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| BSC2.08 | Personalized Breast Cancer Screening Clinical Trial | | |
| Original Policy Date: | January 1, 2016 | Effective Date: | May 1, 2021 |
| Section: | 2.0 Medicine | Page: | Page 1 of 18 |

Policy Statement

The validity of using personalized breast cancer screening services to determine an individual's risk for breast cancer and whether this testing can improve that individual's overall health outcome has not been established in the scientific literature. Blue Shield of California is undertaking a joint clinical study with the Athena Breast Health Network to determine if personalized breast cancer screening services can improve the overall health on an individual.

Therefore:

Personalized breast cancer screening services administered by the Athena Breast Health Network under the established clinical trial protocol (see Policy Guidelines) are considered **medically necessary** for "coverage with evidence development" (CED) clinical trial purposes (see Policy Guidelines) for identified WISDOM study participants **only**.

Personalized breast cancer screening services, **not** administered by the Athena Breast Health Network under the established clinical trial protocol, are considered **investigational** (see Policy Guidelines).

Individuals enrolled in the study and control arms of the WISDOM trial, as well as non-study participants, continue to be entitled to full conventional, evidence-based breast cancer screening, in accordance with Blue Shield of California Preventive Services benefits and the provisions of the Affordable Care Act.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Personalized Breast Cancer Screening includes determination of:

- Hereditary predisposition by comprehensive genomic profiling (BRCA, a panel of breast cancer risk genes, and single nucleotide polymorphisms)
 - Collected from blood or saliva donation
- Mammographic breast density
 - Collected from mammography images
- Family history of breast and associated cancer, personal history of biopsies and abnormal findings, other hormonal exposures
 - Collected from Athena patient intake questionnaire, and
- Assessment of co-morbidities
 - Assessment of life expectancy to determine the optimal age to stop screening (critical for the Medicare population).

Blue Shield of California's coverage of Personalized Breast Cancer Screening is contingent on compliance with the following:

- CED conditions as outlined in the Medical Policy Committee Policy and Procedures document, AND
- Protocol approval and ongoing monitoring by an Institutional Review Board (IRB) for the Athena personalized breast screening study.

Blue Shield of California, at its discretion, may extend coverage to its beneficiaries under this program beyond the planned five-year duration of this study.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

| Previous | Updated | Definition |
|----------|----------------------------|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

| Variant Classification | Definition |
|-----------------------------------|--|
| Pathogenic | Disease-causing change in the DNA sequence |
| Likely pathogenic | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign | Likely benign change in the DNA sequence |
| Benign | Benign change in the DNA sequence |

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

All claims for the genetic testing under the WISDOM study will be submitted by Color Genomics. There are no specific CPT or HCPS code for the initial Color Genomic Panel.

Panel of Breast Cancer Risk Genes

- **81432:** Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
- **81433:** Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
- **81479:** Unlisted molecular pathology procedure

Screening Mammography

- **77063**: Screening digital breast tomosynthesis, bilateral (List separately in addition to code for primary procedure)
- **77067**: Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed

Assessment

- **96040**: Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
- **96160**: Administration of patient-focused health risk assessment instrument (e.g., health hazard appraisal) with scoring and documentation, per standardized instrument
- **99401**: Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 15 minutes
- **99402**: Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 30 minutes
- **99403**: Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 45 minutes
- **99404**: Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 60 minutes

Description

This custom medical policy enables Blue Shield of California to participate in the Athena Breast Health Network “WISDOM” **clinical trial**, which tests a novel evidence-based algorithm for predicting development of breast cancer based on the presence of known strong genetic risk factors for the disease, specialized genetic testing, conventional imaging when appropriate, and a personalized risk assessment. It is hoped that application of this algorithm will reduce excessive radiographic screening of women thought to be at risk for breast cancer. Also, in women with detected breast lesions, it is hoped that this algorithm will help to identify indolent forms of the disease, which do not require immediate aggressive or extensive treatment, versus potentially highly morbid disease requiring immediate chemotherapeutic, radiation, or surgical treatment.

Personalized breast cancer screening, administered by the Athena Breast Health Network, is a preference-based adaptive learning study of personalized breast cancer risk assessment and screening designed to revolutionize the approach to screening, and subsequently, prevention and treatment, of breast cancer.

Personalized breast cancer screening is designed to optimize breast cancer detection for high risk women by reducing the unintended consequences of current screening practices, and better use of available resources to personalize screening and care of any detected lesions. The program aims to demonstrate via a preference-based randomized control trial that a personalized approach to breast cancer screening is as safe as, more effective, less morbid, and preferred by women compared to current annual screening practices. The personalized screening approach would use assessment of the risk to overall health to determine the age at which to start and stop screening as well as the frequency of this screening.

