

# Journal of Family Practice Oncology

### Issue Number 31, Fall 2018 | www.fpon.ca

## Newer approaches in the treatment of breast cancer

By Dr. Tamara Shenkier, Medical Oncologist, BC Cancer – Vancouver

Breast cancer is the most common cancer diagnosed in females, with 3,480 cases reported in BC in 2015<sup>1</sup>.



cancer is highly curable and women with metastatic breast cancer can live for years. This translates into close to with a

Early breast

Dr. Tamara Shenkier

25,000 females in BC living with a prior diagnosis of breast cancer in the previous 10 years<sup>2</sup>. Therapy for early (curable) and advanced (treatable) breast cancer continues to improve. This article will highlight a few of the recent developments in hormone receptor (HR) positive breast cancer, which accounts for 75% of new diagnoses.

Women with HR positive breast cancer, some of whom are treated with adjuvant chemotherapy, contend with the residual and late side-effects of this treatment. They also remain at risk for recurrence many years after diagnosis. New approaches address both the potential for overtreatment and undertreatment.

For forty years the choice of adjuvant systemic therapy for early breast cancer was predicated on the stage and biomarker profile of the cancer. Now a 21-gene expression assay, the Oncotype DX™ Breast Recurrence Score, has

# Join us @ the BC Cancer Summit for Primary Care Oncology CME



This November 23-24, BC Cancer celebrates 80 years of excellence in cancer care and will mark the occasion with the BC Cancer Summit, a two-day conference at the Sheraton Vancouver Wall Centre. The event provides critical education, professional development and unique relationship building opportunities for oncology professionals from all specialties and disciplines. The Family Practice Oncology Network's two most significant oncology CME events for primary care, GPO Case Study Day (November 23) and Family Practice Oncology CME Day (November 24), will be held as part of the Summit. Our format will follow that of previous years, with

#### Register today at bccancersummit.ca

feedback enriched content. Register today at bccancersummit.ca and take advantage of this plethora of learning and networking opportunities!

continued on page 3



# A new era in endometrial cancer care: advances in molecular classification

By Dr. Jessica N. McAlpine, Associate Professor, Gynecology and Obstetrics, Division of Gynecologic Oncology, Dr. C. Blake Gilks, Professor, Pathology and Laboratory Science, and Dr. Aline Talhouk, Assistant Professor, Gynecology and Obstetrics, University of British Columbia

Cancer care in the last decade has seen a dramatic shift towards a 'subtype-specific' approach. We are on the cusp of a new era in endometrial cancer (EC) care, with new molecular tools coming in to standard clinical care and transforming current practice patterns across Canada and globally. Herein, we share a snapshot of the new molecular classifiers now seen on pathology reports and what else is coming in the very near future.

# Why is this molecular approach to endometrial cancer (EC) needed?

Unlike ovarian cancer where pathologists can reliably distinguish subtypes and subsequently direct care for that individual, evaluation of EC under the microscope is inconsistent. Consequently, treatments administered vary widely and determining the 'best' treatment for an individual has been impossible.

# How can we overcome these challenges?

We have developed a molecular classification tool that reliably categorizes tumours and provides prognostic information for women with EC. Based on The Cancer Genome Atlas (TCGA); an in-depth characterization of ECs that identified four genomic subgroups with distinct clinical outcomes, we pared down the complex components of testing to three low-cost, easily performed tests. This combination of tests has been validated in different patient populations and reproduces the TCGA subgroups, but is applicable to endometrial biopsy samples and could be used in any cancer centre. That it can be achieved on biopsy/curetting specimens is critical, as this provides earlier information for patients and their physicians. Internationally, these same tools are now recognized and being implemented. We have named this tool 'ProMisE' (Proactive Molecular Risk Classifier for EC), the key components of which are outlined below and in Figure 1.

## MMR

Mismatch repair (MMR) is a type of DNA repair commonly interrupted in ECs and other solid tumours. Deficient MMR can be inherited (e.g. Lynch syndrome) or acquired. Identifying Lynch syndrome is important to both patients and family members (i.e., increased screening for other cancers, risk reducing surgeries), but in addition, certain treatments work better in MMR-deficient tumours so identification may improve outcomes. Immunohistochemistry to test ECs for MMR is low cost (~\$80-100) and now routinely performed across BC and in some other provinces at no cost to the patient. Pathology reports show these results and may prompt additional tumour testing and/ or referral to the hereditary cancer centre.

## POLE

DNA polymerase epsilon or POLE is also involved in DNA repair. When not functioning, POLE mutant tumours become highly mutated across many genes. Remarkably, women with POLE mutated ECs have excellent outcomes with extremely rare recurrence events or death from their disease. POLE testing can be achieved in research labs, but a clinically-approved laboratory test is in active development and will be implemented in the very near future. Although not available or reported today, we foresee widespread access to POLE testing in the next year or two. Knowing POLE status of an EC may enable simple surgery to be performed in a community hospital (not a cancer centre) and spare adjuvant treatment.

## p53

p53 is a tumour suppressor protein, i.e., its activity stops the formation of cancers. Loss of function of p53 is common in cancers, and detection by IHC is reliable and cheap (~\$40-50). Increasingly, p53 IHC has been assessed by BC pathologists to help identify aggressive subtypes of EC. Women with ECs harbouring p53 abnormalities have very poor outcomes. Identification of these women is therefore imperative so that the most aggressive surgeries, and additional treatments (e.g., chemotherapy, radiation, new trials) can be administered.

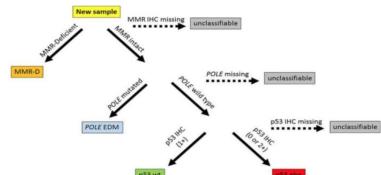
## Summary

We are in a new era of molecular classification and subtype-directed management in EC. Although the full assembly of ProMisE is not 'live' in BC or anywhere in the world (outside of clinical trials/research), several components of this tool ARE available now (MMR and p53) and seen on your pathology reports from diagnostic biopsies and/or hysterectomies. Patients may ask about these tests as public knowledge increases. Understanding what these results mean, what actions to take, and what is coming in the near future will help improve care today and help prepare for tomorrow. We are currently assessing ProMisE in over 1,000 ECs across Canada to determine how it can be used to best direct clinical care and to assess health economic/ resource implications. Stay tuned as we look to improve outcomes for women with EC!

