Cigna Medical Coverage Policy

Subject **Prophylactic Oophorectomy or Salpingo-oophorectomy With or Without Hysterectomy**

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Table of Contents

Hyperlink to Related Coverage Policies

Colorectal Cancer Screening and Surveillance
Genetic Counseling
Genetic Testing for Susceptibility to Breast and Ovarian Cancer (e.g., BRCA1 & BRCA2)
Genetic Testing for Susceptibility to Colorectal Cancer
Genetic Testing of Heritable Disorders
Prophylactic Mastectomy
Proteomic Pattern Analysis of Blood for the Early Detection of Ovarian Cancer

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Coverage Policy

Cigna covers prophylactic oophorectomy or salpingo-oophorectomy as medically necessary when ANY of the following criteria is met:

- genetic mutation confirmed by molecular testing for breast and ovarian cancer susceptibility genes (BRCA1 or BRCA2)
- personal premenopausal history of steroid hormone receptor-positive breast cancer
- personal history of breast cancer and **one** first-degree* relative with a history of ovarian cancer
- two or more first-degree* relatives with early onset ovarian and/or breast cancer
- known familial cancer syndrome associated with increased risk of ovarian cancer (e.g., hereditary nonpolyposis colorectal cancer [HNPCC])

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

Cigna covers prophylactic hysterectomy as medically necessary when performed with bilateral oophorectomy for those who have been diagnosed with HNPCC, found to be carriers of

HNPCC–associated mutations, or are members of HNPCC families as determined by a pattern of occurrence of HNPCC-related cancers.

General Background

Ovarian cancer is the fifth leading cause of cancer death among women in the United States and has the highest mortality rate of all gynecologic cancers. Ovarian and breast cancer are components of several inherited cancer syndromes including familial site-specific ovarian cancer; hereditary breast/ovarian cancer; and Lynch syndrome, which is a combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers. For the general population of women, the lifetime risk of developing ovarian cancer is 1.39%; the lifetime risk of dying from ovarian cancer is 1.04%. Most hereditary breast and ovarian cancer are caused by inherited mutations in the BRCA1 or BRCA2 genes, which lead to lifetime risks of ovarian cancer of 20–50%. Considering family history in the absence of specific information on BRCA1/2 mutation status, unaffected women who have two or three relatives with ovarian cancer have a cumulative ovarian cancer risk of about 7%. Women who have a mother or sister with ovarian cancer have a cumulative lifetime risk of ovarian cancer of about 5%. (National Cancer Institute [NCI], 2013c). Women with a family history of cancer of the breast, uterus, colon, or rectum may also have an increased risk of ovarian cancer (NCI, 2006). According to the NCI, features of hereditary cancer include the following (NCI, 2013a):

In the individual patient:

- multiple primary tumors in the same organ
- multiple primary tumors in different organs
- bilateral primary tumors in paired organs
- multifocality within a single organ (e.g., multiple tumors in the same breast all of which have risen from one original tumor)
- younger-than-usual age at tumor diagnosis
- tumors with rare histology
- tumors occurring in the sex not usually affected (e.g., breast cancer in men)
- tumors associated with other genetic traits; congenital defects; an inherited precursor lesion; or another rare disease;
- tumors associated with cutaneous lesions known to be related to cancer susceptibility disorders (e.g., the genodermatoses)

In the patient's family:

- one first-degree relative with the same or a related tumor and one of the individual features listed
- two or more first-degree relatives with tumors of the same site
- two or more first-degree relatives with tumor types belonging to a known familial cancer syndrome
- two or more first-degree relatives with rare tumors
- three or more relatives in two generations with tumors of the same site or etiologically related sites

