Clinical Policy Title: Prophylactic salpingo-oopherectomy

Clinical Policy Number: 13.03.03

Effective Date: January 1, 2017
Initial Review Date: October 19, 2016
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:
CP# 00.00.00 Prophylactic mastectomy
CP# 02.01.10 Colaris testing for Lynch syndrome

Coverage policy

Keystone First considers prophylactic salpingo-oopherectomy (PSO) to be clinically proven, and, therefore, medically necessary for a woman when any of the following criteria is met:

- A positive test result for the breast cancer susceptibility gene (BRCA 1 or 2) gene mutations exist.

- A personal history of breast cancer with at least one first-degree relative (mother, sister, or daughter) with a documented history of ovarian cancer.

- One or more first- or second-degree relatives (maternal or paternal aunt, grandmother, or niece) have a history of ovarian cancer.

- Two or more first-degree relatives (mother, sister, or daughter) have a history of ovarian and/or breast cancer.
• One first-degree relative (mother, sister, or daughter) and one or more second-degree relatives (maternal or paternal aunt, grandmother, or niece) have a history of ovarian cancer.

• The woman is beyond childbearing age and has been diagnosed with a known familial cancer, such as Lynch syndrome (hereditary non-polyposis colorectal cancer [HNPCC]), a hereditary ovarian cancer syndrome.

In addition, Keystone First considers prophylactic hysterectomy medically necessary when performed in conjunction with PSO when any of the following criteria are met:

• A Lynch syndrome II mutation is documented.

• The woman meets criteria for PSO and, after a risk and benefit discussion with her physician, chose to have prophylactic hysterectomy in conjunction with oophorectomy.

Limitations:

Before a PSO is performed for a woman in her reproductive years, a sterilization consent form may be required.

Keystone First considers PSO to be investigational, and therefore, not medically necessary, for all other conditions.

Alternative covered services:

Prophylactic mastectomy (PPM).

Background

Hereditary susceptibility to cancer is now expanding with the growing knowledge of genetic mutation patterns. The National Cancer Institute (NCI) defines criteria for hereditary susceptibility in both the individual patient, and in the patient’s family (NCI 2013a). The list of criteria in the patient is extensive, and includes existence of multiple tumors, age, histology types, and other genetic traits. NCI defines hereditary susceptibility in the patient’s family to include any of:

• 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 at 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 at the same site or etiologically related sites.

As of 2015, there are 21 genes associated with increased risk of breast and ovarian cancer. These can be subdivided into three groups (i.e., high-, moderate-, and newer risk). The high- and moderate-risk genes have been well studied, and can increase risk for other cancers; they differ in that breast or ovarian cancer risk is typically elevated at least four-fold for high-risk genes and two – three fold for moderate-risk genes. Precise risks for the newer genes are still being calculated (GeneDx 2015).

The BRCA 1 and 2 genetic mutations, first identified in 1994, are most common and best understood. They can be inherited from a woman’s father or mother. These mutations account for 5 percent to 10 percent of all breast cancers and 10 percent of ovarian cancers. BRCA mutations mean an increased risk of breast cancer for women by age 70. This elevated risk is 55 percent – 65 percent for BRCA1-positive women and 45 percent for BRCA2-positive women (Antoniou 2003). The normal lifetime risk of the disease is 12 percent (NCI 2015).

There is considerable variation in BRCA prevalence by racial and ethnic groups of the estimated 300,000 U.S. women with the mutation. A survey of 1,727 women with breast cancer under age 65 provided the basis for prevalence estimates of the BRCA1 mutation in Northern California. Jewish women of Ashkenazi descent were highest at 8.3 percent, followed by Hispanics (3.5 percent), non-Hispanic whites (2.2 percent), African Americans (1.5 percent), and Asian Americans (0.5 percent). The authors speculate that the Hispanic rate may be somewhat inflated by the presence of unrecognized Jewish ancestry (John 2007).

The total prevalence of women with hereditary susceptibility to breast and ovarian cancer is higher than the cited figures, as they only include BRCA1-positive women and not BRCA2-positive or other known and unknown mutations. In addition, hereditary mutations are not always detected in high-risk women. For example, in a sample of 236 Ashkenazi Jewish women with breast cancer and a family history of breast or ovarian cancer, the likelihood of detecting a mutation was 32.1 percent (Robson 1997).

