received (Levine, Julian, Eisen, Trudeau and Pritchard). The study which included 1,000 women found that the RS changed oncologists' recommendations in approximately half of the patients; pretest and post-test remained the same in 48% of patients, changed from unsure or chemotherapy to no chemotherapy in 38%, and changed from unsure or no chemotherapy to chemotherapy in 15%. As a result of the test, chemotherapy was avoided in a large number of patients. Based on these results, the MOHLTC is continuing to fund the Oncotype Dx test. The results of the study were presented at ASCO and published in the *Journal of Clinical Oncology* (4).

Radiation Therapy:

The goal of the radiation program in ECRI Clinical Trials is to evaluate new radiation therapy (RT) technologies and biomarkers to improve outcomes for patients with cancer. The focus has been on common cancers such as breast, prostate and lung. Two of these trials, PROFIT and RAPID, recruited patients a number of years ago and patients are currently in the follow-up phase with the analyses planned for 2016. The results are likely to have an impact on clinical practice.

PROFIT (Julian, Levine): In this trial (PIs, Drs. C. Catton, PMH and H. Lukka, JCC), 1,204 men with intermediate risk early prostate cancer were randomized to a short course of RT (50.4 Gy in 12 fractions over 2.4 weeks) compared to a conventional fractionation course (78 Gy in 39 fractions over 8 weeks) between 2006 and 2011. The trial is funded by CIHR. If there is no loss of efficacy and no increase in toxicity with the shorter treatment then it will likely become standard therapy for patients with intermediate risk prostate cancer.

RAPID (Whelan, Julian, Levine): Based on the results of the OCOG HYPO trial, three weeks of breast irradiation is the current standard RT regimen following breast conserving surgery (BCS) in North America. We have investigated new approaches to RT after BCS to further improve the convenience and tolerance of the treatment. RAPID (funded by CIHR) compared large doses of radiation per fraction over five days to only part of the breast called accelerated partial breast irradiation (APBI) and standard whole breast irradiation (WBI) (PIs, Drs. Whelan and Olivotto, BC). Between 2006 and 2011, 2,135 patients were recruited from 43 sites in Canada and Australia and are currently in the follow-up phase. An 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 (presented in the plenary session at the

American Society of Radiation Oncology (ASTRO) and published in the *Journal of Clinical Oncology* (5)). The study is still ongoing to evaluate the primary outcome of local recurrence. The results have limited the unfettered adoption of the new approach in Canada and the US, which had been increasingly used in North America without proper evaluation.

MA20 (Whelan, Levine): Post-mastectomy RT to the chest wall and regional nodes (supraclavicular, axillary and internal mammary lymph nodes) called regional nodal irradiation (RNI) in women with node positive breast cancer reduces the risk of local recurrence and prolongs survival. The NCIC CTG MA20 trial (PI, Whelan) evaluated whether RNI reduced distant spread and mortality in women who received breast irradiation after BCS. RNI reduced both loco-regional and distant recurrence (presented at *ASCO* and published in *NEJM (6)*). As a result, RNI is now increasingly used to treat such women following BCS.

LUMINA (Bane, Whelan): Radiation is standard therapy after BCS to reduce the risk of local recurrence. A trial has been initiated to identify a subgroup of patients after BCS who can be spared RT. The objective of the Lumina trial is to determine if women with both low risk tumour clinical characteristics (age > 55, node negative and tumour size < 2cm) and the luminal A subtype on IHC and who will receive endocrine therapy are at sufficiently low risk of local recurrence (defined as < 10% at five years) to avoid radiation. The design is a prospective cohort study involving 22 Canadian centres; 160 of 500 patients have been enrolled. The trial is funded by the Canadian Breast Cancer Foundation (CBCF). If LUMINA confirms that selected 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. This will undoubtedly have a significant impact by avoiding the inconvenience and morbidity of RT and by reducing costs.

LUSTRE (Swaminath, Whelan, Julian, Wright): Surgical resection is considered the standard of care for patients with Stage I NSCLC. However, approximately 20% of patients with NSCLC cannot undergo surgery because of significant comorbidities, such as severe chronic obstructive pulmonary disease or cardiac disease. Radiotherapy is the preferred treatment option in such patients. Conventional RT for NSCLC is typically given as a prolonged course of treatment (15-30 fractions over 3-6½ weeks). Studies of RT in such patients have reported local control rates of 50-70% and two year survival rates of 35-50%. A randomized trial funded by the Canadian Cancer Society Research Institute (CCSRI) is currently underway to evaluate a new radiotherapy technique, stereotactic body radius therapy (SBRT), which can deliver radiation precisely to the tumour in very high doses and for a very limited number of treatments – a potentially game changing strategy.

BRACHY (Sur, Wright, Whelan, Julian): Many NSCLC patients present with advanced disease not amenable to surgery. They are often treated with external beam RT with the aim of palliating symptoms, but the success of this treatment and duration of benefit are limited. Uncontrolled studies suggest that high dose rate brachytherapy that delivers an additional dose of radiation to the centre of the luminal disease by the insertion of a radiation source may be associated with improved patient symptom control compared to RT. The BRACHY trial (funded by the CCSRI) compares external RT alone with the same RT regimen followed by the brachytherapy in patients with advanced stage or recurrent NSCLC who have thoracic symptoms. The hypothesis is that brachytherapy added to external RT provides improved local tumour control that will result in

improved symptom control and quality of life. Currently, 120 patients are on study and it is due to close to accrual in early 2016. This is one of the few randomized trials evaluating brachytherapy.

ALMERA (Tsakiridis, Wright, Pond, Whelan): Locally advanced Stage III NSCLC is normally managed with RT and concurrent chemotherapy. Laboratory studies suggest that metformin may increase the effects of radiation and chemotherapy by stimulating AMP-activated protein kinase, a mediator of radiotherapy cytotoxicity. The objective of the ALMERA trial is to determine if metformin given concurrently with chemotherapy and RT improves progression-free survival compared to usual concurrent RT and chemotherapy. This is a randomized Phase II trial funded by CIHR. Should metformin be shown to improve progression-free survival in our trial, it will identify an innovative approach to improve current therapy.

Early Phase Trials:

OCOG has focused on collaborating with basic scientists at McMaster and conducting first in patient proof of principle trials. There are considerable challenges in moving discoveries from the laboratory into the clinic and OCOG has developed considerable experience in this type of research.

IMPACT (Levine, Gulenchyn, Pond, Valliant): Dr. Levine evaluated novel functional imaging methods to evaluate response to therapy in breast cancer. In the multicentre IMPACT trial, FLT PET and BOLD MRI were studied to determine whether they predicted response to chemotherapy in 30 women with locally advanced breast cancer. The trial was funded by OICR. Unfortunately there was no association between the imaging tests and response to chemotherapy.

PETRA (Reilly, Levine, Gulenchyn, Pond): In the first in patients PETRA trial, ^{131}I radiolabelled pertuzumab is being evaluated to determine whether it can predict response to trastuzumab in patients with HER2 positive metastatic breast cancer. The trial (funded by OICR) is based on the experimental work of Dr. Reilly at the University of Toronto. Both pertuzumab and trastuzumab bind to the HER2 receptor but at different sites. It is hypothesized that a small dose of radiolabelled pertuzumab can be used to study binding of trastuzumab to the receptor and subsequent internalization of the receptor. If this was demonstrated, then trastuzumab, which is expensive, would only be given when it would have a high likelihood of working.

THORIDAL (Foley, Bhatia, Julian, Levine): Laboratory research showed that the antipsychotic drug thioridazine induced the differentiation of a neoplastic human pluripotent stem cell. When applied to leukemia, this treatment reduced AML blasts without affecting normal hematopoietic stem progenitor cells. Mechanistically, this was postulated to be mediated by the blockade of dopamine receptors (DRs) overexpressed on neoplastic stem cells. In a first in human Phase I trial, the safety of using thioridazine in addition to cytarabine in elderly patients with relapsed or refractory AML is being investigated. Currently, eight patients have been entered. The trial is funded by the McMaster Boris Endowment.

Quality Care & Knowledge Translation (KT)

ECRI has a cadre of exceptionally talented health services researchers. They focus on the areas of survivorship, palliative care, quality of care in cancer surgery, models of care, knowledge translation and implementation science. There is synergy between ECRI research interests and JCC cancer program priorities.

Survivorship

In 2013 Dr. J. Sussman took on the role of clinical lead for survivorship care at Cancer Care Ontario. This newly created leadership role is focused on developing and implementing province-wide strategies to support optimal survivorship care that includes aspects of both physical and psychosocial recovery from a cancer diagnosis and treatment. He is the lead author of a practice guideline on models of survivorship care that are used to guide the implementation and evaluation of new models of care for cancer survivors (7). In 2014 he led a province-wide study of transitions of breast cancer patients to primary care that demonstrated the safety and efficacy of this approach (recently published in the *Journal of Oncology Practice* (8)).

In addition, Dr Sussman is the specialist lead for the cancer survivorship component of the national CIHR funded study (PI, Dr. E Grunfeld) that will design and evaluate a shared care model involving primary care and oncology across the cancer care trajectory for patients with breast cancer. This study will be completed in 2018 and will set the standard for shared care in cancer patients.

In 2014 Dr. Sussman received grant support from the Canadian Partnership against Cancer (CPAC) to design and evaluate three strategies to address gaps in integration between primary care providers and oncology programs. This will study key aspects of provider integration in Ontario, British Columbia and Manitoba. The goal is that it is completed in 2017. In studying vertical integration, a scan of current practices to support repatriation of cancer patients who need to come back for assessment and treatment is nearing completion. In studying functional integration, the use of electronic care plans is being evaluated in three regions in Ontario and one in British Columbia to determine if an electronic platform is feasible and seen to be of benefit in transitioning patients to primary care. The third project addressing clinical integration involves the development and evaluation of a national curriculum in survivorship care that will be delivered in British Columbia, Ontario and Manitoba. Shared learning that involves both oncology and family medicine trainees, which has never before been attempted, will evaluate the potential benefits of early interdisciplinary exposure and experience in addressing gaps in provider integration.

Palliative Care:

Dr. Hsien Seow is an international leader in palliative care. His program of research focuses on understanding the palliative care system in Canada, investigating strategies to improve palliative and end-of-life care experience for patients and their families, and creating policy relevant research that can be used by decision-makers to improve the palliative and end-of-life care system. Some key contributions in this area are discussed.

Examining the Provision of End-of-Life Homecare Services in four provinces (BC, NS, ON and AB): The study team have completed administrative data research to demonstrate a sizeable and consistent association between providing increased generalist homecare nursing and specialized palliative care nursing separately and on reducing emergency room visits and hospitalizations throughout the last six months of life across all provinces. They also demonstrated that although costly, investment in palliative nursing is associated with lower relative hospital costs and lower total costs. These findings imply that the association on late life hospitalizations and standard nursing, and especially end-of-life nursing, neither appear to be solely a function of the organization of the homecare system (which differs province to province), nor the individual healthcare providers' expertise (which differs individual to individual) published in *Journal of Pain and Symptom Management* and *Journal of Oncology Practice* (9,10). This data has been useful to policymakers as it shows potential avenues for cost-savings and has provided common outcomes and measures for end-of-life cancer care that can be used for bench-marking and quality improvement. The team is currently conducting an analysis looking at regional and community size variation on access to palliative homecare nursing and a policy analysis to examine reasons for provincial and regional variation.

Evaluating and Scaling Effective Interprofessional Palliative Care Teams in the Community: In this study, over a dozen diverse interprofessional palliative care teams in the community who work to provide palliative care to patients at home were studied. The research demonstrated that community based specialist palliative care teams, despite variation in team composition and geography, appear effective at reducing acute care utilization and hospital deaths at the end-of-life. Current inquiries are examining opportunities for cost avoidance. The team was able to identify the key components necessary to enable the scaling and spread of this palliative care service model. Publications of this research are found in the *British Medical Journal* (11) and *Journal of Palliative Medicine* (12). This work is having a significant impact on the Ontario Provincial Hospice Palliative Care Steering Committee's work plan, and at the regional hospice palliative care networks and planning tables.

Using Bereaved Caregiver Surveys to Measure Patient/Caregiver Experience: This study has piloted a bereaved caregiver survey that measures both patient and caregiver experience in the last three months of life to examine the use in multiple care settings (home care, hospices and long term care facilities) and to validate against a gold standard end-of-life satisfaction tool. This work was endorsed by the provincial hospice palliative care steering committee and the goal is to establish adequate measurement properties so that it can be scaled up and used provincially. It is currently being tested in hospitals and long-term care. It has been adopted as the tool to be used for all Community Care Access Centres for the next three years of patient experience reporting for end-of-life clients.

Defining Palliative Care Quality Indicators: Dr. Seow led a project to develop key palliative care performance indicators for the province. This work has involved an extensive literature review of existing palliative care quality indicators (over 750 indicators were identified) and going through a modified-Delphi process to identify the six most "ready" indicators for implementation. These indicators have been endorsed and adopted by the province of Ontario, and also are being adopted by Canadian Partnership Against Cancer's System Performance

group, and regional LHINs. Health Quality Ontario has also endorsed these indicators and will begin to report and measure these regularly in future years as part of accountability and public reporting. There is continued work to strengthen measurement and expand the indicator list and work on developmental indicators, particularly around quality of care and patient experience.

Knowledge Translation and Implementation Science:

Dr. Brouwers is an internationally recognized knowledge translation (KT) researcher with particular expertise in evidence-based decision-making to improve patient outcomes and strengthen health systems. Her work represents a cross-cutting research theme for ECRI: specifically, investigating KT research-driven solutions to facilitate the adoption of translational, clinical and health services research advancements by knowledge users. Some of the key successes from Dr. Brouwers are AGREE and Cancer Care Ontario (CCO)'s Program in Evidence-Based Care (PEBC).

AGREE Enterprise: Dr. Brouwers is the principal investigator of the international AGREE (**A**ppraisal of **G**uidelines **R**esearch & **E**valuation) research program. In this capacity she has led a consortium of scientists in a series of KT projects aimed to create new methods and tools to support the development, evaluation and adoption of clinical and health system guidance (13,14).

- AGREE II: AGREE II is the international standard for clinical practice guideline development, reporting and evaluation. The tool has been translated into 40 languages and is incorporated into practice guideline programs, graduate courses and journal reporting requirements. Associated with the tool and as part of the larger implementation agenda is the online AGREE system (www.agreetrust.org) that provides users access to the RCT-tested training program, the online collaborative system (MY-AGREE Plus), and access to information about all AGREE-related research projects. More than 18,500 individuals are registered with the platform and greater than 6,500 visit the website each month.
- AGREE Health Systems (HS): Developed in collaboration with the international research community and representatives from each of the World Health Organization regions, the AGREE HS facilitates health systems level guidance development, reporting and evaluation. A first of its kind, the tool has been released and a series of prospective validation studies are currently planned in Canada (with Cancer Care Ontario) and internationally in Suriname, Columbia and Cameroon.
- Other AGREE-related projects include AGREE-REX (Recommendations Excellence) and AGREE UPDATE.

Program in Evidence-based Care: Dr. Brouwers is the Scientific Director of the renowned Program in PEBC, the practice guidelines (PG) initiative of Cancer Care Ontario (CCO) and academically linked to ECRI (15). She oversees more than 20 guideline panels with participation of over 200 clinical policy research and methods experts to create clinical and cancer system guidance for Ontario and a program of research to advance the science of practice guidelines and their use. Several ECRI scientists and associate members are actively involved in the PEBC (Sussman, Elit, Denise-Bryant Lukosius, Hotte, Ellis, Simunovic, Hirte, Arnold), as is the larger provincial and national scientific community.

The PEBC guidelines directly impact policy, patients' access to new treatments and the design of the cancer system (refs). For example:

- PGs are required in Ontario drug funding policy deliberations and formulary design
- The Diagnostic Assessment Program Standards are now implemented in many Ontario regions, including our LHIN
- PG adoption is publicly reported in the Cancer System Quality Index (www.csqi.on.ca)
- The Models of Systemic Therapy led to system redesign to improve quality, access and safety of chemotherapy treatments
- PEBC methods/strategies are used by other PG programs
- The Ontario PGs are adapted for use in other jurisdictions (e.g. Nova Scotia)

The PEBC methodological research investigations have led to rigorous yet practical solutions to manage the limited human and financial resources available to ensure principles of evidence-informed decision-making are adhered to by CCO.

