The Clinical Cancer Letter

February 2014 • www.cancerletter.com • Vol. 37 No. 2

Glioblastoma

Phase III Avastin Trial Fails Primary Endpoints

A phase III study of Avastin failed to increase overall survival or statistically significant progression-free survival for glioblastoma patients in the frontline setting. The international study was a collaboration among the cooperative groups RTOG, NCCTG, and ECOG.

The randomized, double-blind, placebo-controlled study enrolled 637 newly diagnosed glioblastoma patients. The study was designed with two primary endpoints: PFS and overall survival OS. The study was published in the New England Journal of Medicine, and was first presented at the plenary session of the American Society of Clinical Oncology 2013 Annual Meeting.

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Biomarkers

Preventive Ovarian Surgery Recommended For Women with BRCA1 Mutations by Age 35

A summary of a large study concluded that women with BRCA1 genetic mutations should undergo preventive ovarian surgery by age 35 to achieve the greatest reduction in their risks of breast and ovarian cancer.

The study also found that women with mutations in the BRCA1 or BRCA2 genes who had this surgery experienced a 77 percent reduction in their overall risk of death by age 70.

The large, international prospective study, published in the Journal of Clinical Oncology, suggests that waiting until a later age appears to increase the risk of ovarian cancer before or at the time of the preventive surgery. Women with a BRCA2 mutation, however, do not appear to be at an increased risk by age 35, suggesting they may delay this procedure until later.

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Head and Neck Cancers

Two Studies Suggest Positive HPV Status Can Indicate Improved Patient Outcomes

Two studies presented at the 2014 Multidisciplinary Head and Neck Cancer Symposium suggested that positive HPV status could be used as a biomarker indicator related to improved survival.

By evaluating next-generation sequencing data and associated clinical records of head and neck squamous cell carcinoma patients from several institutions, made available through The Cancer Genome Atlas, researchers found that combining Mutant-Allele Tumor Heterogeneity as a biomarker with the patient's HPV status provided an effective indicator of improved patient outcome.

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Avastin Glioblastoma Trial Fails to Identify Subgroup

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Participants underwent surgery to resect some or most of the tumor, received the standard of care of chemoradiation with temozolomide, and were randomized to receive either Avastin (bevacizumab) or placebo.

The authors reported data at a median follow-up time of 20.5 months, which revealed no statistical difference in overall survival between the two study arms (median 16.1 months for the standard-treatment arm vs. 15.7 months for the Avastin arm).

Although there was a difference in progression-free survival (7.3 months for the placebo arm vs. 10.7 months for the Avastin arm), the pre-established level of benefit for PFS was not reached.

Study participants were stratified equally across study arms by prognostic molecular markers of tumor O6-methylguanine-DNA methyltransferase methylation status and a tumor-based, nine-gene assay. Investigators did not find a subgroup of patients based on the molecular marker analysis who survived longer from first-line Avastin administration.

Because Avastin is known to confound magnetic resonance imaging examination results used to assess GBM tumor progression, investigators incorporated a "net clinical benefit" component in the trial design to determine if quality of life, symptom burden and neurocognitive function test results corroborate MRI-reported stable or improved disease status.

More than 80 percent of study participants agreed to take part in the net clinical benefits component, which demonstrated a greater decline of cognitive function for patients in the Avastin arm compared with those in the placebo arm. Avastin was also associated with a higher rate of toxicities, including hypertension, bleeding, deep vein thrombosis and pulmonary embolism, and gastrointestinal perforation.

Avastin is a monoclonal antibody against VEGF-A, which is produced by glioblastoma to stimulate blood vessel growth. The angiogenesis inhibitor first showed promise in glioblastoma as clinicians reported positive results treating the disease under approved compassionate use.

Several institutional studies then found similar results. In May 2009, the FDA granted an accelerated registration of Avastin in the second-line setting. Before this trial, no randomized, double-blind studies with the drug in glioblastoma had been conducted.

The Clinical Cancer Letter

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Website: http://www.cancerletter.com

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $129 per year, by The Cancer Letter Inc.

Melanoma

Lymphatic Mapping Techniques Can Outperform "Watch-and-Wait"

Research on lymphatic mapping and sentinel-node biopsy has confirmed that these techniques significantly prolong patients' disease-free and melanoma-specific survival over traditional "watch and wait" techniques.

