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

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

**Note: This does not affect processing of tumor or other pathology specimens as they are not performed by Invitae/Prevention.*

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
Breast Cancer Index™ CPT 81518	**Effective until February 1, 2024** Send cases to MD for review. **Effective February 1, 2024** 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
ENDOPREDICT® CPT 81522	There is insufficient evidence in the published medical literature to show clinical utility.
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.
Clopidogrel (Plavix) Pharmacogenetics - CYP2C19 Gene CPT 81225	MCG* A-0631 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Tamoxifen Pharmacogenetics – CYP2D6 Gene CPT 81226, 0070U, 0071U, 0072U, 0073U, 0075U, 0076U	MCG* A-0647 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.

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Genetic Test	Criteria Used
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 Oncotype DX – Prostate CPT 0047U	Colon MCG* A-0651 and Prostate MCG* A-0712- 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*.
Opioid Pharmacogenetics - CYP450 Polymorphisms, OPRM1 Gene, and Gene Panels CPT 81225, 81226, 81227, 81230, 81231, 0031U, 0070U, 0071U, 0072U, 0073U, 0075U, 0076U, 0078U	MCG* A-0992 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*.
Platelet Function Testing (VerifyNow P2Y12 Assay) CPT code 85576	Medical necessity review no longer required

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Genetic Test	Criteria Used
Psychotropic Medication Pharmacogenetics - CYP450 Polymorphisms CPT 81225, 81226, 81479, 0070U, 0071U, 0072U, 0073U, 0075U, 0076U Psychotropic Medication Pharmacogenetics – ABCB1, ADRA2A, BCNF, COMT, DRD, FKBP5, GNB3, HTR, MC4R, OGFRL1, SLC6A4, and TPH1 Genes CPT 81403, 81479, 0032U, 0033U	MCG* A-0692 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*. MCG* A-0859 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*.
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*.
Azathioprine and 6-Mercaptopurine Pharmacogenetics - NUDT15 and TPMT Genes CPT 0034U, 0169U, 81335, 84433	**Effective until February 1, 2024** Current role remains uncertain **Effective February 1, 2024** 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 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

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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 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,

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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 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

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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).

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

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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.*

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

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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: Clinical validity: ChemoFx assay was not prospectively compared head to head to another cellular or molecular chemo responsive test or gold standard. Two retrospective cases series correlated the results of ChemoFx with cancer free survival in ovarian cancer patients, and one small series correlated its results with pathological complete response of small breast lesions to neoadjuvant therapies. Gallion, and colleagues 2006, retrospectively correlated the results of ChemoFx assay to progression free interval (PFI) in a case series of 304 patients with ovarian or peritoneal carcinoma. The study was a case series with potential selection and observational biases. It was not blinded, had no comparison group, and while selection of chemotherapy was at the discretion of the treating physician, some used the results of the assay to help determine the appropriate regimen. Overall, the results of show that 256 cases had an exact or partial match between drugs assayed and received, and 135 cases had an exact match. In the latter group the median PFI was 9 months for patients treated with drugs assayed as resistant, 14 months for those treated with drugs assayed as intermediate and had not been achieved (during study period) for those with drugs assayed as sensitive. The calculated hazard ratio for progression of the resistant group vs. the sensitive group was 2.9 (95% CI: 1.4-6.3), and that of the intermediate vs. sensitive group was 1.7 (95% CI; 1.2-2.5). Clinical utility: The literature search did not identify any published randomized or nonrandomized controlled trials that evaluated the effect of ChemoFx testing on individualizing chemotherapeutic regimen and /or its impact on survival. Other observational non-comparative prospective studies examining the outcomes associated with the use ChemoFx are underway. 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: *Plavix:* Analytic validity
No published studies on the accuracy of commercially available tests for detecting CYP2C19 variants were identified. Clinical validity A recent meta-analysis investigated the relationship between CYP2C19*2 polymorphisms and adverse clinical outcomes in patients with coronary artery disease (CAD) being treated with clopidogrel. Results from this analysis showed that the presence of the 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). There was significant heterogeneity between the studies. Studies varied with regard to clopidogrel dose, duration of follow-up, and patient type. Additionally, not all studies adjusted for confounding factors. Because only one CYP2C19 variant was studied misclassification is possible (Sofi 2010). While the majority of data suggest that patients possessing at least one variant CYP2C19 allele are at an increased risk for adverse cardiovascular events, not all studies have found this association. A genetic sub-study of the Impact of the Extent of Clopidogrel- Induced Platelet Inhibition on Clinical Event Rate (EXCELSIOR) study, found that the CYP2C19 genotype was not associated with risk of death or myocardial infarction (MI); however, increased platelet reactivity was associated with the risk of death or MI and patients with at least one CYP2C19*2 allele had increased platelet reactivity. The study was not powered to address this issue (Trenk 2008). Clinical utility No published studies were identified that prospectively compared patient outcomes managed with and without CYP2C19 genotyping. Conclusion: Analytic validity: 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

