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Genetic Testing for Mental Health Disorders

Policy Number: AHS – M2084 – Genetic Testing for Mental Health Disorders	Prior Policy Name and Number, as applicable: • AHS – M2084 – Genetic Testing for Mental Health Conditions
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I. Policy Description

Mental disorders encompass a range of clinical phenotypes characterized by a clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress in social, occupational, or other important activities (APA, 2013).

This policy focuses on the genetic testing for the diagnosis of and/or susceptibility to mental health disorders. For pharmacogenetic testing for patients on therapies for mental health disorders, please refer to policy AHS-M2021 Pharmacogenetic Testing.

II. Related Policies

Policy Number	Policy Title
AHS-M2021	Pharmacogenetic Testing
AHS-M2145	General Genetic Testing, Germline Disorders
AHS-M2146	General Genetic Testing, Somatic Disorders

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. 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 or the manual website

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

1. Genetic testing for mutations associated with mental health disorders and/or genetic testing panels for mental health disorders **DO NOT MEET COVERAGE CRITERIA** in all situations, including, but not limited to, the following:

    a. To confirm a diagnosis of a mental health disorder in an affected individual.

    b. To predict future risk of a mental health disorder in an asymptomatic individual.

IV. Scientific Background

Mental health disorders are believed to be caused by a variety of factors, including the environment, neurochemistry, and inherited traits (APA, 2013). These disorders can affect daily living and may be accompanied by many symptoms including fatigue, insomnia, sudden weight loss, and an overall depressed mood (HQO, 2017). According to the 2017 National Survey on Drug Use and Health (NSDUH), approximately 51.5 million (20.6%) American adults had a mental illness in 2019 (SAMHSA, 2020). Further, about half of Americans will meet the criteria for a DSM-IV disorder sometime in their lifetime, with first onset usually in childhood or adolescence (Kessler et al., 2005).

Treating mental illness is challenging because people with a mental health disorder often avoid asking for professional help due to stigma associated with the condition. Further, when these individuals do seek treatment, a combination of therapies is often required, including psychotherapy (such as cognitive behavioral therapy), one or more medications (such as antidepressants), or both (HQO, 2017).

Panels of genetic tests have been developed and proposed for use in the diagnosis of mental illnesses and in the identification of asymptomatic high-risk individuals. Gatt, Burton, Williams, and Schofield (2015) state, “major efforts have been directed at family-based association and case control studies to identify the involvement of candidate genes in the major disorders of mental health. What remains unknown is whether candidate genes are associated with multiple disorders via pleiotropic mechanisms, and/or if other genes are specific to susceptibility for individual disorders.”

Mood Disorders

Mood disorders primarily encompass depressive disorders, bipolar disorders, and their ilk. According to the 2017 National Survey on Drug Use and Health (NSDUH), approximately 17.3 million adults and 3.2 million adolescents experienced a major depressive episode (SAMHSA, 2020). Diagnosis of a depressive disorder has traditionally depended on a clinical history and examination, as screening tools do not provide a diagnosis. Symptoms of this set of disorders include anhedonia, depressed mood, fatigue, insomnia, and more (Lyness, 2020).

Biological testing has seen mixed utility. Identifying co-morbid conditions or drugs of abuse is necessary for management of these disorders, but other avenues such as identifying those predisposed to depression without other clinical symptoms need further data (Lyness, 2020). The impact of any one gene on depression has been limited thus far; depression usually requires significant environmental influences in addition to numerous genetic effects to manifest. Several genetic features such as certain loci on chromosome 10, polymorphisms in corticotropin-releasing hormone type 1 receptor gene (*CRHR1*), and many more have been suggested by studies to correlate with depressive disorders, but these results are typically not replicated. Malfunction of several

neurotransmitters such as serotonin, dopamine, GABA, glutamate, and norepinephrine is typically involved with major depressive disorders (Krishman, 2021).

Epigenetic changes have also been associated with depression and suicide. An epigenetic change is a functional modification of a gene by methods such as methylation. Lockwood, Su, and Youssef (2015) report that many researchers have identified a relationship between depression and suicide; specifically, the hypermethylation of *BDNF* (Brain-derived neurotrophic factor) and *TrkB* (tropomyosin receptor kinase B) have been associated with suicide in several studies.

Direk et al. (2017) performed a meta-analysis of two genome-wide association meta-analyses to examine any genetic associations with a broad depression phenotype (encompassing both major depressive disorder and depressive symptoms). The "discovery" stage (two previous studies) included 70017 items, and the "replication" stage of the meta-analysis included 28328 items. One novel locus on chromosome 3 was found to correlate with the broad depression phenotype, and this finding was replicated on an independent sample and on the meta-analysis of both the discovery and replication stages (Direk et al., 2017).

