KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Pharmacogenomic Testing

- ALK Gene Rearrangement and Non-Small-Cell Lung Cancer
- BRAF-v600E Mutation
- Breast Cancer Index
- ChemoFx® Assay
- Conductance Regulator (CFTR) Gene
- Cytochrome P450 Genotyping Test Drug Metabolizing Enzyme Genotyping System
- EndoPredict
- Epidermal Growth Factor Receptor (EGFR) Testing for Predicting Response of Patients with NSCLC to Tyrosine Kinase Inhibitors (TKIs)
- G551D Mutation in the Cystic Fibrosis Transmembrane
- IL28B (IFNL3) Polymorphisms in Patients with Hepatitis C
- Invader UGT1A1 Molecular Assay
- KRAS/NRAS
- Oncotype DX
- Platelet Function Testing (VerifyNow P2Y12 Assay)
- Prosigna Breast Cancer Prognostic Gene Signature Assay
- Warfarin Sensitivity DNA Test

Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees (for in-network coverage).

Prevention and Invitae/LabCorp Genetics are the preferred labs for genetic testing, when the test(s) is/are available at Prevention or* LabCorp *and medical necessity criteria are met.*

LabCorp's test catalog can be found here: LabCorp Test Catalog
Prevention test catalog can be found here: Prevention Test Catalog
Invitae test catalog can be found here: Invitae Test Catalog

**Note: This does not affect processing of tumor or other pathology specimens as they are not performed by LabCorp*

PPO/POS members may use non-preferred labs at the out of network cost share.

Exceptions
For the genetic test(s) listed below, please use the lab specified:

- ***Next Generation Sequencing for Advanced Cancer*** **–** —Any of these three labs can be used:
  - CellNetix SymGene Panel
  - Oncoplex (University of Washington)
  - Caris Life Sciences

Related Policies:

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Genetic Panel Testing
Genetic Screening and Testing

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	
National Coverage Determinations (NCD)	Pharmacogenomic Testing for Warfarin Response (90.1)
Local Coverage Determinations (LCD)	MolDX: Pharmacogenomics Testing (L38337) MolDX: Molecular Diagnostic Tests (MDT) (L36256) MolDX: Breast Cancer Index™ (BCI) Gene Expression Test (L37824) (CPT 81518) MolDX: ENDOPREDICT® Breast Cancer Gene Expression Test (L37311) (CPT 81522) MolDX: NRAS Genetic Testing (L36339) (CPT 81311, 81479) MolDX: Breast Cancer Assay: Prosigna (L36386) (CPT 81520)
Local Coverage Article	Billing and Coding: MolDX: Pharmacogenomics Testing (A57385)

Palmetto GBA is the Medicare contractor for Molecular Diagnostic Testing – this site has the most up to date Medicare coverage guidelines for genetic testing.
MolDX® Program (Administered by Palmetto GBA)

For Non-Medicare Members

Members must meet **ALL the following** criteria:

1. The member is at clinical risk for a genetic condition because of current documented symptoms being displayed or a strong family history of the condition.
2. The test is scientifically valid and can be adequately interpreted.
3. The results will directly affect a member's clinical management or reproductive decisions.
4. After appropriate clinical work-up, and informed consent by the appropriate practitioner, the genetic test is indicated.

Genetic testing is not covered for the medical management of a family member who does not have Kaiser Permanente coverage.

*For **specific tests listed** below the member must meet the criteria above **AND** the specific test criteria below:
For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.

Genetic Test	Criteria Used
Abacavir HLA-B*5701 CPT 81381	This test is covered when: 1) Prior initiation of therapy with abacavir
Anaplastic Lymphoma Kinase (ALK) Gene Rearrangement Testing for Locally Advanced or Metastatic Non-Small-Cell Lung Cancer CPT 88377	No longer requires review

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Genetic Test	Criteria Used
Atomoxetine Therapy	MCG* A-0775 *Not covered per MCG
Behavioral Health Medication Pharmacogenetics - Gene Panels	MCG* A-0681
Breast Cancer Index™ CPT 81518	Considered medically necessary for a woman with early-stage breast cancer when **ALL of the following** criteria are met: • Testing will be used to inform medical decision making regarding extending endocrine therapy • Breast cancer was diagnosed within the last five years • Patient was diagnosed with early-stage disease {Tumor, Node, Metastasis (TNM) stage T1-3, pN0-N1, M0} • Patient has completed at least four years of endocrine therapy • Molecular testing demonstrates that the patient's cancer was estrogen receptor (ER) and/or progesterone receptor (PR) positive • Molecular testing demonstrates that the patient's cancer was human epidermal growth factor receptor 2 (HER2) negative • There is no evidence of active cancer, local recurrence or distant metastasis, at the time of testing request
Carbamazepine Pharmacogenetics - HLA-B*1502 Allele CPT 81381	MCG* A-0649 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
ChemoFx Assay CPT 89240, 81535, 81536	There is insufficient evidence in the published medical literature to show clinical utility.
Colorectal Cancer - BRAF V600E Testing CPT 81210	Does not require medical review
Colorectal Cancer - KRAS and NRAS Genes	Does not require medical review
Clopidogrel Pharmacogenetics - CYP2C19 Gene	MCG* A-0775
Cytochrome P450 Pharmacogenetics - Gene Tests and Gene Panel	MCG* A-0775
ENDOPREDICT® CPT 81522	There is insufficient evidence in the published medical literature to show clinical utility.

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Genetic Test	Criteria Used
GenoSure Archive CPT 87900, 87901, 87906 Trofile DNA phenotype CPT 87999	These tests are covered when: 1) Maraviroc is being considered, AND 2) A positive test is required to initiate use of this drug
CYP2: • CYP2B6/CYP3A4/CYP2A6 Efavirenz CPT 80299, 81401, 81479 • CYP2C19 Proton Pump Inhibitors (PPI) for Treating Helicobacter Pylori CPT 81225, 81226, 81227, 81401, 81479 • Immunosuppressants for Organ Transplant CYP3A5 and CYP3A4 CPT 81401	There is insufficient evidence in the published medical literature to show clinical utility.
Epidermal Growth Factor Receptor (EGFR) Testing for Predicting Response of Patients with NSCLC to Tyrosine Kinase Inhibitors (TKIs) Such as VeriStrat CPT 81235	No longer requires review
IFNL3 (previously IL28B) Polymorphisms in Patients with Hepatitis C CPT 81283	There is insufficient evidence in the published medical literature to show clinical utility.
5-Fluorouracil Pharmacogenetics - DPYD, MTHFR, and TYMS Genes CPT 81232, 81291, 81346	MCG* A-0665 - Kaiser Permanente will not cover this per MCG guideline. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Irinotecan Dosing - UGT1A1 Gene (Invader) CPT 81350	MCG* A-0624 Current role remains uncertain For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
KRAS and/or NRAS KRAS: CPT 81275, 81276, 0111U NRAS: CPT 81311, 0111U	No longer requires review
Malignant Melanoma (Cutaneous) - BRAF V600 Testing CPT 81210	Does not require medical review
Oncotype Dx – Breast CPT 81519, S3854	Covered when the following criteria are met: 1. Axillary node biopsy is negative for tumor or is positive only for micrometastasis, defined as no focus of tumor > 2 mm diameter. 2. Newly diagnosed invasive ductal carcinoma of breast, stage I or II 3. Outcome of testing will guide decision making regarding adjuvant chemotherapy. 4. Patient is female. 5. Primary tumor is estrogen receptor positive. 6. Primary tumor is HER-2 receptor-negative.
Oncotype DX – Colon Cancer CPT 81525	Colon MCG* A-0651 and Prostate MCG* A-0712- Current Role Remains Uncertain. For access to the MCG Clinical Guidelines criteria,

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Genetic Test	Criteria Used
Oncotype DX – Prostate CPT 0047U	please see the MCG Guideline Index through the provider portal under *Quick Access*.
Opioid Pharmacogenetics - CYP450 Polymorphisms and OPRM1 Gene	MCG* A-0775 *Not covered per MCG
Platelet Function Testing (VerifyNow P2Y12 Assay) CPT code 85576	Medical necessity review no longer required
Prosigna Breast Cancer Prognostic Gene Signature Assay CPT 81520	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Rasburicase Pharmacogenetics - G6PD Gene CPT 81247, 82148, 81249	MCG* A-0653 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Statin Pharmacogenetics - SLCO1B1 Gene CPT 81328	MCG* A-0981 Current role remains uncertain. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Tacrolimus Pharmacogenetics - CYP3A4 and CYP3A5	MCG* A-0775 *Not covered per MCG
Tamoxifen Pharmacogenetics - CYP2D6 Gene	MCG* A-0775 *Not covered per MCG
Azathioprine and 6-Mercaptopurine Pharmacogenetics - NUDT15 and TPMT Genes CPT 0034U, 0169U, 81335, 84433	MCG* A-0628 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Warfarin Sensitivity DNA Test CPT 81227, 81355, G9143	This test is covered once in a lifetime to guide the Warfarin dosing strategies when the patient has had no more than 5 doses of Warfarin prior to testing.

***MCG Manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser

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Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting any of these services, please send the following documentation to support medical necessity:

- Any genetic counseling notes if applicable
- Last 6 months of specialist notes of that is being reviewed (neurological - neurology notes)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Pharmacogenetics is defined as the study of the genetic basis for differences in a population's response to a drug. It seeks to identify polymorphisms (genetic variations) that result in different systemic concentration levels of drugs, which may help explain differing responses to the same medication. The field of pharmacogenetics began as the study of gross ethnic variations (e.g., variation by ethnic groups) and evolved into the study of variations of genes and proteins within individuals. Kaiser Permanente is evaluating the evidence for each test as the evidence is published.

Evidence and Source Documents

ALK Gene Rearrangement and Non-Small-Cell Lung
Breast Cancer Index
Cancer BRAF-v600E Mutation
ChemoFx Assay
Cytochrome P450 Genotyping Test Drug Metabolizing Enzyme Genotyping System
Epidermal Growth Factor Receptor (EGFR) Testing for Predicting Response of Patients with NSCLC to Tyrosine Kinase Inhibitors (TKIs)
IL28B (IFNL3) Polymorphisms in Patients with Hepatitis C
Invader UGT1A1 Molecular Assay
KRAS
Oncotype DX
Platelet Function Testing (VerifyNow P2Y12 Assay)
Prosigna Breast Cancer Prognostic Gene Signature Assay
Warfarin Sensitivity DNA Test

Medical Technology Assessment Committee (MTAC)

ALK Gene Rearrangement and Non-Small-Cell Lung Cancer

BACKGROUND

Lung cancer is one of the most common causes of cancer death, accounting for over 1 million deaths annually. Lung cancer is comprised of two histological types: small-cell lung cancers and non-small-cell lung cancers. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. Traditionally, treatment decisions have been based on histological type. For patients with NSCLC, platinum-based chemotherapy constitutes standard first-line treatment. However, a therapeutic plateau has been reached with conventional chemotherapy for NSCLC patients. Advances in the knowledge of molecular mechanisms of carcinogenesis have led to a change in the treatment strategy for patients with NSCLC. Research efforts are now focusing on new therapies that target molecular subtypes of NSCLC (Janku 2010, Pao 2011, Sasaki 2010). Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that is not normally expressed in lung cancer. Fusions of ALK with echinoderm microtubule-associated protein-like 4 (EML4), an upstream promoter, were found in NSCLC in 2007. However, EML4 does not appear to be the exclusive fusion partner with ALK. Biologically, these fusions result in constitutive activation of the kinase. It has been reported that approximately 3 to 7% of tumors harbor EML4-ALK fusions. Although associations with clinical and pathological characteristics are not well established, research suggests that EML4-ALK fusions are associated with never smokers or light smokers, younger patient age, patients with adenocarcinomas, and patients with more advanced NSCLC. While the frequency of epidermal growth factor receptor (EGFR) mutations also

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increases in patients with these characteristics, EML4-ALK rearrangements are generally not found in patients with EGFR or KRAS mutations (Janku 2010, Pao 2011, Sasaki 2010). Currently, clinical trials are underway to determine the safety and efficacy of ALK kinase inhibitors for the treatment of NSCLC in patients with EML4-ALK rearrangements.

