Select Health

Select Health Medical Policies

Genetic Testing Policies

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Select Health

MEDICAL POLICY

GENE EXPRESSION PROFILING FOR MONITORING ACUTE REJECTION IN CARDIAC TRANSPLANT PATIENTS (ALLOMAP)

Policy # 357

Implementation Date:7/1/07
Review Dates: 6/19/08, 6/11/09, 8/16/11, 8/16/12, 8/15/13, 8/20/15, 8/25/16, 8/17/17, 7/20/18, 6/13/19, 2/21/23, 2/15/24
Revision Dates: 11/10/08, 8/16/10, 8/28/14, 6/17/15, 7/17/15, 8/2/19, 7/1/23, 12/6/23, 1/20/25

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Cardiac transplantation is considered the definitive therapy for end-stage heart disease. Continuing advancements in organ procurement, surgical techniques, and immunosuppressive drugs have reduced mortality rates in the early post-transplant period. A common complication to arise post-transplantation is rejection of the donor heart. This may result in significant morbidity and mortality. The incidence of rejection peaks about one month after transplant and then rapidly declines. Biopsy evidence of rejection usually is present before other signs and symptoms of myocardial compromise, and cardiac rejection is often asymptomatic. Endomyocardial biopsy has been the standard of care for rejection monitoring and drug titration management. However, this is an invasive and imperfect measure of rejection that has risks for significant adverse events.

Less invasive indicators of early rejection (e.g., echocardiography) have been studied, but all have limited sensitivity and specificity compared to endomyocardial biopsy. One test, gene expression profiling of peripheral blood lymphocytes, attempts to quantify the relative levels of messenger RNA (mRNA) for large numbers of genes in specific cells or tissues. The goal is to measure differences in the level of translation (expression) of different genes and utilize patterns of differential gene expression in order to identify early changes in the immune system that correlate with rejection of the transplanted organ.

AlloMap is the only commercially available gene expression profile test currently available for heart transplant patients. The test identifies 11 genes that distinguish transplant rejection from quiescence (i.e., ISHLT grade 0). These genes are *ITGA4* (associated with T-cell infiltration at the site of inflammation); *PDCD1* (limits potential autoreactivity); *PF4* and *G6b* (associated with rejection and expressed by platelets); *MIR*, *WDR40A* (erythrocytes), and *SEMA7A* (granulocytes; expressed by immature lymphocytes and elevated in rejection); *IL1R2*, *ITGAM*, and *FLT3* (expressed in monocytes; level of expression correlates with increasing steroid doses); and *RHOU* (involved in modulation of cytoskeletal organization; undetermined role in rejection). The assay also measures expression levels of an additional nine "housekeeping" genes that serve as reference standards.

Reverse transcription polymerase chain reaction (RT- PCR) is used to measure the relative expression of these 20 genes in peripheral blood mononuclear cells. A proprietary algorithm is applied to the results to generate a score ranging from 0−40 and the corresponding 95% confidence interval. The value of the score is then used to predict the likelihood of rejection. The exact cut-point for low-risk of rejection varies depending on the time since the initial transplant.

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Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic expression profiling for monitoring acute rejection in cardiac transplant patients using the AlloMap when ordered by an Intermountain Health Transplant Provider or Intermountain Health Cardiovascular Provider; or when the following criteria are met:

Criteria for coverage:

Criteria for coverage include meeting the criteria for the IMAGE trial, and after a physical and echocardiogram have been performed.

IMAGE Trial Guidelines:

1. Heart transplant recipients who are ≥ 55 days post-transplant
2. Age > 15 years
3. Stable outpatient being seen for routine monitoring of rejection. Stability is defined as absence of prior or current evidence of either severe cardiac allograft vasculopathy (CAV) or antibody-mediated rejection (AMR) with associated hemodynamic compromise
   - Severe CAV is defined as either
     - 50% left main stenosis;
     - ≥ 50% stenosis in ≥ 2 primary vessels (proximal 1/3 or middle 1/3 of the LAD or LCx, RCA to takeoff of PDA in right-dominant coronary circulations) or
     - Isolated branch stenosis of > 50% in all 3 systems (diagonal branches, obtuse marginal branches, distal 1/3 of LAD or LCx, PDA, PLB, and RCA to takeoff of PDA in non-dominant systems)
   - AMR with associated hemodynamic compromise is defined as AMR (defined according to local criteria) with either:
     - A left ventricular ejection fraction (LVEF) ≤ 30% or at least 25% lower than the baseline value,
     - A cardiac index < 2 l/min/m2, or
     - The use of inotropic agents to support circulation
4. Left ventricular ejection fraction ≥ 45% by Echocardiography, Multiple Gated Acquisition (MUGA) scan, or ventriculography at study entry (baseline/enrollment study).
5. Testing being performed as part of an established post-transplant surveillance protocol*

Exclusion Criteria:

1. Any clinical signs of declining graft function:
   - Symptoms of congestive heart failure (CHF)
   - Signs of decompensated heart failure, including the development of a new S3 gallop
   - Elevated right heart pressures with diminished cardiac index < 2.2 L/min/m^2 that is new compared to a previous measurement within 6 months
   - Decrease in LVEF as measured by echocardiography: ≥ 25% compared to prior measurement within 6 months.

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Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

2. Rejection therapy for biopsy-proven ISHLT Grade 3A or higher during the preceding 2 months
3. Major changes in immunosuppression therapy within previous 30 days (e.g., discontinuation of calcineurin inhibitors, switch from mycophenolate mofetil to sirolimus or vice versa)
4. Patient receiving hematopoietic growth factors (e.g., Neupogen, Epogen) currently or during the previous 30 days
5. Patients receiving ≥ 20 mg/day of prednisone-equivalent corticosteroids
6. Patient enrolled in a trial requiring routine surveillance endomyocardial biopsies
7. Patient received transfusion within preceding 4 weeks
8. Patients with end-stage renal disease requiring some form of renal replacement therapy (hemodialysis or peritoneal dialysis)
9. Pregnancy
10. Age < 15 years

*Current Intermountain protocol based upon the study for which AlloMap gained approval, lists the following biopsy frequency post-transplant.

1. 1st year post-transplant:
    a. Monthly until month 7
    b. Every 6 weeks (until month 10)
    c. Then at 1st year annual
2. 2nd year post-transplant: every 3 months
3. 3rd year post-transplant: every 4 months
4. 4th year post-transplant: every 6 months
5. 5th year: Once

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Three studies have been published that attempt to use gene expression profiling of blood samples to detect rejection in cardiac transplant patients. Schoels et al. in 2004 collected 58 blood samples from 44 patients. The blood samples included 32 with < ISHLT grade 2 rejection and 26 with ≥ ISHLT grade 2 rejections. The authors used rt-PCR to amplify 39 candidate genes selected for analysis based on their suspected association with transplant rejection. Discriminate analysis identified 5 gene products that discriminated between grade ≥ 2 rejection and grade < 2 rejection. The optimal cutoff led to a sensitivity of 82% and specificity of 84%; no cross-validation was reported.

Horowitz et al. biopsied 409 endomyocardial samples from 189 transplant patients, of which 81% showed no evidence of allograft rejection (ISHLT grades 0, 1A, or 1B) and 6% showed clinically significant rejection (≥ grade 3A). Of these, blood samples from 7 patients with ≥ grade 3A rejection (rejection) and 7

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Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

patients with grade 0 or 1A rejection (controls). Using an Affymetrix microarray with 22,215 transcripts, the investigators initially identified 91 candidate gene products that differentiated between rejection and controls. Of these, 40 transcripts representing 30 unique gene products maximally differentiated between rejection and non-rejection. Validation of the 91 candidate gene markers involved 7 additional rejection patients who underwent augmented immunosuppressive resulting in resolution of rejection to ≤ grade 2. The change in these gene markers before and after therapy was consistent with a response to immunosuppressive therapy.

Deng et al. reported on the results of the CARGO study, which formed the basis of the AlloMap test. This study involved several phases that identified and validated candidate genes that discriminate between rejection and quiescence. The gene discovery phase used a custom microarray of 7,370 gene sequences to identify 97 candidate genes in 285 samples, 98 cardiac transplant patients. The investigators used rt-PCR in 145 samples (36 rejections; 109 quiescent samples) to further refine that number to 68 genes that distinguished between rejection and quiescent samples (ISHLT grade ≥ 3A vs. grade 0). A discriminate function equation yielded a group of 11 genes (5 from the gene discovery phase and 6 from the literature) that best distinguished between rejection and quiescence.

The primary validation involved 63 samples (63 patients not included in the first phases of the study). The secondary validation included these 63 samples (31 grade ≥ 3A; 32 grade 0) and an additional 184 samples, 30 of which were also used in the gene discovery phase. Using a prospectively defined score ≥ 20 as the rejection threshold, the test had a sensitivity of 84% (95% CI 66%−94%) and a specificity of 38% (95% CI 22%−56%). The secondary validation study yielded similar results (sensitivity 76%, specificity 41%). The authors also noted that time since transplant was highly correlated with AlloMap scores and suggested a cutoff of 28 at ≥ 6 months and 30 for ≥ 1-year post-transplant.

The authors also conducted a prevalence population study to determine the predictive value of test results in a population that more closely represented the distribution of patients likely to be encountered in clinical practice (the initial study phases over-sampled for rejection). This validation sample included samples from 166 patients ≥ 1-year post-transplant. These included 160 (56.9%) grade 0 samples, 68 (24.1%) grade 1A, 23 (8.1%) grade 1B, 21 (7.4%) grade 2, and 9 (3.2%) grade ≥ 3A, a distribution representative of the entire CARGO database. At a threshold of 30, the positive predictive value was 6.8% while the negative predictive value was 99.6%.

Evans et al. assessed economic implications of using the AlloMap test for monitoring cardiac transplant patients relative to endomyocardial biopsy. Their analysis examined the outpatient costs of biopsy and did not include costs for hospitalization and right heart catheterization. They estimated average reimbursement for biopsy to range from $3,581 and $4,140. Their analysis further assumed a roughly 60% reduction in the number of routine biopsies performed during the first-year post-transplant, replaced by AlloMap testing; 20% of AlloMap tests would be followed by a biopsy. In years 2−5 post-transplant, the number of routine biopsies per year is reduced by 80% with approximately 20% follow-up biopsies. The price of AlloMap testing was estimated at $2950. Using these parameters, Evans et al. assumed a per patient savings between $4,193 and $6,511 over 5 years. They estimated an annual savings to U.S. health insurers of approximately $12 million.

The last study by Yamani et al. evaluated the validity of AlloMap test results in patients with transplant vasculopathy. The authors found that patients with vasculopathy had higher AlloMap scores than control patients. The authors conclude that prospective studies are needed to determine the predictive capacity of the AlloMap test in identifying patients at risk for transplant vasculopathy without concomitant transplant rejection.

The primary weakness in this literature is a lack of prospective research to examine the predictive utility of the AlloMap test in clinical populations. The primary study of this test (Deng et al.) used multiple overlapping patient samples and suggests the test has poor positive predictive value in clinical populations. The negative predictive value is high (99.6%), though, it should be noted that if the test had classified all the samples in this study as negative, the negative predictive value would be 96.8%. In other words, because of the low prevalence of biopsy-proven rejection, a negative AlloMap test contributes only a small amount of negative predictive value to the evaluation.

A 2006 evaluation by the California Technology Assessment forum further noted that none of the 11 genes used for the AlloMap test match the genes identified by Horowitz et al. or Schoels et al., which raises concerns about the ability to generalize this particular gene set to other cardiac transplant

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populations. Moreover, the time-dependent cutoffs proposed by the authors also require additional validation. Finally, the Yamani et al. study highlights the complexities of interpreting AlloMap findings in light of multiple clinical factors, the effect of which on AlloMap scores have not been adequately reported in the literature. At a minimum, a validation study in an independent population would increase confidence in the predictive utility of AlloMap test results. More informative, would be a prospective randomized controlled trial in which the utility of AlloMap and cardiac biopsy could be examined.

Due to the FDA approval of the AlloMap test a re-review of the literature was undertaken in October 2008. This review identified an ongoing prospective, randomized clinical trial (also multicenter, non-blinded), the Invasive Monitoring Attenuation Through Gene Expression (IMAGE) trial: "… designed to test the hypothesis that a primarily non-invasive rejection surveillance strategy utilizing GEP testing is not inferior to an invasive EMB-based strategy with respect to cardiac allograft dysfunction, rejection with hemodynamic compromise (HDC) and all-cause mortality."

All previous studies are retrospective, case-control studies. In this regard: "… the limitations of a case–control study design restricts the clinical and causal conclusions one can make." Mehra also states that: "… we call for validation [of AlloMap] within the context of randomized intervention trials that seek to study conventional surveillance vs. gene expression profiling–based patient management in the early time-period after transplantation. Additionally, Deng et al. state that: "… additional clinical experience is needed to establish the role of molecular testing for clinical event prediction and immunosuppression management."

Also, there have been additional publications reflecting the continued questions and concerns about the value and use of endomyocardial biopsies. Hamour et al. for example, suggests that the "frequency of such biopsies should be reevaluated in light of their low yield with current immunosuppression." These conclusions are supported by multiple other studies. The recent trend away from protocol-based EMBs, independent of the introduction of the AlloMap test, reflects the recognition that the benefits of the procedure have moved toward parity with its risks, especially after the first year.

A technology assessment performed in July 2010 identified a new article by Pham et al. presenting their data from the IMAGE trial. This was a prospective, randomized non-blinded study utilizing AlloMap in patients with a recent cardiac transplantation to assess rejection post-transplant (> 6 months). This study compares outcomes between the standard of care approach, endomyocardial biopsy and gene expression testing. Primary outcomes were defined as: 1) rejection with hemodynamic compromise; 2) graft dysfunction due to other causes; 3) death; or 4) retransplantation.

Statistical analysis required a 95% confidence interval to satisfy a non-inferiority position for gene-expression testing. Key aspects of the study showed primary outcomes were fewer in the genetic expression group, 14.5% vs. 15.3%, biopsy frequency was 0.5 vs. 3.0 per patient year in favor of the gene expression group and death from any cause was more frequent in the gene expression group, 6.3% vs. 5.5%. The authors concluded that gene expression testing decreases the complications and frequency of endomyocardial biopsy without jeopardizing risk of rejection or all-cause mortality. Their assumptions were tempered by numerous design concerns of the protocol and results of the study.

The study was biased; physicians could determine which patients could be enrolled. Only 20% of the initial candidates eventually became randomized. This raises the concern that the patient selection favored patients with less risk of rejection. This would favor the gene expression arm of the study due to AlloMap's high negative predictive value. The study also included patients with inherent low risk. The criteria for "low risk" were not fully described in the study, thus, making it difficult for physicians to determine how this test would be utilized in clinical situations.

Patients with antibody mediated rejection were excluded from the study, yet an estimated 15%−40% of transplant recipients will experience a form of antibody mediated rejection. How this influenced the outcome of the study is unclear.

The study only included patients 6 months post-transplant. The literature demonstrates the dramatic increase risk of cellular rejection in the first 6 months and the dramatic decrease in rejection after 24 months post-transplant. Endomyocardial biopsy which may detect rejection prior to physical or echocardiographic changes of rejection would still be required early post-transplant. Discouraging, is the result that of all the patients in the gene expression group who underwent an endomyocardial biopsy, most had a biopsy done due to physical findings of echo findings (28/34) and not due to the genetic

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Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

expression score. The use of AlloMap during the first 6 months would not help determine early rejection if used alone in the clinical assessment.

Rejection rates varied among the groups. Eighty-one discrete rejection episodes occurred. Fifty-nine percent of the rejections in the gene expression group were detected by overt heart failure on clinical exam or by echo. Only 18% of rejection episodes were detected by gene expression alone. This compared with the rate of 47% in the endomyocardial biopsy group who were asymptomatic. This observation illustrates not necessarily the non-inferior status for gene expression testing but raises the concern that studies are needed to address the current protocol for monitoring post-transplant patients. Treating only those with clinical or echocardiographic findings of worsening cardiac function should be treated. This raises the issue of overly aggressive treatment of rejection since those in the gene expression group undoubtedly had silent rejection but were not treated and yet did well without an increase in rejection.

In an editorial by Jarcho, he states: “This observation suggests that, even if rejection is not identified until graft dysfunction is present, the clinical outcomes may not be substantially worse than when rejection is detected early. Perhaps it is time to perform a randomized trial that compares a strategy for continuing endomyocardial biopsies indefinitely with that of discontinuing routine endomyocardial biopsies at some specified interval.”

Finally, the wide confidence interval allows for extreme statistical variability. The trials reduced power was reflected in a relatively wide confidence interval that does not exclude the possibility of a 33% decrease in primary event rates or a 68% increase among patients in the gene-profiling group. This troubling analysis raises serious questions about the reliability of AlloMap despite its 99.2% negative predictive value seen in the CARGO trial. The poor sensitivity of AlloMap is reflected in that 54% of patients who tested above the 34-value (positive test) had no evidence of rejection.

Several positive aspects of the IMAGE trial were the improved quality of life perceived by the patients enrolled in the gene expression group and the associated decrease in complications and costs due to the reduction in endomyocardial biopsies associated with the use of gene expression testing.

A review article by Lipshultz et al, published in 2014 covers the use of AlloMap in acute rejection monitoring. It stated that current practice entails use of the test in patients 15 years of age or older. This is also the age of use referred to in the International Society of Heart and Lung Transplantation (ISHLT) Guidelines from 2010 (Rogers et al., 2010) for use of Allomap. AlloMap scores in patients less than age 15 years remain to be validated.

A review of the literature in mid-2016 found one publication presenting the results of the CARGO II study on gene expression profiling (GEP) in cardiac rejection surveillance (Crespo-Leiro et al., 2016) to further clinically validate GEP. The results based on 938 biopsies continue to show high negative predictive value and low positive predictive value (due to the rarity of rejection) confirming previous studies.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

0018M	Transplantation medicine (allograft rejection, renal), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma
0087U	Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score
0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA
81479	Unlisted molecular pathology procedure

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Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

81560 Transplantation medicine, measurement of donor and third party-induced CD154+T-cytotoxic memory cells

81595 Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score

HCPCS CODES

No specific codes identified

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
12/6/23	For Commercial Plan Policy, removed previous Exclusion #1: "Patients < 7 calendar months or > 5 years after heart transplantation."
1/20/25	For Commercial Plan Policy, added the following language to coverage criteria as an option for qualifying for this testing: "Select Health covers genetic expression profiling for monitoring acute rejection in cardiac transplant patients using the AlloMap ***when ordered by an Intermountain Health Transplant Provider or Intermountain Health Cardiovascular Provider;*** or when the following criteria are met …"

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Select Health

MEDICAL POLICY

GENE EXPRESSION PROFILING: CUTANEOUS MALIGNANCIES

Policy # 667

Implementation Date: 7/1/23
Review Dates: 7/11/24, 8/6/24
Revision Dates: 9/1/23, 7/22/24, 9/3/24

Related Medical Policies:

#680: Gene Expression Profiling: Uveal Melanomas

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cutaneous malignancies (skin cancers) are more common than all other cancers combined, and, collectively, their incidence is rising faster than that of any other cancer.

Cutaneous melanoma (CM) is a malignant tumor formed from pigment-producing cells called melanocytes. This type of skin cancer has highest mortality rate and has demonstrated a rising incidence over the last several decades. Data provided by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimate that there were 97,610 new melanoma cases in the United States in 2023, a nearly three-fold increase in the rate of new cases per 100,000 people per year since 1975. It is now the fifth most common newly diagnosed cancer in the United States, representing 5% of all new cancer cases.

Cutaneous squamous cell carcinoma (CSCC), also known as squamous cell carcinoma (SCC), is a type of skin cancer that starts in the epidermis, or outer layer of the skin. It is the second most common form of skin cancer, after basal cell carcinoma. While the prognosis of cutaneous squamous cell carcinoma (SCC) is generally favorable, an estimated 6% of the greater than 1,000,000 cases diagnosed annually develop regional or distant metastasis, with approximately 2% dying from this disease.
Gene expression profile (GEP) tests aim to provide more accurate prognostication based on an individual patient's own tumor tissue. Several GEP-based tests are currently available and are used in some situations for the clinical management and prognostication of CM and SCC in the absence of high-quality prospective clinical trials. In addition to identifying targets for treatment, gene expression profiling (GEP) also allows for the identification of groups of genes that when expressed together as a "signature" can serve as a biomarker for the prognosis of certain cancers, including predicting recurrence or metastatic risk.

GEP brings us closer to understanding tumors on an individual basis, and to tailoring treatment and surveillance to a specific tumor rather than using generalizations. As such, there are innumerable efforts in this arena to better understand and optimize the use of GEP in clinical decision making. It is important to recognize that currently, neither the American Academy of Dermatology (AAD) nor the National Comprehensive Cancer Network (NCCN) endorse GEP testing. Randomized clinical trials that study patient outcomes based on the results of GEP tests are not yet available, and it remains unclear how these tests should best be interpreted and utilized in clinical practice.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers DecisionDx-Melanoma for either of the following indications (3 or 4):

3. Patients with T1a-HR*, T1b, T2a or T2b melanoma**/*** to guide sentinel lymph node biopsy (SLNB) decisions; **OR**

4. Patients with clinical or pathological Stage I or II melanoma to inform subsequent follow-up imaging, screening frequency, referrals and/or additional management protocols.

Select Health does not cover the myPath Melanoma test or non-invasive gene expression tests (e.g., DermTech Pigmented Lesion Assay) in the evaluation of cutaneous melanomas, as there is a lack of evidence available in peer-reviewed literature which would support either sufficient sensitivity or specificity that would be necessary in defining a valid clinical role. This meets the plan's definition of experimental/investigational.

Select Health does not cover the DecisionDx-SCC in the evaluation of squamous cell carcinoma, as there is a lack of evidence available in peer-reviewed literature which would support either sufficient sensitivity or specificity that would be necessary in defining a valid clinical role. This meets the plan's definition of experimental/investigational.

*HR (High Risk) - includes melanomas with an elevated mitotic rate, young patient age, regression, a transected base (where the true depth of the melanoma is not known), limited sampling of a larger lesion.

**Table 1 – UpToDate, AJCC 8th edition melanoma TNM definitions

Primary tumor (T)		
T category	**Thickness**	**Ulceration status**
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration

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	0.8 to 1 mm	With or without ulceration
T2	>1 to 2 mm	Unknown or unspecified
T2a	>1 to 2 mm	Without ulceration
T2b	>1 to 2 mm	With ulceration
T3	>2 to 4 mm	Unknown or unspecified
T3a	>2 to 4 mm	Without ulceration
T3b	>2 to 4 mm	With ulceration
T4	>4 mm	Unknown or unspecified
T4a	>4 mm	Without ulceration
T4b	>4 mm	With ulceration

***Table 2 – UpToDate, AJCC 8th edition melanoma TNM prognostic stage groups

When T is...	And N is...	And M is...	Then the clinical stage group is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

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SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Billing/Coding Information

CPT CODES

0314U Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)

81479 Unlisted molecular pathology procedure

81529 Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis; Decision Dx

81599 Unlisted multianalyte assay with algorithmic analysis

84999 Unlisted chemistry procedure

Not covered for the indications listed above

0315U Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (i.e., Class 1, Class 2A, Class 2B)

0089U Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)

0090U Oncology (cutaneous melanoma) mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a categorical result (i.e., benign, indeterminate, or malignant)

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Revision History

Revision Date	Summary of Changes
9/1/23	For Commercial Plan Policy, added the DermTech Pigmented Lesion Assay to list of excluded tests.
7/22/24	For Commercial Plan Policy, added coverage criteria for the Decision DX-Melanoma test.
9/3/24	Modified title of policy to include broader term of "Cutaneous Malignancies" whereas previously was just "Cutaneous Melanomas" – and added the DecisionDx-SCC in the evaluation of squamous cell carcinoma as an excluded test.

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Gene Expression Profiling: Cutaneous Malignancies, **continued**

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Select Health

MEDICAL POLICY

GENE EXPRESSION PROFILING: UVEAL MELANOMAS

Policy # 680

Implementation Date: 3/8/24
Review Dates:
Revision Dates:

Related Medical Policies:
#667: Gene Expression Profiling: Cutaneous Melanomas

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Description

Uveal melanoma is a rare malignancy that arises from melanocytes within the uveal tract of the eye, which includes the iris, ciliary body, and choroid. Uveal melanoma comprises approximately 85 percent of all ocular melanomas, with the remainder arising mostly from the conjunctiva (5 percent) or other sites (10 percent).

The molecular pathogenesis of uveal melanoma is distinct from that of cutaneous melanoma and other melanoma subtypes, including conjunctival melanoma. Uveal melanomas usually harbor specific initiating mutations in GNAQ, GNA11, or other members of the G protein alpha subunit signaling pathway, as well as secondary driver mutations with prognostic significance in genes such as BAP1, SF3B1, and EIF1AX.

Patients with metastatic uveal melanoma should have their tumors assessed using next generation sequencing (NGS) or gene expression profiling. While molecular alterations that are targetable for treatment are limited in uveal melanoma, some alterations may offer insights into prognosis as well as clinical trial options.

COMMERCIAL PLAN POLICY/CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health considers gene expression profiling for patients with a diagnosis of primary, localized uveal melanoma to be medically necessary; one test per diagnosis.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

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please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

Covered when the above criteria are met

81552 Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RTPCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis

Key References

1. Carvajal, R. D., & Harbour, J. W. Metastatic uveal melanoma. *UpToDate*. Last updated: Nov 03, 2023.

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Select Health

MEDICAL POLICY

GENE EXPRESSION TESTING FOR INDETERMINATE THYROID NODULE BIOPSY

Policy # 538

Implementation Date: 8/13/13

Review Dates: 10/15/15, 10/20/16, 12/19/18, 10/15/20, 11/18/21, 9/12/22, 3/14/23, 6/12/24

Revision Dates: 10/13/14, 1/30/17, 1/25/18, 2/28/18, 8/7/18, 1/29/21, 10/24/22, 7/1/23, 7/15/24

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Description

A thyroid nodule is an abnormal structure that is anatomically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be visible or palpable when they are big enough or superficially located; however, most nodules are found incidentally on an imaging study performed for a different purpose. Nodules may be single or multiple and may occur with or without symptoms of thyroid hormone excess or deficiency. Most thyroid nodules are benign, but they may be malignant in 5% to 15% of cases. The primary objective of the evaluation of a thyroid nodule is to determine whether the nodule is benign or malignant; the secondary objective is to determine whether the nodule is associated with thyroid dysfunction.

The prevalence of thyroid nodules varies depending on the population studied and is estimated at 2% to 6% with palpation, 19% to 35% with ultrasonography and 8% to 65% at autopsy. Nodules are found up to six times more often in women, based on clinical examination, with smaller differences when imaging is used. The rates of malignancy in nodules are higher in men.

Ruling out malignancy in thyroid nodules historically depended on thyroid resection and histopathological evaluation until fine needle aspiration (FNA). Thyroid FNA biopsy identified most thyroid nodules as benign, obviating the need for surgery in over half of the patients. However, 15%−30% of thyroid FNAs yields an indeterminate cytological interpretation that leads to surgical biopsy, even though most of these biopsied nodules prove to be benign. These indeterminate nodules harbor an approximate 24% risk of malignancy; too high to ignore but driving surgery where most nodules are benign. FNA is the preferred technique for obtaining thyroid follicular cells from thyroid nodules in the office setting. Cytopathologic examination of these cells provides the best information available, short of surgical excision, to assess whether a nodule is benign or malignant.

Several genetic testing panels, also known as molecular markers, have been developed to improve diagnosis of thyroid FNA. These include the Afirma Gene Sequencing Classifier (GSC) test (Veracyte, Inc., South San Francisco, CA) and the ThyroSeq Gene Classifier (GC) test (Sonic Healthcare, USA), which tests have been developed and can be run on the FNA sample to predict which cytologically indeterminate thyroid nodules are benign and to potentially avoid surgery on these nodules. These tests assess PAX8-PPARγ translocation, PPARγ-$CREB_3L_2$ fusions, RAS mutations, $LGALS_3$ expression, BRAF mutations, RET-PTC rearrangements, $PCSK_2$ $CCDN_2$ and PLAB expression and TFF_3 expression among other abnormalities have all been associated with thyroid cancer with varying degrees of evidence; in recent years the positive predictive value (PPV) and specificity for these tests has increased substantially.

The Afirma Thyroid FNA Analysis combines specialized cytopathology (if requested) and the novel Afirma GSC Physicians submit to Veracyte thyroid nodule FNA samples collected in a single patient visit. Alternatively, an FNA sample is submitted for GSC alone only after a local cytopathologist has made a diagnosis of a Bethesda 3 or 4 nodule. Then, a thyroid cytopathology specialist at Thyroid Cytopathology

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Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

Partners (TCP), an independent partner of Veracyte, performs cytopathology assessment of a thyroid nodule FNA sample under the microscope. If the cytopathology diagnosis is benign or malignant, the analysis is complete. Only when TCP's cytopathology diagnosis is indeterminate (a recent study showed TCP's indeterminate rate to be 16%) is the proprietary Afirma GSC performed. ThyroSeq GC is also based on next-generation sequencing of DNA and RNA. However, it is expanded to analyze 112 genes, providing information on > 12,000 mutation hotspots and > 120 gene fusion types. The test detects 4 classes of genetic alterations: mutations (SNVs, indels); gene fusions; gene expression alterations; and copy number variations (CNVs). The test utilizes a proprietary genomic classifier (GC) based on the algorithmic analysis of all detected genetic alterations to report the test result as positive or negative.

ThyraMIR and ThyGenX were developed in-house by Interpace Diagnostics, Inc. and are performed in a laboratory regulated by and certified under the Clinical Laboratory Improvement Amendments. ThyraMIR is a PCR-based micro-RNA (miRNA) expression classifier which evaluates the expression of 10 miRNA genes. ThyGenX performs targeted next-generation sequencing (NGS) analysis to identify over 100 genetic alterations within 5 thyroid cancer-relevant genes. The test combination has been designed to both rule out malignancy as well as confirm it if present.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic testing for indeterminate thyroid nodule biopsy using the Afirma GSC test, ThyroSeq GC, or ThyGeNEXT/ThyraMIR, when criteria are met:

A. One fine needle aspiration (FNA) of the thyroid nodule interpreted as meeting one of the Bethesda guidelines (either III or IV) listed below*

Bethesda Guidelines:
I. Nondiagnostic
II. Benign – This includes macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto's thyroiditis
III. Follicular lesion or atypia of undetermined significance (FLUS or AUS) – This includes lesions with atypical cells, or mixed macro- and microfollicular nodules
IV. Follicular neoplasm – This includes microfollicular nodules, including Hürthle cell lesions
V. Suspicious for malignancy
VI. Malignant

Select Health does NOT cover genetic testing using Afirma XA as current evidence is inadequate to reach conclusions on the clinical and statistical validity of these tests; this test meets the plan's definition of experimental/investigational.

Select Health does NOT cover other genetic testing for indeterminate thyroid biopsies/fine needle aspirates as current evidence is inadequate to reach conclusions on the clinical and statistical validity of these tests; these tests meet the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

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please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Thyroid cancer is most found on routine physical examination as a palpable thyroid nodule. A fine-needle aspiration (FNA) biopsy is usually performed to rule out malignancy. In some cases, the nodules are not clearly benign or malignant based on FNA results alone. Those patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though, most of these nodules turn out to be benign. The 2013 guidelines from the National Comprehensive Cancer Network (NCCN) state that: "Molecular diagnostics ... using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate." Several tests have been developed to reduce the incidence of nondiagnostic biopsy results to better guide surgical decision making. The bulk of the literature focuses on the Veracyte, Afirma test. The literature on the other genetic tests used in the evaluation of indeterminate thyroid biopsies is inadequate to draw conclusions regarding the clinical validity and clinical utility of these tests.

Afirma: No approval by the FDA is required for the Afirma analysis, as it was developed in-house by Veracyte, Inc. All tests are performed by Veracyte in their laboratory which is certified under the Clinical Laboratory Improvement Amendments.

A single study has examined the analytical validity of the Afirma analysis. Chudova and colleagues (2010) reported on the development process and performance validation of the GEC. Microarray data was generated from 178 thyroid tissue specimens representing the 8 most common types of benign and malignant lesions. Messenger RNA transcripts were used to develop a molecular classifier. After testing of the final test set, the sensitivity was determined to be 100%, and the specificity at 73.3%, to yield a negative predictive value (NPV) of 96%.

Clinical validity of the GEC was evaluated by Alexander et al. (2012) in a multicenter study of independently and prospectively collected thyroid FNA specimens. Of 3,789 samples, 265 were classified as indeterminate, had an adequate specimen for analysis, and had results of a histopathological examination, and were included in the analysis. 142 genes were used in the main GEC, which would classify the FNA samples as benign or suspicious. Of the 265 indeterminate specimens, 85 were classified as malignant after evaluation of thyroid tissue. Of these 85 specimens, 78 were correctly classified as suspicious by the Afirma® analysis for a sensitivity of 92%. There were therefore 7 incorrectly classified malignancies. Of the 180 nonmalignant samples, 93 were correctly classified as benign by the GEC for a specificity of 52%. For the entire set of test samples, the positive predictive value (PPV) and NPV was reported at 47% and 93%, respectively.

A single study by Duick et al., in 2012 has documented the impact of the Afirma FNA analysis on the management of patients with indeterminate thyroid nodules. In a retrospective, multicenter study, the researchers evaluated data from endocrinology practices that ordered the Afirma analysis for which the result was benign for at least three patients. A total of 51 endocrinologists from 21 centers reported data on a total of 368 patients. Physicians reported on their management decisions for each patient. According to the survey, surgery was performed in 28 patients with a benign GEC result; the reasons most often given for surgery was nodule size, a nodule causing symptoms of pressure, and a rapidly growing nodule. Hemithyroidectomy was performed in 19 and total thyroidectomy was recommended in 8. The percentage of patients who were operated on (7.4%) represented a significant decrease from the previously reported rate of diagnostic surgery (74%).

ThyraMIR and ThyGenX: The tests were developed in-house by Interpace Diagnostics, Inc. and are performed in a laboratory regulated by and certified under the Clinical Laboratory Improvement Amendments. No approval by the FDA is required.

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Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

In terms of analytic validity, the methodologies used in these tests are reliable, well-known, and reproducible. ThyraMIR is a PCR-based micro-RNA (miRNA) expression classifier which evaluates the expression of 10 miRNA genes. ThyGenX performs targeted next-generation sequencing (NGS) analysis to identify over 100 genetic alterations within 5 thyroid cancer-relevant genes. The test combination has been designed to both rule out malignancy as well as confirm it, if present.

Clinical validity has been studied prospectively using a high number of samples in multiple settings. In a recent study by Labourier et al. in 2015, 638 FNA and surgical specimens were tested for 17 validated gene alterations. The molecular results were compared to surgical histopathology to determine the diagnostic accuracy. miRNA testing correctly identified 64% of malignant cases and 98% of benign cases, Negative predictive value was reported at 94%. The authors reported that the rate of avoidable diagnostic surgeries was reduced by 69%. In another study by Beaudenon et al., 2014, in a prospective, multicenter, double-blind study, 769 FNAs were evaluated. Based on the high rate of cancer detection when present, the authors concluded that the use of molecular testing decreases the rate of two-stage thyroidectomy surgeries.

Clinical utility specific to this testing has not been established and relies on the general acceptance of molecular genomic testing in avoiding unnecessary surgeries and reducing the need for two-stage surgeries.

ThyroSeq: The ThyroSeq test was developed by researchers at the University of Pittsburgh Medical Center. The available evidence for this test is not as decisive as that for the other commercially available tests, but the methodology used is established, and known to be reproducible. There is adequate validation that ThyroSeq can accurately identify point mutations in the genes and fusions in an FNA sample, facilitating treatment decisions in patients with indeterminate thyroid FNA biopsies. The latest version (ThyroSeq GC) offers detection of more than 1,000 cancer “hotspots” (single nucleotide polymorphisms, or SNPs) on 14 thyroid cancer-related genes and 42 fusion genes known to occur in thyroid cancer. In a validation study of 143 consecutive FNA samples with indeterminate diagnosis of follicular neoplasm or suspicious for follicular neoplasm, the test resulted in 104 benign nodules and 39 malignant nodules, which correlated with surgical pathology results for a 90% sensitivity, 83% positive predictive value, and negative predictive value of 96%.

Billing/Coding Information

CPT CODES

0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)
0362U	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB,

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	PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81479	Unlisted molecular pathology procedure
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

HCPCS CODES

No specific codes identified

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Select Health

MEDICAL POLICY

GENE EXPRESSION TESTING FOR INDETERMINATE THYROID NODULE BIOPSY

Policy # 538

Implementation Date: 8/13/13

Review Dates: 10/15/15, 10/20/16, 12/19/18, 10/15/20, 11/18/21, 9/12/22, 3/14/23, 6/12/24

Revision Dates: 10/13/14, 1/30/17, 1/25/18, 2/28/18, 8/7/18, 1/29/21, 10/24/22, 7/1/23, 7/15/24

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

A thyroid nodule is an abnormal structure that is anatomically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be visible or palpable when they are big enough or superficially located; however, most nodules are found incidentally on an imaging study performed for a different purpose. Nodules may be single or multiple and may occur with or without symptoms of thyroid hormone excess or deficiency. Most thyroid nodules are benign, but they may be malignant in 5% to 15% of cases. The primary objective of the evaluation of a thyroid nodule is to determine whether the nodule is benign or malignant; the secondary objective is to determine whether the nodule is associated with thyroid dysfunction.

The prevalence of thyroid nodules varies depending on the population studied and is estimated at 2% to 6% with palpation, 19% to 35% with ultrasonography and 8% to 65% at autopsy. Nodules are found up to six times more often in women, based on clinical examination, with smaller differences when imaging is used. The rates of malignancy in nodules are higher in men.

Ruling out malignancy in thyroid nodules historically depended on thyroid resection and histopathological evaluation until fine needle aspiration (FNA). Thyroid FNA biopsy identified most thyroid nodules as benign, obviating the need for surgery in over half of the patients. However, 15%−30% of thyroid FNAs yields an indeterminate cytological interpretation that leads to surgical biopsy, even though most of these biopsied nodules prove to be benign. These indeterminate nodules harbor an approximate 24% risk of malignancy; too high to ignore but driving surgery where most nodules are benign. FNA is the preferred technique for obtaining thyroid follicular cells from thyroid nodules in the office setting. Cytopathologic examination of these cells provides the best information available, short of surgical excision, to assess whether a nodule is benign or malignant.

Several genetic testing panels, also known as molecular markers, have been developed to improve diagnosis of thyroid FNA. These include the Afirma Gene Sequencing Classifier (GSC) test (Veracyte, Inc., South San Francisco, CA) and the ThyroSeq Gene Classifier (GC) test (Sonic Healthcare, USA), which tests have been developed and can be run on the FNA sample to predict which cytologically indeterminate thyroid nodules are benign and to potentially avoid surgery on these nodules. These tests assess PAX8-PPARγ translocation, PPARγ-$CREB_3L_2$ fusions, RAS mutations, $LGALS_3$ expression, BRAF mutations, RET-PTC rearrangements, $PCSK_2$ $CCDN_2$ and PLAB expression and TFF_3 expression among other abnormalities have all been associated with thyroid cancer with varying degrees of evidence; in recent years the positive predictive value (PPV) and specificity for these tests has increased substantially.

The Afirma Thyroid FNA Analysis combines specialized cytopathology (if requested) and the novel Afirma GSC Physicians submit to Veracyte thyroid nodule FNA samples collected in a single patient visit. Alternatively, an FNA sample is submitted for GSC alone only after a local cytopathologist has made a diagnosis of a Bethesda 3 or 4 nodule. Then, a thyroid cytopathology specialist at Thyroid Cytopathology

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Select Health

MEDICAL POLICY

GENE THERAPY, TESTING, AND COUNSELING

Policy # 123

Implementation Date: 7/98

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Revision Dates: 3/8/04, 9/14/06, 6/25/07, 12/17/09, 10/21/10, 10/12/11, 6/7/17, 6/5/18, 12/5/18, 6/26/23, 8/18/23, 10/6/23, 11/27/23, 1/10/24, 5/24/24, 9/4/24, 12/12/24

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Gene Therapy

Gene therapy or gene-based therapies are any treatments which modifies a person's gene(s) to treat or cure disease. This includes technology such as plasmid DNA, viral vectors, bacterial vectors, human gene editing technology, and patient-derived cellular gene therapy products.

Genetic Testing

Genetic testing is the analysis, for clinical purposes, of human genetic material (i.e., DNA, RNA, and chromosomes), proteins, and metabolites to detect abnormalities related to an inheritable disorder or trait. There are seven categories of germline genetic testing: diagnostic, predictive/pre-symptomatic, carrier testing, pharmacogenetics, prenatal testing, newborn screening, preimplantation testing. Testing may also be done on somatic tissue to determine disease prognosis or treatment.

Genetic Counseling

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing.

and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

I. Select Health covers gene therapy (gene-based therapy) when the P&T committee AND the Chief Medical Officer (CMO) determine that the proposed gene therapy will affect clinical outcome.

II. Select Health covers genetic testing as follows when any of the following are met (A or B or C or D):

A. **Genetic Testing for Inherited Disease:** Genetic testing to establish a diagnosis or susceptibility for an inherited condition may be **medically necessary** when all the following criteria are met:

1. Member exhibits clinical features or signs/symptoms of an inherited condition or is at significant risk of an inherited condition based on family history; and
2. Diagnostic results from physical examination, pedigree analysis, and conventional testing are inconclusive and a definitive diagnosis is uncertain; and
3. The clinical record must document:
    i. How test results will guide decisions regarding disease treatment, prevention, or management, such as averting treatment for other possible diagnosis; and
    ii. That the test being performed is the most appropriate according to currently accepted literature or guidelines.

