Fighting cancer is hard enough—your government should not make it worse.
SPECIAL THANKS to all the cancer patients and patient-centred cancer groups who offered their insight and support for this publication. In particular: the Best Medicines Coalition, the Canadian Breast Cancer Network, the Canadian Cancer Society, the Canadian Testicular Cancer Association, the Canadian Cancer Action Network, the Canadian Lung Association, the CLL Patient Advocacy Group, CML Society of Canada, GIST Sarcoma LifeRaft Group Canada, the Global Lung Cancer Coalition, Lung Cancer Canada, the London and District Multiple Myeloma Support Group, Ovarian Cancer Canada. Many other organizations and individuals generously share their experiences and ideas with us all year, including cancer agencies, policy and research institutes, think-tanks, elected officials and health professionals from coast to coast. We applaud the renewed mandate of the Canadian Partnership Against Cancer to bring the cancer community together in constructive collaboration.

A NOTE OF APPRECIATION to Cohn & Wolfe for a generous amount of pro bono public relations work on our behalf and for their spirited commitment to the cause.

BOARD OF DIRECTORS
Dauna Crooks (Co-Chair) RN, DNSc, is currently the Dean of the Faculty of Nursing, University of Manitoba as well as an Associate Professor at both the University of Toronto and McMaster University. Dauna is also a member of seven professional organizations and has numerous grants and publications.

Douglas Emerson has spent the last decade working in communications, public affairs and government relations. He lost his father to cancer in 2005.

James Gowin (Past Chair) BA, MB, BS, FRCP, founded the community cancer clinic in Cambridge, ON and established the National Conference on Community Cancer Clinics. He has been an advocate for community cancer care and cancer control throughout his 40-year medical career.

Darwin Kealey (Past Chair) BA, MA, is a former executive public servant and international entrepreneur with extensive advocacy experience.

Kong Khoa (Vice Chair) MD, FRCP, is a Medical Oncologist based in the Southern Interior of British Columbia in Kelowna.

Pierre Major (Co-Chair) MD, has worked in Medical Oncology for 30 years and has a special interest in treating elderly patients with cancer. He has over one hundred publications and is actively involved in developing novel treatments for cancer including using viruses to attack cancer cells.

Jackie Manthorne, BA, BED, is CEO of the Canadian Breast Cancer Network (CBCN), a member of the Metastatic Breast Cancer (MBC) Global Advocacy Advisory Board, the global Breast Cancer Dialogue Series, the Community Capacity Building Committee (CCBC) of the Canadian Breast Cancer Initiative (CBCI) and CBCC Ambassador-at-Large.

Robert Pearcey MA, MBBS, FROR, FRCP, is a practicing academic Radiation Oncologist and Professor of Oncology in Edmonton. He also has 14 years of previous administrative experience in Radiation Oncology and is the current chair of the specialty committee in Radiation Oncology for the Royal College of Physicians of Canada.

Joseph Ragaz MD, FRCP, is a Senior Medical Oncologist and breast cancer researcher. Clinical Professor, Faculty of Medicine and School of Population Health, University of British Columbia, Vancouver, B.C.

David Saltman MD, PhD, FRCP(C) is the Chair and Professor of the Discipline of Oncology, Faculty of Medicine, Memorial University. His current interests include cancer advocacy, community oncology and telehealth.

Sandeep Sehdev MD, FRCP, is a community focuses Medical Oncologist at the William Osler Health Centre in Brampton, Ontario—one of Canada’s largest community hospitals—where he has worked since 1992. He is past chair (five years) of the Pharmacy and Therapeutics Committee.

Elizabeth (Liz) Whamond has a long and distinguished history in the Canadian cancer community. In 2001, Ms. Whamond was one of the founding members of the Canadian Cancer Action Network and currently serves as Chair as well as the CCAN representative on the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer.

Sandi Yurichuk (Vice Chair) BS, MBA, PhD candidate, is a cancer advocate and management consultant in the field of oncology.

BOARD SUPPORT

Daniel Gillespie BSc, is a graduate of the University of Toronto. He has been a consultant and research assistant to the Cancer Advocacy Coalition of Canada for the past five years.

Colleen Savage is a public affairs and communications consultant serving as President & CEO for the CACC.

© 2011, CACC except where otherwise noted.

All photos supplied by the individuals and used with their consent.

CANCER ADVOCACY COALITION OF CANADA

REPORT CARD
ON CANCER IN CANADA

VOLUME 13, WINTER 2010–11

CACC EDITORIAL ADVISORY COMMITTEE
Pierre Major, David Saltman, Sandi Yurichuk, Colleen Savage

STATEMENT OF NON-CONFLICT: Authors were not compensated for the articles in this publication; the work is entirely theirs and original.

DESIGN Bob Wilcox

WARNING: Cancer Advocacy Coalition of Canada (CACC) provides the Report Card for general information related to current events and topics relevant to cancer in Canada. While CACC makes best efforts to ensure the accuracy and timeliness of the information contained in the Report Card the information is taken from various public and private sources so that no responsibility can be assumed by CACC for the accuracy or timeliness of this information. The opinions expressed in the Report Card are those of the individual authors of individual articles and material. Their views do not necessarily reflect the views of CACC.

DISCLAIMER: Cancer Advocacy Coalition of Canada (CACC) provides the Report Card for general information related to current events and topics relevant to cancer in Canada. While CACC makes best efforts to ensure the accuracy and timeliness of the information contained in the Report Card the information is taken from various public and private sources so that no responsibility can be assumed by CACC for the accuracy or timeliness of this information. The opinions expressed in the Report Card are those of the individual authors of individual articles and material. Their views do not necessarily reflect the views of CACC.

WARNING: CACC’s Report Card should not be used for the purpose of self diagnosis, self treatment or as an alternative to medical care. If you have any concerns arising out of the information contained in CACC’s Report Card, you should consult your own physician or medical advisor. If you suspect you have cancer, seek professional treatment immediately.

About the Cancer Advocacy Coalition of Canada

The CACC is a full-time, registered, non-profit cancer group dedicated to advocacy, public education, policy analysis and evaluation of health system performance. The CACC is not a charity and operates on unrestricted grants from sponsors based on guidelines that ensure the organization's autonomy. The CACC publishes Canada’s only independent evaluation of cancer system performance, the annual Report Card on Cancer in Canada. The Board of Directors is comprised of unpaid volunteer oncologists, health sector executives and patient advocates from across the country.

Our Vision for the Cancer System

An effective, comprehensive, evidence-based cancer system that offers Canadians the best chances for preventing and treating this disease, and addresses the emotional, physical and financial needs of patients and survivors.

Our Goals: to benefit cancer survivors and all Canadians

• Consistent adherence to best practices in cancer care and prevention, making best use of financial and human resources
• Accountability to patients, survivors and taxpayers
• Transparency of decision-making, priority-setting and performance measurement
• Reduction of the emotional, physical and financial distress associated with a cancer diagnosis
• Access to best practices in disease prevention and timely, effective treatment options
• Increased awareness of prevention choices
IN THIS ISSUE

TRIBUTE
4 A Tribute to Linda Jalbert
by Joseph Ragaz, MD, FRCPC

EDITORIAL
5 by Pierre Major, MD and Colleen Savage

The Cancer Patient’s Challenging Journey

ADVOCACY
8 Open Letter to Physicians
from Alberta Health Services

Walking the Tightrope: Physician Advocacy and Institutional Fidelity
by David Saltman, MD, PhD

PREVENTION
10 Cancer Prevention in Canada: The Sooner the Better
by Joseph Ragaz, MD, FRCPC

Prevention Update: Smoking
Rare Cancers Update: Orphan Drugs

LIVING WITH CANCER
16 Chronic Lymphocytic Leukemia
Ovarian Cancer
Testicular Cancer

UPDATE ON LIVING WITH CANCER
18 Chronic Myelogenous Leukemia
Multiple Myeloma
Neuroendocrine Tumours
GIST

THE ORGANIZATION OF CANCER CARE
21 Waiting Times
by Pierre Major, MD

Should Clinical Trials be Considered Part of “Standard of Care”?
by Susan F. Dent, BSc, MD, FRCPC and Sandi Yurichuk, BSc, MBA, Ph.D. candidate

The Role of the Nurse Practitioner and Clinical Pharmacist
by Jonathan Edwards, BSc, Scott Edwards, PharmD, and David Saltman, MD, PhD

Bone Marrow Transplantation: Improving Outcomes for Canadian Patients
by Ronan Foley, MD, FRCPC

Personalized Medicine: What is Missing?
by Jennifer Levin Carter, MD, MPH with Jillian Lokere

The 21-Gene Assay: Canada’s Uneven Response
by Joseph Ragaz, MD, FRCPC

Noteworthy
by James D. Gowing, BA, MB, BS, FRCPC
Style, grace and courage. Three little words that sum up how Linda Jalbert lived and faced life’s biggest challenges. Ever the optimist, Linda’s vivacious personality and sense of humour were inspirational and infectious—she was loved by all who knew her.

Linda’s personality seemed perfectly suited to her career in the hospitality industry and over the years she worked for some of Montreal’s best hotels—as Director of Sales for the Ritz Carlton, the Four Seasons and the Loews Hotel Vogue. Her passion for her work radiated from her, and impressed colleagues and clients alike with her professionalism, spirit and energy.

Her fervor for her career was matched by that of her beloved husband, Renaud, himself a General Manager of luxury hotels. Their love, friendship and partnership was evident to all who knew them, and Renaud was a constant source of support for Linda, always at her side through the ups and downs that came their way.

And challenges certainly came their way. At only 49, Linda was diagnosed with high-risk breast cancer. But, as only she could, Linda faced this battle head on—never complaining, the epitome of courage and optimism. While undergoing rounds of chemotherapy and radiation, she remained bubbly and witty, never allowing friends, loved ones, hospital staff or even other patients around her to feel down.

And thus, Linda’s new role as a cancer advocate was born. In 2005, she was one of the first patients in Canada to receive Herceptin, but was concerned not by her own condition, but about other women who may not get access to this drug. She took her story to the Globe & Mail and through hard work and dedication was able to help thousands of other patients across the country gain access to a valuable treatment.

Inspired to continue helping other cancer patients, accepting a seat on the Board of the CACC was a natural next move and her energy, enthusiasm, solid counsel and efficiency were appreciated by all of us who had chance to work alongside her.

With her breast cancer undetectable, she seemed to have beaten the odds. And none of us were surprised that a woman with her determination and optimism could overcome such an aggressive disease. But, cancer dealt Linda another cruel blow. Diagnosed with lung cancer in 2008, she again remained true to form, battling courageously while retaining her spirit and zest for life, right until the end.

We all know too well the devastation and grief that cancer leaves in its wake. While we can never fill the hole that Linda has left in our hearts, we can keep her memory alive by continuing her work with the same spirit, energy and passion that she shared with so many.

by Joseph Ragaz, MD, FRCP
As Canadians go the polls this year, federally and in five provinces and at least one of the territories, we repeatedly tell pollsters that our number one priority is health. In all these jurisdictions we will hear the candidates conclude: first, that health already consumes too much of the budget; second, that they agree we should do more; and third, that their solutions are the best choices, given all the competing demands.

We all know it will not be enough. This edition of the Report Card is meant to help every political candidate in the country understand what it means to carry the physical, emotional and financial burdens of cancer. For the cancer patient, Winston Churchill said it best, “if you are going through hell, keep going.”

During the cancer patient’s challenging journey, the current health system can seem self-absorbed, tilted toward overhead and paper processes rather than direct patient services. The weight of administration comes as a direct result of governments’ belief that rigid guidelines, forms and applications will provide a speed bump for utilization and a veil for service denial. A clever strategy, until it is over-used. Today’s health system often appears locked up, with creativity aimed solely at finding new ways to say no.

Front-line health care professionals are not responsible for the design and funding of Canada’s multiple health systems. Our governments are. In fact, the health professionals in this country work against discouraging odds to adjust to increasing constraints, shifting priorities, growing caseloads and a lack of capital and human resources. They save our lives. What does your government do for you?

The people we elect this year will become responsible for negotiating a new federal/provincial/territorial health accord. The new health accord will establish priorities, targets, timelines and a new funding base for the delivery of health services in Canada. How will cancer fare?

**Cancer prevention.** The science for cancer prevention continues to improve, consistently linking cancer with lifestyle choices, harmful products or environments, as well as genetic markers. Funding for cancer prevention lags behind this knowledge, leaving 50 per cent of all avoidable cancer diagnoses looming in the future, for lack of action today. In many of these situations legislative protections are needed, in other cases, active medical intervention is best, including counselling to improve lifestyle choices, or drug therapy.

**Waiting times.** The last accord defined five priority areas, with targets and new funding to address the increasing problem of waiting times for health services. For cancer, that list included only radiation oncology. Indeed, as the illustration on the following page shows, the waits at every point of activity quickly accumulate to become a substantial delay, with overwhelming fear and anxiety for the patient.

Provinces agreed to address the five priorities over five years and report annually to their citizens on progress. For this, the provinces received $5.5 billion as part of the $41 billion health accord deal. The definitions of a waiting time for cancer care, other than radiology, remain impossibly different across the country, other than a general preference to start counting at “ready to treat” (meaning post-surgery); not the first suspicious test result, not even the diagnosis, but somewhere farther down the path. Added to these manoeuvres is the unanswered practical question: if the waiting time for one type of surgery in your province has dropped significantly in the past few years, what happened to the waits for other surgical procedures?

**Catastrophic drug coverage.** Some perspective, please. Creating a new pharmacare plan, with expanded eligibility so more citizens have coverage for a limited list of drugs, is not the same as protection from financial ruin caused by extraordinary prescription drug costs. The provinces that claim to offer a catastrophic drug plan do no such thing. Federal and provincial officials duck responsibility, pointing at each other, invoking amnesia of past promises, while cancer patients are dealt another crushing blow. A Canadian who has to choose between the treatment recommended by the oncologist or the financial solvency of the family has no happy ending. True catastrophic drug coverage would mean Canadians are not confronted with that decision. One payer cannot handle such a plan. The health accord is an ideal instrument to formulate a multi-payer plan.

**Accountability.** As taxpayers, we object to the layers of government fighting over our wallets. We expect clear, honest answers for the “difficult funding decisions” that impede timely access to cancer care. How does one priority supersede another?

Provinces insist their constitutional authority for the delivery of healthcare relegates the federal government to the role of ATM. This ATM needs better rules: more flexibility to deliver our money back to us for services we want; and a higher degree of surveillance over the provincial spending of that money. More importantly, the federal role for establishing and ensuring national standards in healthcare is the only mechanism that will alleviate the persistent inter-provincial disparities in access to care. If a new health accord is to offer financial incentives to the provinces for meeting healthcare targets, an equivalent range of penalties are needed for failure.

By the end of 2011, our newly elected governments across the country will be deeply engaged in negotiations for a new health accord. In the last two years, approximately 345,000 Canadians were diagnosed with cancer—and this year will bring more. Eighty-two per cent of Canadians report cancer has touched their lives either through their own illness or that of a close friend or family member. It would appear to be a substantial group of voters. This is the year to be heard.  

by Pierre Major, MD, Co-Chair of the Board of Directors, and Colleen Savage, President & CEO
The Cancer Patient’s Challenging Journey

**1 Routine visit to Doctor**

First suspicious test result
- Tests to rule out simple explanations
  - no referral
  - GP Disbelief/Misdiagnosis

**4 Follow-up**

- Recovery and more tests
- More chemo
- More radiation
- More clinical trials
- More surgery

**5 Later**

- Supportive/palliative care
- DEATH
- Go back to step 3

**6 Five years later**

-Congratulations! You’re alive.
- Rapid assessment, go to DIAGNOSIS

- More tests
- Distraction—find “miracle” cure online
- More chemo
- More radiation
- More clinical trials
- More surgery

**DEAD END**

- TREATMENT NOT SUFFICIENT
- How much more?
- What drugs?

- TOUGH DECISIONS
  - risks
  - side effects
  - quality of life
  - financial impact

- Supportive/palliative care
- RECURRENCE
- DEATH

**GOOD NEWS**

- GP Disbelief/Misdiagnosis
- REPORT CARD ON CANCER IN CANADA, 2010–11
2 Diagnosis

UNTREATABLE
Go to step 5, supportive/palliative care

IFFY NEWS
Preventative measures
Medical, surgical, lifestyle interventions

GOOD NEWS

• Wait for referral to specialist
• Wait for referral to surgery

IT'S A TREATABLE CANCER

Referral to oncologist
Referral to surgery

WAIT

STAGING
Schedule surgery

WAIT

CHEMOTHERAPY

Referral to oncologist

RADIATION

Referral to surgery

SURGERY

STEM CELL, BONE MARROW TRANSPLANT

DRUGS NOT COVERED

• Private payment
• Fund raising

RECOVERY

More tests, pathology, images

If necessary, return to oncology or surgery to choose another round of treatment

3 Treatment

This illustration is intended solely to portray the long and arduous path for cancer patients as they fight for their lives. It cannot be considered complete or accurate for every type of cancer—because there are hundreds—or every patient—because there are hundreds of thousands in Canada, right now.
Open Letter to Physicians

From the Alberta Health Services Website:
www.albertahealthservices.ca/4052.asp
March 16, 2011

It is our responsibility as clinical leaders, as it is the collective responsibility of all physicians and health care practitioners, to unequivocally address public concerns that our colleagues are restricted in any way from advocating on behalf of their patients.

