

Human papilloma virus vaccines

New horizons in the prevention of cervical cancer

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Background

In July 2006, Health Canada approved Gardasil™ (Merck Frosst Canada, Ltd.), a vaccine designed to prevent infection with human papilloma virus (HPV), the virus that causes cervical cancer. This marks the most significant advance in the prevention of cervical cancer among Canadian women since the initiation of Papanicolaou (Pap) smears more than 40 years ago. Another vaccine, Cervarix™ (GlaxoSmithKline Inc.) is soon to follow. Since Gardasil™ was approved, its use has been endorsed by the National Advisory Committee on Immunization (NACI) and the Public Health Agency of Canada as well as many professional organizations dedicated to improving the health of women, including the Society of Obstetricians and Gynecologists of Canada and the Society of Gynecologic Oncologists of Canada.^{1,2} The Federal Government has allocated \$300 million to the Provinces and Territories to allow implementation of publicly-funded HPV immunization programs and, in turn, Nova Scotia was the first of four Provinces (including Prince Edward Island, Newfoundland, and Ontario) to announce commencement of publicly-funded, school-based immunization programs to begin this fall.

This article reviews the epidemiology of HPV and its associated diseases in Canada, the

scientific data supporting the recommendation for the use of Gardasil™ in Canadian girls and women, and outstanding questions which must be answered as we move forward with this exciting public health initiative.

Epidemiology of HPV in Canada

Human papilloma virus is a ubiquitous human pathogen transmitted primarily through genital skin-to-skin contact. In fact, HPV is the most common sexually transmitted infection, infecting up to 80% of sexually active adults over their lifetime, making it a virtually inevitable part of most of our lives.³ There are over 100 known types of HPV, approximately 40 of which infect the human genital tract. Human papilloma viruses are designated as high or low-risk based upon their oncogenic potential - their ability to cause cervical cancer. Worldwide, HPV types 16 and 18 cause 65-77% of both squamous carcinoma and adenocarcinomas of the cervix; HPV types 31, 33, 35, 45, 52, and 58 account for an additional 20%.⁴ In Canada, HPV types 16 and 18 cause 70% of cervical cancer.¹ Among low-risk HPV types, types 6 and 11 are the most clinically important, causing 90% of external genital warts.⁵

The prevalence of HPV varies by age, ethnicity, geography and risk factors such as number of sexual

partners, age of onset of sexual activity, oral contraceptive use and immunosuppression. Population-based studies of Canadian women have demonstrated an overall prevalence of HPV of any type of 16.8% and of HPV types 16 and 18, the most important of the cervical cancer-causing strains, of 10.6% and 3.5%, respectively.^{1,5-7} Higher rates of infection with high-risk HPV have been reported in Nunavut among Inuit women and cervical cancer rates are also higher in this population.¹ It is important to recognize that the peak incidence of HPV infection occurs in young women (teens and early twenties), shortly after they become sexually active. In fact, among virgins not infected with HPV who were followed prospectively, incident HPV infection occurred in 25% of women by 12 months following first sexual intercourse and 62% within 48 months of first sexual intercourse.⁸

Infection with HPV is associated with a wide variety of diseases. Arguably the most important of these, from a public health perspective, is cancer of the cervix. Persistent infection with high-risk HPV is a necessary cause of cervical cancer; HPV DNA can be detected in 99.7% of cervical cancer specimens.⁹ While about 80% of women who become infected with HPV will clear the virus spontaneously over 1-3 years, those persistently infected remain at risk of

Table 1: Vaccine characteristics of Gardasil™ and Cervarix™

Characteristic	Gardasil™	Cervarix™
References	15-21	22-25
Vaccine type	Quadrivalent VLP HPV 6,11,16,18	Bivalent VLP HPV 16,18
Expression system	<i>Saccharomyces cerevisiae</i>	Hi-5 Baculovirus
Antigen concentration	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18	20 µg HPV 16 20 µg HPV 18
Adjuvant	Alum: 225 µg Aluminum Hydroxyphosphate Sulphate	ASO4: 500 µg Aluminum Hydroxide 50 µg 3-deacylated Monophosphoryl Lipid A
Dosing Schedule	0.5 mL IM* at 0, 2, 6 months	0.5 mL IM at 0, 2, 6 months