08/15/2011: MTAC REVIEW
ALK Gene Rearrangement and Non-Small-Cell Lung Cancer
Evidence Conclusion: Analytic validity: Several methods are available for detecting EML4-ALK rearrangements in patients with NSCLC; however, there is currently no gold standard method. Clinical validity: There is insufficient evidence to determine the clinical validity of testing for EML4-ALK rearrangements in patients with NSCLC. Clinical utility: There is insufficient evidence to determine the clinical utility of testing for EML4-ALK rearrangements in patients with NSCLC.
Articles: Assessment objective: Analytic validity: Are the clinical assays for the detection of ALK gene rearrangements accurate and reliable? Clinical validity: Does the presence of an ALK gene rearrangement predict clinical outcome? Clinical utility: Will the results of the clinical assays for the detection of ALK gene rearrangements alter clinical management and improve clinical outcomes? Several methods including polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) are currently being evaluated for the detection of ELM4-ALK rearrangements. Each of these methods has its advantages and limitations. Currently, there is no gold standard method for detecting EML4-ALK rearrangements in patients with NSCLC (Sasaki 2010). A small retrospective cohort study was identified that addressed the clinical validity of testing patients with NSCLC for EML4-ALK gene rearrangements; however, this study was not selected for review as it only included 19 patients with EML4-ALK rearrangements. Results from this study suggest that patients with EML4-ALK rearrangements have similar response rates to platinum-based combination chemotherapy as patients without these mutations. Additionally, patients with EML4-ALK rearrangements do not appear to respond to tyrosine kinase inhibitors (Shaw 2009). Larger studies are needed to confirm these findings. To date there are no FDA approved agents for the treatment of NSCLC in patients with EML4-ALK gene rearrangements. Results from a phase 1 open-label, prospective case-series that included 82 subjects with EML4-ALK rearrangements suggest that crizotinib, an orally available small-molecule inhibitor of the ALK tyrosine kinase, may be effective for the treatment of NSCLC in patients with EML4-ALK rearrangements. The overall response rate, which included confirmed partial and complete responses, was 57% and 33% of patients had stable disease. The most commonly reported adverse effects were nausea (54% of patients) and diarrhea (48% of patients) (Kwak 2010). Phase 3 clinical trials are now underway to determine the safety and efficacy of crizotinib compared to pemetrexed or docetaxel in patients with advanced NSCLC and EML4-ALK gene arrangements (ClinicalTrials.gov number, NCT00932893).

> The use of ALK gene rearrangement does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

$BRAF^{V600E}$ Mutation
BACKGROUND
In the past year, several therapies for late-stage melanoma have been approved, including peg-interferon α-2b (Sylatron) and ipilimumab (Yervoy). Until now, ipilimumab was the only agent to demonstrate an improvement in overall survival for patients with advanced melanoma. Vemurafenib is approved for the treatment of advanced melanoma as well but targets a specific patient population. It is an inhibitor of mutated forms of BRAF serine-threonine kinase, including $BRAF^{V600E}$, and also inhibits other kinases at similar concentrations. Some mutations in the BRAF gene, including V600E, result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Confirmation of $BRAF^{V600E}$ mutation-positive melanoma as detected by the cobas® 4800 V600 Mutation Test, is required for selection of patients prior to administration of vemurafenib. This test is designed to detect $BRAF^{V600E}$ mutations in DNA isolated from formalin-fixed, paraffin-embedded human melanoma tissue. This test is marketed by the same company that manufactures vemurafenib, and its FDA approval is based on the same data that supported approval of vemurafenib.

09/2011: Pharmacy and Therapeutics Committee (P&T) $BRAF^{V600E}$ Mutation
Evidence Conclusion: From P&T Committee: Evidence of benefit[2-4]: Preliminary data from BRIM-2, a phase 2 trial, showed that patients with $BRAF^{V600E}$ mutation + melanoma who had received prior treatment and were subsequently treated with vemurafenib, had an objective response rate >50%. Based on this data, the FDA recommended modification of the statistical plan for BRIM-3, a phase 3 trial, to accommodate an interim analysis and accelerate the

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approval process. Median follow-up in BRIM-3 was ~3 months. In the BRIM-3 trial, vemurafenib, 960mg BID was superior to dacarbazine in progression-free survival (5.3 months vs 1.6 months; p<0.001) and objective tumor response rate (48% vs 5%, p<0.001).
Complete responses were seen in 2 patients (0.9%) of patients in the vemurafenib group and 0 in the dacarbazine group. Median overall survival was not reached in the vemurafenib group, but was 7.9 months in the dacarbazine group. At 6 months, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group; p<0.001.
In BRIM-2 and BRIM-3, all enrolled patients tested positive for the $BRAF^{V600E}$ mutation using the cobas® 4800 V600 Mutation Test. Evidence of harm[1-3]: The most common adverse reactions of any grade (≥ 30% in either study) reported in patients receiving vemurafenib were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus and skin papilloma. The most common (≥5%) Grade 3 adverse reactions were cutaneous squamous cell carcinoma (cuSCC) and rash; 24% of patients treated with vemurafenib were reported to have at least one cuSCC. These lesions were excised, and none required dose-modifications. The incidence of Grade 4 adverse reactions was ≤ 4% in both studies. In BRIM-3, the incidence of adverse events resulting in discontinuation was 7% in the vemurafenib arm and 4% for the dacarbazine arm. There are no contraindications to vemurafenib. Safety issues addressed in the package insert include cuSCC, serious hypersensitivity reaction, Stevens-Johnson syndrome and toxic epidermal necrolysis, QT-prolongation, liver laboratory abnormalities, photosensitivity, uveitis and other ophthalmologic reactions, and new primary malignant melanomas. Pregnancy category D, may cause fetal harm based on its mechanism of action. Women of childbearing potential and men should be advised to use appropriate contraceptive measures during therapy and for at least 2 months after discontinuation.

Articles: Table 1. Summary of results from BRIM-2: an open-label, single-arm, Phase II trial

Study population	Outcome	Vemurafenib 960mg BID (95% CI) , n=132
$BRAF^{V600E}$ mutation + melanoma who have completed prior 1st line therapy	Best overall response rate	52.3% (43, 61)
	Median duration of response	6.8 months (5.6, not reached)
	Median PFS	6.2 months (5.6, 6.8)

Table 2. Summary of results from BRIM-3: a randomized double-blind placebo-controlled Phase III trial

Study population	Outcome	Vemurafenib n=337	Dacarbazine n=338	HR (95% CI) *p*-value	ARR (95% CI)	NNT (95% CI)
Unresectable stage IIIC or IV melanoma, + $BRAF^{V600E}$ mutation, treatment naïve	Overall survival	Median not reached 84% at 6 months	7.9 months (7.3, 9.6) 64% at 6 months	0.37 (0.26, 0.55) *p*<0.001	20% (13, 26)	5 (4, 7)
	Progression-free survival	5.3 months (4.9, 6.6)	1.6 months (1.6, 1.7)	0.26 (0.2, 0.33) *p*<0.001	NA	NA
	Objective tumor response rate	48% (n=219)	5% (n=220)	*p*<0.001	43% (35, 50)	2 (2, 3)

HR – Hazard ratio ARR – Absolute Risk Reduction NNT – Number Needed to Treat to benefit one person

This was not considered at MTAC but went to P&T instead.

Breast Cancer Index

BACKGROUND

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett et al., 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several molecular tests including the Breast Cancer Index (BCI).

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The BCI is a reverse transcriptase polymerase chain reaction (rt-PCR) test that helps to guide treatment decision in women with early stage breast cancer who are ER+, LN- or LN+, and are distant recurrence-free (https://www.breastcancerindex.com/). The test assesses the overall (10 years) and late distance recurrence (5-10 years) (prognostic) and who benefits from extended endocrine therapy (predictive) after an initial 5-years of endocrine therapy (https://www.breastcancerindex.com/). The test can also be performed after treatment has begun to determine late distance recurrence and the likelihood of benefit from extended endocrine therapy.

The assay is a combination of two markers, the HOXB13/IL17BR (H/I) which is based on two genes, and a proliferation marker which is the molecular grade index (MGI) (based on 5 genes) (Sanft et al., 2015; Dennis C Sgroi, Carney, et al., 2013). These markers evaluate the prognostic component by generating a risk score that varies from 0 to 10. For overall risk, BCI score is classified into three categories: BCI score <5.1 is low risk; 5.1 ≤ BCI score ≤6.5 is intermediate risk, and BCI score ≥6.5 is high risk (Sanft et al., 2015). For the risk of late distant recurrence in patients with lymph node negative, BCI score is classified as low risk BCI < 5.0825 and high risk BCI ≥ 5.0825 (Hayes, 2016). In addition to gene expression, BCI score is determined in N1 patients by adding tumor size and grade (https://www.breastcancerindex.com/about-breast-cancer-index).

The predictive part is based on the quantitative molecular assessment of estrogen signaling pathways (based on H/I) and is indicative of who benefits from extended endocrine therapy after an initial course (5 years) of endocrine treatment (https://www.breastcancerindex.com/about-breast-cancer-index#).

06/05/2017: MTAC REVIEW

Evidence Conclusion:

- Analytic validity: there is insufficient evidence to recommend for or against the analytical validity of the BCI assay in ER+, LN- or LN+ breast cancer patients.
- Clinical validity:
  - Level IB evidence (based on Simon et al. 2009 revised determination of levels of evidence using elements of tumor marker studies) supports the prognostic effect of early recurrence, distant recurrence, and distant recurrence over 10 years in ER+, LN- breast cancer patients. In addition, there is insufficient evidence to assess clinical validity in LN+ patients.
  - Low evidence supports extended use of endocrine therapy in high risk patients with ER+, LN- breast cancer patients.
- Clinical utility: there is insufficient evidence to make a conclusion on the clinical utility of the BCI assay in ER+, LN- or LN+ breast cancer patients.

Articles: PubMed was searched through April 10, 2017 with the search terms breast cancer index bci with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded 20 articles; however, six met our criteria.

The use of Breast Cancer Index for predicting response of solid tumors to chemotherapeutic agents does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/10/2023: MTAC REVIEW

Evidence Conclusion:

- Analytical validity: Evidence is insufficient
- Clinical validity: Low quality evidence suggest that BCI is significantly predictive of response to extensive endocrine therapy and adds a prognostic value beyond clinicopathologic characteristics in ER+, LN- or LN+ breast cancer patients. The test may be clinical useful in terms of optimizing duration of endocrine therapy.
- Clinical utility: One new study indicates that BCI test may influence treatment recommendation. However, the quality of evidence is very low.

Articles: PubMed was searched from 2018 to January 25, 2023, with the search terms breast cancer index bci. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications.

The use of Breast Cancer Index for predicting response of solid tumors to chemotherapeutic agents does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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ChemoFx® Assay

BACKGROUND

It is widely recognized that patients with the same histological stage and grade of cancer may vary considerably in their clinical response and tolerability to chemotherapy. An individual may be resistant to one chemotherapeutic and sensitive to another, suggesting that there is considerable clinical heterogeneity in tumor chemosensitivity. Unfortunately, resistance to chemotherapy cannot be predicted by clinical or histological examination. The administration of an ineffective therapy is associated with unnecessary toxicity, delay of potentially useful drug, added risk of the development of resistant clones, and needless cost. Many attempts have been made over the years to develop an ex-vivo test that would provide clinically relevant tumor-specific information, i.e. measures how a patient cancer cells respond to specific types, doses and combinations of chemotherapy (Gallion 2006, Cree 2007). A number of in-vitro chemosensitivity response tests have been, and are currently used. These include assays that measure cellular metabolic activity, tests that measure radioactive precursor incorporation, and tests that measure cell viability. Chemoresponse assays are not intended to be used as an alternative to the traditional empiric methods for selecting chemotherapy but as an aid to the oncologists when selecting the most appropriate chemotherapy regimens on an individual basis especially when a number of equivalent options are available (Ness 2002, Gallion 2006, Cree 2007). ChemoFx® (Precision Therapeutics) is an ex-vivo, cell death assay based on the biological phenomenon that when cells that grow adherent in culture as a monolayer, die they lose their adherent qualities and lift from the culture surface. The test is reported to use as little as 35 mg of tissue, and have the results available in about 3 weeks after receiving the specimen. It involves growing tumor cells (excised from individual cancer patients through biopsy or surgery, or recovered from fluid specimens), in primary cultures as monolayers. Once a sufficient number of cells are grown, they are exposed to a variety of chemotherapeutic agents in a range of concentrations. A full dose-response curve is generated for each drug evaluated, and the data are presented graphically as the cytotoxic index (% kill), defined as 1-[No of cells in treated wells/No. of cells in control wells] x100. Features of each dose-response curve are used to score a tumor's response to each ex vivo treatment as responsive, intermediate response, or nonresponsive. Drug responses are scored from 0-5 and is determined by the number of drug doses where the cytotoxic index was >35%. Collectively these scores may be used by the oncologist in his treatment decisions (Peters 2005, Zhibao 2008).