This is not a political issue up for debate. It is not opinion or commentary.

As physicians and practitioners, it is our duty to our patients, our colleagues and our profession to represent and articulate the needs and best interests of our patients, and the health system as a whole. It is a standard set centuries ago within the Hippocratic Oath and it remains the touchstone for our profession to this day. As such, it is an expectation of the College of Physicians and Surgeons of Alberta Code of Conduct, and of the Canadian Medical Association Code of Ethics.

This, an open letter to all Alberta physicians, is our personal commitment to do all in our power to enable every physician in Alberta to meet this standard. As medical leaders, we must intervene, even at the risk of being drawn into the current debate, because we have a higher and greater obligation to our patients. We want to make it clear to our patients and the public that caregivers can and must advocate without hesitation.

Today, we are stating for the record, as per the Alberta Health Services Medical Staff Bylaws & Rules, developed by physicians and practitioners for physicians and practitioners, that medical staff and AHS share joint responsibility and accountability for the provision of health services to Albertans. Furthermore, the AHS Medical Staff Bylaws & Rules describe the behaviour and professionalism expected of individual medical staff members and AHS leaders. Included is an explicit statement confirming the right and responsibility of medical staff members to advocate for their patients.

The Bylaws & Rules also ensure a system of protection that affords due process and procedural safeguards for physicians with respect to their actions and interactions with AHS. In addition, the Bylaws & Rules provide multiple avenues and mechanisms for physicians, and medical staff, to discuss and report patient care issues, and to participate proactively with AHS in improving the health care system.

These words represent more than bylaws in and of themselves. They are founded on a set of principles, and Alberta Health Services will not allow these principles to be undermined. These principles as defined in the AHS Code of Conduct are intended to guide all actions and interactions, and underpin all AHS bylaws, policies, procedures, standards, guidelines, regulations and directives that must be followed by AHS and those who provide services on behalf of AHS. We must work in the best interests of patients and clients, we must exercise our best judgement, we must raise our hands if we see something we think is not best for our patients or our organization, and we must have the courage to stand up for what is right.

The AHS Code of Conduct does not restrict a physician or other practitioner to speak out, quite the opposite. In essence, we are required to bring our concerns forward; we are not merely given permission to do so. The Code sets out a number of options for raising issues including speaking to a manager or a physician leader, speaking to the Ethics and Compliance Officer or by contacting the External Confidential Reporting and Disclosure Service.

Today, we are speaking personally as physicians, and making a commitment as leaders, that we support our physician colleagues in upholding their duty and responsibility to advocate for their patients. This is a commitment that goes beyond any policy and to the heart of the oath made by all of us.

Now, and as we move forward in the weeks and months ahead, we have an opportunity to define the future and to develop a partnership that ultimately benefits our individual patients, and the health system as a whole.

Sincerely,

Dr. Chris Eagle, Acting CEO & President, Alberta Health Services
Dr. David Megran, EVP and Acting Executive Lead for Quality and Service Improvement
Dr. Francois Belanger, Acting EVP and Chief Medical Officer
The American Medical Association defines physician advocacy as action by a physician to promote those social, economic, educational, and political changes that ameliorate the suffering and threats to human health and well-being that he or she identifies through his or her professional work and expertise. The spectrum of opportunities for physician advocacy in our society is very broad. It ranges from advocating on behalf of a single patient, to advocating for a community or for society as a whole.

Despite the public endorsement of advocacy by medical educators, national accreditation bodies and professional medical associations, evidence suggests that physicians infrequently get engaged in advocacy activities at a local or national level. There are some notable exceptions. Probably the most famous is Dr. Helen Caldicott, the Australian pediatrician and antinuclear activist. Dr. Fernand Turcotte from the University of Laval has been a strong advocate for banning tobacco products and the mining and sale of asbestos.

Physician advocacy groups include the International Physicians for the Prevention of Nuclear War, an organization that was awarded the Nobel Peace Prize in 1983. The Ontario College of Family Physicians and many individual doctors advocated successfully for banning cosmetic pesticides in Ontario. The Canadian Association for the Protection of the Environment (CAPE) has more than 5,000 members and advocates for a number of environmental issues that affect Canadians. Physicians in Northern Alberta have spoken publicly about the concerns of possible increased rates of cancer in communities near or downstream from oil sands projects and uranium mines, despite opposition from within the medical profession, Health Canada, industry and governments.

There have been many ideas put forward as to why more physicians don’t engage in advocacy activities. Perceived barriers include a lack of advocacy training, physicians’ busy lives and concerns about the negative effect public advocacy may have on career advancement. We are more likely to endorse and celebrate physicians who are involved in direct patient care, basic sciences, drug development and education but less likely to acknowledge the efforts of physician advocating for changes in public policy or protection of the environment. These views may often be in conflict with the values we try to instill in medical students and residents.

The vast majority of oncologists in Canada are salaried employees of healthcare institutions. Many have clinical or full-time university appointments. Those who do advocate internally or externally may find that their cause or agenda could be at odds with their employer and academic institution. Many of these institutions have either formal or informal fidelity agreements, which severely limit an advocate’s ability to speak publicly about a number of issues, even those that do not involve confidentiality issues. Advocacy activities may result in physicians being in conflict with government healthcare priorities and agendas. In an era when hospitals and cancer centres are run as big business, corporate loyalty and other values may sometimes override the best interests of society and the environment.

The recent endorsement of community and societal advocacy as a requirement for successful completion of undergraduate medical training in this country by the Medical Council of Canada and by some residency programs, will hopefully lead to more physician advocates. Healthcare administrators and Deans of our Medical Schools need to encourage and facilitate advocacy activities. Public discourse about how cancer drugs are funded in Canada, concerns about secondhand smoke, the use of cosmetic and agricultural pesticides and other relevant issues should be welcomed by our hospitals and universities and not seen as an attempt to undermine those institutions or the political process.

David Saltman, MD, PhD is the Chair and Professor of the Discipline of Oncology, Faculty of Medicine, Memorial University.

References
by JOSEPH RAGAZ, MD, FRCPC

The objective of this report is to show that prevention is the single most cost-effective initiative Canada could successfully escalate quickly in the fight against breast (and other) cancers. The report will provide an updated review of the research on breast cancer prevention and reveal its current potential impact for breast cancer risk reduction. The scientific community has already been made aware of these data through the normal scientific channels, albeit not all clinicians are aware. So now it is imperative that the information be presented to all the medical community and the other stakeholders - the Canadian public and administrative and medical policy decision makers.

The research shows that if individual lifestyle factors and the identified preventive medical interventions were applied consistently to high risk women, then hormone receptor positive breast cancer could be prevented in 20-50 per cent of cases. The result would be several thousand fewer breast cancers each year in Canada. This report will summarize the data and identify some of the challenges that delay implementing these interventions.

Background
Breast Cancer mortality has decreased by approximately 25-30 per cent in most parts of the western world over the last two decades, with variations across Canada depending on local services.\(^1,2\)

The main factors known to impact breast cancer mortality include:
1. Widespread public education about breast cancer leading to earlier diagnosis particularly by using screening mammography.
2. Evidence-based therapy i.e., effective surgery, adjuvant chemotherapy, hormonal therapy, radiotherapy and post-recurrence therapy.

Breast cancer incidence rates have stabilized since the mid 1990s and slowly decreased since the late 1990s. This has been attributed, according to some reports, to the reduced use of hormonal replacement therapy (HRT) based on the U.S. Women’s Health Initiative group (WHI) publication of adverse HRT effects.\(^3\) However, breast cancer incidence rates had already stabilized in the mid-1990s, and thus other reasons ought to be considered.

Some aspects of breast cancer prevention, common to cardiovascular and breast cancer pathogenesis and related to lifestyle, have been increasingly practised by small cohorts of mostly urban-located western populations – such as weight reduction and diet focused on vegetables, fruit and exercise. In addition, across the western world there has been increased use of anti-cholesterol and anti-inflammatory interventions,\(^4\) which may also beneficially affect breast cancer risk rates.

Despite the decreasing mortality rates for breast cancer over the last decade, more than 22,000 women are still diagnosed each year in Canada and of these, close to 20 per cent will die, with absolute numbers of breast cancer deaths increasing annually (from 4,335 in 1986 to 5,066 in 2007).\(^5\) The ongoing breast cancer morbidity and the anguish of those affected remain one of the largest public health concerns of the female population.

Practical Aspects of Cancer Prevention
Of all breast cancer cases diagnosed in Canada annually, less than five per cent are associated with the expression of identified mutations in the two known genes: the BRCA1/BRCA2. Carriers of these genes have a 60–80 per cent lifelong chance of developing breast cancer and a 40–60 per cent lifelong risk for ovarian cancer, particularly those with the BRCA-2 mutations.\(^6,7\)

These patients and their families are now part of the genetic counselling programs in most cancer institutions across the country, involving professional counsellors, with emphasis on two important steps.
1. Preventive surgery in the form of bilateral mastectomy and/or bilateral oophorectomy.
2. Medical interventions with tamoxifen and raloxifene.

However, the remaining breast cancers, although still likely having some genetic component other than BRCA-1/BRCA-2,
cannot be identified by a single genetic test before diagnosis and thus are not sought out by organized initiatives aimed at prevention. There is evidence that a large sector of this population of women would benefit from the lifestyle and medical interventions described in this review.

To implement population-based breast cancer prevention as part of the accepted clinical guideline programs across Canada will, however, require infrastructure changes and initiatives, including the formation and funding of dedicated breast cancer prevention clinics, ideally associated with, or under the auspices of existing cancer facilities. Currently, only a few U.S. based cancer centres provide prevention counselling by oncologists to non BRCA-1/BRCA-2 women, and there are currently no dedicated breast cancer counselling centres in Canada for the purpose of breast cancer prevention. Due to expected population health gains and related long-term societal cost savings as described below, this should be a high priority.

At least three steps are required:
1. identify which breast cancer risk reduction interventions are evidence-based and most cost-effective;
2. identify women at higher risk using quantitative prediction tools and preferentially counsel this group;
3. finalize the cancer prevention logistics: identify who should do the counselling, who should fund it and consciously expand the focus from diagnosis and treatment of established disease to include prevention.

Risk Factors and Risk-reducing Interventions

Risk measure, named as relative risk (RR) or hazard rates (HR), is a statistical term that compares events with or without a given risk factor or intervention. If risk is unaltered, RR=1.0; if risk increases, for example by 20 per cent, it is expressed as RR=1.2; if risk is reduced by 20 per cent, RR=0.8.

Current literature indicates that the impact of some of the risk-reducing interventions could be profound, with ranges of 20–50 per cent fewer new hormone receptor positive breast cancers annually, (i.e., RR=0.5–0.8) depending on the individual intervention. These data permit estimates that if risk-reduction interventions are practiced with a higher level of compliance, several thousand new breast cancer cases in Canada could be avoided annually. What are these individual risk factors and possible interventions?

1. Excess weight and obesity
The current western diet (based on high carbohydrates, animal fat with high cholesterol and too few vegetables and fruits), associated with obesity and higher body mass index (BMI), has a well-established link to higher breast cancer rates, particularly if associated with a sedentary lifestyle. High breast densities on mammogram and or higher serum estrogen hormonal levels are probably markers of these metabolic phenomena. Obesity, with adipose tissue as a source of carcinogenic molecular growth factors, has been described as increasingly relevant in the recent literature.

The impact of long-term dietary and weight-reducing interventions on breast cancer risk is not precisely known, as no long-term validated intervention studies have been done for breast cancer. The proposed prevention clinics aimed at high risk populations will have potential to study the impact of these interventions. In addition, new data are accumulating on the adverse effects of obesity after a breast cancer diagnosis, showing potential for improving survival rates through lifestyle initiatives, in women already diagnosed with breast cancer.

What about interventions leading to obesity reduction, with dieting and exercise and or more targeted interventions? Old literature did not support a substantial influence of dietary manipulation on either breast cancer rates or breast cancer outcomes after the diagnosis. However, more recent studies come to a different conclusion. George et al.11 showed, in 670 women with breast cancer, that patients consuming better-quality diets (as defined by higher Healthy Eating Index-2005 scores) had a 60 per cent reduced risk of death from any cause when compared to ordinary diet, (HR=0.40, 95 per cent CI: 0.17, 0.94) and an 88 per cent reduced risk of death from breast cancer (HR=0.12, 95 per cent CI: 0.02, 0.99)

2. Exercise
Recent evidence associates regular aerobic exercise with reduced breast cancer incidence rates and improved survival in women with diagnosed breast cancer. In 2008, Irwin et al.15 reported that when compared with inactive women, the multivariate hazard ratios (HRs) showed a 31 per cent reduction of total deaths for women who are physically active in the year before diagnosis – meaning approximately two to three hours per week of brisk walking. (HR=0.69, 95
per cent CI 0.45 to 1.06; P=.045.) In patients who exercised two years after diagnosis, even larger benefits were seen, with a 67 per cent reduction of deaths (HR=0.33, 95 per cent CI, 0.15 to 0.73; P=.046).

The estimates for risk reduction depend on the quality of the study, the duration of follow-up and the intensity of exercise, but fall in the range of 20-30 per cent (RR=0.7-0.8) or more with prolonged exercise. On the basis of 20-30 per cent risk reduction, comparing 1,000 women who do not exercise with 1,000 women who do, the sedentary group would produce 100 cases of breast cancer while the exercising group would produce 80 or less. Thus, a large number of the annual 22,000+ new breast cancers in Canada could be avoided through lifestyle changes that incorporate regular exercise, simultaneously reducing cardiovascular risk.

3. Alcohol
There is rising evidence for an association of increased breast cancer risk with alcohol intake,16,17,18 with some data indicating dose dependence: the more alcohol, the higher breast cancer incidence. More than six drinks per week would increase the risk by 30-90 per cent compared to less than one to two drinks per week (RR=1.3–1.9). The mechanism is likely related to metabolic changes leading to increased breast tissue estrogen effect, which is considered carcinogenic.17

4. Medical interventions with breast cancer prevention agents

i. Tamoxifen. At least four randomized trials have documented a 40–50 per cent risk reduction of estrogen positive invasive and in situ breast cancer rates by tamoxifen (RR=0.5-0.6) given to women at high risk of breast cancer. High risk was determined by the Gail model, based on first degree family history at a young age, or abnormal pathology (atypia lobular carcinoma in situ, etc.).19 Prolonged adverse publicity associating tamoxifen with uterine cancer and increased thromboembolism (clotting), cited in the early years when they were identified but not rated accurately, has negatively affected its use in prevention. More recent updates of tamoxifen net-effect in patients with established breast cancer clarify the picture.

- Incidence rather than mortality from uterine cancer is increased (i.e., more uterine cancers are diagnosed on tamoxifen, but because of early diagnosis most are cured), with reduced breast cancer mortality leading to a much larger net gain: reduction of overall mortality.20
- Thromboembolism rates are similar to those on birth control pills and or hormone replacement therapy, so the rates are not disproportionately increased with tamoxifen.
- Updated data from the original NSABP P-1 prevention trial show minimal risk of uterine cancer or thromboembolism among younger women, under age 55, while the benefit of breast cancer risk reduction of 40–50 per cent is significant.21
- Most recently, Noah-Vanhoucke et al.22 provided one of the most comprehensive cost-benefit analysis of tamoxifen. Their meta-analysis of four randomized trials indicated that tamoxifen chemoprophylaxis, for postmenopausal women under age 55, is cost-effective in reducing breast cancer incidence and improving life expectancy.

