Medical Policy

Miscellaneous Genetic and Molecular Diagnostic Tests

Table of Contents

- Policy: Commercial
- Coding Information
- Policy: Medicare
- Description
- Authorization Information
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 712
BCBSA Reference Number: 2.04.121
NCD/LCD: N/A

Related Policies
Gene Expression Profiling for Uveal Melanoma, #683
General Approach to Evaluating the Utility of Genetic Panels, #734
General Approach to Genetic Testing, #735
Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes, #226
Identification of Microorganisms Using Nucleic Acid Probes, #555
KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer, #104
Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer, #318

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

All tests listed in this policy are considered INVESTIGATIONAL and grouped according to the categories of genetic testing outlined in medical policy #735.
- Testing of an affected (symptomatic) individual’s germline to benefit the individual (excluding reproductive testing)
- Diagnostic testing
- Prognostic testing
- Therapeutic testing
- Testing an asymptomatic individual to determine future risk of disease.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.
CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>81327</td>
<td>SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis</td>
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Description
TESTS ADDRESSED IN THIS EVIDENCE REVIEW
Tests assessed in this evidence review are listed in Table 1. Three types of tests are related to testing of an affected (symptomatic) individual’s germline to benefit the individual (excluding reproductive testing): diagnostic testing, prognostic testing, and therapeutic testing. The fourth type of test reviewed is testing of an asymptomatic individual to determine future risk of disease.

Table 1. Genetic and Molecular Diagnostic Tests in This Evidence Review

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Date Added</th>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Therapeutic</th>
<th>Future Risk</th>
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<tr>
<td>Celiac PLUS</td>
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<td>●</td>
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<td>SEPT9 methylated DNAβ</td>
<td>Severalc</td>
<td>Oct 2014</td>
<td>●</td>
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<td>TransPredict Fc gamma 3A</td>
<td>Transgenomic</td>
<td>Oct 2014</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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Castle: Castle Biosciences; Dxs: Diagnostics; Gxcs: Genetics.
a In a joint venture with Innovative Diagnostic Laboratory.
b For example, ColoVantage®, Epi proColon®.
c ARUP, Quest, Clinical Genomics, Epigenomics.
DIAGNOSTIC TESTS
Multiple Conditions

Single-nucleotide variants (SNVs) are the most common type of genetic variation, and each SNV represents a difference in a single nucleotide in the DNA sequence. Most commonly, SNVs are found in the DNA between genes and can act as biologic markers of genes and disease association. When SNVs occur within a gene or a gene regulatory region, they can play a more direct role in disease by affecting the gene’s function. SNVs may predict an individual’s response to certain drugs, susceptibility to environmental factors, and the risk of developing certain diseases.

DNA specimen provenance assays can be used to confirm that tissue specimens are correctly matched to the patient of origin. Specimen provenance errors may occur in up to 1% to 2% of pathology tissue specimens and have serious negative implications for patient care if the error is not corrected. Analysis of DNA microsatellites from tissue specimens can be performed by analyzing long tandem repeats (LTR) and comparing the LTRs of the tissue specimen with LTRs from a patient sample.

Test Description: DNA Methylation Pathway Profile
The DNA Methylation Pathway Profile (Great Plains Laboratory) analyzes SNVs associated with certain biochemical processes, including methionine metabolism, detoxification, hormone imbalances, and vitamin D function. Intended uses for the test include clarification of a diagnosis suggested by other testing and as an indication for supplements and diet modifications.

Test Description: Know Error DNA Specimen Provenance Assay
The Know Error test (Strand Diagnostics) compares the LTRs of tissue samples with LTRs from a buccal swab of the patient. The intended use of the test is to confirm tissue of origin and avoid specimen provenance errors due to switching of patient samples, mislabeling, or sample contamination.

Celiac Disease
Previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, or idiopathic steatorrhea, celiac disease is an immune-based reaction to gluten (water insoluble proteins in wheat, barley, rye) that primarily affects the small intestine. Celiac disease occurs almost exclusively in patients who carry at least 1 human leukocyte antigen DQ2 or DQ8 allele; the negative predictive value of having neither allele exceeds 98%. Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide (DGP) support a diagnosis of celiac disease, but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.

Test Description: Celiac PLUS
Celiac PLUS (Prometheus Therapeutics & Diagnostics) is a panel of 2 genetic and 5 serologic markers associated with celiac disease. Per the manufacturer, Celiac PLUS is a diagnostic test that also stratifies future risk of celiac disease. Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease; serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-DGP antibodies, IgG anti-DGP, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for disease (eg, with an affected first-degree relative) or with symptoms suggestive of disease.