*intramuscular

precancerous cervical dysplasia (cervical intraepithelial neoplasia-CIN) and, if untreated, progression to invasive cervical cancer over a period of 1 to 20 years following infection.¹ Although screening for cervical dysplasia using routine Pap smears has been associated with a dramatic decline in the incidence of cervical cancer in Canada from 14.7 per 100,000 in 1978 to 4.7 per 100,000 in 2006, the promise of Pap smears to eliminate cervical cancer has not been fulfilled and cervical cancer remains a serious threat to Canadian women.¹⁰ Despite widespread availability and endorsement of regular Pap testing, rates of cervical cancer have plateaued over the last decade owing, in part, to the fact that only approximately 66% of Nova Scotia women, over the age of 15 years, have been screened within three years and even among these, many have not been screened as frequently as recommended.³⁶ Twenty-four per cent of cervical cancers in Nova Scotia occur in women who regularly undergo their recommended Pap smears (at least every 3 years),

while almost 60 per cent occur in women who participate irregularly or not at all in Pap screening programs.³⁶

Cervical cancer remains the second most common cancer in Canadian women aged 20 to 44 years with a lifetime risk of 0.7% or 1 in 138 Canadian women, resulting in approximately 1350 cases of cervical cancer and 400 deaths annually.¹⁰ Nova Scotia has 55 cases of cervical cancer and 20 deaths annually.³⁷ Concerns have also been raised that the incidence of cervical adenocarcinoma and adenosquamous carcinoma, uncommon types of cervical cancer less successfully detected by Pap smears, has increased, particularly among women aged 20 to 49 years.¹¹

In addition to the burden of cervical cancer, HPV types 16 and 18 cause 41-57% of high-grade CIN, 15-32% of low-grade CIN, and 8-19% of atypical squamous cells of undetermined significance (ASCUS).⁴ A considerable proportion of the remaining cases of ASCUS are caused by HPV 6 and 11.⁴ In Canada, this

amounts to approximately 400,000 abnormal Pap smears annually, a tremendous physical and psychosocial burden for Canadian women and financial burden for the Canadian healthcare system.¹⁰

High-risk HPV is also associated with the development of other less common cancers including cancer of the penis, anus, vulva, and vagina.¹ Additionally, up to 72% of squamous cell cancers of the mouth and oropharynx can be attributed to HPV.¹²

While the burden of illness associated with external genital warts (EGW) is less well-defined than that of cervical cancer, available data suggest that it is considerable. There are an estimated 85,000 consultations due to EGW and 36,000 new cases of EGW in Canada each year.¹⁰ In Ontario, 1.1% of women aged 15 to 49 years presenting for Pap smears were reported to have EGW.¹³ In the United States in 2000, the incidence of EGW was 1.67 and 1.65 per 1000 person years among males and females, respectively, with the highest

Table 2: Efficacy of Gardasil™ and Cervarix™

Disease Endpoint*	Gardasil™ % (95% CI)	Cervarix™ % (95% CI)
Persistent infection† with HPV 16 and 18	VE 93.5% (83%-98%)	VE 80.4% (70%-87%)
HPV 16 or 18-related CIN 2 or higher	VE 98% (93%-100%)	VE 90.4% (53%-99%)
HPV 16 or 18-related vaginal or vulvar intraepithelial neoplasia (≥Grade 2)	VE 97% (79%-100%)	No data
Persistent infection† with HPV 45	No data	VE 59.9% (3%-85%)
Persistent infection† with HPV 31	No data	VE 36.1% (.5%-60%)
Protection from genital warts	VE 96% (86%-99%)	No data

Note: VE = vaccine efficacy; CI = confidence interval

**Efficacy data are presented for the intention-to-treat study population defined as all participants who were seronegative and PCR negative at enrolment for all HPV types contained in the vaccine and who received at least one vaccine dose.*

† Persistent infection is defined as 4 months in Gardasil™ trial and 6 months in Cervarix™ trial.

incidence among women 20 to 24 years (6.2 per 1000 person years) and among men 25 to 29 years (5.0 per 1000 person years).¹⁴

These data demonstrate that the burden of HPV-associated diseases remains considerable in Canada.