Uncertainty: Given the pervasiveness of uncertainty in decision-making, Dr. Brouwers, in collaboration with her colleagues at the University of Manitoba, undertook a program of research aimed to identify sources and types of uncertainty that exist, to assess the impact of these sources and types of uncertainty on decision-making, and to create a tool to help decision-makers navigate uncertainty so that decisions can be made in a more systematic, deliberate and transparent manner. While originally explored within the context of policy, we will also be looking at this in the context of clinical decision-making.

Models of Care:

Dr. Bryant-Lukosius is an international leader in the area of innovative nurse-led service delivery models of cancer care. She has led a comprehensive research program utilizing an integrated knowledge translation approach to pioneer the introduction and evaluation of specialized and advanced nursing roles, the development of evidence-informed practices and policies to better integrate advanced practice nurses into the healthcare system, and cost effectiveness of these approaches (16).

She is the founding director of the Canadian Centre of Excellence in Oncology Advanced Practice Nursing (OAPN) located at the JHCC. This is dedicated to building research capacity and providing education, mentorship and knowledge translation to support the development of nursing roles in cancer control. Dr. Bryant-Lukosius is a bridge between the ECRI scientists and the clinical program priorities through her participation on key quality improvement teams at the JCC related to urgent care, symptom management and survivorship.

Cancer Surgery:

Dr. M. Simunovic is a surgical oncologist with special expertise in colorectal cancer. His research focuses on knowledge translation (KT) and surgeon-directed quality initiatives. He led a province-wide trial that evaluated a KT strategy to improve rectal cancer surgery. Although the results were negative, they informed the design of the subsequent region level surgeon-

directed Quality Improvement in Colorectal Cancer in LHIN4 (QICC-L4) project. This latter study is an example of using 'LHIN 4 as a laboratory'. The underlying premise of his research is that for cancer surgeries, region level solutions are required to address quality gaps in patient care observed at the hospital and individual surgeon level.

There are a number of studies within the QICC-L4 project. Innovative KT interventions such as Internet and Hospital Collaborative Cancer Conferencing have been evaluated. Collaborative conferencing involves surgeon-to-surgeon prospective review of cases with radiology support. These interventions were developed to address current logistical barriers to multidisciplinary cancer conferencing for every LHIN4 patient undergoing complex colorectal cancer surgery. Results have shown a consistently high rate of change from original surgeon treatment plan to final consensus treatment plan; in the range of 30-60%. More recent work has demonstrated a high rate of fidelity to consensus recommendations (> 90%), and has identified key factors leading to changes in recommendation (e.g., suboptimal evaluation of eventual surgical margins) (17). Based on the data, the conclusion is that every patient being planned for complex colon or rectal cancer surgery should undergo some form of pre-operative Collaborative or Multidisciplinary Cancer Conferencing. This is currently not occurring for the majority of such patients in Ontario. Another study used the considerable data collected through the QICC-L4 to demonstrate improving surgical and pathology performance over time, and the need for a consensus in the methods and definition of a positive surgical margin in rectal cancer (18).

Translational Research

Translational research has evolved considerably since 2011. ECRI has focused its translational research in targeted areas, e.g. biomarkers, immunology/cell based therapies, imaging and prevention. This program is a work-in-progress, but the expertise in ECRI's other two research themes, i.e. methodology of trials and KT methodology, is being leveraged by ECRI's translational researchers to enable basic scientists to move their discoveries into patients.

In 2009 the Ontario Institute of Cancer Research (OICR) established the Translational Research Team (TRT) Program and a team from Hamilton was successful in receiving a $1M OICR TRT award. This was an important step in catalyzing the evolution from a local research program focusing on drug development into a broader initiative building on local basic science and clinical research strengths. The Hamilton TRT was co-led by Dr. S Hotte, a medical oncologist, and Dr. A. Bane, an anatomic pathologist with special expertise in breast cancer and molecular pathology. The Hamilton OICR-funded TRT became the focus for the translational research component of ECRI. The original goal of the TRT was to bring together researchers and clinicians from a variety of disciplines including basic science, medical and radiation oncology, clinical trials, anatomic pathology, diagnostic imaging, surgery and biostatistics/epidemiology in order to assess current clinical needs and to develop high impact clinical trials (OICR term for translational research trials) that could utilize the expertise of the entire team. More specifically, the aim was to move new discoveries from the laboratory into a clinical setting faster than had been previously possible.

Biomarkers:

Breast Cancer Radiation (Bane, Whelan, Pond, Levine): The relative lack of well characterized predictive biomarkers for radiation therapy in breast cancer was identified by ECRI researchers as a significant unmet clinical need. Tumour grade, intrinsic molecular subtype as determined by six biomarkers (ER, PR, HER2, EGFR, CK5/6 and Ki67) and tumour hypoxia as measured by three markers (HIF1α, CAIX, GLUT1) were studied to determine whether they predicted risk of local recurrence (LR) and response to hypofractionated versus conventional whole breast irradiation in women who had participated in the OCOG HYPO trial comparing two types of radiation following BCS. The study found only molecular subtype was significantly prognostic for local recurrence, with the HER2 enriched and luminal B subtypes having the worst outcomes (19). In addition, the study did not demonstrate a significant interaction of any biomarker examined with radiation regimen, supporting that patients with any grade or molecular subtype of breast cancer can be treated with the more convenient and less costly three week hypofractionated radiation following BCS.

Triple Negative Breast Cancer:

Development of signatures (Bane, Whelan, Pond, Levine): Triple negative breast cancer (TNBC), a subtype of breast cancer defined by the absence of ER, PR and HER2 expression, accounts for 15-20% of all newly diagnosed cases. TNBC has sparked considerable scientific and clinical interest because it is often associated with a poor prognosis and lacks any targeted form of therapy. However, not all TNBC patients have a poor prognosis. Currently, there are no tests that can reliably divide TNBC patients into two different prognostic groups. As a consequence, most patients with TNBC, even those with small tumours and negative axillary lymph nodes, are recommended for aggressive systemic chemotherapy. A method that would be able to accurately stratify TNBC patients into high and low risk groups was identified by Dr. Bane and colleagues as an important unmet clinical need.

An innovative *in silico* approach was used to identify in an unbiased manner gene and pathway that are associated with outcome in TNBC. This work yielded seven modules each comprised of eight or more genes and the module gene score was predictive of outcome in TNBC (HR 3.0). An initial validation of the prognostic ability of the module gene score was undertaken again *in silico*. The module gene score was again a strong predictor of patient outcome (HR =3.1) (20,21).

The next step was to convert this gene module into a clinical assay that could be readily applied to formalin fixed paraffin embedded (FFPE) tumour samples in standard pathology laboratories. A three gene IHC assay was derived containing JUN, CD8 and CD20. These were tested for expression in a local cohort of TNBC samples from Hamilton Health Sciences. A robust relationship between the IHC assay and survival was observed; 10-year survival in the low risk score group was 98% compared to 71% in the high risk score group (HR 6.2; $p<0.0039$). Currently studies are ongoing to validate the prognostic utility of this signature in an independent cohort of TNBC with long-term follow-up.

Immunotherapy:

One of the highlights over the last five years of the Hamilton TRT has been the creation of a functional, successful and enthusiastic immunotherapy group. This group arose organically from the observation that most of the TRT's interest in translational work came from McMaster immunotherapy scientists, e.g. Dr. J. Bramson, already world leaders in their field. Dr. Bramson is credited with reaching out to the clinical investigators in ECRI to initiate and consolidate this relationship. The informal immunotherapy working group includes 13 very committed researchers who meet quarterly after hours to discuss new research opportunities, goals and current clinical needs that can be met through the basic research activities of our members from the McMaster Immunology Research Centre (MIRC).

Natural Killer Cells (Ashkar, Hotte, Hirte, Dhesy, Juergens): Dr. Ali Ashkar at the MIRC has an interest in natural killer (NK) cell function and using the patients' own NK cells to fight their cancer. Studies are underway to compare the NK cells isolated and activated between blood and ascites from patients with ovarian cancer with respect to tumour killing capabilities (Hirte). A new technology is being developed to take advantage of the large numbers of NK cells found in ovarian ascites in order to re-activate them *in viv*o, directly within the peritoneum via IP injection to fight the tumours without the need for isolation, expansion and re-infusion of the patient's own NK cells. Drs. Ashkar, Dhesy, Bane and Levine are planning a first in human study that will test NK cell therapies in patients with locally advanced breast cancer (LABC). A grant application was recently submitted to the CBCF. If it is successful we will be the first in Canada to do this type of research. These studies will be coordinated through OCOG, forming a link between the translational and clinical trials aspects of ECRI.

Oncolytic Viruses (Lichty, Hotte, Juergens): Dr. Brian Lichty, also at MIRC, is an expert in oncolytic viruses; which are live viruses capable of selectively infecting and killing cancer cells. Research from his laboratory has led to a first in human trial through the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Drs. Hotte and Juergens are investigators on this trial which is assessing an oncolytic vaccine which entails the combination of an adenoviral vaccine containing the MAGE-A3 protein followed by administration of an oncolytic virus, the Maraba virus. MAGE-A3 is a known tumour antigen in lung cancer. Drs. Juergens and Lichty are collaborating on the next step of this project which aims to combine this oncolytic vaccine with another immuno-oncology agent, a PD-1 inhibitor, pembrolizumab, in patients with lung cancer.

Imaging:

An important research theme for OICR is imaging. Dr. Valiant had established the Centre for Probe Development & Commercialization (CPDC) at McMaster. Dr. Gulenchyn, Head of Nuclear Medicine at the Hamilton hospitals, wanted to foster research in her department. Dr. Juergens was recruited as an OICR Clinical Scientist in Imaging. Dr. Levine was interested in the challenges of conducting imaging trials. These four individuals came together to form an innovative research group.

Dr. Juergens is leading a first in human Phase I trial of a novel imaging probe, CPD-1028 (developed by Dr. Valliant), which targets the insulin-like growth factor receptor 1 (IGF-1R). The goal of this work is to develop a platform where surface proteins can be detected through molecular PET imaging and subsequently targeted with therapeutic radiopharmaceuticals. To date they have begun their first imaging trial. Patients must have pathologically confirmed over-expression of IGF-1R prior to proceeding with the imaging. Nine patients have been screened for overexpression of IGF-1R and two patients have been imaged. This diagnostic and treatment platform is applicable to multiple tumour types.

Dr. Levine evaluated novel functional imaging methods to evaluate response to therapy in breast cancer. He led the OCOG IMPACT trial which studied, FLT PET and BOLD MRI in locally advanced breast cancer. In the OCOG PETRA trial, ^{131}I radiolabelled pertuzumab is being evaluated to determine whether it can predict response to trastuzumab in patients with HER2 positive metastatic breast cancer. In the THORN trial, Drs. Pond, Gulenchyn, Valliant and Bordeleau (Hereditary Breast Cancer Clinic at the JCC) evaluated the feasibility, acceptability and safety of Molecular Breast Imaging (MBI) using a novel breast-specific gamma camera and 99mTc-sestamibi in 42 patients with a high risk of breast cancer. Both trials are supported by OICR.

Prevention:

Dr. Paola Muti is leading two chemoprevention trials which are innovative and unique. Both are being done in collaboration with OCOG.

MELODI (Muti, Bane, Rana, Hodgson, Lovrics, Levine): In the first trial called MELODI, the potential anticancer effects of Vitamin D and melatonin are being studied with funding support from the JCC Foundation. Women who have been recently diagnosed with breast cancer are randomized to Vitamin D, melatonin or placebo for approximately three weeks. They then undergo definitive surgery for their cancer. The original tumour sample from the diagnostic biopsy is compared with the tissue from the surgery for Ki67, a marker of proliferation. It is postulated that the agents may reduce cancer cell proliferation. If either of these agents or the combination is found to be efficacious then this will provide preliminary evidence for larger prevention trials.

ABOCA (Muti, Julian, Kavsak, Kolb, Cox): the second trial is ABOCA. Laboratory studies on mesothelioma cell lines conducted by Dr. Muti's team in Italy showed that a phytocomplex extract from a type of artichoke, Cynara Scolimus, induced a strong reduction in cell viability, reduction in cell proliferation and invasiveness. Patients with asbestosis (a lung disease caused by occupational exposure to asbestos) are receiving the artichoke phytocomplex in a Phase II trial. The outcomes of the study are both circulating mesothelin, a protein associated with asbestosis and mesothelioma, and miRNA profile modulation. The trial has been developed through a collaboration established between Dr. Muti's team and clinical respirologists (Drs. Kolb and Cox) at the Firestone Chest & Allergy Unit at St. Joseph's Hospital, Hamilton. Dr. Kavsak's laboratory is performing the mesothelin assays. If this proof of concept trial is positive then large scale Phase III trials evaluating the artichoke substance as a preventive agent

can be conducted in workers exposed to asbestos and at risk for mesothelioma, a cancer with high lethality and for which there are limited therapies. The trial is funded by ABOCA Inc.

Laboratory Research (Muti, Steinberg, Blandino): With Dr. Greg Steinberg, Dr. Muti is investigating the biological interaction between two anti-cancer agents, salicylate and metformin, for the inhibition of prostate and lung cancer cell proliferation thus indicating a possible avenue of new clinical research for lung and prostate cancer prevention. Another area of research activity focuses on experimental studies of chemoprevention based on the discovery of agents that activate AMPK (a central cellular energy sensor that suppresses mTOR, one of the most potent oncogenic pathways) and inhibits lipogenesis, one of the main biochemical pathways supporting cancer development. Both are potential exciting candidates for testing in future cancer prevention clinical trials. Dr Muti has received CFI funds to build a new laboratory for studies of molecular epidemiology and cancer prevention.

Cardio-oncology Biomarkers (Kavsak, Dhesy and Leong):

Dr. Kavsak is a clinical chemist with expertise in cardiac biomarker testing. He and Dr. Dhesy have been conducting a prospective cohort study on women with HER2 positive breast cancer receiving trastuzumab. This agent can be associated with cardiac damage. In this study, high-sensitivity cardiac troponin is being measured to see if it can predict early cardiac damage. This is a bridge to the cardiac biomarker research at HHS led by Dr. P. Devereaux.

SCIENTIFIC COLLABORATIVE LINKAGES WITH OTHER GROUPS

Within the Institution (McMaster and HHS)

ECRI has been strategic in building scientific collaborations with basic scientists on the McMaster Campus. ECRI is important for translating their laboratory discoveries to the clinic.

<u>Immunology and cell-based therapy</u>:

In recent years there has been a series of research meetings between ECRI scientists (Drs. Hotte, Dhesy, Hirte, Juergens and Levine) and scientists from the McMaster Immunology Research Centre (Bramson, Ashkar, Lichty and Mossman) to plan translational research that will result in basic research moving into the clinic. Dr. Bramson has been appointed an Associate Member of ECRI. The first initiative that will move forward is a program of NK cell therapy. Recently a grant application was submitted to the Canadian Breast Cancer Foundation (CBCF) for a Phase I trial of NK cell therapy in women with locally advanced breast cancer (LABC) by Drs. Ashkar and Dhesy. Dr. Juergens has established a collaboration with the Chair of Biochemistry, Dr. Mossman. Dr. Bane is working with Dr. Lichty from McMaster to apply a gene signature which profiles immune function to triple negative breast cancer. Drs. Hotte and Lichty are collaborating on developing a vaccine for prostate cancer.

Imaging:

ECRI scientist, Dr. Juergens, is working with Dr. Valliant from CPDC and Dr. Gulenchyn, the Head of Nuclear Medicine at HHS, on the development of an IGFR-1 radiolabelled probe that can target tumour cells. Dr. Levine has collaborated with Drs. Valliant and Gulenchyn on the IMPACT trial which evaluated whether novel functional imaging with FLT PET and BOLD MRI could predict response to chemotherapy in patients with LABC.