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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 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: *Atomoxetine* The literature search did not reveal any studies pertaining to the analytic validity or clinical utility of CYP2D6 genotyping to predict response to atomoxetine. Several studies were found that combined data from various clinical trials to address the clinical validity of CYP2D6 genotyping. The results from these studies are presented below. Michelson et al combined data from multiple studies to examine the effect of CYP2D6 on the efficacy and safety of atomoxetine. Efficacy data was available for 589 patients (559 EM and 30 PM). The primary outcome measure was defined as a ≥25% decrease in ADHD total symptoms measured using the Attention-Deficit Hyperactivity Disorder Rating Scale-Parent Version: Investigator Scored and Administered (ADHDRS-IV-Parent:Inv). Significantly more PM than EM responded to treatment (80% vs. 59.4%, P=0.033). However, PM were more likely to experience insomnia (P=0.035), abrasion (P=0.012), tremor (P<0.001), and decreased appetite (P=0.008) compared to EM. Limitations: small sample size, power was not addressed, not controlled for concomitant medications or other confounding factors, subjects were grouped into either PM or EM, included studies differed with regard to dosing and follow-up, and the research was funded by Eli Lilly (Michelson 2007). Another study combined data from two clinical trials to determine the effect of CYP2D6 genotype on the efficacy and tolerability of atomoxetine. Data was available for 1,326 patients (1,239 EM and 87 PM). Unlike the Michelson study, Trazepacz and colleagues did not find a significant difference in response, defined as a ≥25% decrease in the ADHDRS-IV-Parent:Inv, between PM and EM (84.9% vs. 81.6%, P=0.56). There were no significant differences in adverse events or treatment discontinuation. Limitations: power was not addressed, not controlled for concomitant medications or other confounding factors, subjects were grouped into either PM or EM, and the research was funded by Eli Lilly (Trzepacz 2008). Ramoz and colleagues combined data from two cohort studies and also found no significant difference in treatment response, defined as a ≥25% decrease in the ADHDRS-IV-Parent:Inv, between PM and EM (Ramoz 2009). Codeine for nursing mothers No randomized controlled trials or cohort studies were identified pertaining to the analytic validity, clinical validity, or clinical utility of genotyping nursing

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mothers for CYP2D6 status before prescribing codeine. The literature search revealed one case-control study with 17 infants with symptoms of opioid toxicity, central nervous system (CNS) depression, and 55 infants without symptoms of opioid toxicity following exposure to codeine while breastfeeding. Findings from this study indicate that there was good concordance between maternal and infant CNS depression. When the baby exhibited CNS depression, there was a 71% probability (12/17) that the mother also exhibited such signs.
Mothers of symptomatic infants were 8 times more likely to have the combined CYP2D6 UM and UGT2B7*2 genotype. UGT2B7*2 is also associated with higher production of the active morphine metabolite. Results from this analysis are inconclusive as there were only 2 women with the combined genotype (Madadi 2009b).
Efavirenz No studies were identified that addressed the analytic validity or clinical utility of genotyping to predict dosing of efavirenz. The literature pertaining to clinical validity consisted mainly of small cohort studies. Several small studies have demonstrated an association between CYP2B6 poor metabolizers and efavirenz plasma concentration. However, the number of poor metabolizers included in these studies ranged from 6 to 14. Additionally, not all individuals who were poor metabolizers had higher plasma concentrations (Haas 2004, Gatanaga 2007, Leger 2009). CYP2B6 polymorphisms are not the only factors that affect plasma levels, other drugs and enzymes may also predict efavirenz plasma concentration. To date there is insufficient evidence regarding the effects of CYP2B6 polymorphisms on clinical outcomes such as long-term virological and immunological response to efavirenz therapy. Proton pump inhibitors The literature search revealed several studies pertaining to the clinical validity of genotyping to predict response to proton pump inhibitors. The majority of these studies were small and performed in Asian populations, which are known to have a higher percentage of CYP2C19 poor metabolizers, as such the results may not be generalizable to other populations. A small randomized controlled trial was identified that compared *H. pylori* eradication rates in patient receiving rabeprazole with different antibiotic regimens was not selected for review as it did not have adequate power to address differences in eradication rates by CYPC19 metabolizer status (Yang 2009). A meta-analysis of 20 observational studies was selected for review (Zhao 2008). No studies were identified that addressed the analytic validity or clinical utility of genotyping to predict response to proton pump inhibitors. The objective of the meta-analysis was to determine whether CYP2C19 polymorphisms affect *H. pylori* eradications rates obtained with first-line PPI- based triple therapies. Eradication rates using the PPI lansoprazole and omeprazole were significantly higher for PM and IM compared to EM; however, there was no significant difference between PM and IM. There was no significant difference in eradication rates among the three genotypes for therapies using the PPI rabeprazole. The studies included in this analysis were mostly observations and thus are more prone to bias and confounding.
Studies using difference antibiotic combinations were analyzed together. Additionally, other factors such as antibiotic resistance rates may affect *H. pylori* eradication rates (Zhao 2008). Not all studies have found an association between CYP2C19 genotype and *H. pylori* eradication rates. A cohort study conducted in Korea that included 174 subjects and was published after the meta-analysis found no significant difference in eradication rates by CYP2C19 genotype for patient treated with pantoprazole, amoxicillin, and clarithromycin twice daily. As this study was not randomized it may be prone to bias. There were only 39 poor metabolizers included in the study, so it may lack the statistical power to detect a difference between the CYP2C19 genotypes (Oh 2009).
Immunosuppressant for organ transplantation The literature search did not reveal any studies addressing the analytic validity of genotyping to predict response to tacrolimus. With regard to clinical validity, several cohort, case-control, and cross sectional studies were identified that looked at the effect of CYP3A5 polymorphisms on tacrolimus concentrations. A prospective cohort study was selected for review (Hesselink 2008). One randomized controlled trial was identified that addressed the clinical utility of genotyping to predict initial does; however, this study was not selected for review as patients were genotyped after transplantation and tacrolimus was not initiated until 7 days after transplantation (Thervet 2010). RCT are currently underway to determine the efficacy of genotype guided initial dosing. A recent prospective cohort study compared the effect of CYP3A5 genotype on (weight-adjusted) tacrolimus exposure and dose, as well as the incidence of acute rejection after kidney transplantation. Results from this study suggest that CYP3A5 expressers require higher drug doses than non-expressers to reach target pre-dose concentrations. The overall daily tacrolimus dose was 60% higher for CYP3A5 expressers compared to non-expressers (95% CI, 35-89%, P<0.001). Additionally, significantly more CYP3A5 expressers had a pre-dose concentration below 10 ng/ml, which is the recommended minimum pre-dose concentration in the early phase after transplantation, compared to non-expressers on day 3 after transplantation (28 vs. 10%, P=0.02). On study day 10 and thereafter pre-dose concentration was comparable between the two groups. There was no statistically significant difference in the incidence of biopsy-proven acute rejection (P=0.36) (Hesselink 2008). A prospective study of 44 renal transplant patients also failed to find an association between genotype and risk of rejection; however, this study did find that CYP3A5 expressers required a higher dose of tacrolimus to reach target concentrations (Roy 2006). It should be noted that the pharmacogenetics of tacrolimus are complex. Other factors such as genetic polymorphisms in drug transporters, differences between the donor organ and recipient's intestinal