Related Policies

- Coverage with Evidence Development

In order to accelerate the emergence of a high-quality affordable health care system in California, it is the policy of Blue Shield to implement written “coverage with evidence development” (“CED”) medical policies, such as this personalized breast cancer screening policy. CED medical policies will provide coverage for promising new technologies that have

not yet been established as effective according to generally accepted professional medical standards, but (i) would otherwise be considered Medically Necessary; (ii) are safe; (iii) show substantial potential to improve health outcomes; (iv) reduce waste and inefficiency in the health care system; (v) are part of high quality research or clinical study, and; (vi) meet all of the requirements for CED (refer to Coverage with Evidence Development policy).

Generally, CED is **only** for Blue Shield members who are participating in the study and compliant with the study protocol. If those conditions are not met, Blue Shield will not approve payment for CED for that member. Development of CED medical policy is in and at the sole discretion of Blue Shield. Blue Shield is not obligated to establish CED medical policy. Except as required by the EOC, Blue Shield is not obligated to cover any technology if it has not established a CED medical policy for that technology using the CED process.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Color Genomics is performing a custom panel for the WISDOM study. The custom panel includes full gene sequencing analysis and single nucleotide variant reporting on a subset of genes from their commercially available Hereditary Cancer Test which is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background

In the United States, annual mammographic screening for breast cancer is recommended for the majority of women starting at age 40, regardless of personal risk, and to continue until death, regardless of life expectancy. It has been shown that breast cancer screening costs \$8-10 billion per year and results in 600,000 negative biopsies annually. It is estimated that breast cancer is over-diagnosed in 70,000 women each year in the US, accounting for 31% of all breast cancers diagnosed. This means that for those 70,000 women, routine screening detected lesions that would have never developed into clinically significant disease. These diagnoses likely led to aggressive and unnecessary treatment and cost. Conversely, women at higher than average risk may benefit from screening that starts at an earlier age, occurs more frequently, or utilizes more intensive screening modalities than annual mammography. A screening paradigm that offers more intensive or frequent screening to women at higher risk may be more effective in promoting adoption of prevention strategies, and in preventing breast cancer deaths than the current one-size-fits all approach.

It is well understood that breast cancer is not a single disease. Some breast tumors grow very slowly, others very fast, and not all patients will benefit from the same approach to screening, prevention, or treatment. Thus, the opportunity is to move away from a “one-size-fits-all” screening paradigm and engineer an approach that maximizes screening benefit, harnesses all of the major advances in risk assessment and cancer biology, reduces risk of over-diagnosis and over-treatment, and ultimately results in optimal use of available resources to personalize screening and care.

Although there have been large trials (>650,000 women) of mammography screening for breast cancer detection and many systematic reviews of those trials,¹ controversies remain regarding the ages at which to screen women, how often, and with which screening modalities. Women have been caught in the middle of the scientific controversy and placed in the uncertain position of making screening decisions based upon mixed messages from different providers. There are even questions about whether screening does, in fact, work. To provide American women with the best quality care, comfort and advice possible, it is incumbent upon us to try and resolve this scientific controversy and once again provide women with clear, consistent recommendations to restore confidence in their decisions about breast health.

A summary of select guideline recommendations for screening with mammogram of average-risk women is shown in Table 1.

Table 1. Mammogram Screening Guidelines for Women at Average Risk

| Screening | USPSTF (2016) ² | NCCN (2018) ³ | ACS (2015) ⁴ | SBI and ACR (2010) ⁵ | ACOG (2017) ⁶ |
|---------------------|--|---|--|---|---|
| Age to start | <ul style="list-style-type: none"> • 50 y • Individual choice from 40-50 y | <ul style="list-style-type: none"> • 40 y | <ul style="list-style-type: none"> • 45 y • Individual choice from 40-45 y | <ul style="list-style-type: none"> • 40 y | <ul style="list-style-type: none"> • 40 or 50 y • Individual choice |
| Age to stop | <ul style="list-style-type: none"> • 74 y | <ul style="list-style-type: none"> • Not established | <ul style="list-style-type: none"> • Life expectancy <10 y | <ul style="list-style-type: none"> • Life expectancy <5-7 y | <ul style="list-style-type: none"> • 75 y |
| Interval | <ul style="list-style-type: none"> • 2 y | <ul style="list-style-type: none"> • 1 y | <ul style="list-style-type: none"> • 1 y at ages 45-54 y • 2 y at 55+ y | <ul style="list-style-type: none"> • 1 y | <ul style="list-style-type: none"> • 1 or 2 y • Individual choice |

ACOG: American College of Obstetricians and Gynecologists; ACR: American College of Radiology; ACS: American Cancer Society; NCCN: National Comprehensive Cancer Network; SBI: Society for Breast Imaging; USPSTF: US Preventive Services Task Force.