Contact Dr. Jessica McAlpine at Jessica.Mcalpine@vch.ca

## Helpful Resources:

- Spotlight and review of our research: https://researchfeatures. com/2016/12/13/promisingnew-model-for-the-molecularclassification-of-endometrial-cancers/
- Knowledge translation video developed for obstetrician/gynecologists and BC Cancer Tumour Group: http://www.ovcare.ca/endometrial\_ cancer/endometrial\_cancer.php
- Other articles (new research, reviews): www.ovcare.ca/endometrial\_cancer/ lean\_more\_download\_our\_papers/



Newer approaches in the treatment of breast cancer continued from page 1

been prospectively validated to assist in these decisions<sup>3</sup>. The results of the landmark TAILORx study support endocrine treatment alone for women over 50 years old with HR positive, HER2 negative, node negative breast cancer and scores of 25 and lower. For younger women, with scores between 21-25, there may be as much as a 6.5% improvement in distant disease-free survival with adjuvant chemotherapy followed by endocrine therapy. A decision about chemotherapy is best made after discussion with a medical oncologist.

HR positive breast cancer recurrences can occur at any point, including more than 5 years beyond diagnosis<sup>4</sup>. The risk is higher for those with larger tumours and an increased number of involved axillary nodes. Adjuvant tamoxifen has been the mainstay of endocrine therapy for premenopausal women following adjuvant chemotherapy, even for those with residual ovarian function. A recent study shows that adding ovarian suppression to 5 years of exemestane or tamoxifen results in a significant improvement in 8 year disease free survival compared to tamoxifen alone (80.4% vs 76.7% vs 71.4%) at the cost of increased sideeffects<sup>5</sup>. The overall survival data for these

three cohorts is evolving (87.2% vs 89.4% vs 85.1%). Women 35 and younger derive the largest benefit.

Bisphosphonates inhibit osteoclastmediated bone resorption and are used to treat osteoporosis. In addition, a large meta-analysis of randomized clinical trials shows that using bisphosphonates as adjuvant therapy can improve breast cancer outcomes in postmenopausal women, with small but definite improvements in recurrence and survival compared to placebo (HR 0.82, CI 0.73-0.93)<sup>5</sup>. This treatment is beneficial in HR positive and HR negative disease. In view of these data, BC Cancer now funds adjuvant zoledronate (BRAJZOL) for postmenopausal women with stage II or III disease. The risks include postinfusion flu-like illness, renal impairment and osteonecrosis of the jaw. Patients need baseline dental assessment and blood work (Cr, Ca<sup>2+</sup>) prior to infusions.

There is a new standard of care for first line therapy of advanced HR positive, HER2 negative breast cancer. With letrozole alone, postmenopausal patients could expect control of their metastases for a median of about 12 months. A new class of drugs, which blocks G1 to S phase transition, leads to cell cycle arrest and potentiates the effect of aromatase inhibition. These oral, small molecule, cyclin dependent kinase 4 and 6 inhibitors (CDK4/6i) (palbociclib, ribociclib) double the median progressionfree survival to about 24 months<sup>7,8</sup>. Fatigue and neutropenia are common side-effects, the latter managed with dose reductions or delays. Febrile neutropenia is rare (< 2%). Additional side-effects seen with ribociclib include hepatotoxicity and QTc prolongation.

> View the full 2018 webcast on this topic at www.fpon.ca – Continuing Medical Education.

This article has touched on newer approaches to management of breast cancer. Family physicians can expect to see tailoring of adjuvant systemic recommendations for their pre and postmenopausal patients with HR positive breast cancer. They will have postmenopausal patients with stage II or III breast cancer receiving adjuvant zoledronate. They may also notice their patients with HR positive advanced breast cancer enjoying a prolonged period of disease control with the use CDK4/6 inhibitors.

Contact Dr. Tamara Shenkier at tshenkie@bccancer.bc.ca

see References on page 13

Join us @ the BC Cancer Summit continued from page 1

## November 23: GPO Case Study Day 5.75 Mainpro+ Credits

If you are General Practitioner in Oncology (GPO), a Nurse Practitioner, or a primary care provider keen to tackle prevalent and emerging challenges in cancer care through case-based discussion, this is the event for you. Our third annual GPO Case Study Day will focus on cases in lung cancer, Non-Hodgkin's Lymphoma, prostate cancer, cardio-oncology, and radiation oncology complications. Presentation and discussion of each case will be led by a GPO accompanied by a supporting specialist.

GPO Case Study Day runs from 10:15 a.m. – 5:00 p.m. and provides an excellent environment to learn and connect with colleagues who provide a similar level of cancer care in communities throughout BC, the Yukon, and beyond. Full details and registration at bccancersummit.ca (and at www.fpon.ca). This event sold-out in 2017 so be sure to register early!

## November 24: Family Practice Oncology CME Day 5.75 Mainpro+ Credits

This one-day event is a great opportunity for family physicians and primary care providers to learn about new developments and practice changing guidelines in cancer care, and to build helpful cancer connections.

"All of the information and expertise shared will be targeted to the needs of primary care," notes the Network's Medical Education Lead, Dr. Raziya Mia. "Among the insightful presentations planned for this year are: PSA Testing – Simplified At Last, Follow-up Care of Breast Cancer Patients, and Evidence-Based Guidelines for the Management of Oral Side-Effects of Cancer Therapy, to name a few."

Don't miss this chance to connect with your colleagues in cancer care and to gain knowledge on the most in-demand oncology topics for primary care. Full details and registration at bccancersummit.ca (and at www.fpon.ca).

Contact Jennifer Wolfe at jennifer.wolfe@bccancer.bc.ca or 604.219.9579

# Watch for late effects in survivors of childhood cancers

## By Dr. Karen Goddard, Radiation Oncologist, BC Cancer – Vancouver

Adult childhood cancer survivors (ACCS) often have long-term health problems and risks (late effects) as a result of their previous illness and therapy. The severity and types of these health risks depend very much on the type of childhood cancer and treatment received. Therapies for solid tumours such as sarcomas and brain tumours are generally associated with multiple severe health problems. However, some patients previously treated for diseases like leukemia may be at low risk for late effects.

## View the full webcast on this topic at www.fpon.ca – Continuing Medical Education.

The Family Practice Oncology Network's May 2018 Webcast describes the different causes of late effects including which different organ systems can be affected by childhood cancer treatment. For each organ system there is also a discussion about the nature of that damage. The risk for the development of second neoplasms many years after therapy is also addressed. Some of these tumours are benign (e.g. meningiomas may occur years after any type of brain radiation therapy) and some are malignant (e.g. the risk of breast cancer is very much increased after Hodgkin's Lymphoma chest radiation therapy, especially in adolescent girls).