Thus, tamoxifen for breast cancer prevention in young women, under age 55, at high risk of developing future breast cancer, is generally much safer than many other medical interventions and is currently substantially underutilized.20

ii. Raloxifene (Evista). In a recently completed randomized trial of tamoxifen against raloxifene in a high risk population of postmenopausal women (the STAR trial), raloxifene produced similar risk reduction to that of tamoxifen, while being associated with significantly lower uterine cancer and thromboembolism.21,23

Therefore, the 2010-2011 St. Gallen’s-based consensus conference on breast cancer prevention24 recommends tamoxifen for premenopausal women and raloxifene for postmenopausal women at high risk, indicating that “Because of its proven effectiveness and well understood side-effect profile, tamoxifen is presently deemed to be the preventive agent of choice in most high-risk women, especially in premenopausal women or those with atypical hyperplasia or lobular carcinoma in situ.”

iii. Lasofoxifene. The newest agent, lasofoxifene is a modified SERM, with more cholesterol-reduction and less uterine cancer rates than tamoxifen.25,26 Furthermore, lasofoxifene was associated with significantly reduced risk of bone fractures, a very significant (more than 80 per cent) reduction in ER-positive invasive breast cancers and more than 30 per cent reduction in coronary heart disease and strokes. In addition, there was a reduction of more than 30 per cent in coronary heart disease and strokes. Thus, in postmenopausal women with osteoporosis, lasofoxifene presents a favourable prevention profile. Longer follow-up is required to confirm these promising results. The agent is not yet available in Canada for clinical use.

iv. Bisphosphonates are a class of medications approved in North America and Europe for prevention of bone loss. These drugs have been recently shown to prevent bone fractures not only in cases with advanced metastatic breast cancer (where their use in Canada has been approved), but also to reduce rates of metastases in hormone sensitive breast cancer cases treated with hormonal therapies in the adjuvant setting, just after the primary surgery, to prevent recurrences.27

Recent analysis of one of the largest breast cancer epidemiology studies has shown a strong association of oral bisphosphonates taken by women without breast cancer, with a significant reduction of primary breast cancer in the range of 32 per cent (RR=0.68; 95 per cent CI, 0.52 to 0.88; P < .01).28

v. COX 2 inhibitors such as aspirin,29,31 celecoxib (Celebrex)31-35 and many non-steroidal anti-inflammatory agents, have been known to reduce carcinogenesis in animal studies. Recent human studies in colon cancer and more recently breast cancer confirm almost a 40–50 per cent reduction of new cancers in subjects with regular use of aspirin—a strong anti-inflammatory and a Cox2 inhibitor—compared to non-aspirin users.29,31,36,39 There is promising potential of celecoxib or ibuprofen as examples of a more powerful Cox2 inhibitor. Confirmation of their cost-benefit impact is needed in future studies.36-39
Interpretation of Prevention Studies
These estimates are relevant to the prevention issues under discussion: if all prevention initiatives were put into practice today, with high adherence by high risk Canadian women, several thousand breast cancers could be prevented in Canada annually.

Conversely, if prevention is not practiced, and the present status quo is perpetuated, Canadians will be confronted with several thousand additional breast cancers each year.

Thus, delays in incorporating appropriate interventions into guidelines result in higher rates of death in our population, compared to the decreasing rates if optimum prevention interventions were adopted today.

Low Profile of Breast Cancer Prevention in North America
There are several reasons why prevention of breast cancer is not systematically practiced.

First, no medical specialty in Canada has a mandate for practising prevention at the present time simply because none is claiming this practice as their main domain. Oncologists within cancer institutions accept cases only after biopsy-confirmation of cancer.

Surgeons, even those specialized in breast cancer, do not deal with cancer cases unless a surgical procedure is contemplated. Even then, most lack the knowledge base and the time required to counsel high risk women. Family physicians also lack the specialized background required. They refer cancer patients to oncology centres only when a cancer diagnosis is imminent and or biopsy-proven.

Second, no provincial funding is available for the sustained operation of cancer prevention counselling services. Such a clinical infrastructure would require dedicated oncologists, non-specialty physicians, nurses, social workers, physiotherapists, and nutritionists.

Additional skills would be required in risk assessment and selection of cases for the counselling clinics. Educational resources are required to introduce, reinforce, and monitor recommendations for lifestyle change. Dedicated activity would involve prescription of the appropriate preventive agents and monitoring of their use. These activities are analogous to those involved in operating well-established and funded cancer clinics.

One of the most important steps in planning a targeted prevention practice is to narrow down as much as possible the at-risk population, so that costly preventive initiatives will be focused on those who need them most.

The risk of getting breast cancer can be assessed by a refined new generation of risk assessment tools—most of them expanding on the original Gail risk model, taking into consideration, besides the family history and pathology, also weight, body mass index, exercise and alcohol intake. Attempts are underway to integrate these established risk factors prospectively with screening mammography criteria such as high breast density.

These risk models define a quantitative risk prediction of an individual woman to develop breast cancer and if the risk exceeds a certain level, the woman would be a candidate for a prevention trial or ideally, for prevention initiatives once incorporated into guidelines.

Summary
Data increasingly indicate that breast cancer prevention initiatives should be at the forefront of action. Today, however, despite these data, obesity rates are on the rise, particularly among young teenage girls and generally among women with low socio-economic or aboriginal background. This in turn is related to higher rates of sedentary lifestyle associated with lower exercise in the western population as a whole.

The data forecast a very promising impact of obesity reduction on breast cancer rates, through a combination of diet and exercise. A similar effect is apparent on general health outcomes, including profound cardiovascular and stress-relief benefits, with an associated high cost-benefit to the health system. Professional counselling to promote exercise and sensible diet, in a dedicated prevention clinic, deserves priority attention from health planners and administrators.

Both tamoxifen and raloxifene are substantially underutilized for breast cancer prevention, mostly due to the biased perception of their side effects, despite randomized trials showing Level 1 evidence for their large scale benefit in breast cancer. The tamoxifen/raloxifene underutilization is made worse by these drugs not being approved and funded for prevention in Canada, where only Quebec funds their use for breast cancer prevention. In contrast, in the U.S., insurance companies fund these agents for prevention if indicated by an oncologist.

In Canada, in general, we lack dedicated prevention facilities and systematically organized cancer prevention programs. One of the first such programs in Canada, proposed by the University of British Columbia, is the Breast Cancer Prevention Clinic to open in Vancouver in the late Spring of 2011.

Conclusion
The main objective of this report is to alert Canadians to the issues of cancer prevention using breast cancer as an example and to document the huge potential for avoiding a large number of breast cancers if all evidence-based prevention initiatives were systematically applied to high risk women. While prevention interventions with medication are clearly indicated due to their documented impact and cost-benefit, the advantages of aggressive weight and diet control, with escalating exercise, are undeniable for both breast cancer and cardiovascular disease. Furthermore, large societal cost savings for Canadian taxpayers will follow, as in the long-term millions more would be spent to cure a developed breast cancer than to prevent it today.

It is the intention of this report to provide compelling support for the development of dedicated breast cancer prevention clinics supervised by trained oncologists, staffed with the related counselling team of nurses, dietitians, physiotherapists and social workers. Truly, an ounce of prevention is worth many pounds of cure. The sooner the better.

Joseph Ragaz, MD, FRCPC, is a Director of the CACC and a Senior Medical Oncologist, Breast Cancer Researcher, Clinical Professor, Faculty of Medicine and School of Population Health, University of British Columbia, Vancouver, B.C.


References
Prevention Update

Smoking

Smoking is the most preventable cause of lung cancer and harms anyone in the near environment. In 2009, 20 per cent of adult Canadians were smoking, with provincial rates varying from a low of 16 per cent in British Columbia, up to 22 and 23 per cent from Quebec all the way to Newfoundland and Labrador. The territories are terrifying, with smoking rates of 36 per cent in the Yukon and NWT, but a jaw-dropping 61 per cent in Nunavut. In subsets, males are smokers more often than women in each province or territory. Excluding the territories for a moment, merely because the numbers betray a phenomenon more diverse than tobacco alone, males in Alberta, Nova Scotia and Newfoundland and Labrador are smoking more than anyone in the country, at rates of 26 and 27 per cent.

Smoking rates have dropped, slowly, for decades. All it took was decades of aggressive anti-tobacco campaigns, massive amounts of public education and health promotion, numerous controls on the marketing of tobacco products, frequent price increases for tobacco products, smoking bans extending out from restaurants and bars to all public buildings, transit systems, parks, entire communities. The vigilance and creativity of the anti-tobacco movement is impressive, as is the commitment by most governments to deny a safe haven to a lit cigarette. Alberta and Quebec are the only provinces that have not introduced legislation for smokeless cars when children are present. Newfoundland and Labrador will implement the ban in May, 2011.

With all this activity, so clearly focused on one goal, why is one out of every five Canadians still smoking? Why is the smoking rate for teenage girls increasing and the overall rate for all adults apparently levelling off?

There may be answers in the unique resistance of some smokers to standard quit techniques. Perhaps a more formalized program of counselling and medical intervention is needed, but are physicians ready for this role? Perhaps a more stringent regulatory environment is appropriate, or more targeted health promotion messages, perhaps a more tailored form of government spending to reach the resistant smoker. This year the CACC will pursuit the subject in tailored form of government spending to reach the resisters.

RARE CANCERS UPDATE

Orphan Drugs

Ontario and Alberta each have an established framework for dealing with rare diseases but no other Canadian jurisdiction has taken that step. In a standard drug review, where each province tries to decide whether a new drug is important, effective and affordable, there are fairly rigid rules about the extent and quality of evidence that must be delivered before a drug can be considered a worthwhile expenditure.

However, rare diseases are exactly that and there are an insufficient number of patients to run the full-scale clinical trials that are common to research on other diseases. With incidence rates in the single digits per 100,000 or even 200,000 people a rare cancer is hard to diagnose, hard to put in front of the rare clinician who knows it well, and hard to explain. The trials are small and often deemed unconvincing. Furthermore, the discovery of a treatment for any of the rare diseases is likely a breakthrough, which can cause the trial to be suspended for ethical reasons – it is improper to withhold an effective drug from the control arm of the trial.

In short, the usual standards and processes stack against a new, orphan drug. It is for this reason that two provinces developed a special policy to consider more relevant criteria for these drugs reviews. Otherwise the new orphan drugs fail the reviewers’ analysis and are rejected.

The pan-Canadian Oncology Drug Review (pCODR) is a new review process initiated by the provinces and territories to conduct expert reviews and provide recommendations on the clinical merits and cost-effectiveness of a new cancer drug. The provinces then have common, expert advice on which to base their funding decisions. If pCODR had a rare cancers policy, the entire nation would reap the benefits of an insightful analysis of these orphan drugs. But that is not the case. As it stands, only two provinces will be able to sensibly evaluate the merits of such products.

For a disease like cutaneous T-cell lymphoma, that strikes approximately one person out of 150,000 the inability to count on a drug review process that knows your disease can be unnerving. Cutaneous T-cell lymphoma is a general term for many lymphomas of the skin. There are no proven causes, but the usual arsenal of cancer weapons is applied, including radiation and chemotherapy along with ultraviolet light and topical treatments. A new treatment option is, to say the least, welcome.

It is encouraging to hear that Ontario will spur the other provinces into a common rare diseases policy, allowing all jurisdictions to benefit from the analyses already conducted and the expert recommendations for a new set of best practices in these special reviews. The test will be whether orphan drugs survive or fail the new pCODR process.
B-cell Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) are cancers of the white blood cells that are characterized by a proliferation of B cell lymphocytes. According to Statistics Canada (2006), about 1900 new patients are diagnosed every year. SLL primarily involves the lymph nodes while CLL affects the blood, bone marrow and lymph nodes. CLL and SLL are now considered to be different manifestations of the same disease. Resulting anemia, low platelets and frequent infections because of low immunity are common.

Most cases of CLL are diagnosed in people over age 50 and its incidence increases with age. CLL tends to be indolent in the early stages and is often diagnosed as a result of routine blood tests. In many cases, a watchful waiting period begins as there are little benefits to early treatment. This period often lasts several years during which patients often complain of various levels of fatigue and anxiety. Proper diagnosis is critical as a subset of patients have an aggressive form of CLL and need to make the best therapy choices quickly.

CLL symptoms leading to treatment include fever and/or chills, severe weight loss, soaking night sweats and overwhelming fatigue. Chemotherapy agents such as fludara-bine (Fludara) and cyclophosphamide (Procytox, Cytoxan) are typically used in combination with monoclonal antibodies such as rituximab (Rituxan) in order to reduce these symptoms. This combination, known as FCR has become the gold standard for treatment. However it tends to be quite toxic and typically leaves patients in a more immune-compromised state. Younger or high-risk patients may be offered an allogeneic stem cell transplant. Clinical trials are one way patients can receive emerging drug combinations while waiting for provinces to fund drugs officially approved by Health Canada. These trials tend to be restricted to patients who meet stringent criteria and who have access to a cancer centre offering the trial. Many patients are frustrated that there is no standard of practice for CLL in Canada as treatment depends on which province you live in.

CLL is due to DNA genetic damage during cell division, as part of the B-cell regenerative process. Defective B-cells accumulate and can eventually lead to bone marrow failure, if left untreated. Genetic biomarker testing such as FISH (Fluorescent In Situ Hybridization) and the more recent introduction of Chromosomal Microarray Analysis known as array Comparative Genomic Hybridization (aCGH) are expanding the field of genetic markers in CLL. FISH testing is done for patients in clinical trials but they are generally not given the results. The aCGH is currently not available to Canadian patients unless they make their own arrangements to have it completed out of the country. Advances in treatment, a better understanding of how the cancer functions and mapping of the chromosome damage that causes CLL has led to greatly increased response rates and durations of response. Treatments can be repeated but they typically result in shorter remissions. Not much advance has been made in extending overall survival, however. Canada does not have a Centre of Excellence for CLL. We are fortunate to have a dedicated group of clinicians and researchers who form the Canadian CLL group and meet in Manitoba every year. CLLPAG is a national volunteer organization of patients committed to advocacy, awareness, education and equal access to care on behalf of Canadians affected by CLL and SLL. The Leukemia and Lymphoma Society of Canada, Lymphoma Foundation of Canada and Juravinski Cancer Centre in Hamilton, ON support CLLPAG in organizing an International Conference on CLL every few years. This unique event, organized by CLL patients for CLL patients and practitioners, provides a world-class forum to learn about the latest developments on the treatment of this complex, heterogeneous disease.

As we learn more about the genetic variations in CLL/SLL, there will be a growing need for individualized treatment and advanced biomarker testing. These will require further treatment approvals based on new criteria, new ways of thinking about the disease, new technologies and a greater emphasis on targeted therapies that closely match the needs of the patient. Personalized medicine will save money by reducing ineffective or unnecessary treatments. Canadians should be able to receive optimal health care no matter where they live. It is imperative that the cancer care agencies of Canada and provincial and federal health ministries support research into new treatments and technologies as well as fast-track approval of selective inhibitors which are newer, innovative, less toxic treatments. A great deal of progress has been achieved with the approval of FCR as the therapy of choice for most untreated CLL patients. Approval of FCR or FR for repeat therapy and select alternatives, such as bendamustine (Treanda), for older patients is paramount.

Submitted by members of the CLL Patient Advocacy Group www.cllpag.ca
© 2011 CLLPAG. Used with the kind permission of the authors.

Ovarian Cancer

While considered rare compared to some cancers, Canadian women have a 1 in 70 lifetime risk of developing ovarian cancer. Approximately 2,600 women are diagnosed and there are 1,750 deaths from the disease each year. Seventy per cent of women with ovarian cancer do not survive five years—making the disease Canada’s most fatal gynecologic cancer. Although ovarian cancer is most common among women over the age of 50, it also affects younger women. About 10 per cent of ovarian cancers are hereditary—usually due to a mutation to the BRCA1 or BRCA2 (Breast...
Cancer 1 or 2) gene. One in 50 Ashkenazi Jews carries one of these gene mutations that increases their risk for breast, ovarian and related cancers. Segments of the French Canadian pop-
ulation may also be at increased risk. As the country’s sole charity dedicated to overcoming ovarian cancer, Ovarian Cancer Canada has a continuous dia-
logue with women and families living with the disease, other families who have lost loved ones, health professionals who deliver care and researchers who study ovarian cancer. Our stakeholders speak with one voice when they say that their biggest frus-
tration is the absence of a screening test for the early detection of ovarian cancer. The need for increased resources to support Canada’s most promising research in this area cannot be overstated. When detected and treated at an early stage, five-year survival of ovarian cancer can be as high as 90 per cent. Unfortunately, the lack of a screening test and the fact that symptoms can be vague and attributed to other causes means ovarian cancer is usually diagnosed in later stages, when the disease has already spread to other parts of the body.

The signs and symptoms of ovarian cancer—including swelling or bloating of the abdomen, pelvic discomfort or heaviness, difficulty eating or feeling full quickly and emptying the bladder frequently—are not well known among Canadian women and many primary health care providers. This lack of awareness and the absence of a screening test for early detection can result in a longer wait for a correct diagnosis compared to other cancers. Until an early detection test is available, knowledge and awareness of the signs and symptoms are the best defence against this disease. A woman who experiences one or more symp-
toms that persist for three weeks should see her doctor for a full investigation.

If ovarian cancer is suspected, the family doctor or gynecologist should refer the patient to a gynecologic oncologist, a specialist with five years of postgraduate training in obstetrics and gynecology plus an additional two years of cancer training. The gynecologic oncologist will manage treat-
ment—usually surgery and chemotherapy. Studies have shown that there are better outcomes for ovarian cancer when surgery is performed by a gyneco-
logic oncologist. Canada has 82 of these specialists and more are needed to meet the growing demand for care.

Women with ovarian cancer tell us that the wait to see a gynecologic oncologist, and the wait for surgery and other treatment to begin, can be very stressful. A shortage of specialists plus other challenges, such as limited access to operating rooms and inconsis-
tencies in available therapies across the country—intraperitoneal chemotherapy, for example—are other frustrations they experience.

It is estimated that the incidence of gynecologic cancers in Canada will rise by 47 per cent between 2001 and 2014. The Society of Gynecologic Oncology of Canada (GOC), in part-
nership with Ovarian Cancer Canada, is now conducting a study of wait times and treatment protocols for gynecologic cancers across the country with an aim to improve care for women requiring treatment.