In addition to age, genetic, lifestyle, and environmental risk factors affect a women’s likelihood of developing breast cancer. Several tools have been developed to estimate a women’s personal risk of developing breast cancer using models incorporating family history, breast density, endocrine exposures, gene variants, and/or atypia.⁷⁻¹⁷

More intense screening recommendations have been suggested for women of above-average risk by several societies but the US Preventive Services Task Force concluded that “trial data are too limited to directly inform the question of what the best screening strategy is for women or how clinicians can best tailor that strategy to the individual.”

The WISDOM (Women Informed to Screen Depending On Measures of risk) study is supported by the Patient-Centered Outcomes Research Institute. WISDOM includes a randomized controlled trial comparing a risk-based (or personalized) breast cancer screening strategy with annual screening to evaluate whether risk-based screening is as safe, less morbid, facilitates prevention, and is accepted by women.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of

life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Personalized Breast Cancer Screening

Clinical Context and Study Purpose

The purpose of personalized breast cancer screening is to develop strategies based on a women's risk of developing breast cancer. The goal is to reduce overdiagnosis, false-positive mammograms, and overtreatment of indolent disease while continuing to detect dangerous cancers.

The question addressed in this evidence review is: Does personalized breast cancer screening improve the net health outcome for women?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women without prior breast cancer or bilateral mastectomy.

Interventions

Personalized breast cancer screening is screening for which timing (starting, stopping, and frequency) and screening modality (mammogram alone or mammogram with magnetic resonance imaging or other imaging) are determined by a woman's personal risk of developing breast cancer (see Appendix Figure 1). Tools exist to estimate a women's personal risk of developing breast cancer using models incorporating family history, breast density, endocrine exposures, gene variants, and/or atypia.⁷⁻¹⁷

Comparators

The following practice is currently being used: standard screening, such as annual or biennial screening (see Appendix Figure 2). Some medical societies have additional screening suggestions for women at increased risk.

Outcomes

The beneficial outcomes of interest are overall mortality and breast cancer mortality. The harmful outcomes of interest are (1) false-positive results, which lead to unnecessary additional imaging, biopsies and anxiety, and (2) overdiagnosis or treatment of noninvasive and invasive breast cancer that would otherwise not have become a threat to a woman's health during her lifetime.

Timing

Systematic reviews of trials of screening mammography that have found a benefit of screening have generally accumulated more than a decade of follow-up.¹⁸⁻²⁰

Setting

Primary or secondary care settings are of interest.

Evidence

No RCTs comparing standard screening strategies with personalized or risk-based screening strategies were identified.

Simulation models have suggested that the risk and benefit trade-offs of screening differ by risk and that risk-based or personalized screening intervals may lead to improved health outcomes or be more cost effective than uniform screening intervals based on age.²¹⁻²⁴

Design of WISDOM Study

The questions addressed in the Women Informed to Screen Depending On Measures of risk (WISDOM) study are: Is personalized, risk-based screening (1) an improvement over annual screening; as safe and less morbid and (2) does it enable prevention; and (3) as a participant-centered alternative to annual screening, is it readily accepted by women?

Population

The WISDOM study design includes both an RCT cohort and an observational cohort (see Appendix Figure 3). Women are encouraged to enter the randomized cohort, in which they are randomized to routine annual screening or personalized screening. Women who have a strong personal preference for annual or personalized screening will be enrolled in the observational cohort.

The WISDOM study is enrolling women ages 40 to 74 years of age without prior breast cancer or ductal carcinoma in situ or prior prophylactic bilateral mastectomy. The RCT target enrollment is 65,000 women. This sample size would provide 85% power with a noninferiority margin of 0.05% for the difference in annual risk of diagnosis with stage IIB or higher cancers assuming²⁵:

- proportions of participants in the biannual, annual, and high-risk groups will be 40.4%, 28.2%, and 2.5%, respectively
- rate of stage IIB cancers is estimated to be approximately 0.05% per year
- annual hazard ratios for stage IIB cancer are 0.041%, 0.077%, 0.28%, and 0.020% in each of the personalized screening groups, respectively
- 1-sided type I error rate of 0.025

An additional 35,000 women are expected to enroll in the observational cohort. The total study sample size goal is approximately 100,000 women.