10/05/2009: MTAC REVIEW

ChemoFx® Assay

Evidence Conclusion: There is insufficient evidence to date to determine the clinical validly and utility of ChemoFx in selecting the most appropriate chemotherapy regimens and improving survival of cancer patients.

Articles: The published literature on ChemoFx® is very limited. There were only two case series (N=304, and N=18) that retrospectively evaluated the predictive value of ChemoFx assay by correlating its results with progression free interval (PFI) in patients with ovarian cancer, and another small case series among 34 women with breast cancer, that correlated the pathological complete response to a neoadjuvant chemotherapy with the results of ChemoFx® testing. As regards the clinical utility of the test, the literature search did not reveal any randomized or non-randomized controlled trials that compared outcomes among patients managed with and without ChemoFx® testing. The larger case series on the predictive value of ChemoFx was critically appraised Gallion H, Christopherson WA, Coleman RI, et al. Progression –free interval in ovarian cancer and predictive value of an ex vivo chemo responsive assay. Int J Gynecol Cancer 2006;16:194-201. See Evidence Table

The use of ChemoFx Assay for predicting response of solid tumors to chemotherapeutic agents does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Cytochrome P450 Genotyping Test Drug Metabolizing

BACKGROUND

Pharmacogenetics is the study of the genetic causes of individual variation in drug response. There has been growing interest in the use of pharmacogenetics to predict response to medications in terms of safety and efficacy. Cytochrome P450s, in particular CYP3A4, CYP2D6, CYP2C19, CYP1A2, and CYP2B6, have a central role in the metabolism of many clinically used drugs. Genetic polymorphisms in the cytochrome P450 enzymes may help to explain the observed variation in the concentrations of certain drugs and their metabolites. Genetic variability can significantly affect drug metabolism and lead to distinct subgroups of the populations that differ in their ability to metabolize various drug. The resulting phenotypes are poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultra-rapid metabolizers (UM). Clinically, the most important phenotypes are ultra-rapid metabolizers and poor metabolizers. Subjects who possess the ultra-rapid metabolizer phenotype may

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experience a reduced response to standard doses of medications because their ability to rapidly metabolize these medications makes it difficult to sustain therapeutic levels. They are also more likely to suffer from adverse drug reactions due to the formation of toxic metabolites and excess levels of the active drug. Because poor metabolizers have low metabolic capacity, usual doses may lead to higher than expected drug concentrations, placing them at increased risk for adverse drug reactions. Additionally, PM may not respond to drugs that require activation by the enzyme in question (Ingelman-Sunberg 2010). It is thought that knowledge of the genetic metabolizer status may enable physicians to more accurately identify the appropriate drug and/or drug dose that maximizes efficacy and minimizes toxicity in each individual patient. The AmpliChip test uses microarray DNA chip technology developed by Affymetrix. The microarray chip is similar to a computer microchip, but instead of circuits, the microarray chip contains millions of DNA fragments, called probes, that are chemically synthesized at precise locations on the coated quartz surface. The genetic test is performed by extracting DNA from the patient's blood. Prepared DNA samples are applied to the array and matched to the sequence of the probe molecules. The AmpliChip cytochrome P450 genotyping test was cleared for marketing by the FDA in December 2004. It is the first FDA-approved laboratory gene test to evaluate genetic information for medication selection.

PLAVIX In the Unites States, cardiovascular disease is the leading cause of death in both men and women (Heron 2009). Clinical trials have shown that clopidogrel (Plavix), an anti-blood clotting medication, reduces the morbidity and mortality associated with several cardiovascular diseases. However, there is a significant amount of inter-individual variability in clopidogrel responsiveness, which leads some patients to experience decreased platelet inhibition (poor response) with clopidogrel (Momary 2010b). It is thought that the primary source of variability in clopidogrel responsiveness lies in the pharmacokinetics of clopidogrel. Clopidogrel is a pro-drug that is metabolized into its active metabolite through the action of several enzymes (CYP2C19, CYP1A2, CYP3A4, CYP3A5, and CYP2B6). A polymorphism in any of the enzymes could result in decreased responsiveness. One of the enzymes associated with clopidogrel non-responsiveness is CYP2C19. Patients with the wild-type CYP2C19*1 allele have normal metabolic activity. However, four variant CYP2C19 alleles are associated with reduced metabolic activity. Drug interactions, clinical factors, such as diabetes and increased weight, and patient non- compliance are other proposed mechanisms of clopidogrel non-responsiveness. The prevalence of clopidogrel resistance varies from 3-30% (Momary 2010a, Momary 2010b, Ma 2010). On March 12th, 2010, the FDA added a boxed warning to the label for clopidogrel to alert healthcare professionals and patients of the reduced effectiveness of clopidogrel for patients who are poor metabolizers and includes information on the role of CYP2C19 genotype in clopidogrel responsiveness. There has been growing interest in the use of CYP2C19 genotyping to identify patients who are non-responsive to clopidogrel. The AmpliChip CYP450 Test (Roche Diagnostics Inc, Indianapolis, IN) has received FDA approval for CYP2C19 genotyping.

TAMOXIFEN Aside from non-melanoma skin cancer, breast cancer is the most common form of cancer in women. It is the number one cause of cancer death in Hispanic women, and the second leading cause of cancer death in white, black, Asian/Pacific Islander, and American Indian/Alaska Native women (CDC 2010). Tamoxifen is used as an adjuvant endocrine therapy to prevent estrogen receptor-positive breast cancer recurrence, as a treatment for metastatic breast cancer, and to prevent disease in high-risk women with ductal carcinoma in situ (Lash 2009). Tamoxifen is a "pro-drug", several enzymes (CYP2B6, CYP2C8, CYP2C9, CYP2C10, CYP3A4, CYP3A5, and CYP2D6) transform the pro-drug into its active metabolites 4-hydroxytamoxifen (4-OH tamoxifen) and 4-hydroxy-N-desmethyltamoxifen (endoxifen). Research indicates that both endoxifen and 4-OH tamoxifen have nearly 100-fold higher affinity for estrogen receptors than tamoxifen; however, endoxifen is found at a 6 to 12 fold higher concentration than 4-OH tamoxifen. Every secondary tamoxifen metabolite except for endoxifen is formed by two enzymes CYP3A4 and CYP3A5. Endoxifen production is almost totally dependent on the enzymatic activity of CYP2D6. In vivo studies suggest that endoxifen is the major active metabolite of tamoxifen (Higgins 2009). The observed variation in the concentrations of tamoxifen and its metabolites might be explained through genetic polymorphisms in the genes that encode the CYP2D6 enzyme. There are more than 100 allelic variants of CYP2D6 with incidence varying according to race and ethnicity. The most prevalent allele is the wild-type allele CYP2D6*1. Patients with two copies of this allele produce an enzyme with normal activity. Because individuals have two CYP2D6 alleles, various combinations of the alleles result in a spectrum of CYP2D6 function ranging from no activity to increased activity. In the Caucasian population, approximately 5-10% of patients are poor metabolizers and 10-15% of patients are intermediate metabolizers of tamoxifen. It is thought that tamoxifen- treated patients who are poor metabolizers and intermediate metabolizers are at an increased risk for recurrence (Dezentjé 2009, Higgins 2009, Lash 2009). CYP2D6 inhibiting drugs, such as SSRIs, may also decrease tamoxifen metabolism (Lash 2009). Due to the association between tamoxifen metabolism and the CYP2D6 genotype, there is growing interest in the use of CYP2D6 genotyping to direct treatment for patients with breast cancer. *Atomoxetine* Atomoxetine is a norepinephrine reuptake inhibitor that is used to treat attention-deficit hyperactivity disorder (ADHD). Atomoxetine is metabolized via the CYP2D6 enzyme and has a broad therapeutic window. Currently,

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dosing is determined by the patient's weight with dose adjustments according to clinical response and adverse effects. Studies have suggested that in PM the plasma concentration of atomoxetine is higher and the half-life is longer compared to EM (Michelson 2007). *Codeine for nursing mothers*
Opioid analgesics, such as codeine, are commonly used for pain relief in labor and postpartum. Codeine is a pro-drug that is predominantly metabolized by the CYP2D6 enzyme into morphine. While codeine is effective for the majority of individuals, a subset of patients, CYP2D6 poor metabolizers, do not possess any active gene copies and experience poor analgesia due to the deficient formation of the active metabolite (morphine). Additionally, approximately 2-40% of individuals (depending on ethnic background) are ultra-rapid metabolizers and possess functional duplications of the CYP2D6 gene. These duplications lead to enhanced biotransformation of codeine into morphine and have been associated with adverse effects including death in breastfed infants (Madadi 2009a, Alfirevic 2010). *Efavirenz* Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Treatment with efavirenz plus two nucleoside reverse transcriptase inhibitor (NRTI) is recommended among the first line regimens in patients initiating highly active antiretroviral therapy (HAART). In addition, efavirenz is used with other antiretroviral agents as a part of post exposure prophylaxis regimen to prevent HIV transmission. Efavirenz is metabolized primarily by CYP2B6 with partial involvement from CYP3A4 and CYP2A6. It is hypothesized that polymorphisms in these genes may contribute to interindividual differences in efavirenz plasma concentration and half-life. Studies have found that poor metabolizers were at greater risk of high plasma levels of efavirenz. It had been suggested that high plasma levels may be associated with central nervous system (CNS) side effects, such as abnormal dreams, dizziness, somnolence, insomnia, and impaired concentration (Rakhmanina 2010, Tozzi 2010). *Proton pump inhibitors (PPI) for treating Helicobacter pylori* H. pylori infection is closely related to many gastrointestinal diseases, including gastritis, peptic ulcer disease, and gastric cancer. Eradication of H. pylori is important for reducing the relapse rate of ulcers and the risk of gastric cancers. Current treatment for the eradication of H. pylori consists of a PPI and two antibiotics (amoxicillin and either clarithromycin or metronidazole). The majority of proton pump inhibitors are metabolized primarily by the CYP2C19 enzyme. PPIs work by raising the intragastric pH, which increases the stability and bioavailability of antibiotics making them more effective. Factors associated with treatment failure include, but are not limited to: antibiotic resistance, non- compliance, smoking habits, bacterial and host-related factors, and CYP2C19 genotype (Yang 2010, Sugimoto 2009). *Immunosuppressants for organ transplant*
Immunosuppressant drugs are used in transplant patients to prevent rejection. Regimens usually include a combination of different drugs. Immunosuppressants have a narrow therapeutic range. Overdosing can lead to infection, malignancy, and organ toxicity, whereas under dosing can lead to rejection. The current approach to prevent over- or under dosing is therapeutic drug monitoring where blood or plasma concentrations are measured and dosage is adjusted to ensure that drug concentrations remain within a narrow therapeutic range. The first 72 hours after transplantation is the most critical time as inadequate drug exposure increases the risk for rejection. Therapeutic drug monitoring is not useful for predicting the initial dose.
Thus, there has been growing interest in using a pharmacogenetic approach to predict initial dose. Tacrolimus is a calcineurin inhibitor that is metabolized by CYP3A5 and CYP3A4. Patients with a functional copy of the CYP3A5 enzyme are referred to as functional expressers; patients without a functional copy of the CYP3A5 enzyme are referred to as functional non-expressers. CYP3A5 expression is thought to be associated with reduced tacrolimus exposure following oral administration, thus patients who are functional expressers may be more likely to experience rejection (Ware 2010, Staatz 2010). *Selective serotonin reuptake inhibitors (SSRIs)*
SSRIs are a popular class of antidepressant medications. CYP2D6 and CYP2C19 are the primary CYP450 enzymes involved in the metabolism of SSRIs. Other CYP450 and non-CYP450 enzymes also play a role in the metabolism of some SSRIs. It is thought that polymorphisms in the CYP450 enzymes can lead to variability in response to some SSRIs. Knowing a patients genotype may be helpful in choosing an initial SSRI that is more likely to be effective (Berg 2007).