HPV Vaccines

The recognition of the causative link between HPV and cervical cancer and the epidemiology of HPV, demonstrating that a limited number of HPV genotypes are responsible for the majority of HPV disease burden worldwide, offered opportunity for development of multivalent vaccines with the potential to significantly impact overall disease burden. Two such vaccines currently exist—Gardasil™, the only licensed product in Canada, and Cervarix™, expected to become available for use in Canada in late 2007. Key similarities and differences between the vaccines are highlighted in Table 1.

Gardasil™ is a quadrivalent vaccine containing virus-like particles (VLP) from four strains of HPV-

high-risk HPV types 16 and 18 and low-risk types 6 and 11. Cervarix™, also a VLP vaccine, contains VLPs from only HPV types 16 and 18. The surface of HPV is comprised of two capsid proteins, the L1 and L2 proteins. The L1 protein is the major antigen recognized during natural infection, resulting in the development of neutralizing antibodies. Thus, the capsid L1 protein was selected as the vaccine antigen in both HPV vaccines. The gene that encodes each of the L1 proteins is expressed in a cell vector and the protein product produced self-assembles into a non-infectious VLP that is identical in size and shape to the natural virus but contains no DNA so cannot replicate. The VLPs of each type produced are purified, adsorbed onto an adjuvant, and combined for intramuscular injection.

Vaccine immunogenicity and efficacy

The immune response to and efficacy of Gardasil™ and Cervarix™ have been studied in 20,853 and 18,644

women, respectively, in published Phase 2 and 3 clinical trials involving young women from many industrialized and developing countries around the world (Table 2).¹⁵⁻²⁵

Data on the immune response to both vaccines are derived from trial participants who were polymerase chain reaction (PCR) and antibody negative to HPV types contained in the vaccines at enrolment and until one month following the third vaccine dose. Both Gardasil™ and Cervarix™ are highly immunogenic in 16-26 year old women, eliciting an antibody response to all HPV types contained in the vaccine in more than 99% of trial participants.^{16, 22} While the absolute antibody concentration reported in clinical trials cannot be compared between the two vaccines because of differences in the assays used to measure antibody levels, by one month following the third vaccine dose, both vaccines elicit antibody levels to all HPV types contained in the vaccine much higher than those observed following natural infection-

Gardasil™ antibody titres 11-105 times higher than that following natural HPV infection; Cervarix™-82-107 times higher.^{16, 22} Antibody titres for both vaccines peak one month following the third dose and then plateau by 18-24 months with no further decrease in antibody levels for at least 5 years.^{17, 23} Although the proportion of participants remaining seropositive to HPV type 16 two years following the last dose of Gardasil™ remains 96%, only 68% of participants were seropositive to HPV 18 at this time point;²⁴ the significance of this finding is unknown given that Gardasil™ has been shown to induce immune memory.²⁶ All women who received Cervarix™ remained seropositive to HPV 16 and 18 51-53 months following the last dose.²³ It is important to remember that the amount of antibody needed for protection against HPV infection, or the correlate of protection, is not known.

Immunogenicity to both vaccines has also been studied in adolescent girls aged 9 to 15 years and both vaccines have been shown to be highly immunogenic, eliciting antibody titres 1.7 to 2.4 times higher than those observed in adults.²⁷⁻²⁹ In fact, among adolescents aged 10-15 years, two doses of Gardasil™ administered 2 months apart elicited antibody levels as high as those observed after 3 doses of vaccine (0, 2, and 6 months) in adults.²⁷ This interesting observation suggests that the immune response to Gardasil™ among young adolescents may be robust enough to permit administration of only 2 doses of vaccine in this population. To further explore this hypothesis, academic investigators from British Columbia, Quebec and Nova Scotia, with funding from those Provincial Governments, are now enrolling adolescent girls aged 9-13 years in a clinical trial assessing the immunogenicity of 2 versus 3 doses of Gardasil™.

Because the period between HPV infection and the development of cervical cancer is generally many years and because it would be unethical to observe as trial participants progress from infection to cervical cancer without intervening, assessment of the efficacy of HPV vaccines has focused, on the recommendation of the World Health Organization, on vaccine efficacy against the surrogate disease endpoints of persistent HPV infection (6 months or longer) and Grade 2 or Grade 3 CIN. Efficacy data reported in Table 2 are derived from the intention-to-treat population, those participants who received at least one dose of vaccine, as results from this population most closely reflect the expected performance of HPV vaccines in “real-world” clinical practice. Overall, among women not previously infected with vaccine-type HPV, both Gardasil™ and Cervarix™ are highly efficacious in preventing the disease outcomes studied.^{17, 18, 20, 21} In addition to the vaccine type-specific protection demonstrated for both vaccines, Cervarix™ also provided some cross protection against persistent infection with HPV type 45 (vaccine efficacy 60%), type 31 (vaccine efficacy 36%) and type 52 (vaccine efficacy 32%)²⁵; collectively, HPV 45, 31, and 52 cause 12% of cervical cancer.³ While cross-protection data has not yet been reported for Gardasil™, early promising results with Cervarix™ suggest that these vaccines may provide protection broader than what can be expected from prevention of vaccine-type HPV alone.