Unfortunately, the risk of late effects for any ACCS continues to increase with time. Patients treated intensively for childhood cancer need life-long follow-up. The focus of the Webcast is the Late Effects,

Assessment and Follow-up (LEAF) Clinic which has been operating for the last two years. The program is designed to meet the needs of ACCS in British Columbia. Young adult patients previously followed by the BC Children's Hospital pediatric oncology team are transferred to the LEAF program for ongoing care. We have also developed a program to contact ACCS who may have been "lost to follow-up" across the province, to reassess their health and ensure that they are receiving informed and appropriate primary care.

We meet with patients in person or by videolink, review their previous medical records, and assess their current health

status. In light of that information, we evaluate the risk for potential late effects and offer management recommendations for these chronic health problems. We provide a summary outlining previous therapies,

> potential long-term health problems and risks, together with screening recommendations and healthy lifestyle advice. Our summary is designed to meet the needs of the patient and their primary

care practitioner. We are also involved in patient and health care professional education programs, and in research. Psychosocial support is a critical element of our program, and the clinic has two family counsellors who organize support group activities, in addition to counselling on an individual basis.

We would really encourage you to participate in our CME module about late effects after treatment for childhood cancer at: https:// elearning.ubccpd.ca/login/index.php

Please contact us if you have any questions. LEAF Clinic:

www.bccancer.bc.ca/our-services/services/ late-effects-assessment-follow-up 604.877.6070 or ACCS@bccancer.bc.ca

# CanIMPACT: a multi-province study of delivery of follow-up care by primary care physicians

By Mary McBride, Distinguished Scientist, Cancer Control Research, BC Cancer – Vancouver

This article is a follow-up to our Fall 2017 report on our multi-province study of family physician care of cancer patients in Canada (the CanIMPACT study). This study was funded based on a recognition of the critical role that primary care plays in improving cancer patient outcomes and quality of life, and the strength of primary care in providing continuous, coordinated, and comprehensive patient care.

A recently-published CanIMPACT analysis (Kendell C. et al; *Curr Oncol.* 2017 Apr;24(2):81-89) examined breast cancer follow-up delivered in the primary care and specialist (including oncology) care settings, in three Canadian provinces (British Columbia, Manitoba, and Ontario). The study reviewed follow-up care for all women with incident invasive breast cancer in each province from 2007 to 2012 (2011 in Manitoba), who successfully completed surgery with or without adjuvant or neoadjuvant therapy (that is, treatment with curative intent).

According to the US Institute of Medicine, follow-up care should involve these essential components: (1) prevention and detection of new and recurrent cancer; (2) surveillance for cancer spread, recurrence, or second cancers; (3) intervention for the consequences of cancer and its treatment (for example, physical issues such as such as lymphedema, pain, and fatigue, and psychosocial issues such as anxiety and distress); (4) coordination between specialists and primary care providers (PCPs) to ensure that a survivor's overall health needs are met (National Cancer Policy Board; Hewitt M, Greenfield S, Stovall E, eds. From cancer patient to cancer survivor. 2006. www.nap. edu). Importantly, cancer survivors also often require care for non-cancer-related health issues such as chronic disease screening and management.

Although specialists and PCPs both play a role in addressing these needs, several studies, including studies in Canada, have found that PCPs are both willing to take on a greater role in cancer follow-up care than previously, and able to provide follow-up that is as effective as specialist follow-up care. Patients also report higher satisfaction with follow-up care led by PCPs (Rubin G et al. *Lancet Oncol* 2015: 16: 1231–72; *continued on page 5* 



# Psychiatric issues in oncology: Side-stepping communication pitfalls and promoting resilience

By Dr. Elaine Drysdale, Clinical Professor, Psychiatry, University of British Columbia and Psychiatric Consultant to the Leukemia/Bone Marrow Transplant Program of BC

Every discussion with a patient has the potential to improve, or aggravate his/her ability to cope with a cancer diagnosis. This article, summarizing communication elements of the Webcast, "Psychiatric Issues in Oncology", discusses key points regarding word choices with patients. Even with good intentions, we can unwittingly add to a patient's anxiety, frustration, and

despair. Instead, busy family practitioners can use the strategies that follow to avoid common communications pitfalls and improve patients' resilience.

Discussions about treatment and consent, for example, can lead to overwhelming anxiety, even to PTSD, and what I term "false despair". Always provide information that is easy for patients to understand and emphasize that there are always exceptional patients.

Never say "There's nothing (or nothing more) we can do." No matter the prognosis, patients need to feel there is always hope. Always let them sense that the physician will stand by and support when cure is not possible. The phrase, "We don't have a cure....yet!" implies hope for the future. With increasing development of novel and genetic approaches a "hopeless" diagnosis one year may become a "chronic illness" the next. What is hoped for may gradually shift with disease progression, but a sense of hope for something is vital for the human spirit. The book, "How to Break Bad News" by Dr. Robert Buckman, is a helpful resource.

The expression "Just be positive!" should be

avoided. It places tremendous expectations on the patient creating guilt, resentment, and tension. For this reason, I coined the phrase, "the tyranny of positive thinking" in 1990, which resonated with clinicians across North America! It is far preferable to suggest "a fighting spirit" as a coping strategy. If that seems daunting for a weary or nauseated patient, I elaborate that "a

Dr. Elaine Drysdale

fighting spirit" refers to an underlying "decision to survive and do what it takes to get better." This takes the pressure off both the patient and caregiver who might each be feeling anxious and helpless that the patient "isn't positive enough."

Queries arise regarding why some patients reject medical reassurances over their worries, and experience seemingly disproportionate psychological distress? Any symptom or side-effect may have unique significance and meaning to an individual. The following scenarios illustrate this:

 A patient referred for anxiety developed a medication induced side-effect of muscle pain. However, he believed information about his condition was being withheld because muscle pain was the presenting symptom of his cancer diagnosis. He was sure that the recurrence of muscle pain implied recurrence of cancer. Merely asking why he could not accept staff reassurances, revealed the real cause of his increased anxiety.

- A leukemia patient refused to accept her good medical prognosis because she secretly believed she would have the same outcome as her fiancé, who died on the same ward. In fact, her situation differed in various ways regardless of their similar diagnoses.
- Similarly, mild cognitive side-effects of chemotherapy (often referred to as 'chemobrain') may be misinterpreted by a patient as an ominous indicator of brain metastases.