Wray et al. (2018) performed a genome-wide association meta-analysis to identify loci related to major depressive disorder (MDD). The authors investigated a total of 135,458 cases and 344,901 controls and found a total of 44 "independent and significant loci." An important association found was genetic risk of MDD with education, high body mass and schizophrenia. The authors concluded that a "continuous measure of risk" belies the clinical phenotype of MDD (Wray et al., 2018).

Persons affected by bipolar disorders experience both depressive and manic symptoms; on the other hand, unipolar disorder patients characteristically experience only depressive or manic symptoms. Bipolar disorders, such as bipolar I disorder and bipolar II disorder, may present with similar symptoms to major depression. However, bipolar I disorder presents with more severe manic episodes than bipolar disorder II (Bobo, 2017). As with depressive disorder, several genetic features have been associated with bipolar disorder. Corticotropin releasing hormone signaling, endothelin 1 signaling, glutamate signaling, and phospholipase C signaling have all been investigated as possible links to bipolar disorder. A calcium channel regulator, *CACNA1C* has seen consistent association with bipolar disorder as well. Other genetic components, such as gene expression and epigenetic features, have been studied (Stovall, 2020). Hughes et al. (2018) has reported that *Ankyrin-3* (*ANK3*) is one gene that is consistently associated with bipolar disorder by multiple genome-wide association studies.

Ikeda, Saito, Kondo, and Iwata (2018) performed a meta-analysis of genome-wide association studies on bipolar disorder. Twenty-six studies encompassing over 200,000 subjects were included. The authors found a total of 39 single nucleotide polymorphisms (SNPs) with genome-wide significance. However, their primary conclusion was "that the effect size of the susceptibility SNP is extremely small (e.g., odds ratio ~1.2), and the magnitude was similar to that of SCZ [schizophrenia] and MDD [major depressive disorder]." The authors also stressed "that common genetic variants do not have a large impact on the diagnosis for BD [bipolar disorder]" (Ikeda et al., 2018).

Stahl et al. (2019) published a genome-wide association study (GWAS) focusing on bipolar disorder. A total of 20352 cases and 31358 controls of European descent were evaluated, and a follow up analysis (with an additional 9412 cases and 137760 controls) was performed on the 822 variants with a P value of 1×10^{-4}. Eight of 19 variants that were genome-wide significant ($P < 5 \times 10^{-8}$) in the discovery GWAS were not significant in the combined analysis. Overall, 30 loci were found to be genome-wide significant, and 20 of these loci were newly identified. Notable and significant loci included genes

encoding ion channels, neurotransmitter transporters, insulin secretion regulation, and synaptic items. The authors noted that bipolar I disorder is more correlated with schizophrenia while bipolar II disorder is more correlated with major depressive disorder (Stahl et al., 2019).

Qi et al. (2020) completed an integrative analysis of a GWAS and a regulatory SNP annotation dataset that included 20,352 cases of bipolar disorder and 31,358 controls in the first dataset, and 7,481 cases of bipolar disorder and 9,250 controls in the second dataset. A comparative analysis of the two datasets was completed. The authors note that "After the integrative analysis, we identified 52 TFBRs [including transcription factor binding regions] target genes, 44 TADs [topologically associated domains] target genes, 55 CIRs [circular RNAs] target genes and 21 lncRNAs [long non-coding RNA regions] target genes for BD [bipolar disorder] (Qi et al., 2020)." Some of the most important genes identified include *ITIH4*, *ITIH3*, *SYNE1* and *OPRM1*; this study shows that regulatory SNPs are important in the development of bipolar disorder.

Psychotic Disorders

Psychosis of the mind is loosely defined as a disconnection with reality. Psychotic disorders primarily include schizophrenia, schizotypal disorder, and delusional disorder. Other psychiatric conditions, such as bipolar disorder, may include psychotic symptoms. Major psychotic symptoms include delusions (loosely defined as "strongly held false beliefs that are not typical of the patient's cultural or religious background"), hallucinations, thought disorganization, agitation, and more. Diagnosis of these psychotic disorders typically involves excluding other possible causes of these symptoms. Once other causes (such as foreign substances or other pathological conditions) have been ruled out, a psychiatric disorder should be considered (Marder, 2021).

Genetic risk factors have been modestly associated with schizophrenia, as heritability studies (twin studies, adoption studies, et al.) have demonstrated useful results. However, the specific genes involved in the etiology of schizophrenia have yet to be identified. Other pathological risk factors, such as environmental (infections, inflammation, and even immigration) and neurological (dopamine, glutamate, GABA, et al.), have been proposed to contribute to schizophrenia and this realm of disorders (Fischer, 2020).