Stem Cells:

In laboratory experiments in the Stem Cell & Cancer Research Institute at McMaster, Dr. M. Bhatia has shown that the drug thioridazine (which used to be used in patients with mood disorders) is effective in killing leukemic stem cells. A first in human Phase I clinical trial which is evaluating this agent in patients with AML has commenced. The research team includes Drs. Foley (hematologist, McMaster/HHS), Bhatia (stem cell biologist), Julian (biostatistician, OCOG) and Kim (clinical pharmacologist, UWO).

Cancer Biology:

Dr. Bane has established a collaboration with Dr. Hassell (cancer biologist, McMaster). Their main shared interest has been in deciphering the biology behind differing outcomes in basal-like breast cancer, a subtype of triple negative breast cancer.

Cancer Prevention:

Dr. Muti has established a collaboration with Dr. Steinberg at McMaster. She has space in his lab for her post doc to work. They have examined the relationship between metformin, ASA and breast cancer. Collaborations have been established with surgeons in Hamilton; Drs. Hodgson and Lovrics (MELODI trial) in which Vitamin D and melatonin are being studied and Drs. Kolb and Cox (pulmonary medicine, St. Joseph's Hospital) for the ABOCA trial which is studying artichoke extract in patients with asbestosis.

Quality of Life Models of Care:

Dr. Bryant-Lukosius has collaborations with local research teams (e.g. hematology, pediatrics, McMaster Health Forum) that focus on transitions in care and symptom management from a clinical and policy perspective.

Education:

ECRI has strong ties with the Department of CE&B. A number of ECRI scientists teach in this Department and supervise graduate students in the Health Research Methodology Program and the PhD Health Policy Program. Dr. Brouwers has designed the Knowledge Translation course for the HRM and leads it. Dr. Seow has recently designed and launched a new course in the HRM on innovation. He is a member of CHEPA.

Economic:

Dr. Levine has collaborated with Drs. Serrano (Surgery) and Gafni (CE&B and CHEPA) on an economic analysis of the PET CAM trial.

Cardio-oncology:

There is recognition that there is a unique relationship between cancer and disease of the heart. A collaboration has been established between Drs. Leung (cardiologist, HHS and PHRI), Dhesy and Kavsak. Research on cardiac biomarkers that could detect very early heart damage is ongoing. Approximately 20% of patients with breast cancer who are receiving adjuvant trastuzumab are unable to complete the full year of treatment because of a significant drop in their cardiac ejection fraction. Based on these considerations, Drs. Leung and Dhesy have recently prepared grant applications to Hamilton Academic Health Source Organization and the HHS Strategic Research Initiative for a Phase I trial of angiotensin converting enzyme-inhibitors (ACE-I) and beta blockers for those who develop mild cardiac dysfunction. The aim is to normalize the ejection fraction so that the patient can continue on with the trastuzumab.

Outside the Institution

Regional:

LHIN4: Dr. Simunovic is actively involved with regional surgeons as part of his ongoing surgical quality research program and has established an extensive network of community surgeons practicing in all hospitals in the region. Dr. Seow works closely with community partners in palliative and hospice care and consults extensively with local policy and planning bodies in the region. Dr. Sussman works closely with the Department of Family Medicine and with a number of local family health teams to engage in initiatives to improve provider integration and knowledge for cancer survivor care.

Along with Dr. Sussman and the JHCC Cancer Survivorship Working Group, Dr. Bryant-Lukosius has led several participatory action research initiatives with community-based primary healthcare providers to co-design new models of cancer survivorship care and to optimize nursing roles within these models.

Provincial:

OICR: ECRI scientists have been actively engaged with OICR programs including the Translational Research Team (TRT) and High Impact Clinical Trials (HICT) program. We have three OICR Clinician Scientists and hold a number of operating grants from OICR in support of individual studies (BOLD, PETRA, BIANCO and ATOM). Drs. Brouwers, Seow and Sussman are members of the HSR team of OICR and have received research funding. Dr. Brouwers is a member of the OICR HSR-KT Advisory Panel. Dr. Levine was a member of a special ad hoc subcommittee of the OICR Board to help prepare the OICR 2016-2021 Strategic Plan.

MOHLTC: OCOG worked very closely with two branches of the MOHLTC, the Medical Advisory Secretariat (now part of Health Quality Council) and the Out of Country Branch, to develop and execute the Oncotype Dx Field Evaluation. Dr. Seow has worked closely with Health and Research, Quality and Standards and the Provincial Steering Committee for Palliative Care.

CCO: Approximately five years ago CCO took over the sponsorship of the PET in Oncology program from the MOHLTC. This transfer was seamless and the OCOG team related to CCO for the trials described in the earlier section on research activity. Several of the ECRI scientists have leadership roles with CCO. Dr. Brouwers is the provincial leader of the Ontario cancer guidelines program, the Program in Evidence-Based Care. Dr. Sussman is the clinical lead for the Survivorship Program at CCO and has led projects in survivorship care transitions for both breast and colorectal cancer patients across the province. Dr. Bryant-Lukosius has held several leadership roles at CCO focused on optimizing health human resources and cancer care redesign, e.g. member of the Patient Reported Outcomes (PROs) and New Ambulatory Care (NAMOC) Advisory Committees. Dr. Seow is on the Palliative Care Advisory Committee.

ICES: Dr. Seow has continued his collaborations with ICES scientists. In addition, he has served on an important committee at McMaster which is responsible for bringing an ICES hub to McMaster. OCOG is working with Dr. Earle, the Head of Health Services Research at OICR and an ICES Scientist, to use administrative databases to collect outcome data in clinical trials.

National:

CPAC: Between 2007 and 2013 Dr. Brouwers oversaw the Capacity Enhancement Program of CPAC. Dr. Sussman is actively involved in CPAC provider integration policy and research and sits on a number of advisory committees.

Canadian Cancer Clinical Trials Network: Dr. Arnold has championed this new enterprise, the aim of which is to increase recruitment to academic trials. He has established a strong local network including St. Catharines and Cambridge. He was recently appointed Chair of the Provincial Steering Committee.

NCIC CTG: ECRI scientists continue to be actively involved in the CTG. Dr. Whelan is the co-chair of the breast group and Professor Julian and Dr. Wright sit on their data safety monitoring board.

KT Canada and KT Canada Strategic Training Initiative in Health Research (STIHR):
Dr. Brouwers is a member of Knowledge Translation Canada Research Network and McMaster University. She co-leads the KT Canada STIHR initiative.

International:

Dr. Bane is a member of pathology working groups to standardize measurement of biomarkers: the Ki67 International Working Group led by Torsten Nielsen (UBC) and the TILs International Working Group led by Carsten Denkert (Charité University, Berlin). Dr. Brouwers is the

principal investigator of the international research consortium AGREE Enterprise, which has established international standards related to guideline development and application (AGREE II, AGREE Health Services, AGREE Update and AGREE Recommendations). Dr. Muti has continued a strong collaboration with Dr. Blandino at the Italian National Cancer Regina Elena in Rome.

Dr. Bryant-Lukosius has research and graduate education collaborations in Switzerland (University of Basel, University of Lausanne) and also the University of Eastern Finland related to the evaluation of advanced practice roles in cancer and other sectors.

RESEARCH PRODUCTIVITY

Details of ECRI scientists' productivity in terms of publications and funding are summarized in Table 3 and Table 4, respectively.

Table 3: Summary of Publications (2011-2015)

Member		Publications*	1st Author	PEBC Guidelines
Andrew	Arnold	4		2
Anita	Bane	10	3	
Jonathan	Bramson	29		
Melissa	Brouwers	38	11	3
Denise	Bryant-Lukosius	9		1
Ian	Dayes	7	2	1
Bindi	Dhesy	13	2	
Laurie	Elit	58	19	4
Peter	Ellis	29	10	2
Karen	Gulenchyn	12	1	1
Hal	Hirte	29	1	
Sebastien	Hotte	34	1	1
Rosalyn	Juergens	7	2	
Jim	Julian	24		
Pete	Kavsak	54	27	
Mark	Levine	46	5	
Som	Mukherjee	22	3	
Paola	Muti	50	5	
Gregory	Pond	84	11	
Hsien	Seow	30	8	
Marko	Simunovic	25	8	1
Jonathan	Sussman	18	3	2
Anand	Swaminath	11	2	1
Tim	Whelan	24	4	
Jim	Wright	16		
		669	**131**	**19**

* Publications are not double counted.

Table 4: Summary of Funding (2011-2015)

Member	Principal Investigator			Co-Investigator*
	Peer Reviewed	Other	Industry Grants	
Andrew Arnold	$0.00	$1,000,000.00	$0.00	$0.00
Anita Bane	$2,304,645.00	$186,240.00	$0.00	$350,000.00
Jonathan Bramson	$4,855,000.00	$1,605,000.00	$398,000.00	$8,380,460.00
Melissa Brouwers	$6,637,159.00	$12,542,826.00	$0.00	$49,142,776.00
Denise Bryant-Lukosius	$385,500.00	$494,000.00	$0.00	$620,887.50
Ian Dayes	$215,504.00	$0.00	$0.00	$84,000.00
Bindi Dhesy	$0.00	$31,064.36	$0.00	$213,330.20
Laurie Elit	$1,285,524.51	$124,884.00	$68,000.00	$1,411,686.00
Peter Ellis	$0.00	$58,705.54	$0.00	$30,000.00
Karen Gulenchyn	$30,000.00	$0.00	$757,506.00	$1,632,950.00
Hal Hirte	$0.00	$0.00	$440,774.17	$0.00
Sebastien Hotte	$999,131.00	$0.00	$353,130.00	$1,272,499.88
Rosalyn Juergens	$1,450,000.00	$100,000.00	$500,000.00	$2,337,852.00
Jim Julian	$0.00	$0.00	$0.00	$5,294,685.00
Peter Kavsak	$394,135.00	$336,517.00	$158,486.00	$3,820,854.20
Mark Levine	$1,999,309.00	$1,296,586.00	$0.00	$3,712,271.00
Som Mukherjee	$100,000.00	$0.00	$0.00	$0.00
Paola Muti	$1,526,000.00	$0.00	$180,000.00	$300,000.00
Gregory Pond	$257,624.00	$0.00	$0.00	$1,185,695.00
Hsien Seow	$1,059,529.00	$1,414,066.00	$0.00	$1,211,565.60
Marko Simunovic	$2,019,562.00	$24,285.00	$0.00	$3,734,006.00
Jonathan Sussman	$1,120,000.00	$225,195.00	$100,000.00	$3,717,762.20
Anand Swaminath	$1,290,186.00	$0.00	$0.00	$568,514.00
Tim Whelan	$2,744,699.00	$120,813.00	$0.00	$6,057,458.00
James Wright	$0.00	$13,975.00	$0.00	$188,250.00
Total Funding	**$30,673,507.51**	**$19,574,156.90**	**$2,955,896.17**	**$95,267,502.58**

* Co-investigator funding only counted if ECRI scientist is not PI

RESEARCH PLANS (2016-2021)

Sutcliffe Review:

To prepare for ECRI's second five year term, the Scientific Director asked Dr. Simon Sutcliffe to conduct a review of ECRI's performance to date and to provide advice on ECRI's future direction with an eye to optimize its strengths and opportunities for success. Dr. Sutcliffe is an oncologist and is considered a senior statesman for Canadian oncology. He was previously President of the Princess Margaret Hospital, President of the British Columbia Cancer Agency, Chair of Canadian Partnership Against Cancer and Chair of the International Cancer Control

Congress. He is currently President of Two Worlds Cancer Collaboration. The review took place in the spring of 2015. In May 2015 Dr. Sutcliffe provided ECRI with a full report (see Appendix I). The two primary highlights of his report are as follows:

"Its First Five Years: ECRI, A Success in Uncertain Times"

Dr. Sutcliffe contrasted the research environments before the mid-2000s to more recent times. Specifically, Dr. Sutcliffe articulated that before the mid-2000s research institutes across the country were established relatively easily and frequently. In part, because of the greater ease to recruit research academics and the greater availability of research dollars. Since the mid-2000s the environment has become much more challenging on both fronts. 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. Despite this challenging environment, Dr. Sutcliffe concluded that ECRI has been extremely successful. The research dollars brought in from peer-review funding agencies, publications (number and quality), and the significance and breadth of collaborations and leadership roles among its members attest to its successful. Dr. Sutcliffe attributed the success of ECRI to the collaborative culture, the steadfast determination among its scientists and to the quality of the leadership that has enabled the ECRI members to work relatively unencumbered to do the science and not the administrative or operational aspects of the science. Dr. Sutcliffe encouraged ECRI members and its sponsors to celebrate this success and to not let the challenging environment impede its efforts to move forward.

"Its Next Five Years: ECRI Lead with Research-Driven Solutions to Cancer Problems"

Dr. Sutcliffe recommended that ECRI define itself by the problems it wishes to solve and to optimize the intellectual and collaborative capacity among its members to achieve its goals. To this end, he recommended that ECRI not be bounded by traditional research institutional governance, professional affiliations or allegiances. But rather, to enable fluidity in the roles and intensity of participation of its members so that research teams are tailored to ensure that the best combination of scientists and collaborators are brought together to solve a prioritized cancer challenge. In other words, ECRI's competitive edge should be that it provides the space by which scientists with common goals can create solutions. Practically, this would require shifting away from crafting research projects solely along the traditional themes of clinical trials, health services research and translational research and to a more "McMaster*ish*" problem-based philosophy – optimizing the intellectual capital and innovation of ECRI members and their collaborators to solve cancer problems. In addition, Dr. Sutcliffe described the biomedical research paradigm in a series of three sequential sinusoidal curves; discovery, validation and application, and that ECRI's greatest potential for significant impact was with the application phase of research.

Each ECRI scientist received a copy of the Sutcliffe Report. It was discussed by both the ECRI Executive and ECRI scientists at meetings over the summer and fall of 2015. The recommendations were enthusiastically embraced. Moving forward with the recommendations

is a work in progress. First, we discussed what to call the research entity envisioned by Dr. Sutcliffe and we agreed on **Strategic Research Collaboration (SRC)**. This was defined as an interdisciplinary team of ECRI members marshalling their expertise and focusing it to design and conduct studies that address an important cancer problem. We wanted to identify several SRCs. Identifying the theme for our first SRC was based on what was perceived by ECRI members as research strengths, unmet clinical need, magnitude of the problem, potential for alignment with JCC clinical program and the results of the body of research considered to have a very high potential for clinical and health system impact. As problems are addressed, new ones will be identified, with new collaborative teams forming to address this problem. This fluid approach represents a unique model of research collaboration which resonates with McMaster's problem-based learning and ensures that ECRI scientists will stay closely in tune with the most pressing problems for the cancer system. Meanwhile, individual ECRI scientists would continue their own portfolios of research to ensure that an exciting successful research enterprise provided the environment and foundation to fuel the SRCs.

Strategic Research Collaborations

To begin, we have identified four potential SRCs at various stages of development. These are all works in progress. The furthest along in its development is *Survivorship Care* which is the closest to being launched. Next in development is *Palliative Care*. The SRCs are built on existing strong ECRI research programs and the results they have generated in recent years. Processes that need to occur in the coming months include, but are not limited to: identification of SRC team members; refining the research agenda including deliverables; and defining a relationship with the JCC clinical program. In addition, two additional SRC programs have been identified that are in the incubation stages. One called, "Application and evaluation of precision medicine", looks at cancer risk stratification and implications for policy. The second will look at the role of uncertainty and its implications for clinical practice and health policy in breast cancer. In the coming months these will be developed more fully and launched. In time it is anticipated that we will have established a conceptual and methodologic framework which will enable us to roll out a number of SRCs.