View the full 2018 webcast on this topic at www.fpon.ca – Continuing Medical Education.

If a patient appears overly distressed by a fact or symptom, clarifying its unique significance and context may be essential.

How can physicians learn to use language that subliminally communicates potential hope and resilience? The Canadian Society of Clinical Hypnosis, BC Division, provides an annual workshop on how to best use phrases that imply future possibilities rather than reinforcing despair. For example, "You are not feeling well...yet," or "I wonder whether it will be two days or three before you feel more like eating," imply underlying expectations of improvement.

The Webcast covers a large array of topics of "Psychiatric Issues in Oncology," including chemobrain, management approaches and tips for depression, anxiety, fear of dying, and delirium. Tune in!

Contact Dr. Elaine Drysdale at elaine.drysdale@vch.ca

### CanIMPACT

#### continued from page 4

Grunfeld E and Earle C. J Natl Cancer Inst Monogr 2010;40:25–30; Grunfeld E. J Clin Oncol 28:658s, 2010 (9090).

Our study showed that at least two-thirds of women in each province received care from both primary care and oncology providers for the four years following initial treatment (defined as ending at one year postdiagnosis), although the average number of breast cancer-specific visits to primary care and oncology declined with each follow-up year. Considerable interprovincial variation was observed in the type of provider and pattern of care, with greater surgeon followup in Nova Scotia, greater oncology follow-up in Ontario, and greater primary care followup in BC. Provincial differences could reflect variations in policies and recommendations (i.e, for timing of "discharge" of patients from oncology to primary care), and resources or infrastructure to support PCP-led follow-

up care, including information on patientspecific cancer-related later health risks.

The key next question we evaluated was: does a difference in provider affect adherence to guidelines for breast cancer follow-up care (www2.gov.bc.ca/gov/content/health/ practitioner-professional-resources/bcguidelines/breast-cancer-management)? A report on our findings will follow.

For further information, please contact Mary McBride at mmcbride@bccrc.ca



# Nanaimo GPO, Dr. Steve Kulla: job satisfaction through close to home cancer care



Even though it's a serious place with a serious purpose, BC Cancer's Clinic at Nanaimo Regional Hospital is an amazing place to work according to

General Practitioner in Oncology (GPO), Dr. Steve Kulla – a place with continuity where all members of the team are valued and dedicated to providing the best cancer care possible.

Dr. Kulla explains:

I'd had my own family practice in Nanaimo for about five years, including serving on the palliative care team at the hospital, when I was asked to consider the GPO role. The decision was difficult as I was happy in my family practice, but my interest in cancer and palliative care prevailed, and the result continues to reward. We have an outstanding team in Nanaimo including four GPOs, chemotherapy nurses, pharmacists, a social worker, a dietician, and nurse leaders who all contribute to an excellent work environment where the job is always interesting. We cover all the tumour groups with no oncologist on site, so our team works closely with oncologists at BC Cancer – Victoria and occasionally with those at BC Cancer – Vancouver. Their responsiveness and the level of communication that we share is a huge bonus to our effectiveness.

Our clinic ensures that cancer patients from Nanaimo as well as Parksville, Qualicum, Uclulet, Tofino, and Port Alberni can receive their treatment and supportive care close to home rather than having to travel to Victoria. The latter can prove an extremely long day – exhausting both physically and financially to the point where many patients would not be able to follow through. Our small clinic provides a big service to these communities as patients remain near to family, their family physicians, and in a community they are familiar with. These

## Next GPO education course begins February 4, 2019

The GPO Education Program is an eight-week course offering rural family physicians and newly hired BC Cancer GPOs the opportunity to strengthen their oncology skills and knowledge, and provide enhanced cancer care. The program covers BC and the Yukon and includes a two-week Introductory Module held twice yearly at BC Cancer – Vancouver followed by 30 days of flexibly scheduled clinical rotation. Full details at www.fpon.ca are important advantages for folks going through chemotherapy who may already be feeling unwell, fatigued, or in pain. We save them a long journey, and it's much easier for family or friends to accompany them to appointments. Plus they get used to us here and that can be comforting as well.

Going forward, we would one day like to be able to provide radiation treatment in Nanaimo as patients do still need to travel to Victoria for this purpose. We have recently started providing Radium 223 for prostate cancer patients which previously had to be administered in Victoria. Another long term goal is to run clinics several times a month in Port Alberni, where the demand for our services is high and the need continues to grow. This would benefit not only patients in Port Alberni, but also those from Tofino and Uclulet.

Finally, Dr. Kulla speaks well of the Family Practice Oncology Network's GPO Education Program, a requirement for all new GPOs in BC/Yukon, which he completed in 2015. "The program provided a great deal of knowledge well delivered over a short time," he notes, "all of which was reinforced through clinical practice. It was beneficial to learn how cancer care is provided through BC Cancer, the specific details of the treatment regimens, and to meet members of the huge team to which we belong." There are currently 106 GPOs practising in 35 different BC/Yukon communities.

Contact Dr. Steve Kulla at steve.kulla@bccancer.bc.ca

# Recall process change for colon screening program fecal immunochemical testing

## By Laura Gentile, Operations Director, BC Cancer Colon Screening

The BC Cancer Colon Screening program is committed to removing barriers and increasing accessibility to colon cancer screening in British Columbia. Based on feedback from patients and primary care providers, the program will be changing the process for how patients are recalled for fecal immunochemical test (FIT) re-screening. As of September, the process for colon screening recall is as follows:

- 1. Patients due for FIT re-screening will receive a recall letter and a completed lab requisition (that includes FIT ordered for the patient on behalf of the provider) that the patient can use to pick up a FIT directly from the lab.
- 2. The Colon Screening program will notify providers when their patient has been recalled for FIT. Notifications will be sent to the primary care provider on file for the patient.
- 3. The remaining FIT screening process remains unchanged. The patient completes their FIT and returns it to the lab. Test *continued on page 7*

# Corridor Consults – Medical Cannabis Q&A

## By Dr. Pippa Hawley, Medical Leader, BC Cancer Pain & Symptom Management/ Palliative Care Program

Many of you will have had conversations with your patients about use of medical cannabis as part of their cancer care. Some patients will also be taking it in some form without your knowledge, at significant expense and at some risk to their health if improperly used. It is important that patients feel comfortable discussing cannabis use with their health care providers, and that those health care professionals feel sufficiently informed to be able to counsel their patients effectively.