10/03/2005: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing
Evidence Conclusion: There is no published evidence on using the AmpliChip cytochrome P450 genotyping test to help select medications or doses of medications. The ideal study would compare the safety and effectiveness of medications selected with and without the results of the AmpliChip cytochrome P450 genotyping test, preferably in a randomized trial. This type of study has not been published.
Articles: No empirical studies were identified that reported on medication selection using the AmpliChip test, or clinical outcomes following medication selection guided by the AmpliChip test. Several articles on the Affymetrix GeneChip were identified, but none of the mentioned using the technology with the AmpliChip test. In addition, the studies on the Affymetrix GeneChip used it for genetic profiling (e.g., to estimate prognosis of colon cancer patients), not to aid physicians in the selection of medications.

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The use of in the evaluation of does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/16/2010: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing Evidence Conclusion:
There is insufficient evidence to determine whether CYP2C19 genotyping assays accurately and reliably detect variant CYP2C19 alleles. Clinical validity: There is insufficient evidence to determine whether the presence of CYP2C19 variant genotypes predict clinical outcomes. Clinical utility: There is insufficient evidence to determine if using CYP2C19 gene testing for predicting clopidogrel responsiveness will improve clinical outcomes.
Tamoxifen: Analytic validity No published studies on the accuracy of commercially available tests for detecting CYP2D6 variants were identified. Clinical validity the results of the published studies on the clinical validity of CYP2D6 gene testing for tamoxifen metabolism were conflicting. Goetz et al conducted a retrospective review of archived sample of patients from the North Central Cancer Treatment Group RCT (89-30-52) tamoxifen only arm. The objective of this study was to determine the effect of CPY2D6 metabolism on breast cancer recurrence and survival. By taking into account genotype and CYP2D6 inhibitor use, patients were classified as either poor metabolizers, intermediate metabolizers, or extensive metabolizer (normal). When extensive metabolizers were compared to decreased metabolizers (intermediate and poor metabolizers), patients with decreased metabolism had significantly shorter time to recurrence (p=0.034), relapse-free survival (p=0.017), and disease-free survival (p=0.027). Overall survival did not differ significantly between extensive and decreased metabolizers. When poor metabolizers were compared to extensive metabolizers, poor metabolizers had significantly shorter time to recurrence (p=0.007), relapse-free survival (p=0.005), and diseases-free survival (p=0.008) than extensive metabolizers. Overall survival did not differ significantly between poor and extensive metabolizers. There was no significant difference in any of the measures of recurrence or survival between intermediate and extensive metabolizers. The major advantage of this study is that is accounted for CYP2D6 inhibitor use. One of the limitations of this study is that there were only sixteen poor metabolizers and forty intermediate metabolizers. Because of the small number of subjects, the study may lack the power to detect significant differences. Also, the study only accounts for one CYP2D6 variant. Because only one variant was studied there is the possibility for misclassification (Goetz 2007). A retrospective analysis of 1,325 subjects from German and U.S. cohorts found that patients with reduced or absent CYP2D6 function had significantly shorter time to recurrence, event-free survival, and disease-free survival compared to extensive metabolizers. There was no difference in overall survival between decreased and extensive metabolizers. Patients from the 89-30-52 trial, the same population studied by Goetz, were included in this analysis. One of the limitations of the study was that the cohorts that were combined had different lengths of follow-up. Additionally, the study did not account for CYP2D6 inhibitor use. Advantages of this trial include its size and that it accounted for 5 different variant alleles (Schroth 2009). Another retrospective cohort study also found that relapse-free survival and event-free survival were significantly poorer for decreased metabolizers compared to extensive metabolizers (Schroth 2007). Not all studies have shown an association between CYP2D6 metabolism and treatment outcomes. Nowell and colleagues conducted a retrospective review of 337 archived samples. The objective of this study was to determine whether genetic variability in the tamoxifen metabolic pathway influenced overall survival in breast cancer patients treated with tamoxifen. In the study, extensive metabolizers were compared to decreased metabolizers (intermediate and poor metabolizers). Relapse- free and overall survival did not differ significantly between extensive and decreased metabolizers. One of the limitations of the study was that the authors did not control for CYP2D6 inhibitor use. Because of the small number of subjects the study may lack power to detect significant differences. There is a potential for misclassification as only one CYP2D6 allele was accounted for. Additionally, the effects of CYP2D6 genotype on tamoxifen metabolism were not assessed separately for poor and intermediate metabolizers (Nowell 2005). Clinical utility
No published studies were identified that prospectively compared patient outcomes managed with and without CYP2D6 genotyping. Conclusion: Analytic validity: There is insufficient evidence to determine whether CYP2D6 genotyping assays accurately and reliably detect variant CYP2D6 alleles. Clinical validity: There is insufficient evidence to determine whether the presence of CYP2D6 variant genotypes predict clinical outcomes.
Clinical utility: There is insufficient evidence to determine if using CYP2D6 gene testing for predicting tamoxifen metabolism will improve clinical outcomes.
Articles: *Plavix:* Assessment objective: Analytic validity: Do the CYP2C19 genotyping assays accurately and reliably detect variant CYP2C19 alleles? Clinical validity: Does the presence of CYP2C19 variant genotypes predict clinical outcome? Clinical utility: Will the results of the CYP2C19 genotype assay alter clinical management and improve clinical outcomes? Medline was searched through June 2010 with the search terms *clopidogrel*, *Plavix*, and *CYP2C19* with variations. The search was limited to English language publications and human populations. The

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reference lists of relevant studies were reviewed to identify additional publications. Sofi F, Giusti B, Marcucci R, et al. Cytochrome P450 2C19*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J 2010;* 30 March 2010. [Epub ahead of print] See Evidence Table *Tamoxifen:* Assessment objective: Analytic validity: Do the CYP2D6 genotyping assays accurately and reliably detect variant CYP2D6 alleles? Clinical validity: Does the presence of CYP2D6 variant genotypes predict clinical outcome? Clinical utility: Will the results of the CYP2D6 genotype assay alter clinical management and improve clinical outcomes? No randomized controlled trials were identified. The literature consisted mainly of retrospective case series and cohort studies. The results from the studies evaluating the association between tamoxifen metabolism and breast cancer recurrence and survival were conflicting, with some showing a positive association and some showing a negative association. The study by Goetz et al was selected because it took into account CYP2D6 inhibitor use. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 2007; 101:113-121**.** See Evidence Table U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2006 Incidence and Mortality Web-based Report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2010. Available at: http://www.cdc.gov/uscs.

The use of in the evaluation of Plavix and Tamoxifen metabolization does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/20/2010: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing
Evidence Conclusion: There is insufficient evidence to determine the analytic validity, clinical validity, or clinical utility of genotyping for the following indications: Atomoxetine (dosing), Codeine (deciding whether to prescribe codeine for nursing mothers), Efavirenz (dosing), *Helicobacter pylori* (managing treatment), Immunosuppressant for organ transplantation (dosing), Selective serotonin reuptake inhibitors (selection or dosing)
Articles: There is limited evidence pertaining to the analytic validity, clinical validity, and clinical utility of CYP450 genotyping. The majority of studies identified were small observational studies that addressed the association between CYP450 genotype and intermediate outcomes. A prospective cohort study that evaluated the effect of CYP3A5 genotype on tacrolimus exposure, dose, and incidence of acute rejection, and a meta-analysis that looked at the association between CYP2C19 polymorphisms and H. pylori eradication rates were selected for review. The following studies were critically appraised: Zhao F, Wang J, Yang Y, et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008; 13:532-541. See Evidence Table Hesselink DA, van Schaik RHN, van Agteren M, et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients. Pharmacogenetic Genomics 2008; 18: 339-348. See Evidence Table

The use of in the evaluation of Atomoxetine, Codeine for nursing mothers, Efavirenz, Proton pump inhibitors (PPI) for treating Helicobacter pylori, Immunosuppressants for organ transplant, and selective serotonin reuptake inhibitors (SSRIs) metabolization does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

02/13/2012: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing
Evidence Conclusion: Analytic validity No published studies on the accuracy of commercially available tests for detecting CYP2C19 variants were identified. Clinical validity Results from the 2010 MTAC review were based on a meta-analysis that included 7 cohort studies. Results from the meta-analysis showed that the presence of CYP2C19*2 allele was associated with an increased risk of a subsequent cardiovascular event (RR 1.96, p=0.02) and stent thrombosis (RR 3.82, p<0.01); however, there was significant heterogeneity between the studies. Studies varied with regard to clopidogrel dose, duration of follow-up, and patient type. Because of this, it was determined that there was insufficient evidence to determine whether the presence of CYP2C19 variant genotypes predict clinical outcomes (Sofi 2011). Results from both of the most recent meta-analyses suggest that there is no significant association between major cardiovascular events and CYP2C19 genotype. Both studies also found some evidence that the loss of function genotype may be associated with stent thrombosis; however, the quality of this evidence is weak due to evidence of publication bias. Meta-analyses are only as good at the studies that they include. The majority of the studies included in these analyses were small, there was variation between the studies with regard to the components of the primary endpoint, and misclassification is possible as not all alleles were typed (Bauer 2011, Holmes 2011).Clinical Utility No published studies were identified that prospectively compared patient outcomes managed with and without CYP2C19 genotyping.

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Articles: The literature consisted mainly of cohort studies and genetic sub-studies of randomized controlled trials. No studies were identified that examined the analytic validity of CYP2C19 genotyping. Several meta-analyses were identified that evaluated the association between CYP2C19 and the clinical efficacy of clopidogrel. However, only 2 of these analyses included additional studies that were not included in the 2010 MTAC review. Both of these meta-analyses were selected for review. Several studies were identified that looked at the effect of higher doses of clopidogrel or other medications on platelet reactivity in patients with the CYP2C19 loss of function genotype; however, since platelet reactivity is an intermediate marker, none of these studies were selected for review. No studies were identified that looked at the effect of CYP2C19 genotyping on long term clinical outcomes such as major cardiovascular events. The following studies were critically appraised:
Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ.* 2011;343:d4588. See Evidence Table Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA.* 2011;306:2704-2714. See Evidence Table

The use of in the evaluation of Plavix and Tamoxifen metabolization does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

EndoPredict

BACKGROUND

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett et al., 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several molecular tests including the EndoPredict test. Based on the manufacturer, a tumor section from the FFPE block is needed to perform the test. The tissue collected is treated and the RNA is isolated. The reverse transcription and quantitative PCR are performed, and the levels of gene expression are measured. These genes include eight disease-genes and four reference genes. Results are exported from the EP device into the EP software which generates EP scores and classifies patients into low or high risk of distant metastasis within 10 year. The EP score is a number that ranges from 0 to 15; EP score ≤ 5 is indicative of low distant recurrence risk under endocrine therapy; EP score > 5 indicates high distant recurrence risk. The molecular features are coupled with clinicopathological parameters including tumor size and nodal status to determine the EPclin score. The test is believed to predict distant metastasis in ER-positive, HER2-, node negative or node positive breast cancer treated with endocrine treatment alone (Kronenwett et al., 2012). It is also believed that it can be performed in decentralized laboratories (Denkert et al., 2012; Kronenwett et al., 2012).

06/05/2017: MTAC REVIEW
EndoPredict
Evidence Conclusion:
Conclusion

- Analytic validity: Three studies with low to moderate evidence show that EndoPredict may be reproducible and reliable in ER+, LN-, or LN+ breast cancer patients.
- Clinical validity: Seven studies with level IB evidence show that EndoPredict test may be prognostic of distant recurrence in ER+, LN-, or LN+ breast cancer patients. In addition, studies assessing the predictive value of the test are lacking and women who benefit from chemotherapy are unknown.
- Clinical utility: One study, that provides low evidence, assessed the impact of EndoPredict on treatment decision; thus there is insufficient evidence to recommend for or against the clinical utility of the test.
- Based on one study, EP may be more prognostic than Oncotype Dx.