Irritable Bowel Syndrome
Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the general population in the United States and worldwide. Symptoms include abdominal pain and/or bloating associated with disordered bowel habit (constipation, diarrhea, or both). Pathophysiology is poorly understood but may be related to chronic low-grade mucosal inflammation and disturbances in GI flora. Recommended treatments include dietary restriction and pharmacologic symptom control. As living microorganisms that promote health when administered to a host in therapeutic doses, probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials (RCTs) have found evidence to support efficacy, but results from recent RCTs have been mixed. This discrepancy may be due in part to the differential effects of different probiotic strains and doses.
Test Description: GI Effects Comprehensive Stool Profile
The GI Effects Comprehensive Stool Profile (Genova Diagnostics) is a multianalyte stool assay. The test uses polymerase chain reaction (PCR) to quantify 26 commensal gut bacteria and standard biochemical and culture methods to measure levels of other stool components (eg, lipids, fecal occult blood) and potential pathogens (ova and parasites, opportunistic bacteria, yeast). The test is purported to optimize management of gut health and to differentiate IBS from inflammatory bowel disease (IBD).

Inflammatory Bowel Disease
IBD is an autoimmune condition characterized by inflammation of the bowel wall and has clinical symptoms of abdominal pain, diarrhea, and associated symptoms. Crohn disease (CD) and ulcerative colitis are the 2 main entities under the category of IBD. The diagnosis is typically made by endoscopy or colonoscopy with biopsy and histologic analysis. This requires a semi-invasive procedure; as a result, a blood test to diagnose IBD could avoid the need for the procedures.

Test Description: IBD sgi Diagnostic
IBD sgi Diagnostic (Prometheus Therapeutics & Diagnostics) is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory biomarkers (n=5). A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent with CD, or inconclusive for UC vs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.

Colon Cancer
Early detection of colorectal cancer (CRC) reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy. A simpler screening blood test may have the potential to encourage screening and decrease mortality if associated with increased screening compliance. Serum biomarkers that are shed from colorectal tumors have been identified and include Septin 9 hypermethylated DNA (*SEPT9*). The Septin 9 protein is involved in cell division, migration, and apoptosis and acts as a tumor suppressor; when hypermethylated, expression of *SEPT9* is reduced.

A cofounder of the biotechnology firm GeneNews developed a patented platform technology based on the sentinel principle. The sentinel principle posits that because blood interacts with all bodily tissues, “subtle changes occurring in association with injury or disease, within the cells and tissues of the body, may trigger specific changes in gene expression in blood cells reflective of the initiating stimulus.” In this way, blood cells (specifically, leukocytes) may act as sentinels of disease. In studies that led to the formulation of this principle, investigators compared gene expression (total RNA levels) in blood samples with cataloged genes from 9 different organs (brain, colon, heart, kidney, liver, lung, prostate, spleen, stomach) and estimated that 66% to 82% of genes encoded in the human genome are expressed in human leukocytes.

Test Descriptions: SEPT9 Methylated DNA
ColoVantage (various manufacturers) blood tests for serum *SEPT9* methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration (FDA) approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to ARUP and Quest. ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (eg, DNA preparation, PCR primers, probes). Sensitivity as high as 90%, with 88% specificity and 99.9% negative predictive value (4% positive predictive value) have been reported for ColoVantage. By comparison, reported sensitivity and specificity for Epi proColon were 68% and 80%, respectively. Serum *SEPT9* methylated DNA testing is intended for individuals 50 years of age or older who have an average risk of CRC.

Test Description: ColonSentry
ColonSentry (GeneNews; Innovative Diagnostic Laboratory) is a PCR assay that uses a blood sample to detect expression of 7 genes found to be differentially expressed in CRC patients compared with
controls. Per the company website, these genes are early-warning signs of colon cancer, and test results can indicate the odds of having CRC compared with an average-risk person. An average-risk person is defined as one who is “at least 50 years old, is asymptomatic for CRC, has no personal history of benign colorectal polyps, colorectal adenomas, CRC, or inflammatory bowel disease, and does not have a first-degree relative with CRC.” The test is intended for use in adults who are averse to colonoscopy and/or fecal occult blood testing. “Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules.”

PROGNOSTIC TESTS
Crohn Disease
Recent studies have identified serologic and genetic correlates of aggressive CD that is characterized by fistula formation, fibrostenosis, and the need for surgical intervention. Prometheus has developed a blood test that aims to identify patients with CD who are likely to experience an aggressive disease course.

Test Description: Crohn’s Prognostic
Crohn’s Prognostic (Prometheus Therapeutics & Diagnostics) is a panel of 6 serologic (n=3) and genetic (n=3) biomarkers. Limited information about the test is available on the manufacturer’s website.