Because Phase 3 trials of Gardasil™ did not exclude women who were or who had previously been infected with one or more HPV types, analysis of vaccine efficacy in the total trial population, more representative of the sexually active adult population than the intention-to-treat population previously described, is possible. In the total population, 24% of whom

were infected with one or more of the vaccine HPV types (6, 11, 16, or 18) at enrolment, overall efficacy against cervical disease was low (44-55% against vaccine-specific types and 17-20% against all types). This confirms that Gardasil™ is not effective in women already infected with vaccine-type HPV.^{18, 19, 21} This data, cited by some vaccine critics as evidence predicting failure of Gardasil™ in the “real-world”,³⁰ was in fact key in the decision-making by NACI which led to the recommendation to target Gardasil™ for young adolescents, aged 9 to 13 years, before they are likely to have begun sexual activity or to have been infected by HPV.¹ In this population, given the data demonstrating equivalent or superior immune response to the vaccine compared to adult trial participants, vaccine efficacy can be expected to approximate that observed in the intention-to-treat population in the Phase 3 trial. While some might argue that the poor vaccine efficacy observed in the total trial population argues against recommending Gardasil™ to older, sexually active women, it is important to remember that Gardasil™ will provide women with protection against vaccine-types to which they have not previously been exposed. While type-specific HPV testing is not currently routinely available and it is therefore not possible to provide individual women with estimates of their expected personal benefit from the vaccine, analysis of the total population of women in the Gardasil™ trial revealed that only 0.2% of women were positive for both HPV 6 and 11, only 1% were positive for both HPV 16 and 18, and only 0.1% were positive for all four HPV types contained in the vaccine.¹ Thus, most women would be expected to derive benefit from receipt of Gardasil™ and all women aged 9 to 26 years for whom the vaccine is licensed should be offered the vaccine, regardless of

Table 3: Summary of the recommendations of the National Advisory Committee on Immunization for the use of Gardasil™ in Canada

Population	Recommendation*	Notes
Females aged 9-13 years	Recommended	<ul style="list-style-type: none"> • Key target population as prior to the onset of sexual activity for most; vaccine efficacy expected to be highest in this population
Females aged 14-26 years	Recommended	<ul style="list-style-type: none"> • Even if sexually active, unlikely to be infected with all vaccine types • Offer even if prior history of abnormal Pap, cervical cancer, known HPV infection, or genital warts • Counsel patient on risk of prior infection with HPV
Females > 26 years	No recommendation	<ul style="list-style-type: none"> • Use may be considered in individual circumstances
Females < 9 years	Not recommended	<ul style="list-style-type: none"> • No data available regarding safety, efficacy, or immunogenicity in this group
Males	Not recommended	<ul style="list-style-type: none"> • Efficacy of Gardasil™ in males not yet known
Immunocompromised persons	Recommended	<ul style="list-style-type: none"> • As Gardasil™ is not a live virus vaccine, its use in persons with immunocompromise is not contraindicated • As with other vaccines, immune response to Gardasil™ in this population may be less than in immunocompetent persons
Pregnant women	Not recommended	<ul style="list-style-type: none"> • Delay administration of Gardasil™ until after pregnancy • No intervention required if vaccine inadvertently administered during pregnancy • Data on immunization during pregnancy limited • No increase in adverse pregnancy or fetal outcomes observed in 1,115 women who became pregnant during clinical trials

**Receipt of Gardasil™ is not a substitute for routine Pap screening. All women and girls should be counseled about the ongoing risk of HPV-associated cervical disease and advised to participate in currently recommended Pap screening programs.*

personal history of HPV infection, genital warts, or abnormal Pap smears.¹ While it is known that both Gardasil™ and Cervarix™ are highly immunogenic in women older than 26 years, trials assessing the efficacy of the vaccine in this population are ongoing and no recommendation can yet be made for this group. However, use of the vaccine in this population may be considered in individual circumstances.¹ No data regarding the efficacy of Gardasil™ in males is yet available and the vaccine is not currently recommended for males. Recommendations of NACI are summarized in Table 3.