Women across Canada also tell us that they experience high stress in the period immediately following completion of their treatment. By this point in their ovarian cancer journey, they have educated themselves about the disease and know that they have to live with the possibility of recurrence. Issues ranging from survivorship to recurrence, palliative care and end-of-
life care mean women with ovarian cancer and their families need support services close to home.

Since our organization was founded 13 years ago, Ovarian Cancer Canada has worked diligently with survivors, volunteers and the cancer community toward the goal of overcoming ovarian cancer by:

• supporting women and families living with the disease
• educating the public and health professionals about ovarian cancer
• and raising funds for research into early detection and, ulti-
mately, a cure.

We believe that success can best be achieved through a collaborative national cancer strategy that brings greater focus and improved research opportunities for diseases that are as lethal as ovarian cancer. We also believe that a coordinated national approach can best address the human and financial resource issues, and ensure equal access to the best evidence-based care and support for all Canadian women and their families living with ovarian cancer.

Elisabeth Ross is Chief Executive Officer of Ovarian Cancer Canada. www.ovariancanada.org
She also co-chairs the National Survivorship Working Group of the Canadian Partnership Against Cancer.
© 2011 Elizabeth Ross. Used with the kind permission of the author.

Testicular Cancer

Testicular cancer starts in the cells of a testicle. The testicles are part of a man’s reproductive system. They are the two egg-shaped organs found in the sac of loose skin (scrotum) at the base of the penis. The testicles are held in the scrotum by the spermatic cord. The spermatic cord contains the ductus deferens, some lymph nodes, veins and nerves.

Testicles make the male sex hormone testosterone and sperm. Sperm begins to form in “germ” cells inside the testicles. Most testicular cancers start in the germ cells and are called germ cell tumours.

There are two main types of germ cell tumours: seminomas and non-
seminomas. Each type grows different-
ly and is treated differently. Both types can be treated successfully.

Testicular cancer, although a rare cancer in the spectrum of cancers overall, is still the most common can-
cer for males from 15–29 years of age. On average, one out of every 273 males in Canada will be diagnosed
The highest overall incidence of testicular cancer occurs in Alberta, then Nova Scotia and Saskatchewan. However, it is the age-specific incidence rates that reveal the poignant truth about the impact of this disease.

The highest rate of testicular cancer in one age group occurs in Nova Scotia, for men 25–29 years of age. Across the country, the highest incidence occurs in young men between the age of 25 and 34, with only Manitoba having a higher rate in the 35–39 age group. The incidence of testicular cancer increases from age 15 and decreases after age 40.1

While this cancer has the highest curability rate for all men’s cancers at 97 per cent, the aftershock following diagnosis causes deeper problems and complications for survivors.

The stigma of an orchiectomy (semi or full surgical castration), creates typically unaddressed issues for the survivor and his sense of masculinity. Akin to breast cancer mastectomy and reconstruction, testicular cancer survivors who opt for a testicular implant do have a quick recovery time and generally are sent home to recover, either with a surety of having been cured or getting a finite chemotherapy schedule as the next, final step to being cured. What is left untreated is the how the patient feels as a man.

The psychological impact of testicular cancer is as relevant as any other cancer, regardless of the curability factor. The emotional effect following an orchiectomy is parallel to a mastectomy for a woman. Only in moments of intimacy or examination would someone know the man in front of them has had testicular cancer.

The typical responses by TC survivors are either, “sweep it under the carpet”—living in denial that it ever happened—or a gradual acceptance of the new reality, depending on the survivor’s personal sense of security and whether a social support system is in place.

Cancer is a catalyst for confronting one’s mortality. It offers a perspective like no other, bringing issues to the forefront. What once seemed important and/or tolerable becomes insignificant and/or intolerable, leaving you with your world upside down, asking “where do I go from here?”

In men, this experience is difficult to adjust to, as we do not often express feelings liberally and honestly. When combined with the age group involved—often as young as 15—the impact on personal, emotional development can be severe.

TCTCA offers a peer support system for survivors to network via email, telephone, or in person. As the only registered non-profit charity for Canadian testicular cancer awareness, if every TC survivor were to approach our group at once, we would be overwhelmed accommodating an entire country of males in need.

Testicular cancer is one face to the young adult cancer issue in Canada, where we are effectively “a lost generation.” With so much effort focused on paediatric/geriatric cancer care and support programs, hospitals and cancer treatment centres do not have as many young adult survivor outreach programs in place yet. This is mostly due to the lack of a young adult approach within the cancer system, stemming from the insecurity and fear of patients who retreat from drawing attention.

Encouraging an open forum for testicular cancer patients at the time of diagnosis is just as important as the diagnosis itself. Hopefully this leads to easier adjustment in developing self-identity through any/all treatments, approaching friends and/or family for emotional support and security as men following cancer’s touch.

Peter Laneas is a two-time testicular cancer survivor and the national spokesperson for The Canadian Testicular Cancer Association. For more information on testicular cancer, www.tctca.org.

(c) 2011 Peter Laneas. Used with the kind permission of the author.

References
1 Sources: Surveillance and Risk Assessment Division, CCDPC, Health Canada; Statistics Canada and the Canadian Council of Cancer Registries

UPDATE

Chronic Myelogenous Leukemia

Key issues last year were disease resistance and patient intolerance to current front line therapy, imatinib (Gleevec). Newer second-generation drugs are now available to treat these issues. In August 2010, Health Canada approved nilotinib (Tasigna), which joined dasatinib (Sprycel) as second line therapies. The approval of nilotinib is good news, but because each province must approve the drug for reimbursement on their provincial formularies, it has been very difficult for some Canadian patients to access this drug. In BC, Alberta, Saskatchewan and Quebec, nilotinib has been approved on provincial formularies as a second line treatment. However, in Ontario, nilotinib funding is only available for third line treatment, setting up a potential disaster for some patients. Some patients linger longer on the first line treatment while their health deteriorates to the point that when they may be able to access sec-
ond and third line therapies, neither of them offers any improvement. We must be able to trust our doctors to protect our health.

The next issue we addressed was purchasing our oral cancer therapy through private employer insurance, with some assistance from provincial drug plans. For some patients, the gap leaves them paying $1,500 that is not reimbursable. Why are we subjecting these patients to something that sounds like a “cancer tax”? Additionally, colleagues frown upon co-workers with diseases on “designer” priced drugs, as premiums are increased or benefits are scaled back to meet the costs. BC and Alberta continue to be the only provinces that provide oral cancer drugs through their cancer and rare disease drug programs.

Our third issue was asking the government to step in and get involved in supporting drug combination trials or stopping drug trials for CML. This is happening in Europe. The data from Europe indicate that 10 per cent of CML patients on the current front line therapy, imatinib, may be candidates to safely stop taking drugs. This figure could be as high as 40 per cent if we factor in the superior responses that patients achieve on the second line drugs such as dasatinib and nilotinib. We hear rumours that industry is stepping up to the plate, but where is our government?

We would like the governments to support a personalized medicine approach with regards to CML. If we could allow our physicians to conduct appropriate diagnostic tests up front for CML patients, such as immunophenotyping, mutation detection combined with cytogenetics, PCR, FISH and standard blood tests, as well as other tests that may be deemed appropriate, we may be able to ensure that the right patient gets matched with the right drug, at the right dose, at the right time.

Next year we hope to report that these critical issues are resolved, with improvements in patients’ quality of life and return to good health.

Cheryl-Anne Simoneau is President of the CML Society of Canada. 
© 2011 Cheryl-Anne Simoneau. Used with kind permission of the author.

Multiple Myeloma

Have there been improvements in our access to drug treatments? This year’s answer—maybe yes, maybe no.

There are two parts of the equation. First there is the funding approval and then, the challenge of physically getting the drug.

The Pan Canadian Oncology Drug Review is to be a more transparent, accountable system of cancer drug review. pCODR is a step forward as more public inclusion has been desired and requested—including patient sub-

missions. It is a modest step, but we welcome it and look forward to further openness and understanding.

Then each province and territory will make their own funding decisions based on the pCODR evaluation of effectiveness and cost-benefit. Even assuming, with great optimism, that the provinces and territories all accept a positive recommendation from pCODR and decide to fund a new cancer drug, there are always conditions and restrictions.

The second part of this equation is receiving the needed drug therapy.

The actual receipt of a needed drug may be either a simple or an onerous task—most stressful and unfair when one’s life is hanging in the balance. Ontario’s Expanded Access Program puts restrictions on access with the intent of protecting the patient. A perfect example is lenalidomide (Revlimid). Processes must be and have been put in place because of the historical birth defect issue. So this is good. However, the organization or administration of this program is a convoluted nightmare.

An application to receive a drug under the EAP is supposed to receive a decision within two weeks. Approvals have been taking up to two months. This system has forced some physicians to spend extraordinary amounts of time on paperwork rather than providing patient care. Hospitals already hire “reimbursement navigators” to help patients and doctors find a way to obtain the many treatments not covered by the provincial drug plan.

Would you, as a patient with an advancing cancer, want to wait two months simply because of paperwork to find out if your EAP application is approved? Whether or not the health ministry feels any sense of urgency, the cancer patients certainly do.

Physicians who work with this system 24/7 are strong proponents for positive change. But patients also can, and must, have a voice. It is the responsibility of the patient population to become more informed, more involved and more outspoken.


Neuroendocrine Tumours

Neuroendocrine tumours, now known more commonly as NET cancers, is the umbrella term for a group of unusual, often slow-growing cancers, which develop from cells in the diffuse endocrine system. They are found most commonly in the lung or gastrointestinal system, but they can also originate in other parts of the body such as the pancreas, ovary, and testes, among other sites.

Increased awareness of NET cancer has developed as a result of media coverage of Apple founder Steve Jobs’ pancreatic NET cancer. We are now recognized as the fastest growing cancer community worldwide (BBC, Belfast, September, 2010).

Despite increased media exposure, NET cancer still remains, for the most part, a no-name cancer. Although the
Canadian Cancer Encyclopedia now boasts a Neuroendocrine Cancer chapter, it is filed under the category of “other endocrine.” Usually NET cancers do not originate from a specific site. This seems to confound provincial health ministries and cancer agencies when it comes to identifying us properly.

An important NET cancer diagnostic scan, the octreoscan, still has no billable code, which means hospitals have to individually foot the bill for our scans, making us an expensive and unattractive patient group for hospitals worried about their bottom line.

For most of last year, the only centre in Canada accepting patients from all over the country were the Neuroendocrine Cancer Centres in Calgary and Edmonton. The Cross Cancer Centre in Edmonton was actually the first location in Canada to begin to treat patients with the not-yet-approved rare nuclear isotope Lutetium 177, which targets all NET cancer cells and is regarded as a significant treatment option for a substantial segment of our community.

The London Regional Cancer Centre, which in the past had accepted patients from all over Canada, had been closed to patients outside the Local Health Integrated Network, (LHIN) for 2009 and much of 2010, but in the second half of 2010 Ontario bowed to patient pressure and the London HSC opened its doors again.

Currently Cancer Care Ontario has an Expert Panel and Steering Committee looking at the delivery of radioisotope treatment for qualifying patients in Ontario. CNETS Canada is acting in a consultative capacity.

Our Vancouver International Conference in May 2010, with 35 faculty from six countries, focused on the best and most innovative practices worldwide and our DVDs are available for distribution across Canada to medical and patient libraries everywhere.

On June 2, 2010, CNETS Canada spoke of the need for radioisotope treatment at the Health Committee of the House of Commons. On October 10, 2010 the Canadian NET Cancers community took part in the first World NET Cancer Awareness Day by hosting information tables in key hospitals and making sure our newly published information leaflets were in the stacks. We will host more hospital information tables and put leaflets into many more hands in 2011.

Maureen Coleman is the President of CNETS Canada. www.cnetscanada.org

© 2011 Maureen Coleman. Used with the kind permission of the author.

GIST

In last year’s Report Card on Cancer in Canada, Life Raft Group Canada noted the many difficulties faced by patients living with GIST (gastrointestinal stromal tumour), a rare sarcoma of the gastrointestinal tract.

Drug access is a particular problem for patients with rare cancers. Imatinib (Gleevec) was the first approved targeted chemotherapy for GIST.

Subsequently, several other drugs, including sunitinib (Sutent), nilotinib (Tasigna), and dasatinib (Sprycel), have either been approved or are in trial for GIST. All of these drugs cost thousands of dollars per month, and provincial drug plans have been slow to provide coverage.

There are unacceptable differences in drug coverage between provinces: a “patchwork quilt” or “postal code lottery.” A particular problem right now is access to “adjuvant” Gleevec, that is, treatment intended to delay or prevent recurrence of GIST, following surgery. This treatment is known to be highly effective, based on results of several published clinical trials, but remains unavailable to many Canadian GIST patients, because of financial barriers. Novartis Pharma-ceuticals had provided access, through its compassionate-use program, but this program was shut down to all new patients, as of Feb. 1, 2011.

So, we monitor the provincial funding decisions and we press the case for improved access.

- In B.C., funding approval for adjuvant Gleevec was given, with some restrictions, in 2009.
- In Quebec, funding can be provided through the Exceptional Patient Program.
- In N.S., funding was approved in Dec. 2010.
- One month later, in N.B., funding was denied.
- In Ontario and Alberta, decisions have not yet been made. Ontario is a key province, and its pending decision could make a huge difference. For now, many patients needing adjuvant Gleevec have no options, and can only wait and hope that their cancer does not return.

David Josephy

These capricious and arbitrary differences in drug funding across Canada must end. The provinces must harmonize their coverage at the Best Practices/highest standard of care that can be achieved. Our patients cannot be left without access to needed drugs!

David Josephy is the President, GIST Sarcoma Life Raft Group Canada.

www.liferaftgroup.ca

© 2011 David Josephy. Used with the kind permission of the author.
Waiting for Personalized Cancer Care

BY PIERRE MAJOR, MD

The word cancer is frightful. When there is a suspicion of cancer, access to timely diagnostic tests and care is important to allay fears and offer the patient some sense of action, control and movement that is away from danger and toward solutions.

This year the CACC team set out to document what patients encounter when faced with a potential diagnosis of cancer. We could not find any reliable information on wait times from the initial referral by family physicians to specialists and definitive diagnostic procedures and treatment. We searched provincial health ministry web sites and government e-publications.

The ministry of health of Ontario has a web site with wait times for several surgical procedures but no comprehensive database is currently available on wait times for cancer diagnostic procedures. Ontario’s cancer agency has brought much greater transparency to access times for medical and radiation oncology services. This is an important first step in identifying bottle necks and improving access to diagnostic and surgical services.

All provinces need to bring greater transparency to their cancer care resources. What consistently contrasts the perceptions of physicians and patients on the front line about wait times is the lack of a sense of urgency from health care authorities. This leaves a very unsatisfactory perception that the concerns of the individual patients are lost in the far-removed discussions of administrators.

Information on wait times is important for health care managers/planners. For the individual patient this is less useful. The patient first brings symptoms of concern to their family physician who then has to arrange medical specialist referrals for definitive diagnostic tests and then to a surgeon for treatment. Primary care physicians develop patterns of referral with a limited number of specialists in their geographic areas.

Wait time information throughout a province, as is available in Ontario, does not frequently influence the referral pattern of the family physician. It is only when a surgeon declines a referral because his operating room time constraints would jeopardize timely care that the patient and primary care physician will look for alternatives. This brings uncertainty to the patient; there is also a growing body of information that shows that delays in initiating treatment not only caused patient anxiety but may adversely affect the outcome of treatment for certain cancers.

There is no information on the effect of delays in access to cancer care and outcomes. What we have is information from Europe. When the U.K. decided to investigate the cause of having the worst outcomes from cancer compared to western European countries, delays in accessing cancer care appeared to be the only variable capable of explaining this large disparity. In response, the U.K. has channeled increased resources to cancer care.
Similarly, delayed access to drug therapy in Canada is often caused by the multiple layers of review, from the initial federal review for safety and efficacy, to price reviews that establish an acceptable market price, to the inter-provincial clinical and cost-benefit review and then to the individual provinces for a funding decision. A new drug that is rapidly adopted in the U.S. does not become an insured treatment in Canada until years of this regulatory consideration are completed. And then, as with all aspects of our health system, the patient access will vary from province to province.

The international disparities in access to new medicines for cancer treatment were reported last year by the U.K.’s own Sir Michael Richards, National Cancer Director. The U.K. placed 12th on a list of 14 countries surveyed; Canada placed 13th. The uproar in the U.K. caused an immediate influx of funding for new cancer drugs and dismissal of the drug review committee responsible for rejecting these treatment options.

Canada has relatively fewer hospital beds per population than most European countries and Ontario has the fewest hospital beds for its patients than any other province. This situation is chronic; better productivity of the Canadian hospital system that could explain our lower need for acute care beds is an undocumented assumption that needs to be challenged. Navigating the hospital network is daunting for primary care physicians and detrimental to patient care.

The discourse on the need for patience while hospital administrators look for solutions is of little solace to the patient who needs care now.

The first five priority areas for improved wait times are considered to have been successful. Reporting on the results for 2010, the Canadian Institute for Health Information states that eight out of 10 patients received their priority procedures within the recommended time frames.