The Schizophrenia Working Group of the Psychiatric Genomics Consortium performed a "multi-stage schizophrenia genome-wide association study of up to 36989 cases and 113075 controls." A total of 108 SNPs were found to associate independently with schizophrenia. The authors noted that "associations were enriched among genes expressed in tissues that have important roles in immunity," and suggested that this result "provided support for the speculated link between the immune system and schizophrenia" (Ripke et al., 2014).

Gandal et al. (2018) performed meta-analyses of transcriptomic studies covering five major psychiatric disorders, including schizophrenia (SCZ), autism (ASD), bipolar disorder (BPD), alcoholism, and depression, and compared cases and controls to identify co-expressed gene modules. Patterns of shared and distinct gene-expression perturbations were identified across these conditions. The degree of sharing of transcriptional dysregulation is related to polygenic (SNP–based) overlap across disorders, suggesting a substantial causal genetic component. This comprehensive systems-level view of the neurobiological architecture of major neuropsychiatric illness demonstrates pathways of molecular convergence. The authors note, "we have replicated broad transcriptomic and cell-type specific patterns independently for ASD, SCZ and BD, providing an organizing pathological framework

for future investigation of the mechanisms underlying specific gene and isoform-level transcriptomic alterations in psychiatric disease (Gandal et al., 2018)."

Huckins et al. (2019) performed a transcriptomic imputation to identify associations between schizophrenia and gene expression. A total of 40,299 cases and 65,264 controls were evaluated, and 413 genic associations were found. Sixty-seven non-MHC [major histocompatibility complex] genes were identified, of which 14 were not within previous GWAS loci. Finally, 36 biological pathways were recognized as having a potential association with the clinical phenotype (Huckins et al., 2019).

Kowalczyk et al. (2018) completed a study with 1,080 Polish subjects (401 with schizophrenia and 679 healthy controls). The purpose of the study was to determine if genetic variants in the *HSPA1A* (rs1008438, rs562047) and *HSPA1L* (rs2075800) genes are associated with the risk of development of paranoid schizophrenia. While previous studies have reported an association between *HSPA1A* and *HSPA1B* SNPs and schizophrenia symptomatology, no statistically significant relationships were identified in this study.

Guan et al. (2020) completed a study which researched the relationship between the *WBP1L* (WW Domain Binding Protein 1 Like) gene and schizophrenia. An initial group of 2,128 patients with schizophrenia and 3,865 controls were recruited for this study; a second group of 1,052 patients with schizophrenia and 2,124 controls also participated. Thirty-two SNPs located in the *WBP1L* gene were analyzed. "To conclude, SNPs rs4147157 and rs284854 were associated with SCZ [schizophrenia] in the Chinese Han population. Additionally, rs4147157 was significantly associated with specific symptom features of SCZ (Guan et al., 2020)."

(Mojarad et al., 2021) studied how whole genome sequencing (WGS) broadens the range of copy number variants that play a clinical role in schizophrenia. Genomic data of 259 schizophrenic adults was analyzed for any rare high-impact variants including single nucleotide variants, insertions/deletions, and tandem repeat expansions. (TREs). This study identified more TRE variants (one in DMPK; two in ATXN8OS) and an ultra-rare loss-of-function SNVs in ZMYM2 which suggests that it plays a bigger role in schizophrenia than previously thought. Of the 233 patients with no pathogenic copy number variants, WGS identified 26 individuals with pathogenic rare copy number variants and 17 individuals with other types of rare high-impact variants that have potential clinical relevance. This indicates that individuals with schizophrenia, including many with no broadly defined learning disability, had a high-impact small number variant or TRE that was not detectable by CMA, but it was detected by WGS. The authors conclude that this study provides " important evidence of the enhanced performance of WGS compared to CMA in the detection of genome-wide clinically relevant variants, and an initial indication of features that could help identify individuals with schizophrenia who are most likely to benefit from clinical genetic testing and genetic counselling (Mojarad et al., 2021)."

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is one of the most common childhood behavioral disorders, which commonly continues into adulthood. Evaluation of this disorder typically includes medical, developmental, educational, and psychosocial examination, and this condition is often comorbid with other psychiatric disorders, such as anxiety or substance use. Symptoms typically include inattention, impulsivity, restlessness, and other dysfunction in certain environments, for example, in school (Krull, 2019).