Risk Assessment

All women will undergo risk assessment using the Breast Cancer Surveillance Consortium (BCSC) risk model. The BCSC risk assessment tool was developed and validated in a cohort including more than 1 million multiethnic women in the United States in whom about 18,000 were diagnosed with invasive breast cancer.¹⁷ The cohort was constructed from women in 7 mammography registries participating in the National Cancer Institute-funded BCSC. The tool was independently validated in an analysis including more than 4000 women from 3 studies (Mayo Mammography Health Study cohort, Mayo Clinic Breast Cancer Study, Bavarian Breast Cancer Cases and Control Study).²⁶ A version of the tool is available online and includes factors for age, race/ethnicity, family history, history of breast biopsy, and breast density.²⁷

Treatment Groups

Women will be randomized to the personalized screening group or the annual screening group. Randomization will be stratified by clinical site, age less than 50, no prior mammogram, and BCSC risk score (3 categories; cutoffs not specified).²⁵

Personalized Screening Group

The personalized screening group will receive genetic testing, performed by Color Genomics using a custom panel. The initial panel will include several rare high- and moderate-penetrance variants including the following: *BRCA1*, *BRCA2*, *ATM*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11*, and *TP53*. New genes may be added to the panel during the study. Participants will also be genotyped for 157 common, lower-risk genetic variants (single nucleotide variants [SNVs]) that have an established association with breast cancer risk in white, African American, Asian (Chinese), and Latino populations identified by the Breast Cancer Association Consortium of the Collaborative Oncological Gene-environment Study.

For the women in the personalized screening group, the WISDOM study will perform risk assessment with a recently updated version of the BCSC model that includes additional SNVs as a polygenic risk score, and was validated in 3 case-control studies with more than 3000 cases and controls.²⁶ An estimate of each woman's 5-year risk of breast cancer will be calculated using a Bayesian method based on the BCSC estimated risk including results from genetic testing.²⁵

Following genetic testing and risk determination, the personalized screening group participants will be offered breast health specialist counseling performed by a certified genetic counselor.

The screening recommendations based on risk are shown in Table 2 (adapted from the WISDOM protocol).²⁵ A woman falls into a lower risk category only if she does not meet criteria for any of the higher risk categories.

Table 2. WISDOM Screening Classifications in the Personalized Screening Arm

| Risk Category | Criteria/Threshold | Screening Recommendation |
|-----------------|---|---|
| Highest | For any age: <ul style="list-style-type: none"> • <i>BRCA1</i>, <i>BRCA2</i>, <i>TP53</i>, <i>PTEN</i>, <i>STK11</i>, <i>CDH1</i> variants, or • <i>ATM</i>, <i>PALB2</i>, or <i>CHEK2</i> variant carrier with positive family history of breast cancer • 5-y risk $\geq 6\%$ or • History of chest wall radiotherapy before age 35 y | Annual mammogram plus annual magnetic resonance imaging |
| Elevated | <ul style="list-style-type: none"> • Ages 40-49 y with extremely dense breasts or • 5-y risk of developing estrogen receptor-breast cancer $\geq 0.75\%$ based on susceptibility, age, and ethnicity or • Top 2.5th percentile of risk by 1-y age category or • <i>ATM</i>, <i>PALB2</i>, or <i>CHEK2</i> variant carrier without a positive family history of breast cancer | Annual mammogram |
| Average | <ul style="list-style-type: none"> • Ages 50-74 y, or • Ages 40-49 y with $\geq 1.3\%$ 5-y risk | Biennial mammogram |
| Lowest | <ul style="list-style-type: none"> • Ages 40-49 y (who do not meet any criteria for the higher risk categories) | No screening until age 50 y |

Adapted from the WISDOM protocol (2016).²⁵

Annual Screening Group

Women in the annual screening group will be assigned an annual screening schedule. However, women in the annual screening group who are assessed as being in the highest 5% five-year risk for their age group have the opportunity for counseling and/or referral to a high-risk clinic. These women will follow standard of care for highest risk that may include more frequent screening.²⁵

Outcome Measures

The WISDOM study has 2 coprimary outcomes: safety and morbidity. The safety primary outcome is measured by the rate of cancers diagnosed at stage IIB or higher and is a

noninferiority outcome. The morbidity primary outcome is measured by the rate of breast biopsy and is a superiority outcome.²⁵

There are several secondary outcomes:

- Rate of stage IIB and clinically detected interval cancers
- Rates of systemic therapy
- Recall rates and follow-up procedures
- Rates of ductal carcinoma in situ
- Rates of chemoprevention
- Proportion of women who agree to enroll in the study who choose risk-based vs annual screening in the self-assigned cohort vs opting to be randomized
- Adherence to the assigned screening schedule in the randomized cohort
- Patient-Reported Outcomes Measurement Information System anxiety score²⁸
- Breast Cancer Risk Worry score²⁹

Recruitment and Follow-up

Women will initially be recruited from Athena Breast Health Network sites, including University of California at San Francisco, University of California at Davis, University of California at Los Angeles, University of California at San Diego, University of California at Irvine, and Sanford Health System. Recruitment will open to women outside Athena during the second phase of the study.²⁵

The total duration of WISDOM support from the Patient-Centered Outcomes Research Institute is 5 years. Accrual was expected to begin within 6 months of trial start and complete within 2 to 3 years. This would correspond to between 1.5 and 4.5 years of follow-up for the women enrolled.²⁵ The investigators aim to secure additional funding support beyond the Patient-Centered Outcomes Research Institute award.