Though cannabinoid medicine is a complex field, the core knowledge required can be compressed into a few key questions:

## 1. What cancer treatment symptoms can medical cannabis help with?

There is evidence of benefit from THC (tetrahydrocannabinol) and CBD (cannabidiol) for pain, nausea and vomiting, muscle spasm, anxiety, anorexia, and sleep disturbance, and anecdotal reports of benefit in a variety of other symptoms. CBD alone can have anticonvulsant, antipsychotic and antiinflammatory effects.

## 2. How should patients take medical cannabis?

Always recommend oils as the first choice: absorption is faster transmucosally than if the product is swallowed, plus there is no risk of harm from inhalation.



# 3. What product should patients look to buy?

It is important that patients realize that cannabis products developed for recreational use all contain primarily THC, which may not be well-tolerated and may be less effective for their symptoms than a THC/CBD mix. CBD moderates the effects of THC on cannabinoid receptors. Advise patients to start with a 1:1 ratio of THC to CBD in order to minimize the side-effects and maximize the effectiveness. In a frail elderly person, one might recommend even less THC.

# 4. Where should patients make their purchase?

Until such time as Health Canada changes the current regulations regarding distribution, always recommend patients purchase medical cannabis from a Licensed Producer (LP), not a storefront dispensary. There is not yet such an entity as a legal licensed dispensary. If purchased anywhere other than through an LP, the product will not have been checked for pesticide contamination or mold, and the constituent cannabinoids written on the label cannot be guaranteed.

## 5. How can patients locate find a Licensed Producer of medical cannabis?

LPs can be chosen from the list on Health Canada's website. Search "Health Canada Licensed Producers", click on "Authorized Producers of Cannabis for Medical Purposes", and then scroll down to the table. Patients can compare prices, register with a preferred producer, and follow that LP's instructions.



# 6. Do I need to fill in a form as the primary care provider?

All LPs require a similar, brief medical document be completed by a patient's physician or nurse practitioner. The only question, other than your name and address, is the recommended limit on amount of product. Start with "Oil in dose up to equivalent of 1g/day of dried product". If a higher dose is required, up to equivalent of 3g/day of dried product is still considered within a reasonable medical use range.

# 7. Can't I just write a prescription for Cesamet or Sativex?

Nabilone tablets (Cesamet) contain a synthetic THC analogue and have none of the "entourage" cannabinoids in plant cannabis that play a role in increasing effectiveness and minimizing side-effects from THC. Nabiximols buccal spray (Sativex) is an excellent plant-derived THC/CBD mix product, but is prohibitively expensive.

8. Can cannabis cure cancer?

Though there is interesting in-vitro data, and many anecdotal reports on the internet, there is as yet NO clinical trial evidence that any commercially available cannabis product can cure cancer or slow cancer growth. CBD clearly has complex effects on the immune system and could potentially reduce the effect of immunotherapies.

Contact Dr. Pippa Hawley at phawley@bccancer.bc.ca

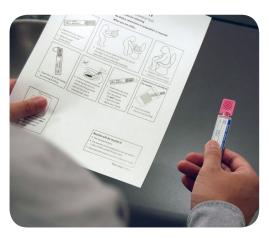
Recall process change continued from page 6

results and follow-up recommendations are sent to the patient and their provider.

Previously, patients were mailed a recall notice when they were due for re-screening and asked to see their primary care provider to obtain a requisition for the FIT. Patients then took the requisition to the lab to obtain their test kit. The Colon Screening Program received a number of concerns and complaints since the program's inception from patients and providers suggesting that the process had too many steps and added barriers for patients to engage in regular screening. The new process removes the need for the patient to visit their provider in order to obtain the FIT from the lab.

This process has been endorsed by the Society of General Practitioners and the BC Nurse Practitioners Association, and is supported by the Divisions of Family Practice.

For more information please contact the Colon Screening Program at screening@bccancer.bc.ca



# An ounce of prevention...

By Dr. Malcolm Moore, President, BC Cancer

Every year the Canadian Cancer Society (CCS) publishes a report on Cancer Statistics.

Ryan Woods, who works in our Population Oncology Department, is one of the authors of this report. As well as providing important information on Cancer Incidence and Mortality, the CCS typically will have one area of focus with each report. A couple of years ago they highlighted the oncoming Cancer Tsunami driven by the aging of the Canadian population. This highlighted

the need for all provincial cancer agencies to create sufficient capacity to care for this 'tsunami' and is why building this capacity is such an important part of our BC Cancer plan. This year's report (http:// www.cancer.ca/en/cancer-information/ cancer-101/canadian-cancer-statisticspublication/?region=on) is well worth reading. The focus is on cancer incidence by stage and highlights that, despite the availability of organized screening programs



Dr. Malcolm Moore

in 2 (49%) colorectal cancers are diagnosed at a late stage (stage III or IV). It also shines a light on the fact that we still have less than

in most Canadian provinces and territories, 1

half the eligible population in Canada (including in BC) being regularly screened for colorectal cancer.

With their longitudinal patient relationships, primary care physicians play a critical role in cancer screening. This is both in informing patients of the value of screening as well as initiating screening tests based upon what is recommended. At present in BC, we have

population screening for cervical, breast and colorectal cancer (as well as an HPV vaccination program to prevent HPV related cancers). As we look to the future, this role will become more complex as new screening programs are added (we have a proposal before the Ministry to launch a lung cancer screening program in high-risk individuals); and others modified (we will be moving to an HPV screening program for cervical cancer). Screening will also become more personalized based upon patient characteristics such as smoking history, comorbidity, and patient preference around tolerance of risk for screening tests where the increasing detection of early disease is balanced by the morbidity associated with testing and dealing with false positive results. Screening recommendations will increasingly also rely on genetic factors that define cancer risk such as BRCA germline mutations.

There is good evidence that engagement with primary care providers can improve cancer screening rates even in the presence of organized screening programs that approach patients directly. At BC Cancer we are committed to working closely with Primary Care to improve screening rates and to provide you with the appropriate information you need to discuss this with patients. This will become increasingly important as we move into an environment where screening recommendations are tailored to the individual patient based upon genetic and other factors.

