CANCER ADVOCACY COALITION OF CANADA

REPORT CARD ON CANCER IN CANADA™

Volume 15 • 2014-2015

Reflections on 2014

For many there are reasons to be thankful ... yet for others there is only hope yet to be fulfilled

CANCER ADVOCACY COALITION OF CANADA

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CACC Editorial Advisory Committee Dauna Crooks, James Gowing, Darwin Kealey, David Saltman and Colleen Savage

Special thanks to all the cancer patients and patient-centred cancer groups who offered their insight and support for this publication. Many other organizations and individuals generously share their experiences and ideas with us all year, including cancer agencies, policy and research institutes, think-tanks, senior officials in health ministries, elected officials and health professionals from coast to coast.

A note of appreciation to Cohn & Wolfe for a generous amount of pro bono public relations work on our behalf.

BOARD OF DIRECTORS

The Cancer Advocacy Coalition welcomes nominations to the Board of Directors. Send your CV and a letter describing your interests to our Nominations Committee at the main email address.

BOARD SUPPORT

Daniel Gillespie BSc, is a graduate of the University of Toronto and an independent consultant to the CACC, providing executive support and research services to the Board. Colleen Savage is an independent consultant serving as CEO.

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The Cancer Advocacy Coalition welcomes submissions from authors who wish to publish original articles on issues that are important to patients, showcase innovation in the organization and delivery of care, identify gaps and solutions, explore the potential benefits and guidance required for emerging technologies, evaluate the effectiveness of cancer policies and practices, or tell the story of your own cancer experience, particularly with a rare cancer, a new technology or an innovative service arrangement.

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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 health professionals, business 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 decisionmaking, 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

A Tribute to Maureen Coleman

In 2013 we lost one of our greatest champions of cancer patients, Maureen Coleman, the Founder and Past President of the Carcinoid Neuroendocrine Society Canada, also known as CNETS Canada. As we reach the one-year anniversary of Maureen's passing, it's important to reflect on the tremendous impact she had on the NET cancer community.

Maureen's contribution began in 2001 when she was diagnosed with neuroendocrine tumours, a rare form of cancer. Maureen and a few other Toronto-based patients funneled their feelings of loneliness in their diagnosis into a passionate drive to support each other and share information among themselves and other patients. This support group became CNETS Canada in 2007 and obtained charitable status in 2008.

Maureen's passion touched many people and she developed a worldwide reputation as a staunch NET cancer advocate with an entrepreneurial ability to approach the topic from many different angles. She learned as much as she could about neuroendocrine cancers, travelling the world to attend conferences so that she could bring back vital information for Canadian patients. Back home, Maureen developed NET cancer conferences across Canada, featuring world-renowned experts. The agendas provided important Continuing Medical Education (CME) credits that physicians are required to earn to retain their licenses and which was both an incentive and a mark of credibility for the content that was delivered.

She implemented a support model that offered direct patient support by phone and through in-person meetings of support groups. She fought for access to diagnostics and treatment options, spearheaded CNETS Canada's financial support of neuroendocrine cancer-specific research and built a partnership with the Cancer Research Society that resulted in the CNETS Canada annual NET Cancer Fundraising Day. Maureen was also one of the founding members of INCA (International NET Cancer Alliance) and held a strong vision of a NET cancer community without borders.

Beyond Maureen's passion as a cancer advocate she was a mom, a daughter, a partner, a sister and a dear friend to many. She loved all of these roles and fulfilled them

A passionate NET cancer leader, educator and friend

with great intensisty. She was a warm, compassionate, intelligent and genuine individual who always put the needs of others above herself and never let people down when they asked for support.

Maureen was tenacious and courageous. She was also an educator, a profession that served her well as she worked to educate patients, medical professionals and governments about the complexities of NETS and patients' unique needs. Though there were times when she was leading the way virtually on her own, she never faltered. She dedicated herself to our cause and pushed ahead to accomplish great things personally and on behalf of CNETS Canada and the NET patient community.

Maureen's legacy lives on in CNETS Canada. There are no words to accurately express the immense loss we continue to feel. We are in awe of everything Maureen accomplished and so proud to continue carrying out her dream. Maureen's beautiful smile and energy continue to shine on us as we think of her. As has been said before, she was a rare gem, worthy of our remembrance.

By Jackie Herman, President, CNETS Canada

Editorial

Oh for just one time . . .

The HMS Erebus was found exactly where 166 years of Inuit folklore said it would be. But for all that time and all the searches, nobody thought that information was relevant.

Solutions to the gaps and disparities in cancer care will be found exactly where patients have been pointing for far too long: more choices, better choices, up-to-date choices, fewer financial barriers to those choices and, if you don't mind please, can these health professionals work together and coordinate all the pieces of my care?

In many ways, the cancer system is better than it was fifteen years ago when we began this publication. Prevention initiatives are found throughout the country, in anti-smoking laws for example. There are national standards for several of the waits that cancer patients face, organized screening programs are more fully developed and include colorectal cancer, and might even include lung cancer in our lifetimes. The provinces are much more likely to publicly report on their performance and admit when they missed a target, fell below a standard or simply cannot cope with all the demands they face. Multidisciplinary care is less often the rarity and more often the first approch to meeting a set of patient needs. Nurse navigators and advanced practice nurses can be found working in innovative models of care delivery that make a world of difference to patients who are easily lost in the labyrinth. A superb project in Ottawa connects oncologists with cardiologists so that patients with both problems receive timely care that is fully coordinated.

Cancer research is booming in fields that hold so much promise: assessing the future risk of cancer, detecting its presence much more accurately and quickly, bringing personalized treatments to market that are precisely focused on the unique cancer cells that threaten us. The diagnostic tools available to clinicians have never been so effective (and expensive).

At the same time, a string of stubborn problems remain unresolved. Wait times are uneven - better of course, but there are still large disparities between provinces and within provinces and numerous examples of ups and downs for exactly the same type of wait in the same province. The Wait Time Alliance has done an impressive job detailing these facts for ten years and deserves a medal. Health ministers across the country have jumped on every opportunity to talk about patient-centred care and yet the wait times being reported reflect small portions of the patient journey. The initial focus for measuring wait times is still inward-looking: what is our silo willing to be accountable for? The wait times for a diagnosis are particularly erratic and need to be resolved.

Cancer prevention still relies heavily on nagging people toward a healthier lifestyle. An HPV vaccine for boys, which could prevent future cancers, is funded in only two provinces although every province and territory offers the vaccine to girls.

Provincial coverage of new discoveries is still too slow, whether the discovery relates to new cancer drugs or the biomarkers that identify when to use them, or to precision medicine discoveries that are gathering dust. Canadians give generously to research and expect to benefit from the results.

On the subject of research, we see a continuing imbalance of investments toward a few cancers that are widely known while the stigma of lung cancer curtails the research necessary to overcome an extraordinary fatality rate. And who will look for answers to rare cancers?

Policy gaps abound, as they did fifteen years ago. A patient receiving IV chemotherapy faces no charges of any kind while a patient taking a chemotherapy pill might be asked to pay thousands of dollars every month for the privilege of taking that medication at home. About half of all chemo is now in pill form, but a few provinces are stuck in the past while patients have to choose between living, or protecting the family's financial future.

There will come a time when this Report Card can publish more of the great successes and fewer of the glaring inequities. Like you, we eagerly look forward to that day. Maybe, for just one time, we could write that cancer care in this country is the best in the world.

Dauna Crooks, Chair of the Board
Colleen Savage, President & CEO

The Postal Code Lottery of Human Papillomavirus Vaccination in Canada

BY JAIME MCDONALD, BSCPHARM, PHARMD

Background

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections in Canada, with nearly 75 per cent of sexually active men and women having at least one infection in their lifetime.[1] In addition to causing genital warts, infection with HPV has been linked to various malignancies, the most infamous being cervical cancer which is caused almost exclusively by infection with HPV. However, HPV is also a major cause of malignancy in both men and women, including anal and oropharyngeal cancers, as well as penile cancer in men. Male cancers related to HPV, although rare, still represent a significant burden and their incidence is on the rise.[2]

Multiple HPV strains are capable of causing anogenital infection and the majority of immunocompetent adults are able to successfully clear the virus without any long-term sequelae. However, chronic infection with certain high-risk oncogenic strains, notably HPV types 16 and 18, has been implicated in roughly 70 per cent of cervical cancers, 88 per cent of anal cancers, 61 per cent of oropharyngeal cancers and 50 per cent of penile cancers.[3] In men specifically, 92 per cent of anal cancers, 63 per cent of penile cancers, and 89 per cent of oropharyngeal cancers are attributable to HPV types 16 and 18. HPV types 6 and 11 cause nearly 90 per cent of genital warts.[4]

Two recombinant, adjuvanated vaccines are commercially available in Canada; a quadrivalent vaccine against HPV types 6, 11, 16 and 18 (Gardasil) and a bivalent vaccine against HPV types 16 and 18 (Cervarix). Both vaccines are Health Canada approved for females between the ages of nine and 45 for protection against the development of precancerous and cancerous lesions of the cervix. A detailed comparison may be found in Table 1.

The differing indications for cancer prevention are unlikely to be clinically relevant, not only for biological reasons, but clinical trials have shown both the bivalent and quadrivalent vaccines to be effective in girls and women.[5]

Cost-Efficacy

Cost-efficacy analyses are so far inconclusive, with some for and against expanding HPV vaccination programs to include males. Most Canadian cost-efficacy analyses are unable to recommend expanding vaccine programs to males, unless uptake in females is less than 50 per cent, and instead encourage increased uptake in females as a more cost-effective strategy.[6] However, the Public Health Agency of Canada warns that the quality of life and economic burden of HPV-related disease in Canadian males is significant and should be considered when reviewing vaccination programs.[4]

Keeping this in mind, there has been a lower than desired uptake of HPV vaccine with 2011-2012 data showing only 70 per cent of eligible females were vaccinated in Ontario and a growing rate of vaccine refusal among parents of school-age children.[7] Female vaccination rates of 80 per cent have been used in most cost-efficacy analyses,[4] limiting the extrapolation of any comparative cost-efficacy analyses until a time when that threshold has been definitively reached.

Interestingly, there is preliminary evidence that bivalent vaccine may possess higher immunogenicity and cross-protective efficacy for other HPV types,[4,5] which may confer long-term cost-efficacy. Based on cost alone (Table 1), Cervarix appears to be an attractive option, however when non-cancer outcomes (i.e., genital warts) are considered, the cost-efficacy difference is minimized.[4] Head-to-head clinical studies comparing the bivalent to the quadrivalent vaccine are lacking at this time, however cost and efficacy comparisons are beyond the scope of this article as currently only the quadrivalent vaccine is licensed by Health Canada for use in males.

Table 1 **Comparison of HPV vaccines available in Canada***

	Quadrivalent vaccine	Bivalent vaccine
HPV types	6, 11, 16, 18	16, 18
Cost **	$149.95	$94.95
Indications	**Women 9 to 45 years** • Genital warts • Cervical intraepithelial neoplasia grades 1, 2 & 3 • Cervical adenocarcinoma in situ • Vulvar and vaginal cancer • Vulvar and vaginal intraepithelial neoplasia grades 2 & 3 **Women 9 to 26 years** • Anal cancer • Anal intraepithelial neoplasia (AIN) grades 1 & 2 **Men 9 to 26 years** • Anal cancer • AIN grades 1, 2 & 3 • Genital warts	**Women 9 to 45 years** • Cervical intraepithelial neoplasia grades 1, 2 & 3 • Cervical adenocarcinoma in situ
Schedule	0, 2 & 6 months	0, 1 & 6 months 0 & 6 months (ages 9 to 14)

* As per Cervarix and Gardasil product monographs.
** Average acquisition cost per dose (McKesson Canada), tendered prices unknown.

Supporting Evidence

Substantial evidence exists to support HPV vaccination for adolescent females. Two international, randomized, placebo-controlled studies have been conducted that have included over 17, 000 women.[8,9] If naive to HPV infection, women experienced almost complete protection against the HPV-related outcomes under study including abnormal cytology of the vulva and cervix, anogenital warts and cervical cancer. Although the trials were relatively short in duration at only three years follow-up, and some would argue too short to make conclusions with respect to cervical cancer, there was little hesitancy to adopt a widespread vaccination program for females.

There are no studies assessing the effects of HPV immunization in males on the prevention of male to female transmission or the incidence of cervical cancer. As well, the World Health Organization (WHO) does not recommend vaccination of boys solely for the purpose of cervical cancer prevention, assuming greater than 70 per cent uptake in females. However, models show that expanding HPV vaccination programs to males would further reduce the incidence of HPV disease and cervical cancer deaths by an additional 30 and 23 percent, respectively.[11]

Cervical cancer prevention notwithstanding, there are several studies showing benefits to HPV vaccination for males. A randomized, double-blind, placebo-controlled trial enrolling equal proportions of male and female children, has shown that seroconversion rates were greater than 99 per cent over the entire population with rates in boys non-inferior to those in girls.[12] A randomized, placebo-controlled, double-blind trial published in the New England Journal of Medicine in 2011[13] showed that a three-dose vaccination series with a quadrivalent HPV vaccine was 65 per cent effective in preventing genital lesions caused by HPV 6, 11, 16 or 18 in 4,056 males aged 16 to 26. In patients negative for HPV at baseline, efficacy was nearly 90 per cent.

A planned substudy of the aforementioned trial included 602 HIV-seronegative men who have sex with men (MSM) and aimed to assess vaccine efficacy in preventing AIN, a precursor for anal cancer. In the intent-to-treat population, the incidence of AIN due to HPV 6, 11, 16 or 18 declined by 50 per cent; incidence declined by 78 per cent in the

per-protocol population.[14] While the evidence in males is definitely less robust than for females, this landmark trial provides sufficient scientific rationale for the consideration of gender-neutral vaccination programs.

MSM have been identified as a population at increased risk of infection and adverse outcomes related to HPV,[4] including both anogenital warts and cancers. However, a recent study conducted at McGill University showed significant rates of oral HPV infection among heterosexual males.[15] More than seven per cent of men in the study had oral HPV infection, with higher rates among males who smoked, performed oral intercourse on their partner more frequently, or who had multiple partners. Prevalence was highest among males whose partner had an oral HPV infection, with rates reaching 28.6 per cent.