Summary of Evidence

For individuals who are adult females without prior breast cancer or bilateral mastectomy who receive personalized breast cancer screening, the evidence includes simulation studies. Relevant outcomes are overall and disease-specific survival, morbid events, quality of life, medication use, and resource utilization. Annual breast cancer screening mammography is known to lead to overdiagnosis and false-positives. The WISDOM study is an ongoing RCT designed to compare personalized breast cancer screening with annual screening. WISDOM will test whether the rate of recalls and breast biopsies can be reduced with personalized screening while still detecting a similar number of dangerous cancers. Simulation models have suggested personalized screening can reduce harm and cost compared with the current standard practice; initial evidence from year 1 of the WISDOM study suggests the study is feasible. The WISDOM study meets the criteria for coverage with evidence progression as outlined in Blue Cross and Blue Shield Association Coverage with Evidence Progression Framework.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines for breast cancer screening (v.1.2020) and for genetic/familial high-risk assessment (v.3.2019) make the following recommendations regarding breast cancer screening and diagnosis for asymptomatic women without history of breast cancer (see Table 3).^{3,30} Note that the guidelines encourage all women to be “familiar with their breasts” and promptly report changes.

Table 3. Breast Cancer Screening Recommendations

| Population | Mammography and MRI Screening Recommendation |
|--------------------------------|--|
| Ages 25-39 y with average risk | None |

| Population | Mammography and MRI Screening Recommendation |
|--|--|
| Ages ≥40 y with average risk | Mammography every year |
| Ages ≥35 y with 5-y risk of invasive breast cancer ≥1.7% | Mammography every year |
| Lifetime risk >20% based on history of LCIS or ADH/ALH | <ul style="list-style-type: none"> • Mammography every year beginning at age of diagnosis but not before age 30 y • MRI every year beginning at age of diagnosis but not before age 25 y (based on emerging evidence) |
| Lifetime risk >20% based on family history | <ul style="list-style-type: none"> • Mammography every year beginning at 10 y prior to when the youngest family member was diagnosed with breast cancer, but not prior to age 30 y or age 40 (whichever comes first) • MRI every year beginning at 10 y prior to when the youngest family member was diagnosed with breast cancer, but not prior to age 25 y or age 40 y (whichever comes first) |
| Received prior thoracic irradiation between ages 10-30 y | <ul style="list-style-type: none"> • Mammography every year beginning 8 y after radiotherapy but not before age 30 y • MRI every year beginning 8 y after radiotherapy but not before age 25 y |
| BRCA variant–positive | <ul style="list-style-type: none"> • MRI every year from ages 25-29 y • Mammography and MRI every year from ages 30-75 y |
| Li-Fraumeni syndrome | <ul style="list-style-type: none"> • MRI every year from ages 20-29 y • Mammography and MRI every year from ages 30-75 y |
| Cowden syndrome | Mammography and MRI every year starting at age 30-35 years or 5-10 years before the earliest known breast cancer in the family (whichever comes first) |
| ATM, CHEK2, NBN variant–positive | Mammography every year starting at age 40 y, consider MRI |
| CDH1, PALB2 variant–positive | Mammography every year starting at age 30 y, consider MRI |
| NF1 variant–positive | Mammography every year starting at age 30 y, consider MRI from ages 30-50 y |

ADH: atypical ductal hyperplasia; ALH: atypical lobular hyperplasia; LCIS: lobular carcinoma in situ; MRI: magnetic resonance imaging.

American Cancer Society

The American Cancer Society guidelines for breast cancer screening in average-risk women (2015) and for breast screening with magnetic resonance imaging as an adjunct to mammography (2007) made the recommendations on breast cancer screening (see Table 4).^{4,31}

Table 4. Breast Cancer Screening Recommendations

| Population | Mammography and MRI Screening Recommendation |
|--------------------------------|---|
| Ages 40-45 y with average risk | Option for mammography every year |
| Ages 45-54 y with average risk | Mammography every year |
| Ages ≥55 y with average risk | Mammography every year or every other year until life expectancy is <10 y |
| High risk ^a | Mammography every year starting at age 30 y |

MRI: magnetic resonance imaging.