<u>Survivorship Care</u>:

The Problem: Improvements in screening, which led to detection of cancer at an earlier and more treatable stage, and advances in treatments generally, have resulted in many more patients surviving a cancer diagnosis. It is estimated that by 2020, there will be 2 million cancer survivors living in Canada. The traditional measurement of five year survival rates are becoming increasingly obsolete as these do not accurately reflect the long-term implications of a cancer diagnosis, nor adequately capture the effects of a cancer diagnosis and therapy on the many thousands of patients who are now being cured every year. It is increasingly being recognized that the diagnosis and treatment of cancer can have lifelong implications. In many cases, the long-term toxicities of newer cancer therapies are not known. The increasing prevalence of cancer survivorship has created unique pressures and challenges within the health system with the recognition that new models of care need to be developed and evaluated if the cancer system is to optimally deliver care and remain sustainable. Cancer survivorship research strives to understand the long-term impact of a cancer diagnosis on patients, providers and the health

system. Survivorship research includes studies with a biological focus to understand the short and long-term effects of cancer therapies within the context of individual genomic profiles and health services research to understand the social and health system impacts of cancer diagnoses and therapies. Cancer survivorship has been poorly studied to date, presenting a unique opportunity for ECRI to take a leadership role in this area.

Strategy: Building on the research expertise and success of ECRI scientists over the next five years, survivorship-themed initiatives are planned in Models of Care and Late Effect Toxicities. For the former theme, a number of projects will be conducted:

- ECRI scientists and their collaborators will develop and test an inter-professional curriculum for trainees around survivorship care that involves family medicine and oncology. The pilot phase of this work has been funded by the Canadian Partnership against Cancer and is planned to be carried out in Ontario, British Columbia and Manitoba through 2017. Additional funding will be sought to extend this to a fully national initiative to train the next generation of clinicians in survivorship care as well as extend the initiative to other professional groups including nursing and pharmacists.
- A shared-care model of cancer survivorship care that addresses the complexity of survivor populations that cannot be fully transitioned for follow-up in a cancer program will be developed and tested.
- In order to understand the effects of implementing changes in the models of care (from oncology to primary care or shared care), ECRI scientists plan to measure the shifts in patterns of care over time and study adherence to follow-up guidelines and age appropriate preventive care to determine quality of surveillance for cancer survivors (breast, colorectal, prostate, lymphoma). This work aligns with national initiatives such as "Choosing wisely Canada".
- To study the extent to which self-management can be incorporated into survivorship care, projects are currently being crafted to design, implement and evaluate self-care in cancer survivors.

To develop a better understanding of the late effect toxicities of new cancer therapies on survivors, a series of targeted projects will be developed which will include:

- Understanding the gaps and opportunities in survivorship care from the perspective of a modern provincial cohort of cancer survivors through a comprehensive survey procedure that is funded by the Canadian Partnership against Cancer (2016) and to use the results of this study to inform the development and evaluation of supportive care strategies for survivors and community providers.
- Develop and test a strategy to efficiently and effectively collect toxicity data within the context of ongoing follow-up through clinical trials in the cancer centre as well as the community which will be led by clinical trials. We will explore the possibility of developing a survivorship cohort in the LHIN.
- Understand the implications of cancer therapies on heart function and outcomes through a series of projects within a specialized group of cardio-oncology research scientists.
- Leverage findings emerging from the translational team and other such researchers to determine patient populations for whom more or less intensive clinical surveillance strategies would be of benefit and to consider the implications for the types of follow-up and access to specialist care that will be required.

This is an ambitious research agenda. It will be led by Dr. Sussman. It is recognized that some of our research is national and provincial in scope. An important principle of the survivorship SRC is the engagement of the JCC cancer program in research, including patients, nurses and physicians.

Palliative Care:

The Problem: Despite advances in cancer treatment and improved survival rates for many cancers, there are still nearly 30,000 patients dying of cancer each year in Ontario. Palliative care is an approach to care that improves the quality of life of patients facing life-threatening illness and their families through the prevention and relief of suffering, pain and other problems related to the physical, psychosocial and spiritual domains. The need for access to palliative care in multiple settings is substantial, especially towards the end of life and the need will grow as the population ages and more cancer deaths are predicted. Studies estimate that only 30% of patients who die receive palliative care. Palliative care delivery through interprofessional teams can reduce symptom burden, improve quality of life and satisfaction, and reduce anxiety and depression. Furthermore, care through such interprofessional teams has been beneficial in multiple settings (e.g. hospital outpatient, hospital inpatient, home and hospice). There has also been a growing body of research demonstrating the economic benefits of providing palliative team-based care, as it helps to avoid unnecessary late-life hospitalizations which account for 50-70% of costs in the final year of life. Finally, although 80% of Ontarians prefer to die at home, 65% die in hospital.

Although the benefits of interprofessional team-based palliative care are well documented, the optimal model of care delivery across multiple settings is not clear. Research suggests that the optimal model depends largely on local contextual factors, and a one size fits all program model is not effective when spreading and scaling. Therefore, an important area of future research involves identifying the key components of effective palliative care models, how to adapt these components to diverse settings and local contexts, and the key factors for successful implementation and spread of sustainable care models. Additionally, as these models are being rolled out further research is required to measure their impact on the patient, family and the health system. ECRI scientists have the clinical and research expertise to lead this work in Ontario and nationally.

Strategy: Over the next five years, palliative care themed initiatives are planned in interprofessional team-based palliative care and quality indicator measurement. For the former theme, a number of projects will be conducted:

1) ECRI scientists and their collaborators will investigate the science of how to enhance palliative care in the home and community setting through interprofessional primary care teams, using a capacity-development model. This work aligns with provincial priorities to enhance palliative care capacity.
2) Improving clinical care within the inpatient hospital setting will be explored through enhanced interprofessional collaboration, capitalizing on the existing multidisciplinary providers within the cancer centre.

3) Exploring collaborations with oncology specialists and primary care providers to work in a more integrated and collaborative approach so that patients requiring palliative care can move more seamlessly between settings.
4) In the local LHIN, ECRI scientists will identify clinical processes to identify cancer patients who would benefit from palliative care earlier in their disease progression and implementing appropriate care pathways to better manage symptoms and reduce unmet needs.

To advance quality measurement in palliative care, a series of targeted projects will be considered, which will include:

1) ECRI scientists will advance existing measures of health system performance (e.g. over aggressive care, such as rates of emergency department visits in the last two weeks of life) by reporting variation and benchmarking rates by cancer type and regional cancer centre.
2) Optimizing the use of existing electronic medical records with clinical data to measure quality of symptom management for palliative cancer patients.
3) Developing a reliable and valid set of patient and caregiver-reported outcomes that measure the experience of care and quality dimensions across multiple settings. This will also include identification of optimal survey methods, testing in diverse settings and comparing outcomes by cancer types.
4) Testing of the patient and caregiver-reported outcome for cancer patients in the local LHIN hospitals to identify areas of excellence and areas for improvement.

This research agenda will be led by Dr. Seow (palliative systems) and Dr. Brouwers (implementation science) and a palliative care clinical co-lead (who will be appointed). It is recognized that some of the palliative care research is national and provincial in scope. Through this co-leadership model we will be able to accelerate health system and clinical advances in palliative care to have a measureable impact on patients, families and our community. It will support oncology providers to work in effective interprofessional teams so that care is more integrated and coordinated across care settings. This means that patients and families will receive more timely, efficient and effective palliative care services in our local LHIN, across the province and nationally.

<u>Application and Evaluation of Precision Medicine</u>:

The Problem: Precision medicine refers to the tailoring of oncologic treatments to the unique characteristics of the patient and his/her tumour. It is dependent on biomarker testing of the cancer, often genetically-based, to identify unique abnormalities that predict outcome and/or response to particular treatments. While the goals of such an approach are admirable there are inherent challenges: evidence supporting the clinical utility of biomarker tests is often scant and of poor quality and the accompanying cascade costs to the health system can be considerable. Explicit consideration of the cost utility of candidate tests is rarely factored into the scientific inquiry. Yet there is advocacy from patients, oncologists and researchers for the use of such tests in practice.

Biomarker testing in translational oncology has focused largely on risk stratification and the identification of targets that can direct treatment decisions. For example, in breast cancer

commonly used tests include the Oncotype Dx® Recurrence Score (RS), and the Prosigna® RS which is based on the PAM50 gene signature. These tests can risk stratify patients and potentially predict response to chemotherapy, although validation of the latter is yet to be obtained. The costs of both of these tests are ~ $4,000 U.S. per patient.

Ontario has a publicly funded health care system and the healthcare budget is fixed. Ideally, any new innovative test that is adopted for a clinical indication should displace a less effective test of similar cost. To do this, we have to answer the question: Is the clinical utility of this test worth the costs? At the core of our new emerging SRC theme is the hypothesis that there are less expensive alternatives to some of the genomic biomarkers that have enticed the research community and been widely adopted by oncologists for risk stratification and prediction of treatment response. Our research in this area will include development of reliable, valid and efficient tests; evaluating the cost utility of the tests; and assessing the system capacity to support adoption of the tests.

Strategy: We have identified key areas of inquiry to begin to develop the CRC theme:

- The LUMINA trial will explore if a simpler and less expensive marker of cell proliferation, Ki67 measured by IHC, can in addition to ER/PR testing identify low risk node negative breast cancer patients who can avoid WBI following BCS surgery and to response to regional nodal irradiation in patients with node positive breast cancer.
- Recent research demonstrating that NSCLC can be associated with a number of genetic abnormalities that may revolutionize the treatment for patients. At present, different genetic abnormalities are tested separately in different laboratories. This is logistically challenging and expensive. We will explore the role multiplex testing (a type of assay that simultaneously measures multiple analyses in a single run) as an alternative that is more efficient, patient friendly and cost effective approach.
- In the BIANCO study we are trying to determine whether a combination of routine tests, e.g. ER, PR, grade, and Ki67 can be used to identify a group of patients who do not require Oncotype DX® testing. If this methodology is successful then we will apply it to other expensive molecular biomarker tests.

ECRI Scientist Portfolios

Clinical Trials:

Muscle-invasive bladder cancer (Levine, Pond, Mukherjee): During the last 12 months a new trial entitled, "Impact of Positron Emission Tomography (PET) Imaging in Muscle-invasive Urothelial Carcinoma of the Bladder Staging (PET MUSE)" has been developed and the first patient should be enrolled in December 2015. Patients with muscle invasive bladder cancer are staged prior to radical cystectomy and bilateral pelvic and iliac lymph node dissection. Such patients will be randomized to staging with PET-CT or no PET-CT. Our hypotheses are that staging with PET-CT will identify more extensive metastases: 1) pelvic and para-aortic lymph nodes resulting in more aggressive surgery (e.g. extended lymphadenectomy), 2) distant disease (e.g. liver, lung and bone) resulting in avoidance of cystectomy and administration of palliative therapy, and 3) the detection of more extensive local disease will stimulate increased use of neoadjuvant chemotherapy. The PIs are Drs. Srikala Sridhar (medical oncologist, PMH),

Nicholas Power (urologist, London Regional Cancer Centre) and Som Mukherjee (medical oncologist, JCC). The trial is funded by CCO.

ATOM (Krzyanowski, Grunfeld, Julian, Howlett, Levine)*:* Approximately 25% of Ontario breast cancer patients receiving adjuvant chemotherapy visit the emergency room or are admitted to hospital because of uncontrolled nausea/vomiting, febrile neutropenia, or drug-induced pain (range, 5%-35% across sites). Such toxicity events affect the quality of life of the patient and place a substantial economic burden on the system. Dr. Krzyanowski (medical oncologist, PMH) and her colleague Dr. Grunfeld (Department of Family Practice, University of Toronto) have developed a nursing intervention which contains both education and care components in order to reduce the rate of toxicity events. OCOG is coordinating an OICR-funded cluster randomized trial involving 20 Ontario sites. It is anticipated that the trial will commence in the first quarter of 2016.

Continuation of Previous Radiation Trials: The RAPID trial will complete follow-up in the next 2-3 years and a final analysis is planned. The LUMINA trial will continue accrual for a further two years with a planned analysis toward the end of five years. The BRACHY trial is expected to complete accrual in early 2016 with an analysis performed towards the end of that year. The LUSTRE and ALMERA trials will continue accrual over the next 2-3 years with planned analyses in 2020.

OPAR (Kim, Whelan, Julian): The results of our RAPID trial show an adverse effect of APBI on breast cosmesis. We postulate that based on radiobiology principles, the twice daily schedule was the cause of the adverse cosmesis. We recently received funding from the Canadian Breast Cancer Foundation (CBCF) for a randomized Phase II study to compare two candidate schedules for APBI delivered once a day (30Gy or 27.5Gy both in once daily fractions over five days). If one of these schedules is demonstrated to have acceptable toxicity it will be taken forward for a direct comparison with the current standard approach of hypofractionated WBI in a large randomized trial.

SBRT for Oligo-metastatic Breast Cancer (Whelan, Swaminath): It is hypothesized that in patients with oligo-metastatic disease (limited, i.e. $\leq$ 3 metastases), ablative therapies directed at metastatic sites may improve prognosis by reducing tumour burden and preventing reseeding by tumour cells. Our goal is to prospectively determine if treatment of oligo-metastases with SBRT in addition to systemic therapy in patients with ER positive breast cancer improves outcome compared to systemic therapy alone. A randomized Phase II trial is under preparation. If SBRT is confirmed to improve progression-free survival and overall survival it will establish this modality as a viable option for patients with oligo-metastatic disease.

Ductal Carcinoma in situ (Whelan, Rakovitch, Parpia, Levine): Ductal carcinoma in situ (DCIS) is a premalignant condition of the breast that is typically detected on screening mammography. Most cases of DCIS are indolent and do not develop into invasive cancers. Nonetheless, most cases are treated with breast conserving surgery followed by radiation. There is general agreement that DCIS is over-treated because it is not possible to distinguish those cases of DCIS which will become invasive from those that are benign. Genomic Health Inc. has developed a 12 gene test which may identify a group of DCIS patients with a very low risk of developing

invasive cancer. These patients could potentially avoid breast irradiation. Dr. Whelan and team will conduct a cohort study to evaluate if the use of the DCIS score changes the treatment recommended by the radiation oncologist and changes the treatment preference of the patient. The trial is funded by Genomic Health.

Quality Care & Knowledge Translation (KT):

Note: Survivorship and Palliative Care are discussed in SRC section

KT Challenges (Brouwers)*:* Over the next five years, Dr. Brouwers will extend her research to investigate why advancements made by KT scientists are not adopted by knowledge users to solve real-world health challenges. She will investigate research-driven and knowledge user-centred solutions which are practical and usable and carefully consider the issue of context features (e.g. values & preferences, system & organizational design). Specifically, within the context of cancer, Dr. Brouwers will study how usability and context features mediate/moderate the effectiveness of KT interventions aimed to improve the uptake of evidence in the cancer field. She will explore the theoretical underpinnings of these relationships and identify predictable patterns where usability and context features optimize effectiveness of KT interventions in the cancer field. Using these data, Dr. Brouwers she will create effective and usable solutions that translate the most promising advancements in KT science to solve real world cancer problems, with a particular focus on survivorship and palliative care.

Quality of Life and Patient Experience, Integrated Care and Effectiveness (Bryant-Lukosius): Dr. Bryant-Lukosius' research plan for the next five years aligns with McMaster's strategic area of priority for Integrated Health Research and CCO's (2015) Cancer Plan IV priorities for Quality of Life and Patient Experience, Integrated Care and Effectiveness.

The overall goal of this program of research is to collaborate with a design team of patients, cancer and community-based primary healthcare providers, and healthcare decision makers (CCO, primary care, LHINs, MOHLTC) to develop and evaluate patient and provider targeted interventions to promote patient activation and optimize self-management support across the cancer journey. As a first step, funded by the Ruth and Lewis Sherman Foundation to 2017, a mixed method study will be undertaken to examine current evidence, evaluate current practices and examine patient, provider, team, organization and system barriers to promoting patient activation and self-management support for cancer survivors. Using a participatory approach, interventions targeting patients and providers will be designed to improve patient health and quality of life and their healthcare experiences through increased patient engagement in their healthcare and optimal self-management support. This first study will provide a foundation about the components needed for a patient-activation and self-management program and factors to tailor it to different communities. This study will be followed by pilot studies to test candidate implementation intervention strategies (e.g. interprovincial education) and the requirements for a cluster randomized controlled trial to enable the evaluation of the effectiveness and costs associated with this program.