Vaccine safety

Both Gardasil and Cervarix have excellent safety profiles and were well-tolerated in clinical trials.¹⁵⁻²⁵ The most common, and expected adverse event following receipt of both vaccines is pain, swelling and redness at the injection site, occurring in up to 85% of recipients, or 6% to 8% more common than produced by an alum placebo.^{22,31} While fever ($\geq 37.8^{\circ}\text{C}$) occurred in 10% of participants, it was not more frequent among those who received Gardasil™ than those who received placebo.³¹ The incidence of other systemic events such as nausea, vomiting, and diarrhea was

not higher than that observed among recipients of placebo.³¹ Serious adverse events following immunization were rare and the proportion of participants experiencing a serious adverse event were similar in the vaccine and placebo groups.³¹

Since the licensure of Gardasil™, over 7 million doses have been distributed in the United States. As of June 30, 2007, a total of 2,531 reports have been received by the Vaccine Adverse Event Reporting System (VAERS).³² Nearly 95% of reports received have been classified as non-serious, with local injection-site reactions and fainting at the time of

vaccine administration predominating. Overall, less than 6% of reports to VAERS regarding Gardasil™ have been deemed serious. In comparison, the overall average in VAERS for any serious adverse event ranges from 10-15%. Thirteen reports of Guillain-Barre Syndrome (GBS) following Gardasil™ have been reported.³² Of these, only 2 cases meet the case definition for GBS, occurred within 6 weeks of vaccination, and had received Gardasil™ alone. Because GBS occurs at a rate of 1-2/100,000 person years during the second decade of life, it is expected that some cases of GBS will occur after vaccination but will not be due to vaccination. The reported rate of GBS following vaccination with Gardasil™ is not greater than the number of reports that could be expected to occur by chance alone after a vaccination. Seven deaths have been reported among persons who have received Gardasil™, one involving a blood clot, one involving a pulmonary embolism, and one due to myocarditis in a patient with proven Influenza A infection.

All reports of death following immunization are under review by an expert panel. At this time, though the deaths are temporally related to vaccination, there is nothing to suggest that the deaths were caused by the vaccination and the total number and pattern of deaths reported does not differ from that expected in the absence of immunization. It is important that physicians and patients alike understand that, in the context of a large-scale medical intervention of any kind, adverse events are going to happen and may, coincidentally follow, but not be caused by the intervention. Passive surveillance systems such as VAERS in the United States and the Canadian Adverse Events Following Immunization Surveillance System in Canada as well as more active surveillance systems such as the Vaccine Safety Datalink in the US allow real-time oversight of

adverse events following immunization, permitting early detection and investigation of concerning events. It is important that physicians are aware of these safeguards and the fact that they have been successful in identifying unexpected vaccine adverse events in the past. Parents should be reassured that despite alarming reports of serious events following vaccination with Gardasil™ reported by the lay press,³³ careful ongoing review of these databases by experts have failed to identify any safety concerns following distribution of more than 7 million doses of Gardasil™ in the United States.

Knowledge gaps

It is undeniable that questions remain about HPV vaccination, as is the case at the time of implementation of any new immunization program. While it is clear that these vaccines are highly effective at preventing precancerous lesions of the cervix, it will take many years to see this translate into demonstrated protection against cervical cancer. What we do know, however, is this. HPV causes cervical cancer. Gardasil™ prevents infection and disease caused by 2 types of HPV known to cause 70% of cervical cancer. Based upon demonstrated efficacy in clinical trials, the number of 12 year old girls needed to prevent one case of cervical cancer is only 324 and immunization of only 729 girls is needed to prevent one cervical cancer death!³⁴ In comparison, 21,000 people must be vaccinated to prevent 1 death due to meningococcus, 34,000 must be vaccinated to prevent a death due to varicella (chickenpox), and 5,000 must be vaccinated to prevent a death due to influenza.³⁴ Yet routine immunization against all of these is widely accepted! Even if protection from HPV vaccine is not lifelong and a decision is made to provide a booster dose in the future, these vaccines compare very favourably with other

vaccines used in publicly-funded immunization programs.