OR

B. **Genetic Testing Not Related to Inherited Conditions:** Genetic testing for indications *other than* determining risk or establishing a diagnosis for a genetically inherited disease (e.g., genetic expression analysis in breast cancer) may be considered **medically necessary** when all the following criteria are met:

1. An association of the marker with the natural history of the disease has been established; and
2. The clinical records must document:
    i. How test results will guide decisions regarding disease treatment or management; and
    ii. That the test being performed is the most appropriate according to currently accepted literature or guidelines.

OR

C. **Familial Variant Testing:** Single gene or single variant testing is considered **medically necessary** when there is a known pathogenetic or likely pathogenic variant in a close (first, second, or third-degree) relative and test results will directly impact the individual's medical management.

1. **Select Health does not cover testing for Variants of Uncertain Significance (VUS).** This meets the plan's definition of experimental/investigational.

OR

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i. Both parents are known carriers of an autosomal recessive disease; OR
ii. At least one parent is a known carrier of an autosomal dominant, sex-linked, or mitochondrial condition; OR
iii. At least one parent is a carrier of a balanced structural chromosome rearrangement.

Select Health will only cover preimplantation genetic testing for aneuploidy (PGT-A) when performed in concert with either preimplantation genetic testing for mutation (PGT-M) or preimplantation genetic testing for chromosome structural rearrangements (PGT-SR). Select Health does NOT cover PGT-A alone, due to a lack of sufficient evidence supporting efficacy of this testing; this meets the plan's definition of experimental/investigational.

Select Health considers duplicative genetic testing (a test with the same genetic content as a previous test) to be not medically necessary, unless sufficient clinical rationale to support the need for repeat testing is documented in the clinical notes.

Select Health does NOT cover genetic testing under the following circumstances:

- Direct-to-consumer genetic testing (e.g., 23andMe, AncestryDNA)
- Other genetic tests for population screening

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

"A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up the gene (direct testing), looking at markers co-inherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing)." Genetic tests are conducted for various purposes, including predicting disease risk, newborn screening, determining clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in an individual, families, or populations.

General Categories of Genetic Tests

Diagnostic Genetic Testing: Occurs in a symptomatic patient with a clinical presentation in association with or without a family history that leads the clinician to suspect a genetic disorder. Test results may confirm the suspected diagnosis, provide prognostic information, and assist in care management decisions, including treatment, preventative care recommendations, and condition specific surveillance.

Predictive Genetic Testing for Disease Assessment: Occurs in a patient with or without symptoms which would indicate a high probability of a genetic mutation; this test should be prognostic and assist in

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care management decisions including treatment, preventive care recommendations and condition-specific surveillance.

Prenatal Genetic Testing: A diagnostic test of the fetus to predict disease.

Population Genetic Screening applies to testing individuals without regard to the family history or phenotypic expression of a genetic disease, which may include newborn screening, maternal serum screening, or screening as specific ethnic population.

Newborn Screening: May include genetic and metabolic testing for early, presymptomatic detection, when diagnosed and treated, and prevents possibly irreversible health consequences.

Preimplantation Testing: Preimplantation genetic testing is a technique used to identify genetic defects in embryos created through in vitro fertilization (IVF) before pregnancy. Preimplantation genetic testing-mutation (PGT-M) refers specifically to when one or both genetic parents have a known genetic abnormality and testing is performed on an embryo to determine if it also carries a genetic abnormality. In contrast, preimplantation genetic testing - aneuploidy (PGT-A) refers to techniques where embryos from presumed chromosomally normal genetic parents are screened for aneuploidy.

Carrier Genetic Testing: Used to evaluate the potential of transmission of genetic mutations in asymptomatic, disease-free individuals; this includes testing parents in the preconception or prenatal periods to assess risk of having a child with a genetic disorder in a planned or ongoing pregnancy.

Billing/Coding Information
Covered: ONLY for the conditions outlined above

CPT CODES

0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested
81170-81383	Gene Analysis: Tier 1 Procedures
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81400	Molecular pathology procedure level 1
81401	Molecular pathology procedure level 2
81402	Molecular pathology procedure level 3
81403	Molecular pathology procedure level 4
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
81406	Molecular pathology procedure level 7

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81407	Molecular pathology procedure level 8
81408	Molecular pathology procedure level 9
81410-81471	Genomic Sequencing
81479	Unlisted molecular pathology procedure
81490-81599	Multianalyte Assays with Algorithmic Analyses
88245	Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)
88249	Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (eg, diepoxybutane, mitomycin C, ionizing radiation, UV radiation)
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88264	Chromosome analysis; analyze 20-25 cells
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3841	Genetic testing for retinoblastoma

Not covered for the indications listed above

0396U	Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions

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5. National Society of Genetic Counselors (NSGC) Position Statements. https://www.nsgc.org/POLICY/Position-Statements Accessed August 6, 2024.

Revision History

Revision Date	Summary of Changes
6/26/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
8/18/23	For Commercial Plan Policy, added qualifying option of criteria #C: "If there is a known pathogenetic familial variant, then genetic testing is allowed for that variant." Also, added new Section II for coverage criteria of Preimplantation Genetic Testing.
10/6/23	For Commercial Plan Policy, added the following exclusion: "Select Health considers situations in which a duplicative germline test was performed for the same genetic content as a previous test to be not medically necessary.
11/27/23	For Commercial Plan Policy, added language to coverage criteria to clarify which type of tests should be performed: "How test results will guide decisions regarding: disease treatment, prevention, or management, such as averting treatment for other possible diagnosis; ***and that the test being performed is the most appropriate according to currently accepted literature or guidelines.***"
5/24/24	For Commercial Plan Policy, added the following clarifying language to the Preimplantation Genetic Testing section: "**Select Health will cover preimplantation genetic testing of up to 16 oocytes per case.** **Select Health will only cover genetic testing for aneuploidy (PGT-A) when performed in concert with PGT-M. Select Health does NOT cover preimplantation genetic testing for aneuploidy (PGT-A) separately,** due to a lack of sufficient evidence supporting efficacy of this testing; this meets the plan's definition of experimental/investigational."
9/4/24	For Commercial Plan Policy, modified overall coverage criteria to align with current clinical standards, and updated the following exclusions: "Select Health considers duplicative genetic testing (a test with the same genetic content as a previous test) to be not medically necessary, unless sufficient clinical rationale to support the need for repeat testing is documented in the clinical notes. Select Health does NOT cover genetic testing under the following circumstances: • Direct-to-consumer genetic testing (e.g., 23andMe, AncestryDNA) • Other genetic tests for population screening"

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Gene Therapy, Testing, and Counseling continued

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Select Health

MEDICAL POLICY

GENETIC TESTING FOR PROSTATE CANCER PROGNOSIS

Policy # 544

Implementation Date:11/11/13

Review Dates: 6/11/15, 6/16/16, 10/20/16, 10/19/17, 5/17/21, 11/17/22, 1/17/23, 2/15/24, 12/13/24

Revision Dates: 9/9/21, 7/1/23, 11/8/23, 7/29/24, 12/19/24

Related Medical Policies:

#510 Genetic Testing: PCA3 Testing for Prostate Cancer

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Prostate cancer is the most common cancer among men, with over 200,000 new cases identified each year in the United States. Gene expression testing (Decipher, OncotypeDx Prostate, Prolaris) has been developed to aid in risk stratification of biopsy-positive patients. These tests are prognostic for determining specific endpoints such as distant metastasis or adverse pathology, and intended to help inform on treatment decisions, such as active surveillance vs definitive therapy.

One such test is the Decipher Prostate Biopsy Genomic Classifier. This test is a whole-transcriptome RNA expression oligonucleotide microarray performed on FFPE tissue post-positive biopsy. Results are given as a Decipher score: indicating low (0-0.45), intermediate (0.45-0.60), or high (0.6-1.) risk of metastasis in the next 10 years.

Oncotype Dx Genomic Prostate Score Test is a gene expression test which measures specific RNA markers in FFPE tissue post-positive biopsy. It generates the Genomic Prostate Score (GPS) which is purported to assist in determining the aggressiveness of an individual's prostate cancer and assist in determining the appropriate approach to management.

Prolaris is a quantitative RT-PCR test assessing 46 genes via FFPE tissue post-positive biopsy and combines this information with PSA and Gleason score to generate the Prolaris Molecular Score which predicts the patient's risk for disease-specific mortality and metastasis.

Decipher Prostate RP Genomic Classifier is a whole-transcriptome RNA expression oligonucleotide microarray performed on FFPE tissue post-radical prostatectomy (RP) with adverse pathology or persistent PSA. Results are given as a Decipher score: indicating low (0-0.45), intermediate (0.45-0.60), or high (0.6-1.) risk of metastasis and cancer mortality following the RP.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers certain prostate tumor-based molecular assays [Decipher Prostate Biopsy Genomic Classifier, Genomic Prostate Score (GPS), and Prolaris] when:

a) Patient has NCCN low, favorable-intermediate, unfavorable-intermediate, or high-risk disease*, AND

b) Life expectancy ≥ 10 years.

4. Select Health covers Decipher RP to inform adjuvant treatment decisions when

a) Adverse features** are found post-radical prostatectomy (RP); AND

b) Decipher testing has not been previously performed.

**NCCN prostate Initial Risk Stratification and Staging workup for clinically localized disease. Version 4.2023.*

***Adverse features can include, PSA persistence, rising PSA (above nadir); pathology showing positive margins, seminal vesicle invasion, extracapsular extension, pT3, or pT2 with positive margins; distant metastases, or pelvic recurrence.*

Table 2. AJCC Prognostic Groups#

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
Stage IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
Stage IIB	T1-2	N0	M0	PSA <20	2
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA <20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

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Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

[#]NCCN Clinical Practice Guidelines in Oncology. Version 4.2024.

Select Health does not cover the ArteraAI Prostate Test as peer-reviewed medical literature does not support this test as having sufficient sensitivity or specificity to define a valid clinical role; this meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Currently, no systematic reviews or primary literature are available regarding the Oncotype DX Prostate Test. A validation study was presented at the 2013 American Urology Association annual meeting, which is purported to: "… strongly predicted disease aggressiveness (p = 0.002) offering information beyond currently available clinical factors, such as PSA and biopsy Gleason Score." However, that presentation is not available nor have these findings been published.

As no literature on this technology has been published to date, an assessment regarding safety or efficacy of the test is not possible at this time (GRADE 2C).

Billing/Coding Information

Covered for the indications listed above when criteria are met

CPT CODES

0047U Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score

0376U Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate

81479 Unlisted molecular pathology procedure

81541 Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score

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81542 Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score

81551 Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a

81599 Unlisted multianalyte assay with algorithmic analysis

Not Covered for the indications listed above

0376U Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer specific mortality, includes predictive algorithm to androgen deprivation therapy response, if appropriate

HCPCS CODES

No specific codes identified

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Active Surveillance

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Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
11/8/23	For Commercial Plan Policy, added coverage criteria for the Decipher PR Test.
7/29/24	For Commercial Plan Policy, consolidated coverage criteria for individual tests in criteria #3 (Decipher Prostate Biopsy Genomic Classifier, OncotypeDx Prostate, and Prolaris) into one uniform set of criteria to align with updated NCCN guidelines. Also, added exclusion of the ArteraAI Prostate test.
12/19/24	For Commercial Plan Policy, modified requirements in criterion #1 in first section: "Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history. Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing."; and changed name of the OncotypeDX Protate test to the Genomic Prostate Score (GPS) test in criteria #3, to reflect current branding.

Disclaimer
This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult with appropriate healthcare providers to obtain needed medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member's individual benefit plan that is in effect at the time services are rendered.

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MEDICAL POLICY

GENETIC TESTING: 5-FLUOROURACIL TESTING IN CANCER PATIENTS

Policy # 594
Implementation Date: 1/13/17
Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24
Revision Dates: 7/1/23

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#590 Pharmacogenomic Testing for Drug Metabolism

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cancer is the second leading cause of death in the United State behind heart disease. Fluoropyrimidine drugs, such as 5-fluorouracil (5-FU) and capecitabine (oral FU), are a mainstay in the treatment of numerous solid tumors, including colorectal cancers, breast, stomach, and pancreatic cancers. These drugs work to interfere of the synthetic pathway for thymidine, a critical component in DNA synthesis required for cell division. This interference in turn stops cancer cell proliferation. The levels of this drug may fluctuate in different patients due to genetic propensities of these individual patients. Theoretically, identifying individual doses may improve outcomes for patients as it may result in optimal levels of the medicines available in the patient's system to treat their condition. 5-FU is used alone or as part of combination therapies.

5-FU degradation occurs in all tissues, including tumor tissues, but is highest in the liver. In humans, 70%–90% of an administered dose of 5-FU is degraded by dihydropyrimidine dehydrogenase (DYPD). Severe and even lethal toxicity reactions occur in 10-40% of patients treated with fluoropyrimidine. Toxicity due to reduced enzyme activity may result in hand-foot syndrome, fever, mucositis, stomatitis, severe diarrhea, nausea, vomiting, rectal bleeding, andneurologic abnormalities such as cerebellar ataxia (uncoordinated muscle movement) and changes in cognitive ability. Variants in the *DPYD* gene that result in reduced, or absent, DPD enzyme activity can cause this toxicity. Testing for genetic variants in DPYD is beneficial for reducing the risk of toxicity as there are Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for prescribing and dosing fluoropyrimidines based on an individual's *DPYD* genotype.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, **continued**

Select Health considers testing for genetic variants in DPYD either by gene sequencing or targeted genotyping as medically necessary for individuals considering or currently on therapy with any 5-FU containing drug including, but not limited to:

- 5-fluorouracil (Fluorouracil, Adrucil)
- Capecitabine (Xeloda)
- Fluorouracil topical formulations (Carac, Efudex, Fluoroplex)

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Fluoropyrimidine drugs are frequently used for treating solid tumors. Toxicity from fluoropyrimidines have been reported in 10-40% of patients. Genetic variants in the *DPYD* gene can increase the chance of this toxicity. There are CPIC guidelines for prescribing and dosing fluoropyrimidines based on an individual's *DPYD* genotype.

There is mounting evidence about the utility and cost-effectiveness of *DPYD* genetic testing. A study by Lunenburg et al. in 2016 prospectively genotyped *DPYD* in 275 patients prior to their first fluoropyrimidine treatment and found 5% had variants that required 25–50% dose reductions. None of these patients developed toxicity. A larger, prospective, multi-center study was conducted by Deenen et al. in 2016 on 2,038 patients and variants were found in 1% of patients who were dose adjusted. In this group the risk of grade III toxicity was significantly reduced to 28% compared to 73% in historical controls ($p < 0.001$) and the drug induced rate was reduced from 10% to 0.

The group also evaluated the cost-effectiveness and found that the overall cost for screening was less than for usual care. Another cost simulation study by Cortejoso et al. in 2016 also argue that testing of 1000 patients at their center will be cost-effective in preventing neutropenia given their costs for genotyping and treatment of neutropenia given the published rates of neutropenia.

The Lunenburg reviewed concluded that there is "convincing evidence to implement prospective DPYD genotyping with an upfront dose adjustment in DPD deficient patients. Immediate benefit in patient care can be expected through decreasing toxicity, while maintaining efficacy."

Although none of the studies they cite were randomized, they point out that such studies have been attempted but have been halted due to deaths in the standard care arm, suggesting that randomized control studies will not be forthcoming (and serving as further argument for the utility of this testing).

Billing/Coding Information

CPT CODES

81232	DPYD (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)

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Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, **continued**

81346	TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
81479	Unlisted molecular pathology procedure

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
S3722	Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil

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Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, **continued**

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Select Health

MEDICAL POLICY

GENETIC TESTING: 5-FLUOROURACIL TESTING IN CANCER PATIENTS

Policy # 594

Implementation Date: 1/13/17
Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24
Revision Dates: 7/1/23

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#590 Pharmacogenomic Testing for Drug Metabolism

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cancer is the second leading cause of death in the United State behind heart disease. Fluoropyrimidine drugs, such as 5-fluorouracil (5-FU) and capecitabine (oral FU), are a mainstay in the treatment of numerous solid tumors, including colorectal cancers, breast, stomach, and pancreatic cancers. These drugs work to interfere of the synthetic pathway for thymidine, a critical component in DNA synthesis required for cell division. This interference in turn stops cancer cell proliferation. The levels of this drug may fluctuate in different patients due to genetic propensities of these individual patients. Theoretically, identifying individual doses may improve outcomes for patients as it may result in optimal levels of the medicines available in the patient's system to treat their condition. 5-FU is used alone or as part of combination therapies.

5-FU degradation occurs in all tissues, including tumor tissues, but is highest in the liver. In humans, 70%–90% of an administered dose of 5-FU is degraded by dihydropyrimidine dehydrogenase (DYPD). Severe and even lethal toxicity reactions occur in 10-40% of patients treated with fluoropyrimidine. Toxicity due to reduced enzyme activity may result in hand-foot syndrome, fever, mucositis, stomatitis, severe diarrhea, nausea, vomiting, rectal bleeding, andneurologic abnormalities such as cerebellar ataxia (uncoordinated muscle movement) and changes in cognitive ability. Variants in the *DPYD* gene that result in reduced, or absent, DPD enzyme activity can cause this toxicity. Testing for genetic variants in DPYD is beneficial for reducing the risk of toxicity as there are Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for prescribing and dosing fluoropyrimidines based on an individual's *DPYD* genotype.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

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Policy # 594

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MEDICAL POLICY

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Policy # 594

Implementation Date: 1/13/17
Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24
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MEDICAL POLICY

GENETIC TESTING: AGE-RELATED MACULAR DEGENERATION

Policy # 530
Implementation Date: 6/27/13
Review Dates: 4/17/14, 5/7/15, 4/14/16, 4/27/17, 7/18/18, 4/14/19, 3/7/23, 5/10/24
Revision Dates: 7/1/23

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

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Description

Age-related macular degeneration (AMD) is a progressive eye disorder most often found in individuals over age 50. Age, family history, and gender are the most common variables contributing to its development. It is a major cause of blindness and visual impairment in older adults (age > 50 years). There are two types of AMD: wet and dry. Central geographic atrophy, the "dry" form of advanced AMD, results from atrophy of the retinal pigment epithelial layer below the retina, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye. No medical or surgical treatment is available for this condition. Neovascular or exudative AMD, the "wet" form of advanced AMD, causes vision loss due to abnormal growth of fragile and leaky blood vessels in the macula. Several intraocular therapies have been approved in recent years to treat this condition. These therapies may slow the vision loss through their reduction in new blood vessel production and associated macular edema.

Several genetic tests have been developed to assess for the potential development of "wet" AMD, or the probability of it progressing. These tests differ in the number of genetic markers as well as the methods used for calculation of risk. However, the American Academy of Ophthalmology currently does not recommend genetic testing for AMD.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing for age-related macular degeneration. It is considered experimental/investigational due to the lack of demonstrated clinical utility.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit

their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Laboratory-developed genetic testing evaluates the risk of patients with early or intermediate age-related macular degeneration (AMD). These tests are done by either a blood sample or swabbing the inside of the cheek. It combines a patient's disease stage with genetic predisposition, age, and smoking history to provide the probability of converting to AMD. Studies demonstrating the value of predictive testing for AMD are limited. Published studies have not identified the clinical validity or clinical utility of genetic testing in predicting the speed of advancement of AMD in those already at increased risk based on age or early evidence of AMD. This concept has been validated in a study by Hagstrom et al. in 2013. This study analyzed 834 patients; each patient was genotyped for the four genetic variants that are associated with AMD. After one year of treatment, researchers compared genotypic frequencies to therapeutic response. The study determined the genetic tests didn't serve a significant purpose helping with treatment.

Ivana et al. also reviewed genetic testing for AMD. This study found that at the present time there does not appear to be significant ethical, legal, and social implications of genetic testing for AMD, but should only be considered for early-stage disease and not for young pre-symptomatic individuals. However, it was possible to assess the risk of advanced AMD without necessarily doing the genetic test and continue to explore how the results of testing will be applied to the management of patients with AMD.

In addition to the lack of definitive published evidence, statements from specialty societies regarding the use of genetic testing for AMD do not support this testing. All saying similar statements, for example, the American Academy of Ophthalmology (AAO) has reiterated its position that eye physicians and surgeons should avoid genetic testing for age-related macular degeneration (AMD). They request testing avoidance until specific trials have shown a benefit of its use. Recommending genotyping of such patients should only be for research studies because this genetic testing has not been shown to improve clinical outcome.

Billing/Coding Information

CPT CODES

0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81479	Unlisted molecular pathology procedure

HCPCS CODES

No specific codes identified

Key References

1. AAO Task Force on Genetic Testing. (2014). Recommendations for Genetic Testing of Inherited Eye Diseases – 2014. https://www.aao.org/education/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d
2. Assel MJ, Li F, Wang Y, Allen AS, Baggerly KA, Vickers AJ. Ophthalmology, 2018 Mar;125(3):391-397. doi: 10.1016/j.ophtha.2017.09.008. Epub; 2017, Oct 9.
3. DeAngelis MM, Silveira AC, Carr EA, Kim IK. Genetics of age-related macular degeneration: current concepts, future directions. *Semin Ophthalmol*, 2011, May 26; (3):77-93.
4. Stone, E. M. (2015). "Genetic testing for age-related macular degeneration: not indicated now." *JAMA Ophthalmol*, 133(5): 598-600.
5. Warwick A, Lotery A. Genetics and genetic testing for age-related macular degeneration. Eye (Lond). 2018 May; 32(5): 849–857.

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MEDICAL POLICY

GENETIC TESTING: APOLIPOPROTEIN (APOE) TESTING

Policy # 339
Implementation Date:4/19/07
Review Dates: 4/24/08, 4/26/09, 5/19/11, 6/21/12, 5/7/15, 4/14/16, 4/27/17, 6/21/18, 4/12/19, 2/14/23, 2/15/24, 2/18/25
Revision Dates: 2/18/10, 5/29/13, 7/1/23

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Dementia is a disorder that is characterized by impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function). The term dementia does not imply a specific cause or pathologic process. Indeed, symptoms of dementia may arise from several etiologies. This policy addresses genetic testing for Alzheimer's and frontotemporal dementias.

Alzheimer's disease (AD) is the most common form of dementia in the elderly, accounting for 60% to 80% of cases, and it is estimated to affect more than 4.2−5.8 million Americans. Because of increased life expectancy, the number of people living with AD is expected to triple.

Four major types of familial AD have been identified. Types 1, 3, and 4 are classified as early-onset AD because their signs and symptoms appear before age 65. Of early onset cases, 61% have a family history of AD (i.e., early onset familial Alzheimer's disease [EOFAD]) and less than 2% of all AD cases can be attributed to EOFAD. The diagnosis of EOFAD is made in families with multiple cases of AD, in which the mean age of onset is before age 60−65 years. Type 2 AD is classified as late-onset AD because its signs and symptoms appear after age 65. Other than age of onset, these 2 forms of AD present very similarly.

Frontotemporal dementia (FTD) is a heterogeneous term for a spectrum of diagnoses that includes disorders such as Pick's disease, progressive non-fluent aphasia, semantic dementia, FTD with Parkinsonism-17, FTD/motor-neuron disease, and progressive supranuclear palsy. FTD is characterized by focal atrophy of the frontal and temporal lobes in the absence of Alzheimer pathology. Onset usually occurs between the ages of 35−75 years, and only rarely after age 75; the mean age of onset is the sixth decade. The exact prevalence is unknown, though some estimates place FTD at 10% of dementia cases. Clinically, the disorder presents in a variety of ways, but 2 signs are typically associated with FTD: 1) gradual and progressive behavioral change, and 2) gradual and progressive language dysfunction. The most common presenting symptom is word-finding difficulty. However, decreased fluency or hesitancy in producing speech, difficulty with language comprehension, and motor speech difficulties (e.g., dysarthria) are also common.

Coronary heart disease risk assessment is another clinical circumstance in which ApoE is being used. ApoE plays a key role in lipoprotein metabolism and cardiovascular disease, which removes excess cholesterol from the blood and transports cholesterol to the liver for processing. ApoE genetic testing has been proposed for use in predicting risk of cardiovascular disease (e.g., heart attack, stroke) hyperlipoproteinemia type III, and therapy response. Testing for ApoE may sometimes be ordered to help guide lipid treatment. In cases of high cholesterol and triglyceride levels, statins are usually considered

the treatment of choice to decrease the risk of developing CVD; however, there is a wide variability in the response to these lipid-lowering drugs that is in part influenced by the Apo E genotype. Some evidence suggests though appropriately responsive to a low-fat diet, people with ApoE e4 may be less likely than those with ApoE e2 to respond to statins by decreasing their levels of LDL-C and may require adjustments to their treatment plans. At present, the clinical utility of this type of information is yet to be totally understood. Dietary adjustment and statin drugs are the preferred agents for lipid-lowering therapy. ApoE testing may also be ordered occasionally to help diagnose type III hyperlipoproteinemia in a person with symptoms that suggest the disorder and to evaluate the potential for the condition in other family members.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing for Alzheimer's disease or *any* type of dementia. This meets the plan's definition of experimental/investigational.

Select Health does NOT cover Apolipoprotein E (apoE) testing for assessing increased risk of cardiovascular disease. This meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Alzheimer's disease. The early-onset forms of AD (types 1, 3, and 4) are inherited in an autosomal dominant pattern (i.e., 1 copy of the altered gene in each cell is sufficient to cause the disorder). In most cases, an affected person inherits the altered gene from one affected parent. Researchers have identified three missense gene mutations that cause these forms of AD: the APP gene on chromosome 21 (21q21), the PSEN1 gene on chromosome 14 (14q24.3), and the PSEN2 gene on chromosome 1 (1q31-q42). Penetrance for these genes is around 100%.

The APP gene codes for the amyloid precursor protein and the PSEN1 and PSEN2 genes code for the presenilin-1 and presenilin-2 proteins, respectively. These proteins are part of a process in which amyloid precursor protein is cut into smaller segments (peptides). One of these peptides, soluble amyloid precursor protein (sAPP), has growth-promoting properties and may play a role in the formation of nerve cells in both embryonic and adult brain tissue.

More than 140 PSEN1 mutations have been identified in patients with type 3 AD and approximately 11 PSEN2 mutations have been shown to cause type 4 AD. At least 22 APP mutations have been described in patients with type 1 AD. Mutations to these genes appear to negatively affect the processing of amyloid precursor protein, which leads to increased production of amyloid beta peptide, which can build up in the brain and form the amyloid plaques characteristic of AD. Amyloid plaques may lead to the death of nerve cells and the progressive signs and symptoms of this disorder.

PSEN1 mutations account for 30%−70% of cases of early-onset familial AD. PSEN2 mutations account for less than 5% of early-onset familial AD cases. APP mutations are responsible for about 2%−15% of all

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early-onset familial AD cases. Kindreds with autosomal dominant EOFAD with no identifiable mutations in the PSEN1, PSEN2, or APP genes have been described; thus, it is likely that other causative genes will be identified. Penetrance of PSEN1 is 100% by age 65. Penetrance of PSEN2 is 95%.

The genetic causes of late-onset (type 2) familial AD are less clear. This disorder is likely related to mutations in one or more risk factor genes in combination with lifestyle and environmental factors. Mutations to the APOE gene on chromosome 19 (19q13.2) are associated with increased risk for late-onset familial AD. The APOE gene codes for apolipoprotein E and packages and transports cholesterol (and other fats) through the bloodstream and then delivers them to the appropriate locations in the body for processing and use. Apolipoprotein E is a major component of very low-density lipoproteins (VLDLs), which remove excess cholesterol from the blood to the liver for processing.

There are 3 common APOE alleles (ε2, ε3, ε4) and 6 possible genotypes. Evidence for a genetic risk factor in late onset AD is strongest for the ε4 allele of APOE. The APOE ε4 allele is associated with an increased number of amyloid plaques in the brain tissue of people with AD. There appears to be a dose-response effect of ε4: each additional copy is associated with an increased risk of AD and earlier age of onset; 68 years in ε4 homozygotes, 77 years for heterozygotes, and about 85 years for no ε4 allele. However, while the APOE ε4 allele conveys an increased risk of developing AD, not all people with AD disease have the ε4 allele, nor will all people with the ε4 allele develop the disease. APOE mutations appear to predispose to the psychiatric complications associated with AD and ε4 may also affect the risk for development of vascular dementia.

A 2003 Hayes Directory on gene mutations portending risk for AD concluded that genetic testing for APP and Presenilin mutations has utility in suspected cases of early onset AD but that testing is of limited additional clinical value in young (under age 50) symptomatic patients with a confirmed autosomal dominant family history of AD. The review also gave a 'B' rating for use of this testing to predict risk for AD in asymptomatic patients younger than 50 with a confirmed history of early-onset AD. The basis for the 'B' rating lies in the benefits conferred by a positive test result; namely, that such information affords patients the luxury of making health and family decisions in the context of almost certain disease risk. No literature has been published which suggests that genetic testing for early onset AD has any impact on clinical management of the disease.

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The literature offers minimal support for genetic testing for APOE alleles either to diagnose AD or identify persons at risk for developing the disease. While the literature suggests a potential use of APOE genotyping to predict the rate of cognitive decline or treatment response AD patients, the research is not consistent in this area. A positive APOE test may also provide confirmatory evidence of an AD diagnosis, but there is little evidence to suggest that such information would have any impact on subsequent treatment decisions. Given the high prevalence of ε4 alleles in the population, APOE genotyping in asymptomatic individuals, is unlikely to further clarify an individual's risk for AD over other information such as family history or cognitive test results. Consequently, APOE genetic testing is more appropriately used in a research context as opposed to a clinical tool for diagnosing AD.

The American College of Medical Genetics practice guideline for genetic testing in Alzheimer's disease (Goldman et al) recommends against testing for APOE alleles. If a genetic cause for EOAD is found, its clinical utility is debatable since there are no medical treatments for EOAD. However, it may be beneficial for asymptomatic individuals in the same family to be tested (for planning purposes) and on a societal level identifying individuals with these known mutations may allow participation in research studies or trials to try and discover more about causes/treatments for AD. A case for testing in families with autosomal AD and possible parameters/guidelines are in the ACMG guideline (Goldman et al).

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Genetic Testing: Apolipoprotein (APOE)Testing, **continued**

Frontotemporal Dementia. While 40%–50% of FTD patients have some family history of dementia or neurodegenerative disease, only 5%–10% of FTD patients have a family history suggestive of an autosomal dominant pattern of inheritance, i.e. a clear pattern of FTD-type diagnoses being passed from parent to child, with virtually every patient having an affected parent and each child of an affected person having a 50% chance to inherit the disorder. The age of onset can often be younger with familial and inherited forms of FTD (30s and 40s) and the disease may progress more rapidly.

Mutations of the microtubule-associated protein tau (MAPT) gene on chromosome 17 (17q21-22) are responsible for about 10% of familial FTD cases but up to 50% of autosomal dominant FTD. MAPT codes for the tau protein. Thirty to 40 different MAPT mutations causing FTD have been identified most of which are located between exons 9 and 13. Mutations form mutant tau proteins in cells or change the proportion of the forms of tau normally expressed in the brain. These changes promote tau aggregation into filaments and harm the ability of tau to bind to microtubules.

MAPT mutations are associated with one inherited form of FTD called Frontotemporal Dementia with Parkinsonism-17 (FTDP-17). MAPT mutations account for approximately 70% of autosomal dominant FTDP-17 and 33% of cases with a positive family history.

In some families with frontotemporal dementia showing with an inheritance pattern suggestive of linkage to chromosome 17q21.1, neither mutations in the MAPT gene nor tau pathology at neuropathologic examination has been found. Moreover, heterogeneity in clinical presentation is observed even within families with the same MAPT mutation. These findings suggest that additional gene mutations and other risk factors likely play a role in development of FTD and its phenotypic expression. Indeed, recent studies point to mutations of the progranulin gene as playing some role in the development of sporadic ubiquitin-associated FTD.

The primary literature on genetic testing for FTD is still in the early stages with articles focused primarily on describing genetic mutations. Although there are no systematic reviews on genetic testing and FTD, several literature reviews have been published, which summarize the extant research on the genetics of FTD and the clinical utility of testing. These reviews suggest several conclusions about the state of genetic testing for FTD:

- FTD is a complex disorder with a heterogeneous presentation and poorly understood neuropathology. Knowledge about the genetics of this disorder is rapidly emerging.
- Persons with a family history of dementia or neurodegenerative disorders are at higher risk for developing FTD than the general population. Individuals with a clear history of FTD are at extremely high risk.
- Tau pathology occurs in a percentage FTD cases and is particularly common in persons with an autosomal dominant pattern of FTD.
- MAPT mutations linked to tau pathology are associated with FTD, particularly among persons with a family history of autosomal dominant FTD. Goldman et al. estimates the risk of having a tau mutation to be 80% in persons with more than three family members with a history of fulminate FTD.
- The penetrance of the many MAPT mutations is variable, though penetrance of some may be 100%.
- Many additional genes and other risk factors likely play a role in the development of FTD and its phenotypic expression.
- For a particularly rare form of FTD, FTDP-17, genetic testing for certain MAPT mutations may be informative.
- The clinical utility of genetic testing for FTD in most patients with dementia has not been established.

A literature review performed in February 2010 identified a study by Mihaescu at al. recognized that genotyping is not considered useful for screening, presymptomatic testing, or diagnosing Alzheimer's disease. They concluded their study by stating "Most research on genome-based applications in AD is still in the first phase of the translational research framework, which means that massive research is still needed before their implementation can be considered."

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Apolipoprotein E (apoE) testing for risk of coronary heart disease. Multiple studies and reviews have evaluated the relationship between apo E genotypes (particularly the apo E4 allele) and both LDL-cholesterol and the incidence of CHD. However, these reports may have been both underpowered to detect the true relationship and also subject to publication bias. The largest meta-analysis of the impact of the presence of the apo E allele on LDL-cholesterol levels and CHD risk came to the conclusions that there was an approximately linear relationship of apoE genotypes (when ordered E2/E2, E2/E3, E3/E3, E3/E4, and E4/E4) with LDL-cholesterol. There was a weakly inverse relationship of these genotypes with HDL-cholesterol level and a non-linear relationship with triglycerides, with the E3/E3 genotype having the lowest triglyceride levels. The lack of predictability in use of ApoE as a screening test for clinically defined atherosclerotic disease was also verified in systematic review published in 2002. The study suggests that apoE genotype may be related with lipid levels and CAD but is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered not an effective predictor of CAD, when compared to other established procedures.

Similarly, the role of apolipoprotein E (APOE) phenotypes in cerebrovascular disease and ischemic stroke is unsettled. This apolipoprotein is a ligand for hepatic chylomicron and VLDL remnant receptors, leading to clearance of these lipoproteins from the circulation, and for LDL receptors. The APOE e4 allele has been reported to be a stroke risk factor in some but not other studies.

Billing/Coding Information

CPT CODES

81401	Molecular pathology procedure, Level 2

HCPCS CODES

S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease
0355U	APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)

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Select Health

MEDICAL POLICY

GENETIC TESTING: BREAST, OVARIAN, PANCREATIC, AND PROSTATE CANCER

Policy # 664
Implementation Date:7/1/23
Review Dates: 8/16/24
Revision Dates: 11/8/23, 4/19/24, 9/4/24, 12/20/24

Related Medical Policies:
#438 Genetic Testing: PTEN Mutation Analysis

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Nearly 2 million individuals are diagnosed with cancer each year in the United States. Breast and prostate cancer are the most common, respectively accounting for 16% and 15% of all cancer diagnoses. Ovarian and pancreatic cancers are less common but associated with significant mortality. While most cancer is sporadic, 5-10% of individuals have hereditary cancer, meaning there is an underlying genetic variant that predisposed the individual to developing cancer. Several genes are known to increase the risk of developing breast, ovarian, pancreatic, and/or prostate cancer, with many of these genes increasing the risk for multiple of these types of cancers. This includes, but is not limited to, *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11*, and *TP53*.

Personal and family history factors which suggest an individual may have a genetic cancer predisposition include early-onset cancer, multiple family members over several generations with cancer diagnoses, or a history of certain types of cancers. For individuals who have suggestive personal or family histories, genetic testing for cancer susceptibility genes (i.e., germline testing) may be useful for determining whether there is an underlying genetic cause. Identifying a genetic variant causing a hereditary cancer susceptibility can help guide an individual's cancer-related screening and management, to improve health outcomes. Diagnosing a genetic cancer susceptibility can also help identify at-risk family members who may also benefit from genetic testing.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

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3. **Select Health covers panel testing for breast, ovarian, prostate, and pancreatic cancer susceptibility genes, which must include at minimum the following genes: *BRCA1*, *BRCA2, CDH1*, *PALB2*, *PTEN*, *STK11*, and *TP53***, when one of the following criteria are met (A−G):

   A. Personal history of breast cancer diagnosed ≤ 50 years; **OR**

   B. Personal history of breast cancer at any age and one of the following (1−8):
      1. To aid in systemic treatment decisions using PARP inhibitors[a] for breast cancer in the metastatic setting, or
      2. To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer; or
      3. Triple-negative breast cancer; or
      4. Multiple primary breast cancers (synchronous or metachronous); or
      5. Lobular breast cancer with personal or family history of diffuse gastric cancer; or
      6. Male breast cancer; or
      7. Ashkenazi Jewish ancestry; or
      8. ≥ 1close blood relative[b] with any of the following (i−vii):
         i. Breast cancer at age ≤ 50; or
         ii. Male breast cancer; or
         iii. Ovarian cancer; or
         iv. Pancreatic cancer; or
         v. Prostate cancer at any age with metastatic[c], or high- or very-high-risk group*; or
      9. ≥ 3 total diagnoses of breast and/or prostate cancer (any grade) on the same side of the family, including the patient with breast cancer; **OR**

   C. Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; **OR**

   D. Personal history of exocrine pancreatic cancer; **OR**

   E. Personal history of prostate cancer and any of the following (1−4):
      1. Metastatic or high- or very-high risk group per NCCN.
      2. ≥1 close blood relative[b] with one of the following (i−v):
         i. Breast cancer at age ≤ 50 years; or
         ii. Triple-negative breast cancer at any age; or
         iii. Male breast cancer at any age; or
         iv. Ovarian cancer at any age; or
         v. Pancreatic cancer at any age; or
         vi. Metastatic, high- or very-high risk group prostate cancer.
      3. ≥ 3 close blood relatives[b] with prostate cancer (any grade) and/or breast cancer at any age on the same side of the family, including the patient with prostate cancer;
      4. Ashkenazi Jewish ancestry; **OR**

   F. An affected individual (not meeting testing criteria listed above) or unaffected individual with any of the following:
      1. a first- or second-degree blood relative meeting any of criteria A−C (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making[d]); or
      2. a first-degree blood relative meeting any of criteria D−E; or
      3. a personal or family history of a known pathogenic or likely pathogenic variant in a breast, ovarian, pancreatic, and/or prostate cancer susceptibility gene who have a family history suggesting a different syndrome in addition to the known variant; **OR**

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G. An affected or unaffected individual, who otherwise does not meet the criteria above, but has a probability > 5% of a BRCA1/2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk); must be performed by the ordering physician.

Note: If a multigene cancer panel is performed, the appropriate panel code should be used.

a- The two FDA approved PARP inhibitors - olaparib and talazoparib are included as a category 1, preferred options for those with germline BRCA1/2 mutations. The NCCN Panel recommends assessing for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the NCCN Panel supports use in any breast cancer subtype associated with germline BRCA1/2 mutations.

b- Close blood relatives include first-, second-, and third-degree relatives on the same side of the family.

c- Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes.

d- This may be extended to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable P/LP variants and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT Codes

0037U Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden [FoundationOne CDx]

0102U Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication)]

0103U Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only)]

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Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

0131U Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U)

0129U Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)

0132U Hereditary ovarian cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U)

0134U Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)

0135U Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)

0137U PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)

0138U BRCA1(BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)

0172U Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score

0235U PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

81162 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis

81163 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81164 BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

81165 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81166 BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

81167 BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

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Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

81212 BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants

81215 BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81216 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis

81217 BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant

81307 PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence

81308 PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant

81321 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

81322 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant

81323 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

81351 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence

81352 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)

81353 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)

81432 Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53

81433 Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

81449 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF,

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Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis

81445 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

81451 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81479 Unlisted molecular pathology procedure

88271 - 88275 Molecular cytogenetics

Key References

1. Centers for Disease Control and Prevention (CDC). Genetic Testing for Hereditary Breast and Ovarian Cancer.
2. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3.2024 – February 12, 2024.

Revision History

Revision Date	Summary of Changes
11/8/23	For Commercial Plan Policy, modified overall coverage criteria regarding required panel of genes to be tested (changed *should* to *must*): "Select Health covers panel testing for high-penetrance breast cancer susceptibility genes, which **must** include the following genes (BRCA1/2, CDH1, PALB2, PTEN, and TP53)"
4/19/24	For Commercial Plan Policy, added the STK11 gene as part of the required genes to qualify for panel testing: "Select Health covers panel testing for high-penetrance breast cancer susceptibility genes, which must include the following genes (BRCA1/2, CDH1, PALB2, PTEN, STK11, and

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	TP53" and modified criterion #E3: "3. > 3 close blood relatives with prostate cancer (any grade) and/or breast cancer at any age on the same side of the family including the patient with prostate cancer; …"
9/4/24	Modified title of policy to include addition of "Ovarian, Pancreatic, and Prostate Cancer," and for Commercial Plan Policy, incorporated coverage criteria for evaluation of genetic testing for these cancers, and modified overall coverage criteria to align with current clinical standards; and added the following note: "If a multigene cancer panel is performed, the appropriate panel code should be used."
12/20/24	For Commercial Plan Policy, modified requirements in criterion #1 in first section: "Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history. Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing."