Cancer Surgery (Simunovic): Over the next two years we will complete the CIHR-funded evaluation of the QICC-L4 that compares relevant measures in LHIN4 versus other regions of

Ontario for the years 2006-2012. Over the next five years we will continue to explore more effective ways of optimizing the delivery of colorectal cancer surgery. For example, we have done preliminary work on a Surgical Events Reporting System (SERS). SERS is ostensibly a root cause analysis of a negative patient outcome (local tumour recurrence). We recently completed a pilot evaluation of negative events among 14 LHIN4 patients and found that in 12 of 14 cases a deficiency could be identified in one or all of the following: radiology performance, pre-operative surgeon performance or intra-operative surgeon performance. We will also explore the potential of the QICC-L4 project to facilitate accrual of patients to clinical trials. We have recently secured funding to enroll patients in a complex rectal cancer trial called RAPIDO. While RAPIDO is exploring a compelling clinical question, our main interest is in determining if the QICC-L4 study team can do the following:

1) Use the CCO e-Path pathology system to identify new patients with rectal cancer
2) Use the OneView radiology data repository to review cross-sectional imaging and determine if individual patients are eligible for RAPIDO
3) Have the involved surgeon make a timely referral to the Walker Family Cancer Centre in St. Catharine's or the JCC and potential enrollment in RAPIDO. Accrual rates (accrued/eligible) are usually in the single digits for colorectal cancer trials in LHIN4 and in Canada.

We hypothesize that by engaging surgeons early in the accrual process, accrual rates can be markedly increased.

Translational Research:

Triple Negative Breast Cancer (Bane, Whelan): Our work to date in TNBC has highlighted the importance of the host immune response and the tumour immune microenvironment for determining outcome in this often poor prognosis group of patients. Over the next 2-3 years our plan is to expand on this work and profile our entire cohort of 163 TNBC for the immune related genes described and examine the relationship with patient survival. In addition, we will attempt to reduce the number of immune genes required for TNBC subgroup classification, from the current > 700 genes to a more manageable and cost-effective set. The resulting immune gene signature will be tested prospectively on samples from patients with TNBC in the MA21 randomized trial, conducted by the NCIC-CTG that compared three different chemotherapy regimens in early stage breast cancer. A validated gene signature which could be adopted in the clinic would significantly improve risk stratification for TNBC patients and improve decision-making around adjuvant chemotherapy.

If we succeed in validating our signature for clinical use to risk stratify TNBC patients, we would then seek to examine whether the signature could potentially be used to predict which patients with TNBC would derive benefit from the use of immunotherapies.

Biomarkers in Radiation Therapy (Bane, Whelan): We anticipate completing accrual to the LUMINA trial in 2018 and following patients to assess the five year local recurrence rates.

The NCIC CTG MA.20 (PI, Whelan) was described earlier. Based on an exploratory analysis of this trial, we hypothesize that molecular subtype of breast cancer can predict response to RNI.

We plan to acquire the tumour blocks from patients enrolled in this trial and test them for molecular subtype using a panel of six IHC antibodies (ER, PR, HER2, Ki67, EGFR and Ck5/6) and evaluate the ability of molecular subtype to predict response to RNI in patients with node positive disease. This work will continue to build on the concept of improved risk stratification for breast cancer patients and therapy avoidance in select low risk individuals.

Immunotherapy-NK Cells (Ashkar, Dhesy, Hirte, Juergens, Hotte, Levine): Proof of principle Phase I trials are planned in patients with locally advanced breast cancer and ovarian cancer.

Immunotherapy-oncolytic virus (Lichty and Hotte): Dr. Lichty's expertise in oncolytic virus research and Dr. Hotte's interest and expertise in oncolytic virus clinical trials, developmental therapeutics and prostate cancer have led to an exciting collaboration in a $5M Movember grant (PI, Dr. Bell, Ottawa) to develop a targeted oncolytic virus vaccine for the treatment of prostate cancer. The primary objective of this project will be to adapt our novel Oncolytic Virus Vaccine (OVV) approach for the context of prostate cancer and evaluate its potential in a clinical trial. As a second objective, we will develop the next generation of oncolytic virus vectors and therapeutic approaches tailored to prostate cancer. Specifically, we will use patient specimens to evolve oncolytic virus platforms to grow more effectively in prostate cancer. We will also develop a combination therapy approach employing docetaxel, a gold standard for treatment of advanced prostate cancer that we have found to be a "viral sensitizer" that can enhance the activity of oncolytic viruses.

Prevention (Muti): Dr. Muti's is now focusing on the anticancer effect of a Mediterranean diet that is characterized by a high intake of vegetables and fruits, plant proteins, whole grains, fish, olive oil and low fat dairy. Systematic reviews and meta-analyses of observational studies have provided strong evidence that adherence to a Mediterranean diet confers significant protection against cancer incidence and mortality, including breast cancer. However, the precise mechanism is still unknown. Dr. Muti has recently submitted an application to the CCSRI to examine the association between Mediterranean diet and miRNA profiling (or miRNA as single entity) with the hypothesis that the Mediterranean diet down-regulates expression of multiple miRNAs impacting on a complexity of pathways connected to the inhibition of oncogenesis.

ORGANIZATION

Leadership:

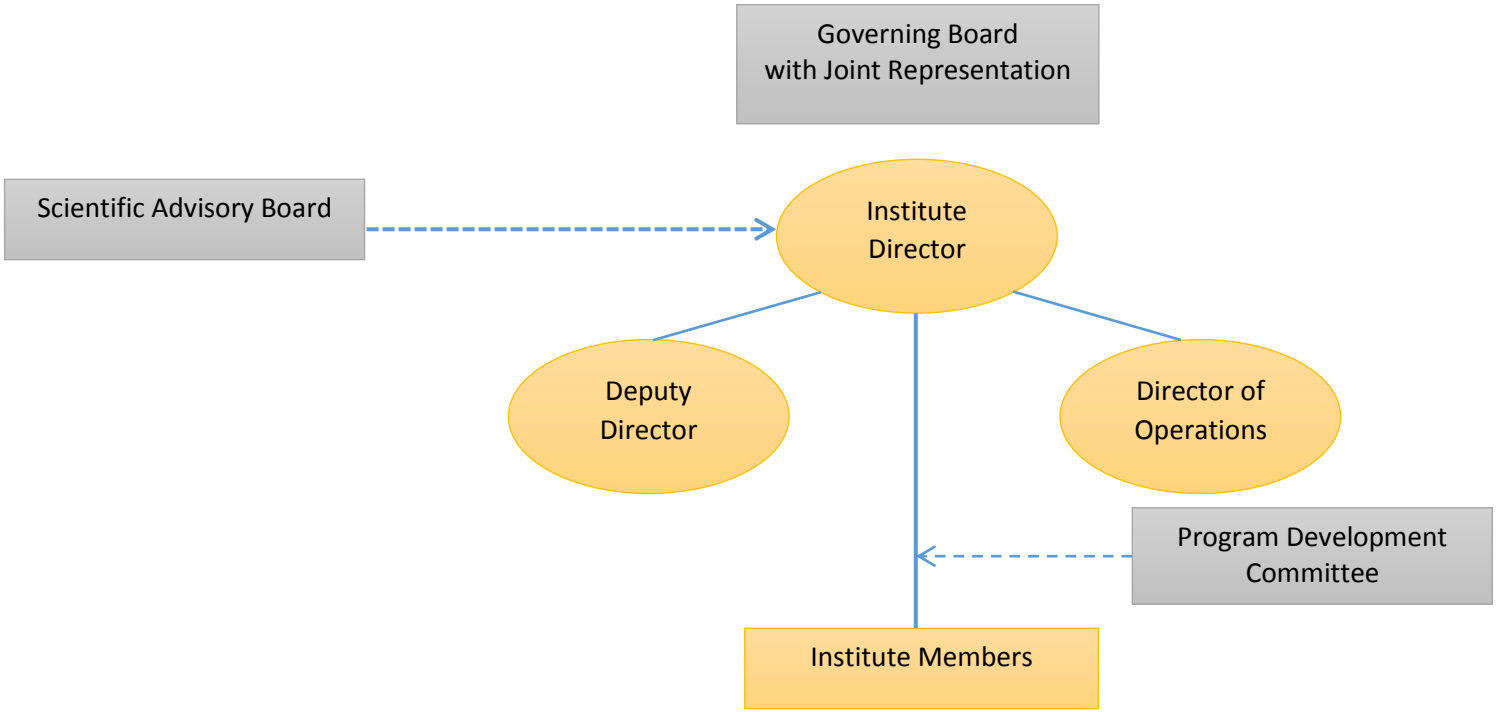
Dr. Mark Levine is the *Scientific Director* of ECRI. Dr. Levine is Head of Cancer Research at Hamilton Health Sciences and Chair of the McMaster Department of Oncology. While these leadership roles are not necessarily intended to be synonymous, it has been extremely important for Dr. Levine to hold these multiple leadership roles while ECRI was being established. The Scientific Director is responsible for developing and leading the scientific program; for reporting to the governing board on ECRI performance; for recruiting and mentoring scientists; for conducting annual reviews of scientists; for leading fundraising initiatives to support the institute; and for liaising with the President of the Cancer Centre in the development of a research agenda that is synergistic with the priorities of the cancer program.

The *Deputy Director* of ECRI, Dr. Melissa Brouwers, is responsible for reviewing and recommending Associate Members; for representing the Scientific Director in development of the research agenda; for chairing quarterly meetings of theme leads; and for contributing to the annual performance reviews of scientists.

The initial ECRI research agenda was conceptualized around three thematic areas: clinical trials, quality health care and knowledge translation, and an emerging area of focus in translational research, which was buttressed by a four year $1M grant from the Ontario Institute for Cancer Research (OICR) (2011-2014). ECRI *Theme Leaders* are expected to hold regular meetings of theme members in order to foster research collaboration; work with the group to monitor and pursue relevant granting opportunities; and identify potential research collaborators. Theme leaders include Drs. Anita Bane and Sebastien Hotte (translational research), Tim Whelan (clinical trials), and Hsien Seow (quality health care and knowledge translation). These leaders are members of the Program Development Committee.

The *Director of Operations* for ECRI, Anne Snider, is responsible for the development of a business plan for the institute; for liaising with Hamilton Health Sciences and McMaster University in the development of policies and practices; for liaising with research managers affiliated with ECRI; and for ensuring goals associated with communications, IT, facilities, grants, contracts, meetings, seminars, the annual research day, the annual retreat and reporting requirements for the institute are supported.

Figure 1: Organizational Structure



Organizational Structure:

ECRI has a relatively flat organizational structure (Figure 1), which reflects its infancy as a research institute, its collaborative model of operation and its limited organizational infrastructure. Apart from the individuals listed in the Leadership section above, all of whom carry multiple responsibilities, there have been no dedicated staff positions to support ECRI activities. Staff in the Department of Oncology has been informally seconded to support specific activities such as organization of the annual research day or completion of an IT infrastructure needs assessment.

The ECRI structure respects the organizational structure of pre-existing research groups which came together to form ECRI. Research groups such as the Ontario Clinical Oncology Group (OCOG), the Supportive Cancer Care Research Unit (SCCR Unit) and the Canadian Centre for Oncology Advanced Practice Nursing (OAPN) were established prior to 2011 and continue to fulfill their individual mandates which include specific internal and external lines of accountability. The co-location of the Cancer Care Ontario Program in Evidence-Based Care with ECRI provided an important enabler and driver of the ECRI health services and knowledge translation research agenda while retaining its own internal structure and mandate. The Juravinski Cancer Centre Clinical Trials Department provided an important enabling infrastructure for the ECRI clinical trials research agenda and reflected a longstanding integration of clinical trials research within the cancer centre's quality of care delivery framework.

ECRI Scientists:

All ECRI Scientists hold full time faculty appointments at McMaster University. Their funding is supported by their home departments (Table 5). Home departments include Oncology, Surgery, Ob/Gyn, Pathology and Molecular Medicine and the School of Nursing. Full members of ECRI are expected to have an active scholarly research program in an area relevant to the cancer research goals of the institute and to hold peer-reviewed funding. Associate members of ECRI are expected to be collaborating with full members on projects of relevance to the mission of the institute or to have held peer-reviewed funding for less than two years.

Table 5: Current salary support for ECRI scientists

Name	Source of salary support
Arnold	ONT-MOA
Bane	OICR Career Scientist, HRLMP, Department of Oncology
Brouwers	Department of Oncology, Cancer Care Ontario
Bryant	McMaster School of Nursing
Elit	Gyn/Oncology ONT AFP
Hotte	ONT-MOA
Hirte	ONT-MOA
Juergens	OICR Clinician Scientist, Department of Oncology
Julian	HHS
Kavsak	Department of Pathology and Molecular Medicine
Levine	Buffett Taylor Endowed Chair, HHS, McMaster, ONT-MOA
Muti	ArcelorMittal Endowed Chair, Department of Oncology
Pond	OICR Career Scientist, Department of Oncology
Seow	CIHR Career Award, CRC Tier II
Simunovic	Department of Surgery , HHS
Sussman	Rad onc ONT AFP
Whelan	Tier I CRC, Radiation Oncology ONT AFP

Decision-making:

Program Development Committee

The Scientific Director, Deputy Director, Director of Operations and Drs. Bane, Whelan and Sussman and representatives/leaders each of the themes, form the ECRI *Program Development Committee* which meets on a monthly basis to steer the development of the institute. In addition to setting institute priorities, the Program Development Committee provides strategy and direction for pursuing opportunities for crosscutting and multidisciplinary research programs and projects.

Scientific Advisory Board

To date, ECRI has not established a Scientific Advisory Board, largely because its program of research has been in a formative stage. In May 2015, Dr. Simon Sutcliffe, who has held significant cancer research leadership positions including former Head of the BC Cancer Agency, President and CEO of the Ontario Cancer Institute of the Princess Margaret Hospital and Board Chair of Canadian Partnership Against Cancer, was invited by Dr. Levine to conduct an informal evaluation of ECRI and to advise on how ECRI might focus its research priorities in order to maximize its success and impact going forward. Dr. Sutcliffe's report has formed the basis for the vision for the future outlined in section on Research Plans.

Setting a Collaborative Agenda with the Cancer Program

Two of the core and founding principles of ECRI were to create a research institute that would be highly integrated in purpose with the priorities of the Juravinski Cancer Centre at Hamilton Health Sciences; and to create a program of research that would lead to immediate and demonstrable benefit for cancer patients and their families in the region served by Hamilton Health Sciences. The *LHIN as a Lab* concept has been used to describe this approach. The ECRI Scientific Director and President of the Cancer Centre hold regular meetings to discuss opportunities for collaboration. Successful pilot projects and cross-collaboration between clinicians, administrators and scientists have led to the formulation of a focused research agenda for ECRI for the next five years which reflects this important collaboration.

COMMUNICATION STRATEGIES

Communication strategies:

Branding

Branding materials were developed over the 2013-14 year. The ECRI website http://www.everypatientmatters.ca was launched in the fall of 2014. Branding materials were developed to be used by ECRI members for business cards, email signatures, PowerPoint slides and letterhead. ECRI members are encouraged to include reference to ECRI in publications and at academic conferences.

Annual Research Day

ECRI hosts an *annual research day* designed to bring together ECRI scientists, their staff and trainees. The goal of the research day, held onsite at the JHCC, is to share and celebrate science, to facilitate collaboration, and to stimulate new ideas. To date three research days have been held. Key note speakers and ECRI collaborators speaking at the research day have included Drs. Allison Sekuler, Associate Vice President and Dean of the McMaster School of Graduate Studies; Brian Lichty, McMaster Immunology Research Centre; Ms. Susan King, Director of the Hamilton Niagara Haldimand Brant Regional Hospice Palliative Care Program; and Dr. Ralph Meyer, President of the Juravinski Cancer Centre and Regional Vice President Cancer Care Ontario.

At the most recent research day, held on January 30, 2015, over 100 researchers, staff and students participated in the day titled, *Personalizing Medicine: Improving Cancer Care from Cells to Communities* (http://ecri.ocean.factore.ca/posts/8-ecri-research-day).