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genotype, and drug interactions may all contribute to differences in the pharmacogenetics of tacrolimus. Selective serotonin reuptake inhibitors (SSRIs) The literature search revealed several case-control and cohort studies pertaining to the clinical validity of genotyping patients to predict their response to SSRIs. No studies were identified that addressed analytic validity or clinical utility. In general, studies of clinical validity were limited by inadequate power, poor and intermediate metabolizers were analyzed together, studies grouped different SSRIs together or with other classes of antidepressant medications, and studies did not provide information on variables such as diet, other medications, race/ethnicity, and other genetic factors that may influence SSRI efficacy and tolerability. The majority of studies evaluating the clinical validity of genotyping patients to predict their response to SSRIs found no association between genotype and adverse drug reactions (Murphy 2003, Roberts 2004, Suzuki 2006, Peters 2008). One study did find an association between genotype and the occurrence of adverse events; however, there were only 8 (29%) poor metabolizers and 3 (19%) UM included in the study (Rau 2004). 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.
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

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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: Analytical validity: Three studies were identified (Denkert et al., 2012; Kronenwett et al., 2012; Varga et al., 2013). Two were validation studies and one was a retrospective comparison between EndoPredict and the Oncotype Dx. Patients were ER+, HER2-. Sample size ranged from 10 to 34. The majority of the sample was node negative in two studies; node status is unknown in the second study. The studies show that EndoPredict test is reproducible (correlation coefficient: 0.994 to 0.995). The test is also reliable (variance of EP scores 0.15 for proficiency test to 0.18 in an independent lab). Sensitivity and specificity were evaluated in one study and were 100% (Denkert et al., 2012). Analytical accuracy was evaluated in one study (Kronenwett et al., 2012) and found that the difference between reference EP scores and reported EP scores was less than 1.0 EP units for 9 out of 10 samples with mean deviation of 0.15. The study that compared EndoPredict to Oncotype Dx showed moderate positive linear correlation and concordance between these tests.
Nevertheless, the results should be interpreted with caution due to the small sample size, and financial ties between authors and Sividon, the reference laboratory. In light of these limitations, the studies provide low to moderate evidence to support the reproducibility and reliability of the test. **Clinical validity:** Seven studies (Bertucci, Finetti, Viens, & Birnbaum, 2014; Buus et al., 2016; Dubsky, Filipits, et al., 2013; Filipits et al., 2011; Fitzal et al., 2015; Martin et al., 2014; Martin et al., 2016) were identified. The studies were retrospective-prospective in design. Patients were ER+, HER2-, LN- or LN+, treated with endocrine therapy alone or chemotherapy or chemotherapy followed by endocrine therapy. Sample size was up to 1702 patients and age ranged from 23-80 years. Patients were postmenopausal women in four studies. Most of these studies were conducted in Europe. The primary outcome was the assessment of prognostic performance of EndoPredict test. The prognostic performance was evaluated by assessing distant recurrence, or metastasis-free survival (MFS), or distant-relapse free survival (DRFS). One study (Bertucci et al., 2014) assessed the predictive value of the test; another study compared EP versus Oncotype Dx (Buus et al., 2016). These studies demonstrate that the EndoPredict test is highly prognostic of distant recurrence or metastasis-free survival. Based on Simon et al. 2009 (Simon, Paik, & Hayes, 2009), the studies provide level IB

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evidence. However, limitations include one or more of the following: lack of data on premenopausal women, lack of assessment of the predictive value of the test, low to moderate quality trials, clinicopathological factors varied between studies, small sample size, financial ties with manufacturer, and low events suggesting an overestimation of the prognostic performance. **Clinical utility:** One retrospective study (Muller et al., 2013) with 167 patients reported that EP may change treatment decision in ER+, HER2-, LN+/LN- breast cancer patients. The change in treatment decision occurred in 38% of patients with 25% changed to endocrine treatment alone. The main limitations include the retrospective nature of the study.