Contact Dr. Malcolm Moore at malcolm.moore@bccancer.bc.ca

# GENOVA program: why refer women with ovarian and endometrial cancers for hereditary cancer screening?

By Anna Tinker, BC Cancer Medical Oncologist, Janice Kwon, BC Cancer Gynecologic Oncologist, Sophie Sun and Kasmintan Schrader, Co-Medical Directors, BC Cancer Hereditary Cancer Program, and Jennifer Santos, BC Cancer GENOVA Nurse Coordinator

# **GENOVA** (Genetic testing of **EN**dometrial and **OVA**rian

cancer), a new initiative from BC Cancer's Gynecologic Oncology Tumour Group and Hereditary Cancer Program (HCP) has been launched, with the aim of improving referral rates to the HCP for patients with ovarian and endometrial cancers that are at risk of being related to a cancer susceptibility gene.



Approximately 10% of all cancers are due to an inherited cancer susceptibility syndrome. Those harboring an inherited susceptibility to cancer represent a unique population for whom it is possible to: a) predict cancer risk and b) take proactive measures to prevent or detect cancers early through effective screening or risk-reducing surgeries. The two most common hereditary cancer syndromes, *BRCA1* and *BRCA2*-Associated Breast and Ovarian Cancer Syndrome and Lynch Syndrome, are strongly associated with gynecologic cancers.

Patients with non-mucinous epithelial ovarian cancer have a ~20% risk of harboring a germline *BRCA1* or *BRCA2* gene mutation. Inherited mutations in one of these genes significantly increase the risk of developing ovarian or breast cancer, but other cancers also occur at higher rates, including prostate, pancreatic and skin cancers.

Patients with DNA mismatch repair (MMR) gene (MSH2, MLH1, MSH6, PMS2)- deficient endometrial cancer have up to a 50% risk of Lynch Syndrome. Lynch syndrome is associated with the classic doublet of continued on page 9

# Landmark BC study shows HPV testing detects cervical pre-cancer earlier than the Pap smear

## By Laurie W. Smith RN(c) BN MPH, Research Program Manager, HPV FOCAL|HPV Related Diseases Research, BC Cancer – Vancouver

According to the HPV FOCAL trial, a large study involving thousands of British Columbia women, testing for the human papillomavirus (HPV) is more accurate at detecting cervical pre-cancer than the Pap test. FOCAL study results indicate HPV testing for screening could replace the Pap test as the primary screening tool in the future.

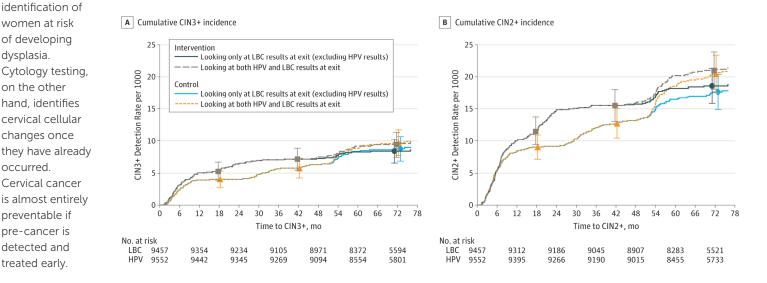
It is now well established that virtually all cases of cervical cancer are caused by high-risk HPV types. In most cases, HPV is transient and spontaneously regresses without any implications. In a small percentage of the population, an HPV infection can persist for many years and may cause pre-cancer or cancer. HPV testing detects HPV DNA and can determine if high-risk strains of the virus are present,

Results of the HPV FOCAL Study, conducted collaboratively by BC Cancer, the BC Centre for Disease Control, and the University of British Columbia were recently published in the Journal of the American Medical Association (JAMA) in July 2018. HPV FOCAL is the first study of its kind to directly compare HPV testing to cytology. There were 19,009 BC women randomized to the intervention (HPV testing) and control arms (cytology testing). Women were recruited through over 200 collaborating metro Vancouver and Greater Victoria health care providers. Results demonstrated that HPV testing every 4 years detected cervical precancer earlier than Pap testing every 2 years. At the 4 year study exit, fewer women in the HPV tested group were found to have precancer than women in the Pap tested group. This was attributed to earlier identification of women eligible for follow-up and treatment. Women screened for HPV were almost 60%

less likely to have a pre-cancerous lesion 4 years later compared to those who had Pap testing.

HPV FOCAL findings demonstrate that HPV testing can be performed less frequently, in addition to detecting cervical precancer earlier. These findings could have implications for the future of cervical screening in BC. BC Cancer is working with the BC Ministry of Health and other stakeholders to assess the future of HPV testing in the provincial cervical screening program. HPV FOCAL provides vital information needed to inform this process. This pivotal study would not have been possible without the commitment and collaboration of hundreds of BC health care providers, and of course...thousands of BC women!

Contact Laurie Smith at laurie.smith@bccancer.bc.ca



## GENOVA program continued from page 8

leading to early

colorectal and endometrial cancer, but included in this syndrome is a greater risk of developing gastric, ovarian, small bowel, urothelial cancers and other cancer types.

Approximately 1,000 new cases of ovarian and endometrial cancers are diagnosed in BC annually. <u>The HCP has determined that</u> only about 50% of eligible cases are being referred to the HCP for consideration of **genetic testing**. However, there is a need to proactively identify patients and families carrying mutations associated with the two major hereditary cancer syndromes in order to offer them cancer screening and risk-reducing interventions, with the goal of saving lives.

The program will utilize the provincial synoptic pathology reporting system to identify patients with non-mucinous ovarian cancers and MMR-deficient endometrial cancers. Gynecologists and general practitioners involved in the care of highrisk women will be sent a letter identifying the patient eligible for referral. They will be encouraged to discuss directly with patients the risk of harboring a hereditary cancer mutation and to complete a referral to the BC Cancer HCP. The GENOVA Nurse Coordinator will also be available for clinicians who are seeking additional information.

Contact the GENOVA Program at GENOVA@bccancer.bc.ca

# Supportive cancer care services: enhancing and extending care

Effective care of cancer patients extends well beyond diagnosis and treatment to include those services which address the emotional, spiritual and physical impacts that cancer can bring to the forefront. At BC Cancer, these services are known as Supportive Cancer Care Services and include Patient and Family Counselling, Psychiatry, Pain and Symptom Management/Palliative Care, and Nutrition and Rehabilitation. All are available through each of BC Cancer's six Centres including various options to connect inperson, by telephone or online. Services are intended for cancer patients with immediate acute needs, with the intent of transition to community services when stabilized.