Not only does this study suggest that HPV may be prevalent among heterosexual males, it also suggests that transmission can occur via oral-oral and oral-genital routes. As mentioned above, HPV infection is more closely associated with oropharyngeal cancers than with penile cancers, with the former being much more common.

It is clear that clinical evidence and medical opinion support the expansion of HPV vaccination programs to include both males and females.

Some advisory committees have recommended targeting MSM for publicly funded vaccination programs[4,16] as these patients are unlikely to benefit from herd immunity conferred by a female-only vaccination strategy. Models have shown favourable cost-efficacy when MSM are targeted at an age of 12 years.[17] However, the identification of high-risk males who are likely to engage in high-risk sexual behaviours , or even smoke, is probably not feasible before the age of 12. Young boys are unlikely to declare sexual preference before the onset of sexual maturity when vaccines are likely to confer the most benefit, further supporting a non-selective vaccination strategy for males as has already been implemented for females, regardless of risk.

Indeed, grade 8 students in Canada, the target population for some vaccination programs as discussed below, are typically 13 or 14 years of age. A survey released by the Public Health Agency of Canada in 2011 reported that by the time they had reached 14 years of age, 16 per cent of females and 18 per cent of males have had sexual intercourse.[18]

In major clinical trials, vaccination is overwhelmingly less effective when participants with baseline HPV infection are included. In one trial, efficacy dropped from 98 per cent to 44 per cent.[8] As well, high-risk women and men, including those with multiple sexual partners and those with a history of abnormal PAP smears were typically excluded from clinical trials showing efficacy.

Most importantly, the ethical implications of withholding public funding for a vaccine that is known to reduce the burden of disease – and potentially cancer – in a specific population must be considered. While direct evidence that vaccination against HPV reduces cancer in males is lacking, the preliminary evidence is difficult to ignore. Health Canada and the Food and Drug Administration have already taken this leap of faith upon approving quadrivalent vaccine for the prevention of anal cancer in men and women, despite a lack of studies reporting hard outcomes.

Vaccination Programs

In 2013, Prince Edward Island became the first and only Canadian province to offer the HPV vaccine to boys as part of their routine, publicly funded vaccination schedule. However, beginning in September 2014 the Alberta school immunization program includes Grade 5 boys with a four-year catch-up program for Grade 9 boys. Publicly funded immunization programs are listed by province in Table 1. The provinces vary with respect to the timing of vaccination, ranging from Grade 4 in Quebec and the Northwest Territories to Grade 8 in Ontario.

Quebec and British Columbia are notable exceptions in that these provinces offer only two doses of vaccine, compared to the other provinces, which offer three doses. This decision is based on good evidence from randomized, controlled trials and is supported by the WHO. The WHO recommends this schedule for younger women aged nine to 14 years.

However, there are fewer data, especially long-term, to support a two-dose series and a Canadian model showed cost-efficacy only if the duration of protection from the vaccine is at least10 years and likely at least 20 years.[5] Data for protection are only available for approximately five to six years following vaccination, with models predicting 20 years or more of protection.[19] Quebec also offers, free of charge, the vaccine to immunocompromised women aged 18 to 26, including those infected with HIV, however there is no evidence for a two-dose series in this population.

As of 2014, the American Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with quadrivalent HPV vaccine for all boys in a three-dose series at age 11 or 12 years and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years should also be vaccinated, particularly those with certain high-risk medical conditions.[20]

To keep things in perspective, the ACIP evidence grade and subsequent strength of recommendation, is higher for HPV vaccination in males than for other vaccine-preventable

Table 2 HPV vaccination programs 2014

Province / Territory	Ages	Gender
NL	Grade 6	Females
PEI	Grade 6	Females and Males
NS	Grade 7	Females
NB	Grade 7	Females
QC **	Grade 4	Females
ON	Grade 8	Females
MB	Grade 6	Females
SK	Grade 6	Females
AB	Grade 5	Females and Males
BC *	Grade 6	Females
YT	Grade 6	Females
NU	Grade 6	Females
NWT	Grade 4	Females

* 2 doses.
** 2 doses, includes immunocompromised women 18-26 years.

illnesses such as meningococcal and pneumococcal disease, for which vaccines are routinely covered for all Canadians and usually without age restriction.

Closer to home, the National Advisory Committee on Immunization (NACI) recommends the HPV vaccine for females (bivalent or quadrivalent) and males (quadrivalent) between nine and 26 years of age including MSM. In December of 2014, the committee expanded their recommendations, stating the vaccine may now be administered to males and females over 26 years of age.

The committee also expressed agreement with the WHO in that a two-dose series age at 0 and 6 to 12 months may now be considered for immunocompetent individuals 9 to 14 years of age. There is no direct evidence for a two-dose series in males, however there is no indication that the response would be any different than that observed in female studies. Immunocompromised or HIV-infected patients who receive their first dose after 15 years of age should continue to receive three doses.[21]

Starting in 2007, with varying degrees of catch-up programs for eligible females, Canadian provinces began offering publicly funded HPV immunization programs. As of 2010, every province in Canada had implemented a vaccine program for school-aged girls. However, as seen in Table 2, provincial uptake of the NACI recommendations for males is lagging. Several professional organizations including the Canadian Medical Association, the Canadian Dermatology Association, the Canadian Society of Obstetricians and Gynecologists, the Canadian Cancer Society, and the Registered Nurses Association of Ontario, among others, vocally support expansion of HPV vaccination programs to males.[22] On a global stage, Australia, the United States and Austria have all expanded their HPV vaccination programs to include males.

Conclusions & Recommendations

Unfortunately, public health policy with regards to HPV vaccination programs is not driven purely by scientific evidence. Public funding for vaccination against a sexually transmitted infection is subject to considerable public debate and opinion, much like other "lifestyle" illnesses such as smoking and drug abuse.

However, it is clear that clinical evidence and medical opinion support the expansion of HPV vaccination programs to include both males and females. Cost-efficacy concerns, while legitimate, are estimates at best and even female vaccination rates have been unable to meet the criteria for cost-efficacy assumed in most models. As such, the Cancer Advocacy Coalition of Canada supports the following recommendations:

- The HPV vaccine should be offered to all Canadians, regardless of province of residence, gender or sexual orientation. Specifically, the quadrivalent HPV vaccine should be offered to all males older than 9 years, with catch-up programs made available.
- Vaccination programs should target children before the age of sexual maturity, as early as nine and as late as 12 years of age, keeping in mind the duration of protection is currently not known.
- As a cost reduction measure, a two-dose series of bivalent or quadrivalent HPV vaccine may be offered to immunocompetent individuals nine to 14 years of age.
- Long-term studies assessing the efficacy of HPV vaccination in the prevention of HPV-related disease and cancers in men are warranted. Other areas of interest include estimating the duration of protection and necessity for booster doses.

Jaime McDonald, BSCPharm, PharmD is a pharmacist in Ottawa and a Director of the CACC.

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NO EVIDENCE THAT GIRLS BECOME PROMISCUOUS AFTER THE HPV VACCINE

The concern among some families that the HPV vaccine could encourage promiscuity in their young daughters should be put to rest, according to new research from McGill published in the Canadian Medical Association Journal.[1]

The authors followed 260,493 Grade 8 girls in Ontario for an average of four and a half years – until the end of Grade 12. Half the girls had the vaccine in Grade 8 in the first two years it was offered, the other half had been in a two-year cohort just before the vaccine became available at school and did not receive the vaccine.

The study used two clinical indicators of sexual behaviour: pregnancy or a sexually transmitted infection. Checking anonymized medical records, the authors found no evidence that vaccination increased the risk of either outcome. Indeed, the authors concluded that their findings are "strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls. These results suggest that concerns over increased promiscuity following HPV vaccination are unwarranted and should not deter from vaccinating at a young age."

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Cardiac Oncology:
Improving Cardiac Safety, Advancing Cancer Care

Ottawa Cardiac Oncology Program

BY JEFFREY SULPHER MD FRCPC, NADINE GRAHAM BSC, CHRISTOPHER JOHNSON MD FRCPC, MICHELE TUREK MD FRCPC, SHREY MATHUR BSC, ANGELINE LAW MD FRCPC, ELLAMAE STADNICK MD FRCPC, JASON WENTZELL BSCPHARM, ACPR AND SUSAN DENT MD FRCPC

OCOP Members (Left to right): Dr. Michele Turek, Dr. Susan Dent, Sean Hopkins, Dr. Jeffrey Sulpher, Dr.. Christopher Johnson, Nadine Graham. Absent: Dr. Angeline Law, Dr. Ellamae Stadnick, Jason Wentzell

Introduction

Cancer and heart disease are the two leading causes of death in the Canadian population.[1] The development of targeted cancer therapies (e.g., trastuzumab) have resulted in improved patient outcomes.[2] However, targeted cancer therapies may also increase the risk of side effects, including those involving the heart (cardiac toxicity). Cardiac toxicity is now the second leading cause of long-term morbidity and mortality among cancer survivors.[3] Although cardiac toxicities associated with conventional chemotherapy are well known, the short and long-term effects of targeted treatments on the heart are less well understood.

For patients and their families, receiving a cancer diagnosis can be devastating. Navigating the complexities of the cancer care system is a significant challenge. These difficulties are compounded if cardiac complications from cancer treatment arise, thus justifying the need for a multidisciplinary, patient-centred approach in managing these risks.

The Ottawa Cardiac Oncology Program (OCOP) was established at the Ottawa Hospital in 2008. This multidisciplinary team, the first of its kind in Canada, consists of a medical oncologist, cardiologists, and a clinical pharmacist. OCOP provides patients with an integrated approach to cancer therapy, and promotes seamless communication between health-care providers. OCOP has three mandates: clinical service, research, and education. Through our cardiac oncology clinic (COC), patients benefit from timely access to cardiac assessment and treatment, resulting in improved quality of patient care. While the initial focus of the clinic was directed at women with early stage breast cancer exposed to chemotherapy and/or trastuzumab,[4] the widespread adoption of targeted therapies in oncology has led to the referral of a much broader patient population. To date over 550 cancer patients with a wide variety of cardiac issues (e.g. high blood pressure, rapid heart rates) have been evaluated through this program, and the COC model is being used for similar clinics throughout Canada.

Research Program

The goal of OCOP's research program is to develop a national cardiac oncology patient registry, in order to facilitate the development of evidence-based guidelines for diagnosis and treatment of cardiac toxicity. In collaboration with basic scientists, we are in the process of establishing a translational research program that will evaluate the role of novel biomarkers and specialized cardiac imaging techniques in predicting early signs of cardiac toxicity.

The goal of the educational component of the program is to educate patients, practitioners, and other health care professionals at various stages of training. The educational needs of trainees are currently met through clinical rotations supplemented by self-directed learning activities. Future efforts will focus on producing electronic learning resources.

We have established bimonthly multidisciplinary cardiac oncology rounds to foster education of our staff, residents and fellows. In July 2013, OCOP established a cardiac oncology research fellowship at the University of Ottawa, the first of its kind in North America. This research fellowship is designed to provide trainees with the opportunity to increase their knowledge and expertise in the detection and treatment of cardiac complications related to systemic cancer therapy (including chemotherapy and targeted agents). Future education activities will focus on web-based information about the interactions between cancer therapies and the heart.

In recognition of these efforts, the Ottawa Cardiac Oncology Program received the 2013 Innovation Award from the Cancer Quality Council of Ontario (http://www.cqco.ca/awards/recipients_2013).

Collaboration

As OCOP gained clinical expertise in the management of cardiac toxicity related to cancer therapy, it became apparent that a national organization devoted to furthering this area of cancer care was necessary. In 2011, the Canadian Cardiac Oncology Network (CCON) was established to facilitate collaboration among health care professionals interested in the emerging field of cardiac oncology. CCON's vision is to optimize cardiac care for cancer patients receiving potentially cardiotoxic therapy. CCON's missions are to: 1) gain a better understanding of cardiac complications related to oncology treatments, 2) develop early detection and intervention strategies to optimize cardiac health, and 3) optimize patient outcomes by collaborating with allied healthcare professionals.

In order to accomplish these goals, several projects and initiatives are currently in progress. To date, CCON has hosted four National cardiac oncology conferences in Ottawa, with a growing interest from a number of health care providers including: oncologists, cardiologists, nurses, pharmacists, radiologists and basic scientists. Our fourth conference was held in Ottawa May 8-9, 2014, and several international speakers shared their expertise and perspective on cancer care and heart health. CCON has also developed a one day workshop in Ottawa for visiting health care professionals to facilitate the establishment of cardiac oncology clinics at their respective centres. In October 2015, CCON will co-host the first global cardio-oncology summit with the International CardiOncology Society.

CCON, in collaboration with the Canadian Cardiovascular Society (CCS), is in the process of formulating a national position statement on best practices for monitoring and management of cancer therapy-related cardiotoxicity. Dr. Susan Dent, founder of CCON, is working with members

Patient Perspective

"It was so organized, and it all happened very quickly. The chemotherapy unit had very close dealings with the cardiologists. The oncology and cardiology teams were very well integrated. It means a great deal to me to know I'm getting such great care and medically these teams know exactly what is happening. I was under the care of one team, not several teams doing different things. There was less confusion."

Elizabeth Lee,
Cardiac Oncology Clinic Patient

The Ottawa Cardiac Oncology Clinic at a glance

		# Patients	%
Referrals 2008-13		428	
Cancer type	Breast	246	57
	Gastrointestinal	63	15
	Genitourinary	52	12
	Lung	17	4
	Hematological	31	7
	Other	19	4
Exposure to potentially cardiotoxic cancer therapy	Total	376	88
	Chemotherapy	207	48
	Targeted Therapy	169	39
Prescribed Cardiac Medication		175	41
Cancer Therapy Outcome	Completed	224	52
	Ongoing	12	3

of the International Cardiac Oncology Society (ICOS) to review current evidence and develop a similar comprehensive consensus statement for international use. In partnership with other leading world-class institutions in cancer care (i.e. Vanderbilt University - Nashville TN, University of Chicago - Chicago IL, MD Anderson Cancer Centre - Houston TX, University of South Florida – Tampa FL, and University of Pennsylvania - Philadelphia PA), CCON is working to develop a North American cardiac oncology fellowship program. This will foster the training of future health care providers in this novel area of medicine.