This method of detecting melanoma metastasis to the lymph nodes allows doctors to determine which patients actually have nodal metastasis and may benefit from having their non-sentinel lymph nodes removed, which consists of approximately 20 percent of patients, while sparing the surgery for the many patients it will not benefit.

The study, published in the New England Journal of Medicine, evaluated outcomes of 2,001 melanoma patients at 10 years of follow-up.

One important finding was that the thickness of the initial melanoma tumor relates to the effectiveness of these treatments in managing nodal and other metastases.

Patients with primary melanoma tumors of intermediate thickness (1.20 to 3.5 millimeters thick) who had sentinel-node biopsies with immediate complete removal of the lymph nodes if the sentinel node contained cancer cells had an overall

disease-free survival of 71.3 percent compared to 64.7 percent for those whose nodes were observed without sentinel biopsy.

The research also found that sentinel-node biopsy prolonged distant disease-free survival and melanoma-specific survival for patients with lymph node metastasis from primary melanomas of intermediate thickness.

A mixture of blue dye and radioactive tracer was injected into the tissues around the primary tumor to find the lymphatic channels that lead to the first tumor-draining lymph node. The dye-isotope mixture follows the same lymphatic path used by the melanoma cells to spread to the sentinel node. The sentinel node is removed and examined by microscopy. If tumor cells are not found in the sentinel node it is highly unlikely that there will be tumor in other non-sentinel nodes and further nodal surgery is considered unnecessary. If cancer cells are found in the sentinel node, all other lymph nodes in the nodal group are removed.

Although some patients with thick primary tumors benefit from having their lymph nodes removed, the findings suggest that the timing of the intervention is not as crucial for them as it is for patients with intermediate thickness primary tumors. Not enough patients with thin melanomas were in this trial to permit conclusions on their benefit from the technique.

Biomarkers

Preventive Ovarian Surgery Recommended By Age 35

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Prior studies have shown that prophylactic oophorectomy reduces the risk of developing breast and ovarian cancers in women with BRCA1 or BRCA2 mutations. This study is the first to show an overall mortality reduction benefit. As many as 70 percent of women in the U.S. who learn they have BRCA mutations choose to have prophylactic oophorectomy.

In the Hereditary Ovarian Cancer Clinical Study, researchers from Canada, the U.S., Poland, Norway, Austria, France, and Italy identified women with BRCA mutations from an international registry, 5,787 of whom completed questionnaires about their reproductive history, surgical history (including preventive oophorectomy and mastectomy), and hormone use.

The study began in 1995, and the women were followed through 2011. Investigators examined the relationship between prophylactic oophorectomy and the rates of ovarian, fallopian tube, and primary peritoneal cancer, and the overall rate of death by age 70.

Among the 5,787 women, 2,274 did not have oophorectomy, 2,123 had already had the surgery when they began the study, and 1,390 underwent oophorectomy during the study follow-up period. After an average follow-up period of 5.6 years, with some women followed as long as 16 years, 186 women developed either ovarian, fallopian tube, or peritoneal cancer.

Overall, the investigators found that oophorectomy reduced the risk of ovarian cancer by 80 percent. For women who carry a BRCA1 mutation, the authors estimate that delaying the surgery until age 40 raised the risk of ovarian cancer to 4 percent; ovarian cancer risk increased to 14.2 percent if a woman waited until age 50 to have the surgery.

In contrast, only one case of ovarian cancer was diagnosed before age 50 among BRCA2 mutation carriers in this study. By comparison, the lifetime risk of ovarian cancer in all women (including those without BRCA mutations) is only 1.4 percent.

Of the 511 women who died during this study, 333 died of breast cancer, 68 from ovarian, fallopian tube, or peritoneal cancers, and the remainder from other causes. Prophylactic oophorectomy reduced the risk of death by any cause by 77 percent, largely by lowering the risks of ovarian, fallopian tube, peritoneal, and breast cancers.

Breast Cancer

Study Shows MammaPrint Test Can Predict 25-Year Risk Levels

Researchers concluded that the MammaPrint genomic breast cancer test can accurately stratify a woman's breast cancer risk for up to 25 years after she is first diagnosed with the disease.