The exact pathology of ADHD is unknown. A combination of genetic, environmental, and neurological factors has been suggested to contribute to the condition, but no definitive correlations have been found. Genes, such as serotonin transporters, dopamine receptors, and glutamate receptors, have all been linked to ADHD development, and possible genetic basis has been supported by twin and family studies (Bukstein, 2021).

Middeldorp et al. (2016) performed a genome-wide meta-analysis to "investigate the genetic overlap of ADHD symptom scores with ADHD diagnosis." The authors examined the "genome-wide single nucleotide polymorphisms (SNPs) and ADHD symptom scores were available for 17,666 children (<13 years of age) from nine population-based cohorts." SNP-based heritability was estimated at 5-34%, but there were no genome-wide significant SNPs. However, three genes were found to have a gene-wide significant association, and one of these genes (WASL) was involved in neuronal development (Middeldorp et al., 2016).

Qi et al. (2019) analyzed a GWAS dataset of 20,183 patients with ADHD and 35,191 healthy controls. This tissue specific transcriptome-wide association study (TWAS) identified 148 relevant brain tissue genes related to ADHD (including *TDO2*, *CHD1L* and *KIAA0319L*); in the mRNA expression datasets, 11 common genes were identified (including *ACSM5*, *CCDC24* and *MVP*) (Qi et al., 2019). These genes may help to further the understanding of the underlying genetic mechanisms of ADHD.

Meijer et al. (2020) studied DNA methylation related to ADHD and associated traits via an epigenome-wide association study. Blood samples were used from participants in the NeuroIMAGE study. Samples from participants with ADHD (n=35) and samples from healthy controls (n=19) were analyzed. The researchers found that "methylated regions provided significant findings showing that hypermethylated regions in the *APOB* and *LPAR5* genes were associated with ADHD persistence compared to ADHD remittance (Meijer et al., 2020)." Both of these genes are involved in cholesterol signaling. It is important to note that this study included a rather small sample size. The authors conclude by stating that "Although we do not wish to draw conclusions before replication in larger, independent samples, cholesterol signaling and metabolism may be of relevance for the onset and/or persistence of ADHD (Meijer et al., 2020)."

In an epigenome-wide association study, Rovira et al. (2020) studied epigenetic dysregulation in adults with ADHD. This study found one CpG site and four regions that are methylated in 103 patients and 100 controls. This study observed whether smoking status, polygenic risk burden, or exposure to stressful life events had an impact on the methylation pattern of ADHD at the CpG site. Stressful life events, polygenic risk burden, and smoking status had no impact on the methylation pattern in ADHD subjects. The authors conclude that "these findings support a role of DNA methylation in ADHD and emphasize the need for additional efforts in larger samples to clarify the role of epigenetic mechanisms on ADHD across the lifespan (Rovira et al., 2020)."

Anxiety Disorders

Anxiety disorders, including general anxiety disorder, phobias, and obsessive-compulsive disorder, are characterized by excessive and persistent worrying that is hard to control and causes significant distress and/or impairment. According to the 2017 NSDUH, approximately 31.1% of American adults will experience an anxiety disorder at some point in their lives (SAMHSA, 2020). In addition to the characteristic worry, anxiety sufferers may also experience other somatic symptoms, such as increased fatigue (Baldwin, 2021).

Several genetic factors have been suggested to contribute to this condition. Neurotransmitter receptors, transporters, and pathways have all been associated with generalized anxiety disorder. Other metabolites, such as 5-hydroxyindoleacetic acid, have been explored. Furthermore, twin studies have demonstrated degrees of heritability; estimates are typically in the range of 30% heritability (Baldwin, 2021; Bennett, 2019).

Smith et al. (2016) performed a genome-wide analysis on neuroticism (a very common personality trait in anxiety disorders) for over 106,000 patients. A total of nine novel loci were found to have significant associations with neuroticism. These loci included genes involving glutamate receptor ionotropic kainate 3 (*GRIK3*), corticotropin-releasing hormone receptor 1 (*CRHR1*), CUGBP (CUG triplet repeat RNA binding protein 1) elav-like family member 4 (*CELF4*) and more (Smith et al., 2016).

Levey et al. (2020) studied the genetics of anxiety disorders and symptoms using the Million Veteran Program, which is one of the world's largest biobanks. Both the Generalized Anxiety Disorder 2-item scale and physician diagnoses were used to identify individuals with an anxiety disorder (n=199,11 and n=224,330 respectively). The strongest genome-wide signals were identified on chromosome 3 (rs4603973) near *SATB1*, on chromosome 6 (rs6557168) near *ESR1* and on chromosome 7 (rs56226325) near *MAD1L1* (Levey et al., 2020). Further, *MAD1L1* "may have implications for genetic vulnerability across several psychiatric disorders (Levey et al., 2020)."