In an effort to reach out to patients, caregivers, and healthcare professionals, CCON launched its official website (www.cardiaconcology.ca) in November 2013. This website provides an opportunity to share the latest information on cardiac oncology, form research partnerships, and promote upcoming events.

Summary

In 2014, more than one million individuals in Canada will be considered cancer survivors. It is imperative that we work together to ensure these individuals do not face long term sequelae from their cancer treatment; in particular cardiac toxicity. Individuals with heart disease may face a diagnosis of cancer - a multidisciplinary approach will be needed to allow these individuals to receive the best cancer care without compromising their heart health. Cardiac Oncology is a new medical discipline that is breaking down the traditional 'silos' to offer individuals a patient-centred approach to cancer care.

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ESTABLISHING A CARDIAC ONCOLOGY CLINIC TIPS FOR ACHIEVING SUCCESS

The organization of a specialized cardiac oncology clinic is a complex process involving multidisciplinary collaboration, administrative support, and institutional resources. Here are tips on forming your own successful COC clinic.

1. **Logistics** – COC clinics require close interaction between oncologists and cardiologists. Choose a clinic location in close proximity to a cancer centre, preferably with an electronic health record and point-of-care access to cardiac imaging.
2. **Expertise** – Cardiologists with imaging experience are well suited to this area of clinical care. Focus on recruitment of specialists who are interested in learning more about cancer therapy and prognosis.
3. **Allied Health Support** – Clinics require significant support from allied health professionals. Consider recruitment of clinic nurses with experience in both cancer treatment and cardiac disease, and who have an interest in clinical research.
4. **Resources** – Cardiac oncology is a rapidly growing field. Access to the latest medical literature and research tools is crucial for clinic success.
5. **Collaboration** – Multidisciplinary clinics work best with consistent communication between health care providers. We recommend regular case review rounds and educational sessions (with participation of clinical fellows and residents) to keep members of the clinic informed and up to date.

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Nurses Challenge the Status Quo in Cancer Care

BY DAUNA CROOKS, RN, DNSC

Introduction

Each year the Report Card seeks out innovations in cancer care. This year we spoke to advanced practice nurses or APNs whose focus is cancer. Advanced Practice Nurses are nurses with advanced degrees, usually masters and/or doctoral degrees who carry the title of Clinical Nurse Specialist or Nurse Practitioner. APNs across Canada were invited to share the innovations they have made to the cancer system and to cancer patient care. What they shared was astounding. This article provides the highlights of interviews with eight APNs from Alberta, Manitoba and Ontario.

ALBERTA

Krista Rawson

Krista Rawson is an NP and Senior Practice Consultant with Cancer Control Alberta (Cancer Plan 2030), who has created a sustainable workforce plan for NPs in cancer care. This feat is unique in cancer systems as little thought is given to the type of practitioner or role needed for excellent patient care and little planning has been done to enhance role implementation for nurses or introduction of new roles in what has traditionally thought to be physician territory. Krista developed a Community of Practice that meets monthly so that NPs in all parts of Alberta can discuss practice, ideas to advance patient care, role implementation, and workplace issues. Mentorship is active and continuous to promote knowledge about and respectful interaction with the health care team, patients and families. Context of the family is viewed as important in educating, dialoguing with and supporting patients and families to make appropriate decisions for their particular context and providing all aspects of supportive care wherever needed. In addition, Krista works with Universities and NP students to create a positive succession plan. Her work serves as a model for Canada.

Krista was charged with creating new models of care to meet specific patient needs across the province. Krista completed an environmental scan to determine what was working and what was not. She modified how roles were introduced and supported in the workplace. Since NPs in Alberta support communities to provide cancer care closer to home, models of care developed differ by region and available resources.

Support to patients and family members is an important part of the NP role.

Care and service innovations have expanded to include: rapid access clinics for lung cancer patients where these clinics provided first point of contact, assessment, treatment, navigation and education. Women with breast cancer on hormone treatment and patients in the curative treatment phase have access to an NP provider clinic offering one to one appointments as well as weekly group education. NPs offer support for sexual health issues where patients are seen by multidisciplinary team and are followed through treatment as needed. NPs follow patients with head and neck cancers and facilitate the transfer home with management of supplemental tube feedings as needed.

Support to patients and family members is an important part of the NP role in addition to assessments and management of treatment symptoms and complications. Similarly, NPs manage chemotherapy for GI patients and provide psychosocial support and education. NPs also follow patients with brain tumours and support the patient and family in advance planning and end-of-life decision-making.

Dr. Edith Pituskin

Dr. Edith Pituskin is an NP with a doctoral degree in Rehabilitation Sciences. She serves currently as a Clinician Scientist for Cross Cancer Centre in Edmonton. Edith has developed a rapid access cardiology clinic where patients have access to diagnostic imaging, dose timing, and surveillance of clinical outcomes. All patients seen in clinic become research partners by giving blood and tissue samples. From

these samples a data set is being built to determine and identify prognostic factors relative to treatment and clinical outcomes. Edith's vision is to identify through the samples and testing those patients at risk where increased surveillance is most useful. Although cardiac issues especially heart failure, have been problematic for patients and physicians for decades, this is the first research-based clinic to actively assess and address those issues. Edith invested in research and education and the result was that physicians now view this clinic as a valuable service and support it. Additionally, her research extends to patient experiences with radiation and caring activities of radiation oncologists and therapists giving radiation.

Edith is involved in the breast cancer clinic mentioned above, managing women on hormonal treatments. Drug adherence for this group is lower than desired for a good clinical outcome. The focus of education and support is around managing medications and using exercise and other means to maintain health, fitness and improve survival advantage.

MANITOBA

Dr. Anne Katz

Dr. Anne Katz is an advanced practice nurse working at CancerCare Manitoba. She is on the graduate faculty at University of Manitoba, Faculty of Nursing. Anne is a certified by the American Association of Sex Education Counselling and Treatment. Her practice is focused on providing information, education and counselling to people with cancer and their partners about sexual changes that can occur during and after treatment. Anne feels it is important for every cancer patient to be able to have a discussion about sexuality with their health care providers. Anne also educates and supports nurses and other health professionals to assess and discuss sexual changes and issues arising during treatment. In addition to face to face individual and couple counselling, Anne has written many books to help the public and health professionals understand the importance of sexual health and managing feelings in changing states such as during cancer treatment.

Anne receives referrals from medical and radiation oncologists, and nurses. Anne is located in the prostate cancer clinic but serves all cancer centre patients. She does brief resolution focused therapy identifying what is happening to the couple and the impact of the issue on their relationship. Anne validates the concerns the individuals have and in dialogue normalizes their concerns. She encourages open discussion with the couple to fully understand what each is thinking about the issues arising and the needs each has to move forward. Erectile dysfunction in prostate treatment interventions, colorectal and bone marrow transplant are common and may or may not be treatable. Information for couples is important and a likely outcome known in advance is somewhat easier to deal with going forward. Women with anal/rectal cancer may require dilation. This fact may increase or decrease emotions but recognition of the facts and how each one might help is useful. Anne recognizes the difficulty in dealing with sexual issue in the face of cancer and treatment but encourages commitment and flexibility as the couple works through the combined issues.

It is important for every cancer patient to be able to have a discussion about sexuality with their health care providers.

An example of Anne's work is found in the following vignette. A woman with breast cancer was treated with an aromatase inhibitor known to promote vaginal stenosis, vulvar atrophy both of which will cause pain with sexual touch. The woman was experiencing excruciating pain in sexual congress. Her partner was feeling guilty for hurting her and the woman felt guilty for not wanting to participate with her partner. Topical and locally applied estrogen was suggested and found to be helpful. Anne's advice for health care practitioners is "Just Ask!" It is important that patients have permission to talk and will look for cues from health care professionals to open a dialogue about treatment and psychological impacts on sexuality.

Kristie Morydz

Kristie Morydz, NP CancerCare Manitoba is part of a team who developed a smoking cessation program for patients, family members, staff members and their families as a primary cancer prevention modality. The idea was presented to ENT and surgical staff to lower risks for surgery and need for excess drug use. Rounds and team meetings were also used to identify issues and to implement this service. Evidence was gathered for a smoking intervention and guidelines for all staff were written, material for cancer patients was also developed on quitting smoking, effects of smoking on body and survival. Nursing students from University of Manitoba created the information booklet to support therapy. Treatment plans are being developed.

Kristie receives 5-6 new referrals each week (self-referral and HCP referral). Referees see the clinic nurse once per week to determine needs, issues and interventions. Pharmacists dispense the treatments and social workers counsel. Follow-up is intensive for 2-4 weeks. Kristie is part of the regional COP for Smoking Cessation and is able to bridge in and out patients without loss of follow-up or treatment. Distant patients are seen by telehealth and medications

are covered by Manitoba Health. Care can be readily coordinated and support sustained to maintain tobacco free lifestyle. Kristie has a primary role in the thoracic disease site group.

ONTARIO

Trillium Health Partners in Mississauga Ontario offered three dynamic advanced practice nurses.

Devi Ahuja

Devi Ahuja, NP Oncology in the Mississauga/Halton Central West Regional Cancer Program developed a survivorship program and well follow-up program. Women with breast cancer who have completed active treatment would normally be transferred back to the care of their GP. The well follow-up includes meeting supportive care needs until the patient feels ready to return to GP care. Quick re-entry is part of the well follow-up plan in the event of an issue or symptom needing scrutiny by oncology specialists. Quick re-entry decreases wait time from suspicion of an issue to testing and/or treatment. Cancer Care Ontario devised the concept and the Credit Valley site implemented it. A colorectal well follow-up clinic will begin soon developed with patient and GP input.

An outcome of this work is enhancement of transparency in communication with GPs and within the health care team onsite: developing care plans, summaries for the GP, toolkits for the GP around what to look for, how to manage patients and when to send them back to oncology. Feedback to date indicates enhanced satisfaction on the part of patients and GPs. Devi also created a lymphedema class with self-management information, physiotherapy assessments and treatment and attention to latent side effects, supportive care issues, diet, exercise and screening.

Charmaine Lynden

Charmaine Lynden, NP focusses on a range of disease sites in her practice in radiation oncology. She set up the processes to make the clinic run smoothly, for example she manages contacts and referrals from other Trillium sites, interacts with Emergency Departments, created processes for referrals, communication channels to GPs and other clinics. She manages lung cancer, esophageal/gastric/pancreatic cancer or anal/rectal cancer patients with concurrent radiation and chemotherapy at high risk for toxicity. Patients may come from any site of Trillium Health Partners so the need to organize and coordinate visits, tests and treatments is essential. She manages side effects and toxicities of radiation treatment. The GU group of patients will see her before surgery and continue to radiation therapy. Charmaine manages radiation patients admitted to hospital, directing their care plan for oncology crises such as spinal cord compression. She consults with palliative care and oncologists as needed.

Kathy Kiteley

Kathy Kiteley, CNS Palliative Care displays the broad scope of the Clinical Nurse Specialist role. She works with the Cancer Care Ontario initiative on the work of APNs in cancer care. She has a significant role in the Dyspnea Management Program developing evidence based guidelines, algorithms, patient information, DVDs that help patients through breathing, relaxation and guided imagery practices to reduce or manage dyspnea. She evaluated the program examining quality of life, and ESAS outcomes. She is seeking funding to sustain a Breathing Wellness Program developed from the earlier work. She is co-lead in the Registered Nurses Association of Ontario Best Practice Guideline on Pain Assessment and Management. She is part of a team looking at the knowledge translation of work done on symptom management. She has worked with other oncology nurses to develop a curriculum for end-of-life care for rural and urban nurses in Thailand. In her work setting Kathy provides palliative care to Trillium patients.

The most problematic issues for patients are fatigue and cognitive memory disruption.

Lynn Hryniuk

Lynn Hryniuk NP works in a private cancer navigation service which provides prevention, assessments, navigation and supportive care complementary to but not the same as that available in the cancer systems across Canada. Lynn is one of a number of Nurse Case Managers across Canada who assist patients to return to work after cancer and/or to rehabilitate to a new life status. Nurse Case Mangers walk patients through the diagnostic process, the diagnosis itself, cancer treatments, and educate on self-help strategies. They assist patients to positively manage side effects both long and short term. Referrals are made to the cancer centres, oncologists and GPs as the need arises.

The care is done by phone as often as the patient needs access to the nurse case manager. Nurses can be contacted for questions or concerns between planned phone contacts. Symptoms, issues and worries are discussed. The most problematic issues for patients are fatigue and cognitive memory disruption. Both influence their activities and successful return to work. Lynn encourages patients to monitor their activity level, need for naps and increasing or decreasing ability to be active. She discusses how to increase exercise tolerance and promotes the activities that patients enjoy. Lynn also examines the diet and promotes foods that increase energy and have a longer lasting effect on energy. Cognitive memory issues are frightening and frustrating and Lynn coaches patients to keep their minds active with reading,

crosswords and puzzles, but more importantly to maintain a sense of humour about forgetfulness when it happens. She counsels patients to do one thing at a time and finish it so that a sense of accomplishment is felt and an incentive to go on. Lynn works with the family physician or oncologist to consider issues with hemoglobin or thyroid when fatigue is prevalent. Specific plans for rehabilitation are made at a pace the patient can manage. Communication with regular health care providers is encouraged and patients are taught how to organize their thoughts, concerns and questions in preparation for these visits. NCCN Guidelines are used to manage care and symptoms arising so that care is the most up to date and evidence based. Medical personnel suggest drug treatments and suggest ways to find funding for these. Referrals are made with the patient's permission to resources and services for symptom management, but self -advocacy is encouraged.

The majority of work from diagnosis to end of life focusses on reclaiming and integrating a new life after cancer.

Back to work issues are raised and recommendations are made to employers for work modification and a guide for reintroducing a cancer survivor to the workplace. Supports for return to work issues in the psychosocial realm are also addressed such as concerns about what people at work will think. While patients may look good on return to work they very often experience fatigue with a new routine. Cognitive memory issues are often voiced as a concern. Plans are made with the patients for actions to be taken and when, for example if they can get through a day with activity at home they could likely mange a half day with the challenges of the workplace.