^a Lifetime risk >20% based on family history, a known *BRCA1* or *BRCA2* variant or first-degree relative with *BRCA1* or *BRCA2* variant, radiotherapy between ages 10 and 30 y; Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, or first-degree relative with one of those syndromes

American College of Radiology

The American College of Radiology guidelines for breast cancer screening made the following recommendations in 2018 (see Table 5).⁵

Table 5. American College of Radiology Breast Cancer Screening Recommendations

| Population | Mammography and MRI Screening Recommendation |
|------------------------------|---|
| Ages ≥40 y with average risk | Mammography every year until life expectancy <5-7 y |

| Population | Mammography and MRI Screening Recommendation |
|---|---|
| <i>BRCA1</i> or <i>BRCA2</i> variant–positive or first-degree family member is <i>BRCA1</i> or <i>BRCA2</i> variant–positive or first-degree variant–positive | Mammography and MRI every year starting at age 30 y |
| Lifetime risk $\geq 20\%$ based on family history or mother or sister with premenopausal breast cancer | Mammography and MRI every year starting by age 30 y or 10 y earlier than age of diagnosis of the youngest affected relative, whichever is later |
| History of mantle radiotherapy between ages 10 and 30 y | Mammography and MRI every year starting 8 y after radiotherapy but not before age 25 y |
| History of LCIS, ADH/ALH, DCIS, breast, or ovarian cancer | Mammography every year starting at time of diagnosis |

ADH: atypical ductal hyperplasia; ALH: atypical lobular hyperplasia; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; MRI: magnetic resonance imaging.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists practice bulletin (2017) for breast cancer screening made the following recommendations on breast cancer screening mammography for average-risk women⁶:

- Mammography should be offered starting at age 40
- Mammography should begin no later than age 50
- Mammography can be either annual or biennial
- The decisions about age to begin and screening intervals should be made through a shared decision-making process
- Mammography should continue until at least age 75

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force published recommendations for breast cancer screening in 2016.² Its recommendations are as follows:

- For women aged 50 to 74 years, biennial mammography (grade B)
- For women aged 40 to 49 years, the decision to start mammography is an individual one (grade C)
- For women aged 75 years and older, the current evidence is insufficient to assess the balance of risks and benefits of mammography

Medicare National Coverage

There is no national coverage determination (NCD) for personalized breast cancer screening. There are also no NCDs for breast magnetic resonance imaging or breast cancer susceptibility panel testing. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

NCD 220.4 describes coverage for screening mammography: "Payment may not be made for a screening mammography performed on a woman under age 35. Payment may be made for only one screening mammography performed on a woman over age 34, but under age 40. For an asymptomatic woman over age 39, payment may be made for a screening mammography performed after at least 11 months have passed following the month in which the last screening mammography was performed."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|-------------|--|--------------------|-----------------|
| Ongoing | | | |
| NCT02620852 | Women Informed to Screen Depending on Measures of Risk (Wisdom Study) (WISDOM) | 100,000 | Dec 2020 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|-------------|--|--------------------|-----------------|
| NCT02619123 | Tailored Screening for Breast Cancer in Premenopausal Women. A Translational, Randomized Population-based Trial (TBST) | 33,200 | Jan 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Appendix 1