## Learn more about this topic at our November 15 Webcast. Register at http://ubccpd.ca/webinars

Patient and Family Counselling helps patients, couples and families cope with the emotional, practical, and social distress that a cancer diagnosis and treatment can trigger. Expert counsellors help manage such challenges as fear, anxiety and depression, family tensions and relationship problems, lifestyle changes, and financial stressors. Individual counselling and group-based programs - including stress reduction - are available at every BC Cancer Centre. No referral is needed and patients, their families or caregivers can call for an in-person or telephone appointment up to eighteen months following treatment. Counsellors also provide connection to community resources.

See bccancer.bc.ca, Our Services, Patient and Family Counselling, for contact details.

General program inquiries program can be addressed to Heather Rennie at hrennie@bccancer.bc.ca

### In Your Community

- The Canadian Cancer Society hosts a Community Services Locator at cancer. ca linking to over 4,000 cancer related services. They help by phone, too, at 1 888 939 3333.
- Cancer Chat Canada provides professionally led, no cost, online support groups for Canadians affected by cancer: https://cancerchat.desouzainstitute.com

**Psychiatry**: BC Cancer psychiatrists with a subspecialty in oncology work closely with Patient and Family Counselling to provide mental health support for patients suffering from complex situations related to cancer and cancer treatment. Their services are available to patients during active treatment with a referral from the patient's family physician or oncologist. To refer, please call 604.877.6000 x672194 to request a referral form, and then fax the completed form to 604.877.6249.

General program inquiries program can be addressed to Dr. Alan Bates at alan.bates@bccancer.bc.ca

Pain and Symptom Management/Palliative Care: Pain and Symptom Management Clinics at each of BC Cancer's Centres provide specialized services to help patients improve pain control and cope with problems such as severe nausea, shortness of breath, and fatigue. Clinic staff also advise on care planning and decision making during care transitions. The aim is to transfer patients back to their family physician once their needs are addressed. Referrals are accepted from any member of a patient's care team and the referral form and clinic details are available on bccancer.bc.ca, under Our Services. Information is also included there to help manage symptoms and sideeffects from both a patient's and a health care professional's perspective.

General program inquiries program can be addressed to Dr. Pippa Hawley at phawley@bccancer.bc.ca

## Learning Opportunities

- Take the free, one-hour, accredited online course – methadone4pain.ca – to become more confident in prescribing methadone for analgesic purposes. A federal exemption is no longer required.
- Register for the November 28 UBC Division of Palliative Care CME Day at the BC Cancer Research Centre. Full details at http://palliativecare.med.ubc.ca/ upcoming-master-class-palliative-carestrong-growth-28th-november-2018/

**Nutrition Services**: BC Cancer dieticians help patients improve and maintain their nutritional status during treatment providing support for issues such as decreased appetite and unwanted weight loss, dry mouth and taste changes, nausea, and constipation or diarrhea. Patients with head and neck, esophageal or gastric cancer are directly referred to these services. Others can selfrefer and can make an appointment by calling the closest Nutrition Services Department listed at bccancer.bc.ca, under Our Services. A wealth of nutritional information, including recipes, is also listed there.

### In Your Community

- Patients can call 811 Health Link BC to speak with a registered dietician at no charge. Patients and family members can also speak directly with an oncology specialized dietician working in partnership with BC Cancer.
- Hospital dieticians are an excellent resource for patients receiving chemotherapy in community-based clinics.

#### Speech Language Pathology (SLP): BC

Cancer, and its Health Authority partners, have expertise to help patients improve speaking and swallowing difficulties caused by cancer or cancer treatments. Patients with head and neck cancer are directly referred while others can self-refer by contacting the appropriate SLP location listed on bccancer. bc.ca, Our Services.

**Exercise Support**: BC Cancer recently added Exercise Support resources to bccancer.bc.ca (under Health Information, Coping with Cancer) to promote the benefits of exercise for cancer patients and to provide tools to get started.

#### In Your Community

 Patients can call 811 – Health Link BC's Physical Activity Service for Cancer – to speak with an exercise professional with cancer expertise – no charge. With a physician referral, patients can speak directly with an oncology specialized exercise specialist.

General program inquiries program can be addressed to Ryna Levy-Milne at rlevymilne@bccancer.bc.ca

Consider donating to BC Cancer's Supportive Cancer Care Services through the BC Cancer Foundation: www. bccancerfoundation.com/supportivecare

# From the needs of patients, to the needs of the community

By Dr. Cathy Clelland, Provincial Lead, BC Cancer Primary Care Program

As BC moves closer to the implementation of the Patient Medical Home (PMH) model supported by Primary Care Networks (PCN) and Specialized Services Programs, this is a good opportunity to reflect on cancer and how our patients' needs are best addressed at various stages. As with all medical conditions, there are aspects of cancer care that are squarely in the world of family medicine



Dr. Cathy Clelland

and primary care, while others require specialized services. There is recognition that a sustainable cancer care system will only be possible with collaborative efforts between all the existing organizations and health care providers involved in cancer prevention, detection, diagnosis, treatment and support of cancer patients.

With the development of Divisions of Family Practice, family physicians have broadened their focus from the needs of patients in their own practice to include the needs of the

population in their community. While BC Cancer, for example, oversees cancer screening programs for cervical, breast and colorectal cancer, the provision of these activities occurs in the community. Historically, participation rates in these programs have been suboptimal for a variety of reasons. The development of the PMH and PCN provides great opportunity to explore

innovative approaches to

increase these rates significantly.

Recognizing the important role of family physicians and other primary care providers, BC Cancer is committed to partnering with primary care to support patients through their cancer journey. A recent needs assessment conducted by the Family Practice Oncology Network and UBC's Division of Continuing Professional Development, indicated that communications and care coordination during active treatment through to post treatment transitioning to primary care, need significant improvement. Development of care plans with clear recommendations for follow-up, as well as resources to support patients, were also identified as priorities. Awareness of specialized supportive services was cited as needing improvement as well. Information regarding BC Cancer's Supportive Cancer Care Services and Late Effects and Follow-up (LEAF) Clinic are featured in this Journal for this reason.