Clinical examination (i.e., bimanual pelvic examination) lacks the sensitivity needed to reliably identify early ovarian cancer, and there continues to be a lack of effective ovarian cancer detection methods. Prophylactic oophorectomy, the surgical removal of the ovaries, is a surgical option to reduce the risk of developing both ovarian and breast cancer in high-risk women (e.g., those with BRCA mutations, site-specific ovarian cancer syndrome, or Lynch Syndrome). Although not technically the same, the term risk-reducing salpingo-oophorectomy (RRSO), which includes removal of the ovaries and fallopian tubes, is used interchangeably with prophylactic oophorectomy. RRSO has been shown to reduce the risk of ovarian of ovarian cancer, fallopian tube cancer, and peritoneal cancer by approximately 85–90% in women with known mutations in BRCA1 or BRCA2. RRSO has been shown to decrease overall mortality in women with a BRCA1 or BRCA2 mutation. The procedure has also been shown to reduce the risk of breast cancer by 40–70%. This protection likely occurs only if patients are premenopausal at the time of risk-reducing salpingo-oophorectomy (American College of Obstetricians and Gynecologists [ACOG], 2009). The degree of risk for ovarian or breast cancer, potential morbidity and mortality of surgery and the risks associated with early menopause should be taken into account when considering prophylactic oophorectomy for high-risk women. Potential adverse effects of bilateral

oophorectomy and premature menopause include vasomotor symptoms, cardiovascular disease, and osteoporosis (NCI, 2006).

Literature Review
Numerous studies have found that women at inherited risk of breast and ovarian cancer have a decreased risk of ovarian cancer following prophylactic oophorectomy. The available evidence evaluating the impact of prophylactic oophorectomy on individuals at high risk for ovarian cancer includes systematic reviews, case-control and cohort studies. Studies have primarily evaluated women with inherited mutations in BRCA1 or BRCA2. A systematic review (n=18 studies) by Bermejo-Pérez and colleagues (2007) assessed the effectiveness of preventive intervention strategies (i.e., prophylactic surgery, intensive cancer screening, and chemoprevention) implemented in women carrying mutations in BRCA1 or BRCA2 genes, in terms of reducing breast and gynecological cancer incidence and/or mortality. Although methodological flaws were identified in all the studies examined, overall, study results indicated that compared to surveillance, oophorectomy or salpingo-oophorectomy led to a reduction in breast cancer incidence in carriers of BRCA mutations (Bermejo-Pérez, et al., 2007).

Case-control and cohort studies (n=170—1828) with median follow-up through 25 years have demonstrated that prophylactic oophorectomy is associated with a significant reduction in the risk of both ovarian and breast cancer (Domchek, et al., 2006; Finch, et al.; 2006; Rocca, et al., 2006; Rebbeck, et al., 2002; Kauff, et al., 2002).

Hysterectomy Performed with Prophylactic Oophorectomy
Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal-dominant condition caused by mutation of one of several deoxyribonucleic acid (DNA) mismatch repair (MMR) genes. This genetic mutation is estimated to account for 5–6% of colorectal cancer cases. Individuals with an HNPCC gene mutation have an estimated 80% lifetime risk of developing colon or rectal cancer (NCI, 2013b). Genetic testing can identify the majority of individuals with HNPCC before they develop cancer. The characteristics of HNPCC include early onset of colorectal cancer (average age at diagnosis is 45 years) and an increased risk of other cancers, predominantly those of the ovary, uterus, stomach and small bowel. Indications of an HNPCC family include multiple relatives with colon cancers, or a colon and endometrial cancer, and clusters of colorectal and other cancers of the gastrointestinal (e.g., stomach, small intestine, pancreas), urinary or female reproductive system. Ovarian cancer risk is reported to be 3.5 times higher in HNPCC families than in the general population. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing surgery that is considered for women in HNPCC families who are ≥ 35 years of age and have no desire to preserve their fertility.

Literature Review: There is limited evidence in the form of controlled studies demonstrating the effectiveness of prophylactic surgery in at-risk HNPCC mutation carriers, and it is unlikely that randomized controlled studies will be performed, given the rarity and nature of this condition. A systematic review of observational studies by Lindor et al. (2006) provided recommendations for the clinical management of those with an inherited predisposition to Lynch syndrome. The authors found fair evidence supporting the efficacy of prophylactic hysterectomy and oophorectomy as an option for women age 35 or older who do not want to preserve fertility (Lindor, et al., 2006).