Annual Retreats

All members of ECRI attend *annual retreats* focused on key aspects of institute development. As much as possible, consensus is sought amongst ECRI members regarding strategic direction for the Institute (Appendix II).

ECRI Research Rounds/Seminars

ECRI scientists, Fellows, and senior research staff meet on a bimonthly basis to present emerging research ideas, research in progress, or to update one another on pending grant applications and opportunities for collaboration.

FINANCIAL STATUS

Current financial status:

ECRI was established in 2011 with no direct operating funds but with significant in-kind or investment support from its host organizations:
Hamilton Health Sciences:

- The allocation of research space for ECRI on the JHCC campus
- The designation of Dr. Levine as Head of Cancer Research at HHS and contribution to his base salary
- Seed salary funding for ECRI Scientists (Bane, Pond, Brouwers)
- The allocation of a portion of a Cancer Program Director (AS) time to support the development of the Institute
- Investment of $30K in 2008 for development of a functional plan for the Institute, completed in 2010
- Investment of $150K in 2011 for development of a design brief for the Institute, completed in 2013.
- $50,000 strategic grant to develop integrated lung cancer research proposal.

McMaster Faculty of Health Sciences and Department of Oncology:

- Seed salary funding for ECRI Scientists (Bane, Pond, Brouwers)
- Salary funding and laboratory space for Dr. Muti
- Support for operating costs to support annual research days
- Support for costs of development of website and branding material
- Faculty time
- Research staff time to support annual research days
- Core operating support for Dr. Muti

Scientist Salaries:

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. There are no endowed faculty positions directly associated with ECRI at this time, but this could be a focus for the future, especially in terms of a future position of Scientific Director, should Dr. Levine retire.

Research staff and trainee salaries:

These are supported by individual researchers through research grants. Trainees, clinical and non-clinical, are seen as excellent mechanisms to facilitate collaborative interdisciplinary

research. Therefore securing funding for ECRI Fellows is a goal for the next five year term of ECRI.

Infrastructure staff:

Apart from a portion of the time of a JCC Director to fulfill the role of ECRI Director of Operations, and a part-time, one-year secondment of research staff to support special projects, 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. The establishment of this infrastructure will be a priority for the next five year term of ECRI.

BUSINESS PLAN 2016 – 2021

In November 2015, Hamilton Health Sciences agreed to direct cancer research funds held by the organization towards a consolidated operating budget for ECRI. The Faculty of Health Sciences also agreed to allow the Department of Oncology to direct residual cancer research funds, in order to match HHS funds, towards a consolidated operating budget for ECRI. Together this will provide the basis of a five year operating budget for ECRI at the level of ~$200,000 per year for five years. This will provide some stability for basic ECRI operations including logistical support, funding for an annual retreat and annual research day, support of the ECRI website and annual funding to support the recruitment of an ECRI Research Fellow. It is also expected that ECRI should form a Scientific Advisory Board (SAB) to help support and guide its development over the next five years. A portion of these infrastructure funds will be used to support travel and honoraria costs of the SAB. With this foundational infrastructure support in place ECRI will be able to start a process of raising capital for longer term sustainability through industry support, donor support or other mechanisms of contributions from ECRI scientists. The proposed allocation of these funds is shown in the spreadsheet below. A detailed five year budget will be prepared once funding arrangements have been confirmed and funding transfers completed.

Table 6: ECRI Annual Operating Budget (2016-21)

Personnel	FTE	$ inclusive of FB
Research Coordinator	1	80,000
Admin Assistant	0.25	20,000
Fellow	1	40,000
Expenses		
Annual research day		5,000
Annual retreat		5,000
Website hosting		1,000
Office expenses		5,000
Communications		5,000
SAB honoraria		10,000
SAB travel		10,000
Total		**181,000**

Fundraising:

Fundraising to support ECRI will be a focus of the next five years and there will be multiple strategies. These will be formally consolidated in a fundraising plan, in consultation with leadership and Foundation/Advancement offices of ECRI host institutions. Examples include:

Patient and Family focused events:

Each year over the past eight years, the Breast Cancer Disease Site Team of the Juravinski Cancer Centre has held the BRIGHT Run (http://www.brightrun.ca/) in the Dundas Valley Conservation Area. Over $2M has been raised to support breast cancer research led by investigators at the JCC, many of whom are ECRI scientists. The BRIGHT Run is a highly visible and positive fundraising event that engages patients, families, cancer centre staff and researchers. Events like these are examples of the type of fundraising that ECRI could engage in in the local community and emphasizes the direct relationship with patients and the community that ECRI research is intended to support.

Industry Partnership:

In addition to holding peer reviewed grants, many ECRI scientists conduct research supported by industry: pharmaceutical, radiation and imaging equipment and biomarker technology industry. There are many potential industry partners who might be approached to support ECRI research projects, Fellows or capital development.

Naming Opportunity/Capital Development:

When ECRI was formed, the name *Escarpment Cancer Research Institute* was used as a placeholder; recognizing there may be a significant naming opportunity, should the capital development of a research institute as envisioned in the functional plan and design brief already completed by HHS move forward. While all ECRI scientists and their staff are currently housed on the JHCC site, they are disbursed across more than one location. The vision of the design brief is to build a dedicated research institute at the heart of the JHCC campus by replacing the aging infrastructure of the G Wing and renovating the original Henderson Research Institute in the H Wing. The opportunity to create a highly visible research and learning hub, open to the public for special events, would certainly catapult the visibility of ECRI in the host organizations and in the community.

Endowed Research Positions:

To date funding for ECRI scientists and the ECRI Scientific Director has been primarily the responsibility of the Chair of the Department of Oncology. As ECRI and its host institutions look to the future, the establishment of secure funding through endowment should be considered.

SUMMARY

Over the last 4½ years ECRI has made substantial progress in meeting its goal of conducting research that impacts on the lives of people affected by cancer. Researchers have benefitted from the consolidation and co-location of their activity and purpose within the new research institute. In addition, ECRI has fostered collaboration with basic scientists at McMaster in order to build on collective expertise and to pursue interdisciplinary avenues of research. By the standard academic metrics of grants and publications, ECRI scientists have been very productive. Furthermore, the results of ECRI studies have changed patient care, benefiting both patients and the cancer system. As a research institute, ECRI has several unique features including: a focus on its research having immediate benefit for patients in our own community; expertise in a number of cross-cutting methodologies such as clinical trials and knowledge translation; and embedment in a regional cancer centre which ensures that the research is clinically relevant and can address the most pressing issues facing cancer patients and the cancer system.

When ECRI was launched in July 2011, the research it conducted was built around the themes of Clinical Trials, Quality Care & Knowledge Translation and Translational Research. This reflects the organization of cancer research generally and was a useful starting point for building initial teams within these thematic areas. Having achieved this initial level of development, ECRI sought external input to help consider ways that the institute might extend its potential for greater impact.

Dr. Simon Sutcliffe was invited to conduct a review of ECRI's performance and to provide advice on ECRI's future direction with an eye to optimizing its strengths and opportunities for success. His review occurred in May 2015. Discussions with Dr. Sutcliffe, one of the most eminent cancer leaders in Canada, were stimulating and very important in terms of shaping the ECRI direction for the next five years. He commended ECRI for having been very successful in

a challenging environment and stated that by all standard academic measures, ECRI and its members had been productive and impactful. Most importantly, he provided advice and strategy on how ECRI could move forward to realize its full potential by embracing a problem-based approach to prioritized cancer challenges through the use of fluid, interdisciplinary teams led by ECRI researchers and including collaborators across multiple disciplinary domains. Practically, this would require shifting away from crafting research projects solely along the traditional themes of clinical trials, health services research and translational research to more of a problem-based approach that optimizes the intellectual capital and innovation of ECRI members and their collaborators to solve cancer problems.

This concept resonated with the ECRI leadership and was embraced by the scientists. To realize this vision, ECRI has developed the concept of a Strategic Research Collaboration. Four Strategic Research Collaborations have been identified, two of which (Survivorship, Palliative Care) are already well established in terms of active research and designated leadership. The other two (Application & Evaluation of Precision Medicine, and Uncertainty) are at an earlier idea and proof of concept stage of development. The identification and activity associated with Strategic Research Collaborations are intended to be fluid and to change over time.

Individual ECRI scientists will continue with their own portfolios of research in order to ensure that an exciting successful research enterprise provides the environment and foundation to not only fuel the Strategic Research Collaborations but also continue to reflect the strength and interests of individual researchers. The reach for ECRI research will continue to be provincial, national and international in scope. Indeed, it is critical that this be the case if ECRI researchers are to be competitive in seeking research funding. Notwithstanding this broad scope, ECRI research will continue to be informed by the pressing needs and priorities of the JCC and regional cancer program. The "LHIN as a Lab" will continue to be a concept that helps drive this commitment. Opportunities to enable effective knowledge translation within the cancer program will be actively pursued in discussion with cancer program leadership.

After just four years, ECRI is established and has gained traction. ECRI is ambitious and is keen to do more. As one looks to the next five years, it is recognized that there are a number of challenges. Healthcare is undergoing dramatic changes and will continue to do so. Research funding is tight and getting more difficult to obtain. Clinician scientists are facing increasing clinical loads which impact on time for research. In such challenging times it is critical that research be focused on significant problems and that the healthcare system is structured in a way to support research and transfer research findings into practice. ECRI is committed and ready to face these challenges because it believes that research leads to improvement in care. The ECRI tagline, "Inspiring Research: because every patient matters" will continue to be the guiding philosophy for ECRI.

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APPENDIX I: REPORT - SUTCLIFFE EXTERNAL REVIEW

Review of the Escarpment Cancer Research Institute

Dr. Simon Sutcliffe

May 2015

INTRODUCTION

The Escarpment Cancer Research Institute (ECRI) was established in 2011 as a joint McMaster University/Hamilton Health Sciences Research Institute. ECRI represented the culmination of many years of discussion and planning and the collective commitment of its founding partners: the Department of Oncology in the McMaster University Faculty of Health Sciences (FHS); Hamilton Health Sciences (HHS) and the Juravinski Cancer Centre (JCC). ECRI will undergo a five year review in 2016. Based upon performance and demonstration of value, it will be eligible for further renewal.

The current review was undertaken at the request of the inaugural and founding Scientific Director, Dr. Mark Levine, to gain an external perspective regarding the performance and positioning of ECRI relative to its anticipated review and potential for renewal. The thoughts and recommendations are based on face-to-face meetings with ECRI members, associate members and research staff (June 4-5), background material made available prior to the review, and a number of conversations after the review with Dr. Levine, Deputy-Scientific Director Dr. Melissa Brouwers, and Director Ms. Anne Snider.

This external, single-person review has been undertaken in the context of a retrospective assessment of performance from 2011-2015, and as a prospective assessment of the strengths and challenges of ECRI's performance to date in a manner that would align with reconsideration and re-positioning of ECRI's strategy for the impending full review in 2016.

THE RETROSPECTIVE REVIEW (2011-2015)

Establishment of ECRI

A number of factors contributed to the plan to establish ECRI:

- The establishment of the Department of Oncology, in the McMaster FHS in 2006.
- An HHS strategic research plan in 2006 aligning priority clinical and research programs at the Henderson site.
- Emergence in 2008 of significant cancer research opportunities through the establishment of the Ontario Institute for Cancer Research (OICR) and a desire for McMaster to coalesce a research agenda across multiple departments, disciplines and faculties in order to be competitive.

Together these factors enabled the recruitment of scientists/methodologists to the Department of Oncology (Pond, Brouwers, Seow, Muti); enhanced collaboration with other key cancer research groups at McMaster (Immunotherapy – Bramson; Probe Development – Valliant; Stem Cell – Bhatia, Hassell); and led to the recruitment of additional scientists supported by OICR (Juergens, Bane). Research space was made available by HHS to support ECRI. With these enablers, the associated recruitment and building on the strength of pre-existing research groups (OCOG, PEBC, Surgical QI, JCC CTD and OAPN), ECRI was launched with potentially broad ranging multidisciplinary interests and capabilities, all aligned to the idea of making an impact on the burden of cancer in the population.

The Challenges associated with Establishing ECRI

Notwithstanding the importance of the founding enablers for ECRI, the environment was characterized during the initial ECRI years with several potentially destabilizing challenges including the integration of the cancer centre with the hospital; the loss of core CCO operating funds for research; pressure on clinicians to provide more clinical service; the strain on clinical trials units in Canadian cancer centres to maintain sustainability; and an increasingly competitive research funding environment.

It is important to note that despite these challenges in the internal and external environment, ECRI researchers have remained both committed to their research and have continued to be highly productive, using the common measures of publications and research funding.

The Vision, Mission, Core Values and Founding Themes of ECRI

- *Vision*: ECRI will be the national leader of innovative and sustainable solutions that will put research into action for the benefit of people affected by cancer.

- *Mission*: ECRI is dedicated to improving the lives of people affected by cancer. The ECRI research strategy includes clinical advancements, system innovations and knowledge translation.

- *Core values*: Evidence based; multi-disciplinary; burning passion to succeed; committed to community and international in reach.

- *Founding themes*: Translational Research, Clinical Trials and Quality Care & Knowledge Translation.

While the vision, mission, core values and founding themes of ECRI are important and reasonable, they are somewhat standard. At this stage in its development and as it looks to the future, there is an opportunity for the ECRI group to seek a more innovative path, to sharpen its vision and mission by being more specific in terms of action, and to build on its multidisciplinary strength in an integrated way by abandoning the silo structure of the separate themes.

Operating Resources for ECRI

ECRI scientists rely on external funding (peer-review agencies and industry) to conduct research. This is to be expected and would be an expectation in any serious research group. There are explicit guidelines in place defining role expectations for Full and Associate members of ECRI.

<u>Full Membership</u>

- Full membership in ECRI requires an active scholarly research program in an area relevant to the cancer research goals of the Institute.
- ECRI scientists are expected to hold peer-reviewed funding.
- Salary support for ECRI scientists is the responsibility of their primary academic department and may consist of University base funding, endowed Chairs, Canada

Research Chairs, other external career awards, or other hospital or external sources of funding.

- Every effort will be made to co-locate all Full members of ECRI within ECRI designated research space.
- All Full ECRI members will participate in an annual review with the Scientific Director of ECRI.
- ECRI members are expected to reference their membership in ECRI in grants, presentations and publications.
- ECRI members are expected to participate in the development and core activities of ECRI including attending research in progress seminars, participating in scientific events, supporting trainees, and attending ECRI meetings and annual retreats.

Associate Membership

- Associate membership in ECRI is appropriate for faculty members collaborating with Full members or projects of relevance to the mission of the Institute or new members with less than 2 years of peer-reviewed funding in a relevant area.
- Associate ECRI members are encouraged to reference their membership in ECRI in grants, presentations and publications.
- Associate ECRI members are expected to participate in research in progress seminars, and participate in scientific events.
- For larger and more established groups, such as OCOG or PEBC, scientists have been able to create management and infrastructure roles to support overall day to day management and development. For ECRI members who hold appointments in the Department of Oncology, management, finance, and HR support is available within the Department. The host institutions also provide services such as account management, contract management, and external reporting on grants.

However, from an operating point of view, ECRI as an entity lacks operating funds and therefore has been unable to put in place a robust infrastructure to support its activities. Core operating funds to support day to day administration; IT and website management; a broader communication effort; coordination of collaborative ECRI research projects; coordination of ECRI events; and recruitment of trainees are examples of core ECRI activities that would benefit from infrastructure support.

As noted above, there is some reliance on existing support within specific research groups and ECRI uses the infrastructure provided by the Department of Oncology. In addition, ECRI has seconded senior managers from various research groups to help with selective functions, e.g. development of an IT needs assessment; development of a website; support for an annual research day, and support for development of the ECRI research plan and related projects. While productive in some areas, and useful for engaging research staff in the development of ECRI, this model is challenging to sustain and has led to delays in moving good ideas forward in a timely manner, results in diffusion of responsibility or duplication of effort, and hinders ECRI from realizing its full potential. Core operating funds would surely help facilitate ECRI moving from its current state of development and success to a more visible, coordinated and ultimately impactful state.