Thymomas and Thymic Carcinomas
Thymomas and thymic carcinomas are rare epithelial tumors of the thymus. Most are diagnosed in individuals between 40 and 60 years of age. Thymic epithelial tumors range from histologically benign tumors to microscopically or macroscopically invasive low- or high-grade malignant tumors. However, even tumors that are histologically benign can behave aggressively.

Test Description: DecisionDx-Thymoma
DecisionDx-Thymoma (Castle Biosciences) is a gene expression profile test that measures the activity of 23 genes within the thymic tumor. Its intended use is to distinguish between thymic carcinoma and thymoma and to predict tumor aggressiveness by the likelihood that the tumor will metastasize.

Cutaneous Melanoma
Cutaneous melanoma represents less than 5% of skin malignancies but results in the most skin cancer deaths. The incidence of cutaneous melanoma continues to increase, and it is currently the sixth most common cancer in the United States. Standard treatment options for stage I and II melanoma are excision with or without sentinel lymph node examination. Current risk factors to predict localized tumor aggression include Breslow tumor thickness, tumor ulceration, and mitotic rate of the tumor cells. The likelihood of regional lymph node involvement increases with increasing tumor thickness and negatively impacts the rate of survival significantly.

Test Description: DecisionDx-Melanoma
DecisionDx-Melanoma (Castle Biosciences) is a gene expression profile test with a signature of 31 genes, 28 discriminating genes, and 3 control genes. The test is used to measure the risk of metastasis in patients with stage I and II cutaneous melanoma and classifies tumors into 2 groups of risk of metastasis—low or high (classes 1 and 2, respectively). The test purports to give an independent prediction of tumor metastatic risk, independent of currently used metrics of risk assessment (eg, Breslow thickness, ulceration status, and mitotic rate; American Joint Committee on Cancer stage, sentinel lymph node biopsy status), so that patients with high-risk stage I or II disease can undergo more aggressive surveillance treatment than they would otherwise receive. The test is intended to provide additional prognostic information to current staging methods (American Joint Committee on Cancer stage, sentinel lymph node biopsy).

THERAPEUTIC TESTS
Test Description: ResponseDX: Colon
Response Genetics currently markets 2 colon cancer genetic panels to guide treatment selection, as well
as separate tests for 11 genes associated with colon cancer prognosis and/or treatment response. The Driver Profile panel comprises PCR variant testing in KRAS, BRAF, and mismatch repair genes (microsatellite instability), plus NRAS exon 2 and 3 sequencing. The ResponseDX: Colon test comprises the 4 tests in the Driver Profile plus: EGFR expression; PI3K exon 1, 9, and 20 sequencing; TS expression; ERCC1 expression; UGT1A1 SNV testing (rs8175347, rs4148323); VEGFR2 expression; and MET amplification by fluorescence in situ hybridization.

Non-Hodgkin Lymphoma
Rituximab is a humanized IgG monoclonal antibody against the CD20 antigen, which is commonly expressed on B lymphocytes. It is FDA-approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and nononcologic uses (eg, rheumatoid arthritis). Rituximab has demonstrated better response and survival rates in combination chemotherapy regimens in patients with follicular lymphoma, chronic lymphocytic leukemia, and diffuse large B-cell lymphoma than chemotherapy alone, though not all patients responded. Altered binding to lymphocyte-bound rituximab by cytotoxic effector cells (eg, natural killer cells, macrophages) has been identified as a mechanism of reduced rituximab efficacy. Effector cells with a Val158Phe substitution variant in their surface receptors for IgG molecules (eg, rituximab) have impaired binding affinity, and cellular cytotoxicity is reduced. A genetic test for the Val158Phe variant of the gene that encodes the IgG receptor on effector cells (FCGR3A) has been developed and investigated as a means of predicting response to rituximab.

Test Description: TransPredict Fc gamma 3A
Formerly PGxPredict:Rituximab, TransPredict Fc gamma 3 (Transgenomic) is a PCR assay that uses a blood sample to detect the Val158Phe variant of the FCGR3A gene. For patients who are homozygous for valine, the test reports a high likelihood of response to rituximab; for all other patients (homozygous for phenylalanine or heterozygous), the test reports an average probability of response. The test is intended for patients with follicular, CD20-positive, B-cell non-Hodgkin lymphoma who are being considered for treatment with rituximab.