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Select Health

MEDICAL POLICY

GENETIC TESTING: CARDIOMYOPATHY

Policy # 665
Implementation Date: 7/1/23
Review Dates: 8/16/24
Revision Dates: 12/6/23, 9/3/24

Related Medical Policies:
#123: Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cardiomyopathy is a disease where the heart muscle has become abnormally thickened, enlarged, or rigid, making it difficult to pump blood. Over time, cardiomyopathy weakens the heart so that it is less effective in pumping blood throughout the body and maintaining a normal rhythm. This can result in heart failure, arrhythmia, or other complications.

There are several types of cardiomyopathy, including:

- Arrhythmogenic cardiomyopathy: heart muscle is replaced by scar tissue and fat, disrupting the electrical signals of the heart, causing arrhythmias
- Dilated cardiomyopathy: the muscle of the heart (typically the left ventricle) stretches and becomes thinner, causing enlargement of the heart chamber, which decreases the ability of the heart to pump blood effectively; for details on subtypes of dilated cardiomyopathy, see footnote c
- Hypertrophic cardiomyopathy: the walls of the heart chamber become thickened, reducing the amount of blood that can enter the chamber and be pumped out with each heartbeat
- Restrictive cardiomyopathy: the walls of the ventricles in the heart become rigid, making it so they don't relax and fill with blood like they would normally, resulting in enlargement of the atria
- Peripartum cardiomyopathy: a form of dilated cardiomyopathy that occurs in the last month of pregnancy or in the postpartum period
- Cardiac amyloidosis: deposits of amyloid protein build up on the heart muscle, decreasing the ability of the heart to pump blood effectively

Cardiomyopathy can be acquired or inherited. There are many underlying causes for acquired cardiomyopathy including coronary artery disease, congenital heart disease, inflammatory conditions, infection, toxins, thyroid disease, aortic stenosis, radiation, chronic hypertension, and "athlete's heart." For individuals who do not have an identifiable acquired cause for their cardiomyopathy, genetic testing may be useful for determining whether there is an underlying genetic cause. Establishing a genetic cause for cardiomyopathy in an individual can help guide medical management recommendations and identify at risk family members who would also benefit from genetic testing for the known family variant.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers genetic testing for cardiomyopathy when either I or II are met:

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I. **Select Health considers genetic testing for cardiomyopathy as medically necessary,** if recommended by Intermountain Heart Institute;

OR

II. For all other clinicians, Select Health considers genetic testing for cardiomyopathy as medically necessary, when the following criteria are met:

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested; and

3. Select Health considers genetic testing for the following panel tests for cardiomyopathy as medically necessary, when the following criteria are met:

   i. Non-genetic causes of cardiomyopathy have been ruled out, such as prior myocardial infarction from coronary artery disease, valvular and congenital heart disease, toxins (most commonly anthracyclines or other chemotherapeutic agents, various drugs with idiosyncratic reactions), thyroid disease, inflammatory or infectious conditions, severe long-standing hypertension, radiation, aortic stenosis, and extreme physiologic hypertrophy (aka “athlete’s heart”).

   AND

   ii. Meets one of the following criteria (A−F):

   A. Arrhythmogenic cardiomyopathy

   1. The member meets the task force criteria for at least possible arrhythmogenic cardiomyopathy (defined by Corrado, et al. table 1[a] and supplementary figure 1[b])

   OR

   B. Dilated cardiomyopathy (DCM)

   1. The member has a diagnosis of DCM[c] from a cardiologist or documented left ventricular enlargement and systolic dysfunction (e.g., ejection fraction <50%) based on echocardiogram, cardiac MRI and/or left ventricular angiogram

   OR

   C. Hypertrophic cardiomyopathy (HCM)

   1. The member has a diagnosis of HCM from a cardiologist or documented to have unexplained left ventricular hypertrophy with myocardial wall thickness of 15mm or greater (in adults) or a z-score greater than or equal to 2 (in children) based on echocardiogram or cardiac MRI

   OR

   D. Restrictive cardiomyopathy (RCM)

   1. The member has a diagnosis of RCM from a cardiologist or based on echocardiogram showing diastolic dysfunction of a non-dilated ventricle.

   OR

   E. Peripartum cardiomyopathy

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1. The member has a diagnosis of peripartum cardiomyopathy from a cardiologist in the last month of pregnancy or within 3 months following delivery by left ventricular enlargement and systolic dysfunction (e.g., ejection fraction < 45%).

OR

F. Cardiac amyloidosis

1. The member has a diagnosis of cardiac amyloidosis based on pyrophosphate (PYP) scan or biopsy.

Select Health considers genetic testing for ischemic cardiomyopathy to be not medically necessary as the underlying factors that cause this condition are non-genetic.

For genetic testing of a known familial variant in a cardiomyopathy gene, please reference Select Health Medical Policy #123.

a - Table 1 from Corrado, et al.

Table 1

European Task Force criteria for diagnosis of Arrhythmogenic Cardiomyopathy.

Category	RV Phenotype	LV Phenotype
I. Morpho-functional ventricular abnormalities	**Major** • Regional RV akinesia, dyskinesia, or aneurysm and one of the following: • global RV dilatation (increase of RV EDV according to the imaging test specific nomograms for age, sex and BSA)* or • global RV systolic dysfunction (reduction of RV EF according to the imaging test specific nomograms for age and sex)* **Minor** • Regional RV akinesia, dyskinesia or aneurysm of RV free wall	**Minor** • Global LV systolic dysfunction with or without LV dilatation (increase of LV EDV according to the imaging test specific nomograms for age, sex, and BSA)*
II. Structural alterations	**Major** • Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue, at histology **Minor** • Unequivocal RV LGE (confirmed in 2 orthogonal views) in ≥1 RV segment (excluding myocapic valve)	**Major** • "Ring like" LV LGE (subepicardial or mesomyocardial strie pattern) of ≥2 segments (confirmed in 2 orthogonal views). **Minor** • LV LGE (subepicardial or mesomyocardial strie pattern) of 1 or 2 Bull's Eye segment(s) (in 2 orthogonal views) of the free wall, septum, or both (excluding patchy, focal or septal junctional LGE**).
III. Repolarization abnormalities	**Major** • Negative T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals ≥14 year-old (in the absence of complete RBBB and not preceded by J-point/ST-segment elevation) **Minor** • Negative T waves in leads V1 and V2 in males ≥14 year-old (in the absence of RBBB and not preceded by J-point/ST-segment elevation) • Negative T waves beyond V3 in the presence of complete RBBB • Negative T waves beyond V3 in individuals < 14 year-old	**Minor** • Negative T waves in left precordial leads (V_4-V_6) (in the absence of complete LBBB)
IV. Depolarization and conduction abnormalities	**Minor** • Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3) • Terminal activation duration of QRS ≥55 ms measured from the nadir of the R wave to the end of the QRS, including R', in V1, V2, or V3 (in the absence of complete RBBB)	**Major** • Low QRS voltages (<0.5 mV peak to peak) in all limb leads (in the absence of other causes (e.g. cardiac amyloidosis, obesity, emphysema, or pericardial effusion)
V. Arrhythmias	**Major** • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with non-inferior axis **Minor** • Frequent ventricular extrasystoles (>500 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with inferior axis ("RVOT pattern") • History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology	**Minor** • Frequent (<500 per 24 h) or exercise-induced ventricular extrasystoles with a RBBB morphology or multiple RBBB morphologies (excluding the "fascicular patterns") • Non-sustained or sustained ventricular tachycardia with a RBBB morphology (excluding the "fascicular patterns") • History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology
VI. Family history/genetics	**Major** • Identification of a pathogenic ACM gene variant in the patient under evaluation • ACM confirmed in a first-degree relative who meets diagnostic criteria • ACM confirmed pathologically at autopsy or surgery in a first-degree relative **Minor** • Identification of a likely pathogenic ACM gene variant in the patient under evaluation • History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria • Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative • ACM confirmed pathologically or by diagnostic criteria in second-degree relative	

Note: best practice is to use a reference range derived using the diagnostic approach and the same segmentation method as for patients. ACM = arrhythmogenic cardiomyopathy; BSA = body surface area; EDV = end-diastolic volume; EF = ejection fraction; ITF = International Task Force; LBBB = left bundle-branch block; LGE = late gadolinium enhancement; LV = left ventricle; RBBB = right bundle-branch block; RV = right ventricle; RVOT = right ventricular outflow tract.

* Cut-off values of EDV and EF of the European TF criteria for respectively RV dilatation and systolic dysfunction are reported in Table 2.

** Septal junctional LGE at the RV insertion points.

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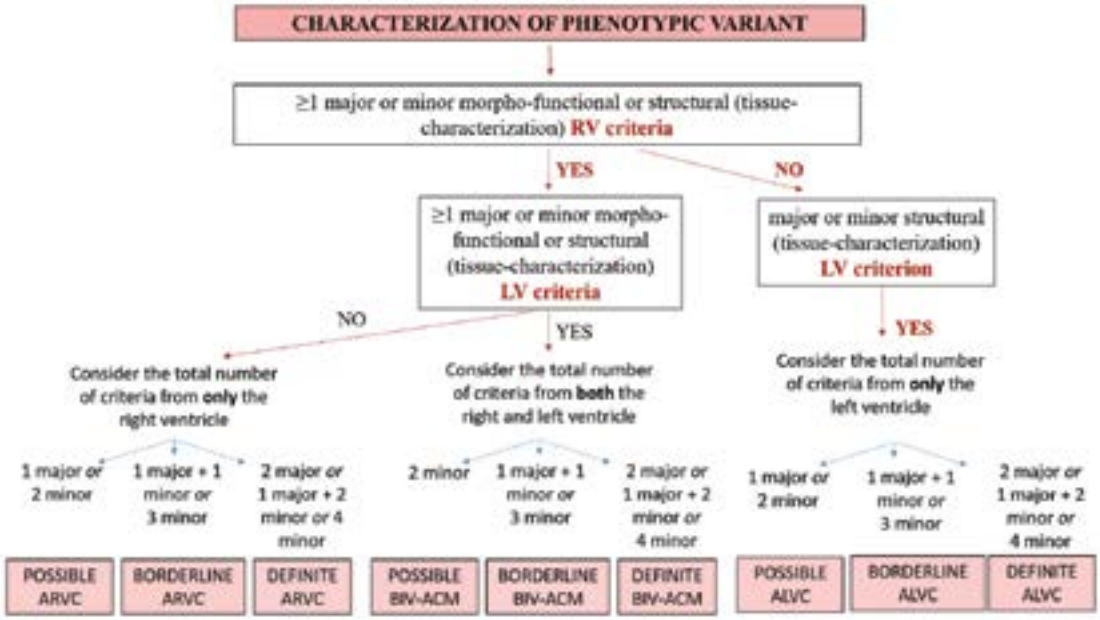
b – Supplementary Figure 1 from Corrado, et al.



c - DCM is the presence of left ventricular dilation and either global or regional systolic dysfunction. This dysfunction is unexplained solely by an abnormal loading condition (such as hypertension, valve disease, or a congenital heart defect) or coronary artery disease. Dysfunction and dilation in the right ventricle may be present as well. Non-dilated left ventricular cardiomyopathy (NDLVC) is the presence of non-ischemic left ventricular scarring or fatty replacement. This can be further delineated into NDLVC with or without systolic function, regional or global. Global and regional wall motion abnormalities and isolated global left ventricular hypokinesia without scarring may be present. This category includes conditions such as arrhythmogenic left ventricular cardiomyopathy (ALVC), left dominant arrhythmogenic right ventricular cardiomyopathy (ARVC), or arrhythmogenic DCM. Often these conditions do not fulfill diagnostic criteria for ARVC.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

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Genetic Testing: Cardiomyopathy, continued

0237U Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

81410 Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK

81411 Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1

81413 Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCHN2, KCNJ2, KCNQ1, RYR2, and SCH5A

81414 Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1

81439 Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)

81479 Unlisted molecular pathology procedure

81493 Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score

Key References

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Revision History

Revision Date	Summary of Changes
12/6/23	For Commercial Plan Policy, modified criteria to include option of recommendation by Intermountain Heart Institute as a qualifying factor.
9/3/24	For Commercial Plan Policy, updated overall criteria to align with current clinical standards, including inputting reference tables to help with evaluation; and added the following exclusion: "Select Health considers genetic testing for ischemic cardiomyopathy to be not medically necessary as the underlying factors that cause this condition are non-genetic."

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Select Health

MEDICAL POLICY

GENETIC TESTING: CELL-FREE FETAL DNA TESTING

Policy # 679
Implementation Date: 3/25/24
Review Dates:
Revision Dates: 7/22/24

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cell-free fetal DNA (cffDNA) testing [also called noninvasive prenatal testing (NIPT) or noninvasive prenatal screening (NIPS)] is a screen for fetal aneuploidies. This testing evaluates short segments of cell-free fetal DNA in the maternal plasma during pregnancy. The clinical utility of cffDNA has been established for detecting fetal trisomy 13, 18, and 21, at ≥ 8−10 weeks gestation with a viable singleton or twin pregnancy. This testing can identify fetuses at increased risk for aneuploidy but cannot definitively diagnose, confirm, or exclude. Screening tests that show increased risk should be confirmed by diagnostic testing prior to any intervention.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers cell-free fetal DNA testing for common aneuploidy (chromosomes 13, 18, 21, X, Y) once per singleton or twin pregnancy.

Select Health does not cover this testing solely for the purposes of fetal sex determination; this is considered NOT medically necessary.

Select Health does NOT cover cell-free fetal DNA testing for the evaluation of the following:

- Microdeletions/microduplications
- Expanded aneuploidies (chromosomes other than 13, 18, 21, X, Y)
- Twin zygosity
- Whole genome or whole exome screening
- Single gene disorders
- Non-viable pregnancies
- Fetal trophoblast cells (such as Luna Prenatal Test)
- Higher order multiple gestation (≥ 3 fetuses)

Use of this testing for these indications meets the plan's definition of experimental/investigational.

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SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

Covered for the indications listed above when criteria are met

CPT CODES

81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed
81479	Unlisted molecular pathology procedure

Not covered for the indications listed above

81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, digeorge syndrome, cri-du-chat syndrome), circulating cell-free fetal dna in maternal blood

Key References

1. American College of Obstetricians and Gynecologists (ACOG). Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020;136(4):e48-e69. Epub 2020/08/18. PMID: 32804883
2. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016;18(10):1056-65. Epub 2016/07/29. PMID: 27467454
3. Palomaki GE, Chiu RWK, Pertile MD, et al. International Society for Prenatal Diagnosis Position Statement: cell free (cf)DNA screening for Down syndrome in multiple pregnancies. Prenat Diagn. 2021;41(10):1222-32. Epub 2020/10/06. PMID: 33016373
4. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. Genet Med. 2022;24(7):1379-91. Epub 2022/05/25. PMID: 35608568

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Genetic Testing: Cell-free Fetal DNA Testing, **continued**

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Select Health

MEDICAL POLICY

GENETIC TESTING: CELL-FREE TUMOR DNA/LIQUID BIOPSY

Policy # 581
Implementation Date:7/8/16
Review Dates: 6/15/17, 9/18/18, 8/8/19, 10/21/20, 5/19/22, 1/17/23, 2/29/24
Revision Dates: 8/21/17, 8/16/19, 9/23/20, 1/29/21, 5/9/22, 7/1/23, 7/24/24, 8/26/24, 3/20/25

Related Medical Policies:

#570 Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Detecting and monitoring cancer recurrence can sometimes be problematic. Additionally, for individuals who have a relapse while on therapy determining optimal approaches to therapy modification can also be problematic as tumor samples may not be accessible via biopsy, or the patient may not be able to well-tolerate an invasive procedure. New methods to identify and characterize the molecular characteristics of persistent or recurrent tumors are being developed, which are intended to eliminate invasive biopsies, but retain similar sensitivities and specificities. One such technology is the "liquid biopsy." This technology uses next-generation sequencing to characterize tumors based on the capture and analysis of circulating tumor DNA (ctDNA). This technology involves a blood test that provides detailed information on the genomic make up of any tumor present, with the ability to identify the percentage of each mutation found in an individual's blood. The concentration of tumor DNA in the blood stream has been speculated to also indicate how advanced cancer may be, and whether current therapies are having any impact.

Laboratories pursuing this technology include Foundation Medicine, Guardant Health, and Tempus, with many more in various stages of development.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

A. **Select Health covers either the Guardant360CDx liquid biopsy assay or FoundationOne LiquidCDx if <u>one</u> of the following is present:**

Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

1. Liquid biopsy may be allowed independently or concurrently with tissue-based CGP (comprehensive genomic profiling) for non-small cell lung cancer (NSCLC) that is locally advanced, which is unresectable stage III or metastatic disease.

   OR

2. Tissue-based CGP is infeasible* and an FDA-approved indication or NCCN recommendation requires information about the presence or absence of a tumor genetic biomarker

   OR

3. Member is considering participating in a clinical trial** intended to assess the effectiveness of targeted therapies based on tumor genetic biomarker, and tissue-based CGP is infeasible*.

   OR

4. Liquid biopsy is allowable independently or concurrently with tissue-based CGP for advanced or metastatic breast cancer.

*Infeasible: i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated

**Clinical trial must meet one (i–iii) of the following clinical conditions:

i. Any advanced stage III or IV solid tumors, or

ii. All lymphomas, or

iii. Multiple myeloma

Select Health does not cover the Guardant Health Shield blood test in the evaluation of colorectal cancer. This test is considered not medically necessary as the clinical utility has not been determined due to a lack of evidence available in peer-reviewed literature supporting either sufficient sensitivity or specificity.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

For individuals who have cancer who receive molecular characterization of tumor using cell-free tumor DNA (ctDNA), the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and

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standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study populations have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of this technology on health outcomes.

Billing/Coding Information

CPT CODES

Covered for the Indications Listed Above

0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer
0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in highrisk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein desgammacarboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood
0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

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81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81451	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, 3 RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure

Not Covered for the Indications Listed Above

0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence

HCPCS CODES

No specific codes identified

Key References

1. Iams, W.T., Mackay, M., Ben-Shachar, R., et al. (2024). Concurrent Tissue and Circulating Tumor DNA Molecular Profiling to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. JAMA Netw Open. 7(1): e2351700. PMID: 38252441.
2. Krebs, M. G., et al. (2022). Practical Considerations for the Use of Circulating Tumor DNA in the Treatment of Patients With Cancer. JAMA Oncology, 8 (12), 1830-1839. PMID 36264554.
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Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, **continued**

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
7/24/24	For Commercial Plan Policy, added criteria #4: "Liquid biopsy is allowable independently or concurrently with tissue-based CGP for advanced or metastatic breast cancer." as an additional qualifying factor.
8/26/24	For Commercial Plan Policy, added an exclusion for the Guardant Health Shield blood test.
3/20/25	For Commercial Plan Policy, modified requirements in criterion #A-1: "Liquid biopsy may be allowed independently or concurrently with tissue-based CGP (comprehensive genomic profiling) for non-small cell lung cancer (NSCLC) that is locally advanced, which is unresectable stage III or metastatic disease."

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Select Health

MEDICAL POLICY

GENETIC TESTING: CHARCOT-MARIE-TOOTH SYNDROME (HEREDITARY MOTOR SENSORY NEUROPATHY)

Policy # 134
Implementation Date: 3/6/10
Review Dates: 7/18/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 9/13/18, 8/7/19, 1/24/23, 2/15/24
Revision Dates: 7/1/23

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Charcot-Marie-Tooth is a spectrum of disorders and is one of the most common inherited neurological disorders, affecting approximately 1 in 2,500 people in the US. It is a polyneuropathic process that can be demyelinating or axonal and affects patients typically in the first or early second decade, but infants may be symptomatic. The neuropathy of CMT affects both motor and sensory nerves.

Hereditary motor sensory neuropathy (Charcot-Marie-Tooth disease) has been classified as types 1−7 and consists of at least 30 different disorders. The major division comprises type 1 and type 2, which together are the most common hereditary peripheral neuropathies, with an estimated prevalence of 40 per 100,000. Common features include both motor and sensory nerve manifestations with distal leg weakness, foot deformities (pes cavus, hammer toes), and sensory deficits.

Early symptoms may include frequent sprained ankles caused by distal muscle weakness or difficulty running and keeping up with peers. The only obvious physical findings may be loss of reflexes, pes cavus foot deformity, and hammer toes. Calf muscle atrophy often occurs, causing the classic "stork leg deformity." Walking is clumsy because of both muscle weakness and sensory loss. Sensory loss is gradual and mainly involves proprioception and vibration. Later changes include atrophy of the intrinsic hand and foot muscles. Palpable enlargement of the peripheral nerves may occur secondary to nerve hypertrophy. In addition, kyphosis or scoliosis often develops.

Treatment is symptomatic. Affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Quality of life has been measured and compared among various groups of individuals with Charcot-Marie-Tooth. Special shoes, including those with good ankle support, may be needed. Affected individuals often require ankle/foot orthoses (AFOs) to correct foot drop and aid walking. Orthopedic surgery may be required to correct severe pes cavus deformity. Some individuals require forearm crutches or canes for gait stability, but fewer than 5% of individuals need wheelchairs. Exercise is encouraged within the individual's capability and many individuals remain physically active. The cause of any pain should be identified as accurately as possible.

HMSN type 1, also known as Charcot-Marie-Tooth type 1 (CMT1) disease, is a demyelinating disorder of peripheral nerves. It has been subdivided based on genetic markers into types 1A, 1B, and 1C, (with type 1A being most common), although the clinical manifestations are similar. Affected patients typically present in the first or early second decade, but infants may be symptomatic. Type 1 disease is caused by mutations in genes that are expressed in Schwann cells, the myelinating cells of the peripheral nervous

system. The types that typically exhibit autosomal dominance have been subdivided into types 1A, 1B, and 1C. However, autosomal recessive and X-linked forms also occur.

CMT hereditary neuropathy needs to be distinguished from acquired non-genetic causes of peripheral neuropathy and other genetic neuropathies. The CMT phenotype consists of motor and sensory neuropathy without an established acquired cause. Individuals with CMT who experience blindness, seizures, dementia, and intellectual disability are not part of the CMT hereditary neuropathy syndrome and should be suggestive of some other diagnosis. The probability of any given group possessing a mutation for CMT is not established. Furthermore, among those with identifiable mutations, the penetrance and expressivity of mutations is also unknown.

Currently, there are no established, effective treatments to either slow or reverse the natural disease process for the various CMT variants, though, multiple treatment regimens are being explored.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover genetic testing for Charcot-Marie-Tooth Syndrome, including inheritable motor/sensory neuropathy. This testing has not been established as medically necessary in the management of patients with peripheral neuropathy.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
Extensive literature has been published on Charcot-Marie-Tooth; this evidence demonstrates the reliability of this testing (statistical validity). From this evidence, it is clear that genetic mutation is responsible, at least in part, for a wide variety of otherwise undiagnosed motor-sensory peripheral neuropathies.

GeneReviews lists 4 major types of CMT with about 30 subtypes. This will likely expand as further research on this group of disorders becomes better understood. However, it is not yet clear from the evidence what the accuracy of available genetic tests is, the penetrance or expressivity of mutations, or the necessity/importance of performing genetic testing vs. clinical testing.

The American Academy of Neurology's guideline from 2009 on genetic testing for neuropathy and subsequently reaffirmed in 2013 (England et al.), noted: "Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A)". Despite this recommendation, there is insufficient evidence to support performing testing in this situation, as it does not alter patient management in a substantive manner nor presents significant clinical utility. The guideline goes on to state, genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C). Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features, and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening.

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Genetic Testing: Charcot Marie-Tooth Syndrome (Hereditary Motor Sensory Neuropathy, continued

There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (Level U).

Currently, there remains a lack of information demonstrating the clinical utility of this testing.

Billing/Coding Information

CPT CODES

81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81403	Molecular pathology procedure, Level 4
81404	Molecular pathology procedure, Level 5
81405	Molecular pathology procedure, Level 5
81406	Molecular pathology procedure, Level 7
81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report

Key References

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2. Bassam, B. A. (2014). "Charcot-Marie-Tooth disease variants-classification, clinical, and genetic features and rational diagnostic evaluation." J Clin Neuromuscul Dis 15(3): 117-128.
3. DiVincenzo, C., C. D. Elzinga, A. C. Medeiros, I. Karbassi, J. R. Jones, M. C. Evans, C. D. Braastad, C. M. Bishop, M. Jaremko, Z. Wang, K. Liaquat, C. A. Hoffman, M. D. York, S. D. Batish, J. R. Lupski and J. J. Higgins (2014). "The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy." Mol Genet Genomic Med 2(6): 522-529.
4. England, J. D. (2014). "The shifting landscape of genetic testing for Charcot-Marie-Tooth disease." Muscle Nerve 49(4): 467-468.
5. Ostern, R., et al. (2013). "Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies." BMC Med Genet 14: 94.
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Genetic Testing: Charcot Marie-Tooth Syndrome (Hereditary Motor Sensory Neuropathy, continued

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MEDICAL POLICY

GENETIC TESTING: CHROMOSOMAL MICROARRAY ANALYSIS (CMA)

Policy # 297
Implementation Date:2/15/06
Review Dates: 5/17/07, 4/24/08, 2/18/10, 5/19/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 6/16/18, 4/17/19, 2/14/23, 2/15/24, 2/17/25
Revision Dates: 4/23/09, 5/26/16, 8/7/18, 7/1/23, 5/24/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#514 Whole Genomic Sequencing (WGS)/Whole Exome Sequencing (WES)

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (CHIP) plans. Refer to the "Policy" section for more information.

Description

Developmental disabilities are a family of chronic disorders of early onset, affecting between 5%–10% of children. Global developmental delay (DD), a heterogeneous subset of developmental disabilities, is defined as significant delay in 2 or more developmental areas and is associated with deficits in adaptation and learning skills. Those deficits are evident in comparison with the skills-attainment of chronological peers. "Significant" delay is defined as performance 2 standard deviations or more below the mean on age-appropriate, standardized norm referenced testing. The term global developmental delay is usually reserved for younger children (i.e., typically less than 5 years of age), whereas the term intellectual disability (ID) is usually applied to older children when IQ testing is more valid and reliable.

Chromosomal microarray (CMA) has been recommended as a first-tier genetic test for individuals with DD/ID, ASD, and/or multiple congenital anomalies (MCA) since 2010. One of the main advantages of CMA is its use as a discovery tool, as it requires no prior knowledge of the chromosome imbalance that is involved.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers chromosomal microarray (CMA) as outlined below.

Criteria for coverage:

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Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued

A. Diagnostic Testing for Symptomatic Individuals:

1) Testing performed on living child or adult; and

2) Diagnosis cannot be made on clinical evaluation alone; and

3) Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis; and

4) At least one of the following presentations:
   i. Isolated developmental delay (DD)/intellectual disability (ID)
   ii. DD/ID associated with other findings that are not consistent with an easily recognizable syndrome
   iii. Autism spectrum disorder
   iv. Multiple congenital anomalies[a] not specific to a well-delineated genetic syndrome.

B. Diagnostic Testing on products of conception for Intrauterine Fetal Demise or Stillbirth:

1) Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis; and

2) At least one of the following:
   i. Multiple congenital anomalies[a] not specific to a well-delineated genetic syndrome
   ii. Fetal demise or stillbirth occurred at 20 weeks of gestation or later
   iii. Recurrent pregnancy loss (beginning at second pregnancy loss).

C. Select Health covers use of chromosomal microarray analysis (CMA) in pregnancy, when the following criteria are met.

1) Any one of the following:
   i. Patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnostic testing
   ii. Patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing

[a]Multiple congenital anomalies defined as 1) two or more major anomalies affecting different organ systems or 2) one major and two or more minor anomalies affecting different organ systems. [Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.]

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

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Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued

Billing/Coding Information
Covered: For the indications outlined above

CPT CODES

0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis [SMASH from New York Genomic Center]
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities [CNGenome from Revvity]
0318U	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood [EpiSign Complete, Greenwood Genetic Center]
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81479	Unlisted molecular pathology procedure

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

Key References

1. ACOG Committee Opinion No. 446: array comparative genomic hybridization in prenatal diagnosis. Obstet Gynecol. 2009 Nov;114(5):1161-1163. doi: 10.1097/AOG.0b013e3181c33cad. PMID: 20168129. (reaffirmed 2021)
2. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018 Nov;132(5): e197-e207. doi: 10.1097/AOG.0000000000002899. PMID: 30157093
3. Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Obstet Gynecol. 2016 Dec;128(6): e262-e268. doi: 10.1097/AOG.0000000000001817. PMID: 27875474.(reaffirmed 2023)
4. Miller DT, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010 May 14;86(5):749-64. doi: 10.1016/j.ajhg.2010.04.006. PMID: 20466091.

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Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued

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Select Health

MEDICAL POLICY

GENETIC TESTING: CHROMOSOMAL MICROARRAY ANALYSIS (CMA)

Policy # 297
Implementation Date:2/15/06
Review Dates: 5/17/07, 4/24/08, 2/18/10, 5/19/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 6/16/18, 4/17/19, 2/14/23, 2/15/24, 2/17/25
Revision Dates: 4/23/09, 5/26/16, 8/7/18, 7/1/23, 5/24/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#514 Whole Genomic Sequencing (WGS)/Whole Exome Sequencing (WES)

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (CHIP) plans. Refer to the "Policy" section for more information.

Description

Developmental disabilities are a family of chronic disorders of early onset, affecting between 5%–10% of children. Global developmental delay (DD), a heterogeneous subset of developmental disabilities, is defined as significant delay in 2 or more developmental areas and is associated with deficits in adaptation and learning skills. Those deficits are evident in comparison with the skills-attainment of chronological peers. "Significant" delay is defined as performance 2 standard deviations or more below the mean on age-appropriate, standardized norm referenced testing. The term global developmental delay is usually reserved for younger children (i.e., typically less than 5 years of age), whereas the term intellectual disability (ID) is usually applied to older children when IQ testing is more valid and reliable.

Chromosomal microarray (CMA) has been recommended as a first-tier genetic test for individuals with DD/ID, ASD, and/or multiple congenital anomalies (MCA) since 2010. One of the main advantages of CMA is its use as a discovery tool, as it requires no prior knowledge of the chromosome imbalance that is involved.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers chromosomal microarray (CMA) as outlined below.

Criteria for coverage:

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MEDICAL POLICY

GENETIC TESTING: CYSTIC FIBROSIS (CF)

Policy # 289
Implementation Date: 12/15/05
Review Dates: 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 4/25/13, 2/11/16, 2/16/17, 2/15/18, 2/18/19, 2/7/23, 2/15/24
Revision Dates: 2/15/07, 2/20/14, 2/11/15, 2/25/19, 7/1/23, 8/7/23

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cystic fibrosis (CF) is a multisystem genetic disease in which defective chloride transport across membranes causes dehydrated secretions. This leads to tenacious mucus in the lungs, to mucous plugs in the pancreas, and to the characteristically high sweat chloride levels. Intelligence and cognitive function are typically normal. More than 25,000 Americans have CF, with approximately 850 individuals newly diagnosed each year. Cystic fibrosis is inherited as an autosomal recessive disorder; the responsible gene, the CF transmembrane conductance regulator (CFTR), was mapped to chromosome 7 and identified in 1989.
Cystic fibrosis has a highly variable presentation and course. Median age at diagnosis is 6–8 months; nearly 2/3 of individuals are diagnosed before 1 year of age. Some individuals have severe pulmonary and/or gastrointestinal disease while others have relatively mild disease with presentation during adolescence and young adulthood. There is a range of outcomes, from early death from pulmonary complications to mild atypical disease in second and third decades, but rarely a normal length of life. Even though median survival has increased from 18 years in 1976 to 30.1 years in 1995, there has been little life-span extension between 1990 and 1995. Survival has improved thus far, through aggressive management of pulmonary, pancreatic, and intestinal complications.

Even though there have been advances in treatment, there is no cure for CF. Severity of lung disease is the key to the quality and length of life. Ninety percent of persons who have CF die from pulmonary complications. Pulmonary function tests, especially forced expiratory volume (FEV1), are predictive of mortality: when the FEV1 is 30%, mortality is 50% in 2 years. Poor prognosis is related to respiratory complications before 1 year of age, malnutrition, and denial of the condition. Better prognosis is indicated from mild symptoms at diagnosis, pancreatic sufficiency, and atypical presentation. A survey in 1995 reported that 35% of young adults with CF worked full-time, and almost 90% had completed at least a high school education.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

Genetic Testing: Cystic Fibrosis (CF), continued

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

1. **Select Health covers genetic testing of cystic fibrosis for members** in any of the following groups:
   a) Couples seeking prenatal care; *or*
   b) Couples who are planning a pregnancy; *or*
   c) Persons with a family history of cystic fibrosis; *or*
   d) Persons with a first-degree relative identified as a cystic fibrosis carrier; *or*
   e) Reproductive partners of persons with cystic fibrosis.

2. Diagnostic Testing for Symptomatic Individuals:

a) Individuals with an intermediate range/equivocal sweat chloride test (30-59mmol/L), or

b) Individuals with a negative sweat chloride test when symptoms of CF are present, or

c) Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or

d) Infants with an elevated IRT value on newborn screening, or

e) Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD), OR

f) Mutation Identification to Guide Pharmacologic Therapy Selection (individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies), OR

3. Prenatal Testing:

a) Either biological parent has a diagnosis of CF, or

b) Family history of CF in a first degree relative, or

c) Both parents are carriers of CF mutations included in the panel, or

d) Echogenic bowel has been identified on ultrasound in a fetus.

4. CFTR Intron 8 Poly T Analysis:

Diagnostic Testing:

a) CFTR mutation analysis performed and R117H mutation detected, or

b) Diagnosis of male infertility (e.g., congenital absence of vas deferens [CAVD], obstructive azoospermia), or

c) Diagnosis of non-classic CF.

Select Health does not cover genetic carrier testing for cystic fibrosis for all other indications as the effectiveness of testing for other indications other than the ones listed above have not been established. Use of this testing in these circumstances is considered experimental/investigational.

Select Health considers a core panel of 40 mutations recommended by the American College of Medical Genetics (ACMG) medically necessary for cystic fibrosis genetic testing. Preauthorization will be required for full sequencing review. The standard CF transmembrane regulator (CFTR) mutation panel is as follows (Available at: http://www.acmg.net):

ΔF508	ΔI507	G542X	G551D	W1282X	N1303K

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R553X	621+1G→ T	R117H	1717-1G→ A	A455E	R560T
R1162X	G85E	R334W	R347P	711+1G→ T	1898+1G→ A
2184delA	1078delT	3849+10kbC→ T	2789+5G→ A	3659delC	I148T
3120+1G→ A					

Select Health considers screening for cystic fibrosis mutations that extend beyond the standard mutation panel recommended by the ACMG to be experimental/ investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Cystic fibrosis is one of the most common genetic diseases in Caucasians, with an incidence of about one in 3,300. The disease also has a fairly high incidence among Hispanics: 1 in 9,500. Cystic fibrosis is a rare disorder in native African and native Asians, estimated to occur in less than 1 in 50,000, but higher incidences are observed in American populations of these ethnic groups (1 in 15,300 and 1 in 32,100, respectively), suggesting Caucasian admixture. Recent surveys of some Native American populations also indicate high incidences: 1 in 3,970 in the Pueblo people, and 1 in 1,580 among the Zuni.

Since the identification of the gene and the major mutation responsible for CF, more than 600 mutations and DNA sequence variations have been identified in the CFTR gene. The Delta F508 mutation is represented in almost all populations, although its relative frequency varies among different geographic locations. The highest frequency is observed in Caucasian populations, where it accounts for approximately 70% of the CF alleles. Delta F508 mutation accounts for large portions of the alleles in other racial/ethnic groups: 48% in African Americans, 46% in Hispanics, and 30% in Asian Americans and Ashkenazi Jews. Some 15–20 other "common" mutations account for 2%–15% of CF alleles, depending on the ethnic composition of the patient group studied. Most of the remaining mutations are rare. The proportion of detectable mutations is an important indicator of the utility of a population-screening program. Combining detection of the Delta F508 with other mutations common to specific ethnic groups, it appears that there are several examples of populations for which 90% to 95% sensitivity can now be achieved with the current technology: the Ashkenazi Jews, Celtic Bretons, French Canadians from Quebec, and some Native Americans. In Caucasians in the United States, it is feasible to approach 90%

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Genetic Testing: Cystic Fibrosis (CF), continued

sensitivity at the current time. Because the remaining mutations are rare, expanding the panel of screened mutations is expected to achieve only marginal gains in the sensitivity. The detection rate in African Americans is about 75%. Despite the relatively high incidence in Hispanics, the detectable alleles account for only 57% of the CF mutations in this group. The promise appears to be weak in Asian Americans at 30% sensitivity.

Studies have shown that interest in CF genetic screening is limited in the general population and that agreement to participate in genetic education and testing procedures occurs primarily among pregnant women and persons with positive family histories. Uptake of prenatal genetic testing for CF varies widely, with acceptance ranging from about 50% to a high of 78% in one HMO population. Participation has been affected by factors relating to convenience, education, cost, views regarding abortion, concerns about the low sensitivity of the test, and the manner of presentation of the testing opportunity. Concerns about confidentiality and insurability and simply "not wanting to know," are often mentioned as reasons to forgo testing.

Guidelines published by the American College of Medical Genetics (ACMG) in 2001 and affirmed by the American College of Obstetrics and Gynecology (ACOG) in their policy statement published in 2001 recommend that genetic testing be offered to individuals with a family history of CF and partners of those with CF. As a group, individuals with a family history have relatively high frequencies of mutations in the CFTR gene. Members of this group have increased awareness of their risk of being carriers, as well as increased familiarity with the disease and its impact on the family. Testing may assist in making informed reproductive choices and decisions regarding family health. To date, over 900 mutations in the CF gene have been identified. As it is impractical to test for every known mutation, the ACMG Accreditation of Genetic Services Committee has compiled a standard screening panel of 25 CF mutations, which represents the standard panel that ACMG recommends for screening in the U.S. population. This 25-mutation panel incorporates all CF-causing mutations with an allele frequency of greater than or equal to 0.1 % in the general U.S. population, including mutation subsets shown to be sufficiently predominant in certain ethnic groups, such as Ashkenazi Jews and African Americans. This standard panel of mutations is intended to provide the greatest pan-ethnic detectability that can practically be performed.

The ACOG's update on carrier screening for CF (2011) added the recommendations stating that a patient previously screened should not be re-screened and the results should be documented and complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.

The NIH, ACOG, and the ACMG also recommend that CF genetic testing be offered prenatally and to couples planning a pregnancy. Data indicates that a significant level of interest in CF testing exists in this group. This is a vulnerable population and because of the inherent time constraints, it is particularly important that they receive adequate and balanced information. This information includes, but is not limited to, the implications of genetic testing, its limitations and strengths, and the risks of ensuing potential therapies and interventions, sensitivity of the test, a description of the range of severity of the disease. Care should be given to ensure decisions of couples considering testing or subsequent reproductive options are completely voluntary and made without coercion from care providers. The NIH Consensus Statement on Genetic Testing for CF and the ACMG has not recommended CF testing for the general population. Given the low incidence and prevalence of CF and the demonstrable lack of interest in the general population, there is little justification for testing. Genetic testing for CF should begin with education concerning CF. It should be clear that the patient has received the material and has had an opportunity for questions to be answered before testing is undertaken—all persons undergoing genetic testing should give written informed consent for the test.

As with any genetic testing, provision of accurate genetic counseling, particularly when the results are provided to the patient or when the intervention strategies are discussed, is essential. The implications of genetic testing, its limitations and strengths, and the risks of ensuing potential therapies and interventions mandate that individuals knowledgeable in genetics provide these services. The counseling skills required must combine respect for a patient's right to make an autonomous decision with an appropriate level of support to facilitate the decision-making process. Any strategy attempting to provide these services to the public carries with it a responsibility to enhance the educational process for physicians and other healthcare providers.

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Billing/Coding Information
Covered: For the conditions outlined above

CPT CODES

81220	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)
81221	; known familial variants
81222	; duplication/deletion variants
81223	; full gene sequence
81224	; intron 8 poly-T analysis

HCPCS CODES

No specific codes identified

Key References

1. American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG). Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Provider Guidelines. ACOG/ACMG Position Statement. Washington, DC: ACOG; 2001.
2. American College of Obstetrics and Gynecology. Policy statement on prenatal Cystic Fibrosis Testing, 12/12/01.
3. American College of Obstetricians and Gynecologists (ACOG). Update on carrier screening for cystic fibrosis. ACOG Committee Opinion No. 325. Washington, DC: ACOG; December 2005
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5. Cystic Fibrosis Diagnosed After 2 Months of Age Leads to Worse Outcomes and Requires More Therapy. Pediatrics. http://pediatrics.aappublications.org/cgi/content/full/119/1/19. 2/14/07.
6. Genetic Testing for Cystic Fibrosis. NIH Consensus Statement Available on-line at http://text.nlm.nih.gov/ or at NIH Consensus Program Information Center, P.O. Box 2577, Kensington, MD 20891, Telephone: 1-888-NIH-CONSENSUS (888-644-2667) Fax: (301) 816-2494.
7. Guidelines for Population-Based Cystic Fibrosis Carrier Screening. Adapted from the American College of Medical Genetics; Genetics in Medicine/01, Vol. 3 No. 2:149-154; on-line at http://www.acmg.net/Pages/ACMG_Activities/Poilicies Statements.htm. American College of Medical Genetics, 9650 Rockville Pike, Bethesda, MD 20814-3998, Phone: 301-530-7127, Fax: 301-571-1895
8. Watson, M. S., et al. (2004). "Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel." Genet Med, 6(5): 387-391.