The Performance of ECRI

The ECRI Faculty:

There were 16 founding scientists in ECRI in 2011 and shortly thereafter a 17th scientist joined (Table 1). The choice of the scientists was based on a number of factors including: time available for research, track record, and training. However, this was somewhat arbitrary and decided on by the Scientific Director. Actual definitions and role expectations for membership were more formally developed after ECRI was established.

One of the unique features of ECRI is that it is embedded within a tertiary academic regional cancer centre. The importance of linking the research program with the JCC clinical cancer program was recognized. For example, in 2013, the clinical program identified palliative care and survivorship as strategic priorities. ECRI is working to build bridges with the clinical program in these areas. In order to further build this bridge between the clinical and research programs a number of associate members were appointed (Table 1). The idea was that these individuals (all clinicians) would bring their clinical experiences to ECRI and partner with ECRI researchers in developing a research agenda. This would be one way of ensuring that ECRI would focus on issues that are relevant to patients and clinicians in the cancer centre and the surrounding community.

The one exception to this approach re associate members was the appointment of a non-clinician, Jonathan Bramson, PhD, in order to enable collaboration between ECRI clinician scientists and immunology researchers, clearly an area of strength in ECRI and at McMaster and an important and promising area of cancer research.

Table 1: ECRI Members

Scientist	Discipline	Theme	Award
Andrew Arnold	Medical Oncology	Clinical trials	
Anita Bane	Molecular pathology	Translational	OICR Scientist
Jonathan Bramson†	Immunology		John Bienenstock Chair in Molecular Medicine, Canada Research Chair in Translational Cancer Immunology
Melissa Brouwers	Psychology	Quality Care & KT	
Denise Bryant-Lukosius	Nursing	Quality Care & KT	
Ian Dayes†	Radiation Oncology	Clinical trials	
Bindi Dhesy†	Medical Oncology	Clinical trials	
Laurie Elit	Gynecology Oncology	Quality Care and KT	
Peter Ellis†	Medical Oncology	Clinical trials	
Karen Gulenchyn†	Nuclear Medicine	Clinical trials	
Hal Hirte	Medical Oncology	Translational	
Sebastien Hotte	Medical Oncology	Translational	
Rosalyn Juergens	Medical Oncology	Translational	OICR Scientist
Jim Julian	Biostatistician	Clinical trials	
Peter Kavsak	Clinical Chemistry		

Table 1: ECRI Members

Scientist	Discipline	Theme	Award
Mark Levine	Medical Oncology	Clinical trials	Buffett Taylor Chair in Breast Cancer
Som Mukherjee†	Medical Oncology	Clinical trials	
Paola Muti	Epidemiology	Translational	Arcelor Mittal Dofasco Chair in Experimental Therapeutics
Gregory Pond	Biostatistician	Clinical trials	OICR Scientist
Hsien Seow	Health Policy	Quality Care and KT	CIHR Investigator, Tier II Canada Research Chair
Marko Simunovic	General Surgery	Quality Care and KT	
Jonathan Sussman	Radiation Oncology	Quality Care and KT	Provincial Radiation Clinician Scientist
Anand Swaminath†	Radiation Oncology	Clinical trials	
Timothy J. Whelan	Radiation Oncology	Clinical trials	Canada Research Chair in Breast Cancer
Jim Wright†	Radiation Oncology	Clinical trials	
† Associate Member			

Performance Parameters for ECRI:

ECRI was launched with three research themes: translational research, clinical trials and quality healthcare & knowledge translation (KT). These themes were established based on existing strengths and research groups. The clinical trials program is vibrant. The Ontario Clinical Oncology Group (OCOG) continues to design and execute a spectrum of trials, from first in-human to large Phase III trials. In some cases the principal investigators are ECRI members or associate members. There has been an effort to link with basic scientists on the McMaster campus and conduct first in-human proof of principal trials (M. Bhatia - stem cells in patients with AML; J. Valliant and K. Gulenchyn - imaging; and J. Bramson - cell based therapies).

The Quality Healthcare and KT team is productive and vibrant. Key programs of research include investigations in supportive cancer care and transitions between active treatment and survivorship, palliative care and models of end of life care, and implementation science with particular focus on the role of evidence and its use by clinicians, policymakers and system leaders. Other areas of inquiry include quality improvement, cancer surgery and roles of advanced practice nurses. In terms of collaborative work, Sussman, Seow, Pond and Brouwers have been particularly successful in pursuing new research initiatives amongst themselves and with other partners (e.g. Ontario Ministry of Health, Cancer Care Ontario, and OICR).

The translational research program is the least developed of the ECRI programs, but has grown substantially from 2011. It has focused on prevention, biomarkers, imaging and immunology/cell based therapies.

Details of ECRI publications are presented in Table 2 and awards/grants in Table 3.

Table 2: Summary of Publications and Funding
ECRI Membership 2011-2015

First name	Last name	ECRI Role	Publications	1st Author	PEBC Guidelines
Andrew	**Arnold**	Member	4		2
Anita	**Bane**	Member	10	3	
Jonathan	**Bramson**	Associate Member	29		
Melissa	**Brouwers**	Member	38	11	3
Denise	**Bryant-Lukosius**	Member	9		1
Ian	**Dayes**	Associate Member	7	2	1
Bindi	**Dhesy**	Associate Member	13	2	
Laurie	**Elit**	Member	58	19	4
Peter	**Ellis**	Associate Member	29	10	2
Karen	**Gulenchyn**	Associate Member	12	1	1
Hal	**Hirte**	Member	29	1	
Sebastien	**Hotte**	Member	34	1	1
Rosalyn	**Juergens**	Member	7	2	
Jim	**Julian**	Member	24		
Pete	**Kavsak**	Member	54	27	
Mark	**Levine**	Member	45	4	
Som	**Mukherjee**	Associate Member	22	3	
Paola	**Muti**	Member	50	5	
Gregory	**Pond**	Member	84	11	
Hsien	**Seow**	Member	30	8	
Marko	**Simunovic**	Member	25	8	1
Jonathan	**Sussman**	Member	18	3	2
Anand	**Swaminath**	Associate Member	11	2	1
Tim	**Whelan**	Member	23	3	
Jim	**Wright**	Associate Member	16		
Total ECRI Publications 2011-2015			**667**	**129**	**19**

Table 3: Summary of Funding
ECRI Membership 2011-2015

Member	Principal Investigator			Co-Investigator
	Peer Reviewed	Other	Industry Grants	
Andrew Arnold	$0.00	$1,000,000.00	$0.00	$0.00
Anita Bane	$2,304,645.00	$186,240.00	$0.00	$350,000.00
Jonathan Bramson	$4,855,000.00	$1,605,000.00	$398,000.00	$8,380,460.00
Melissa Brouwers	$6,637,159.00	$12,542,826.00	$0.00	$49,142,776.00
Denise Bryant-Lukosius	$385,500.00	$494,000.00	$0.00	$620,887.50
Ian Dayes	$215,504.00	$0.00	$0.00	$84,000.00
Bindi Dhesy	$0.00	$31,064.36	$0.00	$213,330.20
Laurie Elit	$1,285,524.51	$124,884.00	$68,000.00	$1,411,686.00
Peter Ellis	$0.00	$58,705.54	$0.00	$30,000.00
Karen Gulenchyn	$30,000.00	$0.00	$757,506.00	$1,632,950.00
Hal Hirte	$0.00	$0.00	$440,774.17	$0.00
Sebastien Hotte	$999,131.00	$0.00	$353,130.00	$1,272,499.88
Rosalyn Juergens	$1,450,000.00	$100,000.00	$500,000.00	$2,337,852.00
Jim Julian	$0.00	$0.00	$0.00	$5,294,685.00
Peter Kavsak	$394,135.00	$336,517.00	$158,486.00	$3,820,854.20
Mark Levine	$1,999,309.00	$1,296,586.00	$0.00	$3,712,271.00
Som Mukherjee	$100,000.00	$0.00	$0.00	$0.00
Paola Muti	$1,526,000.00	$0.00	$180,000.00	$300,000.00
Gregory Pond	$257,624.00	$0.00	$0.00	$1,185,695.00
Hsien Seow	$1,059,529.00	$1,414,066.00	$0.00	$1,211,565.60
Marko Simunovic	$2,019,562.00	$24,285.00	$0.00	$3,734,006.00
Jonathan Sussman	$1,120,000.00	$225,195.00	$100,000.00	$3,717,762.20
Anand Swaminath	$1,290,186.00	$0.00	$0.00	$568,514.00
Timothy J. Whelan	$2,744,699.00	$120,813.00	$0.00	$6,057,458.00
James Wright	$0.00	$13,975.00	$0.00	$188,250.00
Total Funding	**$30,673,507.51**	**$19,574,156.90**	**$2,955,896.17**	**$95,267,502.58**

The Evolving Characteristics of ECRI

"Things may appear the same, but something pretty substantial happened to shore-up the sameness".

"*Success is the ability to sustain a stable productive faculty without their awareness of the ever-present and increasing reality of failure due to the constraints and challenges of the prevailing healthcare and operating environment".*

These statements during the review highlight the changes occurring during the period from 2007 associated with the global financial downturn, healthcare funding constraints, institutional reorganizations and mergers, "downsizing" of faculty and personnel, "retrenchment" of the clinical and scientific research enterprise, erosion of "protected time" for research by clinical staff and increasing competition for diminishing donor funds and peer-research grants. Thus, to remain as a competitive research institution in 2015 with an established program and performance, in and of itself, is a substantial achievement and "against the odds" of the last five years.

These circumstances pertaining to the political, healthcare, fiscal and social environment have shaped the evolution of ECRI:

- *Culture of ECRI*: An allegiance and loyalty to a vision for research and its relationship to practice enhancement, and to personal and collaborative scientific research career development. The culture is accountable to science, research and knowledge application for improved health and illness control.
- *Leadership of ECRI*:
  - Establishment of a secure, supportive environment with minimization of bureaucracy and administrative encumbrance.
  - Creation of an environment in which the vision can be achieved through enabling inclusivity and collaboration, focused research excellence, openness to opportunity within an overall strategy and mitigation of hurdles, barriers and challenges.
  - Non-authoritarian leadership, inspiring "followership by setting a compelling vision, culture and direction".
- *Driving imperatives*: Conducting relevant, health solutions-oriented research for population application; pursuit of new or augmented capabilities, capacity and resources (e.g. CIHR-Foundation, SPOR); and fostering, enabling and equipping "high-performing" teams addressing health research priorities.

PROSPECTIVE REVIEW 2015 ONWARDS
ANALYSIS AND RECOMMENDATIONS

ECRI was established in 2011 and now has almost four years of practical experience in leadership, management and operations. It is anticipated that its formal five-year review will be commissioned in 2016. Thus, the findings and recommendations of the present review (May 2015) serve two purposes: 1) an assessment of performance to date with an opportunity to embellish strengths and to mitigate challenges or deficiencies, and 2) create an opportunity to consider strategic and business planning for ECRI's second five-year term (2016-2021), including principles for succession, new directions and consolidation of its strengths. To this end, a number of ideas are put forward for consideration in strengthening ECRI's focus and impact.

The Vision, Mission, Core Values and Key Directions

Vision:

The current vision: ECRI will be the national leader of innovative and sustainable solutions that will put research into action for the benefit of people affected by cancer.

Considerations in revising the vision statement: The vision is built upon "innovative and sustainable solutions" to transform health systems and services for those affected by cancer through research knowledge applied into clinical practice.

Strengthen the latter ideas in the statement.

Mission:

The current mission: Dedicated to improving the lives of people affected by cancer, the ECRI research strategy includes clinical advancements, system innovations and knowledge translation.

Considerations in revising the mission statement: The current mission statement is not really different or more explanatory than the vision. A key element of the mission includes "improving the lives of those affected by cancer through application of research knowledge". This implies:

- more effective, evidence-based practice through clinical trials,
- more effective and efficient health system interventions to enhance quality of care and the patient experience with cancer,
- development and integration of new approaches for the identification, characterization and selection of interventions to optimize with individual ("personalized") and population-based health outcomes.

Strengthen these action-oriented themes in the statement and create greater distinction between the Vision and the Mission.

Core Values:

The original core values (evidence-based, multidisciplinary, burning passion to succeed, committed to community and international in reach) stated in the 2011 ECRI charter should not change.

Key Directions:

ECRI's research started with three themes and is evolving. The research in clinical trials is a strength, particularly the focus on trials that generate knowledge which contributes to evidence-based medicine and which informs evidence-based care. The health services research in the theme of quality healthcare is also a strength with the unique aim of optimizing individual and societal health and healthcare. Moreover, the health services research directed to knowledge application can drive individual and population-based healthcare and cancer control. While the productivity of the translational research theme is adequate, it is significantly challenged by competing translational research groups elsewhere in Ontario (e.g. Toronto) and elsewhere in Canada (e.g. British Columbia).

In conceptualizing its future, ECRI should examine how it can best leverage its scholarly assets to optimize its impact and productivity.

The Conceptual Model for ECRI

ECRI is at a state of its maturity to reflect upon the questions:

- What makes it strategically different from other cancer research institutes?
- In what does ECRI excel?
- What makes ECRI unique or special?

Considerations when answering these questions include:

- underlying political and organizational relationships
- strategic and clinical research model
- scientist participation model
- business model
- LINH as a "living laboratory" for ECRI

Each of these issues will be addressed in turn.

The Underlying Political and Organizational Relationships:

To be successful ECRI needs to ensure that certain enabling conditions are optimized. To this end, *an analysis identifying key existing and potential collaborators (e.g. McMaster University, Hamilton Health Sciences, Cancer Care Ontario, Faculty of Health Sciences), what ECRI requires from these relationships (e.g. resources, brand, space), and what ECRI offers to these relationships (e.g. innovative research, effective solutions) should be undertaken.* In doing so, ECRI can structure and organize its aims and activities to seek and optimize those collaborations which result in mutually satisfying benefits. Moreover, it will help define expectations in the

relationships with other key leaders required to support the success of ECRI (e.g. administration of JCC, HHS and the University).

A unique aspect of ECRI is the multidisciplinary make-up of its scientists and associate members who come from the McMaster Departments of Oncology, Surgery, Obstetrics & Gynecology, Clinical Epidemiology & Biostatistics, Pathology & Molecular Medicine and the School of Nursing. Many of the members have their academic home in the Department of Oncology, a relatively new department at McMaster (established in 2006). The additional relationships beyond Oncology afford unique opportunities to the ECRI scientists with respect to research innovation and access to expertise. For example, relationships have been established between ECRI clinicians and basic scientists on McMaster campus including imaging (Valiant), stem cells (Bhatia, Hassell) and immunology (Bramson). These occurred for a number of reasons including capitalizing on funding opportunities, mentoring of young scientists and the enthusiasm for translational research. Going forward however, *a decision needs to be made regarding which existing relationships should be pursued and additional relationships that ought to be explored, in terms of net benefit for ECRI in terms of its vision and mission.*

The ground work for ECRI was being laid at the same time as the new Department was conceived. Having the same individual as the Chair of Oncology and the Scientific Director of ECRI has been opportune in terms of having one voice to advocate for cancer research and facilitating access to space and funding. At times, however, it has led to confusion with regards to a common understanding of the different research mandates of ECRI and the Department. *A common and continued communication strategy is warranted and future succession planning should explore the best leadership governance to optimize the success of ECRI.*

<u>The Strategic Clinical Research Model</u>:

Context:

Healthcare is rapidly changing and will continue to do so for the foreseeable future. The burden placed on the Canadian healthcare system by cancer is substantial and increasing. There are a number of reasons for this: the aging population, improvements in treatment and the impact of lifestyle including diet on non-communicable diseases such as cancer, diabetes and vascular disease. Healthcare systems in Canada, the United States and Europe are struggling to cope with the financial burden of healthcare. Major drivers for rising costs include anticancer drugs and new technology, e.g. imaging and genomic testing. There are many challenges to the healthcare system in Ontario. Hospital budgets are stressed. Funding by the MOHLTC is flat-lined, which means each year cuts are necessary to keep up with increased costs as a result of union contracts, drugs and technology. Stringent benchmarks for hospital length-of-stay result in sick patients being discharged home. Community services are stretched to the limit to support patients' out-of-hospital, chronic care and palliative care facilities are limited. As a result, cancer patients and their families have many unmet needs.