Other studies:

Author, year	Findings
(Dubsky, Brase, et al., 2013)	HR: 2.80 (1.81–4.34) P<0.001 first 5 years HR: 3.28 (1.48–7.24) P=0.002 after 5 years EP is highly prognostic of distant recurrence
(Muller et al., 2012)	Correlation r=0.92 between biopsies and surgical specimens

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 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,

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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 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

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Inhibitors (TKIs) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/18/2010: MTAC REVIEW
Epidermal Growth Factor Receptor (EGFR) Evidence
Conclusion: Analytic validity
There are a variety of methods used to detect EGFR mutations. Each of these assays has its advantages and limitations. Rapid detection of EGFR mutations with multiplex PCR and primer was found to be highly accurate compared to direct sequencing. In a sample of 81 tumors the two methods identified the same 26 mutations (Lin 2010). Clinical validity The Iressa Pan-Asian Study (IPASS) was a phase 3, multicenter, randomized, open-label trial comparing gefitinib with carboplatin plus paclitaxel as first-line treatment in 1217 clinically selected patients in East Asia with advanced non-small-cell lung cancer. In the overall population, the median progression-free survival (PFS) was 5.7 months in the gefitinib group and 5.8 months in the carboplatin plus paclitaxel group. The probability that a patient would be free of disease progression was greater with carboplatin-paclitaxel in the first 6 months and greater with gefitinib in the following 16 months. The objective response rate was significantly higher with gefitinib that with carboplatin plus paclitaxel. Overall survival did not differ between the two treatment groups; however, there were less than 100 events in each group. A preplanned subgroup analysis by EGFR mutation status was also performed. EGFR mutation status could be determined for 437 subjects (35.9%). Patients with sensitive EGFR mutations who received gefitinib had longer PFS, higher response rates, and a lower rate of adverse events compared to patients with sensitive EGFR mutations taking carboplatin plus paclitaxel. However, results should be interpreted with caution as EGFR status could only be evaluated for 35.9% of the original study population and patients were not randomized based on EGFR status. The results from this study are generalizable to patients of Asian ethnicity, who were nonsmokers or former light smokers, and had adenocarcinoma of the lung. Another limitation of this study lies in the analysis. The Cox proportional-hazards model is based on the assumption that the hazard ratio of the two treatments is constant overtime. Since the curves cross, this assumption is violated. However, in the subgroup analysis (patients with EGFR mutations) this assumption is not violated (Mok 2009). The results from a preplanned subgroup analysis of the INTEREST trial, a RCT comparing gefitinib to docetaxel in a Western pretreated population, were consistent with the results from the IPASS trial.
However, only 44 subjects in the study were EGFR mutation-positive (Douillard 2010). Clinical utility Two RCT recently evaluated the efficacy of gefitinib compared to chemotherapy in patients with sensitive EGFR mutations and non-small-cell lung cancer. The first trial compared gefitinib to carboplatin plus paclitaxel chemotherapy. Patients treated with gefitinib had significantly longer progression-free survival than patients treated with carboplatin plus paclitaxel (median 10.8 vs. 5.4 months, P<0.001) and higher response rates (73.7% vs. 30.7%, P<0.001). There was no difference in overall survival between the two groups; however, the incidence of severe toxic effects was significantly higher in the chemotherapy group than in the gefitinib group (71.1% vs. 41.2%, P<0.001). The results from this trial are generalizable to nonsmoking patients from Asia who had not previously received chemotherapy (Maemondo 2010). The second RCT assessed the efficacy of gefitinib compared to cisplatin plus docetaxel chemotherapy in patients with sensitive EGFR mutations. Findings from this trial are similar to the afore mentioned trial with progression-free survival being longer (9.2 vs. 6.3 months, P<0.001) and response rate being higher (61.2% vs. 32.2%, P<0.001) in patients treated with gefitinib compared to patients treated with cisplatin plus docetaxel. Results for overall survival could not be determined as data were immature and follow-up is still ongoing. Results from this study are generalizable to patients of Asian origin (Mitsudomi 2010). Conclusion: Analytic validity: 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

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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 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 the analytic validity of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections. Clinical validity A recent genome-wide association study (GWAS) identified seven single nucleotide polymorphisms (SNPs) around the IL28B gene that were associated with SVR in patients with chronic genotype 1 HCV infection. The most strongly associated SNP was rs12979860 followed by rs8099917. Results from this study suggest that the rate of viral response in European-Americans and Hispanics with the CC genotype was twofold higher compared to patients with the TT genotype. The rate of viral response in African Americans was threefold higher compared to patients with the TT genotype. No replication cohort was performed (Ge 2009). Two other GWAS in different populations also found that polymorphisms on the IL28B gene locus were associated with SVR. The first study found that the rs8099917 SNP on the IL28B gene was associated with SVR in Australian patients with chronic HCV infection. These results were replicated in an independent cohort of Europeans from the United Kingdom, Germany, Italy, and Australia (Suppiah 2009). The second study found that in Japanese patients with genotype 1 HCV, SNPs near the IL28B chromosome (rs8099917 and rs12980275) were associated with SVR. These results were replicated in an independent cohort on Japanese patients with HCV infection (Tanaka 2009). Clinical utility No studies were identified that evaluated the clinical utility of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections. 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

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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 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.