U.S. and Dutch researchers, using the longest-term follow-up study of its kind, concluded the 70-gene test has the statistically significant ability to predict whether a newly diagnosed breast cancer patient is at low or high risk of a breast cancer recurrence. Their findings were published in Breast Cancer Research and Treatment.

The study authors looked at two key measures regarding the set of 295 patients who were the subject of an earlier New England Journal of Medicine study: distant metastasis-free survival and overall survival.

The accuracy of results held true for both DMFS and overall survival, regardless of whether patients had

node-negative or node-positive cancer. The data was generated from a group of consecutively treated women who were originally diagnosed between 1984 and 1995 and were less than 53 years of age at diagnosis. Median follow-up on these patients was 18.5 years, with a range of 15 to 25 years.

The test is the first FDA-cleared assay of its kind. Developed by Agendia, MammaPrint is used as part of the Symphony test panel, which also includes the BluePrint assay.

Study: Women at Higher Risk Of Estrogen Receptor Positive Breast Cancer After Smoking

Young women who smoke and have been smoking a pack a day for a decade or more have a significantly increased risk of developing the most common type of breast cancer, according to an analysis published in the journal Cancer.

Researchers conducted a population-based study consisting of 778 patients with estrogen receptor positive breast cancer and 182 patients with triple-negative breast cancer. Estrogen receptor positive breast cancer is the most common subtype of breast cancer, while triple-negative breast cancer is less common but tends to be more aggressive.

Patients in the study were 20 to 44 years old and were diagnosed from 2004-2010 in the Seattle-Puget Sound metropolitan area. The study also included 938 cancer-free controls.

The researchers found that young women who were current or recent smokers and had been smoking a pack a day for at least 10 years had a 60 percent increased risk of estrogen receptor positive breast cancer. In contrast, smoking was not related to a woman's risk of triple-negative breast cancer.

NIH Study Confirms Male Risk Factors For Breast Cancer

An NIH study confirmed risk factors for male breast cancer, in one of the largest studies conducted to date on the subject.

The analysis pooled data from studies of about 2,400 men with breast cancer and 52,000 men without breast cancer and confirmed that risk factors for male breast cancer include obesity, a rare genetic condition called Klinefelter syndrome, and gynecomastia. Only about 2,000 new cases of male breast cancer are expected to be diagnosed in 2014 in the U.S.

Scientists at NCI addressed this issue by pooling risk factor data from over 21 studies on male breast cancer. The study was published in JNCI.

Researchers observed a small but statistically significantly elevated risk for breast cancer in men with a high body mass index. Men with the highest BMI had a 35 percent greater risk of breast cancer compared to men with the lowest BMI. The elevated risk observed with men who have a high BMI (who often have excess breast tissue and elevated estrogen levels) appears similar to the pattern for breast cancer risk in postmenopausal women.

It was also determined that gynecomastia, independent from both Klinefelter syndrome and obesity, was associated with a 10-fold increased risk of breast cancer in men.

The researchers plan to follow up with a deeper analysis of the effects of naturally occurring hormones on the risk of breast cancer in men by testing hormone levels in biological samples available from some of the studies involved with the project.

Head and Neck Cancers

Studies Suggest HPV Status Can be Used with Biomarkers

(Continued from page 1)

The TCGA data available for HNSCC patients included 302 patients, with 35 HPV-positive patients. The researchers' examination confirmed that high tumor MATH at time of surgery is an indicator of poor outcome (high-MATH HR=2.1; 95% CI, 1.4 to 3.2; p = 0.0002, logrank test) and that HPV-positive HNSCC patients have lower average MATH values than HPV-negative HNSCC patients.

In bivariate analysis, both MATH and HPV were significantly associated with survival. When stratified by HPV status, MATH was similarly related to outcome in clinically defined subsets of patients regardless of clinical characteristics such as tumor margins, nodal classification, or tumor staging. Median follow-up with the 173 surviving patients was 22 months.

Genetic heterogeneity of each tumor was assessed by MATH, the percentage ratio of the width to the center of the distribution of tumor-specific mutant-allele fractions. In order to compare to previous studies, analysis was limited to mutant-allele fractions no less than 0.075, and the high-MATH

cutoff value of 32, previously found to distinguish outcome classes, was used. Cox proportional hazards analysis was used to evaluate the relations of MATH and HPV to overall survival.