The majority of work from diagnosis to end of life focusses on reclaiming and integrating a new life after cancer. Lynn helps patients/survivors redefine their life status and manage work and relational issues. Survivors receive a Risk Assessment and focused education about how to further decrease their risk of cancer as well as heart disease, stroke, diabetes and osteoporosis. All survivors and their family doctors receive a Survivorship Care Plan and summary of what has happened in care. This plan indicates long term issues and symptom that may arise. Given the nature of late effects, Lynn is available for her cases to call and discuss issues as they arise for as long as is needed and well past graduation from the program.

End of life issues are raised as appropriate and plans are begun to address issues the patient wishes to resolve or address. Referrals are suggested or made on behalf of the patient to palliative care or pain and symptom management services.

CHALLENGES FOR APNS IN CANCER CARE

Palliative care, primary prevention and survivorship are not central to cancer control services. Still, these are recognized as important features of care by APNs.

Krista plans to create business cases and innovative partnerships around palliative care and survivorship to meet the needs of Albertans. Shared care models for long term metastatic disease are one possibility. Prevention in cancer centres is geared toward secondary prevention with assessments and treatment of late stage side effects. Krista is forward looking in the roles of NPs in cancer care. Strategies to decrease recurrence, weight management, exercise and other supports are being discussed as prevention measures to be integrated into care.

Edith is seeking funds to research the impact of exercise in hormonal treated women and those with metastatic breast disease. She is also seeking space for women to exercise and for an oncology rehabilitation centre that would create patient specific prescriptions for rehabilitation and exercise.

Anne is involved with a new field in Manitoba, onco-fertility and preservation issues for cancer patients. At present procedures and partnerships are being developed for sperm banking, cryopreservation of eggs and a fertility clinic.

Kristie is looking to develop smoking cessation plans with entire families of patients and staff to ensure greater support, positive role models and higher resolution to quit smoking.

Devi is considering the impact of opening new follow-up sites to accommodate the numbers of breast and colorectal patients and the possible need for after-hours clinic time in the Mississauga area. Two hundred patients have been referred to her since last fall. A new human resources structure developed by a nurse would be an exciting event.

Charmaine is examining the evidence for skin care products for patients with anal/rectal issues.

Kathy plans to make a difference in the emotional care of cancer patients by educating nurses in assessment of needs and interventions, how to start conversations and provide emotional care in a timed environment. She plans to study barriers and challenges for nurses, identify how to change viewpoints initiate self-reflection, identify what changes could be made and create a model for nurses to use in conversation and finally to create mentors to keep the movement going on behalf of cancer patients. Kathy is developing sustainable end of life care in a complex study of common practice, desired practices, and prognostic measures of death risk, advanced care planning and partnerships to provide and

maintain the best end of life care for cancer patients.

Lynn has worked in both public and private cancer care. Her hope is that patients get what they deserve, a unified consistent and cogent team that supports patients at all junctures of the cancer journey. The team she works with has published an evaluation of their service and patients agreed that the care they received was consistent, very helpful, timely and accessible and different from the care received in the cancer centre setting.

SUMMARY

APNs have made considerable changes in health care in general and cancer care in particular. Patients have confidence and trust in nurses but cancer agencies and hospitals are slow to utilize the expertise of nurses. The interviews with this group of cancer care providers demonstrated both the constraints they work under but also the drive to improve care for patients regardless of the limitations of cancer centre mandates. The 2014 Cancer System Quality Index released by the Cancer Quality Council of Ontario identified several hot issues in cancer care in Ontario with comparisons to other provinces. Wait times for surgical, medical and radiation treatments were found to be below the standard expected. Ongoing symptom assessment and management is lacking during and after the treatment phase. Survival rates are declining for women with breast cancer. Access to and use of palliative care was another issue raised. Given the expectation of rising cancer rates in the next two decades, it was surprising that no mention was made of human resource planning for cancer care. There is an obvious lack of skilled communication in the care setting about cancer issues, sexuality, end of life and symptom management assessments and interventions. All of these issues have been raised and addressed by the group of APNs.

The APNs interviewed were forward looking in their vision to change both services to patients and the cancer system itself. It behooves cancer administrators and government to access the vast expertise and support developments this group is already working on. The challenge of knowledge translation of these innovations is significant. Hopefully this Report Card will bring the depth of APN innovation to the attention of the public, administrators and government.

Dauna Crooks RN, DNSc recently retired from her position as Dean of Nursing, University of Manitoba and now resides in Dundas, ON. Dr. Crooks is Chair of the CACC.

THE FIRST STEP TOWARD AN ORGANIZED LUNG CANCER SCREENING PROGRAM[1]

Following new evidence that suggests screening via low-dose CT scans could help reduce lung cancer-related deaths in high-risk populations, the Canadian Partnership Against Cancer's pan-Canadian Lung Cancer Screening Initiative has developed the Lung Cancer Screening Framework for Canada to help interested provinces and territories design targeted early detection programs for high-risk populations.

It's estimated that 25,500 Canadians were diagnosed with lung cancer in 2013 and that some 20,200 men and women died from the disease in the same year. The five-year relative survival rate for lung cancer is 17 per cent.

The Framework eliminates duplication of efforts, saving time and resources that interested provinces and territories would otherwise have had to devote to developing their own approaches to lung cancer screening. It provides guidance to provinces that may be investigating the feasibility of lung cancer screening for high-risk populations and provides a framework of how to minimize the negative impact of opportunistic screening.

Lung cancer screening is focused on a defined high-risk population because the risks and complications associated with screening lower-risk cohorts, such as false positive findings, likely out-weigh any potential benefits.

Setting criteria for eligibility to participate in screening requires consideration of multiple factors, aside from risk exposure. Although conditions such as age eligibility should ideally be standardized across the country, as it is for colorectal cancer screening, lung cancer screening will likely evolve differently across the provinces and territories in terms of timing and approaches that best fit the needs of the jurisdiction.

The consensus statements within the Framework were developed through an extensive consultation process and involved clinicians, pathologists, radiologists, smoking cessation experts and thoracic surgeons, among others.

1. Canadian Partnership Against Cancer. Lung Cancer Screening Framework for Canada. 2015.

The Importance of the Multidisciplinary Team in the Acquisition and Processing of Cancer Biopsy Tissue Samples for Biomarker Testing

BY DAVID SALTMAN, MD, PHD, FRCPC

Introduction

Personalized medicine uses the genetic signature of a cancer cell to diagnose and effectively target activating genes and their corresponding proteins (biomarkers).

The therapeutic targeting of these genetic abnormalities often leads to more effective and safer therapies than seen with nonspecific chemotherapy drugs. For example, the response rates and the improvement in progression-free survival achieved in certain subsets of lung cancer that harbour either an epidermal growth factor receptor (EGFR) mutation or an anaplastic lymphoma kinase (ALK) fusion gene is far greater with EGFR and ALK inhibitors than seen with cytotoxic chemotherapy drugs.[1,2]

Similar results are also seen in a number of other cancer types, which historically have been very difficult to treat when in an advanced stage.

At the cornerstone of personalized medicine is the requirement for the accurate, cost effective and easily reproducible identification of the genetic abnormality that is causing the cancer to grow and will be the target for these novel therapies.

A biomarker for cancer can be defined as genetic material (DNA or RNA) or protein that can be isolated from a tumour and is indicative of a normal or abnormal process. While prognostic markers may indicate the probability of a benefit from a treatment intervention, predictive markers are objective indicators of the sensitivity or resistance of a tumour to a specific therapy that is designed to target that gene or protein.

The detection of biomarkers in cancer biopsy samples may not be possible without an adequate volume of high quality tumour tissue.[3] The pathologist's role in this process is obvious but the involvement of the other members of the multidisciplinary team and effective communication between stakeholders is also critically important. This article will use non-small cell lung cancer as a paradigm for the steps that are required for providing the pathologist with cancer biopsy samples for biomarker testing.

The Role of the Respirologist and Thoracic Surgeon

Patients with lung cancer may first enter the healthcare system either with a visit to their family physician or the emergency department. Symptoms such as cough, bloody sputum, shortness of breath and chest pain usually precipitate a cascade of investigations including chest x-rays and CT scans. Abnormalities seen on imaging studies suggestive of a lung cancer will then result in a referral to a respirologist or thoracic surgeon for biopsy confirmation of the diagnosis.

The detection of biomarkers in cancer biopsy samples may not be possible without an adequate volume of high quality tumour tissue.

Unless the patient has advanced disease evident on physical examination or imaging studies, the first attempt at procuring a biopsy sample is often performed by bronchoscopy. If the tumour can be safely visualized within the airways, then the bronchoscopist will attempt a biopsy using tiny forceps. More than one biopsy fragment may be obtained but the samples are often small. Tumours that are outside the airways can be biopsied by directing the bronchoscopist's needle through the wall of the airway with the use an endobronchial ultrasound or EBUS.[4]

Cancer cells can also often be obtained using exfoliation by brushing or washing the involved airways (bronchial lavage) with a saline or salt solution and collecting the fluid for cytology. The number of cells obtained is often very diluted, requiring the concentration of the material by special techniques to allow the pathologist to have adequate cells to examination microscopically. If the amount of the tumour cells in a bronchoscopic biopsy or obtained by bronchial brushing or lavage is small, then it may impact the pathologist's ability to make a diagnosis of cancer, to sub-classify the tumour or test for biomarkers.

Bronchoscopy has a higher sensitivity for the diagnosis of central lesions and a low sensitivity for the diagnosis of peripheral lesions. Lung cancers that are in the peripheral lung zones that are not accessible by bronchoscopy are usually referred for transthoracic needle biopsy (TNB) under image guidance.

The Role of the Interventional Radiologist

With the exception of tumours that can be easily felt and safely biopsied without imaging guidance or sampled by a surgical procedure with direct visualization, many biopsies, whether intrathoracic or extrathoracic, are done with the assistance of imaging. The two most commonly used imaging techniques for obtaining tissue biopsies include ultrasound and CT scanning.

Image guided sampling of tumours for lung cancer diagnosis and molecular testing are performed using either fine needle aspiration (FNA), or by utilizing a core needle biopsy (CNB). FNA is rapid, cost effective and safe.[5,6] The procedure involves inserting a small diameter needle into the tumour and aspirating cellular material for cytology. The procedure is best done with an experienced cytopathologist present to analyse the sample by microscopy and determine on site whether there is adequate and representation cells in the aspirated to make the diagnosis. Inadequate tissue sampling is one the greatest drawbacks of this technique.

Core needle biopsy has an advantage over FNA because it uses a larger diameter needle allowing for a more adequate tissue sample to be obtained. However, unlike FNAs, the CNB may be done blindly and so you may not have any indication of the tumour content until after the sample has been processed and examined microscopically. Depending on the location of the tumour, it may be possible to safely obtain multiple CNB samples. The larger sample size provides more ample tumour tissue to make a histologic diagnosis of non-small cell lung cancer and perform biomarker testing. Core needle biopsy complications will depend on a number of factors including the organ that is being biopsied. Compared with FNA, core needle biopsy does not appear to result in a higher complication rates for hemoptysis (coughing up blood) or pneumothorax (air in the pleural space).[7]

The extent or stage of the lung cancer at diagnosis will often determine the choice of procedures used for obtaining tumour tissue to determine a histologic diagnosis and test for biomarkers. In patients with cancer localized to the lung without involvement of the lymph glands in the centre of the chest (mediastinum) or pleural space, their disease may be classified as stage I or II and therefore potentially curable by resection of the primary tumour. If it is very likely that the patient is a candidate for a curative lung resection, then a FNA may be the preferred technique for obtaining a diagnosis of NSCLC. The amount of tumour available to the pathologist after a lung cancer resection will be more than adequate for biomarker testing.

The approach may be different for patients with inoperable lung cancer, where cure by surgery is not thought to be possible. Since testing for the EGFR and ALK mutations is recommended in advanced stage lung cancer, performing a CNB is more likely to yield sufficient quantities of representative tumour tissue to confirm the diagnosis of NSCLC, subclassify the tumour and have sufficient tissue remaining for molecular diagnostic studies.

Compared to CNB, the interpretation of FNA specimens or exfoliation cytology is limited by the smaller sample size, a sampling error or the lack of a histologic pattern. The size of a biopsy is important, but the sample must obviously be representative of the tumour. For molecular testing, the preference between FNA versus CNB will vary between laboratories but as a general rule specimens with a small amount of tumour but a high tumour cellularity may be more appropriate compared with a larger biopsy with a low cellularity.

It is very important that the respirologists and thoracic surgeons communicate effectively with their radiologist colleagues when ordering image guided biopsies to help determine the best technique to obtain a diagnosis and have ample tissue left over for molecular testing.

The Role of the Pathologist

Regardless of the method used to acquire tumour tissues samples, the specimens will need to be processed in such a way that will allow the pathologist to view the tumours cells and confirm the diagnosis. Cellular material obtained by FNA can be spread onto glass slides for examination by microscopy by the pathologist. Residual material acquired from FNA can be concentrated by centrifugation of the cellular solution to make a pellet, which is then fixed in a formalin solution and embedding in paraffin. Slides made from the paraffin blocks are useful adjuncts for establishing a diagnosis using immunocytochemistry and for molecular testing. For bronchoscopic forceps biopsies and CNBs, the samples are suspended in formalin, then embedded in a

Communication between histo-pathologists, cytologists and laboratory technicians is critical.

paraffin, from which thin slices can be cut to make slides for routine microscopy and immunohistochemistry (IHC). The distinction between subtypes of NSCLC can be made by morphology alone provided there is adequate tissue. In cases where there is no clear differentiation by microscopy, IHC markers, such as the adenocarcinoma marker TTF-1 and the squamous marker P63, can be very helpful in distinguishing subtypes.

An excessive number of slides made from the tumour block for histology and additional IHC markers will limit the amount of sample that can be used for biomarker detection. Communication between histo-pathologists, cytologists and laboratory technicians is critical in preserving biopsy tissue for subsequent molecular testing.

Slides with sufficient tumour cells can later be used for biomarker detection using IHC to detect the ALK fusion protein, or fluorescence in situ hybridization (FISH) to determine the presence of an ALK fusion gene. Although both these assays can be used independently to detect ALK fusions, many labs will perform reflex confirmation of a positive IHC result with FISH.