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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: Analytic validity No studies were identified that directly compared the Response Genetics test to another test. A recent study compared four different methods of *KRAS* mutation testing–Sanger sequencing, array analysis, melting curve analysis, and pyrosequencing. The study included samples from 263 patients with colorectal cancer. Results from this study indicate that there was very good agreement between the four methods (κ >0.9). As to date there is no reliable, predetermined gold standard method for comparison, direct estimates of the sensitivity and specificity of the respective methods is not possible (Weichert 2010). Clinical validity Treatment regimens differed across the studies; however, there was a consistent message that for patients with mutant *KRAS* tumors the addition of the monoclonal antibodies cetuximab and panitumumab did not increase progression-free, overall survival, or response rate compared to mutant *KRAS* tumor patients who were not treated with a monoclonal antibody. *First-Line* Three RCTs conducted retrospective subgroup analyses to investigate the influence of *KRAS* mutation status on progression-free survival (PFS), overall survival (OS), and response rate. The Von Cutsem study analyzed data from the CRYSTAL trial. This trial was a randomized, open- label, multi-centered study that compared 14-day cycles of cetuximab plus FOLFIRI to FOLFIRI alone. For patients with mutant *KRAS* tumors, there was no difference between response rate, PFS, or OS between the two treatment groups. When patients with wild-type *KRAS* tumors were compared to patients with mutant *KRAS* tumors there was no difference between the groups for PFS or OS; however, the response rate was higher for patients with wild-type tumors (Von Custem 2009). Tol et al analyzed data from the CAIRO2 trial. This was an open-label randomized trial that evaluated the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab as first-line treatment in patients with metastatic colorectal cancer. Patients with mutant *KRAS* tumors who did not take cetuximab had significantly longer PFS and OS and higher response rates compared to patients who took cetuximab. Compared to patients with mutant *KRAS* tumors taking cetuximab, patients with wild-type *KRAS* tumors taking cetuximab had longer PFS, OS, and higher response rates. There was no significant difference in PFS, OS, or response rates for between mutant and wild-type patients not taking cetuximab (Tol 2009). Hecht and colleagues used data from the PACCE trial that evaluated panitumumab added to bevacizumab and oxaliplatin- based chemotherapy (cohort 1) or irinotecan-based chemotherapy (cohort 2). There was no significant difference in PFS or OS for patients with mutants *KRAS* tumors in either cohort (Hecht 2008). *Second-Line* No new information was identified since the 2008 MTAC review. Evidence for the 2008 MTAC review: The three retrospective cohort studies evaluated (Lievre 2008; DeRoock 2008; DiFiore 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* tumors. *Third-Line* Two RCTs conducted retrospective subgroup analyses to investigate the influence of *KRAS* mutation status on progression-free survival (PFS), overall survival (OS), and response rate. Amado and colleagues used data from a trial that that evaluated panitumumab monotherapy versus best supportive care (BCS) for patients with chemotherapy-refractory metastatic colorectal cancer. In this trial, patient in the BSC arm could receive panitumumab after disease progression. The effects of panitumumab on PFS were significantly greater for patients with wild-type tumors compared to patients with mutant tumors. As this was a crossover study, reliable overall survival measures cannot be obtained. Response rate data were missing for 19% of the population (13% wild-type *KRAS* and 26% mutant *KRAS*). For patients with wild-type *KRAS* taking panitumumab 17% had a partial response; no responders were identified in any other group (Amado 2008). Karapetis and colleagues used data from a phase 3 trial that examined the effects of cetuximab on patients with chemotherapy-refractory colorectal cancer versus BSC. There was no difference in PFS or OS for patients with mutant *KRAS* tumors between the treatment groups. The effects of cetuximab on PFS and OS were

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significantly greater for patients with wild-type tumors compared to patients with mutant tumors. In the cetuximab group, the response rate was 12.8% for wild-type *KRAS* tumors and 1.2% for mutant *KRAS* tumors. None of the patients in the BSC group had an objective tumor response (Karapetis 2008). All analyses were retrospective and therefore are subject to confounding – other differences between patients with wild-type and mutant *KRAS* genes could have affected the outcome. Patients in the RCTs were not randomized based on their *KRAS* mutation status. A subset of subjects from the RCT was used for analysis. Samples could only be obtained from 45%-92% of the primary analysis populations. Not all *KRAS* mutations were assessed. Mutations in codon 62 would have been missed even though this is a less prevalent mutation (~3% of mutations) it still may result in misclassification. The trials received industry funding. In the study conducted by Hecht and colleagues, censoring could have altered the PFS results. Additionally, response rate data was missing from 19% of the subject in the Amado study. Clinical utility
No studies were identified that specifically addressed clinical utility. However, identifying patients who will not respond to therapy will avoid the administration of an ineffective treatment and its associated toxicities.
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 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.