Figure 1. WISDOM Personalized Screening Arm

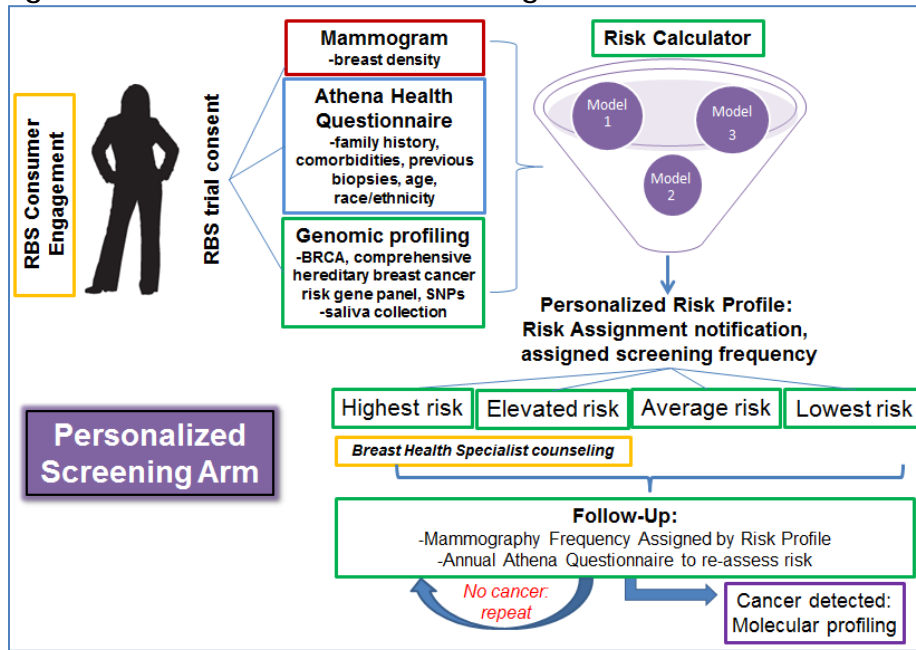


Figure 2. WISDOM Annual Screening Arm

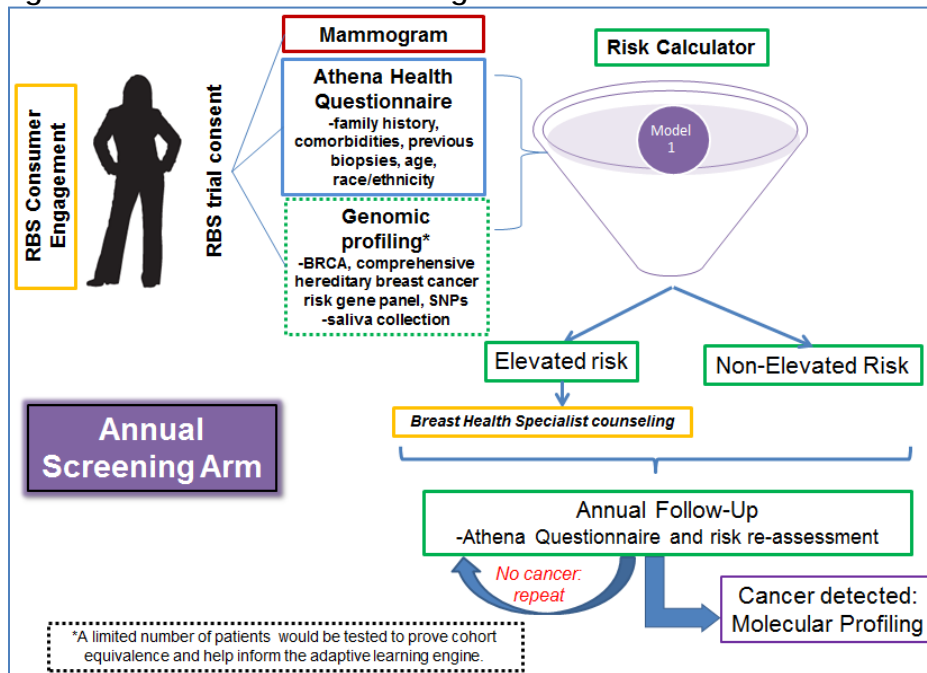
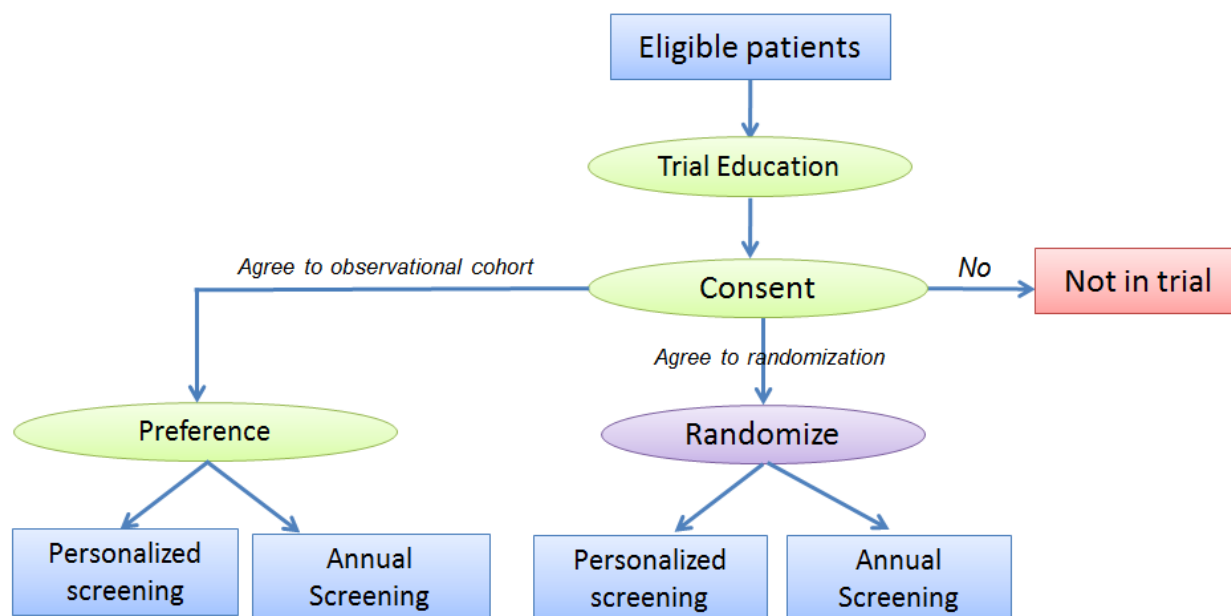


Figure 3. Overview of Risk Based Screening (RBS) Trial Design



Proposed Preference-based Randomized Control Trial Design.