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MEDICAL POLICY

GENETIC TESTING: DONOR-DERIVED CELL-FREE DNA FOR MONITORING OF REJECTION IN HEART AND KIDNEY TRANSPLANTATION

Policy # 671

Implementation Date:7/1/23
Review Dates: 8/20/24
Revision Dates: 1/22/24

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Heart Transplant

Donor-derived cell-free deoxyribonucleic acid (dd-cfDNA) is released from damaged donor heart cells and can be quantified relative to the amount of background circulating recipient cell-free DNA. An increase in the percentage of dd-cfDNA in the blood indicates injury to the transplanted (i.e., donor) heart that may be caused by acute cellular rejection (ACR) or antibody-mediated rejection (AMR), as well as other forms of injury, such as cardiac allograft vasculopathy.

The accuracy of dd-cfDNA for the detection of ACR and AMR was reported in a large prospective study of 171 patients who had undergone transplantation at least seven days prior. The study assessed the ability of dd-cfDNA to detect grade 2 ACR or grade 1 AMR. The study reported the following:

- For the detection of ACR in patients who were at least 14 days post-transplantation, the sensitivity and specificity of dd-cfDNA were 83 and 82 percent, respectively, for the cutoff value of 0.25 percent dd-cfDNA .
- For the detection of AMR in similar patients, the sensitivity and specificity of dd-cfDNA were 88 and 82 percent, respectively, for the cutoff value of 0.25 percent dd-cfDNA . For either AMR or ACR and at the 0.25 percent cutoff, the sensitivity and specificity were 88 and 82 percent, respectively.

- Given the limitations of endomyocardial biopsy to detect ACR and AMR, the study also evaluated dd-cfDNA as the reference standard to assess the accuracy of endomyocardial biopsy. When dd-cfDNA ≥ 0.25 percent was used as the reference standard, the study found that endomyocardial biopsy had a sensitivity of 20 percent and specificity of 99 percent.

After obtaining serologic tests for rejection, confirmatory biopsies are performed based on the test results as follows:

- Simultaneous gene expression and cell free DNA test results: If a GEP test and dd-cfDNA are obtained simultaneously, the result of each test must be considered. If the dd-cfDNA result is positive, a biopsy is obtained regardless of the GEP result. If the dd-cfDNA result is negative and the GEP result is positive, the approach to performance of a biopsy is individualized and may be

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Genetic Testing: Donor-Derived Cell-Free DNA for Monitoring Rejection of Heart and Kidney Transplantation, **continued**

influenced by such factors as the severity and frequency of past episodes of rejection. If both tests are negative, we do not perform a biopsy. This approach is based on the diagnostic characteristics of these tests.

- Isolated gene expression profiling: If an isolated GEP test is negative, an endomyocardial biopsy is not performed. If an isolated GEP test is positive, a biopsy is typically obtained. In patients who have two negative biopsies following elevated GEP test results, further biopsies are not obtained based on GEP results and cease GEP testing. This approach is motivated by the high negative predictive value and low positive predictive value of GEP testing.

- Isolated donor-derived cell-free DNA: In the presence of an isolated positive dd-cfDNA, a endomyocardial biopsy is obtained, while a negative dd-cfDNA result does not require a follow-up biopsy. This approach is motived by the high diagnostic accuracy of the dd-cfDNA test.

Kidney Transplant

The use of routine monitoring of donor-derived cell-free DNA (dd-cfDNA) after kidney transplant may allow clinicians to identify subclinical allograft injury and intervene prior to development of clinically evident graft injury. To evaluate this, data from 1092 kidney transplant recipients monitored for dd-cfDNA over a three-year period was analyzed to assess the association of dd-cfDNA with histologic evidence of allograft rejection. Elevation of dd-cfDNA (0.5% or more) was significantly correlated with clinical and subclinical allograft rejection. dd-cfDNA values of 0.5% or more were associated with a nearly three-fold increase in risk development of de novo donor-specific antibodies (hazard ratio 2.71) and were determined to be elevated a median of 91 days (interquartile range of 30-125 days) ahead of donor specific antibody identification.

Persistently elevated dd-cfDNA (more than one result above the 0.5% threshold) predicted over a 25% decline in the estimated glomerular filtration rate over three years (hazard ratio 1.97). Therefore, routine monitoring of dd-cfDNA allowed early identification of clinically important graft injury. Biomarker monitoring complemented histology and traditional laboratory surveillance strategies as a prognostic marker and risk-stratification tool post-transplant. Thus, persistently low dd-cfDNA levels may accurately identify allograft quiescence or absence of injury, paving the way for personalization of immunosuppression trials.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Donor-derived cell-free DNA (dd-cfDNA) for monitoring of rejection in heart or kidney transplantation is covered if ordered by an Intermountain Health Transplant Provider, or when the following criteria are met:

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested; and

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Genetic Testing: Donor-Derived Cell-Free DNA for Monitoring Rejection of Heart and Kidney Transplantation, **continued**

3. To assess the probability of allograft rejection in kidney and cardiac transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of cardiac or renal biopsy. Frequency of genetic testing to be determined by the transplant provider.

I. Frequency of Testing Recommendations for Heart

A. Year 1:
Starting day 30 post-transplantation; and then, once every 2 weeks x 2; and then, once every 3 weeks x 3; and then, monthly up to 6 months post-transplantation; and then, every 6 weeks till the end of the first-year post-transplantation.

B. Year 2:
Every 3 months.

C. Year 3:
Every 6 months.

D. Year 4:
Once yearly.

E. Year 5 and Beyond:
As needed.

II. Frequency of Testing Recommendations for Kidney

A. These are the recommended frequencies for post-kidney transplant: 2,4,7,10, and 13 months post-transplant.

B. After the 13th month, determinations will be made on a case-by-case basis, or if more frequent testing will be allowed, based on further concern of renal rejection.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

Covered for the indications outlined above when criteria are met

CPT CODES

81479	Unlisted molecular pathology procedure

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Genetic Testing: Donor-Derived Cell-Free DNA for Monitoring Rejection of Heart and Kidney Transplantation, **continued**

Not covered: the following codes are considered experimental/investigational

0540U Transplantation medicine, quantification of donor-derived cell-free DNA using next-generation sequencing analysis of plasma, reported as percentage of donor-derived cell-free DNA to determine probability of rejection

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Revision History

Revision Date	Summary of Changes
1/22/24	For Commercial Plan Policy, revised to provide coverage of this testing with criteria.

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Select Health

MEDICAL POLICY

GENETIC TESTING: EPILEPSY

Policy # 602

Implementation Date: 5/19/17
Review Dates: 7/18/18, 4/12/19, 8/7/19, 4/5/23, 5/10/24
Revision Dates: 7/1/23, 7/21/23

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Epilepsy is a disorder characterized by recurrent, unprovoked seizures. It is a heterogeneous condition that encompasses many different types of seizures and that varies in age of onset and severity. Some individuals experience seizures without any additional clinical symptoms, while others have comorbidities including autism spectrum disorder, developmental delays or regression, intellectual disability, encephalopathy, birth defects, or characteristic facial features. The causes for epilepsy vary and can include trauma, stroke, infection, structural brain abnormalities, autoimmune conditions, and genetic factors. It is estimated that 30% of epilepsies have an underlying genetic cause.

Workup of patients with epilepsy can include EEG, imaging, and laboratory testing for metabolic, autoimmune, toxic, and infectious causes of epilepsy. When these evaluations do not identify a cause, the patient is considered to have unexplained epilepsy. Genetic testing is recommended by the National Society of Genetic Counselors and endorsed by the American Epilepsy Society for individuals with unexplained epilepsy. Identifying an underlying genetic cause for epilepsy can impact treatment, providing guidance on anti-seizure medication, diet, and surgical decisions. It can also provide insight into the natural history of the condition and anticipatory guidance for healthcare providers and families. Further, it can inform recurrence risk. Commercial genetic testing for epilepsy genes is available from numerous companies. Because of the large number of epilepsy-associated genes, testing is often done by multi-gene panel testing, whole exome seqeuncing, or whole genome sequencing.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

A. Select Health covers genetic testing for epilepsy by genome sequencing, exome sequencing, or multi-gene panel, when all the following criteria are met:

1. The patient has epilepsy of unexplained etiology with onset at any age; and
2. Alternate etiologies have been considered and ruled out when possible (e.g., head

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trauma, toxic exposures, stroke, infections, autoimmune conditions, metabolic conditions, tumors, prenatal injury), and

3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.

B. Exclusions

- Genetic testing for epilepsy is considered not medically necessary in individuals who do not meet the above criteria.
- Comprehensive genetic testing for epilepsy is not medically necessary for individuals with a known familial variant unless targeted genetic testing has been performed and is negative.
- Genetic testing is considered experimental/investigational for screening for genetic epilepsy in asymptomatic individuals.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were identified. The available commercial genetic tests for epilepsy are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Genetic epilepsies can be divided into the rare epileptic syndromes that may be caused by a single-gene mutation and the common epilepsy syndromes that are thought to have a multifactorial genetic basis.

Rare Epilepsy Syndromes Associated with Single-Gene Mutations:

There are numerous rare syndromes that have seizures as their primary symptom, some of these include Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus (GEFS+), epilepsy and intellectual disability limited to females (EFMR), and Nocturnal frontal lobe epilepsy. These generally present in infancy or early childhood. Many of them are thought to be caused by single-gene mutations. The published literature on these syndromes generally consists of small cohorts of patients treated in tertiary care centers, with descriptions of genetic mutations that are detected in affected individuals.

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Genetic Testing: Epilepsy, continued

These syndromes can be evaluated by single-gene analysis, which is generally performed by direct sequencing. Direct sequencing is the gold standard for identifying specific mutations. This testing method has an analytic validity of greater than 99%. They can also be evaluated by genetic panel testing, which is generally done by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very accurate, in the range of 95% to 99%.

The literature on the clinical validity of these rare syndromes is limited, and for most syndromes, the clinical sensitivity and specificity is not defined. Dravet syndrome (Hirose and Mulley et al) is probably the most well-studied, and some evidence on the clinical validity of SCN1A mutations is available. The clinical sensitivity has been reported to be in the 70% to 80% range. In 1 series of 64 patients, 51 (79%) were found to have SCN1A mutations. The false-positive rate and the frequency of variants of uncertain significance, is not well characterized.

For the other syndromes, the associations of the genetic mutations with the syndromes have been reported in case reports or very small numbers of patients. Therefore, it is not possible to determine the clinical validity of the putative causative genetic mutations.

One potential area of clinical utility for genetic testing may be in making a definitive diagnosis and avoiding further testing. For most of these syndromes, the diagnosis is made by clinical criteria, and it is not known how often genetic testing leads to a definitive diagnosis when the diagnosis cannot be made by clinical criteria.

Another potential area of clinical utility may be in directing pharmacologic treatment. For Dravet syndrome, the seizures are often refractory to common medications. Some experts (Mulley and Ottman et al.) have suggested that diagnosis of Dravet syndrome may therefore prompt more aggressive treatment, and/or avoidance of certain medications that are known to be less effective, such as carbamazepine. However, there are no studies that examine the frequency with which genetic testing leads to changes in medication management, and there are no studies that report on whether the efficacy of treatment directed by genetic testing is superior to efficacy of treatment without genetic testing.

Therefore, there are numerous rare epileptic syndromes which may be caused by single-gene mutations, but the evidence on genetic testing for these syndromes is insufficient to form conclusions on the clinical validity and clinical utility of genetic testing. The syndrome with the greatest amount of evidence is Dravet syndrome. The clinical sensitivity of testing patients with clinically defined Dravet syndrome is relatively high in small cohorts of patients. There may be clinical utility in avoiding further testing and directing treatment, but there is only a small amount of evidence to suggest this and no evidence demonstrating that outcomes are improved.

Common Epilepsies

The common epilepsy syndromes, also known as idiopathic epilepsy, generally present in childhood, adolescence, or early adulthood. They may be generalized or focal in nature, and may be convulsant (grand mal) or absence type. They are generally thought to have a multifactorial genetic component.

The common epilepsies are generally evaluated by genetic panel testing. The larger, commercially available panels that include many mutations are generally performed by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very accurate, in the range of 95% to 99%. Less commonly, deletion/duplication analysis may be performed; this method is also considered to have an analytic validity of greater than 95%.

The literature on clinical validity includes many studies that report the association of various genetic variants with the common epilepsies. There are a large number of case-control studies that compare the frequency of genetic variants in patients with epilepsy to the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of single-nucleotide polymorphisms (SNPs) associated with epilepsy across the entire genome. No studies were identified that reported the clinical sensitivity and specificity of genetic mutations in various clinically defined groups of patients with epilepsy. In addition to these studies on the association of genetic variants with the diagnosis of epilepsy, there are numerous other studies that evaluate the association of genetic variants with pharmacogenomics of anti-epileptic medications.

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Diagnosis of Epilepsy

The Epilepsy Genetic Association Database (epiGAD) (Tan et al.) published an overview of genetic association studies in 2010. This review identified 165 case-control studies published between 1985 and 2008. There were 133 studies that examined the association of 77 different genetic variants with the diagnosis of epilepsy. Approximately half of these studies (65/133) focused on patients with genetic generalized epilepsy. Most of these studies had relatively small sample sizes, with a median of 104 cases (range, 8–1361) and 126 controls (range, 22–1390). There were less than 200 case patients in 80% of the studies. The majority of the studies did not show a statistically significant association. Using a cutoff of $p < 0.01$ as the threshold for significance, there were 35 studies (21.2%) that reported a statistically significant association. According to standard definitions for genetic association, all of the associations were in the weak-to-moderate range, with no associations reported that were considered strong.

The EPICURE Consortium published one of the larger GWAS of genetic generalized epilepsy in 2012 (12). This study included 3,020 patients with genetic generalized epilepsy (GGE) and 3,954 control patients, all of European ancestry. A 2-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million single-nucleotide polymorphisms (SNPs). In the discovery phase, 40 candidate SNPs were identified that exceeded the significance for the screening threshold (1×10^{-5}), although none of these reached the threshold defined as statistically significant for genome-wide association (1×10^{-8}). After stage 2 analysis, there were 4 SNPs identified that had suggestive associations with GGE on genes *SCN1A*, *CHRM3*, *ZEB2*, and *NLE2F1*.

A second GWAS (Guo et al.), with a relatively large sample size of Chinese patients, was also published in 2012. Using a similar 2-stage methodology, this study evaluated 1,087 patients with epilepsy and 3,444 matched controls. Two variants were determined to have the strongest association with epilepsy. One of these was on the *CAMSAP1L1* gene and the second was on the *GRIK2* gene. There were several other loci on genes that were suggestive of an association on genes that coded for neurotransmitters or other neuron function.

In contrast to the 2 studies, a GWAS published from the UK (Kasperaviciute et al.) failed to show any robust associations of SNPs with partial epilepsy. This study included 3,445 patients with partial epilepsies and 6,935 controls of European ancestry. Using a threshold of an odds ratio greater than 1.3, the authors reported that no SNPs were identified that had a statistically significant association at that level.

In 2012, Heinzen et al. used whole exome sequencing to evaluate the association of genetic variants with genetic generalized epilepsy in 118 individuals with the disorder and 242 control patients of European origin. No variants were found that reached the statistical threshold for a statistical association. From this initial data, the researchers selected 3,897 candidate genetic variants. These variants were tested in a replication sample of 878 individuals with GGE and 1,830 controls. None of the tested variants showed a statistically significant association.

In addition to the individual studies, there are a number of meta-analyses that evaluate the association of particular genetic variants with different types of epilepsy. Most of these have not shown a significant association. For example, Cordoba et al. evaluated the association of *SLC6A4* gene variants with temporal lobe epilepsy in a total of 991 case patients and 1,202 controls and failed to demonstrate a significant association on combined analysis. Nurmohamed et al. performed a meta-analysis of 9 case-control studies that evaluated the association of the *ABC1* gene polymorphisms with epilepsy. There was a total of 2,454 patients with epilepsy and 1,542 control patients. No significant associations were found. One meta-analysis that did report a significant association was published by Kauffman et al. in 2008. This study evaluated the association of variants in the *IL1B* gene with temporal lobe epilepsy and febrile seizures, using data from 13 studies of 1,866 patients with epilepsy and 1,930 controls. Combined analysis showed a significant relationship between one SNP (511T) and temporal lobe epilepsy, with a strength of association that was considered modest (odds ratio [OR]=1.48; 95% confidence interval [CI], 1.1 to 2.0; p=0.01).

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The evidence on genetic testing for the common epilepsies is characterized by a large number of studies that evaluate associations of many different genetic variants with the various categories of epilepsy. The evidence on clinical validity is not consistent in showing an association of any specific genetic mutation with any specific type of epilepsy. Where associations have been reported, they are not of strong magnitude, and in most cases, have not been replicated independently or through the available meta-analyses. Because of the lack of established clinical validity, the clinical utility of genetic testing for the common epilepsies is also lacking.

In conclusion, genetic testing for epilepsy covers a wide range of clinical syndromes and possible genetic defects. For rare epilepsy syndromes, which may be caused by single-gene mutations, there is only a small body of research, which is insufficient to determine the clinical validity and clinical utility of genetic testing. There may be a potential role in differentiating these syndromes from the common epilepsies and from each other, and in improving the efficiency of the diagnostic work-up. There also may be a potential role for genetic testing in identifying syndromes that are resistant to particular medications, and thereby directing treatment. However, now the evidence is limited and the specific way in which genetic testing leads to improved outcomes is ill-defined.

For the common epilepsies, which are thought to have a complex, multifactorial basis, the role of specific genetic mutations remains uncertain. Despite a large body of literature of associations between genetic variants and common epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. This literature does not permit conclusions on the clinical validity of genetic testing. Because of the lack of conclusions on clinical validity, conclusions on clinical utility are also lacking.

Billing/Coding Information

CPT CODES

0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, UnverrichtLundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
81401	Molecular pathology procedure level 2
81403	Molecular pathology procedure level 4
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
81406	Molecular pathology procedure level 7
81407	Molecular pathology procedure level 8
81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, GT.80 | 32 Codes Number Description PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
81479	Unlisted molecular pathology procedure

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	; full gene sequence

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81190 ; known familial variant(s)

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Select Health

MEDICAL POLICY

GENETIC TESTING: BARRETT'S ESOPHAGUS

Policy # 678
Implementation Date: 2/19/24
Review Dates:
Revision Dates: 11/11/24

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Description

The EsoGuard test and the EsoCheck device (Lucid Diagnostics, Inc., New York, NY) have been proposed as a screening kit for the detection of Barrett's Esophagus (BE). The EsoCheck is a specimen collection device in the form of a vitamin-sized, encapsulated balloon. The device is swallowed and surface textures on the balloon collect a gentle brushing of the esophageal mucosa. The balloon is collapsed to protect the collected specimen and drawn back out through the upper esophagus and mouth. The specimen is submitted to a laboratory for EsoGuard testing. The EsoGuard uses next generation sequencing bisulfate converted DNA to detect the presence of Vimentin and CyclinA1 methylation signatures at 31 sites within those genes to identify the presence of BE. The EsoCheck device has received a 510(k) clearance from the FDA while the EsoGuard was granted a breakthrough device designation. Use of the EsoGuard test for detection of BE is not considered in accordance with generally accepted standards of medical practice.

For individuals with Barrett's esophagus who receive multi-analyte assays with algorithmic analyses (MAAAs) TissueCypher Barrett's Esophagus Assay, the evidence includes four case control studies and one prospective cohort study. In a Hayes, Inc. Molecular Test Assessment regarding TissueCypher Barrett's Esophagus Assay (Castle Biosciences Inc.), literature search through October 2023, the overall body of evidence was rated very low quality and insufficient to evaluate the use of this assay. While the limited evidence may suggest that TissueCypher Barrett's Esophagus Assay may identify some patients at high-risk for progression who would be candidates for eradication therapy, the evidence also suggests this test may not reliably identify patients at low risk of progression who would be candidates for reduced surveillance. This questions whether clinical decisions based on this assay result would lead to patient benefit or harm. There were no studies found evaluating whether this testing impacted clinical outcomes. Based on current evidence uncertainty exists due to study limitations that include questions related to test accuracy and the lack of evidence directly evaluating clinical outcomes with testing. Randomized controlled trials (RCTs) are needed to validate the clinical utility of the TissueCypher Barrett's Esophagus Assay in its use to improve patient outcomes in guiding management. The evidence is insufficient to determine if this technology results in an improvement in net health outcome.

For Individuals with eosinophilic esophagitis who receive multi-analyte assays with algorithmic analyses (MAAAs) Esophageal String Test (EST), the evidence includes two prospective case studies. While these studies may be promising, no randomized controlled trials (RCTs) were found, and it remains unclear whether this test could be used to guide management in individual patients. RCTs are needed to validate the clinical utility of the EST in its use to improve patient outcomes in guiding management. The evidence is insufficient to determine if this technology results in an improvement in net health outcome.

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COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing to screen for the likelihood of Barrett's esophagus, esophageal cancer, or esophagogastric junction cancer (e.g., methylation analysis, EsoGuard). The effectiveness of this testing has not been established; therefore, this meets the plan's definition of experimental/investigational.

Select Health does NOT cover multi-analyte assays with biomarker analysis (e.g., TissueCypher, Esophageal String Test) for the management of Barrett's Esophagus and other esophageal disorders such as eosinophilic esophagitis as the effectiveness of this testing has not been established. Therefore, this meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

Not covered: Experimental/Investigational for the indications listed above

CPT CODES

0095U Inflammation (eosinophilic esophagitis), ELISA analysis of eotaxin-3 (CCL26 [C-C motif chemokine ligand 26]) and major basic protein (PRG2 [proteoglycan 2, pro eosinophil major basic protein]), specimen obtained by swallowed nylon string, algorithm reported as predictive probability index for active eosinophilic esophagitis

0108U Gastroenterology (Barrett's esophagus), whole slide–digital imaging, including morphometric analysis, computer-hyphenassisted quantitative immunolabeling of 9 protein biomarkers (p16, AMACR, p53,CD68, COX-hyphen2, CD45RO, HIF1a, HER-hyphen2, K20) and morphology, formalin-hyphenfixed paraffin-hyphenembedded tissue, algorithm reported as risk of progression to high-hyphengrade dysplasia or cancer

0114U Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus EsoGuard™, Lucid Diagnostics, Lucid Diagnostics

Key References

1. Anthem. Clinical UM Guideline. Testing for Oral and Esophageal Cancer. Last Review Date: 05/11/2023.
2. Biomarker Testing for Barrett's Esophagus and Other Esophageal Disorders. Wellmark Blue Cross and Blue Shield. Last Review Date: October 2023.
3. Poppers, D. M., et al. Novel Screening and DNA Testing for the Detection of Esophageal Precancerous Disease. *Gastroenterology & Hepatology*. Volume 18, Issue 5. May 2022.

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Revision History

Revision Date	Summary of Changes
11/11/24	Modified title of policy from "Genetic Testing: EsoGuard" to "Genetic Testing: Barrett's Esophagus" to incorporate consideration of other tests related to Barrett's Esophagus. And for Commercial Plan Policy, added language excluding coverage of the TissueCypher and Esophageal String tests: "**Select Health does NOT cover multi-analyte assays with biomarker analysis (e.g., TissueCypher, Esophageal String Test) for the management of Barrett's Esophagus and other esophageal disorders such as eosinophilic esophagitis** as the effectiveness of this testing has not been established. Therefore, this meets the plan's definition of experimental/investigational."

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The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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MEDICAL POLICY

GENETIC TESTING: EXPANDED CARRIER SCREENING

Policy # 452
Implementation Date: 8/9/10
Review Dates: 9/15/11, 7/18/13, 8/28/14, 5/7/15, 4/14/16, 4/27/17, 2/18/19, 8/16/23, 8/16/24
Revision Dates: 12/5/11, 6/1/17, 1/26/18, 8/17/23, 5/14/24, 9/4/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Genetic diseases inherited through Mendelian genetics impose a significant public health burden on society, with single-gene disorders accounting for at least 10% of pediatric admissions and 20% of infant mortality. Over 6,000 genetic disorders are inherited through Mendelian genetics, each of which affect less than 200,000 Americans, but combine to afflict 25–30 million people worldwide. Because of this heterogeneity, diagnosis and treatment are difficult for most individuals with a genetic disease.

Couples who test positive as carriers have several options to conceive a child without a lethal disease, such as a pre-implantation genetic diagnosis (PGD) or donor gametes with in vitro fertilization. With forewarning of a positive test result, couples might choose to adopt, to conceive naturally and engage in watchful waiting, have an amniocentesis-based genetic test performed for the suspected disease, or decide not to conceive. Finally, those carrier couples who choose to conceive without any intervention at all, will at minimum, benefit from knowing the diagnosis of an affected child; for some diseases ameliorative options are available, involving special drugs or rigorous diets from birth.

New technologies such as next-generation sequencing have made it possible to screen for mutations in many genes more efficiently than testing mutations in a single gene or a small number of population-specific mutations in several genes. Commercial laboratories offer these expanded carrier screening panels. There is no standardization to the makeup of these genetic panels, the composition of the panels varies among labs, and different commercial products for the same condition may test a different set of genes. Although ECS panels may include conditions that are routinely assessed in carrier testing, they also include many conditions that are not routinely evaluated.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers expanded carrier screening, only once per lifetime.*

***Select Health will cover CPT 81443 (at least 15 genes [see code description below]) once per lifetime; and if appropriate, will also cover CPT 81412 (Ashkenazi panel, see code description below) once per lifetime.**

Select Health covers the five genes (*CFTR, SMN1, HBB, HBA1,* and *HBA2*) recommended by the American College of Obstetricians and Gynecologists (ACOG) for carrier testing, when ordered individually.

Select Health does not cover the UNITY Carrier Screen as it does not align with the minimum gene panel recommendations for expanded carrier screening, per the American College of Medical Genetics and Genomics (ACMG) and Select Health guidelines; and could lead to duplication of appropriate testing.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

There is consensus on core conditions that should be offered universally. Some of these conditions are included in one or both of societal guidelines, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG), including cystic fibrosis, fragile X, and spinal muscular atrophy. Recently, these groups co-published a statement (Edwards et al., 2015), which demonstrates an approach for how healthcare providers and laboratories that wish to or that are currently offering expanded carrier screening to their patients. It was not put forward as a replacement to existing guidelines and does not advance the use of large carrier screening panels (beyond those conditions already recommended).

In a recent literature search it was found that the American College of Obstetrics and Gynecologists (ACOG, 2017) now recommends information and counseling about carrier screening should be provided to every pregnant woman, ideally before pregnancy. If the individual or reproductive partner choose to be tested, it should only happen once in a lifetime, and if either are found to be a carrier for a genetic condition, then counseling about potential reproductive outcomes should be offered. The cost to the patient and the healthcare system should be considered when an individual requests a test for a specific condition because the use of expanded carrier screening testing may be cheaper.

Billing/Coding Information

CPT CODES

81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1

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81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
81479	Unlisted molecular pathology procedure

Not covered for the indications listed above

0449U	Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)

HCPCS CODES

No specific codes identified

Key References

1. American College of Obstetrics and Gynecology. (2017) ACOG committee opinion No. 691: Carrier screening for genetic conditions. Obstet Gynecol 129: e41-55.
2. Franasiak, J. M., et al. (2016). "Expanded carrier screening in an infertile population: how often is clinical decision making affected?" Genet Med.
3. Gregg, A.R, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Oct;23(10):1793-1806.

Revision History

Revision Date	Summary of Changes
8/17/23	Reactivated policy; and for Commercial Plan Policy, reimplemented the following guideline: "Select Health covers expanded carrier screening, only once per lifetime."
5/14/24	For Commercial Plan Policy, clarified the following coverage criteria and exclusion: "**Select Health covers expanded carrier screening, only once per lifetime.* *Select Health will cover CPT 81443 (at least 15 genes [see code description below]) once per lifetime; and if appropriate, will also cover CPT 81412 (Ashkenazi panel, see code description below) once per lifetime. Select Health covers the individual five genes (CFTR, SMN1, HBB, HBA1, HBA2)** recommended by the American College of Obstetricians and Gynecologists (ACOG) for carrier testing. **Select Health does not cover the UNITY Carrier Screen** as it does not align with the minimum gene panel recommendations for expanded carrier screening, per the American College of Medical Genetics and Genomics (ACMG) and Select Health guidelines; and could lead to duplication of appropriate testing."
9/4/24	For Commercial Plan Policy, reworded the following guideline for clarification: "Select Health covers the five genes (CFTR, SMN1, HBB, HBA1, and HBA2) recommended by the American College of Obstetricians and Gynecologists

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	(ACOG) for carrier testing, ***when ordered individually***."

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Select Health

MEDICAL POLICY

GENETIC TESTING: GENE EXPRESSION PROFILING IN THE MANAGEMENT OF BREAST CANCER

Policy # 281

Implementation Date:8/30/05

Review Dates: 8/17/06, 8/21/08, 8/13/09, 8/19/10, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 5/25/18, 4/17/19, 9/29/20, 9/15/22, 2/7/23, 2/15/24, 2/18/25

Revision Dates: 9/17/07, 5/3/11, 8/22/14, 11/13/14, 1/1/15, 9/8/15, 5/25/18, 9/17/18, 7/1/23, 7/29/24, 3/10/25

Related Medical Policies:

#664 Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Excluding cancers of the skin, breast cancer is the most common cancer among individuals assigned female at birth (AFAB), accounting for nearly 1 in 4 cancers diagnosed in US women. Breast cancer in individuals assigned male at birth (AMAB) accounts for 1% of all breast cancer, with more than 2,000 men in the United States receiving a breast cancer diagnosis each year. Compared with women, breast cancer in men is typically diagnosed at an older age and more advanced stage, is overwhelmingly hormone receptor–positive and is associated with poorer breast cancer–specific survival and overall survival (OS). Although initial treatment decisions (e.g., mastectomy versus breast conserving therapy, preoperative chemotherapy) may be made based on the size and appearance of the primary tumor, and the presence of palpable axillary nodes (i.e., the clinical stage), the surgical findings are used to determine the pathologic disease stage, which dictates the prognosis and need for adjuvant systemic therapy. Many patients with hormone receptor-positive (HR+) lymph node-positive (LN+) early-stage breast cancer (ESBC) receive adjuvant chemotherapy to reduce the risk of recurrence and improve survival. However, chemotherapy often has considerable short- and long-term side effects. Improved information on recurrence risk and the likely benefit of chemotherapy may help inform decisions about chemotherapy use for individual patients.

Currently, adjuvant chemotherapy decisions may be informed by clinical and pathological information, sometimes via a risk prediction tool. Gene expression profiling (GEP) tests estimate an individual's recurrence risk through integration of tumor biology and may also identify patients most likely to benefit from chemotherapy. Currently, there are multiple commercially available gene expression profile assays.

Available genomic assay data to inform treatment decisions in individuals assigned male at birth (AMAB) are either extrapolated from clinical trials in individuals AFAB or are from retrospective studies.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a

history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers the following gene expression tests for patients with invasive breast cancer in *limited circumstances.* (Only one gene expression test will be covered per new breast cancer diagnosis.)

A. Coverage criteria for Oncotype DX, MammaPrint, EndoPredict:

1. Patient is newly diagnosed with Stage I or II breast cancer with a primary tumor that is over 5 mm, node-negative, estrogen receptor positive (ER+) and/or progesterone receptor positive (PR+), and human epidermal receptor negative (HER2-).

   OR

2. Patient is newly diagnosed with ER + and/or PR+ and HER2- breast cancer involving axillary-node micrometastasis (pN1mi) no greater than 2.0 mm or 1–3 lymph nodes and no distant metastasis.

   AND

3. Patient is a candidate for adjuvant chemotherapy (i.e., chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities) and willing to consider adjuvant chemotherapy.

B. Coverage criteria for Breast Cancer Index to assess necessity of adjuvant chemotherapy or adjuvant endocrine therapy in individuals with recently diagnosed breast tumors (when all the following criteria are met):

1. Patient is newly diagnosed with Stage I or II breast cancer with a primary tumor that is over 5mm, node-negative, hormone receptor positive, and human epidermal receptor negative (HER2-).

   OR

2. Patient is newly diagnosed with hormone receptor positive and HER2- breast cancer involving axillary-node micrometastasis (pN1mi) no greater than 2.0 mm or 1–3 lymph nodes and no distant metastasis.

   AND

3. Patient is a candidate for adjuvant therapy (i.e., adjuvant therapy is not disallowed due to other factors, such as advanced age or comorbidities) and willing to consider adjuvant therapy.

C. Coverage criteria for Prosigna to assess necessity of adjuvant chemotherapy or adjuvant endocrine therapy in individuals with recently diagnosed breast tumors (when all the following criteria are met):

1. Patient is newly diagnosed with Stage I, II or IIIA breast cancer with a primary tumor that is over 5mm, node-negative, hormone receptor positive (HR+), and human epidermal receptor negative (HER2-) or human epidermal receptor positive (HER2+)

   OR

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Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

2. Patient is newly diagnosed with hormone receptor (HR+) positive, and human epidermal receptor negative (HER2-) or human epidermal receptor positive (HER2+) breast cancer involving axillary-node micrometastasis (pN1mi) no greater than 2.0 mm or 1–3 lymph nodes and no distant metastasis.

   AND

3. Patient is post-menopausal, a candidate for adjuvant therapy (i.e., adjuvant therapy is not disallowed due to other factors, such as advanced age or comorbidities) and willing to consider adjuvant therapy.

Select Health does NOT cover gene expression testing to assist in decision-making regarding continuation of endocrine therapy after 5 years because it is not medically necessary.

Select Health does NOT cover use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with non-invasive ductal carcinoma in situ (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery; this is considered experimental/investigational.

Select Health does NOT cover the use of other gene expression assays (e.g., Mammostrat Breast Cancer Test, the Breast Cancer Index 5-Year Test, the BreastOncPx, NexCourse Breast IHC4, TheraPrint, BluePrint, or TargetPrint for any indication, as they are considered experimental/investigational.

13 Clinical risk assessment according to modified Adjuvant!Online

Table S 13: Classification of patients according to clinical risk assessment by the modified version of Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
ER negative	HER2 negative	well differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		moderately differentiated OR poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	Any	Any size	C-high

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SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
Since OncoType Dx first became available, other gene expression profile tests touting to perform similar functions have come to market. Several of these tests have been reviewed multiple times and the information below is intended to provide of summary of multiple previous reviews and technology assessments.

Oncotype DX Breast Cancer Assay
The initial indications for the 21-gene expression profile (Oncotype DX) were newly diagnosed invasive breast cancer patients with stage I or II disease that is node-negative and estrogen-receptor (ER)-positive, who would be treated with tamoxifen. Primary validation studies enrolled node-negative patients; this indication is reviewed first. More recently, Genomic Health has expanded their indication to include all stage II disease (tumor < 2 cm with spread to axillary lymph nodes or 2–5 cm without lymph node involvement); this indication for lymph node-positive disease will be reviewed separate from lymph node-negative disease.

Results from the Oncotype DX 21-gene expression profile are combined into a recurrence score (RS). Based on a study of analytic validity, tissue sampling, rather than technical performance of the assay is likely to be the greatest source of variability in results. The 21-gene expression profile was validated in studies using archived tumor samples from subsets of patients enrolled in already completed randomized controlled trials (RCTs) of early breast cancer treatment. Patients enrolled in the trial arms from which specimens were obtained had primary, unilateral breast cancer with no history of prior cancer and were treated with tamoxifen; tumors were ER-positive, most were human epidermal growth factor receptor 2 (HER2)-negative, and in the case of at least 1 trial, multifocal tumors were excluded.

Lymph Node-Negative Patients
Studies delineating the association between the 21-gene RS and recurrence risk are shown in Table 1. Results indicate strong, independent associations between the RS and distant disease recurrence or death from breast cancer. In secondary reclassification analyses of the Paik et al. data, patient risk levels were individually classified by conventional risk classifiers, then re-classified by Oncotype DX. Oncotype DX adds additional risk information to the conventional clinical classification of individual high-risk patients and identifies a subset of patients who would otherwise be recommended for chemotherapy but who are at lower risk of recurrence (average 7–9% risk at 10 years; upper 95% confidence interval [CI] limits: 11–15%). The analysis does not indicate significant erroneous reclassification, given known outcomes. Thus, a woman who prefers to avoid the toxicity and inconvenience of chemotherapy and whose Oncotype DX RS value shows that she is at very low risk of recurrence might reasonably decline chemotherapy. The lower the RS value, the greater the confidence the woman can have that chemotherapy will not provide net benefit; outcomes are improved by avoiding chemotherapy toxicity.

Table 1. Summary of Oncotype DX RS and recurrence risk studies

Study	Total N	Study Objective	Results

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Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

Paik et al. 2004a (7) TAM arm of NSABP B-14 RCT	668	Predict recurrence	RS risk	% of patients	K-M distant recurrence at 10 yr, % (95% CI)		
			Low (<18)	51	6.8	(4.0–9.6)	
			Intermed (18–30)	22	14.3	(8.3–20.3)	
			High (>31)	27	30.5	(23.6–37.4)	
			All	100	15	(12.5–17.9)	
Paik et al. 2004b (8) Additional analysis of Paik et al 2004a data	668	Reclassification study; determine incremental risk compared to conventional classifier	Risk classification by NCCN [1]	Risk reclassification by Oncotype DX	N	% DRF at 10 yr (95% CI[2])	
			Low (8%)	Low	38	100 (NR)	
				Intermed	12	80 (59–100)	
				High	3	56 (13–100)	
			High (92%)	Low	301	93 (89–96)	
				Intermed	137	86 (80–92)	
				High	178	70 (62–77)	
Bryant 2005 (9) Additional analysis of Paik et al. 2004a data	668	N % recurrence at reclassification	Risk 10-yr classification By Adjuvant! Online[1]	Risk (95%CI[2]) by Oncotype DX			
				Low (53%)	Low	214	5.6 (2.5-9)
					Int-High	140	2.9 (7-19)
				Int-High (47%)	Low	120	8.9 (4-14)
					Int-High	194	30.7 (24-38)
Habel et al. 2006 (10) Case control	255 ER+ TAM+; 361 ER+ TAM-	Predict mortality	RS risk	10-yr absolute risk of death, % (95% CI)			
				ER+, TAM-treated		ER+, No TAM	
			Low (<18)	2.8	(1.7–3.9)	6.2	(4.5–7.9)
			Int (18–30)	10.7	(6.3–14.9)	17.8	(11.8–23.3)
			High (>31)	15.5	(7.6–22.8)	19.9	(14.2–25.2)

Abbreviations: DRF, distant recurrence-free; ER, estrogen receptor; N, total number of patients; NR, not reported; RS, Oncotype DX recurrence score; K-M, Kaplan Meier; NSABP, National Surgical Adjuvant Breast and Bowel Project; RCT, randomized controlled trial; TAM, tamoxifen; NCCN, National Comprehensive Cancer Network (2004); Int/Intermed, Intermediate.

[1]Percentages are percent of total N.

[2]Estimated from graphs. Note that different outcomes were reported between Paik et al. 2004b and Bryant 2005 and could not be converted to similar outcomes with confidence intervals

An additional study, in which samples from a RCT of ER-positive, node-negative breast cancer patients treated with tamoxifen versus tamoxifen plus chemotherapy were tested by Oncotype DX, provides supportive evidence. RS high-risk patients derived clear benefit from chemotherapy, whereas the average benefit for other patients was statistically not significant, although the confidence intervals were wide and included the possibility of a small benefit.

Lymph Node-Positive Patients

Albain et al. evaluated samples from the Southwest Oncology Group Trial 8814, in which randomized node-positive, ER-positive patients treated with tamoxifen for 5 years were compared to those treated with cyclophosphamide, doxorubicin, fluorouracil (CAF) chemotherapy, followed by tamoxifen (CAF-T) for

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5 years. Samples were available for determination of RS for 41% (n=148) and 39% (n=219) of the trial arms, respectively.

In this study, 10-year disease-free survival (DFS) and overall survival (OS) outcomes in the tamoxifen study arm differed by RS risk category (p=0.017 and 0.003, respectively), indicating that the RS is prognostic. When the 2 treatment arms were compared within RS risk categories, only patients in the high RS category significantly benefited from the addition of CAF to tamoxifen (for DFS, 42% [tamoxifen] vs. 55% [CAF-T], p=0.033; for OS, 51% [tamoxifen] vs. 68% [CAF-T], p=0.027), suggesting that RS is also predictive of response to chemotherapy.

A multivariable analysis of RS interaction with DFS, adjusted for number of positive nodes, was significant for the first 5 years of follow-up at p=0.029 and remained significant after adjusting for age, race, tumor size, progesterone receptor status, grade, p53, and HER2. However, the interaction was not significant (p=0.15) after adjusting for ER level (ER gene expression is a component of the 21-gene profile). Interaction results were similar for OS.

Dowsett et al. included a separate evaluation of node-positive patients in their examination of the ATAC trial samples. Of 306 node-positive patients, 243 had 1–3 involved nodes, and 63 patients, 4 or more; these were not evaluated separately. Rates of distant recurrence at 9 years were 17% (95% CI: 12–24%), 28% (20–39%), and 49% (35–64%), respectively. It is not clear that the risk of distant recurrence in low-risk RS patients would be sufficiently low to forgo the choice of chemotherapy. The authors note that their study "… did not directly evaluate the value of RS in predicting the benefit of chemotherapy."

Goldstein et al. evaluated samples from the Eastern Cooperative Oncology Group E2197 trial, which included patients with 0–3 positive lymph nodes and operable tumors greater than 1 cm in size. Patients were randomly assigned to doxorubicin plus cyclophosphamide or docetaxel plus 5 years of endocrine therapy; outcomes were not significantly different for the study arms. A case-control study of samples from this trial found that low-risk RS patients with 0–1 positive node had a recurrence risk of 3.3% (95% CI: 2.2-5%), and low-risk patients with 2–3 positive nodes had a recurrence risk of 7.9% (4.3–14.1%). RS was also a significant predictive of risk regardless of nodal status.