A retrospective study by Schmeler et al. (2006) compared women who had undergone prophylactic hysterectomy (n=61) and those who had undergone prophylactic hysterectomy and bilateral salpingo-oophorectomy (n=47) to mutation-positive women who had not undergone prophylactic procedures (n=210). No endometrial, ovarian, or primary peritoneal cancers developed among the women who had undergone prophylactic surgery, while in the control group, endometrial and ovarian cancers were diagnosed in 69 (33%), and 12 (5%).women respectively.

Burke et al. (1997) reported conclusions of the Cancer Genetics Studies Consortium. It was stated that although no data were available on the efficacy of hysterectomy combined with oophorectomy in the management of HNPCC, the two surgeries should be offered as a combined option for preventing endometrial and ovarian cancer in women known to have HNPCC or to be carriers of HNPCC-associated mutations (Burke, et al., 1997). Despite the lack of robust evidence, available studies in addition to recommendations based upon expert opinion support consideration of prophylactic oophorectomy with hysterectomy for the management of HNPCC.

Professional Societies/Organizations
The National Comprehensive Cancer Network® (NCCN) guidelines for colorectal cancer screening state that prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) should be considered as a risk-reducing option for women with HNPCC (NCCN, 2012b).

The NCCN guidelines state that RRSO has been reported to reduce the risk of both breast and ovarian cancers. The NCCN panel recommends limiting RRSO to women with a known or strongly suspected BRCA1 or BRCA2 mutation (NCCN, 2013c). The ideal age to perform the procedure is between the ages of 35 and 40 and upon completion of childbearing or at an individualized age based on the earliest age of ovarian cancer diagnosed in the family (NCCN, 2013a).

The National Cancer Institute (NCI) guidelines on the prevention of ovarian cancer state that "prophylactic oophorectomy may reduce the risk of developing ovarian cancer for women at high risk. One group for whom this option is considered is women who have an inherited susceptibility to ovarian cancer such as women who have mutations in BRCA1, BRCA2, or hereditary nonpolyposis colon cancer (HNPCC)–associated genes" (NCI, 2013c). Risk-reducing hysterectomy (RRH) with bilateral salpingo-oophorectomy (RRSO) may be presented as an option for women with Lynch syndrome (NCI, 2013b).

According to the ACOG guidelines on Hereditary Breast and Ovarian Cancer (HBOC) Syndrome, risk-reducing salpingo-oophorectomy (RRSO) should be offered to women with BRCA1 or BRCA2 mutations by age 40 or after the conclusion of childbearing (ACOG, 2009). The ACOG guidelines on salpingo-oophorectomy state that for women with HNPCC, the average age of ovarian cancer diagnosis is 42 years and the average age of endometrial cancer diagnosis is 50 years. Therefore, it is reasonable to consider prophylactic surgery in women with HNPCC between ages 35 and 40 if childbearing is no longer desired (ACOG, 2008).

The U.S. Preventive Services Task Force (USPSTF) found fair evidence in the published scientific literature that women with certain specific family history patterns have an increased risk for developing breast or ovarian cancer associated with BRCA1 or BRCA2 mutations. Fair evidence was also found to support prophylactic surgery for these women, as it significantly decreases breast and ovarian cancer incidence. The USPSTF recommendation is that women with the following family history patterns be referred for genetic counseling that will allow for informed decision-making about testing and further prophylactic treatment:

- two first-degree relatives with breast cancer, one of whom was diagnosed at age 50 or younger
- a combination of three or more first- or second-degree relatives with breast cancer, regardless of age at diagnosis
- a combination of both breast and ovarian cancer among first- and second-degree relatives
- a first-degree relative with bilateral breast cancer
- a combination of two or more first- or second-degree relatives with ovarian cancer, regardless of age at diagnosis
- a first- or second-degree relative with both breast and ovarian cancer, at any age
- a history of breast cancer in a male relative

For women of Ashkenazi Jewish heritage, an increased risk in family history includes any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer (USPSTF, 2005).