EGFR mutational analysis and ALK testing are often done sequentially, first by extracting a small amount of genetic material from formalin fixed paraffin embedded (FFPE) biopsy tissue for EGFR testing, and then making slides for ALK fusion gene detection. However, in some cases where there is insufficient tissue in the biopsy sample, the tumour may be exhausted from the paraffin block precluding the possibility of further biomarker testing. A quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) method has been successfully used to detect the presence of ALK fusions in cases of low tumour content in biopsy samples.[8,9] Unlike early allele-specific RT-PCR assays, which can only detect specific ALK fusion RNA expression, newer PCR assays are able to detect any ALK oncogenic fusion transcript and upregulation of the gene.

Analytical methods that test for the presence of multiple, different cancer biomarkers simultaneously will likely replace many single biomarker assays.

Even when biopsy samples are deemed generous, there are a number of factors that can adversely affect the quality of the biomarker nucleic acids and protein hampering their detection. The handling and processing of the tissue biopsy in the bronchoscopy suite, radiology department and operating room is very important. Significant degradation of nucleic acid can occur before the sample is suspended in fixative, so specimens should be fixed in formalin within a pre-specified time of the biopsy for a maximum of 6 to 48 hours. Fixation in formalin beyond 48 hours may modify nucleic acids making biomarker testing difficult to impossible to complete.[10] These times will vary between institutions.

The preservation of the quality of biopsy samples, which have been embedded in paraffin blocks, is very important because archival specimens are frequently used in biomarker testing. Positive EGFR mutation and ALK fusion results have been obtained from specimens acquired five to 10 years earlier. Tumour blocks should be stored without cut surfaces to prevent damage caused by oxidation, light and water exposure, and infestation.

Specialists agreed that acquiring a sufficient quantity of quality tissue remains a challenge in many cases.

The Role of the Multidisciplinary Team

A recent industry sponsored survey has revealed some differing views between lung specialists and pathologists regarding the most appropriate biopsy methods for acquiring sufficient lung cancer tissue samples to test for biomarkers. Both groups of specialists agreed that acquiring a sufficient quantity of quality tissue remains a challenge in many cases. Where the specialists differed in their opinions was in their preferences for either FNA versus CNB for the best method for obtaining tissue for biomarker studies.

The survey also supported the role of the multidisciplinary team (MDT) in lung cancer care, with the majority of specialists reporting that they frequently consulted with their medical and radiation oncology colleagues either informally or as participants in multidisciplinary lung cancer tumour boards or conferences.[11] The role of the oncology MDT in tumour molecular profiling will continue to be relevant as more clinically relevant actionable genetic mutations are discovered and corresponding companion assays and targeted treatments are developed.[12]

It is important that cancer centres, pathology departments and molecular diagnostic laboratories develop effective communication strategies and standard operating procedures (SOPS) for the biomarker testing and reporting of results. Ideally, there should be designated clerical members in cancer centres and pathology departments who coordinate the requisitioning for biomarker testing and transportation of tumour blocks between pathology departments and molecular diagnostic laboratories.

Recommendations

1. **Canadian cancer centres, pathology departments and molecular diagnostic laboratories should collaborate in the development and implementation of clear strategies for biomarker testing.**
2. **Physicians involved in the acquisition and processing of tumour biopsies for biomarker testing should be members of multidisciplinary teams.**
3. **The optimum biopsy technique for obtaining**

an adequate tumour tissue sample for diagnosis and biomarker testing should be discussed within multidisciplinary teams.

4. **Pathology laboratories should have standard operating procedures for the processing, storage, and transportation of tumour samples that may be tested for biomarker.**

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EPIGENOME RESEARCH IN BRITISH COLUMBIA[1]

The BC Cancer Agency was part of a seven year project mapping the epigenome. The term "genome" refers to all the DNA within a cell, and the term "epigenome" refers to the chemical modifications of DNA and proteins that control the structure and activity of the genome. Epigenomes either cause the genome to stay healthy or develop diseases, such as cancer, because they produce the code for cellular properties that distinguish one cell type from another. A better understanding of the epigenome may assist in the design of new treatments. The project, called The National Institutes of Health (NIH) Roadmap Epigenomics Program, provides a core set of data, methodology and infrastructure for studying the role of the epigenome in human health and disease. The original goal was to map 25 normal reference epigenomes, but new technology allowed the team to produce 111 highly detailed maps on how the epigenome varies and operates in different settings.

The Roadmap Epigenomics Program was the first large-scale epigenome mapping initiative in the world, and has inspired similar mapping efforts, which are united by the International Human Epigenome Consortium (IHEC). The IHEC aims to coordinate the production of at least 1,000 human epigenome maps.

Just as the Human Genome Project provided a map of the genes of the human genome, the Roadmap Epigenomics Program offers a resource for understanding how our genetic blueprint is interpreted in different cell and tissue types. The next step will be to map the epigenetic profiles of individuals to understand more about how they vary from person to person and to establish causes between any of these "epigenomic marks" and disease.

IHEC encompasses the Canadian Epigenetic and Environment and Health Research Consortium (CEEHRC), and aims to coordinate the production of at least 1,000 human epigenome maps. All IHEC data is available for use by researchers from around the world, with the ultimate aim of improving human health through a better understanding of disease prevention and potential therapeutic options.

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THEN AND NOW

SOME PROGRESS, BUT ...

BY COLLEEN SAVAGE

CACC began its inter-provincial comparisons of key indicators more than a decade ago, with an early focus on screening programs, wait times and the allocation of prevention research dollars. Over time, other topics of interest were added, such as access to diagnostics (PET scans) and drugs and numerous fields in the organization of care, including the creation of rapid diagnosis centres, secondary prevention programs, cancer care in smaller communities and supportive care. Not every topic is covered in every Report Card, so it is time for an update on two of them: wait times and screening.

WAIT TIMES

In 2003, a year before the Health Accord that motivated provinces to care about wait times, CACC reported on complete disarray in the ability or interest of provinces to capture such data, let alone report any of it.[1] Only five provinces were able to respond to the CACC data request and one year later only four could offer data.

CACC found no common definitions of what constitutes a wait, no commonality in the types of data elements being tracked by the provinces – if any – and widespread obfuscation. Not one province was meeting the two week wait limit for radiation therapy recommended by the Canadian Association of Radiation Oncologists, although BC had created its own standard (four weeks) and claimed to be meeting it, overall. Elsewhere, standards or targets for waits were said to be impossible.

Then the 2004 Health Accord kicked in and waiting times became a priority. The Canadian Institute for Health Information (CIHI) was the designated home for data. The Wait Time Alliance (WTA) was formed the same year and began publishing annual reports in 2005.

Provinces received most of the $5.5 billion federal fund for wait times reduction that year, with a requirement that the five priority areas would see significantly reduced waits by 2007.[2] The only category for cancer was the wait for radiation therapy. The Accord expired in 2014 and has not been replaced.

Progress in the data collection, cooperation of provinces, and public reporting are demonstrated in the contents of Tables 1 and 2. These two tables give reason for both optimism and gloom regarding the willingness of provinces to monitor and be monitored. Information gaps might be caused by workload and technical problems that could be temporary; or there is a continuing pattern of reluctance across the provinces.

To determine which position is more realistic, a check on the annual reports from CIHI and WTA between then and now is revealing.

Just before the 2007 deadline, WTA was writing that provinces were not reporting radiation wait times based on the terms set by their health ministers in 2005 and were meandering about when a wait starts. "We see few attempts to rectify this situation and we remain very troubled by this. Canadians expect and deserve better."[3]

When data for the year end of 2007 were released,[4,5] for the first time every province was included. The provinces continued to use different time frames for when a wait starts and different methods of reporting (median, percentage seen within a target period, or a range of time periods applicable) and different blocks of months/years represented by their data. Every province reported they had achieved and even over-achieved on the four week target.

By 2007, CIHI was routinely reporting on wait times for an oncology appointment, cancer surgery and chemotherapy with data from only three, two and four provinces

Table 1 Wait times for 2002

Source: Report Card 2003-04, Cancer Advocacy Coalition of Canada

Data were collected by a survey sent to all provinces. The full report for this selected year and for other years can be found on the CACC website. Wait time feature articles were published in all the Report Cards between 2003 and 2006

Province	Wait Times in Days					
	SYSTEMIC THERAPY			RADIATION		
	Breast	Prostate	Lung	Breast	Prostate	Lung
NL	30	17	21	53 to 60	51 TO 58	34 to 41
PEI	14	6	5	73	N/A	21
NS	N/A			33		
NB	N/A			N/A		
QC	N/A			N/A		
ON	73			63	76	23
MB	"No wait except for more common cancers"			28 to 35		
SK	N/A			N/A		
AB	N/A			N/A		
BC	N/A			31	31	19

Table 2 Wait times for 2014

Source: Time to Close the Gap, Report Card on Wait Times in Canada 2014, Wait Times Alliance

Grading shows the per cent of population treated within the benchmark.
A+ = 90-100%,
A = 80-89%,
B = 70-79%,
C = 60-69%,
D = 50-59%,
F = less than 50%.

** all body sites combined.*

? Province does not report these wait times.

Province reports these wait times but not in a manner that WTA can grade.

Province	Wait Time Grades Based on Government and WTA Benchmarks 2014					
	Radiation therapy	From referral to consult *	From decision to treat to start of treatment *	Breast	Prostate	Lung
(Benchmark)	4 weeks	14 days	14 days	14 days	14 days	14 days
NL	A+	?	D	?	?	?
PEI	A	A	D	?	?	?
NS	A+	B	B	B	B	B
NB	A+	?	?	?	?	?
QC	A+	?	✍	?	?	?
ON	A+	A	A+	A+	A	A+
MB	A+	?	B	S	F	B
SK	A+	✍	A	?	?	?
AB	A+	D	B	?	?	?
BC	A+	?	B	?	?	?

respectively and the usual variety of reporting methods that make comparison impossible. By 2010, WTA was tracking the waits from referral to consultation and from consultation to treatment, and Table 2 shows the five categories now reported annually.

In 2014 CIHI announced the provinces have adopted a common approach to measuring wait times for cancer surgeries for breast, prostate, colon-rectal, lung and bladder.[6] This initiative does not yet include any benchmarks, but a few provinces have guidelines that set out the stage of cancer and other factors to be considered urgent. A common timeframe for the wait has been adopted, which is the time between the date of booking and the date of surgery.

For this very first report on the new approach to cancer surgery waits,[6] the shortest waits were for breast cancer: half the patients were treated within 17 days and 90 per cent treated within 42 days. The longest waits were for prostate cancer at 37 days and 85 days for the 50th and 90th percentiles. For bladder, lung and colon-rectal cancer surgeries the rates were similar: 18 to 24 days for the 50th percentile and 44 to 59 days for the 90th.

Achievements

- Every province meets the four week target wait for radiation therapy with an A or A+, meaning 80 to 100 per cent of all cancer patients are seen within the target time frame.
- Provinces report at least some wait times on their own websites; CIHI and WTA both publish comprehensive reports annually on a wide range of categories.
- Improved data collection and reporting are notable across the country, compared to 2004. Instead of averages, medians, ranges and estimates, the provinces now provide medians, 50th and 90th percentile waits.
- The original five areas of reporting required by the 2004 Health Accord included only radiation therapy as a cancer measure. CIHI and WTA now report on a wider range of cancer services and waits.
- The new effort to measure waits for cancer surgeries is encouraging. Hopefully the provinces can work from their existing guidelines and move toward establishing one common set of benchmarks reasonably soon.
- Ontario ranked at the bottom of the pack in 2002 and now leads all provinces in reducing wait times, although progress on systemic therapy waits has stalled over the past four years, according to WTA.[7]

Disappointments

- Variations across the country and even within provinces remain disconcerting.
- The WTA continues to point out that current reporting on wait times — from referral to first consult and then from the decision to treat to the start of treatment — exclude the entire block of time spent in waiting for test results, or scheduling diagnostic imaging.[6]
- Most provinces do not report on the wider range of wait time measures sought by WTA. In 2014 only NS and ON reported on all the newer categories of cancer waits identified by WTA; NB and QC reported on none of them, the other provinces were somewhat scattered but four provinces reported on the all-body-sites-combined wait time from referral to consult and eight of 10 provided answers on the all-body-sites-combined wait time from decision to treat to start of treatment.

SCREENING

In 2005 and 2006,[8,9] CACC reported uneven uptake of breast cancer screening programs, peaking between 50-60 per cent of the target population in three provinces and dropping below 30 per cent in three provinces, with the other four provinces in between. At the time, programs complained about inadequate integration with the cancer system, lack of staff, information systems, core funding and even a limited capacity to handle any new cancers that might be caught.

Not all mammograms are for screening purposes, not all screening is done for women within the target age range of 50-69 and many are privately sought outside the organized program. Ten years ago, the CACC survey was exclusively for activity within the organized screening program of the cancer agency or department. Patients who directly accessed a mammogram outside that program were not captured, because no province could verify how much of that activity was for screening.

When these articles were first published, there were no screening programs for colorectal, lung or prostate cancer, although the mortality rates for each were much higher than breast cancer. Screening for colorectal cancer is now in place or in development across the country; for lung cancer the first steps to plan screening are barely begun and for prostate cancer arguments about PSA testing continue, with no sign of resolution.

Breast cancer programs were mostly well established and encompassed all the features necessary for organized screening – although in some cases these features were in development. AB for example, did not introduce its province-wide screening program until 2008. The essential elements include proactive recruitment of the target population, active follow-up and referral, call-backs every two years and reliable data collection. A host of other detail is involved, too elaborate to list here.

CACC had also asked about quality assurance, meaning:

1. is there a formal recall system in place for an abnormal result?
2. is there a written guideline to move a patient to the investigative phase after an abnormal result? and
3. if a cancer develops in the interval between screens, is it flagged to determine what happened with the first test?

For each of these questions, respectively, nine, eight and seven provinces answered yes.

Table 3 **Breast cancer screening 2001-04**

Source: Report Card on Cancer in Canada 2006, Cancer Advocacy Coalition of Canada

Note: Activity represents a mammogram by an organized screening program within the previous two years, except NL. Target populations are generally women aged 50-69 although BC and ON accepted women up to age 74 and 75 respectively. BC, AB and NS accepted women from age 40 and MB wil cover all women on referral. The AB province-wide program did not begin until 2008 and reporting was very limited.