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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 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*

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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 No studies were identified that assessed the sensitivity and specificity of the *Oncotype DX*® colon cancer assay. Clinical validity A recent retrospective analysis of the Quick Simple and Reliable (QUASAR) trial evaluated whether the Oncotype® DX assay can provide clinically relevant information to assist treatment decision making in patients with resected stage II colon cancer. The assay yields a prognostic recurrence score that ranges from 0 to 100 and a treatment score. Results from this trial suggest that recurrence score (RS) was significantly associated with the risk of recurrence even after controlling for other factors such as tumor location, T stage, grade, nodes examined, lymph vascular invasion, and MMR deficient. The estimated recurrence risk at 3 years was 12% for the low recurrence risk group (RS<30), 18% for the intermediate recurrence risk group (RS 30-40), and 22% for the high recurrence risk group (RS≥40). The treatment score was not predictive of chemotherapy benefit (Gary 2011). Clinical utility No studies were identified that assessed the clinical utility of the *Oncotype DX*® colon cancer assay.
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 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: 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:** (Albain et al., 2010) (Evidence table 1) performed a retrospective assessment of the phase 3 trial SWOG-8814. Women with node-positive breast cancer were treated with cyclophosphamide, doxorubicin, fluorouracil followed with tamoxifen (CAF-T) or tamoxifen alone. Patients were postmenopausal women with node positive, ER positive breast cancer. Recurrence score (RS) was found to be highly prognostic (Disease free survival) in the tamoxifen group (HR 2.64, 95% CI, 1.33 – 5.27; p=0.006). The same trend was found for overall survival (OS); HR 4.42 (95% CI 1.96, 9.97; p<0.001). Furthermore, there was no chemotherapy benefit in the low RS; however, disease-free survival was improved with high RS, independent of the number of positive nodes (HR 0.59, 95% CI, 0.35- 1.01; p=0.033). For DFS (disease free survival) as well as OS (overall survival), trend was similar; this means that RS significantly predicted chemo benefit (p=0.053 for DFS and p=0.026 for OS). However, this effect was not constant after 5 years (except for higher RS). The cumulative chemotherapy benefit persisted to 10years. Limitations included a specific population consisting of postmenopausal women limiting extrapolation of finding in premenopausal women. In addition, the sample size was small and some co-authors had ties with the manufacturer. (Dowsett et al., 2010) investigated whether the Recurrence Score (RS) provided information on the risk of distant recurrence (DR) in the tamoxifen and anastrozole arms of the Arimidex, Tamoxifen, alone or in Combination (ATAC) Trial. Outcomes were time to distant recurrence (TTDR), time to recurrence (TTR) and overall survival (OS).Three hundred and six (306) lymph node-positive (LN+) breast cancer in post-menopausal women were examined out of 1231 evaluable

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patients; the median follow-up was 8.5 years. Seventy-four (74) distant recurrences occurred in LN+ patients. In LN+ patients, 52%, 31% and 17% had an RS of <18, 18-30, and ≥31 respectively. The authors reported that the RS was predictive of TTDR in LN+ (HR=3.47, 95% CI = 1.64-7.38; **P=0.002**). After adjusting for clinical variables, the HRs between high and low RS and low to intermediate RS were 2.7% and 1.8% respectively. The 9-year DR rates in LN+ were 17%, 28%, and 49% in the RSs <18, 18-30 and ≥31 respectively. The same trend was observed for OS. The risk of DR was linearly associated with increasing RS. The risk of DR was higher for LN+ than LN- patients. RS was predictive of DR in the same way in patients treated with tamoxifen or anastrozole. Limitations included the small sample size, a specific population consisting of postmenopausal women and the lack of assessment of the chemotherapy benefit. Some authors had financial interest with the manufacturer of the oncotype DX assay. Mamounas (Mamounas et al., 2012) evaluated the association between RS and Paclitaxel (Pac) benefit. The sample used in the current study derived from a study that assessed doxorubicin/cyclophosphamide (AC) with AC followed by Pac (AC→Pac); patients were also treated with tamoxifen. This current study enrolled 1065 patients with ER+, LN+ breast cancer; the median follow-up was 11.2 years. 36%, 34% and 30% had low, intermediate and high RSs respectively. The authors found that RS was significantly predictive of loco-regional recurrence (LRR), disease free survival, distant recurrence and death in patients treated with AC as well as AC→Pac (findings can be seen in the table below).

10-year cumulative incidence (%) of LRR, DFS, DR and death

	Low RS	Intermediate RS	High RS	Log-rank p
LRR				
AC	3.4 (1.4 – 70)	8.3 (4.8 – 13.3)	13.2 (8.3 – 19.1)	**0.004**
AC→Pac	3.1 (1.4 – 6.3)	6.2 (3.3 – 10.4)	11.4 (7.0 – 17.0)	**0.037**
	HR 1.19 (0.45 – 3.16)	HR 0.75 (0.34 – 1.65)	HR 0.80 (0.42 – 1.52)	
DFS				
AC	24.5 (18.8- 31.5)	46.6 (39.5 – 54.4)	54.7 (47 – 62.8)	**<0.001**
AC→Pac	23.9 (18.5 – 30.6)	39.6 (32.8-47.1)	49.5 (42 – 57.5)	**<0.001**
	HR 1.01 (0.69 – 1.47)	HR 0.84 (0.62 – 1.14)	HR 0.81 (0.60 – 1.10)	
DR & death				
Similar trend				

LRR, Loco-Regional Recurrence; RS, Recurrence Score; DFS, Disease Free Survival; DR, Distant recurrence

Furthermore, patients with high or intermediate RS benefited the most from Paclitaxel indicating that chemotherapy may not be warranted in patients with low RS.