As Family Physicians and Divisions of Family Practice assess the needs of their populations to determine the allied care services required in their communities, I have full confidence that the needs of patients with cancer will be more appropriately addressed. As Provincial Lead for BC Cancer's Primary Care Program, I commit to advocating and supporting your work in this critical transformation. Send me your thoughts around these needs, *Cathy.Clelland@bccancer.bc.ca* 

# If I were Tom: an interactive website to support men with prostate cancer

By Dr. John Oliffe, Professor and founder of the Men's Health Research Program, University of British Columbia

If I were Tom (ifiweretom. ca), an evidence-based prostate cancer support website, was developed to help demystify the prostate cancer screening, diagnosis, and treatment processes. The concept for If I were Tom grew out of 15 years of research focused on faceto-face prostate cancer support groups and their many benefits. Members,

both male and female, who attended these groups, were commonly seen to have increased health literacy, prostate cancer specific knowledge, and camaraderie. Although the benefits were far reaching, the barriers to attending meetings were also significant for some folks. And with prostate cancer increasingly being seen as a chronic illness, there was an opportunity to improve

> the accessibility and reach of psychosocial supports reflecting face-to-face groups through an online platform to the growing number of men living with the disease and/or its treatments.

If I Were Tom was launched in January 2017. The current design features a series of interactive video segments that follow Tom, a man facing prostate cancer, through the process of screening, diagnosis, and

treatment. The segments were carefully modeled on stories heard at support groups in ways that authentically represent the reality of those going through the process. **If I Were Tom** also offers men's health resources in the area of exercise, nutrition and mental health, and this content similarly reflects the needs of men observed at face-to-face prostate cancer support

> View the full webcast of this topic at www.fpon.ca – Continuing Medical Education, 2017 Webcasts.

groups. Funded by CIHR and gifted to the Prostate Cancer Foundation BC (www. prostatecancerbc.ca), **If I Were Tom** is regularly updated with new content and has been attracting significant traffic and media attention since it 2017 launch.

An accompanying resource, promoted by the Men's Health Research Program is the **Heads up Guys** website https://headsupguys. org/, a site dedicated to addressing men's depression, which is also a much visited site and resource for men who experience prostate cancer.

Contact Dr. John Oliffe at John.Oliffe@ubc.ca





Dr. John Oliffe

## New resources for managing oral side-effects of cancer therapy

By Dr. Allan Hovan, BC Cancer Provincial Professional Practice Leader, Oral Oncology

As Oral Medicine specialists working at BC Cancer, my colleagues and I see thousands of patients every year experiencing various oral side-effects from cancer therapy whether surgery, radiotherapy or chemotherapy...or a combination of all three. You and your primary care colleagues likely see many such patients as well.

Learn more about this topic at our November 24 Family Practice Oncology CME Day. Register at bccancersummit.ca

In the electronic world we live in, patients often go to the internet for information relating to how to prevent and/or manage these problems. Clinicians sometimes do the same thing. The end result is patients



candidiasis



oral mucositis



aphthous ulcers

sometimes trying unproven, ineffective and, in some cases, dangerous therapies for the management of their oral condition. This was seen as a problem requiring a solution.

Through the Oral Care Study Group of the International Society of Oral Oncology (ISOO) working in partnership with the Multinational Association for Supportive Care in Cancer (MASCC), an exhaustive project was launched several years ago with the goal of establishing evidence-based guidelines for best care. A literature search was conducted using keywords in search engines to identify eligible (English language) published articles based on predetermined inclusion/exclusion criteria. Each article was independently reviewed by two reviewers. Studies were rated according to the presence of major or minor flaws, as per previously published criteria. The body of each intervention in each treatment setting was assigned a level of evidence based on previously published criteria. Guidelines were developed based on level of evidence, with three possible guideline determinations: recommendation, suggestion, or no guideline possible.

As you can imagine, this project involved the review of thousands of articles. In mucositis alone, the literature search identified 8,729 articles, 1,032 of which were retrieved for detailed review based on titles and abstracts. Of these, 570 qualified for final inclusion in the systematic review.

The 9 oral side-effects that were part of these systematic reviews included:

- Salivary Gland Dysfunction/Xerostomia
- Oral Mucositis/Oral Pain
- Dysgeusia (Altered Taste)
- Trismus
- Oral Fungal Infections
- Oral Viral Infections
- Acute and Chronic Oral Graft Versus Host Disease (GVHD)
- Osteoradionecrosis of the Jaw (ORN)
- Medication-Induced Osteonecrosis of the Jaw (MRONJ)

The results of these initial reviews were published as individual articles in the Journal of Supportive Care in Cancer in 2010. Since then, and as new research emerges, these guidelines continue to be updated and published. The question then became how to disseminate these guidelines in a userfriendly and readily accessible format. With this is mind, we created 1-2 page summaries of each of these nine systematic reviews. Currently these guidelines are published in the so-called "Oral Care of the Cancer Patient" document available here: http:// www.bccancer.bc.ca/health-professionals/ networks/family-practice-oncologynetwork/journal-of-family-practiceoncology.

In the near future, we hope to make these guidelines available on both the BC Cancer and Family Practice Oncology Network websites so that clinicians can even more readily access them. Our goal is to make downloadable PDFs available for each of the oral side-effects. The development of a phone app is also in discussion with the BC Dental Association.

I look forward to providing a further update when I present to your group at the BC Cancer Summit on Saturday, November 24, 2018. Register at bccancersummit.ca

Contact Dr. Allan Hovan at ahovan@bccancer.bc.ca

## FOR MORE INFORMATION

To learn more about the Family Practice Oncology Network or become involved please contact: Jennifer Wolfe Tel. 604 219 9579 email: jennifer.wolfe@bccancer.bc.ca

Visit the Network website: www.fpon.ca

The content of articles in this Journal represent the views of the named authors and do not necessarily represent the position of BC Cancer, PHSA or any other organization.

ISSN 2369-4165 (Print) ISSN 2369-4173 (Online) Key title: Journal of family practice oncology

Publications Mail Agreement Number 41172510

Return all undeliverable Canadian Addresses to BC Cancer, 600 West 10th Ave, Vancouver, BC V5Z 4E6 Newer approaches in the treatment of breast cancer continued from page 3

## **References:**

- http://www.bccancer.bc.ca/statisticsand-reports-site/Documents/Incident\_ Cancer\_Report\_2015\_20180410.pdf
- http://www.bccancer.bc.ca/statisticsand-reports-site/Documents/ BCCR\_2016\_Annual\_Report.pdf
- Sparano, J, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2018. 379:111-121
- 4. Pan, H, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med* 2017. 377:1836-1846
- Francis, P, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med 2018. 379:122-137
- 6. Coleman, R etal. EBCTCG Bisphosphonate Working Group. Adjuvant Bisphosphonate treatment in Ear;y Breats cancer; meta-analyis of individual patient data from randomized trials. *Lancet* 2015. 386:1353-1361
- Finn, R, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016. 375:1925-1936
- 8. Hortobagyi, G, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* 2016. 375:1738-1748