It is time for the next step—selecting the next priorities and negotiating the terms of a federal/provincial/territorial agreement on wait times. Our readers are invited to vote on their own priorities.

Vote on our website, www.canceradvocacy.ca
or email to waittimes@canceradvocacy.ca
with your thoughts on priorities for wait time improvement.

---

### ELECTIONS 2011

<table>
<thead>
<tr>
<th>Election</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal Election</td>
<td>May 2, 2011</td>
</tr>
<tr>
<td>Newfoundland and Labrador</td>
<td>October 11, 2011</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>October 3, 2011</td>
</tr>
<tr>
<td>Ontario</td>
<td>October 6, 2011</td>
</tr>
<tr>
<td>Manitoba</td>
<td>October 4, 2011</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>November 7, 2011</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>October 3, 2011</td>
</tr>
<tr>
<td>Yukon</td>
<td>Election possible in 2011</td>
</tr>
</tbody>
</table>
In 2010, an estimated 173,800 new cases of cancer (excluding about 75,500 non-melanoma skin cancers) occurred in Canada. While major inroads have been made in cancer treatment with earlier diagnosis and treatment intervention, 40 per cent of women and 45 per cent of men (based on 2009 incidence rates) will develop cancer during their lifetime. One out of every four Canadians is still expected to die from this disease. Only continued clinical research focused on better methods of cancer treatment and prevention will improve these statistics.

In view of this, should clinical trials be offered as part of standard treatment for Canadians diagnosed with cancer? In order to answer this question we need to address several important issues.

1. How important is clinical cancer research?
2. What is Canada’s contribution to clinical cancer research?
3. What are the barriers to conducting clinical research? and,
4. What are the proposed solutions?

How Important is Clinical Cancer Research?
There is general agreement that in the last four decades the incremental steady improvements in cancer outcomes have largely resulted from carefully planned and executed clinical trials testing new treatments. The last two decades have seen major advances in knowledge of cancer cell biology. Put simply, we now have a better understanding of what turns a “normal” cell into a “cancer” cell and what allows these cancer cells to grow wildly, avoiding all the normal body checks and balances.

In the last decade, based on this knowledge, we have seen the emergence of a new generation of “targeted” cancer therapies. Targeted therapies are generally better tolerated than traditional cytotoxics and have expanded the concept of individually tailored cancer treatment as some of these drugs may be effective in patients whose cancers have a specific molecular target, but may not be effective in the absence of such a target. Clinical trials are important vehicles for evaluating these and other novel therapies that emerge from translational research activities. Moreover, institutions with high participation rates in academic clinical trials have better patient outcomes than institutions with low participation rates.

What is Canada’s Contribution to Cancer Clinical Research?
So, where does Canada stand in terms of participation in clinical cancer research? Accurate data are difficult to determine on the number of cancer patients enrolled in clinical trials and the types of trials in which they are enrolled. A widely quoted estimate is that three per cent of adult cancer patients are enrolled in clinical trials. In 2009, the percentage of patients enrolled in therapeutic clinical trials across Canada ranged from two per cent in the Atlantic Provinces to 11 per cent in Alberta, with a national average of seven per cent (Figure 1). With so few adult patients involved in cancer trials, progress in clinical research is slow. Additionally,
individuals diagnosed with cancer may miss out on opportunities to access potentially effective new treatments. This is in stark contrast to clinical trial participation in the pediatric population. In 2009, pediatric clinical trial participation across Canada ranged from 15 per cent in Saskatchewan to 40 per cent in Ontario with a national average of 37 per cent. These high participation rates have been a key driver in improving survival in the pediatric population with five year overall survival rates for children, 0–18 years, now over 80 per cent.

Despite low participation rates, Canada has an outstanding international reputation for its contribution to cancer therapeutics development from first-in-human studies (Phase I trials) to randomized control trials aimed at changing clinical practice (Phase III). Indeed, when the mean impact factor (indicator of quality of scientific articles) of Canadian clinical cancer research publications was compared with that of other countries, Canada ranked first.

Canadian researchers have made a significant contribution to clinical research. Academic research groups in Canada have conducted and published studies that have led to worldwide changes in clinical practice and standards of care for a number of different cancers, not only with regard to survival but also palliative care, survivor support and symptom control. These academic research groups include the NCIC Clinical Trials Group (NCIC-CTG), core funding from Canadian Cancer Society with institutional members from across the country; the Ontario Clinical Oncology Group (OCOG), core funding from Cancer Care Ontario (CCO) and Hamilton Health Sciences; and the Princess Margaret Hospital Phase II Consortium, core funding from the U.S. National Cancer Institute (NCI).

Numerous advantages pertaining to the conduct of clinical trials in Canada can be cited:

- Centres of Excellence—the number of high quality clinical sites as measured by level of good clinical practice (GCP),
- excellent training,
- experienced clinical trial and site management organizations,
- well-characterized patient populations,
- early-stage initiatives to create centralized research ethics boards, and
- a cost advantage for biotech/biomedical research and development.

![Percentage Distribution of Total Patients in Clinical Trials, by Ontario Cancer Centre](image-url)

**FIGURE 2**

**PERCENTAGE DISTRIBUTION OF TOTAL PATIENTS IN CLINICAL TRIALS, BY ONTARIO CANCER CENTRE**


- **ALL REPORTING CANCER CENTRES**
- Windsor RCC
- London RCG
- Juravinski (Hamilton)
- Carlo Eliah (Pent)
- Odette Toronto Sunnybrook
- UHN/PMH, Toronto
- MDACC (Osche)
- Southeastern RCC
- MDCC (Kingston)
- HRSIR-RCP (Sudbury)
- Northwestern RCC (Thunder Bay)

Report date: February, 2010

Date source: Clinical Trials Program (Ontario Institute for Cancer Research), Cancer Program Scheduling System (PMH)

Activity level Reporting

Prepared by: Cancer Care Ontario, Cancer Informatics
Yet the clinical trial landscape in Canada is changing—for the worse. In 2009, market research conducted by the Canadian Cancer Research Alliance revealed that cancer clinical trials in Canada were under growing threat. This was particularly the case for trials based on ideas developed by the academic sector (i.e., those from cooperative groups). In 2010, CCO reported that cancer patient participation in clinical trials in Ontario from 2007 to 2009 had decreased 28 per cent, (from 5,469 patients enrolled in 2007 to 4,287 patients in 2009) citing a changing environment for supporting clinical trials (Figure 2).

The NCIC-CTG shares similar concerns, according to Dr. Ralph Meyer, Director of the NCIC-CTG. While total patient enrollment in NCIC based clinical trials has remained relatively stable over the past five years, the costs (financial and human) of conducting clinical trials have escalated and there is greater complexity in activating clinical trials.

The Canadian Institute for Health Research (CIHR) has acknowledged that Canada is rapidly falling behind other industrial countries in terms of capacity to undertake patient-oriented research. Failing new action, Canada will rapidly lose its competitive advantage in developing novel therapies and evaluating them in patients.

**What are the Barriers to Conducting Clinical Trials in Canada?**

The barriers to conducting clinical trials in Canada appear to be multi-factorial and include:

- a relative lack of agency funding,
- a declining ability of hospitals/cancer centres to support core clinical trial infrastructure,
- complex regulatory and administrative environments,
- increasingly complex studies, and
- emerging international competition

The lack of agency funding for clinician cancer research is perhaps the most serious barrier. The Canadian Institute for Health Research investment in patient oriented research represents only six per cent ($60 million) of their annual budget which is markedly lower than comparative investments made by the U.S. NIH, the U.K. National Institute of Health Research and Australia’s National Health and Medical Research Council.

In 2007, $398.5 million was spent on peer-reviewed cancer research, from 37 funding agencies in Canada. These statistics reflect a 5.4 percent increase in cancer research funding from federal government programs over a two year period (2005–2007) however, the proportion of funds dedicated to “clinical” cancer research is uncertain (Figure 4). Approximately 45 per cent of research funding was allocated to biology, 11 per cent to...
etiology, two per cent to prevention, 11 per cent to early detection and diagnosis, 23 per cent to treatment, and the remaining 10 per cent to cancer control, survivorship and outcomes (Figure 5). The per capita spending varied widely between provinces, ranging from $0.32 million in New Brunswick to $14.97 million in Ontario (Table 1 and Figure 3).

The tight funding situation for clinical research in Canada has been compounded by a declining ability of hospitals and universities to support core clinical trial infrastructure. Universities have traditionally supported salaries and protected time for research while hospitals have allowed researchers the use of clinical laboratories and diagnostic tests. However, due to fiscal restraints, institutions have moved to a cost-recovery approach. Clinical researchers must find their own funding (through grants and per case funding) to support the infrastructure necessary for conducting clinical research in their institutions.

Emerging international competition poses yet another barrier. In 2007, the pharmaceutical industry spent $1.3 billion dollars in research and development in Canada—$600 million of which was spent on clinical trials. Recently however, there has been a strong shift with industry performing more clinical trials in developing countries in Eastern Europe, Latin America and South Asia. These countries provide rapid access to large numbers of patients while conducting research that costs 30 per cent less than western nations. Consequently, Canada’s participation rate in global pharmaceutical clinical trials decreased 12 per cent in 2007. With a 4.1 per cent share of global clinical trials, Canada ranked fourth behind France (4.3 per cent), Germany (5.7 per cent) and the U.S., which led with 49 per cent.

It is not just shrinking pharmaceutical interest that concerns clinical investigators, it is also the impact on academic clinical trials developed and conducted by cooperative groups and investigators. From coast to coast, individual Canadian researchers and clinicians have also raised concerns that our nation’s clinical trial capacity is eroding in the face of a variety of pressures and barriers. As noted by David Dilts, in a recent editorial on clinical cancer research in the U.S., the current trends are disturbing. While studies by pharmaceutical companies are important, it is essential that academic and cooperative groups continue to flourish.

### TABLE 1
2007 TOTAL CANCER RESEARCH INVESTMENT—BY PROVINCE OF PRINCIPAL INVESTIGATOR/PROJECT LEADER (PI/PL), IN DOLLARS PER CAPITAL INVESTMENT

<table>
<thead>
<tr>
<th>Province</th>
<th>Research Investments of PI/PL ($)</th>
<th>Per Capita ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada, total</td>
<td>398.5 M</td>
<td>12.10</td>
</tr>
<tr>
<td>Ontario</td>
<td>191.6 M</td>
<td>14.97</td>
</tr>
<tr>
<td>Quebec</td>
<td>97.5 M</td>
<td>12.68</td>
</tr>
<tr>
<td>British Columbia</td>
<td>48.2 M</td>
<td>11.18</td>
</tr>
<tr>
<td>Alberta</td>
<td>40.1 M</td>
<td>11.41</td>
</tr>
<tr>
<td>Manitoba</td>
<td>9.1 M</td>
<td>7.65</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>5.8 M</td>
<td>6.25</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>4.6 M</td>
<td>4.56</td>
</tr>
<tr>
<td>Newfoundland and Labrador</td>
<td>1.3 M</td>
<td>2.63</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>0.2 M</td>
<td>1.24</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>0.2 M</td>
<td>0.32</td>
</tr>
</tbody>
</table>

### FIGURE 4
CANCER RESEARCH INVESTMENT BY FUNDER SECTOR IN DOLLARS AND PER CENT CHANGE FROM 2005 TO 2007

![Graph showing cancer research investment by funder sector in millions of dollars from 2005 to 2007.](chart.png)
“Any improvements in cancer care come from clinical trials.”
—Ezekiel J. Emanuel, MD, PhD, Chair, Department of Clinical Bioethics, U.S. National Institutes of Health

Losing the competitive edge has far-reaching implications in our ability to lead the work of translating new discoveries into clinical applications. Clinical trials developed and conducted by Canadian academic investigators could answer the clinical and translational questions that are based on the most promising discoveries from Canadian laboratory researchers. Such trials could address the greatest concerns for the health and well-being of Canadians, in a manner most relevant to the Canadian healthcare system. Thus, the threat to cancer trials, at a time of great opportunity for the translation of research discoveries to clinical testing, is a critical national issue.

The increasing complexity of clinical trials has also had a significant impact on clinical cancer research centres across the county. The NCIC-CTG has seen a two-to-three fold increase in staffing demands necessitated in part by the increase in ethics and regulatory compliance required for conducting clinical studies. The timeline for conducting a trial – the time from activation of the trial to the first patient enrolled in the trial – has also increased significantly.

So what can we do to ensure the future “health” of clinical cancer research in Canada?

What are the Proposed Solutions?
A number of initiatives aimed at promoting the “health” of our research community and preventing further erosion of resources have recently been launched in Canada.

In February 2010, the Canadian Institute of Health Research (CIHR) proposed a 10-year plan to change health care including a strategy for patient-oriented research (SPOR) in Canada. It was proposed that Canada increase its investments and better coordinate its efforts in patient-oriented research to improve the quality, accessibility and cost-effectiveness of health care. The success of such a plan would require support not only from the federal, provincial and territorial governments but also from major stakeholders including research institutions (universities, hospitals, community centres), and clinician scientists as well as private.
and charitable sectors. This strategy would consist of four major components:

1. Improvements to the research environment and infrastructure,
2. Up of mechanisms to better train and mentor health professionals and non-clinicians,
3. Strengthening organizational, regulatory and financial support for multi-site studies, and

Members of the Association of Canadian Academic Health-care Organizations (ACAHO) strongly supported the patient-oriented clinical research initiative. To advance the initiative, the Association proposed that the federal government incrementally invest $10 million that would allow for the implementation of a series of pilot projects that if successful, would move to a broader series of projects across the country. But would this be enough? Comparatively, the National Cancer Research Network funding for cancer research alone in the U.K. is close to four times this amount per year. The U.K. investment in clinical research infrastructure for all diseases (NIH) is hundreds of millions per year. An investment of 10 million dollars in Canada for all diseases is unlikely to have any real impact.

In May 2010, with support from the Canadian Partnership Against Cancer, the Canadian Cancer Research Alliance launched the Pan-Canadian Cancer Research Strategy (PCCRS). This strategy provides a vision for Canadian cancer research achievements over the next five years. Priorities for enhanced funding and collaboration include cancer prevention, basic discovery research (i.e., genomics, cancer initiating cells, new agent discovery, biomarkers), clinical trials, health services/economics and tumour-specific partnered initiatives (e.g., collaboration with Canadian Breast Cancer Research Alliance).

These priorities have resulted in the identification of 24 key action items to be implemented between 2010 and 2012. The plan for clinical trials is to clearly outline the issues facing trials in Canada and make recommendations on how these issues can be resolved. The report will examine jurisdictions with healthy and growing cancer trial enterprises, consider how to engage the pharmaceutical industry and identify ways to maximize patient-oriented clinical research. In addition, the Pan-Canadian Cancer Research Strategy will aim to create an optimal cancer research system - one in which there is a balance of research funding across the three main categories: project grants, infrastructure and research personnel.

Regional initiatives have also been launched to enhance patient enrollment in cancer clinical trials in Canada. In 2004, the Ontario Institute of Cancer Research (OICR) set a goal to double Ontario patient recruitment into cancer clinical trials, within three years, in 28 participating cancer centres throughout the province. With a three year budget of $12.9 million clinical trials recruitment increased from 8.9 per cent in 2004 to 12.4 per cent in 2007 (Figure 2). The success of this program however was based on a business model predicated on self-sustaining fiscal resources from enhanced patient recruitment to pharmaceutical trials. Increasing regulatory requirements and lack of ongoing infrastructure support resulted in a drop in clinical trial enrollment to 8.5 per cent in 2009, a lower figure than before the program went into effect.

In contrast, the National Cancer Research Network (NCRN) was established in the U.K. by the Department of Health in 2001 to provide the National Health Service with the infrastructure to support prospective trials of cancer treatments and support research undertaken by cancer charities. The initial goal was to double the trial enrollment of cancer patients by 2004. With an annual investment of 120 million per year, overall accrual to clinical trials rose from a baseline of less than four per cent of new cases to 14 per cent by 2006. By 2010, recruitment of cancer patients to Cancer Network studies had quadrupled since 2001—from one in 26 patients to around one in six. Unlike the OICR infrastructure program, the Department of Health funding continued beyond the initial three year commitment.

In 2001, stakeholder consultations with researchers, study sponsors, clinical trials sites and regional ethics boards identified inefficiencies in the research ethics review process as a major barrier to the establishment of multi-centre cancer clinical trials in Ontario. In 2003, the Ontario Cancer Research Network responded by establishing the Ontario Cancer Research Ethics Board (OCREB). The board now has 22 member-centres, representing the majority of the province’s hospitals that conduct cancer trials in Ontario. This overarching ethics board markedly reduces the duplication and workload for researchers, sponsors and local ethic boards throughout Ontario. Similar specialized multi-institutional research ethics boards operate in Alberta and British Columbia.

**Recommendations**

If we believe, as a society, that finding a cure for cancer is important then federal and provincial governments, health care organizations, hospitals, universities and foundations must acknowledge and support clinical cancer research. The success of programs such as the Pan Canadian Cancer Research Strategy, and the CIHR Strategy for Patient-Oriented Research, along with other clinical cancer research initiatives will be essential to achieve these goals.