On-going trial:
NCT01272037: A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer with Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Clinical Utility: Summary of evidence Eight observational studies were identified. The studies were retrospective or prospective in design and evaluated the impact of the oncotype DX assay recurrence score on treatment recommendations, patient decisional conflict, patient satisfaction and physician confidence in recommending treatment. Sample sizes were small and ranged from 20 to 282 patients with lymph node-positive, ER+, HER2- breast cancer. Most of the included patients received hormonal therapy or chemo hormonal therapy. These studies showed a change in the treatment recommendations after the oncotype Dx assay was performed. The proportion of the change ranged from 26% to 51%. The principal change was the removal of chemotherapy from the initial treatment recommendation. This suggests that the oncotype DX testing may impact decision-making or treatment plan and reduces the adverse effects caused by chemotherapy. Other findings included patient satisfaction, reduction of decisional conflict. Limitations included the small sample size, the difference between the groups with respect to characteristics of the tumors, and the financial ties between the manufacturer and some authors.
In addition, the retrospective analysis of RCT (evidence table 1) included in the clinical validity section (Albain et al., 2010) found that the addition of anthracycline-based chemotherapy improved disease-free survival (0.59 (0.35 – 1.01); P=0.033) and overall survival (P=0.0271) in patients with high recurrence score.
In conclusion, well-design studies with larger sample size are warranted to assess the patients reported outcomes which evaluate the clinical utility of molecular tests.

Studies assessing clinical utility (Bargallo et al., 2015) in a prospective study (evidence table 2) evaluated the

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impact of the recurrence Score result on the adjuvant therapy decision-making process. The authors reported that for LN+, the change occurred for 41% of the patients. Similarly, treatment recommendations changed for 32% for all patients irrespective of lymph node status and with the use of the oncotype DX assay. A retrospective study (Stemmer et al., 2013) (evidence table 3) compared treatment decisions in N1+/ER+/ HER2-negative breast cancer patients who underwent the oncotype DX assay with a control group composed of patients for whom treatment decisions were solely based on clinicopathologic criteria. Both groups received hormonal therapy with or without chemotherapy. Data of 282 patients who underwent the assay and 669 controls were analyzed. Some differences were noted on the tumor characteristics with patients on oncotype DX group with smaller tumor, lower frequencies of grade 3 tumors and number of positive nodes. The authors reported a lower utilization of chemotherapy in patients who were tested with the assay compared to the control (24.5 vs. 70.1%). In addition, the assay testing was significantly associated with a lower chance of receiving chemotherapy (OR 0.16; P<0.0001) after adjusting for age, tumor size, tumor grade, and nodal status. Nevertheless, limitations included the dissimilarity among groups and the change in adjuvant treatment recommendations for this population. A prospective German study (Eiermann et al., 2013) of 366 patients, of whom 122 were LN+ and 244 were LN- reported a change in treatment decision in 39% of women with LN+ (for LN-, A change of 30% was observed) after performing the oncotype Dx assay. The principal change was from chemo hormonal therapy (CHT) to hormonal therapy (HT) in 28% of all LN+ patients. Similarly, a reduction in chemotherapy was observed. Patient decisional conflict was also reduced by 6% and for both LN- and LN+ patients. Physician confidence in recommending treatment was increased in 45% for both LN- and LN+ patients. However, this was an industry funded study; therefore results should be interpreted with caution. (De Boer, Baker, Speakman, & Mann, 2011) reported that in 50 patients of LN+ patients, a change in treatment decision occurred in 26% of patients. The main change was from chemo hormonal therapy to hormonal therapy alone. Another study (Oratz et al., 2011) showed that 51% (70/138) patients with LN+ early breast cancer had their treatment recommendations changed after undergoing the oncotype Dx assay. The main change included the elimination of chemotherapy from the initial recommendation. A retrospective analysis of a sample of 40 patients with LN+ breast cancer (Nguyen et al., 2014) showed that the oncotype Dx assay was linearly associated with the use of chemotherapy. However, the small sample size constituted a limitation. A prospective study (Yamauchi et al., 2014) of the effect of the 21-gene assay on adjuvant clinical decision-making in Japanese women with hormone-receptor positive, LN- and LN+ breast cancer reported that of the 20 LN+ patients, 65% (95% CI, 41 -85%) had their recommendations changed. 87% (13/15) of LN+ patients had their initial recommendation for chemo hormonal therapy changed to hormonal therapy after performing the oncotype Dx assay. No patients, out of 5 LN+ patients, had their initial recommendations for hormonal to combined chemo hormonal. The results should be interpreted with caution because of the small sample size.