FUTURE RISK IN ASYMPTOMATIC INDIVIDUALS
Immunologic Disorders
Test Description: ImmunoGenomic Profile
The ImmunoGenomic Profile (Genova Diagnostics) is a buccal swab test that evaluates SNVs in 6 genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1β, IL-4, IL-6, and tumor necrosis factor α. According to the company website, variations in these genes “can affect balance between cell (TH-1) and humoral (TH-2) immunity, trigger potential defects in immune system defense, and stimulate mechanisms underlying chronic, overactive inflammatory responses…. The test uncovers potential genetic susceptibility to: Asthma, Autoimmune Disorders, Certain Cancers, Allergy, Infectious Diseases, Bone Inflammation, Arthritis, Inflammatory Bowel Disease, Heart Disease, Osteopenia, and Helicobacter pylori infection (cause of ulcers).”

Summary
There are numerous commercially available genetic and molecular diagnostic, prognostic, and therapeutic tests for individuals with certain diseases or asymptomatic individuals with a future risk. This evidence review evaluates miscellaneous genetic and molecular diagnostic tests not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is the limited evidence on the clinical validity for the test. As a result, these tests do not have clinical utility, and the evidence is insufficient to determine the effect on health outcomes.

Diagnostic Tests
For individuals with symptoms of various conditions thought to be hereditary or with a known genetic component who receive diagnostic testing with a miscellaneous genetic or molecular test (eg, DNA Methylation Pathway Profile, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic, Know Error), the evidence includes case series, cross-sectional studies, diagnostic accuracy studies, and cohort studies. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, change
in disease status, and morbid events. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating the clinical validity of the test. For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

For individuals who are being screened for colorectal cancer who receive SEPT9 methylated DNA testing (e.g., ColoVantage, Epi proColon, ColonSentry), the evidence includes case-control, cross-sectional, and prospective diagnostic accuracy studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The PRESEPT prospective study estimated the sensitivity and specificity of Epi proColon detection of invasive adenocarcinoma at 48% and 92%, respectively. Other studies were generally low to fair quality. It is unclear whether the test is meant to be used in addition to or in place of existing tests. Based on results from these studies, the clinical validity of SEPT9 methylated DNA screening is limited by low sensitivity of the test given that the sensitivity of the test is lower than imaging screening strategies. Compared with stool-based strategies, the sensitivity is in the same range and the specificity is lower. Optimal intervals for retesting are not known. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Prognostic Tests
For individuals who are diagnosed with various conditions (e.g., Crohn disease, thymomas and thymic carcinomas, celiac disease) who receive prognostic testing with a miscellaneous genetic or molecular test (e.g., Crohn's Prognostic, DecisionDx-Thymoma), there are no published studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

For individuals who are diagnosed stage I or II melanoma who receive prognostic testing with DecisionDx-Melanoma, the evidence includes diagnostic accuracy studies and decision impact studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The 3 clinical validity studies enrolled similar or overlapping patient sets and patients outside of the intended use population (American Joint Committee on Cancer stage I or II). They reported follow-up inadequate to determine disease-free survival in some patients, and offered inadequate details about treatments received. One retrospective study has reported that test results are associated with utilization measures but, without sufficient evidence of clinical validity, it is not known whether the changes in management were appropriate. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Therapeutic Tests
For individuals who are diagnosed with various conditions (e.g., Crohn disease, thymomas and thymic carcinomas, celiac disease) who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., ResponseDX: Colon, TransPredict Fc gamma 3A), the evidence includes case series, cross-sectional studies, diagnostic accuracy studies, and cohort studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating the clinical validity of the test. For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Tests for Future Risk of Disease
For individuals with a family history of various conditions thought to be hereditary or with a known genetic component who receive testing for future risk of disease with a miscellaneous genetic or molecular test
(eg, ImmunoGenomic Profile), the evidence includes diagnostic accuracy studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating the clinical validity of the test. For each test addressed, a literature review is conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

### Policy History

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<th>Date</th>
<th>Action</th>
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<tr>
<td>9/2017</td>
<td>Policy statements updated to organize types of tests with language that corresponds to General Approach to Genetic Testing, #735; all tests remain investigational. 9/1/2017</td>
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<tr>
<td>1/2017</td>
<td>Clarified coding information for the 2017 code changes.</td>
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<tr>
<td>8/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


43. Shirts B, von Roon AC, Tebo AE. The entire predictive value of the prometheus IBD sgi diagnostic product may be due to the three least expensive and most available components. Am J Gastroenterol. Nov 2012;107(11):1760-1761. PMID 23160303


69. Weng WK, Lewy R. Immunoglobulin G Fc receptor polymorphisms do not correlate with response to chemotherapy or clinical course in patients with follicular lymphoma. Leuk Lymphoma. Sep 2009;50(9):14941500. PMID 19672774


76. Zimmermann H, Weiland T, Nourse JP, et al. Fcgamma-receptor IIa polymorphism p.158F has no negative predictive impact on rituximab therapy with and without sequential chemotherapy in