The probability of a young woman diagnosed with a BRCA mutation surviving to age 70 without treatment is just 53 percent and 71 percent for BRCA 1 and 2 carriers, respectively, compared to a probability of 84 percent for the general population (Kurian 2010).

Dramatic declines in incidence of breast cancer have been observed in BRCA-positive women after PPM, which has reduced lifetime breast cancer risk by more than 95 percent. In addition, breast cancer risk declined 90 percent among those women who have a strong family history of the disease (Domchek 2010).

BRCA is also an indicator for greater risk of ovarian cancer by age 70. This risk is 39 percent for BRCA1-positive women and 11 percent – 17 percent for BRCA2-positive women (Antoniou 2003). The lifetime
risk of ovarian cancer in the general female population is just 1.3 percent (NCI 2015). PSO has reduced the risk of ovarian and breast cancer by 90 percent and 50 percent, respectively (Guillem 2006).

Needed services among women likely to have a genetic mutation for elevated breast and ovarian cancer risk are underutilized. An estimated 10 percent – 15 percent of at-risk and asymptomatic women have discussed genetic testing with a health professional, 4 percent – 8 percent received advice from a professional to undergo a genetic test, and fewer than 3 percent have had such a test (Levy 2009).

Despite large demonstrated reductions in breast cancer risks to high-risk women, only a minority of women with BRCA mutations elect to undergo prophylactic procedures. A study of 2,677 BRCA-positive and asymptomatic women ages 25 – 79, tracked for an average of 3.9 years, documented the U.S. as the nation with the highest proportion of these women who elect to undergo PPM and PSO (36.3 percent and 71.1 percent, respectively). Poland, whose corresponding numbers are 2.7 percent and 34.9 percent, has the lowest such proportion (Metcalfe 2008). Social beliefs and practices, along with effectiveness of provider counseling, may account for much of this variation.

PPM and PSO were first performed soon after the discovery of BRCA gene mutations and the accompanying genetic tests. Originally, the procedures were performed separately, but now are typically concurrent if the woman elects to undergo prophylactic surgery.

A salpingo-oopherectomy involves removal of the fallopian tubes (salpingectomy) and ovaries (oophorectomy). Removal of both ovaries and fallopian tubes is the standard of care (ACOG 2009), although some women elect to undergo just one of the procedures.

One alternative to PSO to reduce ovarian cancer risk are increased surveillance or more frequent screening exams. Another option is use of oral contraceptives, which reduced ovarian cancer risk by 50 percent over five years, a benefit that lasted for at least 10 years after cessation (Hankinson 1992). Questions remain about how effective these alternatives are at reducing risk, especially for early-stage ovarian cancer.

Women diagnosed with Lynch syndrome, also known as HNPCC, have a 40 percent – 60 percent lifetime risk of endometrial cancer, and a 10 percent – 12 percent chance of ovarian cancer, along with elevated risks of uterine, stomach, and colorectal cancers. Mutations associated with this syndrome include MLH1, MSH2, and MSH6. PSO and hysterectomy, for these women, have been considered as a means of reducing risk of these cancers (Burke 1997).

**Searches**

Keystone First searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on August 23, 2016. Search terms were: “prophylactic salpingo-oophorectomy” and “prophylactic salpingo-oophorectomy.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The most recent version of several guidelines by the National Comprehensive Cancer Network (NCCN) on BRCA-positive women recommends PSO, typically at ages 35 to 40 and on completion of childbearing (NCCN 2016). The American College of Obstetrics and Gynecology (ACOG) also endorses PSO for high-risk women, based on difficulties in detecting ovarian cancer and poor prognosis for treating advanced cases (ACOG 2009). ACOG also recommends PSO include inspection of the peritoneal cavity, pelvic washings, removal of fallopian tubes, and ligation of ovarian vessels at the pelvic brim (AHRQ 2012).

The U.S. Preventive Services Task Force concludes that “fair evidence” exists that PSO effectively prevents breast and ovarian cancer (USPSTF 2005). The Society of Gynecologic Oncology (SGO) recommends that physicians counsel high-risk women to have fallopian tubes removed, followed by ovary removal (SGO 2013). SGO also classifies women with family history of breast and/or ovarian cancer, but with no confirmation of BRCA mutations as “higher-than-average risk” for both diseases (Berek 2010).

The National Cancer Institute recommends that risk-reducing hysterectomy, along with PSO, be considered as an option for women with Lynch syndrome (NCI 2013b).