Vaccine critics purport that routine immunization of young girls is premature because the duration of protection from Gardasil™ is not known.³⁰ How long should we wait for that answer before protecting our daughters? We've acted knowing that protection lasts at least 5 years. Long-term efficacy studies are ongoing to ensure that waning protection does not occur and, if it does, that recommendations for administration of a booster dose are made.³⁵ It is very true that the duration of protection is a key gap in our knowledge regarding these vaccines but decisions about vaccine programs must always be made in the face of this outstanding question. What is the price we would pay for awaiting certainty? How many babies would have died had we waited to begin immunizing against pertussis until we knew they would need a booster as an adolescent? How many of our daughters would be infected with HPV and develop cervical cancer while long term registry studies await efficacy data after 10 years, 15 years, 20 years? Do Canadians really want to participate in **that** experiment?

Will other high-risk types fill the niche left by HPV types 16 and 18, resulting in failure to see overall reductions in the incidence of cervical cancer? While the immunobiology of HPV, very different than that of *Pneumococcus*, would suggest that this is unlikely, long-term population-based post-marketing surveillance has been put in place to ensure that hypothetical concern is addressed.³⁵

Conclusion

While critics of HPV immunization argue that the incidence of cervical cancer in Canada is amongst the lowest in the world and does not justify the "sense of urgency" surrounding Gardasil™,³⁰ the thousands of women and their families who have been affected by

cervical cancer and the parents of young girls with a 1 in 138 chance of developing cervical cancer in the future may well disagree. "If there was an epidemic and people were dropping dead on the street corner, you'd want to do something," Abby Lippman, an epidemiologist who works with the Canadian Women's Health Network argues.³³ Since this is not the case, she argues that "we have the luxury to reflect, think, and act wisely" and questions the implementation of publicly-funded school-based HPV immunization programs for Canadian girls. While Lippmann and her colleagues raise important outstanding questions about HPV vaccines, not dissimilar to the questions outstanding when any new vaccine or other medical intervention is introduced, the facts are clear. HPV is an important public health problem. Cervical cancer remains a threat to Canadian women and Pap screening alone has not been

able to eliminate this threat.

Vaccination with Gardasil™ has been shown to be highly effective at preventing high-grade cervical lesions caused by HPV types 16 and 18 and 95% effective in preventing genital warts. Gardasil™ is associated with acceptable local reactogenicity and no increase in the number of serious adverse events than would be expected in the absence of immunization. Review of clinical and epidemiological data by expert groups around the world, including NACI, has led to the licensure of Gardasil™ in 80 countries and the decision by several Canadian provinces to move forward with publicly-funded school-based programs this fall is being applauded by experts across the country!

Careful, comprehensive plans are being implemented by industry and governments and academic researchers around the world, including Nova Scotia, to evaluate the real-world impact of Gardasil™ and to provide

answers to important, outstanding questions. As Nova Scotian girls head back to school this fall, we must all work to ensure that they and their parents receive honest, accurate, unbiased information about the burden of HPV disease in Canada and the strengths and limitations of Gardasil™, the remarkable, if imperfect, new tool in our armamentarium against cervical cancer.

Let us not allow fear-mongering, born of acceptable and expected scientific uncertainty, to undermine the promise of immunization to augment Pap screening and maximize the protection of our daughters from cervical cancer.

For more information about the HPV vaccine or other questions related to cervical cancer prevention and screening, please call Cancer Care Nova Scotia's Cervical Cancer Prevention Program at 1-888-480-8588.

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Cancer Care Nova Scotia is a program of the Department of Health. Its mandate is to evaluate, coordinate and strengthen the cancer system in Nova Scotia.

Cancer Care Nova Scotia works with and supports professionals and stakeholders in the health care system to bring about patient-centred change. Its ultimate goal is to reduce the burden of cancer on individuals, families, communities and the health care system.

In Practice is a supplement to *Cancer Care Nova Scotia's* newsletter. It is written specifically for primary care practitioners with information that we hope will make a difference in your cancer practice.

Please contact Christine Smith, Communications Coordinator, *Cancer Care Nova Scotia*, by phone at 902-473-2932 or by email at christine.smith@ccns.nshealth.ca with comments or suggestions for future topics.



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