Province/ Territory	Year Program Initiated	Compliance in 2001-02	% of Target Population Screened in 2004
NL	1996	23.2%	30% in 1 yr
PEI	1998	43.5%	N/A
NS	1991	34.0%	45%
NB	1995	51.9%	55%
QC	1998	43.7%	48%
ON	1990	22.4%	26%
MB	1995	48.5%	51.4%
SK	1990	53.0%	approx 57%
AB	1990	12.0%	N/A
BC	1988	50.7%	48%
YT	1990	N/A	N/A
NWT	2003	N/A	N/A

Table 4 **Percentage of eligible women (aged 50-69) reporting a screening mammogram in the last two years - 2008 and 2012 reporting years**

Source: The 2014 Cancer System Performance Report, Canadian Partnership Against Cancer.

Note: Activity represents all self-reported mammograms for screening within the previous two years, both inside and outside organized screening programs.

Province	2008	2012
NL	70.3	72.6
PEI	57.6	59.5
NS	71.0	68.1
NB	74.7	72.1
QC	74.0	74.9
ON	73.0	73.5
MB	70.5	74.1
SK	73.0	63.3
AB	73.6	73.6
BC	67.7	70.2
YT	64.7	57.4
NWT	67.2	66.8

In short, the breast screening programs knew what to do and how to do it but felt constrained.

Tables 3 and 4 show screening for the target population, which is a larger population in Table 3 where the provincial variation in eligible age groups is noted. Table 4 shows only the 50-69 age group.

In 2011 the Public Health Agency of Canada (PHAC) released data on the participation in organized breast screening programs for 2005 and 2006.[10]As a follow-up to the CACC report for 2002 and 2004, it tracks closely and shows the early trend of increased participation as seven provinces instead of four hover around 50 per cent uptake among women aged 50-69. AB was again artificially low because their province-wide program did not yet exist, ON reported 32.4 per cent, NL 35.4 per cent and NWT 26.3 per cent. The national average was 40.0 per cent but when data were compiled for a 30 month period, the national average rose to 43.9 per cent, with proportionately higher rates for each province.

PHAC also included information on the utilization of mammography outside the organized breast screening programs for 2005-2006. Only seven provinces were captured in this material, leaving out NB, NS and PEI. At that time, all mammograms outside the organized program were counted as screening, which produces a misleading result when looking only for screening, but indicates activity that would have included some screening. There was predictably high outside use in AB at 53.7 per cent of all mammograms in the province, followed by ON at 31.1 per cent and NL at 28.5 per cent.

PHAC'S 2013 report,[11] (for 2007-2008) shows a national participation rate for organized programs of 45.9 per cent. Seven provinces reach 50 per cent or more, with PEI leading at 64.1 per cent. ON and NL grow to 40 per cent participation of the target population. These are slow improvements, still far short of everyone's agreed target of 70 per cent.

Statistics Canada captures self-reported mammography and can separate screening from other reasons but does not do so in the public materials on their website; therefore these cannot be regarded as screening reports. CPAC does obtain that breakdown and provides a combined total screening percentage in their system performance reports.

The retention rate for participation in screening is reported by PHAC (2007-2008)[11] as consistently "close to" 70 per cent over a period of years, with individual programs ranging from 55.7 to 81.8 per cent (provinces not identified). Patterns of retention show that after the second screen, women are more likely to continue.

Eligibility for a publicly funded screening mammogram has expanded over the years. Ten years ago BC and ON would welcome women up to age 74 and 75, while BC, AB and NS would permit a screen for women aged 40-49 with a physician's referral. By 2008, every jurisdiction but NL and SK would accept women aged 40-49 on referral and all but PEI would screen women over the age of 75.[10]

By 2012 PEI had the highest rate of screening for women over age 75, at 40 per cent and the lowest rate was in NB at 22.4 per cent.[12]

Achievements

- Provinces routinely provide screening outside the minimum recommended age range of 50-69.
- Between 2008 and 2012, breast cancer screening rates remained relatively stable in most provinces and territories.[13] There have been declines that rebounded and increases that diminished but largely, in spite of the aging population and greater demands on the screening programs, the rates are being maintained.

Disappointments

- Reporting on participation rates has been uneven across all the organizations that have attempted it. Current national information on the volume of breast screening delivered within organized programs and outside those programs is no longer readily available. Some provinces do track this point; for example, an ON report[14] for 2009 shows only 42 per cent of the target population was screened by the organized program. At the same time, the combined inside+outside screening was reported as 72-73 per cent for the same age group.[12] If there are issues to resolve in women's preferences for the provider of the mammogram, surely the first step is to define the problem as precisely as possible.

SCREENING + WAITS

The wait time target for a diagnosis after an abnormal screen is five weeks if no tissue biopsy is needed, or seven weeks if it is needed.

In the CPAC report for 2011, shown in Table 5, nine provinces plus the NWT come in well under the five week target for the median wait time when no tissue biopsy is needed.[15] Data were not available for ON and YT. PEI and the NWT show the longest median wait at four weeks and four provinces, BC, SK, MB and NB, have the shortest median waits, between two and three weeks.

When presented as the 90th percentile of patient waits, not one province meets the five week target, although NB is best at 5.3 weeks, NS and SK are similar at approximately six weeks, BC, AB, MN and PEI hover around eight weeks. NL and NT both hit 10 weeks while QC shows 10.9 weeks.

Overall, in descending order of success, NB, SK, ON, NS, MB and BC all meet the target wait time for 80-89 per cent of women aged 50-69. Even at the lower end of this scale, QC and PEI reach 64.4. and 68.1 per cent of patients seen within the five week target and AB reaches 70.9 per cent.

On the surface, the results might appear similar for the waits encountered when a tissue biopsy is necessary.[15] Seven provinces and the NWT meet the seven week target for median wait times, with the best results in NB, AB and SK showing 5.3, 4.9 and 4.5 weeks. The NWT shows 3.0 weeks,

which is lower than their performance without a tissue biopsy, indicating other factors are at play. MB starts to need eight weeks although without that biopsy they only needed 2.4 weeks. Only QC fails by the same magnitude, but the time gap between their no-biopsy-needed performance and biopsy-needed is smaller than the gap in MB.

The percentage of women diagnosed within seven weeks ranges from the highest in AB and SK at 74.2 and 75 per cent, down to the lowest, at 40.5 per cent in MB and 41.2 per cent in QC. All of the East coast, plus BC and ON are similar in the high-50 and low-60 per cent range. These rates show a slow but steady improvement over previous years.

From the same CPAC report, the 90th percentile wait time for a diagnosis requiring tissue biopsy indicates just how erratic this part of the activity can be. Starting from a modest 9.6 weeks in PEI, the numbers leap. AB, SK, and NB all show the 90th percentile between 12 and 13 weeks. NS needs 13.7 weeks, BC needs 14.9 weeks, MB needs 16.4 and QC needs 17.6 weeks.

What does this mean for patients? Across the provinces, between 25 and 59.5 per cent of new breast cancer cases detected from screening and followed by tissue biopsy are not being diagnosed within seven weeks and some could wait as long as three or four months for a diagnosis. Further research should examine why the need for tissue biopsy generates such extended delays.

From the no-biopsy-needed data it is clear that the follow-up referral process to move the patient to a consult is efficient in most parts of the country. Somewhere, the notion that tissue biopsy could be added to the process and completed within two weeks seemed rational. However, when that task is separated from the aggregate wait (in Table 5), only PEI, SK and AB can achieve that two week goal, even as a median. (NWT does too, but their numbers are outliers.)

There can be many reasons for extended waits, including distance from the follow-up appointment, language barriers, complicating health issues, and whether the biopsy is invasive (surgical) or not. For example, PHAC reports that in 2008, 15 per cent of cases required surgical biopsy, down from 24.5 per cent only four years earlier.[11] These were more common in younger patients and in first-time participants in an organized screening program.

Certainly not every delay is caused by a failure of the health system. But certainly, some of it is.

Ultimately, what these data show is that wait times for a diagnosis remain inconsistent and often far too long, causing unnecessary torment and delaying the start of treatment.

Table 5 **Wait times for diagnosis following breast cancer screening, 2011**
Source: Canadian Partnership Against Cancer, www.systemperformance.ca[15]

Province	Median Wait Between Abnormal Screening Result and Diagnosis (weeks)		Median Wait Time Attributable To the Need for a Biopsy Before Diagnosis (weeks)
	Without tissue biopsy target is 5 weeks	With tissue biopsy target is 7 weeks	
NL	3.0	7.0	4.0
PEI	4.0	6.0	2.0
NS	3.1	6.6	3.5
NB	2.1	5.3	3.2
QC	3.9	8.1	4.2
ON	-	-	-
MB	2.4	8.0	5.6
SK	2.5	4.5	2.0
AB	3.9	4.9	1.0
BC	2.7	6.0	3.3
YT	-	-	-
NWT	4.0	3.0	-1.0

OPPORTUNITIES

1. **Wait times are still reported from the perspective of the health system rather than recognizing that patients experience multiple delays beyond the official waits being compiled. It is time to work on a model that will capture the true patient journey with all its different waits.**
2. **While it is important to know the overall participation rates for breast cancer screening, it is relevant to capture and report on the amount achieved by organized screening programs and compare that to the volume of opportunistic screening outside those programs.**
3. **Waits for a diagnosis require further research. Most provinces easily meet the first (five week) target for a diagnosis after abnormal screening. However, a high percentage of all those needing tissue biopsy fall seriously outside the target (seven week) wait.**

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September 16, 2004
A 10-year plan to strengthen health care

First Ministers agree that access to timely care across Canada is our biggest concern and a national priority. First Ministers have come together and agreed on an action plan based on the following principles:

- universality, accessibility, portability, comprehensiveness, and public administration;
- access to medically necessary health services based on need, not ability to pay;
- reforms focused on the needs of patients to ensure that all Canadians have access to the health care services they need, when they need them;
- collaboration between all governments, working together in common purpose to meet the evolving health care needs of Canadians;
- advancement through the sharing of best practices;
- continued accountability and provision of information to make progress transparent to citizens; and
- jurisdictional flexibility.

First Ministers Meeting on the Future of Health Care 2004
http://www.hc-sc.gc.ca/hcs-sss/delivery-prestation/fptcollab/2004-fmm-rpm/index-eng.php

Coverage of Genotype-Directed Therapy for Non-Small Cell Lung Cancer in Canada: An Update

BY JAIME MCDONALD, BSCPHARM, PHARMD

Introduction

Previous editions of the Report Card have reported on the sporadic reimbursement of companion diagnostic tests for oral tyrosine kinase inhibitors (TKIs) for non-small cell lung cancer (NSCLC). As of the writing of this article, it is our pleasure to report that for the therapies in question, notably crizotinib (Xalkori), afatinib (Giotrif), erlotinib (Tarceva), and gefitinib (Iressa), genotype testing for anaplastic lymphoma kinase (ALK), in the case of crizotinib, and epidermal growth factor receptor (EGFR) mutations is now available to all eligible patients free of charge. However, the mechanism for funding the costs of testing still varies across provinces.

Funding of EGFR and ALK Genotyping

Genotyping for EGFR mutations is now considered standard of care in patients with NSCLC and is publicly funded in all provinces. However, this is not necessarily the case for newer agent coming to market. Traditionally, albeit not exclusively, the manufacturer of the pharmaceutical or companion diagnostic in question has taken on the responsibility of establishing genotyping networks via various pilot programs and laboratories. To make matters worse, these drugs are often launched to market without long-term plans for coverage of testing.

In the case of EGFR, funding of these networks has gradually transitioned from patchwork coverage (via the pharmaceutical industry, manufacturers of companion diagnostics, cancer organizations, interprovincial agreements, etc.) to provincial coverage.[1] At one point in the lifespan of erlotinib and gefitinib, patients were even paying for EGFR testing out of their own pocket.[2] But, as of September 2014, the province of Ontario became the final province to offer provincial funding for EGFR testing.[1] However excellent the news, this announcement comes nearly 10 years after Health Canada's initial approval of erlotinib and gefitinib for NSCLC.

This start-up approach is likely unsustainable for several reasons. Under relatively few circumstances in medicine are pharmaceutical companies, or even patients, responsible for diagnostic costs, nor is their willingness to fund diagnosis likely to continue. Most importantly, an ethical dilemma emerges where the pharmaceutical manufacturer, who is set to profit from use of the drug, is funding the definitive test to determine a patient's eligibility. Needless to say, the convoluted path to provincial coverage for EGFR testing must be streamlined if we are to keep up with the flood of new drugs entering the market. The number of genotype-directed agents in clinical trials has nearly quadrupled in recent years,[3] therefore a systematic approach to coverage for testing must be developed before we reach critical mass.

Testing for ALK fusions, via both immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), is funded in each Canadian province as is crizotinib, the companion oral TKI. The territories usually have health agreements with other provinces (British Columbia, Alberta or Ontario), therefore testing will be performed for these patients at an out of province site. The approval of crizotinib through the pan-Canadian Pricing Alliance was dependent on simultaneous coverage of ALK testing,[4] representing a novel approach to coverage similar to the drug approval process adopted by the Food and Drug administration (FDA) in the United States.[5] The source of funding and type of ALK genotyping still varies across provinces,[1] with Abbott Canada, makers of the Vysis FISH assay, currently funding the cost of FISH testing. This approach provides more security that patients will be eligible for both ALK testing and subsequent treatment with crizotinib without unnecessary delays, representing a definite improvement over the path taken by EGFR testing.

In August 2014, the FDA finalized their guidance for industry that now requires the simultaneous submission and approval of companion diagnostics for genotype-directed therapies; a drug is generally not approved without the simultaneous approval of its companion diagnostic.[5] As companion diagnostics are considered class III medical devices, their approval is required by Health Canada, however these submissions, reviews and approvals do not always occur in tandem with the drug. Although the American model of healthcare reimbursement for both test

Canadian cancer patients find themselves once again in a postal code lottery of drug coverage.

and drug differs significantly, the take-home message is that co-development and approval of drug and diagnostic will ideally expedite time to approval, ensure immediate availability of testing, promote standardization of methods across testing centers, and permit universal access to the same diagnostic testing methods used in clinical trials.