In a separate retrospective analysis of two RTOG studies, researchers found that HPV-positive oropharyngeal patients had a higher overall survival rate than HPV-negative patients.

The study used a retrospective analysis of patients with recurrence of disease after primary therapy in RTOG studies 0129 or 0522, and found that at two years post-treatment, HPV-positive patients had an overall survival rate of 54.6 percent, compared to 27.6 percent in HPV-negative patients.

The analysis included 181 patients with stage III-IV oropharyngeal squamous cell carcinoma with known HPV status (positive = 105; negative = 76), and cancer progression that was local, regional and/or distant after completion of primary cisplatin-based chemotherapy and radiation therapy (standard vs. accelerated fractionation) in RTOG 0129 or cisplatin-AFX with or without cetuximab in RTOG 0522. Tumor status was determined by p16 immunohistochemistry.

Median time to progression was virtually the same for HPV-positive and HPV-negative patients (8.2 months vs. 7.3 months, respectively). Increased risk of death in univariate analysis was associated with high tumor stage at diagnosis (T4 vs. T2-T3), fewer on-protocol cisplatin cycles (=1 vs. 2-3) and distant vs. local/regional recurrent (for all, hazard ratios (HRs) >2.0 and $p<0.05$).

Risk of death after disease progression increased by 1 percent per cigarette pack-year at diagnosis. Rates were estimated by Kaplan-Meier method and compared by log-rank. HRs were estimated by Cox proportional hazards models and stratified by treatment protocol.

In addition, HPV-positive and HPV-negative patients who underwent surgery after cancer recurrence also experienced improved OS compared to those who did not undergo surgery. Recurrence is most commonly in the lungs for both groups of patients.

Lateral Radiation Therapy Results in Regional Control In Advanced Tonsil Cancer

Limiting radiation therapy to lymph nodes on one side of the neck for advanced tonsil cancer resulted in good local regional control and no cancer recurrence on the untreated side, according to a study.

Additionally, the study results indicate that primary tumor location, rather than the amount of lymph node involvement on the tumor side of the neck, dictates the risk for disease in the opposite side of the neck.

The study, presented at the 2014 Multidisciplinary Head and Neck Cancer Symposium, focused on 46 out of 153 total patients with squamous cell carcinoma of the tonsil who received treatment between 1997 and 2012 at Washington University in St. Louis.

Tumor location was well-documented in the 46 patients who received unilateral radiation therapy, with 40 patients (87 percent) having lateralized primary tumors; two patients (4 percent) had non-lateralized tumors, and in four patients (9 percent), lateralization could not be determined retrospectively.

The patients underwent surgical resection and postoperative intensity modulated radiation therapy, with 30 patients also receiving concurrent chemotherapy.

Of the subset of 46 patients treated unilaterally, 72 percent were men, and the average patient age was 59. Sixty-one percent of patients were current or former smokers, and 33 patients were p16 immunohistochemistry positive (72 percent).

The median follow-up period was 2.8 years. There were no local or regional recurrences reported. Distant metastasis developed in four of the patients (9 percent). Two patients developed second primary cancers.

Daily Humidification Improves Quality-of-Life in Phase III Trial

A phase III trial found that patients who received daily humidification of the mouth and throat region from day one of radiation therapy treatment spent nearly 50 percent fewer days in the hospital to manage their side effects.

The study, presented at the 2014 Multidisciplinary Head and Neck Cancer Symposium, was conducted by the Trans-Tasman Radiation Oncology Group and evaluated 210 head and neck cancer patients in

New Zealand and Australia from June 2007 through June 2011.

Patients were randomized to institutional standard of care or humidification using the Fisher & Paykel Healthcare MR880 humidifier. The humidified air is delivered through the nose via a plastic mask that can be worn by patients while sleeping or while sitting.

Patients began humidification on day one of radiation therapy and continued until the ulceration their mouth and throat had resolved. On average, humidification patients spent 57 percent as many days in the hospital to manage side effects (control = 4.1 days vs. humidification = 2.3 days). The return of eating patterns to close to normal was also significantly higher at three months after radiotherapy in the group using humidifiers.

Only 43 patients (42 percent of the patients in the humidification arm) met the defined benchmark of humidification compliance and were able to contribute to the per protocol analysis. The mean average use of humidification for these patients was 3.6 hours per day.