All guidelines emphasize the importance of the provider and patient discussing risks and benefits of PSO before any procedure is performed. Women undergoing PSO frequently experience menopausal symptoms, including osteoporosis, increased heart disease risk, hot flashes, sleep disturbance, and cognitive changes (Domchek 2007). PSO has been shown to reduce breast cancer risk by 47 percent to 68 percent, and reduce risk of cancers of the ovary, fallopian tube, and peritoneum by 71 percent to 96 percent if completed before
menopause, based on six trials (Rebbeck 2009). Several meta-analyses and systematic reviews found that PSO:

- Reduced breast cancer risk in BRCA-positive women. The procedure also significantly reduced all-cause mortality in these women, while PPM did not (Li 2016).

- Was associated with large decreases in breast and ovarian cancer incidence, plus mortality from all causes (Nelson 2014).

- Was associated with a reduction (versus non-surgical BRCA cases) of 68 percent, and a reduction of ovarian cancer risk of 80 percent in studies followed 3.4, 5.6, and 6.2 years (Marchetti 2014).

One report calculated survival gain for BRCA-positive women by age (Kurian 2010). Table 1 shows the percentage survival of these women at age 70, according to age at each type of intervention:

Table 1
Overall survival probability to age 70, in percentage of 25-year-old women with BRCA 1-2 mutation

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>No PSO</th>
<th>PSO at 40</th>
<th>PSO at 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 carriers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No screening, no PPM</td>
<td>53</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td>Screening, no PPM</td>
<td>59</td>
<td>74</td>
<td>69</td>
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<tr>
<td>Screening, PPM age 50</td>
<td>61</td>
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</tr>
<tr>
<td>Screening, PPM age 40</td>
<td>64</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Screening, PPM age 30</td>
<td>66</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>No screening, PPM age 25</td>
<td>66</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>BRCA2 carriers</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No screening, no PPM</td>
<td>71</td>
<td>77</td>
<td>75</td>
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<tr>
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<tr>
<td>Screening, PPM age 40</td>
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<td>82</td>
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<tr>
<td>Screening, PPM age 30</td>
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</tr>
<tr>
<td>No screening, PPM age 25</td>
<td>79</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>General U.S. female population</td>
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<td>84</td>
<td>84</td>
</tr>
</tbody>
</table>

The most efficacious single intervention is PSO at age 40 for BRCA1 carriers (survival 53 percent to 68 percent), versus BRCA2 carriers (71 percent to 77 percent). PPM at age 25 or 30 plus PSO at age 40 yields the greatest survival for BRCA 1-2 carriers (79 percent and 83 percent, versus 84 percent for all U.S. females). Patterns are similar to age 80 (Kurian 2010).

A cost-effectiveness study of BRCA-positive Norwegian women who underwent PSO found an additional 6.4 discounted life years gained in women also undergoing PPM (3.1 for those with just PSO), versus
BRCA-positive women with no intervention. The cost per life year gained was euro 1973 (PSO alone) and euro 1749 (both procedures); researchers concluded these interventions were cost-effective (Norum 2008).

One study compared PSO with prophylactic salpingectomy, with and without delayed oophorectomy. PSO was associated with the lowest cost, greatest life expectancy, and greatest declines in breast and ovarian cancer risk. However, after adjusting for quality-of-life measures, prophylactic salpingectomy with delayed oophorectomy had the highest life expectancy (Kwon 2013). Younger age at PSO was associated with lower social functioning and greater anxiety, while playing a sport and avoiding weight gain were highly related to better quality of life after surgery (Touboul 2011).

Research has addressed whether salpingectomy alone reduces ovarian cancer risk. One large population-based study showed that women with prior salpingectomy had a 35 percent lower risk of ovarian cancer, and a 50 percent reduction with salpingectomy. This finding supports the belief that most ovarian cancers originate in the fallopian tubes (Falconer 2015).

Likewise, studies of oophorectomy alone have demonstrated shown a reduction in ovarian cancer. An analysis of nine studies documented oophorectomy versus ovarian conservation lowered future ovarian cancer rates for women with a family history of breast or ovarian cancer and BRCA1 carriers; evidence for BRCA2 carriers was low quality (Hayes 2013).