A previous study by Chang et al. reported that in women with locally advanced breast cancer treated with neoadjuvant docetaxel (n=97), a complete response was more likely in those with a high RS (p=0.008). Gianni et al. studied 93 patients with locally advanced breast cancer who received neoadjuvant taxane chemotherapy, then post-surgery CMF treatment and tamoxifen (if ER-positive). The authors reported that pathological complete response was more likely in patients with high RS results than with low RS results ($p < 0.01$).

One study surveyed oncologists ordering the 21-gene profile for lymph node-positive patients to determine the effect of the assay results on treatment recommendations and reported that approximately half changed their recommendations after receiving RS results, with 33% recommending endocrine therapy alone, instead of endocrine plus chemotherapy. However, only medical oncologists who were already using the assay (16% response rate) were surveyed, thus biasing the results. Finally, no outcomes were reported, providing no firm evidence of clinical utility.

Additional studies are necessary before it is possible to confidently withhold currently recommended chemotherapy from lymph node-positive invasive breast cancer patients with low/intermediate RS results. The RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) trial, led by the Southwest Oncology Group, will enroll 4,000 women with RS < 25 who have early-stage, hormone receptor-positive, HER2-negative breast cancer involving 1 to 3 lymph nodes. Patients will be randomized to receive either chemotherapy with endocrine therapy or endocrine therapy alone. The primary trial outcomes are expected to be completed in December 2016 (available online at: http://clinicaltrials.gov/ct2/show/NCT01272037).

Patients with DCIS

Ductal carcinoma in situ (DCIS) is breast cancer located in the lining of the milk ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated. The frequency of DCIS diagnosis in the U.S. has increased in tandem with the widespread use of screening mammography, accounting for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. Recommended treatment is lumpectomy (mastectomy is also an option) with or without radiation treatment; post-surgical tamoxifen treatment is recommended for ER-positive DCIS, especially if excision alone is used. Because the overall

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rate of ipsilateral tumor recurrence (DCIS or invasive carcinoma) is about 25% at 10 years, it is believed many women are over treated with radiation therapy. Thus, accurate prediction of recurrence risk may identify those women who may safely avoid radiation.

The Oncotype DX DCIS test uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer. According to the Oncotype website, analyses from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study and the Habel et al. case-control study (10) were used to select genes that predict the risk of recurrence independent of tamoxifen treatment and ER status. Scaling and category cut-points were based on an analysis of DCIS Score results from a separate cohort of patients with DCIS; this study has not yet been published and is available only as a meeting abstract. In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, the Oncotype DX Score for DCIS was compared with the 10-year recurrence risk in a subset of DCIS patients treated only with surgery and some with tamoxifen (n=327). DCIS Score was significantly associated with recurrence outcomes (HR: 2.34 per 50 units; 95% CI: 1.15, 4.59; p=0.02) whether patients were treated with tamoxifen. The standard Oncotype DX Score for early breast cancer was not associated with DCIS recurrence outcomes. This study is available as a meeting abstract but has not yet been published. These studies address the development of the Oncotype DX DCIS Score and the clinical validity (association of the test result with recurrence outcomes). Whether women are better categorized as to their recurrence risk by the Oncotype DX DCIS Score compared with standard clinical indicators of risk has not yet been addressed. Full evaluation awaits publication of studies.

MammaPrint

In the most recent review completed in April 2014, two systematic reviews and thirteen primary literature articles met inclusion criteria for this report. MammaPrint was reviewed May 2011, which concluded, “Of note, to date, no studies have been performed which assess the comparative effectiveness of MammaPrint to any other gene expression profile test such as Oncotype DX to assess whether a seventy gene signature or a twenty-one gene signature or any other gene signature has greater sensitivity or specificity especially given the fact they do not all assess similar genes. Since mid-2011, there have been a number of studies which have compared MammaPrint to other gene expression tests.

One of the two systematic reviews published by Paik et al. speaks to the fact that Oncotype Dx is the only breast cancer prognostic that has reached level IB evidence and that tests such as MammaPrint and MapQuantDx are further behind in their publication of clinically relevant data. However, the group acknowledges that other gene expression tests such as MammaPrint are expected to provide similar information to already marketed adjuvant chemotherapy prognostic tests. Notably, the recently published recommendation by NICE does not advise using MammaPrint in general practice, as there are still unanswered questions regarding its clinical utility and cost-effectiveness.

The primary literature, dating back to the last review, is generally favorable regarding the MammaPrint test. For example, in a prospective comparative trial with MammaPrint and Adjuvant! Online, MammaPrint was able to decrease the number of patients considered to be at high risk, and therefore, in need of adjuvant chemotherapy. Similarly, Drukker et al. showed that fewer patients would continue adjuvant chemotherapy with the use of MammaPrint in a 427-patient prospective study. Though some evidence demonstrates potential clinical utility, no published guidelines, systematic reviews, or society statements illustrate how the test should be used and interpreted within the clinical setting.

Since the last review, new evidence demonstrates Mammaprint offers the potential for use in clinical practice for prognostic stratification and treatment selection for patients with breast cancer, particularly if they are hormone receptor-positive. However, questions remain as to how the test will be employed in the clinical setting.

TargetPrint

TargetPrint is a microarray-based gene expression test that offers a quantitative assessment of ER, PR, and HER2 overexpression in breast cancer. TargetPrint is offered in conjunction with MammaPrint gene expression profiling to provide the physician an even more complete basis for treatment decisions. The manufacturer states that, as compared to Immunohistochemistry (IHC), TargetPrint provides additional information. Whereas IHC provides a semi-quantitative positive or negative result, the gene expression result produced by TargetPrint, provides data on the absolute level of ER, PR, and HER2 gene expression. Published information on the TargetPrint is limited to studies examining its correlation with

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measurements of ER, PR, and HER2 receptors (Gunven et al, 2011; Gevensleben et al, 2010; Roepman et al, 2009). There is a lack of evidence from published prospective clinical studies that demonstrates that quantification of ER, PR, and HER2 gene expression by TargetPrint alters management such that clinical outcomes are improved.

BluePrint

BluePrint is an 80-gene expression assay that classifies breast cancer into basal type, luminal type, or HER2-type. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint®. Krijgsman et al. (2012) noted that classification of breast cancer into molecular subtypes may be important for the proper selection of therapy, as tumors with seemingly similar histopathological features can have strikingly different clinical outcomes. Herein, these researchers reported the development of a molecular subtyping profile (BluePrint), which enables rationalization in patient selection for either chemotherapy or endocrine therapy prescription. An 80-Gene Molecular Subtyping Profile (BluePrint) was developed using 200 breast cancer patient specimens and confirmed on 4 independent validation cohorts (n = 784). Additionally, the profile was tested as a predictor of chemotherapy response in 133 breast cancer patients, treated with T/FAC neoadjuvant chemotherapy. BluePrint classification of a patient cohort treated with neoadjuvant chemotherapy (n = 133) showed improved distribution of pathological Complete Response (pCR), among molecular subgroups compared with local pathology: 56% of the patients had a pCR in the Basal-type subgroup, 3% in the MammaPrint low-risk, luminal-type subgroup, 11% in the MammaPrint high-risk, luminal-type subgroup, and 50% in the HER2-type subgroup. The group of genes identifying luminal-type breast cancer is highly enriched for genes having an Estrogen Receptor binding site proximal to the promoter-region, suggesting that these genes are direct targets of the Estrogen Receptor. Implementation of this profile may improve the clinical management of breast cancer patients, by enabling the selection of patients who are most likely to benefit from either chemotherapy or from endocrine therapy, but current studies are inadequate to prove the clinical utility of this testing in clinical practice. Furthermore, there is no information regarding BluePrint/molecular subtyping from NCCN's clinical practice guideline on "Breast cancer" (Version 2.2013).

The aim of this study was to analyze the correlation between the pathologic complete response (pCR) rate after neoadjuvant chemotherapy and long-term outcome (distant metastases-free survival [DMFS]) in patients with early-stage breast cancer using BluePrint and MammaPrint molecular subtyping versus clinical subtyping using immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) for the determination of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2). Data were analyzed from 437 patients in four neoadjuvant chemotherapy trials. BluePrint and MammaPrint outcomes were determined from 44K Agilent arrays, the I-SPY 1 data portal, or Affymetrix U133A arrays. The pCR rate differed substantially among BluePrint molecular subgroups: 6% in Luminal A-type, 10% in Luminal B-type, 47% in HER2-type, and 37% in Basal-type patients. In the Luminal A-type group (n = 90; including seven HER2-positive patients and eight triple-negative patients by IHC/FISH), the 5-year DMFS rate was 93%. The pCR rate provided no prognostic information, suggesting these patients may not benefit from chemotherapy. Forty-three of 107 (40%) HER2-positive patients were classified as Luminal-type by BluePrint and may have lower response rates to targeted therapy. Molecular subtyping identified 90 of 435 (21%) patients as Luminal A-type (BluePrint Luminal-type/MammaPrint Low Risk) with excellent survival. The pCR rate provided no prognostic information. Molecular subtyping can improve the stratification of patients in the neoadjuvant setting: Luminal A-type (MammaPrint Low Risk) patients have a good prognosis with excellent survival and do not seem to benefit from chemotherapy. We observed marked benefit in response and DMFS to neoadjuvant treatment in patients subtyped as HER2-type and Basal-type. BluePrint with MammaPrint molecular subtyping helps to improve prognostic estimation and the choice of therapy versus IHC/FISH.

Marked differences are observed between BluePrint and MammaPrint (microarray-based) breast cancer subtypes and centrally re-assessed pathological surrogates (based on ER, PR, HER2 & Ki67). The greatest discordance is seen in the substratification of Luminal patients, and in the HR+/HER2+ patients. The observed subtype discrepancies may have an important impact on treatment decision-making. Concordances are in line with recent observation that the four main breast cancer subtypes have common etiology and similar therapeutic opportunities [TCGA, 2012].

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TheraPrint
TheraPrint is a microarray-based gene assay of 55 biomarkers and variant analysis results for 4 genes that have been identified as potential markers for predicting prognosis and therapeutic response to a variety of therapies. It is still in experimental stages and is used in conjunction with MammaPrint. TheraPrint for breast cancer patients provides an individualized genomic fingerprint of the patient's tumor and correlates gene expression and variant analysis results with a likely response or resistance to a variety of hormonal, chemical, and biological therapies. These include important therapies using SERMs, aromatase inhibitors, anti-androgen, alkylating agents, anti-metabolites, anthracyclines, mitotic inhibitors, platinum-based chemotherapy, topoisomerase inhibitors, angiogenesis inhibitors, HER2/EGFR and HER2/PI3K pathway inhibitors, and others.

Breast Cancer Index SM
The Breast Cancer Index is a simultaneous assessment of HOXB13:IL17BR (H/I) Index and the MGISM (Molecular Grade Index). The 2008 TEC Assessment (3) reviewed available studies for the original component assays. There was insufficient evidence to determine whether the H/I Ratio is better than conventional risk assessment tools in predicting recurrence. Ten-year recurrence rates of patients classified as low risk in available studies were 17–25%, likely too high for most patients and physicians to consider forgoing chemotherapy. The Molecular Grade Index is intended to measure tumor grade using the expression of 5 cell-cycle genes and to provide prognostic information in ER-positive patients regardless of nodal status.

Ma et al. evaluated MGI along with H/I in 93 patients with lymph node–negative tumors who received adjuvant hormone therapy and found that each index modified the other's predictive performance. High MGI was associated with significantly worse outcome only in patients with high H/I and vice versa. When the H/I Ratio and MGI were categorically combined into a single predictor, the estimates of 10-year distant metastasis-free survival were 98% (95% CI: 96–100%), 87% (77–99%), and 60% (47–78%) for the low, intermediate, and high-risk groups, respectively.

Jerevall et al. combined the H/I Ratio and MGI into a continuous risk model using 314 ER-positive, node-negative postmenopausal patients from the tamoxifen-only arm of an RCT. The continuous model was also categorized, resulting in proportions of low-, intermediate-, and high-risk patients similar to those reported in the Ma et al. study. This continuous predictor was tested in patients from the no adjuvant treatment arm (n=274) of the same clinical trial, with estimates of rates of distant metastasis at 10 years in the low-, intermediate-, and high-risk groups of 8.3% (95% CI: 4.7–14.4), 22.9% (14.5–35.2), and 28.5% (17.9–43.6), respectively. The estimates of breast cancer-specific death were 5.1% (95% CI: 1.3–8.7), 19.8% (10.0–28.6), and 28.8% (15.3–40.2). An independent population of otherwise similar but tamoxifen-treated patients was not tested.

Jankowitz et al. evaluated tumor samples from 265 ER-positive, lymph node (LN)-negative, tamoxifen-treated patients from a single academic institution's cancer research registry. BCI categorized 55%, 21%, and 24% of patients as low-, intermediate- and high-risk, respectively, for distant recurrence. The 10-year rates of distant recurrence were 6.6% (95% CI: 2.3–10.9%), 12.1% (95% CI: 2.7–21.5%), and 31.9% (95% CI: 19.9–43.9) and of breast cancer-specific mortality were 3.8%, 3.6%, and 22.1% in low-, intermediate-, and high-risk groups, respectively. In a multivariate analysis, BCI was a significant predictor of distant recurrence and breast cancer-specific mortality. In a time-dependent (10-year) ROC curve analysis of recurrence risk, the addition of BCI to Adjuvant! Online risk prediction increased maximum predictive accuracy in all patients from 66% to 76% and in tamoxifen-only treated patients from 65% to 81%.

Mammostrat Breast Cancer Test
Mammostrat is an immunohistochemistry (IHC) test intended to evaluate risk of breast cancer recurrence in postmenopausal, node-negative, ER-positive invasive breast cancer patients who will receive endocrine therapy and are considering adjuvant chemotherapy. The test employs 5 monoclonal antibodies to detect gene expression of proteins biologically independent of each other and not involved in cell proliferation, hormone receptor status, or growth/differentiation, thus potentially allowing integration with clinically routine biomarkers. A proprietary diagnostic algorithm is used to calculate a risk score and to classify patients into high-, moderate-, or low-risk categories.

One published study described the development of the assay but provides no information on technical performance (analytic validity). In a validation study in an independent cohort, a multivariable model

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predicted 50%, 70%, and 87% 5-year DFS for patients classified as high, moderate, and low prognostic risk, respectively, by the test results (p=0.0008). An additional study of the same trial samples used for Oncotype DX validation (NSABP B-14 and B-20 trials) found that among patients with early, node-negative breast cancer treated only with tamoxifen, those stratified by Mammostrat into low-, moderate-, and high-risk groups had recurrence-free survival estimates of 85%, 85%, and 73%, respectively. Both low- and high-risk groups benefited significantly from chemotherapy treatment, but high-risk patients benefited to a greater degree. The moderate-risk group was not well-separated from the low-risk group and thus, moderate-risk results do not appear to provide clinically useful information. A test for an interaction between chemotherapy and the risk group stratification was not significant (p=0.13).

Bartlett et al. used Mammostrat on 1,540 of 1,812 patient samples from a consecutive cohort for which minimum 9-year outcomes were available. The tested samples were from tamoxifen-treated patients; 568 of these were from node-negative patients treated only with tamoxifen and whose tumors were ER-positive. In the latter group, the distant recurrence rates at 10 years for low-, moderate-, and high-risk patients were 7.6% (95% CI: 4.6–10.5%), 16.3% (10.0–22.6%), and 20.9% (12.3–29.5%), respectively. In multivariable analysis, Mammostrat was not a significant predictor of recurrence-free survival in node-negative, ER-positive patients treated only with tamoxifen. However, when all patients (24% node-positive, 20% tumors > 2.0 cm, 18% ER-negative, and 46% treated with chemotherapy) with complete Mammostrat data (n=1,300) were included in a multivariable analysis, Mammostrat scores were independent predictors of recurrence-free survival (p=0.0007). In exploratory analyses of various subpopulations (e.g., node-negative vs. node-positive, ER-negative), Mammostrat appeared to perform similarly in terms of identifying risk groups. However, the numbers of subsets were small.

BreastOncPx

The BreastOncPx test is a reverse transcriptase-polymerase chain reaction (RT-PCR) test performed on formalin-fixed, paraffin embedded tissue that measures the gene expression of 14 genes associated with key functions such as cell-cycle control, apoptosis, and DNA recombination and repair. The results are combined into a metastasis score, which is reported to be associated with the risk of distant metastases in patients who are node-negative and estrogen-receptor positive.

Tutt et al. published information on the development and validation of the test; no information on analytic validity was provided. In order to develop a gene signature that was completely prognostic for distant recurrence and not confounded by treatment prediction, samples from untreated patients with early breast cancer were used. The training set (n=142) was derived from a cohort diagnosed with lymph node-negative stage T1 and T2 breast cancer from 1975 to 1986; ER-positive samples from patients who had had no systemic treatment were selected for analysis. Fourteen genes were eventually selected as most prognostic of time-to-distant metastasis and were given equal weighting in a summary metastasis score (MS). Using a single cutoff, patients are separated into high- and low-risk groups.

The 14-gene signature was validated on ER-positive samples (n=279) from a separate cohort of patients diagnosed with lymph node-negative primary breast cancer between 1975 and 2001. The estimated rates of distant metastasis-free survival were 72% (95% CI: 64–78%) for high-risk patients and 96% (95% CI: 90–99%) for low-risk patients at 10 years' follow-up. Overall, 10-year survival for high- and low-risk patients was 68% (95 CI: 61% to 75%) and 91% (95% CI: 84 to 95%), respectively. After adjusting for age, tumor size, and tumor grade in a Cox multivariate analysis, the HRs for distant metastasis-free survival for the high- versus low-risk group were 4.02 (95% CI: 1.91–8.44) and 1.97 (95% CI: 1.28 to 3.04) for distant metastasis-free survival and overall survival, respectively. However, this difference in risk between groups was not maintained when the analysis was restricted to patients with tumors larger than 2 cm (p value for interaction 0.012).

ROC analysis of the continuous MS for distant metastasis and for death at 10 years, compared to Adjuvant! resulted in slightly higher area under the curves (AUCs) for the MS in each case: 0.715 vs. 0.661 for distant metastases, and 0.693 vs. 0.655 for death. MS was not added to Adjuvant! and compared to Adjuvant! alone.

NexCourse Breast IHC4

NexCourse Breast IHC4 evaluates the protein expression of ER/PR, HER2, and Ki-67 to provide a combined recurrence risk score. The assay technology uses quantitative image analysis to measure immunofluorescent signals, with results that can be combined in an algorithm to generate the recurrence

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risk score. The use of quantitative immunofluorescence is said to increase sensitivity, be more reproducible, and allow specific measurement of tumor cells.

Cuzick et al. evaluated 1,125 ER-positive patients from the Arimidex, Tamoxifen, and Alone or in Combination (ATAC) trial, who did not receive adjuvant chemotherapy, already had the Oncotype DX Recurrence Score (RS) computed, and had adequate tissue for the IHC4 measurements. Of these, 793 were node-negative and 59 were HER2-positive (but were not treated with trastuzumab). A prognostic model that combined the 4 immunohistochemical markers was created (IHC4). In a model combining either IHC4 or Oncotype DX Rs with classical prognostic variables, the IHC4 score was found to be similar to the Oncotype DX RS, and little additional prognostic value was seen in the combined use of both scores. In a direct comparison, the IHC4 score was modestly correlated with the Oncotype DX RS (r=0.72); the correlation was similar for node-negative patients (r=0.68). As an example, for a 1–2 cm, node-negative poorly differentiated tumor treated with anastrozole, 9-year distant recurrence at the 25th versus 75th percentiles for IHC4 and Oncotype DX were 7.6% versus 13.9% and 9.2% versus 13.4%, respectively. The IHC4 score was validated in a separate cohort of 786 ER-positive women, about half of whom received no endocrine treatment. The IHC4 score was significant for recurrence outcomes (HR: 4.1; 95% CI: 2.5–6.8).

Barton et al. assessed the clinical utility of IHC4 plus clinicopathologic factors (IHC4 + C) by comparison with Adjuvant! Online and the Nottingham Prognostic Index (NPI). The study prospectively gathered clinicopathologic data for consecutively treated postmenopausal patients (n=101 evaluable) with hormone receptor-positive, HER2-negative, LN-negative or -positive with 1–2 nodes, resected early breast cancer. Of 59 patients classified as intermediate-risk group by the NPI, IHC4 reclassified 24 to low risk and 13 to high risk. IHC4 reclassified 13 of 32 Adjuvant! high-risk patients to intermediate risk, and 3 of 32 to low risk. In addition, 15 of 26 Adjuvant! intermediate-risk patients were reclassified to low-risk. No Adjuvant! low-risk patients were reclassified as high-risk.

Prosigna

The Prosigna ROR score is an algorithmic calculation that combines gene expression results and clinicopathological parameters/metrics that are specific to each individual patient. In some respects, the Prosigna ROR represents an individual patient prediction tool, fortified with the PAM50 gene assay. The NanoString nCounter Analysis System is one of several next-generation genomic tools that is being applied to clinical applications. The nCounter System is a standalone platform that was FDA 510(k) cleared for use with Prosigna in September 2013. In contrast to first-generation genomic tools such as DNA microarrays and quantitative PCR, the nCounter platform was designed to be an enzyme-free nucleic acid detection system that is easy to use and applicable to clinically-relevant biological samples such as FFPE tissue samples. The NanoString technology directly measures and counts single molecules of nucleic acids and therefore, similar to Next-Generation Sequencing technologies, is a digital technology. The digital data sets apart these next-generation technologies from their first-generation counterparts. The digital data is much more accurate and precise and is simpler to interpret than analog data that must be calibrated to facilitate data interpretation.

The NanoString nCounter system, consisting of a Prep Station and a Digital Analyzer, can be installed locally, hence FFPE samples do not need to be shipped to a centralized lab for analysis. The local pathology laboratory maintains ownership of the diagnostic work-up and remains the service provider. The advantages of this decentralized business model are a more rapid turn-around time and interface with the local care team. NanoString oversees the production and distribution of the consumable Prosigna Kits, consisting of the 50 gene-based CodeSet and 8 controls, other consumables require for the assay, and an associated RNA isolation kit.

In a recent review that was completed in September of 2015, two systematic reviews and 9 primary studies were identified which met inclusion criteria for this report. The literature primarily illustrates the analytical validity and clinical validity of the Prosigna PAM50 gene panel. Meaningful conclusions from the literature include the following:

- PAM50 was prognostic for disease-free survival and overall survival but immunohistochemistry was not.
- PAM50 was predictive of tamoxifen benefit but not statistically significantly.

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Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

- More patients were identified as high-risk and fewer as intermediate-risk with PAM50 than with Oncotype DX.
- PAM50 gene test has shown in one study to be clinically relevant for predicting distant recurrence.
- PAM50 results changed treatment recommendations in 20% of patients.

Billing/Coding Information
Covered: For the conditions outlined above

CPT CODES

0008M	Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement Insight TNBCtype™, Insight Molecular Labs
0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score
0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin- embedded (FFPE) tissue, algorithm reported as a recurrence risk score
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
81479	Unlisted molecular pathology procedure
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score.
81520	Oncology (breast), mRNA, gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis

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Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

81522 Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score

81523 Oncology, mRNA, next-generation sequencing gene expression profiling

81599 Unlisted multianalyte assay with algorithmic analysis

HCPCS CODES

Covered: For the conditions outlined above

S3854 Gene expression profiling panel for use in the management of breast cancer treatment

Key References

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Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards. Also, revised to incorporate coverage criteria for EndoPredict and standard Breast Cancer Index tests (both tests were previously not covered), and added exclusion for Breast Cancer Index 5-Year Test.
7/29/24	For Commercial Plan Policy, consolidated coverage criteria for Oncotype DX, Prosigna, MammaPrint, and EndoPredict tests into one uniform set of coverage criteria that aligns with updated NCCN Guidelines. Also, updated coverage criteria for Breast Cancer Index test to align with updated NCCN Guidelines.
3/13/25	For Commercial Plan Policy, created criteria section C to separate requirements for coverage of the Prosigna test, and added clarifying language to the following exclusion: "Select Health does NOT cover gene expression testing to assist in decision-making regarding continuation of endocrine therapy after 5 years ***because it is not medically necessary***."

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Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

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MEDICAL POLICY

GENETIC TESTING: GENE EXPRESSION PROFILING IN THE MANAGEMENT OF BREAST CANCER

Policy # 281

Implementation Date:8/30/05

Review Dates: 8/17/06, 8/21/08, 8/13/09, 8/19/10, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 5/25/18, 4/17/19, 9/29/20, 9/15/22, 2/7/23, 2/15/24, 2/18/25

Revision Dates: 9/17/07, 5/3/11, 8/22/14, 11/13/14, 1/1/15, 9/8/15, 5/25/18, 9/17/18, 7/1/23, 7/29/24, 3/10/25

Related Medical Policies:

#664 Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Excluding cancers of the skin, breast cancer is the most common cancer among individuals assigned female at birth (AFAB), accounting for nearly 1 in 4 cancers diagnosed in US women. Breast cancer in individuals assigned male at birth (AMAB) accounts for 1% of all breast cancer, with more than 2,000 men in the United States receiving a breast cancer diagnosis each year. Compared with women, breast cancer in men is typically diagnosed at an older age and more advanced stage, is overwhelmingly hormone receptor–positive and is associated with poorer breast cancer–specific survival and overall survival (OS). Although initial treatment decisions (e.g., mastectomy versus breast conserving therapy, preoperative chemotherapy) may be made based on the size and appearance of the primary tumor, and the presence of palpable axillary nodes (i.e., the clinical stage), the surgical findings are used to determine the pathologic disease stage, which dictates the prognosis and need for adjuvant systemic therapy. Many patients with hormone receptor-positive (HR+) lymph node-positive (LN+) early-stage breast cancer (ESBC) receive adjuvant chemotherapy to reduce the risk of recurrence and improve survival. However, chemotherapy often has considerable short- and long-term side effects. Improved information on recurrence risk and the likely benefit of chemotherapy may help inform decisions about chemotherapy use for individual patients.

Currently, adjuvant chemotherapy decisions may be informed by clinical and pathological information, sometimes via a risk prediction tool. Gene expression profiling (GEP) tests estimate an individual's recurrence risk through integration of tumor biology and may also identify patients most likely to benefit from chemotherapy. Currently, there are multiple commercially available gene expression profile assays.

Available genomic assay data to inform treatment decisions in individuals assigned male at birth (AMAB) are either extrapolated from clinical trials in individuals AFAB or are from retrospective studies.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family

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MEDICAL POLICY

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Revision Dates: 9/17/07, 5/3/11, 8/22/14, 11/13/14, 1/1/15, 9/8/15, 5/25/18, 9/17/18, 7/1/23, 7/29/24, 3/10/25

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Review Dates: 8/17/06, 8/21/08, 8/13/09, 8/19/10, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 5/25/18, 4/17/19, 9/29/20, 9/15/22, 2/7/23, 2/15/24, 2/18/25

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MEDICAL POLICY

GENETIC TESTING: GENETIC MUTATION ANALYSIS UTILIZING SOLID TUMOR TISSUE

Policy # 570
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Related Medical Policies:

#581 Genetic Testing: Cell-Free Tumor DNA/Liquid Biopsy

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Cancer is a complex genetic disease influenced by both inherited variants in germline DNA and somatic alterations acquired during formation of the tumor. Prior to tumor genome sequencing, many genes that play a role in cancer were discovered through studies of the germline. Linkage studies in families with inherited, typically childhood cancers, identified rare germline mutations in genes related to DNA damage repair, RAS signaling, or PIK3 signaling. In contrast to childhood cancers, adult tumors have largely been considered 'sporadic'; however, mounting evidence points to a potentially substantial influence from the germline.

Somatic genetic testing for the purpose of cancer management guidance is a rapidly evolving field of molecular medicine. Genetic testing of a solid or hematologic tumor can provide important information regarding the prognosis, risk for recurrence, or help predict tumor response to chemotherapeutic agents. In addition, genetic testing of tissue (e.g., blood) or stool, for evidence of a tumor is becoming an important tool in the early detection of cancer. While this is an area of rapid and ongoing research, clinical validity and utility is proven for only a subset of companion diagnostic genetic tests at this time.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

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Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

Select Health covers multi-marker tumor panels using next-generation sequencing in the diagnosis and treatment of cancer as a method to guide the selection of therapeutic agents for malignant tumors in *limited circumstances*.

Members must meet one of the following (A, B, C, D, or E) of the following to be eligible for next-generation sequencing:

A. Member is considering participating in a clinical trial* intended to assess the effectiveness of targeted therapies based on tumor marker; **OR**

B. Non-small cell lung cancer (NSCLC) regardless of stage; **OR**

C. For any stage III or IV solid organ tumor, and the panel must include BRAF, TMB, MSI, and NTRK; (NTRK using RNA is mandatory in secretory carcinoma of breast and salivary glands; congenital fibrosarcoma; cellular mesoblastic nephroma; thyroid cancer, particularly in children (frequency 2 to 28 percent, depending on the series); glioma (particularly select pediatric high-grade gliomas); specific sarcomas, such as inflammatory myofibroblastic tumor; Spitzoid neoplasms; and suggested in all other tumors with > 1% risk of harboring NTRK fusion); **OR**

D. Comprehensive next-generation sequencing for endometrial cancers, including endometrioid, clear cell, serous and carcinosarcoma subtypes, will be covered if either of the following criteria have been met:

1. Intact mismatch repair (MMR) protein expression with abnormal p53 immunohistochemical staining pattern; or

2. High/high-intermediate risk as determined by GOG 99 criteria with or without abnormal p53 immunohistochemical staining pattern; **OR**

E. A genomic biomarker-linked therapy has been approved by the FDA for their cancer clinical scenario, or there are established genomic biomarker-based treatment contraindications or exclusions.

Specifically related to homologous recombination deficiency (HRD), possibly present in breast, ovarian, pancreatic, and prostate cancer, the following tests must be performed to identify HRD: including BRCA1/2, genomic patterns of loss of heterozygosity (gLOH)[a], number of telomeric imbalances (TAI)[b], and large-scale transitions (LST)[c]

[a] which are regions of intermediate size (>15 MB and < whole chromosome)

[b] which are the number of regions with allelic imbalance which extend to the sub-telomere but not cross the centromere

[c] which are chromosome breaks (translocations, inversions, or deletions)

*Clinical trial must meet one (i–iii) of the following clinical conditions:

i. Any advanced stage III or IV solid tumors*, or
ii. All lymphomas, or
iii. Multiple myeloma

Note: Testing will be allowed once for a specific tumor diagnosis.

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Separate RNA testing will be allowed once, either if DNA testing has been performed previously or is being performed concurrently.

PD-L1 can be billed separately from genetic testing.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Molecular profiling for malignant tumors catalogues specific biomarker information and generates potential treatment options. The personalized tumor molecular profiling services or tests addressed in this document are similar in that they all take an individual's tumor tissue and, from it, produce a molecular profile of the tumor and a list of potential therapies. However, their individual testing methods vary from matching over-expressed genes with drugs to more complex systems biology approaches.

Foundation CDx uses next generation sequencing: "… to interrogate the entire coding sequence of 236 cancer-related genes (3,769 exons) plus 47 introns from 19 genes frequently altered or rearranged in cancer." Foundation CDx helps match the genomic alterations present in a tumor with specific targeted therapies or clinical trials. Recent small studies (Drilon, 2013; Lipson, 2012; Vignot, 2013) have investigated next-generation sequencing in individuals with lung cancer. Others have used next-generation sequencing in those with breast cancer (Ross, 2013a); colorectal cancer (Lipson, 2012), ovarian cancer (Ross, 2013b), and prostate cancer (Beltran, 2013). Limitations of these studies include small sample sizes.

The most widely used of the tumor molecular profiles has been the Target Now Molecular Profiling Service (Caris Life Sciences). According to the Caris Life Sciences website, their tumor profiling service is now being promoted as the Molecular Intelligence Service. The published literature addressing these services is limited. Von Hoff and colleagues (2010) evaluated 86 individuals with refractory metastatic cancer. Progression-free survival (PFS) using a treatment regimen selected by Target Now molecular profiling of a malignant tumor was compared with the PFS of the most recent treatment regimen on which the individual experienced progression. A molecular target was detected in 84 of 86 (98%) participants. A total of 66 (78.6%) individuals were treated according to the molecular profile results with 18 of the 66 (27%) having a PFS ratio (defined as PFS on molecular profile–selected therapy or PFS on prior therapy) of greater than or equal to 1.3 (95% confidence interval [CI], 17% to 38%; P=0.007).

An editorial (Doroshow, 2010) accompanying the study reported that the trial had several significant limitations, including uncertainty surrounding the achievement of time to progression (the study's primary endpoint), and a lack of a randomized design. Additional limitations include a small number of participants and lack of duplication of study results by an independent dataset. GeneKey and OncInsights have even less validation. To date, there are no studies in the published literature specifically addressing these tests.

In a related study examining intratumor heterogeneity, Gerlinger and colleagues (2012) obtained multiple spatially separated biopsy samples from primary renal carcinomas and associated metastatic sites of 4 individuals. Intratumor heterogeneity was characterized using immunohistochemical analysis, profiling of messenger ribonucleic acid (mRNA) expression, and mutation functional analysis. An unexpected finding

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of this study revealed intratumor heterogeneity at the RNA-expression level, with gene expression signatures of good and poor prognosis detected in different regions of the same tumor. The authors concluded that genomics analyses from single tumor biopsy specimens may underestimate the mutational burden of heterogeneous tumors. It was also noted that this may explain difficulties encountered in the validation of oncology biomarkers owing to sampling bias, contribute to Darwinian selection of preexisting drug-resistant clones, and predict therapeutic resistance.

Molecular profiling has also been investigated for gastric cancer. Lei and colleagues (2013) sought to identify subtypes of gastric adenocarcinomas with particular biological properties and responses to chemotherapy and targeted agents. Gene expression patterns among 248 gastric tumors were compared. Three major subtypes of gastric adenocarcinoma were identified: proliferative, metabolic, and mesenchymal. Tumors of the proliferative subtype had high levels of genomic instability, TP53 mutations, and DNA hypomethylation. Cancer cells of the metabolic subtype were more sensitive to 5-fluorouracil than the other subtypes. Also, in two independent groups of subjects, those with tumors of the metabolic subtype appeared to have greater benefits with 5-fluorouracil treatment. Tumors of the mesenchymal subtype contain cells with features of cancer stem cells, and cell lines of this subtype were particularly sensitive to phosphatidylinositol 3-kinase-AKT-mTOR inhibitors in vitro. The authors concluded that if study results are confirmed and extended in future studies, the classification of gastric adenocarcinomas reported here could guide development of therapies tailored to the molecular subtypes.

In 2012, Tsimberidou and colleagues developed a personalized medicine program at a single facility in the context of early clinical trials. Their goal was to observe whether molecular analysis of advanced cancer and use of targeted therapy to counteract the effects of specific aberrations would be associated with improved clinical outcomes. Participants with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. A total of 175 subjects were treated with matched therapy, and the overall response rate was 27%. Of the 116 subjects treated with non-matched therapy, the response rate was 5%. The median time-to-failure was 5.2 months for those on matched therapy versus 2.2 months on non-matched therapy. At a median of 15 months follow-up, median survival was 13.4 months versus 9.0 months in favor of matched therapy.

Jameson and colleagues in 2012 performed a small pilot study investigating multi-omic molecular profiling (MMP) for the selection of breast cancer treatment. MMP treatment recommendations were selected in 25 cases and original treatment plans were revised accordingly. Partial responses were reported in 5/25 (25%), stable disease in 8/25 (32%) and 9/25 had no disease progression at 4 months. This study was limited by its small size and non-randomization. A large randomized prospective trial is needed for further evaluation. Primarily marketed to researchers, Life Technologies Inc. offers several variations of their Ion Torrent Next Generation Sequencing Ion AmpliSeq panels, according to the company website. The Ion AmpliSeq Comprehensive Cancer Panel analyzes more than 400 cancer-related genes and tumor suppressor genes. The Ion AmpliSeq Cancer Hotspot Panel v2 analyzes the "hotspot" regions of 50 cancer-related and tumor suppressor genes.

The nonrandomized study by Haslem et al. in 2016 adds some support to NGS from both the clinical utility and cost-effectiveness standpoint. In their retrospective matched cohort study of 72 patients (36 tested and 36 matched controls), the precision medicine treated cohort had longer progression-free survival than did the control group (22.0 vs 12-week, p = .002) and had similar weekly costs ($4,665 vs $5000). The study is small, but the findings warrant validation in a larger prospective study. Some studies are finding a high rate of clinical actionability, at least in terms of tumors found to have mutations for which there is a therapy. Hirshfield and coworkers in 2016 found that 96% (88/92) patients with rare refractory tumors had at least one mutation that triggered a guided therapy in 35% of cases, but this study did not report on the effect of this therapy.

Other studies (also small) have been less supportive. Blumenthal et al. in 2016 reported use in 43 patients with glioblastoma. In 13 of these an actionable target was found but none responded to the therapy. Grenader et al. in 2016 studied 30 patients with advanced tumors using tumor sequencing. Ten of the patients received treatments based on genomic profiling. Of these only 3 benefited. Median progression-free survival in this small cohort was actually worse in the profile-guided group (12 weeks) compared to the control group (48 weeks).

In summary, there is a growing body of evidence, which, though insufficient to support the general use of molecular profiling to guide treatment decisions for all malignant tumors, provides a basis for allowing

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limited coverage of this testing in support of advancing current clinical knowledge and potentially improving patient outcomes.

Billing/Coding Information

CPT CODES

Covered for the indications listed above if criteria are met

0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue
0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden
0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection
0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffinembedded (FFPE) tissue, nextgeneration sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

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81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (EG, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or MRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure

Not covered for the indications listed above

0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0538U	Oncology (solid tumor), nextgeneration targeted sequencing analysis, formalin-fixed paraffinembedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant
0539U	Oncology (solid tumor), cellfree circulating tumor DNA (ctDNA), 152 genes, nextgeneration sequencing, interrogation for singlenucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant
0543U	Oncology (solid tumor), nextgeneration sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for singlenucleotide variants, multinucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden

HCPCS CODES

No specific codes identified

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Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
8/17/23	For Commercial Plan Policy, included BRAF and NTRK as genes required to be in panel for criteria #C, and added criteria #E: "E. A genomic biomarker-linked therapy has been approved by the FDA for their cancer clinical scenario, or there are established genomic biomarker-based treatment contraindications or exclusions. Specifically related to homologous recombination deficiency (HRD), possibly present in breast, ovarian, pancreatic, and prostate cancer, the following tests must be performed to identify HRD: including BRCA1/2, genomic patterns of loss of heterozygosity (gLOH), number of telomeric imbalances (TAI), and large-scale transitions (LST); which are regions of intermediate size (>15 MB and < whole chromosome); which are the number of regions with allelic imbalance which extend to the sub-telomere but not cross the centromere; which are chromosome breaks (translocations, inversions, or deletions)."
7/12/24	For Commercial Plan Policy, added the following clarifying language to criteria #C: "For any stage III or IV solid organ tumor, and the panel must include BRAF, TMB, MSI, and NTRK; (NTRK using RNA is mandatory in secretory carcinoma of breast and salivary glands; congenital fibrosarcoma; cellular mesoblastic nephroma;

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	thyroid cancer, particularly in children (frequency 2 to 28 percent, depending on the series); glioma (particularly select pediatric high-grade gliomas); specific sarcomas, such as inflammatory myofibroblastic tumor; Spitzoid neoplasms; and suggested in all other tumors with > 1% risk of harboring NTRK fusion)."
9/4/24	For Commercial Plan Policy, added the following limitation: "Note: Testing will be allowed once for a specific tumor diagnosis."
2/19/25	For Commercial Plan Policy, added the following clarifying notes below sections of criteria: "Separate RNA testing will be allowed once, either if DNA testing has been performed previously or is being performed concurrently; PD-L1 can be billed separately from genetic testing.

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Select Health

MEDICAL POLICY

GENETIC TESTING: HEARING LOSS

Policy # 666
Implementation Date: 7/1/23
Review Dates: 8/20/24
Revision Dates:9/4/24

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Prelingual hearing loss affects about 1 out of every 500 individuals. Approximately 20% of cases are attributed to environmental causes, including viral (cytomegalovirus) or bacterial (meningitis) infection, trauma, prenatal exposure to certain drugs, and other environmental factors. The remaining 80% of cases are thought to be genetic, either as part of a recognized genetic syndrome, or as isolated, non-syndromic hearing loss (NSHL).

70−80% of genetic hearing loss is non-syndromic, with no related systemic findings. Some syndromic forms of hearing loss and deafness may masquerade as non-syndromic in infancy and early childhood, before additional symptoms emerge. For example, goiter does not develop until puberty or adulthood in Pendred syndrome; retinitis pigmentosa emerges in adolescence in Usher syndrome; and males with Deafness-Dystonia-Optic Neuronopathy (Mohr-Tranebjaerg) Syndrome begin having progressive neurological symptoms in their teens.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers panel genetic testing for non-syndromic hearing loss, mild or greater (Decibel level > 25), after testing for secondary conditions has been excluded (e.g., environmental/infectious causes).

The following genes can be tested: *CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1* [this list is not meant to be all-inclusive].

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

81252 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence

81253 GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants

81254 GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6- D13S1854)])

81400 Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)

81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)

81407 Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)

81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)

81430 Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1

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81431 Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes

81479 Unlisted molecular pathology procedure

Key References

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Revision History

Revision Date	Summary of Changes
9/4/24	For Commercial Plan Policy, clarified that for this testing, only panel testing is covered with criteria.

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Genetic Testing: Hearing Loss, **continued**

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MEDICAL POLICY

GENETIC TESTING: HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Policy # 240

Implementation Date: 3/1/04

Review Dates: 1/13/05, 12/15/05, 2/16/06, 2/15/07, 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 4/25/13, 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 2/18/19, 1/31/23, 2/15/24

Revision Dates: 7/1/23

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

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Description

Hereditary hemorrhagic telangiectasia (HHT) results from the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small arteriovenous malformations are called telangiectasias. Telangiectasias present on the nose, lips, and tongue typically vary in size from pinpoint to that of a small pea. Because of their thin walls, narrow tortuous paths, and closeness to the surface of the skin or to a mucous membrane, these vessels can rupture and bleed after only slight trauma. Since the contractile elements in the vessel wall are lacking, the bleeding may not stop spontaneously.