Use Outside of the US
The Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of women with epithelial ovarian cancer states that women at high risk for ovarian cancer can be offered prophylactic oophorectomy. According to SIGN, family history can be used to define women who are at increased risk. Individuals at high risk are those with a first degree relative (mother, father, sister, brother, daughter or son) affected by cancer within a family that meets one of the following criteria (SIGN, 2003):

- two or more individuals with ovarian cancer, who are first degree relatives of each other
- one individual with ovarian cancer at any age, and one with breast cancer diagnosed under age 50 years, who are first degree relatives of each other*
- one relative with ovarian cancer at any age, and two with breast cancer diagnosed under 60 years, who are connected by first degree relationships*

- known carrier of relevant cancer gene mutations (e.g., BRCA1 or BRCA2)
- untested first degree relative of a predisposing gene carrier
- three or more family members with colon cancer, or two with colon cancer and one with stomach, ovarian, endometrial, urinary tract or small bowel cancer in two generations; one of these cancers must be diagnosed under age 50 years
- an individual with both breast and ovarian cancer

* In these categories a second degree relative may be counted if the transmission is via the paternal line (e.g., a sister and a paternal aunt or a sister and two paternal aunts).

Summary
Despite the lack of randomized controlled trials (RCTs), the published, peer-reviewed medical literature indicates that prophylactic oophorectomy may be considered for premenopausal (age 35 or older), high-risk women (i.e., women known to carry the BRCA1 and/or BRCA2 mutation or to have a lineage of familial cancer). The literature also suggests that a hysterectomy may be performed in conjunction with prophylactic oophorectomy in women from families with hereditary nonpolyposis colorectal cancer (HNPCC). For premenopausal women with early breast cancer, ovarian ablation by oophorectomy is a therapeutic option. It is important that women undergoing prophylactic oophorectomy with or without hysterectomy understand that this surgery does not completely eliminate the risk of developing cancer. Counseling regarding the risks and benefits of the procedure is equally important for women considering this preventive measure.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Prophylactic Oophorectomy or Salpingo-Oophorectomy

Covered when medically necessary:

CPT®* Codes	Description
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)
58940	Oophorectomy, partial or total, unilateral or bilateral

Prophylactic Hysterectomy when performed with Bilateral Oophorectomy

Covered when medically necessary:

CPT®* Codes	Description
58150	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)
58180	Supracervical abdominal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)
58210	Radical abdominal hysterectomy, with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling (biopsy), with or without removal of tube(s), with or without removal of ovary(s)
58262	Vaginal hysterectomy for uterus 250 grams or less; with removal of tube(s), and/or ovary(s)
58291	Vaginal hysterectomy for uterus greater than 250 grams; with removal of tubes(s)), and/or ovary(s)

58542	Laparoscopy, surgical, supracervical hysterectomy for uterus 250 g or less with removal of tube(s) and/or ovary(s)
58544	Laparoscopy, surgical, supracervical hysterectomy for uterus greater than 250 g with removal of tube(s) and/or ovary(s)
58548	Laparoscopy, surgical, with radical hysterectomy, with bilateral total pelvic lymphadenectomy and para-aortic lymph nodes sampling(biopsy) with removal of tube(s) and ovary(s), if performed
58552	Laparoscopy surgical, with vaginal hysterectomy, for uterus 250 grams or less; with removal of tube(s), and/or ovary(s)
58554	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 grams; with removal of tube(s), and/or ovary(s)
58571	Laparoscopy, surgical, with total hysterectomy, for uterus 250g or less; with removal of tube(s) and/or ovary(s)
58573	Laparoscopy, surgical, with hysterectomy for uterus greater than 250g, with removal of tube(s) and/or ovary(s)
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)
58940	Oophorectomy, partial or total, unilateral or bilateral

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