Those who agree to randomization will be randomized. For those that do not want to be randomized and have a strong preference will pick the option they prefer and be followed in our observational cohort. Women in the personalized arm will be assigned screening intervals based on their risk. A woman's risk will be reassessed at specified intervals, at a minimum of yearly.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

| Type | Code | Description |
|------|-------|---|
| CPT® | 77063 | Screening digital breast tomosynthesis, bilateral (List separately in addition to code for primary procedure) |
| | 77067 | Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed |
| | 81162 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| | 81163 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| | 81164 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| | 81165 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| | 81166 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) |

| Type | Code | Description |
|-------|----------|---|
| | 81167 | BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| | 81432 | Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53 |
| | 81433 | Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11 |
| | 81479 | Unlisted molecular pathology procedure |
| | 96040-GT | Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family |
| | 96160 | Administration of patient-focused health risk assessment instrument (e.g., health hazard appraisal) with scoring and documentation, per standardized instrument |
| | 99401 | Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 15 minutes |
| | 99402 | Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 30 minutes |
| | 99403 | Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 45 minutes |
| | 99404 | Preventive medicine counseling and/or risk factor reduction intervention(s) provided to an individual (separate procedure); approximately 60 minutes |
| HCPCS | G0452 | Molecular pathology procedure; physician interpretation and report |

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|----------------|--|
| 01/01/2016 | Custom Policy |
| 04/01/2016 | Coding update |
| 02/01/2017 | Coding update |
| 03/01/2017 | Policy revision without position change |
| 03/01/2018 | Policy revision without position change |
| 05/01/2018 | Policy revision without position change |
| 07/01/2018 | Policy statement clarification |
| 01/01/2019 | Coding update |
| 05/01/2019 | Policy revision without position change Coding update |
| 05/01/2020 | Annual review. No change to policy statement. |
| 05/01/2021 | Annual review. No change to policy statement. Literature review updated. |

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

| POLICY STATEMENT (No changes) | |
|--|--|
| BEFORE | AFTER |
| <p>Personalized Breast Cancer Screening Clinical Trial BSC2.08</p> <p>Policy Statement: The validity of using personalized breast cancer screening services to determine an individual’s risk for breast cancer and whether this testing can improve that individual’s overall health outcome has not been established in the scientific literature. Blue Shield of California is undertaking a joint clinical study with the Athena Breast Health Network to determine if personalized breast cancer screening services can improve the overall health on an individual.</p> <p>Therefore:</p> <p>Personalized breast cancer screening services administered by the Athena Breast Health Network under the established clinical trial protocol (see Policy Guidelines) are considered medically necessary for “coverage with evidence development” (CED) clinical trial purposes (see Policy Guidelines) for identified WISDOM study participants only.</p> <p>Personalized breast cancer screening services, not administered by the Athena Breast Health Network under the established clinical trial protocol, are considered investigational (see Policy Guidelines).</p> <p>Individuals enrolled in the study and control arms of the WISDOM trial, as well as non-study participants, continue to be entitled to full conventional, evidence-based breast cancer screening, in accordance with Blue Shield of California Preventive Services benefits and the provisions of the Affordable Care Act.</p> | <p>Personalized Breast Cancer Screening Clinical Trial BSC2.08</p> <p>Policy Statement: The validity of using personalized breast cancer screening services to determine an individual’s risk for breast cancer and whether this testing can improve that individual’s overall health outcome has not been established in the scientific literature. Blue Shield of California is undertaking a joint clinical study with the Athena Breast Health Network to determine if personalized breast cancer screening services can improve the overall health on an individual.</p> <p>Therefore:</p> <p>Personalized breast cancer screening services administered by the Athena Breast Health Network under the established clinical trial protocol (see Policy Guidelines) are considered medically necessary for “coverage with evidence development” (CED) clinical trial purposes (see Policy Guidelines) for identified WISDOM study participants only.</p> <p>Personalized breast cancer screening services, not administered by the Athena Breast Health Network under the established clinical trial protocol, are considered investigational (see Policy Guidelines).</p> <p>Individuals enrolled in the study and control arms of the WISDOM trial, as well as non-study participants, continue to be entitled to full conventional, evidence-based breast cancer screening, in accordance with Blue Shield of California Preventive Services benefits and the provisions of the Affordable Care Act.</p> |