Articles: PubMed was searched through March 28, 2017 with the search terms EndoPredict with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies

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were reviewed to identify additional publications. A total of 14 studies were identified; however, 12 studies were reviewed. The main findings of the two remaining were included under other studies.

The use of in the evaluation of EndoPredict test for breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Epidermal Growth Factor Receptor (EGFR)

BACKGROUND

Lung cancer is one of the most common causes of cancer death, accounting for over 1 million deaths annually. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers and the majority of cases present at an advanced stage. For patients with good performance status, platinum-based chemotherapy constitutes standard first-line treatment. However, a therapeutic plateau has been reached with conventional chemotherapy for NSCLC patients. Advances in the knowledge of molecular mechanisms of carcinogenesis has led to the development of new molecular-targeted agents. Current research efforts focus on a number of promising agents targeted against the epidermal growth factor receptor (Yoshida 2010, Campbell 2010). The epidermal growth factor receptor (EGFR) is normally present on the surface of epithelial cells, and plays an important role in regulating cellular processes such as proliferation, differentiation, survival, and maintenance of normal epidermal tissues. Researchers observed that when the function of EGFR becomes deregulated, it contributes to the growth and survival of cancer cells (Huang 2004, Ettinger 2006). The role of EGFR in carcinogenesis led to the development of several therapeutic agents which specifically target growth factor pathways that are deregulated in tumor cells. Tyrosine kinase inhibitors (TKIs) are one of these agents. Results of clinical trials on TKIs are conflicting and show a significant variability in response and survival rates. Some trials showed an improved survival when used after first or second-line chemotherapy, while others failed to show significant response and/or survival benefit. The investigators attributed the lack of benefit to the lack of patient selection in the trials, i.e. the inclusion of unselected NSCLC population in the studies. This was based on the observation that cancer cell lines and tumors are selectively susceptible to inhibition of the EGFR pathway. Results of subgroup analysis of data from observational studies suggest that the response to TKIs is also associated with a number of clinical and biological factors including gender, ethnic origin, smoking status, and histology of the cancer. More recently in 2004, the clinical responsiveness to the TKIs gefitinib and erlotinib were correlated to specific somatic EGFR mutations in the TK domain in NSCLC. The two most common activating mutations seen in patients are exon 19 deletions, and the exon 21 mutation L858R. Data from retrospective studies suggested that these mutations occurred more frequently among females, non-smokers, patients from East Asia, and those with adenocarcinoma histology (Linardou 2009). Extensive research is underway to identify the optimal molecular or genetic biomarkers that can predict the efficacy of a therapeutic agent for treating NSCLS and other malignancies. Predictive biomarkers include EGFR protein expression, gene copy number, mutation status, and others. A qualitative immunohistochemical (IHC) kit for EGFR gene expression testing (the Dako Cytomation EGFR pharmaDx ^{TM} assay) was approved by the FDA in 2004 as an aid to identify colorectal cancer patients eligible for treatment with the cancer drug cetuximab. In June 2005, the FDA issued an alert that new patients should not be given gefitinib, and limited its use to cancer patients who have already taken the medicine and whose doctor believe it is helping them. Erlotinib is another TKI that was approved by the FDA for treatment of locally advanced or metastatic non- small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. In June, 2005 the FDA issued an alert that new patients should not be given gefitinib, and limited its use to cancer patients who have already taken the medicine and whose doctor believes it is helping them. Erlotinib is another TKI that was approved by the FDA for treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen.

08/04/2008: MTAC REVIEW

Epidermal Growth Factor Receptor (EGFR)

Evidence Conclusion: In order to identify the optimal molecular or genetic biomarkers that predict the efficacy of a therapeutic agent, the biomarker should have a plausible relationship with the biology of the disease, and should have a standardized reproducible test, as regards the reagent, performance, analysis and interpretation. There also should be standards for the tumor sample size and fixation. Several potential biomarkers have been identified, but none was validated in randomized controlled trials, to date. Moreover, as the literature indicates, there is no standardized methodology for tissue sampling, nor a standardized reproducible assay for EGFR- expression that would allow a direct comparison of the results obtained from different laboratories. The majority of the published

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trials on EGFR testing and the use of TKIs in patients with NSCLC were small prospective and retrospective case series. There were variations in the inclusion criteria, time of taking and fixation f the tumor tissue samples, as well as other differences in the study designs, which could be potential sources of bias and confounding. In several studies, biomarker assessment was done among a small proportion of patients due to lack of tissue availability. The studies used different tests and arbitrary cut-offs for identifying EGFR mutations as well as unvalidated techniques with no standardized criteria for quantification, processing, scoring, and reporting of the results. Most importantly TKI therapy was not compared to an alternative therapy. Without an appropriate control it is not possible to differentiate between the predictive and prognostic significance of a biomarker.* Moreover, the published trials retrospectively correlated the response to TKIs treatment and/or survival with the EGFR status based on tumor specimens collected at initial diagnosis. This may confound the correlation analysis of EGFR mutations and response as additional mutations could have occurred during therapy. In conclusion, the role of EGFR expression testing as a predictive factor is not well defined. There is insufficient evidence from the published studies, to determine whether EGFR mutation is a predictive marker of clinical benefit from treatment with TKIs or only a prognostic biomarker of better survival, independent of TKI treatment. ***** A prognostic marker is defined as a characteristic associated with prognosis or outcome, usually in terms of relative hazard, whereas a predictive marker is defined as a characteristic that is associated with, and predicts, treatment response. **Articles:** The literature search revealed over 800 articles on epidermal growth factor receptor (EGFR) and TKIs. There were 4 meta-analyses of observational studies, and a number of phase II and phase III clinical trials that studied the effects of specific TKIs and retrospectively correlated the outcomes with EGFR. The phase III trial (Tsao 2005) that compared erlotinib (a TKI) to placebo retrospectively correlated the outcome to EGFR mutation. The three most recent meta-analyses were critically appraised. Nakamura H, Kawasoki N, Taguchi, et al. Survival impact of epidermal growth factor receptor overexpression in patients with non-small cell lung cancer: a meta- analysis. *Thorax* 2006;61:140-145. See Evidence Table Costa DB, Kobayashi S, Tenen DG, et al. Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers. Lung cancer 2007;58:95-103. See Evidence Table Wu y-L, Zhong W-Z, Li L-Y, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: A meta-analysis based on updated individual patient data from six medical centers in Mainland China. *J Thorac Oncol* 2007;2:430-
439. See Evidence Table

The use of Epidermal growth factor receptor (EGFR) testing in the treatment of NSCLC to Tyrosine Kinase Inhibitors (TKIs) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/18/2010: MTAC REVIEW
Epidermal Growth Factor Receptor (EGFR) Evidence
Conclusion:
There is fair evidence that rapid detection of EGFR mutations with multiplex PCR and primer extension produce good results compared to direct sequencing. However, there is insufficient evidence concerning the reproducibility of this test. Clinical validity: There is fair evidence that for patients with EGFR mutations the use of the tyrosine kinase inhibitors gefitinib and erlotinib is associated with an improvement in progression-free survival and response rate. Clinical utility: There is fair evidence that patients managed with the genetic test had better outcomes than patients managed without the genetic test.
Articles: There were several articles that addressed analytic validity. One of the most recent articles was selected for review. Several trials assessed the clinical validity and clinical utility of EGFR testing. Trials were selected for review if they were published after the 2008 review and addressed the safety or efficacy of TKI in patients with EGFR mutations.

The use of Epidermal growth factor receptor (EGFR) testing in the treatment of NSCLC to Tyrosine Kinase Inhibitors (TKIs) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

***Genetic Testing for IL28B Polymorphisms in Patients with Hepatitis* C**
BACKGROUND
Hepatitis C virus (HCV) is a single-stranded, enveloped RNA virus that is spread through contact with the blood of an infected person. In the United States, roughly 4.1 million Americans have been infected with the HCV, making it one of the most common blood borne pathogens. After acute infection with HCV, approximately 70-80% of infected individuals will go on to develop chronic HCV, which is a leading cause of cirrhosis, liver cancer, and liver transplant in the western world (Armstrong 2006, CDC 2009, Rosen 2011). For patients with chronic HCV infection, treatment includes a combination of pegylated interferon (PEG-INF) plus ribavirin given for 24 or 48 weeks depending on genotype. Results from recent RCTs also suggest that treatment for patients with HCV

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genotype 1, the most common isolate in the United States, may also include a protease inhibitor in conjunction with PEG-INF plus ribavirin. Treatment success, referred to as sustained viral response (SVR), is defined as the absence of virus 24 weeks after treatment completion. Less than 50% of patients HCV genotype 1 respond to therapy with PEG-INF plus ribavirin compared to around 80% of patients with HCV genotype 2 and 3. Besides genotype, female gender, white ethnicity, age less than 45 years, low HCV RNA levels at baseline, and lack of cirrhosis are considered to be predictors of viral response. Treatment for HCV is expensive and associated with numerous side effects such as anemia and neutropenia, which can lead to dose reduction or premature termination, thus increasing the risk of treatment failure. Research is currently underway to identify factors that could help patients and clinicians make more informed decisions regarding the risk and benefit of treatment and the likelihood of treatment response. Recent studies suggest that polymorphisms in the IL28B gene may be a useful predictor of treatment response (Clark 2011, Ghany 2009, Mangia 2011, Rauch 2010, Rosen 2011).
The IL28B gene encodes interferon (INF) lambda, a cytokine that shares the same intercellular pathway of INF alpha, the drug currently used in combination with ribavirin for the treatment of chronic HCV. Genome wide association studies suggest that polymorphisms in the IL28B gene may be associated with response to antiviral treatment with PEG-INF plus ribavirin in patients with HCV genotype 1. However, it is important to note that IL28B polymorphisms do not explain all treatment failure, and patients with the non-responder genotype may still respond to therapy (Ahlenstiel 2010, Mangia 2011).

10/17/2011: MTAC REVIEW
Genetic Testing for IL28B Polymorphisms in Patients with Hepatitis C
Evidence Conclusion:
Analytic validity: No studies were identified that evaluated analytic validity of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections. Clinical validity: Results from several GWAS suggest that SNPs around the IL28B gene may be associated with SVR in patients with chronic genotype 1 HCV infection. Clinical utility: No studies were identified that evaluated the clinical utility of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections.
Articles: The literature search identified several genome-wide association studies that identified polymorphisms near the IL28B gene locus as predictors of response to treatment in patients with chronic hepatitis C infection. The largest study was selected for review. No studies were identified that evaluated the analytic validity or clinical utility of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infection. The following study was critically appraised: Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009;461:399-401. See Evidence Table

The use of IL28B polymorphisms does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

KRAS Mutation Testing for Predicting Response to Treatment in Patients with Advanced Colon Cancer
BACKGROUND
Nearly a million new cases of colorectal cancer (CRC) are diagnosed worldwide each year, and about half a million people die from CRC annually. In the United States, CRC is the most common form of cancer in people aged 75 and older (Boyle and Leon, 2002). The length of survival of people with metastatic colorectal cancer has increased from approximately 12 months to 20 months in the past decade. This improvement has been attributed largely to the introduction of new treatments, including chemotherapeutic agents and novel targeted drugs (Di Fiore et al., 2007). Novel therapies include those that target the epidermal growth factor receptor (EGFR) signaling pathway which is believed to be involved in colorectal carcinogenesis. EGFR expression has been found in 60-80% of colorectal tumors (Heinemann et al., 2008). Two new monoclonal antibody inhibitors, cetuximab (Merck) and panitumumab (Amgen), are designed to block EGFR, thereby preventing the activation of downstream signaling pathways and inhibiting tumor cell proliferation. The new targeted therapies are costly and potentially increase the toxicity of treatment. It is thus desirable to select the patients most likely to respond to these treatments. Research is underway to identify biomarkers that predict response to the EGRF inhibitors. One biomarker under investigation is mutations in the K-ras gene (KRAS). KRAS mutations occur in approximately 20-50% of CRC tumors. It is believed that, in patients with mutant KRAS genes, treatment with the new monoclonal antibody inhibitors does not prevent signaling of EGFR, and consequently that the therapies should only be given to patients with wild-type (i.e. non-mutant) KRAS genes (Heinemann et al., 2008). Research first suggested that KRAS mutation selection might be useful for metastatic CRC patients who failed initial chemotherapy and are considering second-line treatment with cetuximab, as monotherapy, or in combination with irinotecan. KRAS mutation selection is also being proposed for first-line treatment with FOLFIRI, with or without cetuximab.
A genetic test is available to determine whether the KRAS gene contains mutations. Response Genetics (Los

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Angeles) has a PCR-based test. KRAS mutation testing for colorectal cancer patients has not been previously reviewed by MTAC.