The term AVM usually refers to the "large" telangiectasias, greater than 0.5 inch in diameter and sometimes up to 3–6 inches in diameter. Large AVMs frequently cause symptoms and complications when they occur in the brain, lung, or gastrointestinal tract. Complications of large AVMs may be catastrophic and may occur without warning. Common complications include hemorrhage of the nose, mouth, tongue, gastrointestinal tract, lungs, fingers, toes, and occasionally the eyes, liver, and other organs.

Hereditary hemorrhagic telangiectasia presents with unexpected or difficult to control bleeding problems. It can present as iron deficiency anemia. It may not manifest clinical signs to alert patients and their physicians to its presence until age 40 or 50. The most common manifestations are epistaxis (nosebleeds) and telangiectasias. Epistaxis is usually the earliest symptom with an average age of onset of about 12 years of age. As many as 95% of affected individuals eventually experience recurrent epistaxis, with 1/3 having onset by age 10 years and 80%–90% by age 21 years. Bleeding can occur from other sites of telangiectasias also. About one-quarter of all individuals with HHT have gastrointestinal bleeding.

Cerebral AVMs may manifest as a hemorrhage, however, often the presenting symptom may be transient ischemic attacks (TIAs), embolic stroke, and cerebral abscess. Migraine headache, polycythemia, hypoxemia with cyanosis, and clubbing of the nails are other frequent complications of pulmonary AVMs. The presenting signs of pulmonary AVMs are usually exercise intolerance and cyanosis.

Hereditary hemorrhagic telangiectasia is inherited in an autosomal dominant manner. Most individuals have an affected parent. Each child of a proband and the sibs of most probands have a 50% risk of inheriting the mutation.

Indications for HHT genetic testing are: 1) to confirm the diagnosis in symptomatic individuals; and 2) to identify a familial mutation in clinically affected individuals, enabling diagnostic testing of at-risk relatives covered by the health plan. HHT is caused by mutations in 3 genes (ACVRL1, ENG, and SMAD4);

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however, mutations in other genes (RASA1 and BMP9) can cause findings with significant clinical overlap.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic testing for hereditary hemorrhagic telangiectasia (HHT), as available evidence strongly supports its clinical utility, and such testing is the accepted standard of care in the at-risk population.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
No systematic reviews were identified related to HHT. Several recent traditional reviews were identified and obtained. Search of the medical literature database revealed 1,563 "hits" on HHT. Seven clinical trials (5 on epistaxis treatment [total n = 122] and 2 relating to AVMs in the liver [total n = 105]) were identified from this group. Only 1 of these was a randomized controlled trial (RCT). There is a distinct absence of diagnostic studies (e.g., observational trials) on this topic.

Analysis of the available literature identifies significant costs related to the treatment of unrecognized HHT. Given its incidence and prevalence in the U.S., identification of patients with HHT prior to development of significant medical complications and elimination from consideration those patients without the genetically inheritable traits is a cost-effective strategy and in the patient's interest.

Billing/Coding Information
Covered: For the conditions outlined above

CPT CODES

81405	Molecular pathology procedure, Level 6
81406	Molecular pathology procedure, Level 7
81479	Unlisted molecular pathology procedure

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Genetic Testing: Hereditary Hemorrhagic Telangiectasia (HHT), continued

HCPCS CODES

No specific codes identified

Key References

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Select Health

MEDICAL POLICY

GENETIC TESTING: HERITABLE THORACIC AND ABDOMINAL ANEURYSM AND DISSECTION (TAAD) RELATED DISORDERS

Policy # 453
Implementation Date: 8/9/10
Review Dates: 9/15/11, 11/29/12, 12/19/13, 12/18/14, 12/10/15, 12/15/16, 12/21/17, 12/20/18, 3/7/23, 5/14/24
Revision Dates: 4/6/15, 7/1/23, 11/27/23, 12/6/23, 9/9/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Aortic aneurysms, dissections, and rupture have ranked as high as the 15th major cause of death in the United States, accounting for nearly 15,000 deaths annually. Family studies demonstrate that up to 19% of persons with TAAD without a known genetic syndrome have a first-degree relative with TAAD. Heritable thoracic and abdominal aneurysm and dissection (TAAD) related disorders are an overlapping group of conditions that result in dilation of the aorta, and, depending on the condition, other vessels with an elevated risk of dissection and rupture. Included in this growing group of conditions are the better-known syndromic forms of aortopathy, including Marfan and Loeys-Deitz syndromes, but the various types of non-syndromic heritable TAAD are also included.

There is significant overlap in clinical features of heritable TAAD-related disorders such that clinical evaluation and family history is often insufficient to diagnose a specific TAAD disorder. Determining which TAAD-associated gene harbors a mutation has direct implications on treatment and surveillance. Given the inability to clinically discern which specific gene mutation may be present, the use of gene panels allows for an accurate and rapid determination of the most appropriate clinical approach to patients.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers panel genetic testing for thoracic and abdominal inherited aortopathy disorders (TAAD) when either I or II are met:

I. **Select Health considers panel genetic testing for TAAD as medically necessary,** if recommended by Intermountain Heart Institute. (Genes include, but are not limited to: *FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1*);

OR

II. For all other clinicians, Select Health considers panel genetic testing for TAAD as medically necessary, when the following criteria are met:

Genetic Testing: Heritable TAAD-Related Disorders, **continued**

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

AND when the following criteria are met:

3. Select Health covers panel genetic testing for TAAD in limited circumstances when specific criteria are met. (Genes include, but are not limited to: *FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1*.)

a) The patient has had an evaluation for a vascular abnormality either by ultrasound or CT scan, or by cardiology/vascular consult; AND (b or c)

b) The patient is under age 60 and displays 1 major* clinical feature OR a strong clinical suspicion of a TAAD disorder as evidenced by 3 or more minor clinical features**; OR

c) The patient is ≥ age 60 and displays 1 major clinical feature* AND
   i. 3 or more minor clinical features**; OR
   ii. a first- or second-degree relative with a major* clinical feature

Select Health does not cover this testing if the only concern is hypermobile Ehlers Danlos Syndrome and the member does not meet the above criteria as this test lacks clinical utility. There must also be concern for other types of connective tissue disorders with cardiovascular involvement, which first must be excluded.

*Major clinical features, include aortic aneurysm, dilation, or dissection; unexplained arterial rupture; unexplained intestinal rupture; unexplained uterine rupture; ectopia lentis.

**Minor clinical features, include pectus carinatum/excavatum; scoliosis; clubfoot; chronic joint subluxations/dislocations; congenital dislocation of the hips; hypermobility (Beighton score ≥ 4); wrist and thumb sign; mitral valve prolapse; arteriovenous carotid cavernous sinus fistula; acrogeria (aged appearance to extremities, particularly hands); characteristic facial appearance (thin lips and philtrum, small chin, thin nose, large eyes); thin, translucent skin (especially noticeable on chest/abdomen); early-onset varicose veins; easy bruising (spontaneous or with minimal trauma); bifid uvula; gingival recession; pneumothorax/pneumohemothorax; tendon/muscle rupture.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Genetic Testing: Heritable TAAD-Related Disorders, **continued**

Summary of Medical Information

Genetic alterations that lead to abnormalities in connective tissue metabolism predispose to thoracic aortic aneurysm. Genetically-mediated TAA accounts for about 5 percent of TAA. About 20 percent of patients with a TAA/aortic dissection have a family history of aneurysmal disease that is independent of any known genetic connective tissue syndrome. Genetic syndromes such as Marfan syndrome, Ehlers Danlos (ED) syndrome, Turner syndrome, and Loeys-Dietz syndrome, have more aggressive rates of aortic expansion and are more likely than sporadic TAA to require intervention.

Familial TAA refers to patients who have thoracic aortic disease associated with a family history of aneurysmal disease who do not meet strict criteria for known connective tissue syndrome. Familial TAA/dissection is increasingly being recognized and can include patients with a dilated aorta and a family history of dissection, rupture, or sudden unexplained death. The ascending thoracic aorta is involved in about 80 percent and the descending aorta is affected in the remaining 20 percent. Patients with familial TAA generally present at an earlier age (56.8 years) compared with patients with sporadic TAA (57 versus 64 years in one study), and also have faster rates of aortic expansion.

Studies of the family trees of patients with isolated TAA or dissection have found that at least 21 percent of probands have at least one family member with a known arterial aneurysm. The rate of inheritance may be higher, since many family members may not be aware that an aneurysm is present. About 80 percent of familial TAA appears to be inherited in an autosomal-dominant manner, but other genetic patterns are also expressed**.** The reduced penetrance and variable expression of these genetic conditions make obtaining a definitive clinical diagnosis difficult. Mutations in the transforming growth factor beta receptor 2 gene (*TGFBR2*) may be responsible for about 5 percent of familial cases. Other mutations include *ACTA2* and *MYH11*. ACTA2 is the most common cause of familial TAA, accounting for up to 14 percent of genetic mutations associated with familial syndromes.

The location of the TAA in the proband closely mirrors aneurysm location in family members, supporting the notion that the etiology of aneurysmal disease is differentiated proximal and distal to the ligamentum arteriosum. Disease proximal to the ligament is predominantly nonatherosclerotic in nature, whereas disease distal to it, is strongly associated with atherosclerosis.

Marfan syndrome — Marfan syndrome, which is associated with mutations in the *FBN1* gene, is usually localized to the aortic root, but may extend to the ascending aorta and is associated with an accelerated expansion compared with degenerative aneurysms and a high risk of aortic complications at a relatively young age. Aortic root dilatation, aortic regurgitation, and aortic dissection are the main causes of morbidity and mortality. Marfan syndrome is discussed in detail elsewhere.

As recommended in the 2010 ACC/AHA/AATS guidelines for thoracic aortic disease, patients with MFS should have echocardiography performed at the time of diagnosis and six months later to determine the aortic root and ascending aortic diameters and their rate of enlargement.

In adults, if the aortic diameter is documented as stable over time, then annual imaging is recommended if the aortic dimension is less than 45 mm. If the aortic diameter is ≥ 45 mm or shows significant growth over time, then more frequent imaging is suggested (e.g., twice yearly) and surgery may be indicated. More frequent imaging is also recommended if the aortic diameter shows rapid change (≥ 0.5 cm/year) or if there are concerns regarding heart or valve function.

For children with MFS, annual imaging is recommended if the aortic dimension is documented as stable over time and not markedly enlarged. There are no validated age-specific absolute aortic diameters that can be used to determine when more frequent imaging should be performed or when prophylactic aortic surgery is indicated. It is recommended that aortic measurements be compared to the body surface area. Sonographic measurement of aortic diameter should be performed annually, as long as the increase in aortic size remains proportional to the increase in body surface area. Twice-yearly measurements are recommended if aortic size (expressed as a percentage increase) diverges from the height when expressed in the same fashion.

Individuals under 20 years of age with systemic findings suggestive of MFS, but without cardiovascular involvement, should also have annual echocardiograms due to the potential risk of development of aortic disease. Adults with repeatedly normal and stable aortic measurements, without a definitive genetic predisposition for aortic enlargement, but with a sense of predisposition based upon family history or borderline aortic measurements can be seen at two- to three-year intervals

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Loeys-Dietz syndrome — Loeys-Dietz syndrome is an autosomal dominant condition due to mutations in the transforming growth factor beta receptor genes (TGFBR1, TGFBR2). Patients with Loeys-Dietz syndrome have many clinical features in common with patients with Marfan syndrome and are also at high risk for aortic dilation, rupture, or dissection at a young age.

As recommended in the 2010 ACC/AHA/AATS guidelines, complete aortic imaging should be performed at the time of diagnosis, and 6 months after in patients with Loeys-Dietz syndrome or a confirmed genetic mutation associated with aortic aneurysms and aortic dissections (eg, TGFBR1, TGFBR2, SMAD3, TGFB2, FBN1, ACTA2, or MYH11), to determine if aortic enlargement is occurring.

If the aortic dimension is stable and no other specific problem in another vascular segment has been identified, patients with Loeys-Dietz syndrome (potentially caused by mutations in TGFBR1, TGFBR2, SMAD3, TGFB2, or TGFB3) should have serial MRI from the cerebrovascular circulation to the pelvis (with a maximal interval between studies of two years) since they commonly develop aneurysms that are amenable to prophylactic surgical management. Prophylactic repair of the aorta is indicated in these patients at an ascending aortic measurement of 4.2cm by TEE.

Ehlers-Danlos syndrome — The Ehlers-Danlos syndrome is a group of conditions due to defects in type III procollagen that cause hyperelasticity and fragility of the skin and hypermobility of the joints (see Ehlers Danlos Society Diagnostic Criteria). Most types of Ehlers-Danlos are not associated with aortic dilation, although mild mitral valve prolapse is often present. However, in the vascular type (previously Type IV) Ehlers-Danlos syndrome, vascular and connective tissue integrity is markedly impaired and spontaneous rupture of large and medium-sized arteries can occur.

Aneurysm-osteoarthritis syndrome — Aneurysm osteoarthritis syndrome, caused by pathogenic variants of SMAD3 (mothers against decapentaplegic homolog 3), is a recently described autosomal dominant syndrome characterized by aneurysms and arterial tortuosity in combination with early-onset osteoarthritis. Aneurysms are most frequently localized to the aortic root, but can be found throughout the arterial tree, including the iliac, visceral, and intracranial arteries. In one review of 38 patients, 71 percent had aortic root dilation.

Billing/Coding Information
Covered: For the conditions outlined above

CPT CODES

81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
81479	Unlisted molecular pathology procedure

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report

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Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
11/27/23	For Commercial Plan Policy, modified formatting and verbiage of overall criteria, and added the following exclusion: “Select Health does not cover this testing, if the only concern is hypermobile Ehlers Danlos Syndrome and the member does not meet the above criteria, this test lacks clinical utility. There must also be concern for other types of connective tissue disorders with cardiovascular involvement, which first must be excluded.”
12/6/23	For Commercial Plan Policy, modified criteria to include option of recommendation by Intermountain Heart Institute as a qualifying factor.
9/9/24	For Commercial Plan policy, added new criterion #3a: “The patient has had an evaluation for a vascular abnormality either by ultrasound or CT scan, or by cardiology/vascular consult …”; and updated list of Major and Minor Clinical Features.

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Select Health

MEDICAL POLICY

GENETIC TESTING: HERITABLE THORACIC AND ABDOMINAL ANEURYSM AND DISSECTION (TAAD) RELATED DISORDERS

Policy # 453

Implementation Date: 8/9/10

Review Dates: 9/15/11, 11/29/12, 12/19/13, 12/18/14, 12/10/15, 12/15/16, 12/21/17, 12/20/18, 3/7/23, 5/14/24

Revision Dates: 4/6/15, 7/1/23, 11/27/23, 12/6/23, 9/9/24

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Aortic aneurysms, dissections, and rupture have ranked as high as the 15th major cause of death in the United States, accounting for nearly 15,000 deaths annually. Family studies demonstrate that up to 19% of persons with TAAD without a known genetic syndrome have a first-degree relative with TAAD. Heritable thoracic and abdominal aneurysm and dissection (TAAD) related disorders are an overlapping group of conditions that result in dilation of the aorta, and, depending on the condition, other vessels with an elevated risk of dissection and rupture. Included in this growing group of conditions are the better-known syndromic forms of aortopathy, including Marfan and Loeys-Deitz syndromes, but the various types of non-syndromic heritable TAAD are also included.

There is significant overlap in clinical features of heritable TAAD-related disorders such that clinical evaluation and family history is often insufficient to diagnose a specific TAAD disorder. Determining which TAAD-associated gene harbors a mutation has direct implications on treatment and surveillance. Given the inability to clinically discern which specific gene mutation may be present, the use of gene panels allows for an accurate and rapid determination of the most appropriate clinical approach to patients.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers panel genetic testing for thoracic and abdominal inherited aortopathy disorders (TAAD) when either I or II are met:

I. **Select Health considers panel genetic testing for TAAD as medically necessary,** if recommended by Intermountain Heart Institute. (Genes include, but are not limited to: *FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1*);

OR

II. For all other clinicians, Select Health considers panel genetic testing for TAAD as medically necessary, when the following criteria are met:

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MEDICAL POLICY

GENETIC TESTING: INHERITABLE COLORECTAL CANCER

Policy # 222

Implementation Date:4/20/04

Review Dates: 4/14/05, 6/22/06, 7/12/07, 6/11/09, 6/17/10, 8/16/11, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 9/25/17, 9/17/18, 10/15/19, 1/31/23, 7/12/24, 2/14/25

Revision Dates: 6/19/08, 1/16/16, 5/2/17, 9/25/17, 10/2/18, 7/1/23, 7/22/24, 10/29/24, 12/20/24, 1/27/25, 3/13/25

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Of the nearly 150,000 cases of colorectal cancer expected to be diagnosed this year in the US, about 5% are inherited. In these cases, mutations in key genes dramatically increase cancer risk. These mutations give rise to multiple colorectal cancer syndromes, including:

- Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer [HNPCC])
- Familial adenomatous polyposis (FAP)
- Attenuated familial adenomatous polyposis (AFAP), a variation of FAP
- MUTYH-associated polyposis (MAP)

Lynch syndrome, the most common syndrome, is caused by a mutation in one of the specific genes responsible for proteins that repair DNA mismatches. Microsatellite instability is a marker for this syndrome. Usually, the colon cancers are located on the right side of the colon. Familial adenomatous polyposis (FAP) and attenuated AFP (AFAP) are the result of mutations in the gene that codes for the key tumor-suppressor protein adenomatous polyposis coli (APC). MUTYH-associated polyposis (MAP) results from mutations in the MUTYH gene that codes for adenine DNA glycosylase which plays a major role in DNA base excision repair. Unlike Lynch syndrome, FAP and AFAP, which are dominantly inherited conditions, MAP is inherited in a recessive manner.

Although Lynch Syndrome, FAP/AFAP, and MAP are biologically different, families affected with these syndromes exhibit accelerated and amplified colorectal carcinogenesis. This is most obvious in the family's history, which features frequent early-onset colorectal cancer. In the case of MAP, however, the family history may not be significant for multiple cases of colorectal cancer. Screening, early prophylactic surgery, close follow-up, and chemoprevention (when appropriate) are important in managing the disease in individual patients. Gene-based tests are used to diagnose susceptibility to these hereditary colorectal cancer syndromes, specifically Lynch syndrome, Familial adenomatous polyposis (FAP), Attenuated FAP (A-FAP), or MUTYH-associated polyposis (MAP).

Multiple molecular testing laboratories offer colon cancer multi-gene panels specific to the needs of a given patient based on personal or family cancer history. These tests include: (1) panels for Lynch Syndrome that includes gene sequence analysis of the MLH1, MSH2, MSH6, EPCAM and PMS2 genes; (2) panels for polyposis syndromes (FAP, AFAP and MAP) that include the APC and MUTYH genes; (3) single site mutation analyses for individuals with known colon cancer gene mutations via previous testing in a family member.

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Genetic Testing: Inheritable Colorectal Cancer, continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers multi-gene panel testing (must include at a minimum the following genes: *APC, MUTYH, MLH1, MLH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53*) for hereditary colorectal cancer (CRC) syndromes* when any of the following criteria are met:

A. Individuals with personal or family history[a] of, at the time of a colonoscopy:

1) ≥ 10 adenomatous polyps

or

2) ≥ 2 hamartomatous polyps

or

3) ≥ 5 serrated polyps/lesions proximal to the rectum

B. Personal history of:

1) a Lynch syndrome (LS)-related cancer[b] or

2) a personal history of a tumor with deficient mismatch repair (dMMR)[c], or

3) a pathogenic/likely pathogenic variant identified on tumor genomic testing clinical implications if also identified in the germline

4) a Lynch syndrome-related cancer with a diagnosis of a second Lynch syndrome-related cancer in the same individual, regardless of age.

OR

C. Family history of

1) a first-degree relative with colon and/or uterine cancer under age 50[b] or

2) a personal or family history of a known pathogenic or likely pathogenic variant in a colorectal or polyposis susceptibility gene who have a family history suggesting an additional syndrome besides that associated with the known variant

3) a first-degree relative with a Lynch syndrome-related cancer with a diagnosis of a second Lynch syndrome-related cancer in the same individual, regardless of age.

OR

D. Two or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, one of whom was diagnosed before age 50.

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OR

E. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, regardless of age.

OR

F. Personal or family history of one or more of the following: congenital hypertrophy of retinal pigment epithelium (CHRPE), desmoid tumor, or papillary thyroid cancer.

a- Personal or family history of polyps is based on cumulative lifetime history of adenomas, hamartomas, and/or serrated polyps/lesions in the proband or a single family member.

b- LS-related cancers include colorectal and endometrial cancer under or at age 50, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma and medulloblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

c- Any tumor at any age that 1) is microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) or next-generation sequencing (NGS); or 2) has abnormal/ deficient MMR protein expression (dMMR) on immunohistochemistry (IHC) without concurrent MLH1 promoter hypermethylation or BRAF 600E mutation.

*Associated CRC Syndromes:

- Lynch syndrome
- Classical familial adenomatous polyposis (FAP),
- Attenuated FAP (AFAP), BMPR1A, MUTYH-associated polyposis (MAP)
- Rare genetic causes of multiple adenomatous polyps
- Colonic adenomatous polyposis of unknown etiology (CPUE)
- Puetz-Jeghers syndrome (PJS), Juvenile polyposis syndrome (JPS)
- Cowden/PTEN hamartoma syndrome

Note: For known familial variant testing, please see medical policy #123.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The evidence related to the effectiveness of gene-based testing for diagnosis, prognosis, and prediction of increased risk of colorectal cancer has been previously reviewed (SelectHealth Tech Assessment November 2001). Additional information obtained from discussions with genetic testing experts since then continues to support these conclusions.

It is now known that Lynch syndrome results from an inherited mutation in 1 of the mismatch repair (MMR) genes. Normally, MMR genes produce proteins that identify and correct base-pairing mismatches

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that can occur during DNA replication. Consequently, a mutation that inactivates an MMR gene leads to accumulation of other mutations which significantly increases the likelihood of developing cancer. Mutations that disrupt the function of MMR genes (mutations in MLH1, MSH2, MSH6, EPCAM and PMS2) have been linked to Lynch syndrome.

It has been known that germline mutations in MLH1, MSH2, and MSH6 account for most detected mutations in families with Lynch syndrome. More recently it has been discovered that PMS2 and EPCAM also play an important role in Lynch syndrome.

As 1 of the 4 primary mismatch repair genes associated with Lynch syndrome, the functional importance of PMS2 has been clear, but its total contribution to Lynch syndrome was historically considered to be quite low. More recent studies suggest that the prevalence of PMS2 mutations is comparable to MSH6, with as much as 15% of all Lynch syndromes attributable to PMS2.

Finally, the EPCAM gene is a recently discovered contributor to Lynch syndrome, accounting for an estimated 1–3% of all detectable Lynch syndrome mutations. Studies indicate that large deletions in the end of this gene, which is located directly "upstream" of MSH2, can lead to a loss of MSH2 expression and result in Lynch syndrome.

Billing/Coding Information

CPT CODES

0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]
0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)
0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)
0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

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Genetic Testing: Inheritable Colorectal Cancer, continued

0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence 81202 APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; promoter\ methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	;known familial variants
81294	;duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	;known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary duplication/deletion variants duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	;known familial variants
81300	;duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	;known familial variants
81319	;duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81327	SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
81401	Molecular pathology procedure, Level 2

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Genetic Testing: Inheritable Colorectal Cancer, continued

81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons): EPCAM (epithelial cell adhesion molecule) (eg, Lynch syndrome), duplication/deletion analysis
81406	Molecular pathology procedure, Level 7
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	;duplication/deletion analysis panel, must include analysis of at least 5genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

Key References

1. NCCN Guidelines. Colorectal Cancer Screening. Version 3.2022 – September 30, 2022.
2. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Versions 2.2023 – October 30, 2023.
3. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 2.2024 — October 3, 2024.

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
7/22/24	For Commercial Plan Policy, clarified age requirement for qualifying factor of personal history of colorectal cancer: "Personal history of CRC ***age 50 or under"*** and also updated other

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	personal/family history requirements in coverage criteria to align with current clinical standards.
10/29/24	For Commercial Plan Policy, added criterion #B-4, added new criterion #C-1 and #C-2, thereby, making the previous criterion #C-1 and #C-2 as #C-3 and #C-4, and added new criteria for sections D and E, as well as new criteria section F, to align with NCCN updates.
12/20/24	For Commercial Plan Policy, modified requirements in criterion #1 in first section: "Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history. Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing."
1/27/25	For Commercial Plan Policy, modified requirements in criterion #1-C: "Colon and/or uterine cancer under age 50."
3/13/25	For Commercial Plan Policy, modified requirements in criterion #C-2 and #C-3: "2) a personal or family history of a known pathogenic or likely pathogenic variant in a colorectal or polyposis susceptibility gene who have a family history suggesting an additional syndrome besides that associated with the known variant 3) a first-degree relative with a Lynch syndrome-related cancer with a diagnosis of a second Lynch syndrome-related cancer in the same individual, regardless of age."; and added the following note: "For known familial variant testing, please see medical policy #123."

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Genetic Testing: Inheritable Colorectal Cancer, **continued**

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MEDICAL POLICY

GENETIC TESTING: LACTOSE INTOLERANCE

Policy # 318
Implementation Date:8/10/06
Review Dates: 8/23/07, 8/21/08, 8/13/09, 8/19/10, 9/15/11, 11/29/12, 12/19/13, 12/18/14,12/10/15, 12/15/16, 12/21/17, 12/4/18, 2/14/23, 2/15/24, 2/17/25
Revision Dates: 7/1/23

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description
Adult-type hypolactasia (primary lactose malabsorption) is determined by a genetically programmed reduction in lactase activity at the intestinal brush border. It affects most of the world's human population and limits the use of fresh milk due to lactose intolerance. The incidence of lactose malabsorption ranges from 11%−60% in Europe and this condition can cause gastrointestinal symptoms such as abdominal pain, bloating, flatulence, and diarrhea. Lactose intolerance can cause bloating and indigestion from consuming milk or milk products. More than 30 million Americans, mostly African-American or Asian, are prone to the condition. However, the correlation between lactose malabsorption and clinical symptoms is unclear: many malabsorbers are in fact able to tolerate a certain quantity of milk without presenting symptoms, while many cases of self-reported milk-intolerance remain asymptomatic after lactose oral load. The diagnosis of adult-type hypolactasia has been difficult to establish because of unsatisfactory diagnostic methods.

C/T(-13910) single nucleotide polymorphism in the lactase (LCT) gene has been shown to be associated with lactase deficiency.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover genetic testing for lactose intolerance as there is a lack of clinical utility as it relates to this testing; this meet's the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Summary of Medical Information

Carroccio et al., in their study of 323 subjects in 1998 demonstrated the difficulties identifying patients who have lactose malabsorption but no tolerants, and who have lactose malabsorption and intolerants. They concluded that in studies of the general population, the frequency of lactose intolerance is much lower than that of lactose malabsorption. Gastrointestinal symptoms after lactose load in self-reported milk-intolerants are found in only a very low number of these subjects. However, the lay public is very aware of lactose intolerance as a cause of gastrointestinal distress and often adjusts their diet due to concern about this phenomenon risking inadequate nutritional and calcium intake.

Additionally, the symptoms of lactose malabsorption can be ill-defined dependent upon the level of lactase enzyme activity persisting in an individual. These symptoms are the same presenting symptoms seen in Celiac disease (Sprue), early inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS).

Measurement of lactase and sucrase levels in intestinal biopsy specimens is required for a definitive diagnosis of the condition. However, due to the invasive and costly manner of obtaining these specimens, the diagnosis of intestinal malabsorption of lactose has been confirmed by a test of absorption (e.g., lactose absorption test) or malabsorption (lactose breath hydrogen test). Less direct tests, such as low fecal pH or reducing substances in the stool, are only valid when lactose has been ingested, intestinal transit time is rapid, stools are collected fresh, assays are performed immediately, and bacterial metabolism of colonic carbohydrate is incomplete. These tests, however, had significant limits impairing diagnostic accuracy.

The utility of the lactose tolerance test is limited by many false negative results that may occur in patients with diabetes or bacterial overgrowth. Abnormal gastric emptying also can lead to spurious results; the blood glucose may be relatively higher with rapid emptying and depressed with delayed gastric emptying. In adults, the lactose tolerance test has a sensitivity of 75% and a specificity of 96%. However, it is cumbersome (particularly in children), and time-consuming, and has largely been replaced by the lactose breath hydrogen test.

The lactose breath hydrogen test measures lactose non-absorption. It is simple to perform, noninvasive, and has a sensitivity and specificity that are superior to the absorption test. Both false-positive and false-negative results can occur. False-positive results are seen with inadequate pretest fasting or recent smoking; false-negative results can be seen after the recent use of antibiotics, in patients with lung disorders, or in the approximately 1% of subjects who are nonhydrogen producers. A normal breath hydrogen test does not rule out an intestinal mucosal lesion and should not be used to avoid an intestinal biopsy. A significant proportion of patients with symptoms suggestive of lactose intolerance have normal breath hydrogen tests. In two series described above, for example, 30%−42% of subjects with severe symptoms of milk intolerance had normal tests. Other possibilities that must be considered include psychologic factors and intolerance to other factors in milk.

Hogenauer et al., in 2005, confirmed this sensitivity and specificity in their prospective trial comparing the DNA testing to lactose hydrogen breath test. In this study, 97% of patients testing positive for the CC genotype of the -13910 T>C polymorphism suggesting lactase non-persistence also had a positive hydrogen test, 86% with either a TC or a TT genotype suggestive of lactase persistence tested negative on the hydrogen test. They concluded that DNA testing had an excellent correlation between a CC genotype and a positive hydrogen test, whereas the correlation between a TC or TT genotype and a negative hydrogen test result is less strong. Analysis of the -13910 T/C variant can be considered a good test for predicting the presence of lactase non-persistence in a patient population with suspected lactose malabsorption.

Sontonocito, et al., in 2015 examined over 1,400 patients and concluded that use of the variants upstream of LPH (C/T-13910 and G/A-22018 mutations) are not useful for routine screening, support the policy stipulation for use in atypical patients who have not been diagnosed by other means.

Billing/Coding Information

CPT CODES

81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

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HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

Key References

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MEDICAL POLICY

GENETIC TESTING: LACTOSE INTOLERANCE

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Adult-type hypolactasia (primary lactose malabsorption) is determined by a genetically programmed reduction in lactase activity at the intestinal brush border. It affects most of the world's human population and limits the use of fresh milk due to lactose intolerance. The incidence of lactose malabsorption ranges from 11%−60% in Europe and this condition can cause gastrointestinal symptoms such as abdominal pain, bloating, flatulence, and diarrhea. Lactose intolerance can cause bloating and indigestion from consuming milk or milk products. More than 30 million Americans, mostly African-American or Asian, are prone to the condition. However, the correlation between lactose malabsorption and clinical symptoms is unclear: many malabsorbers are in fact able to tolerate a certain quantity of milk without presenting symptoms, while many cases of self-reported milk-intolerance remain asymptomatic after lactose oral load. The diagnosis of adult-type hypolactasia has been difficult to establish because of unsatisfactory diagnostic methods.

C/T(-13910) single nucleotide polymorphism in the lactase (LCT) gene has been shown to be associated with lactase deficiency.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover genetic testing for lactose intolerance as there is a lack of clinical utility as it relates to this testing; this meet's the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

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Select Health

MEDICAL POLICY

GENETIC TESTING: LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Policy # 356

Implementation Date: 6/23/07

Review Dates: 6/19/08, 6/11/09, 6/17/10, 8/16/11, 8/12/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 6/16/18, 6/8/19, 2/21/23, 2/15/24

Revision Dates: 2/21/19, 7/1/23

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Leber's hereditary optic neuropathy (LHON) is a bilateral optic neuropathy that typically produces severe and permanent visual loss. The disorder occurs predominantly in young adult males. The initial symptoms include visual dysfunction with blurring of vision and loss of central vision, most often beginning in the late teens. Painless vision loss is typically the only symptom of LHON. Affected individuals are usually entirely asymptomatic, until they develop visual blurring and clouding, affecting the central visual field (i.e., a centrocecal scotoma or "blind spot"). These vision problems may begin in one eye or simultaneously in both eyes. However, if vision loss starts in one eye, the other eye is usually affected within several weeks or months. Over time, the blind spot enlarges and vision in both eyes worsens with a severe loss of visual acuity and color vision. Visual acuity is typically reduced to finger-counting in most cases. Although central vision gradually improves in a small percentage of cases, in most cases, the vision loss is profound and permanent.

LHON has a mitochondrial pattern of inheritance. This inheritance pattern applies to genes contained in mitochondrial DNA. Because human egg cells, but not sperm cells, contribute mitochondria to the developing embryo, only females pass mitochondrial conditions to their children. Pathogenic variants in the following genes have been associated with LHON: *MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6*, *MT-ATP6, MT-CO3, MT-CO1, MT-ATP6,* and *MT-CYB*.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic testing for Leber's hereditary optic neuropathy (LHON) *in limited circumstances* when standard clinical exams, genetic counseling, and conventional diagnostic studies do not provide a definitive diagnosis.

Genetic Testing: Leber's Hereditary Optic Neuropathy (LHON), continued

Any other circumstances for this testing meet the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The limited research evidence examining the clinical use of genetic testing for LHON suggests that this testing may be most useful in specific situations involving atypical symptoms without a clear pattern of maternal inheritance. For patients with typical signs and maternal inheritance, genetic testing is likely unnecessary for establishing a diagnosis of LHON. In terms of predictive testing, the incomplete penetrance of LHON mutations limits the prognostic value of positive test results, particularly in females in whom penetrance is only about 10%. Penetrance is higher in males, though, still only around 50%. De novo mutations are rare in LHON and confer no risk to siblings or parents. A male (affected or unaffected) with a primary LHON-causing mtDNA mutation cannot transmit the mutation to any of his offspring. A female (affected or unaffected) with a primary LHON-causing mtDNA mutation will transmit the mutation to all of her offspring. But again, presence of a mutation in an asymptomatic individual does not predict occurrence, age of onset, or severity of diseases. A negative test result confers a high likelihood of not developing symptoms, and thus, may be informative in cases where a clear family history is not evident. In most cases, however, clinical and family history are likely sufficient to establish risk for developing LHON.

Billing/Coding Information

CPT CODES

81401	Molecular Path Level 2: includes the following genes: MT-TS1, MT-RNR1, MT-ATP6, MT-ND4, MT-ND6, MT-ND5, MT-TL1, MT-TS1, MT-RNR1
81403	Molecular Path Level 4: includes the following genes: MT-RNR1, MT-TS1
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection

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Genetic Testing: Leber's Hereditary Optic Neuropathy (LHON), continued

HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

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Select Health

MEDICAL POLICY

GENETIC TESTING: LONG QT SYNDROME

Policy # 385

Implementation Date: 11/12/07

Review Dates: 10/23/08, 12/17/09, 10/21/10, 10/13/11, 11/29/12, 12/19/13, 12/10/15, 6/15/17, 7/20/18, 6/13/19, 2/21/23, 2/15/24

Revision Dates: 12/29/15, 6/30/16, 7/1/23, 12/6/23, 7/26/24

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) and an increased risk of sudden cardiac death. A range of dysrhythmias can occur with LQTS, the most common being torsade de pointes (TdP), a form of polymorphic ventricular tachycardia (VT). In the specific case of TdP, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis. The peaks of the QRS complexes appear to twist around the isoelectric line of the recording; hence the name torsade de pointes or "twisting of the points."

Bradycardia (a resting heart rate less than 60 beats/min) is also common in patients with LQTS (20%−31% in recent registry studies). Bradycardia appears to be more common in children during the first 3 years of life and has been reported in fetuses and neonates with LQTS.

Long QT syndrome may be either genetic or acquired. Acquired LQTS usually results from drug therapy, hypokalemia, or hypomagnesemia. Congenital LQTS is associated with 13 genes and two clinical phenotypes have been described that vary with the type of inheritance and the presence or absence of sensorineural hearing loss.

- The more common, autosomal dominant form, **Romano-Ward syndrome,** is characterized by QT prolongation and T-wave abnormalities on the ECG, associated with tachyarrhythmias that include the ventricular tachycardia TdP, which may degenerate into ventricular fibrillation. TdP is usually self-terminating, thus, causing a syncopal event, the most common symptom in Romano-Ward syndrome.
- **Jervell and Lange-Nielsen syndrome (JLNS)**, the autosomal recessive form of LQTS, is characterized by congenital profound bilateral sensorineural hearing loss and long QTc, usually greater than 500 ms. Prolongation of the QTc interval is associated with tachyarrhythmias, including ventricular tachycardia, episodes of TdP tachycardia, and ventricular fibrillation, which may culminate in syncope or sudden death. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. 50% of individuals had cardiac events before age 3 years.

Prolonged QT interval is an essential component of the diagnosis of LQTS. Under normal circumstances, the duration of repolarization depends upon the heart rate. The QT interval is longer at slower rates and shorter at faster rates. As a result, the QT interval is often corrected for heart rate (or the duration of the R-R interval) using a common formula: Corrected QT (QTc) = QT interval ÷ square root of the R-R interval (in sec). While there are many ways of calculating the QTc, I most common method is the Bazett formula as described above.

Genetic Testing: Long QT Syndrome, continued

Testing should be performed using the updated Heart Rhythm Society/European Heart Rhythm Association Expert Consensus Recommendations on LQTS Genetic Testing.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers genetic testing for long QT syndrome (LQTS) when either I or II are met:

I. Select Health considers genetic testing for LQTS as medically necessary, if recommended by Intermountain Heart Institute;

OR

II. For all other clinicians, Select Health considers genetic testing for LQTS as medically necessary, when the following criteria are met:

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

AND when the following criteria are met:

3. Select Health covers genetic testing for LQTS in *limited* clinical circumstances. Clinical circumstances in which LQTS Genetic Testing is covered, include any of the following:

A. Comprehensive LQTS genetic testing by multi-gene next generation sequencing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype; or

B. Comprehensive LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, medications, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc > 450 ms in individuals assigned male at birth or children 12 years and younger and > 460 ms in individuals assigned female at birth; or

C. Testing for a known pathogenic familial variant in appropriate relatives.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health

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Genetic Testing: Long QT Syndrome, continued

Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
There exist few articles discussing the relevance of genetic testing for Long QT Syndrome. The most significant articles are: *The Long QT Family of Cardiac Ion Channelopathies* and *Genetic Testing in the Long QT syndrome*. Both articles focus on the insensitivity of the routine ECG in accurately diagnosing a prolonged QTc. The availability of clinical studies on a large series of genotyped patients with LQTS has highlighted major locus specific differences in the prognosis, and in response to therapy it has shown that carriers of LQTS mutations with a normal QTc who cannot be identified by clinical evaluation have a 10% probability of cardiac events by age 40 years if they are not appropriately treated. These data provide a rational for moving genetic analysis from research to diagnostic laboratories and highlight the need for defining optimal screening strategies to make genetic analysis clinically available, efficient, and potentially affordable.

A recent American College of Cardiology/American Heart Association position paper states that the use of β-blocker therapy is appropriate in patients whose molecular testing is positive, thus, supporting the use of genetic testing in this syndrome. Even though the accuracy of genetic testing is 70% in the most common genotypes, the authors suggest that this test is much more predictive than other older tests which have a high false-negative rate.