In patients who met the compliance benchmark, the area under the curve for Common Terminology Criteria Adverse Events version 3.0 functional mucositis score was reduced (control = 8.63 vs. humidification PP = 6.74). The proportion of compliant humidification patients who never required a feeding tube was also increased (control = 0.73 vs. humidification PP = 0.85).

There was also a trend for patients to report a reduction in symptom burden when using humidification but only in those patients compliant in using the humidifier.

Prostate Cancer

Five Years after Proton Therapy, 75-99% of Men Live Cancer-Free

Five years after having proton therapy for early- and intermediate-risk prostate cancer, 99 percent of men are living cancer-free and with excellent quality of life, according to a study. Three-quarters of those with high-risk prostate cancer are also disease-free.

The study, published in the International Journal of Radiation Oncology Biology Physics, researchers at the University of Florida Proton Therapy Institute tracked 211 patients who participated in prospective IRB-approved trials. In each track, patients were given proton therapy over an eight-week period, a shorter interval than typical with IMRT, which may last nine to nine-and-a-half weeks.

Physician-reported data show cancer-free survival rates at five years for low-, intermediate-, and high-risk patients are 99 percent, 99 percent and 76 percent, respectively, while overall survival rates are 93 percent, 88 percent and 90 percent.

Moreover, the rate of serious gastrointestinal and urologic complications is low, at 1.4 percent and 5.3 percent respectively for all patients. Patients also reported good outcomes with respect to both urologic and bowel function.

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Study: Prostate Cancer Classifier Can Predict Risk Better Than PSA, Gleason Score, Tumor Stage

A study demonstrated that the Decipher Prostate Cancer Classifier outperformed existing clinical risk factors for predicting biochemical failure and distant metastasis following radiation therapy. The genomic test, developed by GenomeDx Biosciences, is capable of predicting the probability of developing metastatic prostate cancer.

In addition, researchers observed significant improvement in outcomes for patients with high-risk results who received radiation therapy early, compared to after surgery. The data was presented at the 2014 ASCO Genitourinary Symposium.

In the study, 139 patients who had undergone radiation therapy after prostatectomy at Thomas Jefferson University between 1990 and 2009 were analyzed. RNA was extracted from the preserved tissue samples and run on the Decipher test. Patient histories were then analyzed to determine if Decipher was able to stratify patients who could have benefited from earlier radiation therapy.

In patients identified as high-risk, those that got early radiation therapy survived for a median of 8 years without biochemical failure, defined as an increase in PSA post-radiation. This was compared to less than 4 years for patients that got late radiation therapy ($p<0.001$). At 8 years following radiation therapy, high-risk patients that got early radiation therapy had a 3 percent cumulative incidence of metastasis compared to 23 percent for patients with high-risk results that got late radiation therapy ($p<0.001$).

Decipher measures 22 genomic biomarkers associated with metastatic cancer to generate a result that indicates the likelihood of metastasis. The result is completely independent of PSA and other existing clinical variables.

Ovarian Cancer

Daily Aspirin May Reduce Risk By 20 Percent, Study Says

NCI scientists found that a daily aspirin regimen may reduce the risk of ovarian cancer by 20 percent, but say further research is needed before clinical recommendations can be made.

Previous studies have suggested that the anti-inflammatory properties of aspirin and non-aspirin NSAIDs may reduce cancer risk overall, however, studies examining whether use of these agents may influence ovarian cancer risk have been largely inconclusive. The study, published in JNCI, is the largest to date to assess the relationship between these drugs and ovarian cancer risk.

Researchers analyzed data pooled from 12 large epidemiological studies to investigate whether women who used aspirin, non-aspirin NSAIDs, or acetaminophen have a lower risk of ovarian cancer. These 12 studies (nine from the U.S.) were part of the Ovarian Cancer Association Consortium. The researchers evaluated the benefit of these drugs in nearly 8,000 women with ovarian cancer and close to 12,000 women who did not have the disease.

Among study participants who reported whether or not they used aspirin regularly, 18 percent used aspirin, 24 percent used non-aspirin NSAIDs, and 16 percent used acetaminophen.

The researchers determined that participants who reported daily aspirin use had a 20-percent-lower risk of ovarian cancer than those who used aspirin less than once per week.