02/02/2009: MTAC REVIEW

KRAS Mutation Testing for Predicting Response to Treatment in Patients with Advanced Colon Cancer

Evidence Conclusion: Analytic validity: No published articles on the accuracy of commercially available tests for detecting KRAS mutations were identified. Clinical validity: The three retrospective cohort studies evaluated (Lievre et al. 2008; DeRoock et al., 2008; DiFiore et al., 2007) all found that second-line treatment with cetuximab monotherapy or combination treatment was not effective in any of the patients with mutant KRAS genes (0% treatment response). The response rate in patients without mutations varied from 28-44%. Two of the three studies found a significantly higher rate of progression-free survival in patients with wild-type KRAS versus mutant forms. Only two studies reported overall survival; both found a significantly higher rate in patients with wild-type versus mutant KRAS. Limitations common to the three studies is that the analyses were retrospective, and subject to confounding--there may have been other differences between patients with wild-type and mutant KRAS genes that affected outcome. In addition, the vast majority of patients in the cohort studies received combination therapy as second-line treatment. Thus, one cannot disentangle the effectiveness of cetuximab from the irinotecan-based chemotherapy. This makes it difficult to make conclusions about what treatment patients should receive. Even if one concluded that KRAS mutation status impacts treatment outcomes, it is not possible from these studies to conclude that a monoclonal antibody inhibitor is necessary for treatment success. The Bokemeyer RCT provides some evidence on the added impact of treatment with cetuximab, as first-line treatment. Overall, there was no significant difference in response rate when cetuximab was added to FOLFOX-4 compared to FOLFOX-4 alone. However, in the sub-analysis by KRAS mutation status, there was a better response when cetuximab was added to chemotherapy for patients with wild-type KRAS genes. Clinical utility: No published articles were identified that prospectively managed patients with and without KRAS mutation testing were identified.

Articles: No published articles were identified on the accuracy of any commercially available test for detecting KRAS mutations. There were several retrospective cohort studies that evaluated the statistical association between KRAS mutation status and clinical outcomes with second-line treatment. Three studies (Lievre et al. 2008; DeRoock et al., 2008; DiFiore et al., 2007) were critically appraised. In addition, there was one published RCT evaluating first-line treatment, with a secondary analysis by KRAS mutation status (Bokemeyer et al., 2008), and this was critically appraised. Two unpublished RCTs were also identified that included analyses of outcomes by KRAS status. Both trials were presented as abstracts at the 2008 annual meeting of American Society of Clinical Oncology. The CRYSTAL study (Van Cutsem et al., 2008) evaluated patients receiving first-line treatment and the EVEREST study (Tejpar et al., 2008) evaluated second-line treatment. In terms of clinical utility of KRAS mutation testing for treatment selection, the ideal study would randomize patients to be managed with and without KRAS testing. For those managed with KRAS mutation testing, only patients with wild-type KRAS genes would receive cetuximab (second-line treatment) or FOLFIRI with or without cetuximab (first-line treatment). No randomized or non-randomized controlled trial that prospectively conducted KRAS testing was identified.

Citations for the studies that were reviewed are as follows: Bokemeyer C et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2008 (Epub ahead of print). See Evidence Table. Lievre A et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008; 26: 374-379. See Evidence Table DeRoock W et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008; 19: 508-515. See Evidence Table DiFiore F et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. Br J Cancer 2007; 96: 1166-1169. See Evidence Table

The use of KRAS mutation testing for predicting response to treatment in patients with advanced colon cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/16/2010: MTAC REVIEW

KRAS Mutation Testing for Predicting Response to Treatment in Patients with Advanced Colon Cancer

Evidence Conclusion:

A medical technology review from Blue Cross Blue Shield (BCBS) in conjunction with Kaiser Permanente from 2008 was identified. BCBS found sufficient evidence to approve the use of *KRAS* mutation analysis to predict non-response to the anti-EGFR monoclonal antibodies cetuximab and panitumumab based on retrospective genetic sub-studies from randomized controlled trials. Analytic validity: There is fair evidence that there is very good agreement between Sanger sequencing, array analysis, melting curve analysis, and pyrosequencing for the detection of a KRAS mutation. However, there is insufficient evidence concerning the sensitivity, specificity, and reproducibility of

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these tests. Clinical validity: There is fair evidence that for patients with *KRAS* mutations the use of the monoclonal antibodies cetuximab and panitumumab in not associated with an improvement in overall or progression-free survival. Clinical utility: There is insufficient evidence to determine that patients managed with the genetic test had better outcomes than patients managed without the genetic test.
However, identifying patients who will not respond to therapy will avoid the administration of an ineffective treatment and its associated toxicities.
Articles: A number of studies comparing different methods of *KRAS* mutation detection were identified. The trial with the largest sample size was selected for review. Several randomized controlled trials were identified that included a retrospective subset analysis of treatment efficacy in relations to *KRAS* mutation status. No studies were identified that addressed the clinical utility of *KRAS* mutation testing. A recent retrospective cohort study that evaluated the efficacy of cetuximab in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab plus chemotherapy was not included in this review as the study population was heterogeneous with regard to treatment regimen and line of chemotherapy. Additionally, approximately one third of the study population was included in previous reports.

The use of KRAS mutation testing for predicting response to treatment in patients with advanced colon cancer does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Oncotype DX

BACKGROUND

Breast Cancer- Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett, Cuzick et al. 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several molecular tests including the oncotype Dx breast cancer assay. The oncotype Dx breast cancer assay is a molecular diagnostic test used in patients with early stage invasive breast cancer. In addition to standard measurements used to make treatment decision, the assay provides three advantages including the assessment of gene expression, the determination of recurrence, and the prediction of chemotherapy benefit. Scientists at Genomic Health, the manufacturer of the assay, utilize the reverse-transcriptase polymerase chain reaction (RT-PCR) to analyze a set of 21 genes in several samples and developed a mathematical formula that led to the breast recurrence score result. The score is also known as the recurrence score (RS). A lower score is indicative of a lower chance of recurrence or a smaller chemotherapy benefit. A higher score suggests a higher likelihood of recurrence or a significant chemotherapy benefit. In general, RS less than 18 suggests a low RS; a RS between18-30 indicates an intermediate RS and RS more than or equal to 31 indicates a high RS.
Eligible patients are patients who are medically eligible for chemotherapy and have been diagnosed with stage I, II or IIIa invasive breast cancer, and whose breast cancer is estrogen-receptor positive (ER+) and Human Epidermal growth factor Receptor-negative (HER2-). The oncotype DX breast cancer assay was initially developed in patients with estrogen receptor-positive (ER+) and lymph node-negative (LN-) early invasive breast cancer. However, the test is believed to predict recurrence and chemotherapy benefit on candidates with lymph node-positive breast cancer. The test is being assessed for the first time on Medical Technology Assessment Committee (MTAC) and has been exempt from FDA clearance. **Colorectal Cancer -** Nearly a million new cases of colorectal cancer (CRC) are diagnosed worldwide each year and about half a million people die from CRC annually. In the United States, CRC is the most common form of cancer in people aged 75 and older (Boyle 2002). The length of survival of people with metastatic colorectal cancer has increased from approximately 12 months to 20 months in the past decade. This improvement has been attributed largely to the introduction of new treatments, including chemotherapeutic agents and novel targeted drugs (DiFiore 2007). Several randomized controlled trials (RCT) have shown that adjuvant chemotherapy improves overall survival in patients with stage III disease; however, a clear benefit for patients with stage II disease has not been established. Findings from the QUASAR trial, a RCT designed to determine the effects of 5-FU/LV (fluorouracil/leucovorin) compared to observation in patients with predominantly stage II colorectal cancer, suggest that stage II patients may benefit from 5-FU-based adjuvant therapy. However, since the majority of patients with stage II disease can be cured with surgery alone it is important to identify patients who are likely to develop metastasis and who will benefit from adjuvant

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chemotherapy (Gangadhar 2010). Currently, the risk of recurrence in stage II disease is clinically determined by histologic staging, extended to include evidence of lymphatic or vascular invasion, tumor grade, and the number of lymph nodes identified and examined in the surgical specimen (Midgley 2010). Biomarkers could also be useful in this assessment. Recently, a quantitative multigene expression assay has been developed with the aim of improving treatment decision-making in the setting of stage II colon cancer and is now being marketed as the Oncotype DX® colon cancer assay (Genomic Health Inc., Redwood City, CA). The Oncotype DX® colon cancer assay was derived from an initial set of 761 candidate genes to create a 12-gene panel assay that uses real-time PCR to measure the expression of 7 genes prognostic for relapse-free survival 5 reference genes used for normalization. The assay is performed on excised tumors and yields a prognostic recurrence score that ranges from 0 to 100. The recurrence score is used to improve patient selection criteria for adjuvant chemotherapy (Kerr 2009).

04/04/2005: MTAC REVIEW
Oncotype DX
Evidence Conclusion: Oncotype Dx is a test that is used to predict risk of distant recurrence in women with node-negative and estrogen-receptor-positive breast cancer. There is one published validation study (Paik, 2004) in which Oncotype test results were divided into three risk categories (low, intermediate or high) and the risk categories were correlated with the likelihood of distant recurrence over 10 years. Significantly fewer patients who were categorized as low-risk experienced distant recurrence compared to those categorized as high-risk (6.8% vs. 30.5%). The risk score contributed information on recurrence beyond that provided by age and tumor size. The Paik study included only patients who were treated with tamoxifen. The primary authors of the published study have substantial financial links to the Genomic Health Inc., the company that developed Oncotype Dx. There are no published data on the use of Oncotype Dx on women who are not treated with tamoxifen. There is no evidence that the recommendation for chemotherapy would change based on Oncotype Dx results or that changing treatment based on Oncotype Dx results would improve health outcomes.
Articles: The search yielded 43 articles. Many were on technical aspects of developing genetic assays. There was one published article on methods used to develop the test; this was not evaluated further because it did not address test accuracy. One published validation study was identified and this was critically appraised. There were also several unpublished abstracts and posters, including presentations at the 27th San Antonio Breast Cancer Symposium (SABCS) in December 2004. One of the SABCS posters reported on a case-control study conducted at Kaiser, Northern California to evaluate the Oncotype Dx recurrence score (Habel et al, unpublished manuscript). The study includes both women treated with and without tamoxifen. In the presentation, findings were primarily presented on the group treated with tamoxifen. The unpublished abstracts and posters do not meet the Kaiser Permanente criteria for evaluable evidence. *The reference for the published validation study is as follows:* Paik S, Shak S, Tang G. et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *NEJM* 2004; 351: 2817-2826. See Evidence Table

The use of Oncotype Dx in the evaluation of the likelihood of distal recurrence in patients with estrogen-dependent, node-negative breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

10/18/2010: MTAC REVIEW
Oncotype DX
Evidence Conclusion: There is insufficient evidence to determine the analytic validity, clinical validity, and clinical utility of the *Oncotype DX*® colon cancer assay.
Articles: No articles were identified that addressed the analytic validity, clinical validity, or clinical utility or the *Oncotype DX*® colon cancer assay. Conclusion: There is insufficient evidence to determine the analytic validity, clinical validity, and clinical utility of the *Oncotype DX*® colon cancer assay.