Billing/Coding Information
Covered: For the conditions outlined above
CPT CODES
Effective 1/01/17 Possibly covered for Commercial, Covered PA for Medicare & Not Covered for Medicaid

0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [when specified as the following]: F2 (coagulation factor 2) (eg, hereditary hypercoagulability), 1199G>A variant
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]: CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2) (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2])
81402	Tier 2 Molecular Pathology Procedures
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following]: ANG (angiogenin, ribonuclease, RNase A family, 5) (eg, amyotrophic lateral sclerosis), full gene sequence GJB1 (gap junction protein, beta 1) (eg, Charcot-Marie-Tooth X-linked), full gene sequence
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]: EGR2 (early growth response 2) (eg, Charcot-Marie-Tooth), full gene sequence HSPB1 (heat shock 27kDa protein 1) (eg, Charcot-Marie-Tooth disease), full gene sequence LITAF (lipopolysaccharide-induced TNF factor) (eg, Charcot-

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Genetic Testing: Long QT Syndrome, continued

	Marie-Tooth), full gene sequence SCN1B (sodium channel, voltage-gated, type 1, beta) (eg, Brugada syndrome), full gene sequence SOD1 (superoxide dismutase 1, soluble) (eg, amyotrophic lateral sclerosis), full gene sequence
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]: ANKRD1 (ankyrin repeat domain 1) (eg, dilated cardiomyopathy), full gene sequence GDAP1 (ganglioside-induced differentiation-associated protein 1) (eg, Charcot-Marie-Tooth disease), full gene sequence HTRA1 (HtrA serine peptidase 1) (eg, macular degeneration), full gene sequence MPZ (myelin protein zero) (eg, Charcot-Marie-Tooth), full gene sequence NEFL (neurofilament, light polypeptide) (eg, Charcot-Marie-Tooth), full gene sequence PRX (periaxin) (eg, Charcot-Marie-Tooth disease), full gene sequence PSEN1 (presenilin 1) (eg, Alzheimer disease), full gene sequence RAB7A (RAB7A, member RAS oncogene family) (eg, Charcot-Marie-Tooth disease), full gene sequence TARDBP (TAR DNA binding protein) (eg, amyotrophic lateral sclerosis), full gene sequence
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]: APP (amyloid beta [A4] precursor protein) (eg, Alzheimer disease), full gene sequence CACNB2 (calcium channel, voltage-dependent, beta 2 subunit) (eg, Brugada syndrome), full gene sequence FIG4 (FIG4 homolog, SAC1 lipid phosphatase domain containing [S. cerevisiae]) (eg, Charcot-Marie-Tooth disease), full gene sequence FUS (fused in sarcoma) (eg, amyotrophic lateral sclerosis), full gene sequence GARS (glycyl-tRNA synthetase) (eg, Charcot-Marie-Tooth disease), full gene sequence GRN (granulin) (eg, frontotemporal dementia), full gene sequence JUP (junction plakoglobin) (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 11), full gene sequence LDB3 (LIM domain binding 3) (eg, familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence MAPT (microtubule-associated protein tau) (eg, frontotemporal dementia), full gene sequence MFN2 (mitofusin 2) (eg, Charcot-Marie-Tooth disease), full gene sequence OPTN (optineurin) (eg, amyotrophic lateral sclerosis), full gene sequence PSEN2 (presenilin 2 [Alzheimer disease 4]) (eg, Alzheimer disease), full gene sequence SH3TC2 (SHE domain and tetratricopeptide repeats 2) (eg, Charcot-Marie-Tooth disease), full gene sequence
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]: APOB (apolipoprotein B) (eg, familial hypercholesterolemia type B), full gene sequence MYBPC3 (myosin binding protein C, cardiac) (eg, familial hypertrophic cardiomyopathy), full gene sequence [for HCM, DCM testing] MYH7 (myosin, heavy chain 7, cardiac muscle, beta) (eg, familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence [for HCM testing] SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (eg, familial dilated cardiomyopathy), full gene sequence [for long QT and Brugada syndrome testing only] TSC2 (tuberous sclerosis 2) (eg, tuberous sclerosis), full gene sequence
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]: FBN1 (fibrillin 1) (eg, Marfan syndrome), full gene sequence RYR1 (ryanodine receptor 1, skeletal) (eg, malignant hyperthermia), full gene sequence RYR2 (ryanodine receptor 2 [cardiac]) (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of >50 exons [for CPVT testing only]
81413	Cardiac ion channelopathies (e.g, Brgada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence

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	analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (e.g. Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ
81479	Unlisted molecular pathology procedure

HCPCS CODES

No specific codes identified

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Genetic Testing: Long QT Syndrome, **continued**

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Select Health

MEDICAL POLICY

GENETIC TESTING: LYMPHOPROLIFERATIVE DISORDERS

Policy # 685
Implementation Date: 8/14/24
Review Dates:
Revision Dates:

Related Medical Policies:
#668: Genetic Testing: Myeloid Neoplasms

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Lymphoproliferative disorders encompass a large and diverse group of clonal lymphoid neoplasms with distinct clinicopathologic features. Current classification schemes (WHO 5th edition, ICC 2022) incorporate a combination of morphologic, immunophenotypic, cytogenetic, and molecular features to classify these entities, allowing for more accurate prognostication and therapeutic decisions. Current classification systems group these disease entities into multiple categories of which broadly include: 1) Small B-cell lymphomas, 2) plasma cell neoplasms, 3) large B-cell lymphomas, 4) mature T-cell and NK-cell lymphomas, 5) Hodgkin lymphomas, and 6) precursor B-cell and T-cell leukemias/lymphomas (i.e., acute lymphoblastic leukemias/lymphomas). For the purposes of this policy only neoplasms that commonly require molecular studies will be included/discussed.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers the following groups of molecular studies when the following criteria are met for each group:

A. Small B-Cell Lymphomas

Select Health covers the following molecular studies in the workup of small B-cell lymphomas (e.g., follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone lymphoma (MZL), Hairy cell leukemia (HCL), splenic B-cell lymphomas, lymphoplasmacytic lymphoma (LPL), mantle cell lymphoma (MCL)):

1. IGHV (immunoglobulin heavy chain variable region genes) mutation analysis by sequencing (MCL, CLL/SLL, HCL).
2. TP53 somatic mutation testing (MCL, CLL/SLL).
    a. May be performed as an individual standalone test or as part of a small lymphoid-specific NGS panel (e.g., CLL NGS panel at ARUP, NeoTYPE CLL profile).

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   b. NeoTYPE CLL profile may be performed with and without the FISH probes. The FISH probes are most appropriate in cases of CLL/SLL, though they may be helpful when the differential includes both CLL/SLL and MCL.
3. BRAF V600 mutation detection by PCR (HCL).
4. MYD88 L265P by PCR (LPL, MZL, IgM MGUS)
   a. MYD88 L265P is present in most cases of LPL but may be used to assist in the workup when the differential includes both MZL and LPL)
   b. CLL mutation panel by NGS or other similar panel that includes MYD88 and CXCR4 is considered acceptable
5. CXCR4 mutation analysis (LPL/Waldenstroms macroglobulinemia).
   a. CLL mutation panel by NGS or other similar panel that includes MYD88 and CXCR4 is considered acceptable

B. Mature T-Cell lymphomas

Select Health covers the following studies in the work-up for mature T-cell lymphomas that may include, but are not limited to T-cell large granular lymphocytic leukemia (T-cell LGL) and peripheral T-cell lymphomas:

1. T-cell clonality screening by PCR (acceptable for all suspected T-cell neoplasms).
2. NGS panel that includes STAT3 and STAT5B (T-cell LGL).

C. B-Lymphoblastic Leukemia/Lymphoma

Select Health covers the following molecular studies in the work-up for B-lymphoblastic leukemia/lymphoma (B-ALL):

1. BCR-ABL1, quantitative and/or qualitative RT-PCR studies.
2. Cytogenomic SNP microarray.
3. ClonoSeq ID and MRD testing.
4. Comprehensive NGS* panel that includes both DNA and RNA sequencing.
   a. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

*Given the importance of identifying recurrent fusions in this disease category the utilization of an NGS panel that detects fusion events is required (i.e., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel).

D. T-Lymphoblastic Leukemia/Lymphoma

Select Health covers the following molecular studies in the work-up of patients with T-lymphoblastic leukemia/lymphoma.

1. Cytogenomic SNP microarray.
2. Comprehensive NGS* panel that includes both DNA and RNA sequencing.
   a. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

*Given the importance of identifying recurrent fusions in this disease category the utilization of an NGS panel that detects fusion events is required (i.e., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel).

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E. Acute Leukemia of Mixed or Ambiguous Lineage

Select Health covers the following studies in the work-up of acute myeloid leukemia that is of mixed or ambiguous lineage:

1. Comprehensive NGS panel that includes both DNA and RNA sequencing (e.g., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel)
2. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

0171U Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence

0306U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD

0307U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD

0340U Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence

0364U Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate

81206 BCR/ABL (T(9,22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative

81207 BCR/ABL1 (T(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative

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Genetic Testing: Lymphoproliferative Disorders, continued

81208 BCR/ABL1 (T(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative

81210 BRAF (V-RAF murine sarcoma viral oncogene homolog B1) (eg, colon cancer) gene analysis, V600 variant

81229 Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis

81261 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

81263 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81264 IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81277 Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities

81278 IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative

81305 MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant

81342 TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81351 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence

81352 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)

81353 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81449 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis

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Genetic Testing: Lymphoproliferative Disorders, continued

81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

81451 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81479 Unlisted molecular pathology procedure

Key References

1. Intermountain Precision Genomics. Genetic Testing for Myloproliferative Neoplasms. June 2023.

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Select Health

MEDICAL POLICY

GENETIC TESTING: METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) POLYMORPHISMS IN CANCER, CARDIOVASCULAR DISEASE, AND NEURAL TUBE DEFECTS

Policy # 426

Implementation Date: 10/12/09
Review Dates: 2/17/11, 2/16/12, 4/25/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 12/19/18, 3/1/23, 6/6/24
Revision Dates: 7/1/23

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#590 Pharmacogenomic Testing for Drug Metabolism

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme encoded by the MTHFR gene which is involved in the folate metabolism pathway. Autosomal recessive pathogenic mutations in the MTHFR gene can cause MTHFR deficiency (homocystinuria), a rare disorder characterized by reduced homocysteine levels, developmental delay, and neurological problems (such as seizures).

Two common *MTHFR* polymorphisms in the general population, C677T and A1298C, have been proposed as risk factors for a variety of complex medical conditions including folate metabolism (neural tube defects, pregnancy loss), cardiovascular disease (specifically thromboembolism), cancer risk.

The American College of Medical Genetics and Genomics (ACMG) issued a practice guideline stating that there is a lack of evidence for MTHFR polymorphism testing in the setting of thrombophilia, a family member with a known polymorphism, or dosing of folic acid supplementation in pregnancy*. Additionally, this testing was not recommended as part of the Choosing Wisely campaign. The American College of Obstetrics and Gynecologists (ACOG) does not recommend MTHFR polymorphism testing in pregnancy.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing for the methylenetetrahydrofolate reductase (MTHFR) polymorphisms. There is a lack of clinical outcome data demonstrating the clinical utility of MTHFR polymorphism testing; therefore, this is considered experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

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Genetic Testing: Methylenetetrahydrofolate Reductase (MTHFR) Polymorphisms In Cancer, Cardiovascular Disease, and Neural Tube Defects, continued

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

One systematic review addressed one aspect of the MTHFR mutation. Their focus was on the role of the enzyme in thromboembolism and homocysteinemia. Homocysteinemia has been proposed to increase the rate of thromboembolism.

Pertinent literature discussing the comparative testing approach for homocysteinemia using MTHFR or other biochemical end products, which include homocysteine, are not available. Most of the literature discusses the potential role of homocysteine as a mediator in cardiovascular disease, cancer, and neural tube defects. It is noted the literature poses unanswered questions related to the need for MTHFR testing as there is the lack of scientific evidence to explain the clinical outcomes observed in patients with polymorphisms. Specifically, questions remain unanswered as to how MTHFR polymorphisms are associated with an increase in the rate of NT defects; the role of homocysteine in the process is unclear.

Articles concerning cancer and MTHFR polymorphsims demonstrate both an increase and decrease in cancer rates/risk depending on the circumstance. Regardless of the association between MTHFR polymorphisms and cancer risk, there are currently no clear clinical pathways leading to improvements in patient outcomes. Outcome studies comparing genetic testing with biochemical markers are not available.

A 2014 review of the literature found limited new data regarding the utility of MTHFR testing. Cohen et al. (2013), in a study of over-utilization of MTHFR genotyping took as fact that: “The methylene tetrahydrofolate reductase (MTHFR) C677T variant has been demonstrated to have negligible utility in patient management” based on expert practice guidelines from the College of American Pathologists (Eldibany et al., 2007) and the American College of Medical Genetics (Hickey et al., 2013) that recommend against MTHFR testing in thrombophilia. Additionally, the expert consensus recommendations from American Heart Association continue to suggest that testing may be appropriate only in the setting of hyperhomocysteinemia (Varga et al., 2005), however no new evidence to support this has been published. No new publications demonstrating utility in neural tube defects or cancer were found. Thus, evidence remains insufficient to recommend coverage of MTHFR for any condition.

Billing/Coding Information

Not covered: Experimental/Investigational/Unproven for this indication

CPT CODES

0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report

Key References

1. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol*, 2013. 122:706–717.
2. Eldibany, M. M. and J. A. Caprini (2007). "Hyperhomocysteinemia and thrombosis: an overview." Arch Pathol Lab Med 131(6): 872-884.
3. Hickey, S. E., et al. American College of Medical Genetics and Genomics Practice Guideline: lack of evidence for MTHFR polymorphism testing, Genet Med 2013:15(2):153–156). https://www.acmg.net/docs/MTHFRgim2012165aFeb2013.pdf.

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Genetic Testing: Methylenetetrahydrofolate Reductase (MTHFR) Polymorphisms In Cancer, Cardiovascular Disease, and Neural Tube Defects, continued

4. Levin BL, Varga E. MTHFR: Addressing Genetic Counseling Dilemmas Using Evidence-Based Literature. J Genet Couns. 2016 Oct;25(5):901-11. PMID: 27130656.
5. Moll S, Varga EA. Homocysteine and MTHFR Mutations. Circulation. 2015 Jul 7;132(1): e6-9. doi: 10.1161/CIRCULATIONAHA.114.013311. PMID: 26149435.
6. Varga, E. A., et al. (2005). "Cardiology patient pages. Homocysteine and MTHFR mutations: relation to thrombosis and coronary artery disease." Circulation 111(19): e289-293.

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Select Health

Select Health

MEDICAL POLICY

GENETIC TESTING: MINIMAL RESIDUAL DISEASE (MRD) ASSESSMENT

Policy # 673
Implementation Date: 7/21/23
Review Dates:
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Minimal residual disease, also called measurable residual disease or MRD, refers to the subclinical levels of residual diseases, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and multiple myeloma (MM). MRD is a postdiagnosis, prognostic indicator that can be used for risk stratification and to guide therapeutic options when used alongside other clinical and molecular data. Many different techniques have been developed to detect residual disease. However, PCR-based techniques, multicolor flow cytometry, and deep sequencing based MRD generally provide better sensitivity, specificity, reproducibility, and applicability than other techniques, such as fluorescence in situ hybridization (FISH), Southern blotting, or cell culture.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers minimal residual disease (MRD) assessment for specific hematologic malignancies, including:

a) acute myeloid leukemia (AML)
b) acute lymphoblastic leukemias
c) chronic lymphocytic leukemia (CLL)
d) chronic myeloid leukemia (CML)
e) multiple myeloma

4. Select Health will also cover MRD assessment in other similar clinical circumstances (such as in the context of clinical trials) in other hematologic malignancies (e.g., hairy cell leukemia, some myeloid/lymphoid neoplasms with eosinophilia, follicular lymphoma, and mantle cell lymphoma).

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The use of MRD assessment is considered experimental/investigational for other conditions, including breast and colon cancer.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

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SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Billing/Coding Information

CPT CODES

Covered for the indications listed above when criteria are met

81479 Unlisted molecular pathology procedure [when specified as NGS tumor DNA testing for MRD]

81599 Unlisted multianalyte assay with algorithmic analysis [when specified as NGS tumor DNA testing for MRD]

0364U Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate clonoSEQ® Assay, Adaptive Biotechnologies

0306U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD

0307U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD

Not Covered for the indications listed above

0340U Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate

0453U Oncology (colorectal cancer), cellfree DNA (cfDNA), methylationbased quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)

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Genetic Testing: Minimal Residual Disease (MRD) Assessment, **continued**

Key References

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MEDICAL POLICY

GENETIC TESTING: MYELOID NEOPLASMS

Policy # 668
Implementation Date: 7/1/23
Review Dates: 7/16/24
Revision Dates: 11/8/23, 7/22/24, 9/30/24, 10/29/24

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Myeloid neoplasms encompass a large and diverse group of clonal myeloid neoplasms with distinct clinicopathologic features. Current classification schemes (WHO 5th edition, ICC 2022) incorporate a combination of clinical, morphological, immunophenotypic, cytogenetic, and molecular features to classify these entities allowing for more accurate prognostication and therapeutic decisions. Current classification systems group these disease entities into categories of which include: 1) myeloproliferative neoplasms, 2) mastocytosis, 3) myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement, 4) myelodysplastic/myeloproliferative neoplasms, 5) myelodysplastic syndromes, 6) acute myeloid leukemia and related precursor neoplasms, and 7) acute leukemia is of mixed or ambiguous lineage.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers the following groups of molecular studies when the following criteria are met for each group:

A. Myeloproliferative Neoplasms

Select Health covers the following molecular studies in the workup and monitoring of myeloproliferative neoplasms:

1. Qualitative and quantitative RT-PCR studies for BCR-ABL1 fusion transcripts
2. BCR-ABL1 mutation analysis for TKI resistance by NGS
3. i. JAK2 V617F mutation by ddPCR, or
   ii. JAK2 V617F mutation by ddPCR with reflex to JAK2 exon 12 mutation analysis; also applicable for abdominal thrombosis evaluation
4. The NGS panel must at a minimum include the following genes: **ASXL1, CALR, CBL, CSF3R, DNMT3A, EZH2, IDH1, IDH2, JAK2, KRAS, MPL, NRAS, PTPN11, RUNX1, SRSF2, SF3B1, SH2B3, TP53, and U2AF1.**

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5. A limited panel that only includes **JAK2, CALR, and MPL**, while not preferred, is considered acceptable.

B. Mastocytosis

Select Health covers the following studies in the workup for systemic mastocytosis:

1. Molecular testing for KIT D816V using an assay with high-sensitivity (i.e., ddPCR).
2. Multigene NGS panel that includes genes such as SRSF2, ASXL1, and RUNX1 (e.g., myeloid-specific NGS panel).
    a. The NGS panel must, at a minimum, include the following genes: **ASXL1, CBL, DNMT3A, EZH2, JAK2, KIT, KRAS, NRAS, RUNX1, SRSF2, TET2**.
    b. The presence of KIT in an NGS panel does not replace the need for KIT D816V mutation testing by a more sensitive method (i.e., ddPCR).

C. Myeloid/Lymphoid Neoplasms with Eosinophilia and Gene Rearrangement

Select Health covers the following studies in the workup for myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement:

1. T-cell clonality studies by PCR
2. Myeloid mutation panel by next generation sequencing* (e.g., myeloid-specific panel).
    a. The panel should at a minimum include the following genes: **ABL1, ETV6, FLT3, PCM1, JAK2, PDGFRA, PDGFRB, FIP1L1, FGFR1, ZMYM2.**

*Given the importance of identifying recurrent fusions in this disease category the utilization of an NGS panel that detects fusion events may be favored (i.e., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel). If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

D. Myelodysplastic Neoplasms/Myelodysplastic Syndromes and Clonal Hematopoiesis

Select Health covers the following molecular studies in the workup of patients with persistent and unexplained cytopenias.

1. Myeloid-specific next generation sequencing panel
    a. The panel should at a minimum include the following genes: **ANKRD26**, **ASXL1, BCOR, CALR, CBL, CSF3R, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KRAS, MPL, NRAS, NPM1, PHF6, PPM1D, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TP53, TET2, UBA1, U2AF1, WT1, ZRSR2.**
2. Cytogenomic SNP microarray-oncology.
3. Qualitative/quantitative RT-PCR studies for BCR-ABL1

E. Myelodysplastic/Myeloproliferative Neoplasms

Select Health covers the following molecular studies in the workup of myelodysplastic/myeloproliferative neoplasms:

1. Myeloid-specific next generation sequencing panel
    a. The panel should at a minimum include the following genes: **ANKRD26**, **ASXL1, BCOR, CALR, CBL, CSF3R, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KRAS, MPL, NRAS, NPM1, PHF6, PPM1D, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TP53, TET2, UBA1, U2AF1, WT1, ZRSR2.**
2. Cytogenomic SNP microarray-oncology.
3. Qualitative/quantitative RT-PCR studies for BCR-ABL1

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F. Acute Myeloid Leukemia

Select Health covers the following studies should in the workup of acute myeloid leukemia:

1. Myeloid-specific next generation sequencing panel
    a. The panel should at a minimum include the following genes: **ANKRD26**, **ASXL1, BCOR, CALR, CBL, CEBPA, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KIT, KRAS, KMT2A (MLL), MPL, NRAS, NPM1, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TP53, TET2, U2AF1, WT1, ZRSR2.**
    b. Rapid NGS panels will be covered only at diagnosis to facilitate immediate management of newly diagnosed AML patients. Rapid NGS panels are typically more limited in scope to facilitate a rapid return of results. Therefore, more comprehensive myeloid-specific NGS panels will also be covered at diagnosis to allow for further risk stratification at diagnosis. A rapid AML NGS panel should, at a minimum, include the following set of genes: **CEBPA, FLT3, IDH1, IDH2, KIT, KRAS, NPM1, NRAS, and TP53.**
2. Cytogenomic SNP microarray-oncology.
3. FLT3 ITD and TKD mutation analysis by PCR
4. Quantitative RT-PCR for CBFB-MYH11 inv(16) if detected by FISH or karyotype
5. Quantitative RT-PCR for RUNX1-RUNX1T1 t(8;21) if detected by FISH or karyotype
6. Quantitative RT-PCR for NPM1 if detected by NGS
7. Quantitative RT-PCR for PML-RARa t(15;17) if detected by FISH or karyotype
8. Qualitative/Quantitative RT-PCR for BCR-ABL1 if detected by FISH or Karyotype
9. KIT mutations in AML by fragment analysis and sequencing or equivalent assay if t(8;21) or inv(16)/t(16;16) detected.
10. Quantitative RT-PCR studies will be covered at diagnosis and during treatment and disease monitoring stages.

G. Acute Myeloid Leukemia of Mixed or Ambiguous Lineage

Select Health covers the following studies in the workup of acute myeloid leukemia that is of mixed or ambiguous lineage:

1. Comprehensive NGS panel that includes both DNA and RNA sequencing (e.g., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel)
2. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For this policy, specifically, there are no CMS criteria available; therefore, the Select Health Commercial policy or InterQual criteria apply. Select Health applies these requirements after careful review of the evidence that supports the clinical benefits outweigh the clinical risks. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health

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Genetic Testing: Myloproliferative Neoplasms, **continued**

Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, 11 NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9

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Genetic Testing: Myloproliferative Neoplasms, **continued**

81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
0027U	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)

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Genetic Testing: Myloproliferative Neoplasms, continued

81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, pLeu265Pro (L265P) variant
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81360	ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin

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Genetic Testing: Myloproliferative Neoplasms , continued

Key References

1. Intermountain Precision Genomics. Genetic Testing for Myloproliferative Neoplasms. June 2023.

Revision History

Revision Date	Summary of Changes
11/8/23	For Commercial Plan Policy, modified coverage criterion #3B: "i. JAK2 V617F mutation by ddPCR, **or** ii. JAK2 V617F mutation by ddPCR with reflex to JAK2 exon 12 mutation analysis; ***also applicable for abdominal thrombosis evaluation.***"
7/22/24	Modified title of policy, was previously titled as [Genetic Testing: Myeloproliferative Neoplasms], and for Commercial Plan Policy, added Section G with coverage criteria for "Acute Myeloid Leukemia of Mixed or Ambiguous Lineage."
9/30/24	For Commercial Plan Policy, added new criterion #5 to criteria section #A (Myeloproliferative Neoplasms), "A limited panel that only includes **JAK2, CALR, and MPL**, while not preferred, is considered acceptable." Also, added new criterion #1-b to criteria section #F (Acute Myeloid Leukemia), "Rapid NGS panels will be covered only at diagnosis to facilitate immediate management of newly diagnosed AML patients. Rapid NGS panels are typically more limited in scope to facilitate a rapid return of results. Therefore, more comprehensive myeloid-specific NGS panels will also be covered at diagnosis to allow for further risk stratification at diagnosis. A rapid AML NGS panel should, at a minimum, include the following set of genes: **CEBPA, FLT3, IDH1, IDH2, KIT, KRAS, NPM1, NRAS, and TP53**."
10/29/24	For Commercial Plan Policy, removed the NF1 gene as part of a required panel of genes to qualify for genetic testing associated with sections A, D, E, and F.

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Genetic Testing: Myloproliferative Neoplasms , **continued**

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MEDICAL POLICY

GENETIC TESTING: *NOTCH3* TESTING FOR CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

Policy # 353
Implementation Date: 6/23/07
Review Dates: 6/11/09, 6/17/10, 8/16/11, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 9/12/18, 8/7/19, 2/14/23, 2/15/24
Revision Dates: 6/19/08, 2/26/19, 7/1/23, 7/25/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling

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Description

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited form of angiopathy affecting small blood vessels. All arteries are affected but the brain is most severely affected. Patients with CADASIL may also be at increased risk of myocardial infarction because of damaged blood vessels in the heart. Most patients with CADASIL do not have the common risk factors for stroke and heart attack, such as high blood pressure and high cholesterol, although in some cases these features may also be present.

Transient ischemic attacks (TIAs) and stroke at a young age (mean age of onset = 46 years) are the most common presentation, occurring in 85%. Cognitive disturbances (dysexecutive syndrome), the second most frequent feature, are observed in about 60% of symptomatic individuals—these disturbances may start as early as age 35 years—and about 75% of affected individuals develop dementia. Migraine occurs in about 40% of individuals, and 90% of individuals with migraine have migraine with aura. Psychiatric disturbance is observed in 30% of individuals with CADASIL, varying from personality changes to severe depression.

Genetic variants in *NOTCH3* (located on chromosome 19p13.2) cause CADASIL. CADASIL is inherited in an autosomal dominant pattern (i.e., only 1 affected allele is sufficient to cause the disorder). In most cases, an affected person has one parent with the condition. In rare cases, a family history is not evident, and a new mutation in the *NOTCH3* gene is identified. Penetrance of the disease approaches 100%, however, pathogenic variants in domains 7-34 are more common and may be associated with milder disease and possibly even reduced penetrance.

A more recently recognized form of CADASIL, type 2, is caused by genetic variants affecting one copy of the *HTRA1* gene. While this form of CADASIL has significant overlap in presentation, the age of onset tends to be later (50-70 years) and additional clinical features such as alopecia, spondylosis, and lower back pain have been reported.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested; and

3. **Select Health covers *NOTCH3* testing for CADASIL, either as a single gene test or as part of a focused panel, under *limited circumstances,*** when all the criteria below have been met.

   Criteria required for coverage:

   A. When the family history is suggestive of an autosomal dominant pattern of inheritance, or there is a strong suspicion of CADASIL; and

   B. Personal or family history of transient ischemic attacks (TIA), cerebral vascular accidents (CVA), and/or vascular dementia; and

   C. MRI brain scan shows unexplained white matter hyperintensities.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The medical and empirical literature reviewed suggests that *NOTCH3* testing provides valuable information confirming the clinical utility of this testing in patients suspected to have CADASIL. This was best identified by Markus et al. in 2002. In this study, the associated mutations were noted to be 100% penetrant with variable expressivity. Additionally, it was identified that this testing and higher sensitivity than the gold standard for diagnosing CADASIL, skin biopsy. This confirmed the findings noted by Joutel et al. in 2001.

CADASIL is an extremely rare disorder, suggesting that *NOTCH3* testing is only appropriate in cases when other more likely diagnoses have been excluded. In symptomatic patients with a clear family history, *NOTCH3* appears to be more reliable than skin biopsy at diagnosing CADASIL. The high penetrance and the fact that children of individuals with a *NOTCH3* mutation have a 50% chance of inheriting the mutation suggests a potential use for presymptomatic testing in these individuals, though, the utility of this indication has not yet been evaluated in the literature.

Lack of clinical guidance is apparent in the literature, but a decrease in extensive laboratory testing may occur if genetic testing for CADASIL is permitted. *NOTCH3* testing may be used as a diagnostic, predictive, or prenatal test. Positive test results are diagnostic for CADASIL. As a predictive test in asymptomatic individuals, testing is not useful in predicting age of onset, severity, type of symptoms, or

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rate of progression. Predictive testing of at-risk individuals should be preceded by testing an affected family member to confirm that the mutation is identifiable by currently available techniques. The mutation detection rate ranges from 57%–96% in individuals with well-defined or biopsy-proven CADASIL. Most authors agree that sensitivity exceeds 90%.

Prenatal testing is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis performed at 15–18 weeks' gestation or chorionic villus sampling at about 10–12 weeks. As with predictive testing, a disease-causing mutation must be identified in an affected family member before prenatal testing can be performed.

Recent literature identified one study by Stojanov et al. (2014) which described a case of a de novo NOTCH3 mutation in a patient with CADASIL, supporting testing in rare instances even when a family history is absent.

Billing/Coding Information

Covered: Under the circumstances listed above

CPT CODES

81406 Molecular pathology procedure, Level 7

HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

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Genetic Testing: *Notch3* Testing for CADASIL, **continued**

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Select Health

MEDICAL POLICY

GENETIC TESTING FOR SCREENING AND DETECTION OF PROSTATE CANCER

Policy # 510

Implementation Date: 9/3/12

Review Dates: 10/24/13, 10/23/14, 10/18/14, 10/15/15, 10/20/16, 10/19/17, 3/16/23, 5/15/24

Revision Dates: 7/1/23, 8/7/23, 9/21/23, 9/13/24

Related Medical Policies:

#544 Genetic Testing for Prostate Cancer Prognosis

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Prostate cancer (PCa) is the second leading cause of cancer death in men, exceeded only by lung cancer; a man's lifetime risk of PCa is 1 in 6. Not everyone experiences symptoms of prostate cancer. Many times, signs of PCa are first detected by a doctor during a routine check-up. Part of the annual exam that men over the age of 50 undergo includes a digital rectal exam (DRE) to feel the prostate and a PSA to screen for asymptomatic prostate cancer. Use of the PSA has become controversial in the last couple of years due to the low sensitivity in screening for prostate cancer. Consequently, new tests which may be more sensitive and specific for identifying early or aggressive prostate cancer are being developed.

Prostate cancer is the most common cancer among men, with over 200,000 new cases identified each year in the United States. The median age at diagnosis is 66 years. Older men are more likely to be affected than younger men, and African American men have higher rates compared to men of other ethnic backgrounds.

Screening programs for prostate cancer allow for its early detection. Screening is typically performed by prostate-specific antigen (PSA) test and digital rectal examination (DRE). Diagnosis is confirmed by prostate biopsy. Biopsy is typically performed by collection of approximately 12 needle biopsy cores. Initial biopsies only detect 65-77% of prostate cancers, and repeat biopsies are frequently performed.9,10 The false negative rate of biopsy may be as high as 25%

The ConfirmMDx test (MDx Health) is a proprietary epigenetic assay that measures gene methylation associated with the presence of cancer. Results are intended to assist in determining which patients likely have a true negative biopsy, and which patients are at increased risk for occult cancer. Results may prevent unnecessary repeat biopsies in unaffected men, and triage higher risk patients for repeat biopsies and treatment, as needed.

SelectMDx is a proprietary test that is designed to identify an individual's risk of prostate cancer without the need for a biopsy. SelectMDx is a urine-based assay that measures mRNA levels of DLX1 and HOXC6 to determine an individual's risk of prostate cancer.

Another test is the urine Progensa PCA3 test. PCA3 (or Prostate Cancer Antigen-3, formerly known as DD3) is a prostate-tissue-specific, noncoding messenger RNA (mRNA) that is over-expressed in virtually all prostate carcinoma specimens compared to normal prostate tissue. These attributes of PCA3 mRNA expression make it a promising prostate-cancer-specific marker. Collecting the specimen is a bit more complicated than simply drawing blood as is done with a PSA test. After massaging each lobe of the prostate 3 times, a urine sample is collected and the amount of PCA3 in the sample is analyzed. The

result is reported as an absolute value but also as positive or negative based upon achieving a pre-specified threshold of 35. Based on the results, a patient's physician may decide whether to continue to biopsy or if active surveillance is more appropriate.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health considers prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility to be medically necessary in the following situations:

i. The member has not had a prostate biopsy, and the member has at least one of the following:

a) Prostate specific antigen (PSA) of > 3 ng/ml, OR
b) A digital rectal exam (DRE) that is very suspicious for cancer, AND
c) The test is one of the following:
- Prostate Health Index (PHI)
- SelectMDx
- 4Kscore
- ExoDx Prostate Test
- MyProstateScore (MPS)
- IsoPSA

OR

ii. The member has had a prostate biopsy, and the result is one of the following:

a) Atypia, suspicious for cancer, OR
b) High-grade prostatic intraepithelial neoplasia (PIN), OR
c) Benign, AND
d) The test is one of the following:
- Prostate Health Index (PHI)
- 4Kscore
- ExoDx Prostate Test
- MyProstateScore (MPS)
- IsoPSA
- ConfirmMDx
- PCA

The use of prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility are for all other indications is considered experimental/investigational.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

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please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

A Medical Technology Assessment performed in August 2012 identified 5 systematic reviews and 30 peer-reviewed journal articles concerning PCA3 testing for PCa indications. The literature spans the years 2006−2012 where more than 9,670 (mean per study ≈322) men were studied. Though the systematic reviews are dated, the addition of more current peer-reviewed literature adds or subtracts very little from the conclusions drawn by the authors of the reviews. Three key points frequently discussed in the literature include: 1) the clinical utility of PCA3, 2) defining the appropriate cut-off value for the PCA3 test, and 3) appropriate patient selection for use of the PCA3 assay.

Clinical Utility: The Hayes GTE update in July 2011 noted that PCA3 detection may be useful for guiding biopsy decisions and that it could possibly improve treatment decision-making in the clinic. This conclusion is largely based on their finding that the diagnostic accuracy of the PCA3 detection test (the ability of the test to predict biopsy outcome) is greater than that of PSA screening. Ultimately, the Hayes GTE report did not find PCA3 testing to be a viable screening test for men considering biopsy, for general population screening, or for disease monitoring, giving it a 'D2' rating. The 2009 BCBS TEC assessment echoes the concerns brought forth in the Hayes review, noting the most significant and persistent finding among all the literature identified for this review, that being: "PCA3 results have not been standardized and clinical utility studies of decision-making for initial biopsy, repeat biopsy or treatment have not been reported."

Similarly, Auprich et al., Henderson et al., Hessels et al., and others have all noted that the exact place of PCA3 as a prognostic test for PCa remains the subject of investigation and that no evidence for the usefulness of PCA3 in active surveillance programs has been presented.

Cut-Off Value: The issue of what constitutes an appropriate cut-off value was addressed throughout the studies (patients whose assay scores are above that cut-off would be qualified as high risk of having PCa). Of note, are the comments by van Poppel et al. who showed that a PCA3 cut-off of < 20 may be the most suitable to select men with clinically insignificant PCa in whom active surveillance may be appropriate. A PCA3 score threshold of 50 may be used to identify men at risk of harboring insignificant prostate cancer. Chun et al. was the only other study that stratified cut-offs correlating to predictive accuracy of PCa upon completion of biopsy. In all, twelve papers used cut-offs of between 17 and 66 with the average being 35. This, once again, points to the fact that PCA3 results and methods have not been stratified in large, prospective, blinded studies.

Where PSA has a relatively high sensitivity and low specificity, PCA3 has a relatively high specificity and low sensitivity. Combining the use of these 2 tests may be postulated to result in improved diagnostic performance. Aubin et al., Ochiai et al., and Pepe et al., all showed that when used in conjunction with PSA, PCA3 testing improves diagnostic accuracy of prostate biopsy for PCa. Only Nyberg et al. showed otherwise. These results came after studying 1,251 patients in total. Despite this, these studies only show potential clinical utility in 13% of all patients reported in this review. It has not been determined, as per the literature, if defining cut-off values for the PCA3 test will raise the sensitivity and specificity of the test to a clinically useful level.

Patient Selection: Though many of the papers illustrated promising outcomes, especially when compared to PSA screening, there is little evidence that PCA3 testing improves patient outcomes because of the lack of standardization and patient segmentation delineating for whom this test is most appropriate. The various studies used different populations and different primary endpoints. This, again, clouds the question as to the clinical utility of this test.

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Genetic Testing: PCA3 Testing for Prostate Cancer, continued

Though PCA3 testing has been shown to have better specificity, AUC, and odds ratio than PSA, currently there is no consensus among societies or authors regarding in whom this test should be performed, what cut-off value should be used to stratify risk or need for biopsy, and under what clinical constraints.

An AHRQ evaluation (Gutman et al., 2013) suggests that further comparative effectiveness research is needed to demonstrate utility of PCA3. Also, in 2013, a report from the EGAPP Working Group found insufficient evidence to recommend PCA3 testing to inform decisions about initial or re-biopsy for prostate cancer in at-risk men. They deemed the clinical validity and net health benefit "low" and recommended against use until additional evidence supports improved outcomes.

Wei et al. in 2014 studied 859 men (mean age, 62 years) from 11 centers who underwent prostate biopsy from 2009−2011 to assess whether PCA3 could improve the positive predictive value (PPV) for an initial biopsy (at a score > 60) and the negative predictive value (NPV) for a repeat biopsy (at a score < 20). PPV was 80% (95% CI, 72% to 86%) in the initial biopsy group, and NPV was 88% (95% CI, 81% to 93%) in the repeat biopsy group.

Recent NCCN Guidelines recommend use of the PCA3 assay in the screening and detection of prostate cancer: "Tests that improve specificity in the post-biopsy setting- including the Sentinel Prostate Cancer Test, percent-free PSA, 4KScore, PHI, PCA3, and ConfirmMDx should be considered in patients thought to be at higher risk despite a negative prostate biopsy." (NCCN Guidelines for Prostate Cancer Early Detection V.1.2022)

Billing/Coding Information

CPT CODES

Covered for the indications listed above when criteria are met

0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer
0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer.
0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch post-digital rectal examination urine (or processed first-catch urine), algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)

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Genetic Testing: PCA3 Testing for Prostate Cancer, continued

81479	Unlisted molecular pathology procedure
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and Human Kallikrein-2 [HK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
81599	Unlisted multianalyte assay with algorithmic analysis

HCPCS CODES

No specific codes identified

Not covered: the following codes are considered experimental/investigational

0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer

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Genetic Testing: PCA3 Testing for Prostate Cancer, continued

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Select Health

MEDICAL POLICY

GENETIC TESTING: PCR FOR BCR-ABL1 IN CHRONIC MYELOGENOUS LEUKEMIA (CML)

Policy # 340
Implementation Date: 3/22/07
Review Dates: 2/21/08, 2/26/09, 2/17/11, 2/16/12, 4/25/13, 2/20/14, 2/11/16, 2/16/17, 2/15/18, 2/18/19, 2/14/23, 2/15/24, 2/18/25
Revision Dates: 7/16/13, 9/17/18, 7/1/23, 3/14/25

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Chronic myelogenous leukemia (CML) is a disorder characterized by uncontrolled production of immature granulocytes (white blood cells). The presence of a greater percentage of immature granulocytes over more mature granulocytes ("leukemic hiatus") is one of the classic findings in CML.

CML is distinguished from other leukemias by the presence of a specific acquired cytogenetic abnormality; the Philadelphia chromosome (Ph). Ph is an abnormally short chromosome that results from a balanced translocation between the distal ends of chromosomes 9 and 22. The breakage on chromosome 22 involves a gene called "BCR" (for breakpoint cluster region), while the breakage on chromosome 9 mutates the Abelson (ABL1) gene. This mutated gene is translocated to chromosome 22 and fused with the remaining part of the BCR gene. This fusion between BCR and ABL1 leads to an abnormal fused gene, called BCR-ABL1.

Since 2008, CML has been defined as BCR-ABL1 positive disease only. Diagnosis of CML therefore requires the detection of the t(9;22)(q34;q11) translocation and/or BCR-ABL in the appropriate clinical and laboratory setting. The NCCN guidelines also recommend testing for BCR-ABL1 in monitoring treatment for CML, follow-up during remission, and to monitor progress when recurrence is evident.

CML occurs in three different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase in developed. Untreated chronic phase CML (CP-CML) will eventually progress to accelerated phase CML (AP-CML) or blast phase CML (BPCML) in 3 to 5 years on average. Progression to AP-CML and BP-CML bridges a continuum of clinical features (i.e., fever, bone pain, spleen size), cytogenetic changes, and blast count.

Quantitative RT-PCR (qPCR) should be done at initial workup to establish the presence of quantifiable BCR-ABL1 mRNA transcripts. qPCR, usually done on peripheral blood, is the most sensitive assay available for the measurement of BCR-ABL1 mRNA and it can detect one CML cell in a background of ≥ 100,000 normal cells. qPCR results can be expressed in various ways, such as the ratio of BCR-ABL1 transcript numbers to the number of control gene transcripts. An International Scale (IS) has been established to standardize molecular monitoring with qPCR across different laboratories with the use of one of three control genes (BCR, ABL1, or GUSB) and a qPCR assay with a sensitivity of at least 4-log reduction from the standardized baseline. IS has become the gold standard of expressing qPCR values.

Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), **continued**

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers BCR-ABL testing when the following criteria are met:

A. BCR-ABL kinase domain point mutation analysis is considered medically necessary in the monitoring of chronic myeloid leukemia (CML) in any of the following circumstances:

1) Workup of individuals suspected to have CML using Quantitative RT-PCR (qPCR) following International Scale (IS), or
2) Evaluation of individuals with CML to determine if treated individuals are manifesting suboptimal response to tyrosine kinase inhibitor therapy indicated by:

i. Lack of a partial hematologic or cytogenetic response at 3 months or greater after treatment onset
ii. Less than a complete hematologic and cytogenetic response at 12 months
iii. Disease progression to accelerated or blast phase

Select Health does NOT cover any other BCR-ABL mutation analysis, as its clinical utility has not been established, and its use meets the plan's definition of experimental/investigational

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

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Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), continued

Summary of Medical Information

Chronic myelogenous leukemia results from a somatic mutation (i.e., not inherited) to DNA of a stem cell in the bone marrow. The mutation confers a growth and survival advantage on the malignant stem cell. The result of this injury is the uncontrolled growth of white cells leading, if unchecked, to a massive increase in their concentration in the blood. Unlike acute myelogenous leukemia (AML), CML allows some white blood cells to mature and function normally, which accounts for the less severe early course of the disease.

Chronic myelogenous leukemia has a triphasic clinical course. Approximately 85%–90% of patients present at the time of diagnosis with relatively indolent disease (chronic phase), which is easily controlled with oral chemotherapy. Untreated, however, CML progresses from a chronic phase to a rapidly fatal blast phase, generally over 3–5 years. Two-thirds of patients will also experience a transition period called the accelerated phase, during which time disease control is more difficult to achieve.