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

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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 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

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(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
Platelet Function Testing (VerifyNow P2Y12 Assay)
Evidence Conclusion: Analytic validity Light transmission aggregometry (LTA) is considered by many to be the gold standard in platelet function testing; however, even though this method is the gold standard it is not without limitations. It is time consuming, it has poor reproducibility, and it requires experienced technicians (Sambu 2011). A recent study evaluated the correlation between platelet function tests to measure clopidogrel-mediated platelet inhibition in 80 patients on dual antiplatelet therapy after percutaneous intervention with stent implantation. The cut-off value for defining residual ADP-platelet aggregation despite treatment with clopidogrel was maximal aggregation ≥62% for LTA and PRU ≥273 for the VerifyNow P2Y12 Assay. There was significant correlation between the two assays (r=0.61). When using LTA as the gold standard, the VerifyNow P2Y12 Assay had a sensitivity of 55% and a specificity of 85% (Gremmel 2009). Clinical validity Results from a recent meta-analysis that included 3,058 subjects suggest that that high on-treatment platelet reactivity (PRU ≥ 230) after percutaneous coronary intervention was associated with cardiovascular events. However, the results of this analysis should be interpreted with caution due to methodological limitations. For example, study quality was not reported and confidence intervals were wide due to the small number of events (Brar 2011).Clinical utility A recent RCT evaluated the effect of high-dose compared with standard-dose clopidogrel in 2,214 patients with high on- treatment platelet reactivity after percutaneous coronary intervention (PCI). Results from this study suggest that the use of high-dose clopidogrel in patients with high on-treatment platelet reactivity after PCI did not reduce the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis compared to standard-dose clopidogrel. Due to the fact that fewer events occurred than anticipated, a treatment effect of high- dose clopidogrel cannot be excluded (Price 2011). 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-

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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 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: Analytic validity: No published evidence was identified.

Clinical validity: A meta-analysis of observational studies (Sanderson et al., 2005) found a statistically significant association between variants of the CYP2C9 gene and both a lower dose of warfarin and lower risk of bleeding. The meta-analysis did not study the VKORC1 gene. Two cohort studies published after the meta-analysis (Schwartz et al., 2008; Wadelius et al., 2008) found significant associations between genetic variants of VKORC1 and efficacy outcomes (time to therapeutic INR or dose of warfarin). Associations with genetic variants of CYP2C9 were significant in one study but not the other. Both cohort studies were underpowered to assess the association between bleeding and genetic variants. Clinical utility: Two RCTs, one pilot study (Hillman et al., 2005) and one completed trial (Anderson et al., 2007) compared outcomes in patients managed with pharmacogenetic-guided dosing and those managed with standard dosing. The Anderson et al., 2007 study did not find a significant difference in the primary outcome, the per-patient percentage of out-of-range INR (30.7% in pharmacogenetic-

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guided dosing, and 33.1% in standard dosing). There was also no significant between-group difference in the secondary outcomes, achieving a therapeutic INR by day 5 or day 8, or the proportion of patients with adverse events. There were, however, significantly fewer dose adjustments (mean of 3.6 vs. mean of 3.0) with pharmacogenetic-guided dosing. The Hillman et al., 2005 focused on the feasibility of pharmacogenetic-guided dosing in a clinical setting, which was found to be feasible. The study also described clinical outcomes but did not do statistical testing. Outcomes (e.g. percent time INR in range and percent of patients with maximum INR>4) were similar in the two groups and the number of adverse effects was somewhat higher in the standard-dosing group. In 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 are several genotyping assays available to detect polymorphisms in the CYP2C9 and VKORC1 genes. King and colleagues compared the accuracy of four commercially available assays. All four methods evaluated had high accuracy compared to bi-directional sequencing (King 2009). Clinical Validity In 2008, based on the results from a meta-analysis and two cohort studies warfarin sensitivity DNA testing was found to have adequate clinical validity. Information from the 2008 review: A meta-analysis of observational studies found a statistically significant association between variants of the CYP2C9 gene and both a lower dose of warfarin and lower risk of bleeding. The meta-analysis did not study the VKORC1 gene (Sanderson 2005). Two cohort studies published after the meta-analysis (Schwartz 2008, Wadelius 2008) found significant associations between genetic variants of VKORC1 and efficacy outcomes (time to therapeutic INR or dose of warfarin). Associations with genetic variants of CYP2C9 were significant in one study but not the other. Both cohort studies were underpowered to assess the association between bleeding and genetic variants. New information since the 2008 review: A recent retrospective cohort study compared the accuracy of three different warfarin dosing

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algorithms. Results from this study suggest that the pharmacogenetic algorithm that included information on CYP2C9 and VKORC1 genotype produced initial warfarin dose recommendations that were significantly closer to the stable therapeutic dose than the clinical or fixed-dose algorithms. This analysis did not address whether a precise initial dose of warfarin would improve clinical endpoints, such as a reduction in the time needed to achieve a stable therapeutic INR, fewer INRs that are out of range, or a reduced incidence of bleeding (Klein 2009).Clinical Utility A recent cohort study compared the six month incidence of hospitalization in patients receiving warfarin genotyping versus historical controls. Compared to historic controls, patients who were genotyped for warfarin sensitivity had 31% fewer hospitalizations (P<0.001). Results from this study should be interpreted with caution. Patients were taking warfarin for a median of 32 days before the physician received the lab results. As there was no further communication with the physician after the lab results were sent, it is unknown if the genotyping results were used to inform treatment. The main limitation of this study is the use of a historical control group. Because a contemporary control group was not selected the possibility that the benefits of genotype-guided warfarin therapy may be exaggerated due to confounding, either in the vigilance by the treating physicians or in the kinds of patients who agreed to participate, cannot be ruled out. Other limitations include the fact that the genotype of the control group was unknown and baseline differences in the prevalence of hypertension and diabetes between the control and intervention group (Epstein 2010). 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 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-

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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 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.**

CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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]	09/05/2023

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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.
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 (81401), EGFR (81235) and KRAS (CPT 81275, 81276, 0111U) and/or NRAS (CPT 81311, 0111U) 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.

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