The use of Oncotype Dx in the evaluation of the colorectal cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/16/2010: MTAC REVIEW
Oncotype DX
Evidence Conclusion:
Analytic validity: There is insufficient evidence to determine the analytic validity of the *Oncotype DX*®
colon cancer assay. Clinical validity: Results from a retrospective analysis suggest that the *Oncotype DX*® colon

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cancer assay recurrence score may be associated with recurrence risk in patients with stage II colon cancer. Results from this study also suggest that the *Oncotype DX*® colon cancer assay treatment score was not predictive of chemotherapy benefit. Clinical utility: There is insufficient evidence to determine the clinical utility of the *Oncotype DX*® colon cancer assay.

Articles: Screening of articles: No studies were identified that addressed the analytic validity or clinical utility of the Oncotype DX® colon cancer assay. The following study was selected for critical appraisal: Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol. 2011;29:4611-4619. See Evidence Table

03/20/2017: Oncotype DX
Evidence Conclusion:
Conclusion:

- Analytic validity: There was insufficient evidence to determine the analytic validity of Oncotype DX breast cancer assay in lymph node-positive breast cancer patients.
- Clinical validity: Moderate evidence shows that the oncotype DX assay predicts recurrence in lymph- node positive breast cancer patients. However, the evidence was insufficient for the predictive effect. Studies with larger sample size are needed to optimally determine who will benefit from chemotherapy (particularly among patients with low or moderate recurrence score).
- Clinical utility: The oncotype DX assay may improve outcomes; however well design studies with larger sample size are warranted.

The use of Oncotype DX for breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Invader UGT1A1 Molecular Assay

BACKGROUND

The Invader UGT1A1 molecular assay tests variations in a gene called UGT1A1 that produces the enzyme UDP-glucuronosyltransferase. The UDP enzyme is active in the metabolism of certain drugs, including irinotecan, a chemotherapy agent commonly used to treat colorectal and lung cancer. The active metabolite of irinotecan, SN-38, is glucuronidated by hepatic UGTs. The main dose-limiting toxicity of irinotecan treatment is diarrhea, which is believed to be secondary to the biliary excretion of SN-38. Diarrhea associated with irinotecan-treatment can be serious and often does not respond to conventional antidiarrheal agents. The diarrhea may be due to direct enteric injury caused by the active metabolite of irinotecan, SN-38. A phase 1 clinical trial found an inverse relationship between SN-38 glucuronidation rates and severity of diarrheal incidence in patients treated with increasing doses of irinotecan. This suggests that decreased glucuronidation of SN-38 increases the risk of irinotecan-induced toxicity. Differential rates of SN-38 glucuronidation may help explain individual variation in toxicity rates among cancer patients treated with irinotecan. There may be a genetic predisposition to the metabolism of irinotecan.

Research has found that the UGT1A1 gene is responsible for SN-glucuronidation. Patients with low UGT1A1 activity, such as those with Gilbert's syndrome, may be at increased risk of irinotecan-induced toxicity. The Invader UGT1A1 molecular assay is marketed as a test to aid physicians in making individualized decisions about treatment and medication dosage. By detecting variations in the UGT1A1, the Invader UGT1A1 molecular assay might be able to predict which patients are at an increased risk of toxicity from irinotecan. The Invader UGT1A1 molecular assay was approved by the FDA in 2005 as substantially equivalent to the AmpliChip cytochrome P450 genotyping test. Both are genetic tests that detect single nucleotide polymorphisms. Since it was approved as substantially equivalent to an existing test, the manufacturer was not required to data on clinical sensitivity and specificity to the FDA. (References: Innocenti and Ratain, 2003; Iyer et al., 1998; Rouits et al. 2004; FDA documents).

06/05/2006: MTAC REVIEW
Invader UGT1A1 Molecular Assay
Evidence Conclusion: There is insufficient evidence to draw conclusions on the diagnostic accuracy of the Invader UGT1A1 molecular assay. No published peer-reviewed studies were identified. The only article with empirical data is a letter to the editor of Clinical Chemistry. The authors of the letter reported that findings from the Invader assay had a high rate of agreement with direct DNA sequencing for detecting UGT1A1 polymorphisms in

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60 patients. Diagnostic accuracy studies that are published and peer-reviewed are needed. There is insufficient evidence that more appropriate therapy is used after application of the Invader assay than would be used if the test were not available. There was no published evidence on the impact on health outcomes of using UGT1A1 genotype information from the Invader test to adjust irinotecan treatment. There is some evidence that the UGT1A1 genotype is associated with irinotecan-induced toxicity. The studies reviewed found statistically significant associations between UGT1A1 genotype and irinotecan-induced toxicity. Two of the three studies (Marcuello et al., 2004; Ando et al., 2000) used multivariate analysis. In general, limitations of the studies were that they had relatively small sample sizes and estimates may be imprecise. Their findings provide preliminary data suggesting that information on UGT1A1 genotype may help physicians make better treatment decisions. Results of the studies reviewed cannot necessarily be generalized to use of the Invader assay to identify UGT1A1 polymorphisms, since this test was not used in any of the studies.

Articles: Accuracy of Invader UGT1A1 molecular assay: No published peer-reviewed studies were identified on the accuracy of the invader test for identifying variations in the UGT1A1 gene. There was a letter to the editor that presented data on test accuracy. Letters to the editor do not meet MTAC criteria for acceptable evidence because the scientific methods are not peer reviewed. Does adjusting the dose of irinotecan treatment based on UGT1A1 genotype identified using the Invader assay result in improved health outcomes? No published studies that directly address this question were identified. However, several studies were identified that examined the association between UGT1A1 variants and rates of toxicity related to irinotecan treatment. If there is a significant association between UGT1A1 genotypes and irinotecan-induced toxicity, then using information on UGT1A1 genotypes to inform irinotecan dosing decisions has the potential for improving health outcomes. The three largest studies evaluating the association between UGT1A1 genotype and toxicity (two cross-sectional studies and one case-control study) were critically appraised. *The studies reviewed were:* Marcuello E, Altes A, Menoyo A et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer 2004; 91: 678-682. See Evidence Table Rouits E, Boisdron-Celle M, Dumont A et al. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity. Clin Can Res 2004; 10: 5151-5159. See Evidence Table Ando Y, Saka H, Ando M et al. Polymorphisms of UDP-Glucuronosyltransferase gene and irinotecan toxicity: A pharmacogenetic analysis. Can Res 2000; 60: 6921-6926. See Evidence Table

The use of Invader UGT1A1 molecular assay in the treatment of polymorphisms in the UGT1A1 gene does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Platelet Function Testing (VerifyNow P2Y12 Assay)

BACKGROUND

In the Unites States, cardiovascular disease is the leading cause of death in both men and women (Heron 2009). Clinical trials have shown that clopidogrel (Plavix), an anti-blood clotting medication, reduces the morbidity and mortality associated with several cardiovascular diseases. However, there is a significant amount of inter-individual variability in clopidogrel responsiveness, which leads some patients to experience decreased platelet inhibition (poor response) with clopidogrel (Momary 2010).

Studies suggest that approximately 4% to 30% of patients treated with clopidogrel do not have adequate antiplatelet response. The mechanism for poor response is not fully understood; however, poor compliance, drug interaction, clinical factors such as increased body mass index and diabetes, as well as genetic factors such as polymorphisms in the enzymes that metabolized clopidogrel into its active metabolite are all proposed mechanisms of clopidogrel non-responsiveness (Fileti 2011).

Platelet function testing is a way to monitor response to clopidogrel. It has been hypothesized that monitoring platelet reactivity and then tailoring treatment accordingly may improve clinical outcomes such as major adverse cardiovascular events. There are several different laboratory-based and point-of-care testing systems used to measure platelet response. These methods all have different definitions of high on-treatment platelet reactivity and are known to correlate poorly with each other. All of these methods have advantages and limitations. This review will focus on the VerifyNow P2Y12 Assay (Acumetrics Inc., San Diego, California), which is a fast, standardized point-of-care testing system that does not require special training to perform. The VerifyNow P2Y12 Assay evaluates platelet aggregation of fibrinogen-coated beads in response to adenosine diphosphate (ADP) and prostaglandin E1. Results are expressed as P2Y12 Reaction Units (PRU) with a common cutoff of ≥240 PRU for indicating suboptimal response to clopidogrel. However, one of the limitations of this test is that the cutoff for suboptimal response has not been firmly established (Sambu 2011, Smock 2011). The VerifyNow P2Y12 Assay has received approval from the FDA.

02/13/2012: MTAC REVIEW

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Platelet Function Testing (VerifyNow P2Y12 Assay)

Evidence Conclusion: Analytic validity: Results from a recent study suggest that when using LTA as the gold standard, the VerifyNow P2Y12 assay has a sensitivity of 55% and a specificity of 85%. Clinical validity: Results from a recent meta-analysis with methodological limitations suggest that high on-treatment platelet reactivity may be associated with cardiovascular events. Clinical utility: Results from a recent RCT suggest that high-dose compared to standard-dose clopidogrel in patients with high on-treatment platelet reactivity may not reduce cardiovascular events.

Articles: The literature search revealed several studies and review articles addressing the analytic validity of platelet function testing. Results of a recent study are presented below. Several observational studies and meta-analyses were identified that addressed the clinical validity of platelet function testing with the VerifyNow P2Y12 Assay. Studies were excluded if they were: retrospective, did not look at clinical outcomes, were not powered to evaluate clinical outcomes, or did not measure platelet function using the VerifyNow P2Y12 Assay. A meta- analysis of studies using the VerifyNow P2Y12 Assay to measure platelet reactivity was selected for review. Two randomized controlled trials (RCTs) were identified that looked at the clinical utility of VerifyNow P2Y12 Assay to measure platelet reactivity. One trial was excluded because it had a short duration of follow-up and the results combined patients who were poor responders to clopidogrel with patients who were poor responders to aspirin and patients who were poor responders to both aspirin and clopidogrel. The GRAVITAS trial, which evaluated the effect of high-dose compared with standard-dose clopidogrel in patients with high on-treatment platelet reactivity, was selected for review. The following studies were critically appraised: Brar SS, ten Berg J, Marcucci R, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. *J Am Coll Cardiol.* 2011; 58:1945-1954. See Evidence Table Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA.* 2011; 305:1097-1105. See Evidence Table

The use of Platelet function testing (VerifyNow P2Y12 Assay) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Warfarin Sensitivity DNA Test

BACKGROUND

Warfarin, an anticoagulant, is used to help prevent and treat blood clots. It is commonly used to treat patients with deep vein thrombosis, atrial fibrillation, stroke, and artificial heart valves. Blood clots are potentially dangerous because they can detach and travel in the bloodstream, where they can get wedged in a blood vessel and block the blood supply to a vital organ such as the lungs, heart or brain (Yin 2007). Blood clots are initiated when platelets clump together at the site of bleeding and produce chemicals that activate clotting factors in the blood. Vitamin K is essential for the production of these clotting factors. Warfarin prevents blood clots by inhibiting the action of vitamin K, thereby preventing the activation of clotting factors. The anticoagulant effect of warfarin is measured in terms of the prothrombin time, the time taken for blood clotting to occur in a sample of blood to which calcium and thromboplastin have been added. This time is expressed as the International Normalized Ratio (INR). The higher the INR, the longer time it takes for blood to clot. If the INR is too high, there is an increased risk of bleeding. If it is too low, there may be an increased risk of clot formation. The goal is to adjust the dose of warfarin so that the INR reaches and stays within a narrow therapeutic range. The initial dose of warfarin is an approximation, generally based on a standard protocol or dosing algorithm. Over the first several weeks on the medication, the patient's INR is tested regularly, and the dose adjusted. The risk of anticoagulant-related bleeding is highest at the beginning of therapy (Tan 2010). Warfarin dosing is influenced by a variety of factors such as sex, age, smoking status, medications, diet, height, and weight. Another factor that may be associated with the optimal dose of warfarin is the presence of certain genetic variants (Jonas 2009). Two relevant genes have been identified: Vitamin K epoxide reductase (VKORC1) is a gene which codes for the enzyme that warfarin targets for its effect. Patients with the sensitive AA halotype generally require a lower dose of warfarin than average. Patients with the BB halotype generally require larger doses. The common halotype is AB. The sensitive AA variant of VK0RC1 is estimated to occur in approximately 35-37% of Caucasians, 10-23% of African Americans, and in up to 89% of Asians. Cytochrome P450 (CYP) 2C9 (called CYP2C9) is a gene which codes for the specific liver enzyme that is largely responsible for metabolizing the most active component of warfarin. Some patients have a genetic variation in the CYP2C9 enzyme that causes them to metabolize warfarin more slowly. Patients with this genetic variation generally require a lower dose of warfarin. The usual variant of CYP2C9 that is associated with normal enzyme activity is CYP2C9*1. The variants associated with slower metabolism of warfarin are CYP2C9*2 and CYP2C9*3. The prevalence of these variants varies considerably by ethnic group with Caucasians having the

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highest prevalence (Tan 2010). In 2007, the FDA approved new labeling for warfarin indicating that patients with variations in CYP2C9 and VCORC1 may respond differently to the drug. Due to the fact that warfarin has a narrow therapeutic window and over- or underdosing of warfarin can lead to catastrophic hemorrhagic or thrombotic complications there has been increasing interest in warfarin genotyping to aid in optimizing initial and maintenance warfarin dosing. There are several FDA-approved warfarin sensitivity genotyping test kits; all of them test for mutations in both the CYP2C9 and VKORC1 genes.