"If Canada is not successful in rewarding innovation, innovation will be developed elsewhere."—Russell Williams, President of Rx&D Canada
initiatives, will depend on the following commitments.

1. A long term financial commitment by government(s) and healthcare organizations to provide stable funding and a system of support for clinical cancer researchers. Funding support could be modeled after the U.K.’s National Cancer Research Network program that has successfully supported clinical cancer researchers and consistently increased patient participation in clinical trials throughout the U.K. over the past ten years.

2. Adequate infrastructure support within cancer based healthcare organizations that facilitate patient participation in clinical trials. This would require sustainable resources for patient recruitment, clinical research associates, data managers and oncology nurses.

3. Measurable indicators that include real time assessment and implementation of what is working well and elimination of what is not.

4. Improved efficiencies in the activation and conduct of clinical trials in order to remain competitive in international markets, to ensure that Canadians have continued access to novel cancer drugs and treatments. This would require the development of a seamless national approach to contract negotiations, research ethics approval, regulatory monitoring and budget negotiations.

All of this could be made possible if each Canadian affected by cancer were offered a clinical trial as a “standard” treatment option. We, the general public, can do our part by accepting the importance of cancer clinical research and endorsing this change in medical practice. No longer would individuals who participate in clinical trials have to feel like “guinea pigs”. Rather, by understanding that participation in clinical cancer trials assures consistent standards and reliable quality of care, concerns about participating in research would evaporate. Participation in a study may lead not only to better outcomes for the patient but may also make a significant contribution to the discovery of new and better cancer treatments. Importantly, cancer control would be immeasurably accelerated.

Susan F. Dent, BSc, MD, FRCPC, is a Medical Oncologist at The Ottawa Hospital Cancer Centre; Associate Professor of Medicine, University of Ottawa. She is a member of the NCIC-CTG Breast Disease Site Group, Cancer Care Ontario Breast Disease Site Guideline Committee and the Ontario Cancer Research Ethics Board.

Sandi Yurichuk, BSc, MBA, PhD candidate, is on the Board of Directors of the CACC. Sandi has her own consulting company based in California and specializes in oncology drug development. She is currently enrolled in a PhD program at the International School of Management in Paris, France.

© 2011 Susan Dent and Sandi Yurichuk. Used with the kind permission of the authors.

References

The Role of the Nurse Practitioner and Clinical Pharmacist

IN COLLABORATIVE PATIENT CARE AND DRUG THERAPY MANAGEMENT IN CANADIAN CANCER CENTRES

by JONATHAN EDWARDS, BSc, SCOTT EDWARDS, PharmD, and DAVID SALTMAN, MD, PhD

Introduction

It is anticipated that because of our aging population the incidence and prevalence of cancer in Canada will continue to increase. The rise in the volume of patients will need to be met with an expansion of oncology services. This should include an increase in the number of healthcare professionals involved in the initial patient assessment, the safe delivery of chemotherapy and supportive care medications, surveillance and palliative care. The current and anticipated shortage in qualified medical oncologists in Canada is being mitigated in many cancer centres by utilizing clinical practice associates or general practice oncologists. Expanding the role of non-physician healthcare professionals, such as nurse practitioners (NPs) and pharmacists, may be another solution to concerns regarding the oncology workforce.

Pharmacists are ideally suited to work in a systemic therapy collaborative practice because of their knowledge of pharmacology, drug toxicities, drug interactions, order entry systems and funding mechanisms in those jurisdictions that do not have a fully funded public drug coverage system. Nurse practitioners also work effectively within cancer care programs as part of a multidisciplinary team. In addition to their ability to prescribe supportive care medications and chemotherapy, they can offer psychosocial care, perform certain procedures and participate in patient education. Nurse practitioners also have formal training in patient assessment and physical examination.

Over the last decade a growing number of nurse practitioners and clinical pharmacists are providing direct patient care as part of a collaborative agreement with oncologists, particularly in the United States. Collaborative agreements may be informal or, more appropriately, a written agreement describing a cooperative practice relationship between a NP or pharmacist and a physician, with legal authority to prescribe medications. In North Carolina, pharmacists can prescribe medications under a collaborative agreement with a supervising physician. The State Board of Pharmacy and Medical Board must first approve this collaborative agreement. Once this process has been completed, the pharmacist is licensed as a clinical pharmacist practitioner (CPP). The scope of practice varies between institutions but may include the ability to assess patients, order supportive care medications (antiemetics, growth factors, anticoagulants, bisphosphonates, blood products, antibiotics, smoking cessation products), order intravenous chemotherapy, depot hormone therapies and order laboratory and imaging investigations.

Similar collaborative agreements exist in cancer centres in California and other states, where CPPs may also prescribe take home oral cancer drugs such as capecitabine and tyrosine kinase inhibitors. Pharmacists and nurse practitioners can also prescribe narcotics but require a special license from the United States Drug Enforcement Agency (DEA). Surveys of state pharmacy organizations and state pharmacy boards in the United States have demonstrated that collaborative practices in the oncology and non-oncology settings have a positive effect on pharmacist-physician relationships.

Although some Canadian provinces now have legislation that allows pharmacists to have limited prescribing privileges in the retail setting, many jurisdictions still don’t have laws which allow hospital or cancer centre pharmacists to prescribe. Nurse practitioners are legislated in several provinces to prescribe. They also directly assess patients and perform a number of other functions historically done by physicians, depending on the scope of their practices as defined by their healthcare authority.

We surveyed comprehensive cancer centres from each province to determine the current status of the nurse practitioner and pharmacist in the setting of a collaborative practice and to see whether they were prescribing supportive care medications and chemotherapy.

Methods

Pharmacists and nurse practitioners working in comprehensive cancer centres in 10 Canadian provinces were surveyed either by telephone or by e-mail. A structured questionnaire was used to determine their scope of practice, involvement in direct patient care and prescribing. A senior pharmacy student or pharmacist conducted the survey. The survey was started on November 1, 2010 and completed on January 18, 2011.

Results

There was one response from each of the 10 provinces (Table 1). In four provinces (AB, ON, NS and NB), both NPs and pharmacists have prescribing privileges in their institutions.
as part of a collaborative agreement. However, the pharmacist does not prescribe in any of the centres surveyed. There are six centres with NPs who prescribe one or more types of oncology medications (Table 2). Two centres (NS and AB) indicated that NPs were involved in prescribing intravenous chemotherapy, oral chemotherapy, hormone therapies and supportive care medications. Three centres (NS, ON and AB) follow patients in their clinics who are no longer on active treatment.

In Manitoba, NPs supervise chemotherapy but do not prescribe the drugs. They do prescribe supportive care medications except narcotics. In the cancer centres in NS and NB that were surveyed, NPs use preprinted orders for chemotherapy, while centres surveyed in Ontario and Alberta used electronic ordering systems. In three of the centres where NPs are prescribing chemotherapy, they treat patients in both the adjuvant and metastatic settings. Centres indicated in the survey that NPs prescribe chemotherapy after the oncologist initiates cycle 1 (Table 2). In those centres where chemotherapy patients were under the supervision of NPs, they are referred back to their oncologists when there are serious adverse events, significant dose adjustments required, after assessment of disease status and at the end of a prescribed number of chemotherapy cycles.

Newfoundland and Labrador does not have legislation that allows institution-based pharmacists to enter into a collaborative agreement with a physician or prescribe. Pharmacists in NL do supervise the administration of oral chemotherapy (capecitabine and temozolomide) for patients receiving combined modality concomitant chemotherapy and radiation but they must have a physician order investigations and sign chemotherapy orders. There is one NP working within a cancer centre in the department of radiation oncology who has authority to prescribe hormone therapies and supportive care medications. There were only two centres where NPs prescribe take home cancer drugs. Cancer centres in Saskatchewan and Quebec that were surveyed indicated they do not have any oncology nurse practitioners. Pharmacists do not have the authority to prescribe in those centres.

The cancer centres with NPs supervising and prescribing drug therapy indicated an improvement in job satisfaction and thought there was a decrease in wait-times for patients to start chemotherapy.

Discussion

Our survey results suggest that the role of both nurse practitioners and pharmacists in Canadian cancer centres is expanding to include more direct patient assessment and drug therapy management. Although several provincial nursing, pharmacy and medical boards allow NPs and pharmacists to enter into collaborative agreements with physicians, only NPs are prescribing cancer therapies at the time this survey was conducted.

The reasons why there aren’t more NPs with prescribing authority in collaborative practice working in Canadian cancer centres is not clear. A 2008 survey of British specialist nurses working in cancer and palliative care looked at the benefits and barriers to uptake of nurse prescribing training.8 The main reason for obtaining prescribing privileges was the prospect of improving care. The main reasons why nurse specialists did not pursue prescribing training were: resource issues, lack of medical support and mentorship, and concerns about the relevance of prescribing as a nursing role.

There are a number of factors that may be limiting pharmacists from expanding their roles in oncology. The separation of prescribing and dispensing is thought to be an important safety or quality control issue. However, within a cancer centre or program, it is likely that a limited number of clinical pharmacists will enter into a collaborative agreement to prescribe, thereby separating the functions and maintaining quality assurance. Healthcare administrators and governments may not support the transition of pharmacists from their traditional roles to those where they would have the

**TABLE 1**
**SURVEYED CANCER CENTRES AND THE CHEMOTHERAPY PRESCRIBING STATUS FOR NURSE PRACTITIONERS (NPs) AND PHARMACISTS**

<table>
<thead>
<tr>
<th>Province</th>
<th>Number of cancer centres surveyed</th>
<th>NPs in collaborative practice</th>
<th>NPs prescribing</th>
<th>Pharmacists in collaborative practice</th>
<th>Pharmacists prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>1</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NS</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NB</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>QC</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ON</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MB</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SK</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>AB</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BC</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Radiation oncology nurse practitioner

**TABLE 2**
**SCOPE OF PRACTICE FOR NPs PRESCRIBING ONCOLOGY MEDICATIONS**

<table>
<thead>
<tr>
<th>Province</th>
<th>Order entry system</th>
<th>Intravenous chemotherapy*</th>
<th>Oral chemotherapy</th>
<th>Hormone therapy</th>
<th>Supportive care drugs**</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>Computer</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NS</td>
<td>Preprinted orders</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td>NB</td>
<td>Preprinted orders</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ON</td>
<td>Computer</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MB</td>
<td>Computer</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>AB</td>
<td>Computer</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Ordered by NP after cycle 1.
** Except narcotics
authority to directly assess cancer patients and prescribe medications. We did not interview oncologists as part of this study to determine their attitudes towards NPs and pharmacists expanding their roles in direct patient care and prescribing. However, the support is likely high because the increased participation of the NPs and pharmacists should in theory free up more time for oncologists to see new patients, formulate treatment plans, participate in research and fulfill their administrative commitments. Many cancer centre pharmacies are short staffed making it difficult for pharmacists to expand their clinical roles. This issue will need to be addressed for pharmacists to increase the scope of their practices.

Unlike nurse practitioners, many pharmacists may lack the clinical assessment and diagnostic skills needed to participate more fully in collaborative practices. These skills could be easily acquired through formal education programs or through supplemental training within cancer centres.

Concerns have also been raised about the attitudes of patients regarding the expanded role for pharmacists in areas like clinical assessment. Our experience with pharmacist-led oral chemotherapy clinics suggests that the patient satisfaction is high. Clients and their families are always instructed that pharmacists are part of a multidisciplinary team, which allows us to better monitor safety and reduce clinic waiting times. Internal audits of our pharmacy-/general practice oncology-led rectal cancer neoadjuvant capecitabine clinics have demonstrated a reduction in serious adverse events.

**Limitations**

This survey was conducted at a limited number of comprehensive cancer centres throughout the country. For the smaller provinces, data from a single centre may be reflective of current practices in the entire province. However, for larger provinces like Ontario with multiple cancer centres and clinics, there may be differences in practice for both NPs and pharmacists that are not reflected in this study. We did not conduct the survey in any of the Territories.

**Conclusions**

The disciplines of nursing and pharmacy are evolving rapidly, thus allowing practitioners to diversify and deliver direct patient care as part of a collaborative practice. Our survey suggests that only nurse practitioners are prescribing chemotherapy in Canadian cancer centres and that more needs to be done to encourage and assist qualified pharmacists who wish to obtain the right to prescribe within their scope of practice. For pharmacists, the decision to enter into a collaborative practice with the authority to prescribe should be based on competency and not necessarily on educational attainment. Pharmacist may be required to complete a multi-step process to demonstrate they have the required competencies, similar to the process used by the Alberta College of Pharmacists. Outcomes from the expanding role of NPs and pharmacists in oncology should be measured to assess their impact. Oncology healthcare professionals, health authority administrators and provincial and territorial medical and pharmacy boards should work together to rapidly facilitate the development of collaborative practice guidelines and regulations.

**Recommendations**

- Implement changes to the Pharmacy Act for those provinces that currently do not incorporate practice standards for pharmacist prescribing in their regulatory guidelines.
- Develop formal collaborative practice agreements. Collaboration with other health providers is an important and integral component to pharmacist prescribing. The pharmacist should develop a collaborative practice model, which includes ongoing two-way communication and documentation regarding drug therapy decisions with other health care professionals.
- Develop educational and competency requirements. The pharmacist should participate in continuing education programs, annually complete a professional development log for review, use a self-assessment tool to identify strengths and opportunities for further development, and participate in assessments of practice.
- Develop a process for notification of other health care professionals. Actions related to prescribing and medication management need to be communicated verbally, in writing or through electronic media, when appropriate, to other health professionals. All actions should be supported by documentation.
- Include the ability to order laboratory tests into the pharmacist’s collaborative agreement. Pharmacists should have the authority to order laboratory tests for the purpose of monitoring drug therapy outcomes.
- Provide for quality assurance. The pharmacist in a collaborative practice should develop, maintain and coordinate a comprehensive quality assurance program to assure the quality of their prescribing.

**References**

Bone Marrow Transplantation

IMPROVING OUTCOMES FOR CANADIAN PATIENTS

By RONAN FOLEY, MD, FRCPC

Clinical Background

Allogeneic bone marrow transplantation (BMT) offers the hope of cure to patients with otherwise fatal blood and hematological malignancies. In its simplest form the process involves replacement of a diseased bone marrow with marrow from an otherwise healthy donor. Although complex, it is now known that a balanced engraftment of both donor hematopoietic blood forming stem or progenitor cells as well as donor immune white blood cell effectors (T-lymphocytes) is required for sustained hematopoiesis and long term eradication of disease. Thus, it is not just the transplant conditioning that destroys host cancer cells but the downstream immunological consequences of a persistent attack from a donor immune system (also known as graft-versus-tumour effect).

Immune function of donor T-lymphocytes contributes to both therapeutic efficacy as well as unwanted post transplant side effects, including at times severe graft versus host disease (GVHD). Shifting the balance of therapeutic efficacy from stem cell replacement to maintenance of a transplanted immune system has led to less intense preparative regimens that focus on stable chimeric donor white blood cell immune survival. These less intense, reduced intensity conditioning (RIC) or “mini” allogeneic transplants are now routinely recommended for older patients with underlying incurable myeloid and lymphoid malignancies. BMT as an option for older patients has increased transplant activity in transplant centres across the country. In addition to RIC, other breakthroughs (i.e., use of cord blood in adult patients) in the field of stem cell transplant are transforming this procedure from a few, to many. During this growth phase we need to confirm that proper infrastructure, regulation and supports are in place to ensure success in this “high stakes” life saving procedure.

Allogeneic Transplants are Saving Lives

Once associated with a mortality of more than 60 per cent, the outcome of allogeneic BMT has dramatically improved through a blend of incremental breakthroughs. These include antimicrobials with greater specificity for bacterial and fungal infections that result from prolonged neutropenia. Preventive treatment strategies to mitigate severe systemic viral infections, rational use of growth factors and advances in general supportive care have also contributed to improved survival.

The process of safely performing allogeneic BMT is complex and requires the experience of a comprehensive multidisciplinary team comprised of oncologists/hematologists, nurse practitioners, primary care nursing staff, pharmacy, social work, dietitians as well as consultation from a wide range of sub-specialities: gastroenterology, dermatology, infectious disease and respirology. Laboratory expertise in stem cell manipulation, enumeration and cryopreservation, utilization of blood products as well as DNA specific HLA-typing are also highly essential components of a successful transplant unit. Despite diverse backgrounds and an extensive list of steps, each specialty must properly perform and coordinate specific roles and responsibilities in an effort to ensure the optimal outcome for any individual patient. As mentioned, the hospital laboratory plays a unique and central role in the management of BMT patients which starts with ensuring that the stem cell product, either blood or marrow derived has been properly managed, modified (if requested), labelled, preserved and characterized. Given that a clinical outcome depends on the predicted performance of a specific product there is little room for error.
Stakes are High: Need for Regulation and Standardization

Bone marrow transplants are performed in 23 centres across Canada and there is a need to standardize transplant policies and procedures. Therapeutic cell products are regulated biologically and evaluation and accreditation of each transplant centre is obtained through inspections from Health Canada (mandatory) and in a growing number of centres by the Foundation of Cellular Therapy (FACT). Both organizations require a comprehensive set of validated Standard Operating Procedures (SOPs) and specific policies that ensure absolute patient/product safety. Evidence of well-developed, highly detailed and validated SOPs ensure that a program functions in an integrated manner under thorough scrutiny. Given many single points of failure, it is this absolute level of detail with a “no stone left unturned” mentality that results in consistent patient outcomes. Seeking and obtaining FACT approval remains important to Canadian transplant centres but does require appropriate support (infrastructure and staff) to establish and properly maintain. These ongoing funding requirements remain a significant current challenge in Canada; however given the direct link to patient safety there is a need to ensure that ongoing developments in transplant accreditation are maintained without compromise.