For non-aspirin NSAIDs, which include a wide variety of drugs, the picture was less clear: the scientists observed a 10-percent-lower ovarian cancer risk among women who used NSAIDs at least once per week compared with those who used NSAIDs less frequently. However, this finding did not fall in a range that was significant statistically.

In contrast to the findings for aspirin and NSAIDs, use of acetaminophen, which is not an anti-inflammatory agent, was not associated with reduced ovarian cancer risk.

Adverse side effects of daily aspirin use include upper gastrointestinal bleeding and hemorrhagic stroke. Therefore, a daily aspirin regimen should only be undertaken with a doctor's approval, caution the scientists.

NCI CTEP-Approved Trials For the Month of February

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month.

Phase II

GOG-0283: A Phase II Trial of DCTD-Sponsored Dasatinib (NSC #732517 IND# 120636) in Recurrent/ Persistent Ovary, Fallopian Tube, Primary Peritoneal, and Endometrial Clear Cell Carcinoma Characterized for the Retention or Loss of BAF250a Expression. Gynecologic Oncology Group; Hyman, David Michael. (212) 639-2000

Phase III

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765) Based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL). Eastern Cooperative Oncology Group; Shanafelt, Tait D. 507-284-2358

Other Phases

AAML13B7-Q: Prognostic Significance of MMRN1 in Pediatric Acute Myeloid Leukemia (AML). Children's Oncology Group; Walter, Roland Bruno. (206) 667-3599

AAML13B8-Q: Global Proteomic and Phosphoproteomic Profiling of Normal B Cells Isolated from COG AAML1031 Study Patients in AML Remission. Children's Oncology Group; Pandey, Akhilesh. (410) 502-6662

ANBL13B9-Q: 3D Nuclear Telomere Organization in Neuroblastoma. Children's Oncology Group; Mai, Sabine. (204) 787-2135

ANBL13B10-Q: The Role of FGFR4 in Neuroblastoma Pathogenesis. Children's Oncology Group; Zage, Peter Eric. (832) 824-4615

AREN13B2-Q: Characterization of the Chromosome 11p15 Imprinting Regulation by Epigenetic and Transcriptomic Analyses in Wilms Tumor Patients. Children's Oncology Group; Michels, Karin B. (617) 732-4895

Drug Development

CHMP Delivers Positive Opinion For Two-Dose HPV Vaccine

The European Committee for Medicinal Products for Human Use delivered a positive opinion for a two-dose schedule for the **Gardasil HPV vaccine** in boys and girls ages 9 through 13.

The license application is supported by a study that demonstrated antibody levels one month after a two-dose schedule (0, 6 months) of Gardasil in 243 girls aged 9-13 years are non-inferior to the ones observed one month after a three-dose schedule (0, 2, 6 months) in 272 women 16-26 years old, the population in which efficacy has been demonstrated.

A CHMP positive opinion is one of the final steps before a final marketing authorization decision is made by the European Commission.

Gardasil, sponsored by Sanofi Pasteur MSD, is the only quadrivalent HPV vaccine. It is Europe's leading HPV vaccine with 29 million doses distributed in Western Europe and approximately 144 million doses distributed worldwide.

It is currently licensed as a three-dose vaccination schedule at 0, 2, and 6 months in both girls and boys from the age of 9 years, for the prevention of cervical cancer causally related to certain oncogenic HPV types.

Health Canada approved the Aptima HPV 16 18/45 genotype assay for use on the Panther system, both developed by Hologic Inc. The assay is the only approved test for genotyping human papillomavirus types 16, 18 and/or 45 in Canada.

Although HPV genotype 45 is fairly uncommon, identified in only 0.4 percent of women with normal cytology, it is the third most common HPV genotype associated with invasive cancer. The addition of HPV genotype 45 is designed to help identify more women at risk for adenocarcinoma, with minimal impact to colposcopy rates.

Health Canada has approved the test for two uses: in patients 21 years and older with atypical squamous cells of undetermined significance cervical cytology results, the assay can test samples from women with Aptima HPV assay positive results to assess the presence or absence of high-risk HPV genotypes 16, 18 and/or 45. The assay can also test samples from women 30 years and older with Aptima HPV assay positive results.

The assay received FDA approval on Hologic's Tigris system in October 2012 and the Panther system in November 2013.