Overall, the literature suggests that BCR-ABL testing using quantitative and/or qualitative PCR is an accurate method of monitoring response to Gleevec therapy and for assessing remission in post-transplant patients. BCR-ABL transcript analysis appears to be more accurate than cytogenetic testing, resulting in fewer false negatives. These test results also impact management decisions regarding initiation or change in treatment modalities. Most of the available literature reports on PCR testing in the context of monitoring for recurrence after stem cell transplantation. Thus, conclusions about this testing in other pre-transplant patients are more limited. Moreover, whether early detection with BCR-ABL testing would prevent blast crises and/or future stem-cell transplantation is unknown. Nevertheless, The National Comprehensive Cancer Network (NCCN) guidelines require BCR-ABL transcript analysis in diagnosis and monitoring of CML. Likewise, an extensive systematic review from the Medical Services Advisory Committee of Australia concluded that BCR-ABL transcript analysis is an accurate and cost-effective method of diagnosing and monitoring CML.

The clinical value of testing for specific BCR-ABL mutations is more controversial and less well-supported in literature. The NCCN recommends ABL kinase domain (KD) mutation analysis in the event of inadequate treatment response. However, the literature is unclear as to the significance of specific ABL mutations, and whether identification of a particular mutation improves clinical outcomes or changes treatment decisions. The exception to this is the T315I mutation analysis. Both dasatinib and nilotinib are effective against most of the known BCR-ABL mutations. Their clinical effectiveness, along with that of imatinib and bosutinib is markedly diminished in the presence of the T315I mutation. Ponatinib, however, retains its clinical effectiveness in the presence of this mutation. Thus, for patients with this mutation, the choice of agent will alter clinical outcomes, and thus, clinical utility has been established. For the other BCR-ABL mutations, their clinical utility is not well-supported in the literature.

A phase II trial of 34 Ph-positive relapsed patients (Benjamini et al., 2014) showed high efficacy of treatment using a regimen that included Desatinib in imatinib resistant patients and depended on genotyping of BCR-ABL genotyping beyond just T315I.

More significantly, a multicenter study of TKI resistance (Zabriske et al., 2014) found that different mutations in BCR-ABL confer different resistance and that compound mutations in the fusion gene let to resistance even to Ponatinib (which had been effective in all single mutations) necessitating complete fusion gene genotyping for rational treatment TKI selection to optimize clinical outcome. These developments show that the use of Ponatinib will not be effective against all mutations and mutational analysis will be needed to guide optimal TKI choice.

In the wake of these findings, the NCCN now includes complete mutation analysis in their latest (v.3.2025) guideline on diagnosis and treatment of CML.

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Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), **continued**

Table 1 Recommended tests for diagnostic workup of CML patients.

From: European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia

	ROUTINE DIAGNOSTIC WORKUP	EXPERIMENTAL/CLINICAL TRIALS[3]
Interphase FISH	**• Recommended for initial screening[*]** Pros: Picks up all *BCR::ABL1* rearrangements irrespective of breakpoint. Usually performed on PB. May be used as primary screen for *BCR::ABL1* or to investigate cases that show discrepant results between cytogenetics and RT-PCR. Cons: does not detect ACAs or identify transcript type therefore positive cases need to be followed up by both cytogenetics and RT-PCR.	**• Acceptable for initial screening**
Qualitative RT-PCR	**• Recommended for initial screening[*]** **• Strongly recommended for determining *BCR::ABL1* transcript type in all confirmed CML patients** **• Mandatory to detect atypical *BCR::ABL1* variants[5]** Pros: Only routine technique to determine exact *BCR::ABL1* transcript type[5]. Usually performed on PB. Cons: No commercial test available to detect most atypical *BCR::ABL1* variants, but essential to cover atypical variants if used as a primary screen. Sequence confirmation may be required. Cannot identify ACAs therefore positive cases need to be followed up by cytogenetics. Nested RT-PCR should not generally be used due to the risk of artefacts and contamination.	**• Mandatory**
Cytogenetics	**• Mandatory for all CML cases** Pros: Only routine technique that can detect prognostically significant ACAs. Can usually be performed on PB but may require BM. May be performed after initial screening by FISH or RT-PCR. Metaphase FISH may be useful to investigate variant translocations. Cons: Up to 5% of CML patients have a normal karyotype therefore not recommended in isolation as an initial screening tool. Positive cases need to be followed up by RT-PCR to determine *BCR::ABL1* transcript type.	**• Mandatory**
Quantitative RT-qPCR	**• Not generally recommended** Pros: may provide additional prognostic information by providing baseline to determine early response kinetics. May be used as an initial screen for CML cases identified by FISH or cytogenetics to identify (by exclusion) those who need investigation for atypical *BCR::ABL1* variants. Cons: approach to determine early response kinetics not standardized.	**• Strongly recommended** GUSB or *BCR* recommended as reference genes in preference to *ABL1* to determine early response kinetics within the first 1–3 months.
NGS panel for myeloid and lymphoid genes	**• Not recommended for CP** **• Suggested for *de novo* BP** Pros: May provide additional prognostic information and identify targets for therapy. Cons: Very limited clinical actionability, even in BC.	**• Strongly recommended for CP and *de novo* BP** *ASXL1* mutations associated with adverse prognosis in some contexts but further studies required to define actionability.
***BCR::ABL1* TKD mutations**	**• Not recommended for either CP or *de novo* BP** Mutations very unlikely to be detected prior to TKI therapy.	**• Not generally recommended (but should be considered)**

[*]FISH and qualitative RT-PCR may be considered as alternative approaches for initial screening, i.e. initial identification of CML patients.

[5]RNAseq may be a better alternative to qualitative RT-PCR but is not widely available.

[3]Depending on trial design and objectives.

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Billing/Coding Information

CPT CODES

0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
0040U	BCR/ABL1 (t (9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	; minor breakpoint, qualitative or quantitative
81208	; other breakpoint, qualitative or quantitative
81401	Molecular pathology procedure Level 2

HCPCS CODES

No specific codes identified

Key References

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7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
3/14/25	For Commercial Plan Policy, added new criterion #A-1: “Workup of individuals suspected to have CML using Quantitative RT-PCR (qPCR) following International Scale (IS), …”

Disclaimer

This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult with appropriate healthcare providers to obtain needed medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member’s individual benefit plan that is in effect at the time services are rendered.

The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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MEDICAL POLICY

GENETIC TESTING: PTEN MUTATION ANALYSIS

Policy # 438
Implementation Date: 3/22/10
Review Dates: 4/21/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 9/18/18, 8/8/19, 3/14/23, 6/12/24
Revision Dates: 7/1/23, 7/15/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#664 Genetic Testing: Breast Cancer

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Colorectal cancer (CRC) and breast cancer are two of the most common cancers in the United States. Although recent improvements in screening and increased understanding of the genetics involved with these cancers has reduced the incidence of these cancers, the morbidity and mortality associated with CRC and breast cancer remains significant. Surgery is the usual approach for tumors that have not metastasized and may be curative. However, chemotherapy, sometimes with radiotherapy, is given to patients with stage III or IV (metastatic) cancer.

PTEN mutations have also been identified in a subset of patients for the PTEN hemartoma tumor syndromes (PHTS). PHTS encompasses many several disorders including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Lhermitte-Duclos disease, Proteus syndrome (PS), Proteus-like syndrome, and autism spectrum disorder.

CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, kidney, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The lifetime risk for renal cell cancer (predominantly of papillary histology) is 34%. The risk for endometrial cancer may approach 28%.

BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS. The targeted therapy Truqap (capivasertib) is a type of drug known as an AKT inhibitor. AKT inhibitors may work better in people with PTEN mutations.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

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Genetic Testing: PTEN Mutation Analysis, continued

1. Select Health orders genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers germline testing for PTEN gene mutations and deletions as a diagnostic tool for ruling out Cowden's syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), or another PTEN-related harmartoma syndrome (PHTS). PTEN gene testing may be considered in individuals with a suspected or known clinical diagnosis of Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), or another PTEN-related hamartoma syndrome; or who have a known family history* of a PTEN mutation.

*Known deleterious family mutation in PTEN identified in 1st, 2nd, or 3rd degree biologic relative.

4. Testing is clinically indicated in the following scenarios:

a) Individual from a family with a known PTEN P/LP variant

b) Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)

c) Individual meeting clinical diagnostic criteria for CS/PHTS

d) Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of:

i. Adult Lhermitte-Duclos disease (cerebellar tumors); or

ii. Autism spectrum disorder and macrocephaly; or

iii. Two or more biopsy-proven trichilemmomas; or

iv. Two or more major criteria** (one must be macrocephaly); or

v. Three major criteria, without macrocephaly; or

vi. One major criterion and ≥ 3 minor criteria***; or

vii. ≥ 4 minor criteria

e) Individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed; individual must have one of the following:

i. Any one major criterion; or
ii. Two minor criteria

f) PTEN P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

For breast cancer germline testing for PTEN see SH MP 664.

Select Health does NOT cover PTEN gene testing on tumor tissue in breast or colorectal cancer when used for the purpose of guiding treatment decisions. There is a lack of direct evidence regarding the role of PTEN somatic testing in these clinical settings. This meets the plan's definition of experimental/investigational.

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**Major criteria: • Breast cancer • Endometrial cancer • Follicular thyroid cancer • Multiple GI hamartomas or ganglioneuromas • Macrocephaly (megalocephaly) (i.e., ≥ 97%, 58 cm in adult female, 60 cm in adult male) • Macular pigmentation of glans penis • Mucocutaneous lesions One biopsy-proven trichilemmoma Multiple palmoplantar keratoses Multifocal or extensive oral mucosal papillomatosis Multiple cutaneous facial papules (often verrucous)

***Minor criteria: • Autism spectrum disorder • Colon cancer • ≥ 3 esophageal glycogenic acanthoses • Lipomas • Intellectual disability (i.e., IQ ≤ 75) • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (e.g., adenoma, nodule[s], goiter) • Renal cell carcinoma • Single GI hamartoma or ganglioneuroma • Testicular lipomatosis • Vascular anomalies (including multiple intracranial developmental venous anomalies)

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

No systematic reviews on the role of PTEN (somatic) testing of tumor tissue for any clinical question were identified for this report. There is limited published evidence concerning the clinical utility of PTEN somatic testing in colorectal or breast cancer.

In CRC, Perrone et al. evaluated, retrospectively, multiple molecular markers in patients who did not respond to cetuximab; 13% of patients showed a decreased PTEN gene copy number and none of these patients responded to cetuximab. Unfortunately, the study is small; uncontrolled (i.e., single-arm only), and PTEN gene status was evaluated for copy number (by FISH) rather than protein expression (by IHC). Reviews of PTEN testing in CRC state inconsistencies in IHC testing methodology are at least partially responsible for the equivocal clinical results in CRC. While there is a substantial evidence base on PTEN gene/protein status, it is currently immature and extremely heterogeneous.

In breast cancer, a study by Capodanno et al. showed a 12.5% incidence of reduced PTEN expression (by IHC) in node negative breast carcinoma (n = 72). HER2 was expressed in 30% of the patients. Lack of PTEN expression was not associated with main clinicopathologic or biological parameters. A multivariate analysis showed that PTEN dysregulation was predictive of disease recurrence. This study was also uncontrolled so can only address prognostic value of measured markers. Studies comparing the PTEN mutation and other prognostic tests such as Onco*type* DX are not available. Studies evaluating the PTEN mutation status and chemotherapy in early-stage breast cancer with clinical outcomes are not available. The evidence base is even larger with PTEN and breast cancer, and even more diverse. Clinical questions and settings addressed in published studies are nearly as numerous as the studies themselves, often with conflicting results.

In both diseases, interpretation of evidence is complicated by the many ways PTEN status is being measured, and includes gene mutations, gene copy number, deletions and duplications, polymorphisms, DNA expression, protein expression, various esoteric RNA moieties, and “systems biology” approaches. Additionally, measurement can be performed either on primary tumor or secondary/metastatic tissue, with widely varying concordance depending on what is being measured and stage of disease.

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As with BRAF and other molecular markers, determination of the predictive value of a biomarker requires, at minimum, retrospective validation (prospectively planned) on a well-designed and conducted RCT. Such a study, which has not yet been published, would then provide sufficient evidence, preferably duplicated in another quality study, to warrant performing a prospective RCT in a practical setting that includes the most appropriate patient-oriented outcome compared to current best practice.

The current published literature fails to answer key questions regarding the specific role of PTEN somatic (tumor) testing. Remaining questions include the role of the multiple additional molecular markers, the role of clinical markers (and their relationships with molecular markers), standardization and reliability of test assays, the value of testing the primary tumor versus or in addition to metastatic tumor tissue, the timing of biomarker measurement, and the most appropriate outcomes to assess the success and failure of decision-treatment protocols. As such, conclusions regarding the role of PTEN somatic testing in guiding colorectal or breast cancer treatment cannot be made.

Billing/Coding Information

CPT CODES

0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

HCPCS CODES

No specific codes identified

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Select Health

MEDICAL POLICY

GENETIC TESTING: RETT SYNDROME

Policy # 586
Implementation Date: 6/6/16
Review Dates: 8/17/17, 8/13/18, 10/13/19, 4/5/23, 6/12/24
Revision Dates: 9/24/18, 7/1/23, 7/15/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Rett syndrome is an X-linked dominant genetic neurodevelopmental disorder. There is wide variability in the rate of progression and severity of the disease Over 80% of patients with classical Rett have pathogenic mutations in the *MECP2* gene. More than 200 mutations in *MECP2* have been associated with Rett. However, 8 of the most commonly occurring missense and nonsense mutations account for almost 70% of all cases. Small C-terminal deletions account for approximately 10%; and large deletions, 8% to 10%. *MECP2* mutation type is associated with disease severity. Whole duplications of the *MECP2* gene have been associated with severe X-linked intellectual disability with progressive spasticity, no or poor speech acquisition, and acquired microcephaly. In addition, the pattern of X-chromosome inactivation influences the severity of the clinical disease in females.

This disorder primarily affects individuals assigned female at birth (AFAB) with an incidence of 1:10,000 AFAB births, making it one of the most common genetic causes of intellectual disability in individuals assigned female at birth. In AFAB, classic Rett syndrome is characterized by apparently normal psychomotor development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, followed by long-term stability. During the phase of rapid regression, repetitive, stereotypic hand movements replace purposeful hand use. Additional findings include fits of screaming and inconsolable crying, autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, and acquired microcephaly. In individuals assigned male at birth (AMAB), this condition presents as severe neonatal-onset encephalopathy characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and breathing abnormalities. Death often occurs before age two years.

The diagnosis of Rett remains a clinical one, using diagnostic clinical criteria that have been established for the diagnosis of classic and variant Rett syndrome. Rett syndrome is usually caused by mutations in the *MECP2* (methyl-CpG-binding protein 2) gene. Genetic testing is available to determine whether a pathogenic mutation exists in a patient with clinical features of Rett syndrome, or in a patient's family member.

Approximately 99.5% of cases of Rett are sporadic, resulting from a de novo mutation, which arise almost exclusively on the paternally derived X chromosome. The remaining 0.5% of cases are familial and usually explained by germline mosaicism or favorably skewed X-chromosome inactivation in the carrier mother that results in her being unaffected or only slightly affected (mild intellectual disability). In the case of a carrier mother, the recurrence risk of RTT is 50%. If a mutation is not identified in leukocytes of the mother, the risk to a sibling of the proband is below 0.5% (since germline mosaicism in either parent cannot be excluded).

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There are currently no specific treatments that halt or reverse the progression of the disease, and there are no known medical interventions that will change the outcome of patients with Rett. Management is mainly symptomatic and individualized, focusing on optimizing each patient's abilities. A multidisciplinary approach is usually used, with specialist input from dietitians, physiotherapists, occupational therapists, speech therapists, and music therapists. Regular monitoring for scoliosis (seen in about 87% of patients by age 25 years) and possible heart abnormalities may be recommended. Spasticity can have a major impact on mobility; physical therapy and hydrotherapy may prolong mobility. Occupational therapy can help children develop communication strategies and skills needed for performing self-directed activities (such as dressing, feeding, practicing arts, and crafts).

Pharmacologic approaches to managing problems associated with RTT include melatonin for sleep disturbances and several agents for the control of breathing disturbances; seizures; and stereotypic movements. Rett patients have an increased risk of life-threatening arrhythmias associated with a prolonged QT interval, and avoidance of a number of drugs is recommended, including prokinetic agents, antipsychotics, tricyclic antidepressants, antiarrhythmics, anesthetic agents, and certain antibiotics.

The identification of a mutation in *MECP2* does not necessarily equate to a diagnosis of Rett. Rare cases of *MECP2* mutations have also been reported in other clinical phenotypes, including individuals with an Angelman-like picture, non-syndromic X-linked intellectual disability, PPM-X syndrome (an X-linked genetic disorder characterized by psychotic disorders [most commonly bipolar disorder], parkinsonism, and intellectual disability), autism, and neonatal encephalopathy.

A proportion of patients with a clinical diagnosis of Rett do not appear to have mutations in the *MECP2* gene. Two other genes, *CDKL5* and *FOXG1*, have been shown to be associated with atypical variants.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers genetic testing for potential carriers and patients suspected of having Rett syndrome.

Rett syndrome should NOT be suspected if an individual has a history of:

- Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurologic problems
- Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

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SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information
According to a large reference laboratory, MECP2 testing for RTT has an analytic sensitivity for sequencing of 99% and for MLPA, 90%; analytic specificity is 99% for sequencing and for MLPA, 98%.

Huppke et al (2000) analyzed the MECP2 gene in 31 female patients diagnosed clinically with RTT. (13) Sequencing revealed mutations in 24 of the 31 patients (77%). Of the 7 patients in whom no mutations were found, 5 fulfilled criteria for classical RTT. In this study, 17 different mutations were detected, 11 of which had not been previously described. Several females carrying the same mutation displayed different phenotypes, suggesting that factors other than the type or position of mutations influenced the severity of RTT.

Cheadle et al (2000) analyzed mutations in 48 females with classical sporadic RTT, 7 families with possible familial RTT, and 5 sporadic females with features suggestive, but not diagnostic, of RTT. (14) The entire MECP2 gene was sequenced in all cases. Mutations were identified in 44 (80%) of 55 unrelated classical sporadic and familial RTT patients. Only 1 (20%) of 5 sporadic cases with suggestive but nondiagnostic features of RTT had mutations identified. Twenty-one different mutations were identified (12 missense, 4 nonsense, and 5 frame-shift mutations); 14 of the mutations identified were novel. Significantly milder disease was noted in patients carrying missense mutations as compared with those with truncating mutations.

The 2 studies previously outlined were included in a summary of 6 articles by Lotan et al (2006) who attempted to disclose a genotype-phenotype correlation (3). The authors found that these studies have yielded inconsistent results and that further controlled studies are needed before valid conclusions can be drawn about the effect of mutation type on phenotypic expression. Two subsequent studies (15, 16) used the InterRett database to examine genotype and RTT severity. Of 357 girls with epilepsy who had MECP2 genotype recorded, those with large deletions were more likely than those with 10 other common mutations to have active epilepsy (odds ratio [OR], 3.71; 95% confidence interval [CI], 1.13 to 12.17; p=0.03) and had the earliest median age at epilepsy onset (3 years, 5 months). Among all girls in the database, those with large deletions were more likely to have never walked (OR=0.42; 95% CI, 0.22 to 0.79; p=0.007). Of 260 girls with classic RTT enrolled in the multicenter RTT Natural History study (NCT00299312), those with the R133C substitution mutation had clinically less severe disease, assessed by the Clinical Severity, Motor Behavior Analysis, and Physician Summary scales. Fabio et al (2014) reported similar genotype-phenotype correlations among 144 patients with RTT in Italy.

Evidence from several small studies has indicated that the clinical sensitivity of genetic testing for classical RTT is reasonably high, in the range of 75% to 80%. However, sensitivity may be lower when classic RTT features are absent. Clinical specificity is unknown, but also is likely to be high, as only rare cases of MECP2 mutations have been reported in other clinical phenotypes, including individuals with an Angelman-like picture, non-syndromic X-linked intellectual disability, PPM-X syndrome, autism, and neonatal encephalopathy.

The clinical utility of genetic testing can be considered in the following clinical situations: (1) individuals with suspected RTT, (2) family members of individuals with RTT, and (3) prenatal testing for mothers with a previous RTT child. These situations will be discussed separately next.

The clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. No studies were identified that described how a molecular diagnosis of RTT changed patient management. Therefore, there is no direct evidence for the clinical utility of genetic testing in these patients.

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There is no specific treatment for RTT, so making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. There are several potential ways in which adjunctive management might be changed after genetic confirmation of the diagnosis:

- Further diagnostic testing may be avoided
- Referral to a specialist(s) may be made
- Heightened surveillance for Rett-associated clinical manifestations, such as scoliosis or cardiac arrhythmias may be performed
- More appropriate tailoring of ancillary treatments such as occupational therapy may be possible

Billing/Coding Information

CPT CODES

0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81479	Unlisted molecular pathology procedure

HCPCS CODES

No specific codes identified

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Select Health

MEDICAL POLICY

GENETIC TESTING: SPINAL MUSCULAR ATROPHY

Policy # 600

Implementation Date: 11/14/16
Review Dates: 12/21/17, 12/11/18, 4/5/23, 5/10/24
Revision Dates: 9/17/18, 7/1/23, 7/25/24

Related Medical Policies:

#123 Gene Therapy, Testing, and Counseling

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Spinal muscular atrophy (SMA) disorders are characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. These diseases are classified as types 0 through IV depending upon the age of onset and clinical course.

- SMA 0 has prenatal onset of severe hypotonia, weakness, and areflexia. This can present as decreased fetal movements during pregnancy. Other findings include arthrogryposis, atrial septal defects, facial diplegia, and respiratory failure at birth. Lifespan is typically less than 6 months.
- SMA I, also known as infantile spinal muscular atrophy or Werdnig-Hoffmann disease, is the most common and severe type of SMA. It typically presents in the neonatal period with loss of head control, joint contractures, and variable difficulties with sucking and swallowing. Symptoms progress rapidly, with median survival reported as ranging from 8-24 months.
- SMA II presents between 6 and 18 months of age. Poor muscle tone is often the first symptom and motor milestones, such as sitting independently, are slowly gained until around five years old. Affected individuals typically have a slow decline in motor function with progressive respiratory muscle weakness leading to restrictive lung disease. Scoliosis and finger tremors are also frequently seen. Life expectancy estimates are not established; one study reported 68% of individuals with SMA II alive at 25 years old.
- SMA III typically presents after 18 months. Affected individuals often can walk independently although, over time, may have trouble with frequent tripping and difficulty with stairs. Similar to SMA II, there is a slow decline in motor function, although respiratory muscle weakness is less common. A retrospective study found no difference in life expectancy between individuals with SMA III and the general population.
- SMA IV usually presents in adulthood. Though manifesting with some muscular weakness and gait dysfunction, loss of ambulation is not usually until after the fifth decade, and these individuals tend to have a normal lifespan.

The inheritance pattern of SMA is autosomal recessive, resulting from biallelic variants in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13.2. Approximately 95% of individuals with SMA have homozygous deletions of exon 7, while the remaining 5% are compound heterozygous for an exon 7 deletion and a *SMN1* sequence variant. SMN protein appears to play a role in mRNA synthesis in motor neurons and may also inhibit apoptosis. The level of SMN protein tends to correlate with the severity of the clinical manifestations.

The *SMN2* gene also encodes for the SMN protein, although it makes several versions of the protein and only one is functional while the others are quickly degraded. While most people have two copies of the

SMN2 gene, the number of copies can vary. For individuals with SMA, having multiple copies of *SMN2* is often associated with less severe disease as the SMN2 gene compensates for some of the SMN protein deficiency resulting from the *SMN1* deletion or sequence variant.

Genetic testing is done to confirm a diagnosis of SMA. Definitive diagnosis may allow for more appropriate therapy beyond supportive care, especially for individuals with SMA I and SMA II.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers genetic testing for spinal muscular atrophy (*SMN1* and *SMN2*) for <u>any</u> of the following groups:

A. Individuals suspected of having spinal muscular atrophy (SMA) who have manifested symptoms suggestive of the disorder; or

B. Couples seeking prenatal care; or

C. Couples who are planning a pregnancy; or

D. Individuals with a family history of SMA; or

E. Individuals with a first-degree relative identified as an SMA carrier.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Spinal muscular atrophy (SMA) is the second most common fatal autosomal recessive disorder after cystic fibrosis, with an estimated carrier frequency of 1/40 to 1/60 in the general population. SMA affects alpha motor neurons in the spinal cord; degeneration of these neurons leads to severe, progressive proximal muscle weakness. Based on age of onset and clinical course, five phenotypes are observed: SMA 0 has prenatal onset of severe weakness and hypotonia with respiratory distress at birth; lifespan is typically weeks to months. SMA I (Werdnig-Hoffmann) presents with severe, generalized muscle weakness and hypotonia are present by six months of age, and death from respiratory failure usually

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occurs before age 2 years. In SMA II, children can sit, although they are unable to stand or walk unaided; survival is typically into early adulthood. SMA III (Kugelberg-Welander) is a milder form—patients can walk unaided—with onset after 18 months of age. SMA IV manifests in adulthood and may result in increased muscular weakness but usually has no impact on lifespan.

ACMG's 2008 guideline, reaffirmed in 2013, recommends carrier testing for SMA in all couples regardless of race or ethnicity. ACOG's 2017 Committee Opinion states: "Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant."

The evidence for carrier testing in individuals who are asymptomatic but at risk for having an offspring with a genetic disease includes mutation prevalence studies, general principles of carrier testing, and accepted practice guidelines from major medical societies; the evidence provides a framework for evaluating these tests because direct evidence on outcomes with carrier testing is lacking. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Reported analytic validity (technical accuracy) of targeted carrier screening tests is high. Changes in management involve family planning. Results of genetic testing can be used to assist individuals with reproductive decisions such as avoidance of pregnancy, preimplantation genetic testing, and adoption. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding Information

CPT CODES

0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications, deletions, and mobile element
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report

Key References

1. Carrier screening for genetic conditions. Committee Opinion No. 691. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017; 129:341–55.
2. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 Dec 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1352/
3. UpToDate – Spinal Muscular Atrophy; accessed on 11/4/16.

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Genetic Testing: Spinal Muscularatrophy, **continued**

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MEDICAL POLICY

PHARMACOGENOMIC TESTING FOR DRUG METABOLISM

Policy # 590

Implementation Date:1/16/17
Review Dates: 12/21/17, 12/13/18, 4/26/23, 7/31/24
Revision Dates: 9/17/18, 7/1/23, 1/24/24, 8/29/24

Related Medical Policies:
#123 Gene Therapy, Testing, and Counseling
#426 Genetic Testing: (MTHFR) Polymorphisms in Cancer, Cardiovascular Disease, and Neural Tube Defects
#594 Genetic Testing: 5-Fluorouracil Testing in Cancer Patients

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1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Pharmacogenomics (PGx) is the study of gene variations within an individual's DNA and how these differences influence an individual's response to medications. An individual's unique genetic makeup helps determine how they respond to a drug and whether side effects or adverse reactions may be experienced. Variations in genes may also cause an individual to metabolize a drug more quickly, more slowly or at the same rate as anticipated, based on dosage.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, ethnicity, and drug-drug interactions. Inherited (germline) DNA sequence variations (or, polymorphisms) in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

PGx tests are indicated when medications are being considered for use (or already prescribed) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A or B).

The selection of the medications in question must be derived from clinical factors/necessity rather than from a PGx test. Once the putative therapeutic agents are selected, and those agents are known to have gene-drug interactions as identified above, then a PGx test may be considered reasonable and necessary as the result of that test would aid physician's prescribing or dosing decisions.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical

Pharmacogenomic Testing for Drug Metabolism, continued

literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

PGx test may be considered reasonable and necessary:

1) When the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug.
2) The selection of the medications in question must be derived from clinical factors/necessity and have been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).

The following pharmacogenomic tests and indications are covered when the member meets the applicable criteria below:

SINGLE GENE: The clinical record must clearly show the use of, or intent to prescribe, a drug that has known drug-gene interactions that require a PGx test (based on CPIC level A or B guidelines) to be ordered to define the safe use of that drug in that patient:

a. If two or more single genes are tested, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary at the time they are ordered.

A multi-gene panel is not considered medically necessary because it is unproven to improve health outcomes.

See Select Health Medical Policy 426: MTHFR, for panels or tests ordered solely for MTHFR testing.

PGx testing is covered for single genes for the following gene-drug pairs:

Gene	Drug	CPIC Level
Abacavir	*HLA-B*	A
Allopurinol	*HLA-B*	A
Amitriptyline	*CYP2C19*	A
	CYP2D6	A
Atomoxetine	*CYP2D6*	A
Azathioprine	*TPMT*	A
	NUDT15	A
Capecitabine	*DPYD*	A
Carbamazepine	*HLA-B*	A
	HLA-A	A
Celecoxib	*CYP2C9*	A
Citalopram	*CYP2C19*	A
Clomipramine	*CYP2D6*	A
	CYP2C19	A
Clopidogrel	*CYP2C19*	A
Codeine	*CYP2D6*	A
Desipramine	*CYP2D6*	B
Dexlansoprazole	*CYP2C19*	B
Doxepin	*CYP2C19*	B
	CYP2D6	B
Efavirenz	*CYP2B6*	A
Escitalopram	*CYP2C19*	A

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Pharmacogenomic Testing for Drug Metabolism, **continued**

Fluorouracil	*DPYD*	A
Flurbiprofen	*CYP2C9*	A
Fluvoxamine	*CYP2D6*	A
Ibuprofen	*CYP2C9*	A
Imipramine	*CYP2C19*	B
	CYP2D6	B
Meloxicam	*CYP2C9*	A
Mercaptopurine	*TPMT*	A
	NUDT15	A
Nortriptyline	*CYP2D6*	A
Omeprazole	*CYP2C19*	A
Oxcarbazepine	*HLA-A*	C
	HLA-B	A
Pantoprazole	*CYP2C19*	A
Paroxetine	*CYP2D6*	A
Piroxicam	*CYP2C9*	A
Simvastatin	*SLCO1B1*	A
Succinylcholine	*CACNA15*	A
	RYR1	A
Tacrolimus	*CYP3A5*	A
Tamoxifen	*CYP2D6*	A
Thioguanine	*TPMT*	A
	NUDT15	A
Tramadol	*CYP2D6*	A
Trimipramine	*CYP2D6*	B
	CYP2C19	B
Voriconazole	*CYP2C19*	A
Warfarin	*CYP2C9*	A
	CYP4F2	A
	VKORC1	A

Other Considerations

For pharmacogenomic tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), **testing will be allowed once per lifetime per gene.** Exceptions may be considered if technical advances in testing or the discovery of novel genetic variants demonstrate significant advantages that would support a medical need to retest.

Testing performed in a CLIA-certified laboratory will be considered for coverage. The use of a specific FDA approved companion diagnostic is not necessary for coverage to be considered.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

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Pharmacogenomic Testing for Drug Metabolism, continued

Summary of Medical Information

Current evidence regarding the use of genotyping tests for the determination of drug metabolizer status indicates that while available testing methods may accurately identify genetic variations in an individual, there is insufficient data to demonstrate that such testing, and the clinical decisions made based on the testing, results in a significant impact on health outcomes. Specifically, clinical trials have not yet adequately demonstrated that such testing results in either enhanced clinical effectiveness, or in decreased short-term or long-term serious adverse events.

A particular variant is not always phenotype specific in that it may have a different impact depending on the drug in question (National Academy of Clinical Biochemistry [NACB], 2010). Racial and ethnic differences in the frequency and nature of genetic variants are also possible and should be recognized in translating outcomes from one population to another. The relation of a gene or gene biomarker and a drug target must be validated for each therapeutic indication in different racial and ethnic groups, as well as in different treatment and disease contexts (Kager and Evans, 2012). Pharmacogenetic testing is not currently recommended for general population screening (National Academy for Clinical Biochemistry [NACB], 2010).

Recently, the FDA has added language to the labels of many approved drugs to include pharmacogenomic information. Wang and colleagues published a study evaluating the evidence that supports pharmacogenomic biomarker testing in drug labels and how frequently testing is recommended (2014). Their analysis found that of the 119 drug-biomarker combinations identified, only 43 (36.1%) had labels that provided convincing clinical validity evidence supporting pharmacogenomic testing related to a specific drug. Furthermore, only 18 (15.1%) provided convincing evidence of clinical utility.

Recommendations on the manner of clinical decisions based on the results of a biomarker test were made on 61 labels (51.3%); but only 36 (30.3%) of these contained convincing clinical utility data. A full description of the supporting studies for these recommendations was included in 13 labels (10.9%). The authors found that less than one-sixth of drug labels contained or referenced convincing evidence of clinical utility of biomarker testing, whereas more than half made recommendations based on biomarker test results. They concluded that it may be premature to include biomarker testing recommendations in drug labels when convincing data that link testing to health outcomes do not exist.

Critical elements of assessing the effectiveness of such genetic tests include: (1) analytic (diagnostic) validity; (2) clinical validity; and (3) clinical utility. Analytic validity measures the technical performance of the test, in terms of accurately identifying the genetic markers to be measured. Clinical validity measures the strength of association between genetic test results and clinical parameters such as dose, therapeutic efficacy, or adverse events. Clinical utility, the ultimate goal of genetic testing, measures the ability of the test to improve clinical outcomes, such as whether prescribing or dosing based on information from genetic testing improves therapeutic efficacy or adverse event rate as compared with treatment without genetic testing.

Testing for genetic polymorphisms has also been proposed for a wide array of drugs, involving many different conditions and enzymes. At this time, the available literature addressing such testing is limited and insufficient to allow any assessment of clinical utility in the treatment of individuals. The outcomes that require further research attention include major adverse events, utilization of health resources, and time to clinically significant changes in condition using appropriate and validated measures.

While the potential of pharmacogenomics is intriguing for many clinical applications, it is not yet clear which are most likely to yield clinical benefit in the near future. As this field evolves and matures, and if pre-prescription testing can be shown to be of clinical utility for specific drugs and individuals, it will be imperative to establish evidence-based guidelines for health care professionals delineating the most effective courses of action based on such genotype testing results.

Several commercial laboratories market multi-test panels for genetic polymorphisms related to drug metabolizer status. While the use of some individual tests included in these test panels may be reasonable under specific circumstances, the use of all the tests within a panel is rarely justified unless there is clinical evidence that the panel provides information that leads to meaningful impact on treatment. At this time, the available published evidence addressing the use of such test panels is limited to a few panel- and condition-specific studies (Altar, 2015; Hall-Flavin 2012, 2013; Winner, 2013a, 2013b). The results of these studies are limited by the study designs utilized by the investigators, with each having some combination of no blinding, small study population, retrospective methodology, selection bias, short

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Pharmacogenomic Testing for Drug Metabolism, continued

follow-up periods, and subjective study outcomes. The data from these studies is weak, and further investigation is warranted using better designed, larger study samples and double-blind randomized controlled methodology.

Billing/Coding Information

CPT CODES

0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (i.e., ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder
0173U	Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
0175U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine Smethyltransferase) (e.g., drug metabolism) gene analysis, common variants
0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
0345U	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
0380U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)

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Pharmacogenomic Testing for Drug Metabolism, **continued**

0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639G>A, c.173+1000C>T)
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81400	Molecular pathology procedure level 1
81401	Molecular pathology procedure level 2
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
81406	Molecular pathology procedure level 7
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

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Pharmacogenomic Testing for Drug Metabolism, continued

HCPCS CODES

G9143 Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

G0452 Molecular pathology procedure; physician interpretation and report

Not covered: the following codes are considered experimental/investigational

0516U Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status

0533U Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function

Key References:

1. Centers for Medicare & Medicaid Services (CMS). LCD – MolDX: Pharmacogenomics Testing (L38294).
2. CPIC. Guidelines. https://cpicpgx.org/guidelines/
3. PHARMGKB. Pharmacogenomics. https://www.pharmgkb.org/

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated this medical policy after Select Health and Intermountain Precision Genomics reacquired responsibility for evaluating genetic testing claims; and updated overall coverage criteria to align with current clinical standards.
1/24/24	For Commercial Plan Policy, clarified that both TPMT ***and NUDT15*** are covered without restriction.
8/29/24	For Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards, including providing more specific requirements for determining the eligibility of single-gene tests; and added the following exclusion: “A multi-gene panel is not considered medically necessary because it is unproven to improve health outcomes.”

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MEDICAL POLICY

WHOLE GENOME SEQUENCING (WGS)/WHOLE EXOME SEQUENCING (WES)

Policy # 514

Implementation Date: 11/9/12

Review Dates: 12/19/13, 12/8/14, 4/21/17, 6/21/18, 4/17/19, 1/7/23, 2/15/24

Revision Dates: 4/14/16, 10/11/18, 7/1/23, 8/17/23, 8/28/23, 7/23/24

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Description

Whole genome sequencing (WGS) in the outpatient setting has evidence and support for use as a first-line test for children with multiple congenital anomalies, neurodevelopmental delays, and for health conditions where there is a need for a timely and efficient diagnostic pathway.

First-line use of WGS reduces costs, avoids redundant or wasteful testing, reduces time to diagnosis, reduces disparities in diagnosis, reduces referrals and multiple visits with different specialists, and provides earlier access to treatment options. WGS is currently available at the same or lower cost compared to genetic panel testing or whole exome sequencing (WES). Studies support that the use of trio-based WGS decreases the likelihood of receiving variants of uncertain significance that require further evaluation, in comparison to many phenotype-based gene panels.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.
   Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

I. Whole Genome/Whole Exome Sequencing

A. Select Health considers whole genome sequencing (WGS) or whole exome sequencing (WES) medically necessary when the member meets all the following criteria in A, and one of the following (B or C):

1) No other causative circumstances (e.g., environmental exposures, injury, prematurity, infection) can explain symptoms; and

Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

2) Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available; and

3) The differential diagnosis list and/or phenotype warrant testing of multiple genes and one of the following (i or ii):

i. WES/WGS is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis; or

ii. WES/WGS results may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing.

AND

B. WGS/WES will be considered medically necessary for any of the following conditions:

1) Unexplained multiple congenital anomalies including structural brain or organ abnormalities; or
2) Neurodevelopmental disorders, including intellectual disability and autism spectrum disorder; or
3) Unexplained conditions with significant potential for influencing medical management and clinical outcomes with need for timely diagnosis, including but not limited to:
   i. Significant or refractory epilepsy and/or EEG or exam consistent with encephalopathy; or
   ii. Abnormal labs and/or presentation concerning for metabolic or mitochondrial disorder; or
   iii. Developmental regression or neurological findings suspicious for a progressive disorder including but not limited to white matter disease, cerebellar atrophy, movement disorders; or
   iv. Unexplained cytopenias, immune dysregulation, and bone marrow failure, as well as a significant family history of multiple family members with cancer of autoimmunity not detected by standard, focused screening.

OR

C. WGS/WES is allowed for fetal testing, when all the following criteria are met:

1) Standard diagnostic genetic testing (chromosomal microarray analysis (CMA) and/or karyotype) of the fetus has been performed and is uninformative; and
2) Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue; and
3) At least one of the following is present:
   i. multiple fetal structural anomalies affecting unrelated organ systems
   ii. fetal hydrops of unknown etiology
   iii. a fetal structural anomaly affecting a single organ system and family history strongly suggests a genetic etiology

II. Whole Exome/Genome Reanalysis: Reanalysis of previously obtained uninformative whole exome or whole genome sequence data is considered medically necessary when the above criteria (A plus B or C) for whole exome/genome sequencing are met, AND

1) When any of the following conditions (i–iii) are met:
   i. Onset of additional symptoms that broadens the phenotype assessed during the original exome/genome evaluation, or
   ii. Birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture, or
   iii. At least 18 months have passed since the last analysis (meaning there could now be new scientific knowledge that would impact the patient's result interpretation).

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**Providers should utilize any no-charge analysis offered by the laboratory prior to submitting a request to Select Health for payment of reanalysis.*

WGS/WES for cardiac arrythmias and cardiomyopathies is considered experimental/investigational.

III. Ultra Rapid/Rapid Genome Sequencing

A. **Select Health covers Ultra Rapid or Rapid Genome Sequencing for acutely-ill infants 12 months of age or younger in the hospital setting**, when all the following criteria (1−4) are met:

1) The etiology of the infant's features is unknown, and a genetic etiology is considered a likely explanation for the phenotype, based on either of the following:
   i. Multiple congenital abnormalities affecting unrelated organ systems,
   or
   ii. Two of the following criteria are met:
      a) Abnormality affecting at minimum a single organ system
      b) Encephalopathy
      c) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia)
      d) Family history strongly suggestive of a genetic etiology, including consanguinity
      e) Laboratory findings suggestive of an inborn error of metabolism
      f) Abnormal response to therapy;

AND

2) Alternate etiologies have been considered and ruled out, when possible (e.g., environmental exposure, injury, infection, isolated prematurity);
AND
3) Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available;
AND
4) A diagnosis cannot be made in a timely manner by standard clinical evaluation.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

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Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

Billing/Coding Information
Covered for the indications listed above when criteria are met:
CPT Codes

0094U Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis

0454U Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping

0469U Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination

81415 Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis

81416 Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)

81417 Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)

81425 Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis

81426 Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)

81427 Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)

96040 Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS Codes

S0265 Genetic counseling, under physician supervision, each 15 minutes

Not covered: considered experimental/investigational/unproven or not medically necessary
CPT Codes

0019U Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents

0036U Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses

0212U Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem

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Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband

0213U Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)

0214U Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband

0215U Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)

0260U Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping

0264U Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping

0265U Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants

0266U Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes

0267U Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing

0297U Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification

0298U Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification

0300U Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification

0329U Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations

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Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

0335U Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants

0336U Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent)

0460U Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes

0532U Rare diseases (constitutional disease/hereditary disorders), rapid whole genome and mitochondrial DNA sequencing for singlenucleotide variants, insertions/deletions, copy number variations, peripheral blood, buffy coat, saliva, buccal or tissue sample, results reported as positive or negative

81349 Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis

81479 Unlisted molecular pathology procedure

Key References

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