Despite important advances in the safety and outcome of allogeneic BMT patients there remains room for improvement in prevention and treatment of severe acute and chronic GVHD as well as relapse of the original disease. While research continues into the biological mechanisms of relapse, efforts to identify the best possible marrow donors in Canada also have the potential to dramatically improve transplant outcomes. In this regard increasing the collective pool of Canadian donors will also increase the likelihood of finding the “best match” thus yielding the best clinical results.

Bone Marrow Donors

Efforts to improve outcomes of patients undergoing BMT are constantly being refined and improved. Perhaps not surprisingly it is now known that the outcome of BMT largely relates to the individual that is providing the bone marrow graft. Obtaining stem cells from a donor can occur in one of three transplant situations.

Stem cells may be collected from a patient to be administered back into that patient. This is referred to as an autologous stem cell transplant and is used to treat patients up to the age of around 70 with multiple myeloma, relapsed non-Hodgkin’s lymphoma and Hodgkin’s lymphoma. Relapse of primary disease remains a predominant issue in this type of transplant.

Stem cells can now be obtained from peripheral blood as well as from the posterior pelvis of a donor under general anesthesia, stem cells contain a greater number of CD34+ progenitor stem cells. Interestingly, a mobilized peripheral blood product usually contains a greater number of CD34+ T lymphocytes and potentially a greater risk of chronic GVHD.

An allogeneic transplant involves the use of a stem cell graft (containing CD34+ progenitor cells) that is provided by a healthy donor to a patient. In this setting a brother or sister, or twin may be called upon to donate blood/marrow stem cells. This is known as a matched-related alloBMT. Family members will be asked to undergo typing to determine if a sibling is a match (25 per cent chance). In Canada a sibling donor may have an option of providing bone marrow (approximately 1 litre – adult) collected from the pelvis while under anesthesia or mobilized peripheral blood progenitors (collected by leukopheresis – CBMTG Canadian phase III study). If a patient does not have a suitable available sibling an unrelated donor search will be initiated.

When an HLA matched unrelated donor is sought many additional issues emerge. These otherwise healthy donors are engaging in an altruistic act with the potential to save a life. At the same time it is important to ensure that the products collected from these donors remain confidential and have the best chance of optimal clinical performance. Whereas the availability of matched related sibling donor transplants may diminish over time due to smaller families, unrelated donors are clearly a future focus for growth and development. With the importance of maintaining a strong young healthy pool of Canadian donors this article will focus on issues that will influence the state of allogeneic BMT in Canada. One relates to science and technology and the other to public or social awareness in our younger generations.

Sources of Marrow Stem Cells

Sources of stem cells have expanded over the past decade. While stem cells were traditionally obtained from the posterior pelvis of a donor under general anesthesia, stem cells can now be obtained from peripheral blood as well as from umbilical cord blood. Each source of stem cells, blood vs. marrow vs. cord, exhibits different biological properties. If one compares a bone marrow graft (approximately 1,000ml) to mobilized blood stem cells collected by leukopheresis distinct differences can be seen in graft composition. Interestingly, a mobilized peripheral blood product usually contains a greater number of CD34+ progenitor stem cells but also a greater number of CD3+ T lymphocytes and potentially a greater risk of chronic GVHD.

The Canadian Bone Marrow Transplant Group (CBMTG) is nearing completion of a large phase III study which will address the issue of optimal graft source by comparing filgrastim-mobilized blood to filgrastim-mobilized marrow in matched related alloBMT. This Canadian-led study will indi-
cate the optimal source of stem cells based on a composite endpoint of relapse/mortality and GVHD, and will also evaluate what is the preferred approach based on the donor's overall experience. Understanding these properties, including the recent use of cord blood derived stem cell products for children and more recently for adults, enables the ability to tailor which graft source should perform best for a given individual clinical situation.

As previously mentioned, a donor may be asked to donate stem cells for a sibling (brother or sister) or other family member (matched related donor) or to join a large national registry (matched unrelated donor). A national marrow donor program will HLA-type potential donors and maintain information in a registry that can be searched for a range of transplant eligible patients in need of a suitable marrow donor. All donors should be in good general health and undergo rigorous donor screening. As the transplant eligible age increases so does the potential donor pool of related siblings. Co-morbidities such as COPD, diabetes, heart disease need to be taken into consideration.

Any potential donor should be in satisfactory health so as to tolerate either anaesthesia-marrow harvest or administration of filgrastim and large volume apheresis. In addition to general health bone marrow donors must be screened for active malignancies (excluding “benign” basal cell skin cancer), transmissible viral disease (HIV, hepatitis B/C, HTLV-I, West Nile virus, syphilis), haematological diseases (sickle cell) as well as bleeding disorders. A combination of comprehensive questionnaires, complete history and physical examination ensure a donor is suitable.

Once screened and considered eligible the most relevant donor factor that predicts success across several clinical endpoints is age. Bone marrow recipients from younger donors (i.e., less than 30 years of age) demonstrate improved five-year overall and disease-free survival. A modest decrease in severe GVHD has been noted with younger donors. Other donor factors that predict success across several clinical endpoints is age.

Finding the Best Match
As in other transplant situations, matches are based on the human leukocyte antigen (HLA) system. HLA is comprised of a series of genes on chromosome that encode cell-surface antigen presenting proteins intrinsically linked to our immune system. The major histocompatibility complex (MHC) is made up of two basic classes involved in antigen presentation and subsequent immune activation. MHC class I is typically involved in presentation of small peptides that result from intracellular digestion. MHC class II presents those extra-cellular antigens to host T lymphocytes. MHC class I includes HLA-A, HLA-B and HLA-C, whereas MHC class II includes HLA-DR, HLA-DQ, and HLA-DP. Proteins encoded by HLA define our unique self and directly instruct the immune system to recognize self versus non-self. In any individual one set (haplotype) of HLA genes comes directly from the mother and the other set from the father, leaving only a 25 per cent chance that any given sibling will match a brother or sister.

Previously, HLA typing was performed using serological testing to identify HLA serotypes. This provides a low-resolution map of an individual's HLA type. Although useful in the related setting, there have been concerns regarding its use in unrelated donors where higher resolution of HLA genetic mapping will lead to a better match. If HLA typing lacked sufficient accuracy this would undoubtedly influence the rate of GVHD. HLA laboratories now perform high resolution molecular or DNA typing to ensure a potential unrelated donor/recipient pair are as highly matched (HLA A,B,C, DR) as possible. Studies suggest that employing a molecular approach can reduce the incidence of severe GVHD and improve survival by as much as 50 per cent.

Careful donor selection and molecular typing have improved the overall quality of unrelated transplants to the point where they are considered nearly as safe as when a related donor is used. However there are downsides, the first being that employing a highly specific molecular analysis will effectively reduce the number of available donors. Moreover the process may increase the time required to identify a potential donor worldwide. On average three to six months may be required and given the nature and stability of primary diseases requiring transplant (i.e., relapsed myeloid leukemia) this may not be feasible. Various algorithms now exist that combine a serological search with latter confirmatory molecular analysis. These steps may improve the time and expense of finding a suitable marrow donor.

Issues such as the number of simultaneous potential donors to be typed by high-resolution include whether a recipient has a rare allele or haplotype as well as the clinical urgency for allogeneic BMT are important. It should also be noted that a single allele mismatch (9/10) when typing for HLA-A, -B, -C, DRB1 and DQB1 (i.e., 10/10) may be considered by some centres. In this regard a single mismatch at B or C may be less of a concern than mismatches at A or DR. Potential Canadian donors are currently represented by OneMatch Stem Cell and Marrow Network. This group is actively developing algorithms to effectively and efficiently screen for possible Canadian donors in the least time possible using the results of a blend of intermediate and high resolution typing techniques.

Despite these challenges the OneMatch national registry has seen a marked improvement in the number of available donors and utilization of Canadian stem cell products (Figures 1 and 2) and continues to provide highly matched bone marrow donors to Canadian patients in need of a transplant.

Donor Registry—The Challenges
Signing up to be a marrow donor is a voluntary act. The strength of any national registry, including our own Canadian registry is the number of potential donors available as well as the time and cost to search the registry in a step-wise efficient manner. In terms of creating a robust national registry Canada faces two challenges.

First, our overall population is relatively small and spread out. Our second major challenge relates to Canada as a highly diverse ethnic population.

As can be seen in Figure 3, the ethnic composition of the current OneMatch database demonstrates a non-representa-
tive proportion of non-Caucasian donors. Thus, there is an urgent need to connect to younger demographic groups. Despite significant advances in acquisition of transplantable stem cells many potential donors have concerns about pain and suffering that may be associated with the process. On the other hand our current “young generation” appears to have a raised level of social consciousness and are becoming increasingly involved. Thus, it becomes critical to provide an accurate message about the feasibility of becoming a bone marrow registrant. Specific issues require thoughtful discussion and an understanding that a collective willingness to become involved will have a direct beneficial clinical impact.

As previously mentioned optimal clinical outcomes are seen when young and healthy donors are engaged. This requires a targeted approach and may include special events within a community or the use of social networking strategies. A complete and accurate PCR-based molecular typing approach can now be undertaken using minute amounts of DNA. This can accurately be completed by a simple swab from inside the mouth with a Q-tip. Use of these buccal swabs has been well received in local marrow donor drives and events.

Summary
Bone marrow transplantation is an exciting and growing field of medicine. BMT remains the only chance of cure for many adults and children with otherwise fatal blood and marrow malignancies. No one should die waiting to find a bone marrow donor.

A blend of incremental improvements has led to significant improvements in the field with more patients living disease-free. Several challenges including an effective therapy for GVHD and reduction in rates of post transplant relapse still need solutions.

The availability or potential for allogeneic BMT is now being extended to additional disease states. Moreover current strategies to reduce treatment related toxicity through reduced-intensity BMT will enable a greater number of patients to safely undergo this procedure. Given that the likelihood of finding a sibling donor will always be only 25 per cent and that family sizes will likely diminish over time, the need to turn to a national registry will increase. Finding a match will depend on how many potential donors sign up. In Canada this number is increasing but we still need to target our younger populations.

We also need to ensure that any potential donor is the best possible donor and employ

---

36 REPORT CARD ON CANCER IN CANADA, 2010–11
high resolution HLA-typing to our matching strategy. Ultimately our goal is to ensure that all transplant eligible patients find a donor (either Canadian or from another registry) in a timely manner and enable all patients the chance of being cured.

Positive clinical outcomes will continue to improve with the implementation of comprehensive accreditation organizations and suitable funding required to maintain the current excellence of BMT transplant units across our country.

Ronan Foley, MD, FRCP, is a clinical hematologist with an active practice in malignant hematology at the Juravinski Cancer Centre in Hamilton, ON. He is Director of the Stem Cell Laboratory and Cell Diagnostic Units. Dr. Foley is an Associate Professor of Pathology and Molecular Medicine at McMaster University, President of CBMTG, a Director of the Clinical Trials Network and a member of the NIH Consensus Panel for the Diagnosis and Classification of Chronic Graft vs. Host Disease along with several other affiliations. Other activities include board membership on OCRB and panel chair for the CIHR CBT panel. Dr. Foley’s current research focus is the development of therapeutic cell-based autologous vaccines. He currently has active grants with CANVAC, OICR, and NCIC.

© 2011 Ronan Foley. Used with the kind permission of the author.

References
Cancer treatment has changed dramatically over the last few years. It is now not only possible, but also often important to go beyond classifying tumours based on where they occur in the body. In fact, two patients with cancer of the same organ of origin may well have two very different cancers that can require different treatment strategies. Decades of painstaking research have demonstrated that each tumour has a unique set of genetic aberrations and molecular changes. Some of these genetic and molecular characteristics have been termed biomarkers since they can mark how well a tumour will respond to certain treatments or how quickly the disease will progress.

The goal of biomarker research in oncology is to personalize cancer treatment based on individual tumour characteristics. In the ideal scenario, each tumour is tested to identify its unique biomarker profile and that information helps to inform decisions about prognosis and treatment. In some circumstances, treatments may be selected more effectively based on the biomarker profile of a patient’s tumour. Drugs that are not likely to work or are not necessary can be avoided, thus saving the significant costs, both financial and personal, of needless therapy.

This is the future of cancer care, but we are not there yet. What is missing? To answer this question, it is instructive to review the progress that has been made. The journey from the general (all breast cancers are the same) to the specific (breast cancers are of several types) to the near-personalized (your breast tumour has biomarkers that indicate it will respond well to a particular treatment strategy) began in the 1970s with the discovery of the first biomarker: the estrogen receptor (ER).

The Biomarker Revolution
In 1971, Elwood V. Jensen at the University of Chicago showed that breast tumours rich in ERs were more likely than ER-poor tumours to respond to treatment that would reduce the amount of circulating estrogen in the body.1 When the anti-estrogen compound tamoxifen2,3 was discovered as part of a fertility control program, its potential for the treatment of breast cancer became the subject of much research. By 1973, tamoxifen was known to interfere with estrogen’s ability to stimulate the growth of breast cancer cells and was recognized as an effective treatment approach for breast cancer rich in ERs (“ER-positive” cancer).4

The real breakthrough in biomarker discovery, however, came a few years later. Before the mid-1970s, researchers knew that certain genes, termed “oncogenes”, seemed to be responsible for the unchecked growth and division characteristic of cancer cells. At the time, it was widely believed that oncogenes were viral in origin, not human, and that the cause of all cancer was infection of human cells by viruses containing these viral oncogenes. In 1976, J. Michael Bishop and Harold E. Varmus of the University of California, San Francisco demonstrated that oncogenes are human in origin and can be found in normal human cells. For this revolutionary discovery, Bishop and Varmus were awarded the Nobel Prize in Physiology or Medicine in 1989.5 Armed with a completely new model for understanding cancer, researchers started to study how normal human genes could change to become cancer-causing oncogenes. The race to uncover new oncogenes was on.

One of those newly discovered oncogenes was HER2/neu. Studies by Genentech scientists in the early 1980s demonstrated that, in normal human cells, the HER2/neu gene produces a protein that regulates cell growth. In 1987, Dennis Slamon at the University of California, Los Angeles and colleagues from the University of Texas studied breast tumour samples and found that cancer cells from 25 per cent of the patients contained many more copies of the gene than did normal breast tissue cells. This resulted in abnormally high levels of the HER2/neu protein (“HER2/neu overexpression”).
Most importantly, they found that patients whose tumours had higher levels of HER2/neu protein had a shorter time to relapse and a shorter overall survival time. In sum, the work showed that a high level of HER2/neu in a patient’s tumour was a reliable biomarker for aggressive tumour growth and a worse prognosis.6

In response to this discovery, researchers from Genentech developed a drug to bind to excessive HER2/neu on breast tumour cells, slowing their growth and triggering the patient’s immune system to destroy them. By May 1998, the resulting molecularly targeted agent, Herceptin (trastuzumab), had been shown to increase response rates by about 50 per cent and improve time to disease progression by about 60 per cent when used with chemotherapy for women with metastatic breast cancer.7 Herceptin was approved by the United States Food and Drug Administration (FDA) later that year, followed by approval by Health Canada in 1999.

During the same time period that HER2/neu was discovered and targeted through the development of Herceptin, another well-known cancer biomarker was exploited for rational drug design: the Philadelphia chromosome. This genetic mutation results from a translocation, or break-and-swap, that results in part of human chromosome 22 being joined to chromosome 9.8 Termed BCR-ABL, this new gene produces a protein that causes uncontrolled white blood cell growth and division in Chronic Myelogenous Leukemia (CML). Researchers at Novartis (then Ciba-Geigy) developed an inhibitor of the BCR-ABL protein, imatinib (Gleevec). By 1999, early clinical trials of Gleevec demonstrated remarkable response rates of greater than 90 per cent.9 In 2001, Gleevec was approved in the United States and Canada for Philadelphia (Ph) chromosome-positive CML.