Meanwhile improvements in genomic technology have given rise to the era of "personalized medicine" (now called "precision medicine") in recent years. It is believed that knowledge of the molecular biology of a tumour and the host (the patient) will enable individualizing

treatments to patients. There has been much excitement related to the potential for precision medicine. There is no doubt that there are examples of the recent success of precision medicine in specific cancers, e.g. trastuzumab in Her2 positive breast cancer, imatinib in CML and GIST, and immune check point inhibitors in melanoma. However, these therapies are very expensive and as of yet the promise of precision medicine has not been realized for many of the common cancers.

Given this environment, the challenge for ECRI is to identify areas where it can have the biggest impact. This involves reflecting on its strengths, potential collaborations and the unmet needs of the patients it serves. There is also the practicality that the domain of drug discovery research falls mainly in the purview of pharma and ECRI per se has only limited basic science research capability.

ECRI Research - the Proposition:

Consider ECRI to be an "open space" in which to address the priority questions – in essence, a "cloud" where the constraints of contextual, circumstantial and relationship issues are without boundaries, where any solution can be pursued and determined within the bounds of sound, disciplined, methodologically rigorous science and medicine. In this proposition, ECRI is not constrained from the outset by the traditional parameters defining the status of research institutions (philanthropy; institutional mandate; employment and funding relationships; inter-institutional relationships; space; access to technology; recruitment by discipline of research, etc.) and the competing considerations of health system, institutional and academic politics. Thus, ECRI provides the environment and intellectual capital to perform clinical applied research rather than the facility, the employer, the technology and the budget within which to host research. These considerations are necessary, but are secondary to the primary purpose of undertaking important and relevant health research.

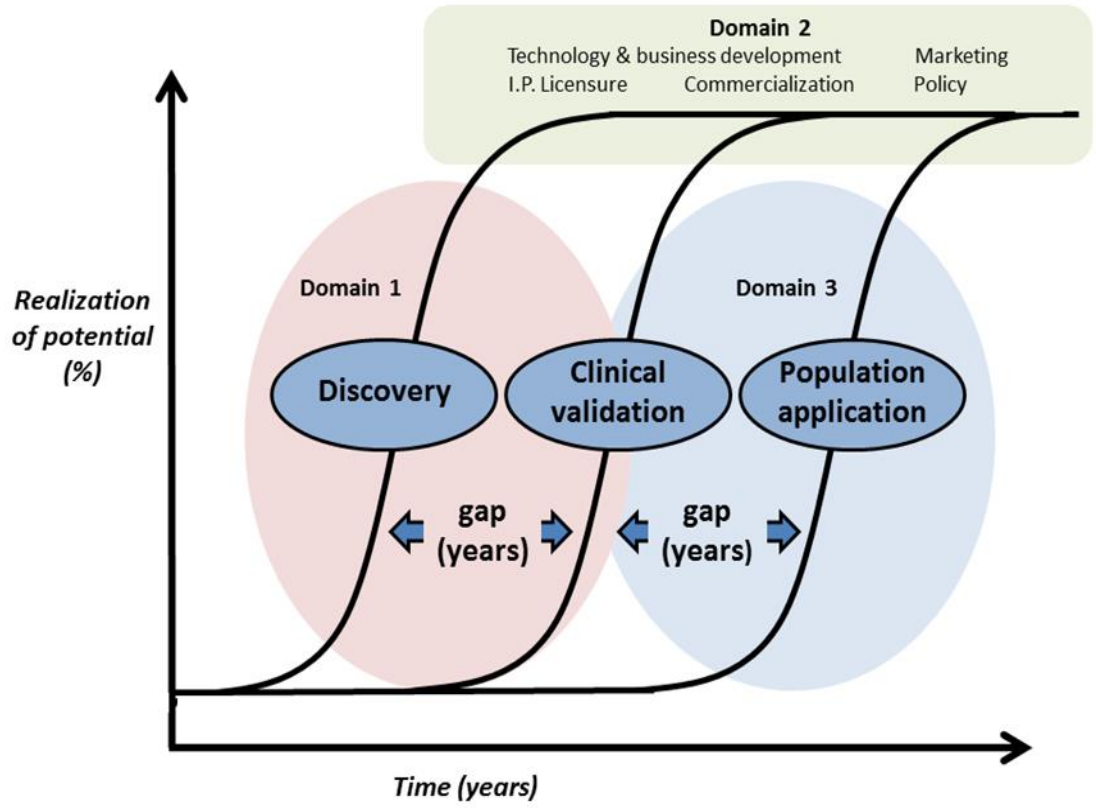
In this model, the starting proposition is to define the focus of the Institute's research. Figure 1 illustrates that the realization of research translation over time engages domains of activity that are driven by different governance, funding and incentives, and populated by a different mix of health professionals, policymakers, patients and publics.

- Domain 1: Discovery science and clinical validation; typically undertaken by biomedical research institutes in tertiary academic environments, usually with robust foundations and access to philanthropy.
- Domain 2: Technology and business development involving intellectual property registration, licensing and commercialization, regulatory practice and policy and marketing.
- Domain 3: The application, uptake and adoption of valid clinical science into population health and illness control, including measures to determine contextual, ethical and socioeconomic aspects of health service interventions.

It is proposed that ECRI's research strength is in Domain 3. This does not preclude engaging in Domains 1 and 2, but rather such engagement needs to be strategic for success in Domain 3.

Using this as a conceptual basis, the next step is to identify and prioritize health research appropriate for ECRI with respect to expertise, interest and commitment to lead.

Figure 1: Research Domains of Activity



To this end, questions/themes/problems will need to be prioritized for ECRI research. This will involve the need to:

- identify the relevant populations for study
- define the relevant and available data sources and methodological innovations
- identify the necessary infrastructure to enable the project
- prepare and submit the application for research funding support

Underpinning these steps is the need to identify the appropriate investigators who may currently exist within the Hamilton academic environment or currently exist in other institutional settings and can be willingly co-opted into the research team, or need to be recruited to bring expertise that is both necessary in the longer term and is required to be a "continuous presence" in the Hamilton/ECRI environment.

In summary, ECRI exists to address and improve cancer control through a predominant focus on knowledge development, transfer and application to health system challenges. To do so effectively can be enhanced by creating the conditions in which health challenges can be addressed without contextual and/or circumstantial boundaries, i.e. "the cloud concept".

Solutions or conclusions may then be contextualized to prevailing circumstances and culture as a means to their realization in current healthcare.

Scientist Participation Model:

It should be noted that there is little operational funding directly attributable to the personnel of ECRI. The support for scientists comes from many sources including career awards from external agencies (e.g. OICR, federal government), endowed chairs, the Dean, McMaster Department of Oncology, HHS and physician practice plans. Research staff are supported through operating grants. Despite this rather heterogeneous funding model, ECRI has been very productive. However, it is important for the following issues to be addressed:

- What are the incentives for performance by ECRI members?
- Over which funded appointments does ECRI have direct or discretionary authority to inform the portfolio of activities undertaken by the scientist?
- What are the criteria for an ECRI appointment at full member, associate member? With a new problem-based approach described above, how can conventional appointments and categories of appointments be used optimally?

The ECRI Business Model:

The ECRI business model is currently built upon the items described below in Table 4.

Table 4: ECRI Business Model

ECRI	No direct operational funding
ECRI-McMaster University	Assignment of endowed Chairs and CRCs Dean's Fund Department of Oncology in-kind & administrative support Home Departments for ECRI members
ECRI-HHS	Access to HHS-appointed clinical staff $150,000 annual support for statistician in OCOG Debt of $600K redirected from CCO to HHS operations
ECRI-JCC	Access to clinical staff
ECRI-JCC Foundation	Some access to research funds. Funds are neither guaranteed nor targeted to ECRI activities.
ECRI-Pharma Industry	Study support: $3 million
ECRI Grants	Peer-review : $30.7 million/4 yrs Other: $19.6 million/4 yrs Co-Investigator grants: $90 million/4 yrs

An analysis of the current business model and future options is warranted. Essentially, there are two strategies for sustainability and growth: 1) to expand the funding (pharma, grants, other non-peer review awards, philanthropy), and 2) focus the available resources in areas of science, on people or platforms with the greatest strategic potential to achieve the vision and mission. The following issues should be considered:

- How can core operational funds be secured and leveraged?
- What are the implications for ECRI if core funding is not secured?
- What is the possibility and probability that the situation could change?

- What are the areas of greatest strategic potential?
- Who are the people with the greatest strategic potential?
- Are they existing and to be retained?
- Existing but need to be "re-positioned" or to be recruited?
- Are there opportunities for commercialization?

The LHIN as a Living Laboratory for ECRI:

One of the unique features of ECRI is that it is embedded within a tertiary academic regional cancer centre. The importance of working closely with the JCC clinical cancer program has been recognized. The clinical programs are ideal for identifying the key questions and issues for patients that ECRI research could address. For example, the clinical program has identified palliative care and survivorship as important issues and ECRI is working to build bridges with the clinical program in these areas. Based on these considerations the "*LHIN as a lab"* was identified as a thematic opportunity for ECRI researchers to rally around. Furthermore, the HHS just announced their strategic priorities which include research on their community.

For the LHIN to be a key enabler of a living laboratory for ECRI research, the LHIN relationship would need to facilitate population access; organizational and professional relationships; data availability (link to population health data sets, including services utilization by geography and cost); definition of LHIN-relevant research questions and research and access to the "levers and controls" for population health performance. There are advantages to the LHIN as a living laboratory:

- Circumscribed population with accessible link to health data sets
- Engagement of health and illness continuums across:
  - Health, illness, treatment, cure, palliation and end-of-life
  - Infancy, childhood, adolescents, young adult and senior life
  - Primary, community, specialty/tertiary, hospice
  - Discovery, validation, application of health innovations

How can this opportunity be better optimized and integrated both strategically and operationally into the ECRI fold?

SUMMARY: FROM CONCEPT TO ACTION

ECRI has demonstrated the potential and performance associated with collaborative relationships between key partners across the academic, tertiary and population domains of the health system. This performance has been based upon capitalizing on strengths and opportunities (assets), but the potential has also been constrained by the challenges inherent within and also external to, ECRI (liabilities). As with any organization, an opportunity to reflect and refine on its strategy and practices enables growth and success. In this review, there have been several questions and issues that the ECRI team is encouraged to work through to provide a foundation for the next stage in its development.

The strengths and opportunities:

The ECRI culture:

- the primacy of knowledge application to outcomes (the focus on Domain 3 – Figure 1)
- inclusivity and collaboration, based upon intellectual contribution, not affiliation or funding source
- mutual accountability and responsibility
- interdisciplinary teams across the continuum of healthcare and health services
- maximizing and optimizing the resources available to perform high quality research
- virtual problem-based "Institute" providing an "open space/cloud" concept for collaborative research

The research concept:

- the creation and sustainability of an "open space/cloud" for the conduct of research, unconstrained by traditional and conventional definitions of "Research Institute", i.e. organization, institution, employer, funder, etc.
- a permissive, secure, unencumbered and enabling environment for the pursuit of research and its application to health service improvement
- performance is the realization of health improvements through ECRI research

The research context:

- clarity of focus based on translating knowledge into health application and optimization
- coherence based upon unifying strengths
- excellence according to the conditions and circumstances for sustainable support

The research content:

- redefining ECRI's research strategy so that it is not about investment in the domains of research, but rather about the investment in the capabilities and capacity to perform relevant health research (science, technology, platforms, personnel, etc.) that can translate into improved health outcomes
- researchers bring different skills to tackle problems that are important for patients
- envisioning and pursuing the future through a platform of core capabilities
- determining what the change in medicine and healthcare will be, and creating the opportunity through ECRI
- recognizing individual strengths and establishing how they can create "collective capacity" for health research
- strategic focus on recruitment, development, retention and succession to ensure security of the ECRI research culture, performance and capability

The weaknesses and threats:

- minimal operating budget and the challenges for securing significant operating funding increases in the prevailing academic, health services and philanthropic climate
- limited ability to facilitate operational support for individual and collective research capacity, e.g. research administrative support, grants preparation and management support, core infrastructure support

- perceived "ambiguity" of overlapping institutional missions, goals and personnel
- real and perceived competitive priorities of partner entities, e.g. McMaster University, Hamilton Health Services, JCC, Department of Oncology and JCC Foundation
- differing cultures, contexts and content of health research priorities between partner affiliates of ECRI
- variable strengths and supports for health research endeavors across Ontario and the proximate strengths of OCI/PMH and the Toronto academic and fiscal environment
- moving from concept to action and facilitating buy-in, agreement, and leadership among the ECRI scientists.

Final Comments

ECRI has demonstrated substantial commitment and performance to the advancement of applied health/cancer research since inception in 2011. This is particularly prescient in the context of research outputs (extensive grants, publications and traditional measures of industry performance) relative to inputs (limited and little secure institutional endowment and/or operational funding). Furthermore, performance and productivity has been established through very challenging and ongoing adverse circumstances for research in Canada.

ECRI has established a particular collection of "assets", possibly arising as a result of this challenging environment that position it in a potentially advantageous way. Its' culture, concept, context and focus promote the concept of an "open-space" for health research ("cloud health research"). An example of this could be, "How can we rationally assess the potential value of health interventions amongst a plethora of competing possibilities in a way that would be transparent, socially and politically responsible, and evidence-based and aligned to the design of appropriate ("hypothesis-proving") studies?" Such a concept aligns to the creation of a virtual space for research – the assemblage of health researchers who are interested (both within and external to the Hamilton environment); assemblage of the database and technology platforms; creation of the virtual working forums and communications; and the design and execution of a mutually agreed health research program.

This concept can clearly be challenged from the perspective of prevailing health research resources, particularly operating and infrastructure support. Whilst relevant, these challenges demand mitigation, not obstruction to the "open space" concept for collaborative research. In reality, the required resources are not substantial – they are the resources necessary to facilitate the business and operations of collaborative teams of researchers assembled to address collectively defined health challenges. The characterization of this resource, and its scalability to accommodate the support of multiple research teams, would be a first step towards the establishment of a revised business plan for ECRI and the development of the funding strategy.

In summary, ECRI has demonstrated performance and capability according to traditional measures of institutional performance. However, its true capacity to perform is yet to be fully realized, based upon its unique opportunity to "rethink" the role and performance of a health research institute in the prevailing present and future health economy.

APPENDIX II: ANNUAL RETREATS

	Objectives	Output
April 2011		
Facilitators: Dr. Heather Arthur, Chief Scientific Officer HHS Heather Pullen Manager, Public Relations & Communications HHS	· Discuss what differentiates ECRI from other research institutes. · Identify how scientists might work together differently. · Develop initial ECRI branding concepts. · Prepare for formal ECRI launch in September.	ECRI tagline: *Inspiring Research: Because Every Patient Matters* Preparation of media stories for ECRI launch in September. Circulation of individual and group research priorities.
November 2012		
Facilitator: Dr. Ralph Meyer Hematologist & Professor Department of Oncology Queens University, Director Clinical Trials Group, National Cancer Institute of Canada	· Review and critically appraise the current research activities and identified priorities of each theme. · Consider current and future state challenges, opportunities and strategies. · Develop an operational and scientific plan of action that will advance the goals of ECRI over the next 2-3 years. · Generate enthusiasm amongst members for the next phase of ECRI development.	Strengths, opportunities and developmental next steps identified for each theme. Action steps identified to bolster communication, strengthen governance structure, consolidate research space and strengthen administrative & research support.
November 2013		
Facilitator: Wendy Hollinshead, Assistant Director, Health Research Services, FHS McMaster University	· Welcome new associate members. · Review progress at theme and ECRI level. · Identify potential grant applications.	Decision to pursue integrated lung research proposal and to use this as a model for other DST proposals linking ECRI research to cancer program.