Under the new FDA approval process, product labeling regulations specify that the safe and effective use of the drug can only be guaranteed when used in conjunction with the approved diagnostic.[5] Use of a specific test is not currently a mandatory requirement of Health Canada however, general suggestions for specific testing are usually recommended for the product monograph. Medico-legally, these suggestions may be left open for interpretation and therefore may vary according to site and even by product monograph. As an example, the product monograph for vemurafenib (Zelboraf), an oral therapy for metastatic melanoma targeting the BRAF V600E mutation, simply states that a validated test must be used.[6] However, the product monograph for crizotinib (Xalkori) lists the specific FISH assay (Vysis) to be used.[7]

Provincial Drug Coverage

Under the current model of Canadian funding, it is possible that a drug may be approved for coverage on a provincial formulary without guaranteed access to companion diagnostic testing. However, it is becoming evident that the opposite is also occurring. While access to diagnostic genotyping is improving, patients now have access to testing without the guarantee of drug coverage. Such is the case for crizotinib in the Northwest Territories, Yukon and Nunavut. Afatinib, which differs from erlotinib and gefitinib in that it irreversibly inhibits EGFR tyrosine kinase and HER2, was approved for the first-line treatment of NSCLC by Health Canada in November of 2013. A year later, most provinces were still debating coverage, while some had already

Table 1 **Provincial coverage of targeted therapies for NSCLC**
Source: Information retrieved from individual provincial formularies

Province	Crizotinib	Afatinib	Erlotinib	Gefitinib
NL	✓	X	✓	X
PEI	✓	X	✓	X
NS	✓	✓	✓	X
NB	✓	✓	✓	X
QC	✓	X	✓	✓
ON	✓	✓	✓	✓
MB	✓	✓	✓	✓
SK	✓	✓	✓	X
AB	✓	X	✓	✓
BC	✓	✓	✓	✓
NU	X	X	✓	X
NWT	X	X	✓	X
YT	X	✓	✓	✓

approved its use (Table 1). This is a clear example of how the lag-time to coverage of new treatments can differ greatly, depending on the province of residence. For rapidly progressive cancers, such as NSCLC, any delays to effective treatment can be costly.

In March 2014, Ontario approved afatinib for coverage under the special access program[8] and now British Columbia does the same. Since then, patients in provinces not offering the drug could theoretically have moved to another province, waited for provincial health coverage and received the drug, all before their home province listed the drug on formulary. In a country that promotes universal healthcare, this should not be necessary.

As outlined in Table 1, gefitinib coverage is also sporadic across Canadian provinces while erlotinib is available ubiquitously. Clinical experience and evidence for efficacy likely favor erlotinib,[9] however the National Comprehensive Cancer Network guidelines list gefitinib as interchangeable with erlotinib[10] and there is limited evidence that the former may be better tolerated.[9]

This problem is not unique to NSCLC. Such is the case for vemurafenib, an oral BRAF kinase inhibitor used in the treatment of melanoma. Testing for the BRAF V600E mutation, which the drug targets, is available free of charge to every Canadian.[11] However, Prince Edward Island has yet to list the drug on its provincial formulary.

Owing to the cost of the oral TKIs, which is about $90,000 per year for crizotinib,[12] they are available almost exclusively through special access programs. Canadian cancer patients find themselves once again in a postal code lottery of drug coverage.

Summary

It is clear that some work remains to be done in terms of optimizing access to oral genotype-directed therapies in NSCLC. The first barrier to treatment is timely access to genotyping. Thankfully, for the agents in question, funding is no longer a short-term issue. However, this is not necessarily the case for other disease states with new molecules entering the market. Therefore, it is imperative that provincial governments and Health Canada strike a balance in terms of approval, standardization and funding of testing.

The final frontier is ultimately ensuring that once a patient is deemed eligible for treatment they do not experience treatment delays due to drug coverage.

Recommendations

1. **The funding of diagnostic genotyping for targeted chemotherapies should not be sustained by private industry or third parties. As is the standard of care in medicine, the funding of diagnostic medicine should remain public.**
2. **The American model of co-development and approval of a drug and its companion diagnostic should be considered by Health Canada in order to expedite access to standardized testing across Canada.**
3. **Provincial approval of funding for both drug and companion diagnostic should occur simultaneously.**
4. **Provinces should make every effort to follow similar timelines for formulary review to avoid interprovincial discrepancies in drug coverage.**
5. **Exceptional use criteria for genotype-directed therapies should be evidence based and reviewed regularly to reduce interprovincial differences in coverage.**

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Recommendations for Change:
Reimbursement and Delivery of Take-Home Cancer Medications in Ontario and Atlantic Canada

BY ROBERT BICK

Introduction

In British Columbia, Alberta, Saskatchewan, and Manitoba, cancer patients have fully funded access to anti-cancer treatments taken at home. Unfortunately, patients in Ontario and Atlantic Canada face significant discrimination when it comes to accessing take-home cancer treatments. In these provinces, if a cancer patient requires an intravenous (IV) drug that needs to be administered in a hospital setting, and it is listed on the provincial formulary, that drug will be 100 per cent funded by the provincial government. However, if the provincially-listed and best-chance cancer drug is something taken outside of hospital (oral or injectable), the patient and family may face significant financial hardship in paying for all or part of their drug costs.

CanCertainty

The CanCertainty Coalition, an unprecedented unification of 35 cancer patient groups, physicians and health care charities from across Canada, has been working to compel governments in Ontario and Atlantic Canada to provide fair and equal access to cancer therapies taken at home. Our position is clear: Cancer's not fair, but accessing treatment should be.

Our hard work is starting to pay off. Change is now being considered in at least two provinces: Nova Scotia and Ontario. In autumn 2014, the CanCertainty Coalition met with Nova Scotia Health Minister Leo Glavine on the issue of funding take-home cancer treatments. Following that meeting, the minister made it clear to CanCertainty, and to multiple provincial media outlets, that his government will work to address this discrepancy in cancer care in Nova Scotia. The CanCertainty Coalition will remain vigilant in ensuring the Nova Scotia government addresses this very important issue.

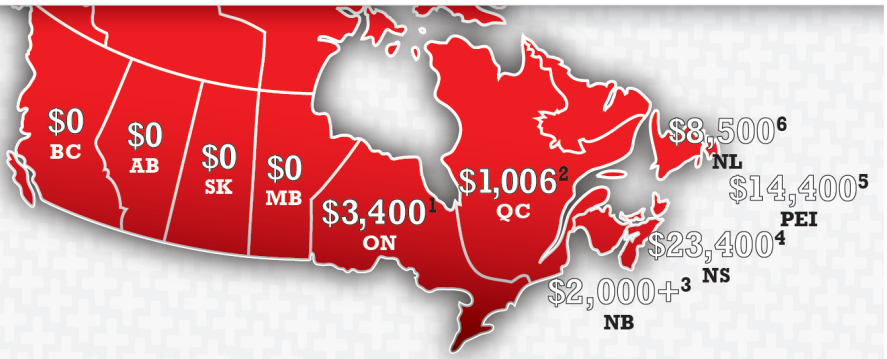
In Ontario, after the Coalition launched the Ontario-focused component of its public awareness campaign in spring 2014, we met with then Ontario Minister of Health and Long-Term Care, Deb Matthews. At that meeting, the minister committed to having the issue of take-home cancer drug funding considered at a Cancer Care Ontario (CCO) policy planning and consultation session with stakeholders. That session, Think Tank: Enhancing the Delivery of Take-Home Cancer Therapies in Ontario, took place on May 8, 2014 in Toronto. Participants included oncologists, pharmacists, nurses, patients, drug access navigators, cancer researchers, pharmaceutical industry representatives, along with government and cancer agency representatives from Ontario and other provinces. Patients were represented at the session by CanCertainty and members of CCO's Patient and Family Advisory Council.

The participants at the session examined the current state of access and delivery for take-home cancer drugs in Ontario and explored opportunities to enhance safety, quality and access for patients. Analysis and review revealed that Ontario's current system for take-home cancer medications lacks comprehensive data collection and sufficient oversight to inform quality improvement processes. System integration weaknesses were examined and linkages between primary care, community pharmacy and hospitals/cancer centres were found to be not sufficiently developed to facilitate responsive and timely cancer care. Safety standards for take-home cancer medications were determined to be needed. The issue of equitable access was examined from multiple perspectives. Take-home cancer drug models outside Ontario were examined and contrasted with Ontario's system.

Along with strong, actionable recommendations to enhance quality and safety, there was general agreement among all participating stakeholders that Ontario must resolve inequitable cancer drug funding and move towards universal funding of take-home cancer medications.

COST OF SAME TAKE-HOME CANCER TREATMENT BY PROVINCE

CANCERTAINTY
EQUAL AND FAIR CANCER TREATMENT FOR ALL



CANCER PATIENTS IN ONTARIO AND ATLANTIC FACE SIGNIFICANT OUT OF POCKET COSTS

[1]Ontario
$3,400 Trillium Deductible
(4% of household net income)

[2]Québec
$1,006 Maximum Individual Deductible

[3]New Brunswick
$2,000+ Annual Insurance Premium per adult, $0 annual deductible, $30 copayment per prescription

[4]Nova Scotia
$23,400 Deductible, $17,550 Copayment, NS Family Pharmacare pays 100% after $29,250

[5]Prince Edward Island
$14,400 Family Deductible under Catastrophic Drug Program = 12% on household income > $100,000

[6]Newfoundland & Labrador
$8,500 (10% Net family income)
Out-of-pocket limit set at 5%, 7.5%, or 10% of net family income

CANCER IS CANCER.
TREATMENT IS TREATMENT.
WHEREVER IN CANADA YOU LIVE.
WWW.CANCERTAINTYFORALL.CA

ASSUMPTIONS

1. Based on total household income of $120,000 ($85,000 net).
2. Oral cancer medication costing $6,000 per month for 12 months.
3. No private insurance.

SOURCES
http://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_trillium.aspx
http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/amount-to-pay-prescription-drugs.aspx
NS Family Pharmacare Calculator: http://novascotia.ca/dhw/pharmacare/family-calculator.asp
NS Family Pharmacare Deductibe must be paid in FULL before patients start to pay "only" the copay amount of 20% per prescription.
NLPD Assurance Plan via http://www.parl.gc.ca/Content/LOP/ResearchPublications/prb0906-e.htm
New Brunswick Drug Plan Premium: http://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/NBDrugPlan/Premiums.html
http://healthpei.ca/catastrophic

Our position is clear: cancer's not fair, but accessing treatment should be.

Table 1 **Potential areas to enhance Ontario's delivery mode for take-home cancer medications**
Source: Cancer Care Ontario Think Tank Proceedings Report, 2014

Dimension	Suggested Enhancements
Quality and Safety	• Provide comprehensive, multidisciplinary, standardized patient education. • Use an electronic method of prescribing with a standardized template. • Establish guidelines for safely prescribing, dispensing and handling take-home cancer medications. • Develop patient and provider tools to monitor adherence. • Create an infrastructure for patient support and side-effect management. • Utilize an integrated error reporting system. • Provide specialized education, training and support to cancer care providers.
Reimbursement and Distribution	• Resolve inequitable cancer drug funding. • Simplify complex reimbursement processes to support ease of access to timely, integrated quality care. • Identify best practices for value-based reimbursement. • Determine the best drug distribution chain for Ontario patients.
Information Management/ Technology	• IM and IT solutions should support continuity of care. • Simplify the system and reduce its administrative burden. • Create a system for robust data collection at all points of care.

In late December 2014, CCO issued a proceedings report that provided an overview and summary of the think tank held on May 8, 2014. The report is available on the CanCertainty website here: www.CanCertaintyforall.ca.

The impressive group of stakeholders assembled for this consultation session generated an excellent set of recommendations for the minister and CCO to address change in Ontario's delivery model for take-home cancer medication. Table 1 summarizes the recommendations generated by participants on how to improve Ontario's current model of delivering take-home cancer medications:

As acknowledged in the report, new take-home cancer drugs that are moving treatment from chemotherapy clinics to home settings introduce new challenges in providing equitable, safe, high-quality and accessible systemic cancer treatment. This report can essentially be regarded as an action plan for the minister and CCO to begin the task of transforming a fractured system of delivery and reimbursement of take-home cancer drugs and addressing, immediately, the inequities that exist in cancer drug access.

The current Ontario Health Minister, Dr. Eric Hoskins, has, of late, been very vocal about two themes: improving access to pharmacare, and strengthening community-based care. Fully funding access to anti-cancer treatments taken at home in Ontario would be an achievement in both of those categories and aligns perfectly with the Minister's "Patients First: Action Plan for Healthcare" (Feb 2015). The report from CCO's policy planning and consultation session provides the Minister with a clear way forward to begin achieving his vision for improved health care in Ontario, and providing fair and equivalent access to cancer medications.

While Canadians from coast to coast ponder the long-term prospect of National Pharmacare, cancer patients and their families urgently require health ministers in Ontario and Atlantic Canada to level the playing field in their respective provinces as a first step. Cancer treatment is cancer treatment. Whether administered in a hospital or at home, the funding mechanisms and reimbursement support at the provincial level must be one and the same.

Robert Bick is a health policy consultant specializing in drug access and reimbursement policy in Canada. He serves on the Board of Directors of Kidney Cancer Canada and is a co-Lead of the CanCertainty Coalition campaign (www.Cancertaintyforall.ca).

SUBSEQUENT ENTRY BIOLOGICS

The term subsequent entry biologic (SEB) refers to new drugs that are similar but not identical to an originator's biologic drug (the reference biologic). Biologics are a class of drugs manufactured from living organisms that cannot be synthesized and the complexities of the manufacturing process mean that every biologic product is unique.

Canadians have long been familiar with generic drugs and the routine substitution by pharmacists for a generic product instead of the brand name product. This is not the case with biologics, indeed Health Canada clearly states that an SEB is not interchangeable with the originator's product.

As patents expire on the first generation of biologics, subsequent entry biologics have started to enter the market. Health Canada operates under a guidance document,[1] not a regulation, which describes the submission and review process for SEBs. The SEB will be given the same chemical name, the International Nonproprietary Name (INN) as the original biologic; the brand name will differ but the INN for both biologics will be the same. This implies much more than similarity and has the potential to create confusion.