10/06/2008: MTAC REVIEW
Warfarin Sensitivity DNA Test
Evidence Conclusion:
There is no published evidence on the accuracy or reliability of commercially available kits for identifying variants in the CYP2C9 and VKORC1 genes. There is fair evidence that variants of the genes are associated with warfarin-related intermediate outcomes (dosing, time to therapeutic INR). There is insufficient evidence due to lack of statistical power that genetic variants are related to risk of bleeding. There is insufficient evidence to determine that managing patients using pharmacogenetic-guided dosing improves outcomes. To date, there is one published completed RCT (Anderson et al., 2007), and this study did not find significant differences in the primary outcome, percentage of out-of-range INR and most secondary outcomes. Several additional RCTs are underway.
Articles: Analytic validity: No published studies were identified that discuss the accuracy or reliability of commercially available test kits for measuring genetic variants in the CYP2C9 and VKORC1 genes. Clinical validity: There is a meta-analysis of studies evaluating the association between CYOP269 genetic variants and bleeds and drug dosing (Sanderson et al., 2005). This study, and the two largest prospective studies evaluating VKORC1 (Wadelius et al., 2008; Schwartz et al., 2008) were critically appraised. Clinical utility: There is one published RCT that compares outcomes in patients managed with pharmacogenetic-guided dosing versus standard dosing (Anderson et al., 2007). In addition, there is an earlier published pilot RCT examining the feasibility of using pharmacogenetic-guided dosing (Hillman et al., 2005). These two studies were critically appraised. The Hillman study was included because, although its primary purpose was examining feasibility, it also included some clinical outcome variables. Several additional randomized controlled trials are underway examining health outcomes in patients starting warfarin therapy who are managed with pharmacogenetic-guided dosing compared to standard methods of dosing. These include the prospective evaluation comparing initiation of warfarin strategies (PRECISE) trial, a study of patients receiving total hip or knee replacement, and a Creighton University study comparing these two types of dosing (ClinicalTrials.gov). *The following studies were critically appraised:* Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose and bleeding risk in warfarin-treated patients: A HuGEnet systematic review and meta-analysis. Genet Med 2005; 7: 97-104. See Evidence Table. Schwarz UI, Ritchie MD, Bradford Y et al. Genetic determinants of response to warfarin during initial anticoagulation. NEJM 2008; 358: 999-1008. See Evidence Table. Wadelius M, Chen LY, Lindh JD et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood 2008. June 23 (E-pub ahead of print). See Evidence Table. Anderson JL, Horne BD, Stevens SM et al. for the Couma-Gen investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation 2007; 116: 2563-2570. See Evidence Table. Hillman MA, Wilke RA, Yale SH et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin Med & Res 2005; 3: 137-145. See Evidence Table.

The use of a DNA sensitivity test to determine the optimal dosing of warfarin does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/18/2010: MTAC REVIEW
Warfarin Sensitivity DNA Test
Evidence Conclusion:
Analytic validity: There is fair evidence that the commercially available assays for determining warfarin genotype are accurate compared to bi-directional sequencing. However, there is insufficient evidence concerning the reproducibility of these tests. Clinical validity: Based on information for the 2008 review, the warfarin sensitivity DNA test was found to have adequate clinical validity. Clinical utility: There is insufficient evidence to determine whether patients managed with the genetic test had better outcomes compared to patients managed without the genetic test.
Articles: The literature search revealed several articles that addressed the analytic validity of warfarin genotyping assays. The study by King and colleagues was selected for review as it assessed the accuracy of four different commercial systems. In the 2008 review, warfarin sensitivity DNA testing passed criterion 3 (clinical validity), since

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then several studies were identified that evaluated the clinical validity of genetic testing to predict warfarin dose. One of the larger cohort studies was selected for review. The study by Epstein and colleagues was the only study identified that addressed the clinical utility of the warfarin sensitivity DNA test. The following studies were critically appraised: King CR, Porsce-Sorbet RM, Gage BF, et al. Performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dosing. *Am J Clin Pathol 2008;* 129:876-883. See Evidence Table. Klein TE, Altman RB, Ericksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med 2009;* 360:753-764. See Evidence Table. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduced hospitalization rates. *J Am Coll Cardiol 2010;* 55:2804-2812. See Evidence Table.

The use of a DNA sensitivity test to determine the optimal dosing of warfarin does not meet all of the *Kaiser Permanente Medical Technology Assessment Criteria.*

Prosigna Breast Cancer Prognostic Gene Signature Assay

BACKGROUND

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett, Cuzick et al. 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several gene expression-based tests including Prosigna breast cancer prognostic gene signature assay.

Prosigna is a genomic test that evaluates the activity of 58 genes and categorizes a patient's tumor into a subtype based on the signature (luminal A, luminal B, HER-2 enriched or basal-like) (Gordon-Craig et al., 2020). It is a gene expression-based test founded on the prediction analysis of microarray 50 (PAM50) gene (Jensen et al., 2018). The PAM50 gene is a gene expression-based test that categorizes the risk of breast cancer. It predicts distant recurrence by defining inherent breast cancer subtypes (Walden et al., 2015). It is reported that Prosigna assay has been validated as a prognostic indicator in postmenopausal patients with ER-positive early-stage breast cancer treated with endocrine therapy and who are low-risk (Alvarado et al., 2015).

Prosigna predicts the risk of distant recurrence. It determines the prognosis for postmenopausal patients with early-stage breast cancer who are estrogen receptor (ER)+ (Jensen et al., 2018). However, it is not clear whether Prosigna predicts chemotherapy benefit (Alvarado, et al., 2015). It is indicated in postmenopausal breast cancer women with stage I or stage II, lymph node-negative, stage II with one to three positive nodes, hormone-receptor-positive, invasive and have undergone surgery and hormonal therapy (https://www.veracyte.com/our-products/prosigna; https://www.breastcancer.org/symptoms/testing/types/prosigna).

Prosigna assesses the activity of 58 genes and produces an estimation of distant recurrence risk of breast cancer within 10 years (after diagnosis). Prosigna produces two outcomes: 1) risk of recurrence score (ROR), a numerical score (1 to 100 scale) that corroborates with the 10-year distant recurrence risk, and 2) an improved risk classification which utilizes predetermined cutoff points associated with clinical outcomes. The risk classification is reported as low, moderate, and high in cancers with negative node, and low or high for patients with positive node. Cancers with negative node are classified as low (0-40), intermediate (41-60), or high (61-100) risk whereas cancers with positive node are classified as low (0-40) or high (41-100) risk (https://www.breastcancer.org/symptoms/testing/types/prosigna).

10/12/2020: MTAC REVIEW

Evidence Conclusion:

- Analytic validity
  - Evidence is insufficient
- Clinical validity
  - Low evidence shows that Prosigna can significantly prognosticate 10-year distant recurrence in post-menopausal patients with ER+, HER2-, LN- or LN+, early breast cancer.
  - Evidence comparing Prosigna and other genomic tests are limited. Two low quality studies showed that Prosigna (ROR) has better prognostic value than Oncotype Dx (RS). According to one low quality study comparing Prosigna, BCI, EPclin, RS, Clinical tx score, immunohistochemical score, Prosigna, BCI, and EPclin

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provide the most prognostic information in LN- cancers during 0 to 10 years and late recurrence. In LN+, all the signatures are weakly prognostic. Similar and more comparative studies are needed to determine the best genomic test.
    - There is insufficient evidence for or against the predictive effect (chemotherapy benefit) of Prosigna.
- Clinical utility:
    - Although, two low quality studies demonstrated the utility of Prosigna, more high-quality studies are warranted to draw a strong conclusion.

Articles:

PubMed was searched through September 16, 2020 with the search terms Prosigna OR PAM50 OR Prosigna Breast Cancer Prognostic Gene Signature Assay with variations. The search was limited to English language publications and human populations. Validation studies, RCTs, and observational studies were included. The reference lists of relevant studies were reviewed to identify additional publications. See Evidence Table.

The use of Prosigna Breast Cancer Prognostic Gene Signature Assay does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

***Note:** Codes listed in the criteria above may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

******To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Date Reviewed	Date Last Revised
04/04/2005	06/04/2013[MPC] 08/06/2013[MPC], 06/03/2014[MPC], 04/7/2015[MPC], 01/05/2016[MPC], 11/01/2016[MPC] '09/05/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC], 10/01/2024[MPC]	11/15/2024

[MPC] Medical Policy Committee

Revision History	Description
06/14/2016	Platelet function testing – VerifyNow changed to "medical review no longer required". CPT code 85576
06/30/2015	Added additional Medicare LCD links and PROOVE® panels
09/08/2015	Revised LCD CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing L36311 and L35472, GeneSight® Assay for Refractory Depression (L36324), Genetic Testing L34101, Cytogenic Studies L34067
03/01/2016	Added Abacavir as a new test, added NRAS as an additional tumor marker, updated criteria for BRAF v600E Mutation
04/04/2017	Added MTAC review for Oncotype Assay for Lymph Node Positive Breast Cancer
08/01/2017	Added MTAC review for Breast Cancer Index and EndoPredict
04/24/2018	Added Oncotype DX Breast criteria revision
04/24/2018	Move BRAF testing to Genetic Screening Policy
06/02/2020	Added section: "Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees" Requires 60-day notice, effective date 10/01/2020.

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10/06/2020	MPC approved the MCG 24th ed. guidelines for Opioid Pharmacogenetics - CYP450 Polymorphisms, OPRM1 Gene, and GeneSight Analgesic Panel: A-0992, Statin Pharmacogenetics - SLCO1B1 Gene: A-0981; added exception for NGS for Advanced Cancer (CellNetix lab) to Invitae as preferred lab section
12/01/2020	Added MTAC review for Breast Cancer Index and Prosigna Breast Cancer Prognostic Gene Signature Assay. MPC approved to adopt non-coverage policy.
05/04/2021	Updated lists of tests, criteria, and applicable codes in Medicare and Non-Medicare sections. MPC voted to adopt MCG* A-0859 for psychotropic medications – this requires 60-day notice, effective date October 1, 2021.
10/27/2022	Updated lab vendor to include Prevention and align with other genetic criteria.
11/18/2022	Updated Medicare Links
12/06/2022	MPC approved to update criteria for ALK, EGFR and KRAS and/or NRAS testing to no longer require review. MPC also approved to move BRAF testing from the Genetic screening/testing criteria page to the pharmacogenomic criteria page. Requires 60-day notice. Effective 05/01/2023.
08/01/2023	Added MTAC review for Breast Cancer Index
09/05/2023	MPC approved medical necessity coverage indications for Breast Cancer Index. MPC approved to adopt Azathioprine and 6-Mercaptopurine Pharmacogenetics - NUDT15 and TPMT Genes, MCG A-0628. Requires 60-day notice, effective February 1, 2024.
06/03/2024	MCG 28th Edition guidelines have been updated where applicable.
06/04/2024	MPC approved to adopt the 28th edition MCG A-0775 policy on Cytochrome P450. Requires 60-day notice; effective November 1, 2024.
11/15/2024	LabCorp acquired Invitae Genetics test. Criteria was updated to reflect acquisition, effective November 15, 2024

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