In 1997, the Cancer Genetics Studies Consortium found insufficient evidence to recommend if prophylactic hysterectomy and salpingo-oophorectomy would reduce cancer risk in women with Lynch syndrome (Burke 1997). Subsequently, a study of Lynch syndrome compared those 61 who underwent hysterectomy (47 also with BPSO) to 210 with no surgery. Cases and controls were followed for an average of 13 and 7 years, respectively. Cases had no subsequent endometrial or ovarian cancer, while controls had 12 cases of ovarian cancer and 69 cases of endometrial cancer (Schmeler 2006).

A review of 21,067 Australian women diagnosed with primary breast cancer from 1997 – 2008 also compared those undergoing hysterectomy, BPSO, both procedures, or no surgery. After tracking women for five to seven years, those with both procedures had an improvement in 10-year survival from 78.5 percent to 85.0 percent), while those with only one of these procedures showed no change (Obermair 2014).

Policy updates:

None.

Summary of clinical evidence:
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li (2016)</td>
<td>Reductions in breast cancer incidence and all-cause mortality after PSO or PBM in BRCA-positive women</td>
</tr>
</tbody>
</table>
| **Key points:**  | - Meta-analysis of 15 studies of women undergoing PSO or prophylactic mastectomy (BPM).  
|                  | - PSO and BPM were associated with decreased breast cancer risk.  
|                  | - PSO was associated with significantly decreased all-cause mortality.  
|                  | - BPM was not associated with significantly decreased all-cause mortality. |
| Nelson (2014)    | Reductions in cancer risk in BRCA-positive women |
| **Key points:**  | - Systematic review of five studies, 2004 – 2013.  
|                  | - BRCA-positive women who did or did not have risk-reducing surgery.  
|                  | - PPM reduced incidence of breast cancer by 85 percent – 100 percent.  
|                  | - PSO (versus no surgery) reduced incidence of breast cancer by 37 percent -100 percent, incidence of ovarian cancer by 69 percent -100 percent, mortality from all causes by 55 percent -100 percent. |
| Kurian (2010)    | Improvements in survival to BRCA-positive women by type of treatment |
| **Key points:**  | - Young women diagnosed with the BRCA 1-2 mutations have a 53 percent and 71 percent chance of surviving to age 70 without treatment.  
|                  | - Survival gain to age 70 for BRCA 1-2 carriers is 15 percent and 7 percent after PSO at age 40.  
|                  | - Survival gain to age 70 for BRCA 1-2 carriers is 24 percent and 11 percent after PSO at 40 plus BPM.  
|                  | - PBM at age 25 offers minimal benefit compared to age 40. |
| Metcalfe (2008)  | Proportions of BRCA-positive women who elect to undergo prophylactic procedures, by nation |
| **Key points:**  | - 2,677 BRCA-positive and asymptomatic women, ages 25 – 79, tracked an average of 3.9 years.  
|                  | - U.S. has highest percentage undergoing PBM and PSO (36.3 percent and 71.1 percent).  
|                  | - Poland has the lowest proportions (2.7 percent and 34.9 percent).  
|                  | - Social beliefs and practices, and effectiveness of counseling, account for differences. |
| **Key points:**  | - Australian women (n=270) with Lynch syndrome.  
|                  | - 61 had hysterectomy (47 of whom also had PSO), others had no surgery.  
|                  | - Surgical and non-surgical groups tracked an average of 13 and 7 years.  
|                  | - Surgical group had zero endometrial, ovarian, or primary peritoneal cancers.  
|                  | - Non-surgical group had 12 ovarian and 69 endometrial cancers. |

**Glossary**

**BRCA 1-2 gene mutation** — Mutations that strongly raise risk of breast, ovarian, and other gynecologic cancers.

**Lynch syndrome** — An inherited condition marked by various genetic mutations that raise risk of colon and other cancers; also known as hereditary nonpolyposis colorectal cancer (HNPCC).

**Mastectomy** — Surgical removal of the breast (represents removal of both breasts).
**Oophorectomy** — Surgical removal of the ovary (represents removal of both ovaries).

**Salpingectomy** — Surgical removal of the fallopian tube (represents removal of both tubes).

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


Clinical trials:

Searched clinicaltrials.gov on August 26, 2016, using term “salpingo-oophorectomy.” Open Studies. 20 studies found, two relevant.


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>58720</td>
<td>Salpingo-oophorectomy, complete or partial, unilateral or (separate procedure)</td>
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<td>Code</td>
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<td>Z80.41</td>
<td>Family history of malignant neoplasm of ovary</td>
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<table>
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