The success of Herceptin and Gleevec paved the way for additional important advances in the field of molecularly targeted therapy. Since 2001, the number of known biomarkers and targeted therapeutics has grown exponentially. We now know that a single biomarker is not always confined to one type of cancer. The Epidermal Growth Factor Receptor (EGFR) is one example. EGFR is a protein that can be overexpressed or abnormally active in the tumour cells from several cancer types, including lung, colon, head and neck, pancreatic, and brain. EGFR is the target of more than one drug: gefitinib (Iressa), erlotinib (Tarceva), cetuximab (Erbitux), Vectibix (panitumumab), and lapatinib (Tykerb).10 Such medications are typically tested in and approved for use in a single type of cancer first, then further trials are conducted in other types of cancer that express the appropriate biomarker. This is the case for Herceptin, a drug originally tested and approved for metastatic breast cancer expressing the biomarker Her2/neu. In late 2010, Herceptin was approved by the FDA and Health Canada for use in HER2/neu-positive metastatic stomach cancer.11

Advances in oncology research have demonstrated that biomarkers are not limited to a paradigm of “one biomarker—one targeted agent.” In fact, the biomarkers present or absent on a patient’s tumour make up a unique molecular profile that can, in some cases, help physicians predict the patient’s response to chemotherapy, targeted therapy, or both. One good example are the multi-gene assays, which are laboratory tests that check a tumour sample for multiple biomarkers at the same time. Such multi-targeted assays are an important area of research. Some examples include Mammastrat and MammaPrint for breast cancer, and Oncotype Dx for breast and colon cancers. Clinical studies have shown that these panels can, for certain cancers, divide patients into groups according to their risk of recurrence. Those in the high-risk group have been shown to benefit from an aggressive course of chemotherapy after surgery, while patients in the low-risk group do not appear to benefit.12,13 Another example is the biomarker KRAS. A 2009 study found that patients with metastatic colorectal cancer whose tumours had a normal KRAS gene were more likely to respond to a combination of chemotherapy and Erbitux than those whose tumours had a specific mutated version of the KRAS gene.14

The strategic use of tumour biomarker profiling can help spare patients from the lost time and potential side effects that come from trying a medication that is unlikely to be effective. Further, tumour biomarker profiling can produce significant savings on a national scale. In the case of KRAS testing, a U.S. pharmacoeconomic study found that upfront KRAS testing of tumours from patients with colorectal cancer would cost $13 million annually but would result in a net savings of $740 million, a savings realized through the avoidance of Erbitux treatment in those patients very unlike—by definition—to patients and to payers—cannot be realized unless a testing program is under strict quality control and produces consistently accurate results. These issues cannot be taken for granted, as made clear by a 2009 study from the University of California, San Francisco that found approximately 20 per cent of HER2 tests conducted today are inaccurate.15 The Commission of Inquiry on Hormone Receptor Testing in Newfoundland, released in 2009, revealed that 383 breast cancer patients of 1,013 tested between 1997 and 2005 had inaccurate ER/PR results, which in many cases led to the omission of appropriate hormone therapy.17 This strongly highlights the need for strict quality control when national programs for biomarker testing are undertaken.

From Targeted Therapeutics to Personalized Medicine

With all of the advances in molecular medicine, it is frustrating to realize that the goal of personalized treatment has still not been attained. The average five-year survival rate for cancer patients in Canada is still just 62 per cent, and about a quarter of cancer types have five-year survival rates under 25 per cent.18 This is the reality even though there are more than a hundred approved cancer drugs in Canada, including 24 molecularly targeted agents. Is the problem that the available drugs are not effective? Certainly continued development of efficacious drugs is needed. Tumours can develop resistance to both standard chemotherapy and targeted agents over time. Yet, a major part of the problem in most countries is the unacceptably long lag time between the attainment of knowledge by the research community and the integration of that knowledge into the standard of care. On average, it takes 17 years for new treatment strategies to become part of published guidelines.19
The reasons for the lag between the research and bedside are complex. Cancer treatment is one of the fastest moving fields in medicine. The explosion of research is overwhelming, and it is challenging even for those who craft the guidelines to keep current. In addition, key opinion leaders do not always agree about whether or not a new medication or treatment strategy has enough data to support its incorporation into the guidelines. Once new research appears in the guidelines, there is a further lag as clinicians incorporate the updated guidelines into practice. A recently published U.S. National Cancer Institute (NCI) Office of Education and Special Initiatives survey of 2,864 oncology practitioners in all types of practice settings found that only 33 per cent indicated that they had adequate time to access best-practice information.20 Regardless of the reasons, the current model for cancer care remains, in some ways, stuck in the past.

For example, the Tumor-Node-Metastasis (TNM) staging system was devised in the 1940s.21 Under this system, all tumours of the same stage and organ of origin are given a similar prognosis and are approached with a similar treatment strategy. Yet, one tumour may respond well to a particular chemotherapy or targeted agent, while another “similar” tumour will continue to grow and progress. Biomarker tools, where they have been developed, may offer a better assessment of risk than does the TNM system. For example, many patients in the clinical trials of multi-gene assays were labeled as high risk by the TNM system but low risk by the assay. These patients would have almost certainly received chemotherapy that followed the standard of care, yet the multi-gene assay revealed that they did not require such an aggressive course of treatment.22 Although these data have been published for four years, multi-gene assays are still not routinely used in the management of breast cancer in Canada, and their cost is rarely covered by the provincial health care plans. In practice, this means that Canadian breast cancer patients will receive unnecessary chemotherapy.23,24 Clearly, something must be done about the lag between the advancement of knowledge and its implementation in the clinic.

As the pace of research and development in oncology treatment continues to accelerate, bridging strategies will become increasingly necessary to make personalized cancer treatment a reality. Busy clinicians will need to find time-sparing and cost-effective ways to bring individualized treatment strategies to their patients. Patients will want a way to play an active role in their disease management in a manner that goes beyond internet searching and recommendations from friends or family. Payers and drug developers have a stake in ensuring that health-care dollars are spent on therapies that have the highest likelihood of producing a disease response. These goals are attainable—if knowledge from research can be quickly moved into the mainstream cancer community. The age of personalized medicine is, indeed, upon us, and it is up to us to seize that opportunity.

Jennifer Levin Carter, MD, MPH, is the Founder, President and Chief Medical Officer of N-of-One Therapeutics, Inc. (www.n-of-one.com). Dr. Carter is a physician, entrepreneur, and former healthcare analyst in bio- and medical technology. She graduated with distinction in Molecular Biophysics and Biochemistry from Yale University. She received an MD from Harvard Medical School and a Masters of Public Health from The Harvard School of Public Health.

Jillian Lokere is a freelance science and medical writer.

© 2011 N-of-One Therapeutics, Inc. Used with the kind permission of the authors.

References
PART 2

The 21-Gene Assay

CANADA’S UNEVEN RESPONSE

By JOSEPH RAGAZ, MD, FRCPC

In 2010, the first part of this series\(^1\) reported that the 21-gene assay recurrence score (RS), when used at the point of diagnosis of breast cancer, can predict the effectiveness of adjuvant chemotherapy in reducing cancer recurrence more accurately than any known biomarker.

Adjuvant chemotherapy is one of the key factors responsible for decreasing breast cancer mortality in the western world. The Oxford-based Early Breast Cancer Trialists' Collaborative Group conducted a review of all randomized trials over the last 20 years, documenting the benefit of adjuvant chemotherapy in reducing recurrences and mortality by 25-30 per cent\(^2\) according to subsets.

However, the benefits of adjuvant therapy are not guaranteed. The molecular classification of the tumour specimen based on the 21-gene assay RS is a vital tool to distinguish those who will have considerable benefits from those who may derive less, or no benefit, from standard chemotherapy.

On a scale of one to 100, a score less than 19 predicts little or no benefit, while a score of 30 or more indicates a very high impact of adjuvant chemotherapy, reducing recurrences by 50-70 per cent. Scores between 19-30 are less clearly predictive, but answers are expected shortly from the recently completed TAILORx trial, which compared the impact of chemotherapy or no chemotherapy in this intermediate group.

The RS score creates an opportunity for physicians to spare cancer patients from any unnecessary toxicity and side effects of chemotherapy. Anyone, especially cancer patients, would wonder why that step is not automatically in place, pursued with enthusiasm. Perhaps the learning curve in Canada is not what it should be.

Since 2007, the American Society of Clinical Oncology (ASCO) and the U.S. National Comprehensive Cancer Network (NCCN) guidelines have recommended that the 21-gene assay (Oncotype Dx) be part of the routine management for early stage breast cancer patients with hormone receptor positive tumours.

However, until 2009, this test was virtually unavailable in Canada outside clinical trials. If the test were more widely used in Canada it could facilitate the avoidance of thousands of rounds of unnecessary, toxic chemotherapy in the sizable patient subset with low RS.

Since our report last year, two Canadian studies have shown the rising value of molecular classification with the 21-gene assay,\(^3,4\) with one of them concluding, “The 21-gene assay appears cost-effective from a Canadian health care perspective.”\(^4\)

With data mounting on the benefit of using the 21-gene assay, Canadian provinces have responded as follows:

- British Columbia began a registration study for the 21-gene assay in 2010. However, it is restricted to node negative cases and until recently was active only in the Vancouver clinic.
- Ontario started funding the 21-gene assay more consistently, using an OHIP provision for out-of-country health services, which requires an application by the oncologist and prior approval from the health ministry.
- In the last few months, Quebec’s RAMQ has started funding an increasing number of 21-gene assay tests.

Table 1 shows the trend of increased use of the 21-gene assay in Canada since 2007.

A significant increase occurred in the number of tests ordered between 2009 and 2010, from 464 to 962. Also, more recently, the medical advisory secretariat to Ontario’s Ministry of Health and Long-Term Care drafted an in-depth analysis and recommendations regarding the 21-gene assay test, basically approving the use of the test for newly diagnosed node negative breast cancer patients with estrogen receptor (ER) positive tumours.\(^5\)

While these are positive trends, there is still massive under-utilization of this predictive tool in Canada. Research data show that of all ER positive tumours more than half will have low RS, whether node negative or node positive. Thus, the test could be used for all node negative and the low risk node positive cases if they are ER positive (70 per cent of all diagnosed) and candidates for chemotherapy (65 per cent of those). Thus, out of the 22,000+ newly diagnosed with new breast cancer each year in Canada, at least 10,000 women

<table>
<thead>
<tr>
<th>Year</th>
<th>Breast cancer patients tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>150</td>
</tr>
<tr>
<td>2008</td>
<td>348</td>
</tr>
<tr>
<td>2009</td>
<td>464</td>
</tr>
<tr>
<td>2010</td>
<td>962</td>
</tr>
</tbody>
</table>

Source: Feb 2011 updates, Genomic Health Database
TABLE 2
RECURRENCE SCORES OF CANADIAN PATIENTS 2007–2010

<table>
<thead>
<tr>
<th>Score</th>
<th>Node Negative Cases</th>
<th>Node Positive Cases</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Per Cent</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>Low (&lt;19)</td>
<td>1,029</td>
<td>55.03%</td>
<td>29</td>
</tr>
<tr>
<td>Intermediate (19–30)</td>
<td>654</td>
<td>34.97%</td>
<td>18</td>
</tr>
<tr>
<td>High (&gt;30)</td>
<td>187</td>
<td>10.00%</td>
<td>5</td>
</tr>
<tr>
<td>Totals</td>
<td>1,870</td>
<td>100%</td>
<td>52</td>
</tr>
</tbody>
</table>

Source: Feb 2011 updates, Genomic Health Database

TABLE 3
ESTIMATED COST-BENEFIT OF THE 21-GENE RECURRENCE SCORE

Based on one year, 10,000 newly diagnosed ER positive cases (i.e., those who are candidates for the 21 gene assay) and variable rates of avoiding chemotherapy.

$ in millions

<table>
<thead>
<tr>
<th>Cost Factors</th>
<th>Rate of Chemotherapy Avoidance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (no test)</td>
</tr>
<tr>
<td>Cost of chemotherapy</td>
<td>$150</td>
</tr>
<tr>
<td>Cost of 21-gene assay</td>
<td>$0</td>
</tr>
<tr>
<td>Health system cost</td>
<td>$150</td>
</tr>
<tr>
<td>Costs Added (+) or Saved (-) /10,000 cases</td>
<td>$0</td>
</tr>
</tbody>
</table>

These estimates are based on $4,000 for the test and a conservative estimate of $15,000 per course of adjuvant chemotherapy, potentially avoided in 2,500, 3,500 or 5,000 patients.

The data indicate that for node negative cases and likely also for the low risk node positive cases, the 21-gene assay could be used for all breast cancer patients with well differentiated, ER positive tumours, whenever adjuvant chemotherapy is potentially indicated, regardless of tumour size or vessel invasion. Once a low RS is doc-
There is still massive under-utilization of this predictive tool in Canada.

umented, chemotherapy should not be given as incurring toxicity for minimum benefits is clearly unacceptable. If the RS is high, chemotherapy ought to be considered even if not originally planned; for intermediate RS cases, individualized decisions need to be made. This approach should become a guideline policy for treatment across Canada.

**Node positive cases.** Preparations are underway in the U.S. for a randomized trial of chemotherapy vs. no chemotherapy in node positive breast cancer cases where RS is low. Canadian participation is expected. This study will be required due to the present international policy of using chemotherapy in all node positive cases. This is still the case despite the study of Albain et al. showing little benefit from chemotherapy in low RS cases among node positive breast cancer patients, regardless of the number of nodes involved, exactly as was the case for node negative cases. The chance of chemotherapy having a meaningful effect among low RS cases in the new study of node positive cases is understandably extremely low, posing a dilemma for prescribing chemotherapy to this cohort of patients, at least to some of the lower risk subsets (e.g., less than four nodes, those with focal nodal involvement only, etc.).

In addition, a related challenge to the present guidelines emerges for patients not participating in the above study: in all situations with low RS, chemotherapy may have to become the “experimental” option.

In summary, several key questions need consideration.

- Is it feasible to obtain, within a reasonable time, much higher levels of evidence in order to bring molecular classification with the 21-gene assay into guidelines? Reviewing the data, this approach seems unlikely, at least not for node negative and low risk node positive cases.
- Which is worse, over-treating large numbers of breast cancer patients with chemotherapy that we already know will be pointless yet toxic and immuno-suppressive, or not treating a few who could receive a slight benefit?
- Can the medical establishment be more pragmatic about accepting the present data into practice guidelines more swiftly and yet continue research into unanswered questions?
- Should patients be informed about these issues and have their own input into pursuing the 21-gene assay and acting on the RS score, i.e., declining or accepting chemotherapy?

**Conclusion**

At this point the 21-gene assay is the only validated test based on molecular classification to guide decisions for or against chemotherapy. Without it, the status quo of empirical approaches towards chemotherapy selection leads to considerable over-treatment with chemotherapy in a large number of low RS cases routinely planned for adjuvant chemotherapy, or in some cases under-treatment in cases with high RS not planned for adjuvant chemotherapy.

Unquestionably, more research is required to refine the molecular classifications for patients with cancer, especially the cost and comparability with surrogate markers. However, the data reviewed in this report document very low expectations of a meaningful benefit from adjuvant chemotherapy for breast cancer patients with low RS scores. If the 21-gene assay became a requirement in Canada, as part of routine policy for all eligible patients, we would see less cost, less toxicity and far less suffering on the part of most patients—and no less effective treatment. We have a choice to make.

**Joseph Ragaz, MD, FRCP(C),** is a Director of the CACC and a senior Medical Oncologist, Breast Cancer Researcher, Clinical Professor, Faculty of Medicine and School of Population Health, University of British Columbia, Vancouver, B.C.

**References**

5. Ontario Health Technology Assessment Series 2010; Vol. 10, No. TBA
PATIENT-CENTERED CARE AND PERSONALIZED PATIENT TREATMENT

Over the last decade the buzz words used by many medical institutions has been “Patient-Centered Care”, but what does this mean? The Royal College of Physicians and Surgeons of Canada has debated the meaning of professionalism and their conclusions include altruism as the hallmark of professionalism and appear to coincide with Francis Peabody’s statement in 1927 that “The secret of the care of the patient is in caring for the patient”.

Today’s medical institutions are using this term when in effect the care of hospitalized patients is based more on process and funding than on caring for the particular needs of the individual patient with their ethnic, cultural, religious and gender differences. We need to change our approach to patients based on caring rather than process.

For many years we treated all cancer patients based on clinical trials that included at best three per cent of the target population and applied it to all. Many of our guidelines are still based on this concept. However, clinicians and patients knew that not all breast cancers behaved the same and with increased research into the differences and our understanding of DNA mutations and intracellular pathways we are now more able to tailor treatments that are targeted to the patient’s cancer. Our knowledge of the cellular changes of all cancers continues to expand and with new tumour markers that truly reflect individual tumours, future treatments will be truly reflective of the needs of individual patients with their individual cancers. Only then will we be delivering personalized patient treatments.

CACC believes in advocacy and is committed to speaking openly about cancer issues, to highlight the concerns of patients and families, and to press governments for a more effective response to the enormity of the cancer problem in Canada. We forego charitable status to retain this freedom. Through the generosity of sponsors and donors, we use unrestricted grants to collect information, consult with cancer experts and families, and lobby governments for improvements. Sponsorship guidelines can be found on our web site.

If you are one of the millions of Canadians concerned about the state of cancer care, tell your federal MP and your provincial MPP/MLA. Make sure the people you elected to govern know that cancer is a priority to you and should be for them.