Quebec recently approved provincial funding for an SEB that is similar to Remicade (infliximab) and used in rheumatoid arthritis, spondylitis, psoriatic arthritis and chronic plaque psoriasis. Of note is that Remicade also has approved uses for other diseases but those are not included in the approved uses for the "new" infliximab (Inflectra). That is a notable detail since Health Canada's guidance document shows that extrapolation of indications will be considered for any SEB and could occur in the absence of rigorous clinical trials or substantive evidence of effectiveness.[1] Health Canada could permit any approved use of the original biologic to be assigned to the SEB, based on evidence that the SEB is similar enough to probably deliver similar outcomes in all the other indications. That evidence does not have to include clinical trials for the other indications. Indeed, stakeholders have pointed out that the limited clinical trials conducted for SEBs tend to be shorter, with earlier endpoints, since the objective is to demonstrate similarity, not equivalence or improvement in patient outcomes. This point alone is greatly disturbing to clinicians who expect very high standard of scientific evidence in drug approvals and who know that biologics cannot be perfectly replicated.

In Quebec, the December 2014 decision to permit – and require – pharmacists to substitute an SEB for an original biologic carries with it the requirement that patients be notified and if they choose the more expensive brand of infliximab the patient may pay the extra money to receive it. That encounter appears to be the only opportunity for choice, whether by the patient, the prescriber or the pharmacist. The prescriber can write "no substitution" on the prescription but must demonstrate "recognized therapeutic concerns" to prevent substitution. Effectively, the Quebec drug plan has created a status of interchangeability that is not recommended by Health Canada and will have unknown impact on patients. As all the provinces start to review SEBs and make decisions about how/if to fund them, the potential for this amount of substitution – for therapeutic equivalence – can become a significant challenge.

Among the concerns raised by stakeholders, such as BioteCanada, is a fear that Canadian physicians, pharmacists and patients are not well informed about SEBs and are ill-equipped to make the decisions they will face. BioteCanada recently released survey results of 427 prescribers from Alberta, British Columbia, Ontario and Quebec in which 41 per cent admitted they either had never heard of SEBs or could not define them. When these physicians were asked what message they receive from the fact that two products have the same non-proprietary name:

- 64 per cent believed the medicines are structurally identical,
- 62 per cent believed that either product would deliver the same results for a patient,
- 49 per cent believed the patient could be safely switched from one product to the other during the course of treatment,
- and 76 per cent believed the medicines are approved for the same indications.

Those responses hint at the complexity of the task ahead, to educate patients and health professionals, to seek more detail, rigor and transparency from regulators about the evidence for SEBs, and to offer choice to prescribers and patients.

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Great Innovations and Stubborn Disparities

Innovations

Prevention

Provinces are making an effort to reduce exposure to second hand smoke as well as ultraviolet light from tanning beds. In Ontario, 102 social housing providers have adopted no smoking policies which prohibit smoking in private and multi-unit dwellings.

Smoking on playgrounds, sports fields and restaurant and bar patios has also been banned in the province. This is good news as until now 12.8 per cent of Canadians aged 12 and older have reported exposure to second hand smoke in public places, well above the 6.3 per cent and 4.7 per cent reported in vehicles and homes respectively. Meanwhile, both PEI and Ontario have prohibited the use of tanning beds for minors.

Screening

The Canadian Medical Association released new recommendations on screening for cervical cancer. They strongly recommend not screening women less than 20 years of age and also strongly recommend screening 30-69 year old women every three years.

However there is still some uncertainty around the routine screening of women aged 20-24 and 25-29. Currently the recommendation is not to screen the 20-24 age group but to actively screen the 25-29 age group every three years. Nova Scotia appears to be one of the first provinces to adopt these new guidelines for cervical cancer screening.

Saskatchewan has made its screening program for colorectal cancer available province wide for the first time. Those aged 50-74 now have access to a paid for in-home test. Those who report being up to date in their colorectal cancer screening has increased in every province between 2008 and 2012, with the highest rates in Manitoba at 59.2 per cent, Ontario at 54.9 per cent, Alberta and Prince Edward Island at 50.3 and 50.1 per cent respectively.

Researchers in Manitoba and Alberta are working on blood tests that distinguish between aggressive and indolent prostate cancer, which could lead to more accurate prediction of when and how to treat the disease.

The Canadian Partnership Against Cancer released a framework for lung cancer screening. The consensus document includes numerous recommendations to the provinces on screening and clinical pathways, multidisciplinary approaches and setting quality standards for screening, diagnosis and treatment.

Staging

The staging initiative of the Canadian Partnership Against Cancer has published its first snapshot report on the stage of cancer at diagnosis, for nine provinces and expects to publish a more comprehensive report late in 2015. The snapshot report shows that the vast majority of breast cancer cases are diganosed at stage l or II, colorectal cancer is most commonly diagnosed at stage III and lung cancer at stage IV.

Personalized Medicine

The Personalized Medicine Partnership for Cancer was launched in Quebec and is focused on developing and delivering personalized medicine to cancer patients. It is a consortium of both public and private sector stakeholders.

Among the programs that will be implemented is one for the development and commercialization of biomarkers for lung, colon and breast cancer. This new organization joins many others in the rest of the country conducting extensive research into the possibilities of precision medicine.

Catastrophic Drug Plans

New Brunswick introduced its drug plan in two phases. Phase 1 began in May 2014 and includes different premium levels for plan members depending on gross income. There is a 30 per cent co-pay at the pharmacy up to $30 per prescription. Phase 2 will begin in April 2015 and will require all those without a private plan to join the New Brunswick Drug Plan. There is a stipulation that all private group drug plans must be at least as effective as the NBDP thereby creating a baseline of equality. As a result, those with private plans will not be included in the NBDP.

PCPA

Established in August 2010, the Pan-Canadian Pricing Alliance conducts joint provincial/territorial negotiations for brand name drugs in Canada. As of June 30, 2014 the PCPA had completed negotiations on 19 brand name cancer drugs while two are currently underway and one cancer drug was recommended to be negotiated by each province/ territory individually. Four cancer drugs will not be negotiated collectively or individually. The negotiations by PCPA are led by

Ontario and Nova Scotia while Quebec and Nunavut are not participating. The remaining provinces that are participating are not bound by the final negotiations or conclusions of the PCPA.

The Fraser Institute reports that delays in the federal regulatory review and provincial reimbursement approval in five of the top 24 oncology drugs could have negatively affected more than 5,000 patients resulting in the potential loss of survival of 1,696 patient years. Further, this loss of extension-of-life has cost between $339.2m and $559.6m.

Wait Times

The Cancer Patient Journey initiative in Manitoba, called In Sixty, is an example of a program aimed at improving cancer patient wait times by increasing efficiencies and improving primary care, diagnostics, specialty care, IT support and communication.

Disparities

Organization of Care

The Health Council of Canada reported that compared to 10 years ago when the 2003 First Minister's Accord and the 2004 10-year health care plan were released, there was an increase in health care spending from $124B to $207B. However this increase has yielded disappointing results, especially when compared to other high income countries.

Despite some improvements in wait times, primary health care reform, electronic health records and drug coverage, we still do not have a high performing system as disparities and inequities persist inter-provincially across the country. The increasing need for greater expenditures in the areas of prevention and primary care have not yet been met. Simply put, there needs to be more equality for all Canadians.

According to a report from the Canadian Partnership Against Cancer, Canadians with low household income and/or are living in rural and remote areas begin at a disadvantage and have a higher cancer risk than those with higher income or living in urban areas.

This result dovetails with the higher smoking rates and higher obesity rates that are found among Canadian women living in low-income households and in rural/remote areas. Men living in high-income neighbourhoods are more likely to undergo PSA testing for prostate cancer but early detection through PSA testing does not seem to lower the likelihood of advanced-stage diagnosis or reduce mortality.

Additionally, distance from a radiation facility has been shown to correlate with a decreased likelihood of a breast cancer patient receiving radiation treatment as well as an increase in the rate of mastectomy. While this might be due to geographical limitations, women from lower income households are also more likely to have mastectomies than women in higher income households.

Patient Perspective

Among the various categories examined in the 2014 Ambulatory Oncology Patient Satisfaction Survey, emotional support was easily the lowest rated. Scoring between 19 per cent and 31 per cent, younger and more educated respondents tended to rate their experience negatively.

Research

Funding data from 2010 indicates that breast cancer has a significantly higher proportion of research funding at 27 per cent relative to its burden of illness which is seven per cent of cancer deaths. Contrasted with lung cancer which is almost the exact inverse; a significantly lower share of funding at eight per cent relative to its burden of illness at 27 per cent of all cancer deaths.

Dr. Kennecke from the British Columbia Cancer Agency (BCCA) compiled data on the effect of resection of metastasis (ROM) in metastatic colorectal cancer (mCRC) from 1995-2010 using outcomes data from the BCCA. It was concluded that the introduction of four or five agents, namely irinotecan, oxaliplatin and 5-fluorouracil, plus one or both of bevacizumab and EGFRI, had a measurable improvement on overall survival from diagnosis versus treatment with only three, one-two or zero agents. This effect was independent of the era in which the data was collected.

Cost of Care

According to Statistics Canada, between 1998 and 2009 there was a 2.9 per cent annual increase in the out-of-pocket expenditures on health care products and services. Households that spent more than 10 per cent of after-tax income rose by 56 per cent. The burden of out-of-pocket expenses is increasingly felt by those in lower income groups, which tends to lead to a reduced use of health services.

pCODR

The first phase of transferring the pan-Canadian Oncology Drug Review into the Canadian Agency for Drugs and Technologies in Health has begun consisting of moving staff, processes, funding, and expertise under the governance of CADTH. The second phase will commence in April 2015 and at that time, evaluation criteria will be merged with the CADTH review process. pCODR has been an international success as a cancer drug review process, while the Common Drug Review (long housed at CADTH) is fraught with credibility issues. It remains to be seen if pCODR will be maintained as the beacon it has become and bring CDR to the same standard.

End of Life Care

The Canadian Hospice Palliative Care Association reports that Canadians believe palliative, hospice and end-of-life care is not only critical but should be made easily available to all that need it. However, many have no idea where or how to access these services. Currently, there is no national palliative care strategy that addresses access to these services.

Accountabability

With the end of the Health Accord came the shut down of the Health Council of Canada, which deserved a better fate.

A SMALL TASTE OF CANADIAN RESEARCH INTO PRECISION MEDICINE

Genome Canada is one of dozens of organizations that are rushing forward with research that has the potential to change the way cancer is predicted, prevented, detected, treated and beaten. The list below[1] is therefore a small sampling of the enormous effort underway in Canada related to precision medicine for cancer. There are hundreds of other projects in health, not to mention agriculture, environment, fisheries, forestries, technologies, etc.

- A compressed sensing framework for identifying differentially expressed isoforms and transcriptomic aberrations in cancer samples
- A Haplotype Map of the human genome – biomedical tool for genetic research in Canada
- Application of pharmacogenomics for rational chemotherapy of lung cancer
- Assessment of risk for colorectal tumours in Canada (ARTIC)
- Better biomarkers of acute and chronic allograft rejection
- Biomarkers for pediatric gliobastoma through genomics and epigenomics
- Cancer Genomics: A multi-disciplinary approach to the large scale high-throughput identificatioin of genes involved in early stage cancers
- Computational interpretation of cancer genomes: defining mutational landscapes for translational genomics
- Development and validation of comparative genomic hybridization arrays for clinical use in cancer
- Early detection of patients at high risk of esophageal adenocarcinoma
- Genetic determinants of human health and disease (including breast, endometrial, prostate, ovarian and melanoma cancers).
- High resolution analysis of follicular lymphoma genomes
- Identification of genetic pathways that regulate the survival and development of cancer and cancer stem cells
- Innovative chemogenomic tools to improve outcome in acute myeloid leukemia
- Integrative genomics for women's health
- Measuring and modeling tumour evolution from next generation sequencing data: enabling clinical study of clonal diversity in cancer patients
- Next generation bioinformatics for clinical genomics: using de novo assembly in personalized medicine
- Personalized cancer immunotherapy
- Personalized risk stratification for the prevention and early detection of breast cancer
- Personalized treatment of lymphoid cancer
- Stratifying and targeting pediatric medulloblastoma through genomics
- Synthetic antibody program: commercial reagents and novel therapy
- The dynactome: mapping spatio-temporal dynamic systems in humans
- The GRID project: Gene regulators in disease
- Tool for proteome-wide identification of regulatory switches

All of this activity is leading to discoveries that could change everything about how your own cancer will be managed. The only question at that point will be whether your cancer team will be allowed to use them.

1. Genome Canada http://www.genomecanada.ca/en/portfolio/project/health.aspx

Noteworthy

A PATIENT PERSPECTIVE

BY LIZ WHAMOND

It seems that every day we hear of breakthroughs with respect to treating cancer and there are more on the horizon. But what about drugs that we already know about, that show at least some hope for treating cancer? How can the necessary trials be funded for those drugs?

Every once in a while we hear of older drugs, that are often used to treat other diseases, having potential to have an impact on cancer treatment or prevention of recurrence. One of those is metformin, which is commonly used in the treatment of diabetes. It's cheap, been around for years and is generally well tole rated. Dr. Goodwin at Toronto's Mount Sinai Hospital spent roughly 10 years finding money to fund research to discover metformin's potential to prevent or control cancer. The evidence to do this study has come from animal models and cell studies, and from basic research scientists. Eventually she was able to fund the research using money from the US government, the Canadian Cancer Society and some US cancer charities. As the patent was about to expire, there was no interest from drug companies to fund new research into other uses for metformin.

So the story continues. In July my ears perked up at the news that aspirin or its generic form may also be effective in the treatment of breast cancer. Dr. Michelle Homes, a Harvard University researcher, claims that she has been turned down several times by US federal funding agencies. This drug is off patent and therefore there is no business case for pharmaceutical manufacturers to fund the approximately $10M price tag to do the trial.

Should a trial show positive results, it would be a cheap way of treating breast cancer in both the developed and developing world. It been around for decades, is reasonably well tolerated and may have the potential to save many lives from breast cancer.

It seems a colossal sin not to fund a clinical trial. So who should fund this research? Surely there are non-profits and others who could form a cross border alliance to raise this money. What about the Canadian Breast Cancer Foundation? What about the Susan G. Komen Foundation? There are many that raise funds in the name of cancer. What about the Terry Fox Foundation? Couldn't the federal governments of both Canada and the US contribute? In the whole scheme of things, $10M is small potatoes compared to what the disease is costing the medical systems in both countries. And many lives could potentially be spared.

We urgently need someone to step up to the plate for this kind of research.

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