Below is a table summarizing selected genes and their potentially associated mental health conditions:

Gene(s)	Mental Health Conditions				
	MDD	Bipolar Disorder	Psychotic Disorders	Anxiety Disorders	ADHD
Serotonin Pathway (*SLC6A4*, 5HT2C, et al.)	X			X	X
Dopamine Pathway (*DRD1*, *DRD2*, *DRD4*, et al.)	X		X		X
Glutamate Pathway	X	X	X	X	X
GABA Pathway	X		X		
SULT4A1 (GeneReview, 2019)			X		
CACNA1C (gated calcium channel)		X			
Corticotropin Pathway (*CRHR1*, et al.)	X	X		X	
Androgen Receptor Signaling Pathway (*ANK3*, et al.)		X			

Many mental health disorder panel tests are produced for pharmacogenetic purposes. However, Invitae has developed the Mendelian Disorders with Psychiatric Symptoms Panel to identify "late onset inborn errors of metabolism that can result in psychiatric symptoms"; this test can analyze up

to 91 genes in hopes to provide “the appropriate clinical and psychological management to achieve the best possible outcome for the patient” (Invitae, 2020).

In a GWAS, Burton et al. (2021) studied the relationship between pediatric OCD traits and genetic variants. 5018 Caucasian children were genetically tested for OCD traits using the Toronto Obsessive-Compulsive Scale (TOCS). The locus, rs7856850, within the intron of protein tyrosine phosphatase δ, was found to be associated with OCD traits. In addition, this study established a possible role of the 9p24.1 region in OCD which is the strongest linkage of pediatric OCD. The authors conclude that " OC traits and OCD share genetic risk, suggesting that the TOCS is capturing traits that are likely to be on a continuum with OCD (Burton et al., 2021)."

V. Guidelines and Recommendations

American Academy of Pediatrics (AAP) (Zuckerbrot et al., 2018)

The AAP (Zuckerbrot et al., 2018) recently published Guidelines for Adolescent Depression in Primary Care which state that the nine depression criteria outlined by the DSM – 5 have been shown to cluster together, run in families and have a genetic basis, but does not recommend specific genetic testing.

American Psychiatric Association (APA) (APA, 2016, 2020)

In their Practice Guidelines For The Psychiatric Evaluation of Adults (3rd Edition), the APA does not make any specific recommendations regarding genetic testing for any psychiatric condition (APA, 2016).

The APA has released a practice guideline for the treatment of patients with schizophrenia. A table is provided in these guidelines titled “assessments to monitor physical status and detect concomitant physical conditions.” The table includes the following relevant recommendation:

- Genetic testing: “Chromosomal testing, if indicated based on physical exam or history, including developmental history[e] (APA, 2020).”

International Society of Psychiatric Genetics (ISPG) (ISPG, 2019)

The ISPG “does not recommend direct-to-consumer genetic testing for medical purposes in patients with psychiatric illness or their families, or in healthy individuals concerned about risk or treatment for psychiatric disorders” (ISPG, 2019).

The ISPG does not recommend using “polygenic risk scores” or “risk allele burden testing” (large numbers of genetic variants considered in aggregate) to identify high-risk individuals or to diagnose psychiatric patients. No recommendation was provided for the analysis of copy number variants for adults with mental illness (ISPG, 2019).

European Network Adult ADHD and the Section for Neurodevelopmental Disorders Across the Lifespan (NDAL) of the European Psychiatric Association (EPA) (Kooij et al., 2019)

These joint guidelines include statements on the genetic component of ADHD. Genetic variants associated with the D4 and D5 dopamine receptor genes typically provided the most consistent findings, but other candidate genes have not shown consistent trends in genome-wide association studies. Several loci have been found to have genome-wide significance, and further research may detect more genomic variants with more genetic samples. Copy number variants have also been suggested to contribute to the condition but findings are inconsistent (Kooij et al., 2019).

American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI) (AACAP, 2013)

The CQI noted that although many different genetic features (loci, genes, copy number variants) have been associated to various degrees with schizophrenia, genetic testing is only recommended if there are "associated dysmorphic or syndromic features" (AACAP, 2013).

In clinical practice guidelines for the assessment of children with anxiety disorders, AACAP states that "At present, there is no clear role for pharmacogenomic testing in medication selection, although this may change as additional evidence accumulates (Walter et al., 2020)."

US Department of Veterans Affairs/Department of Defense (VA/DoD) (VA/DoD, 2016)

The VA/DoD published a clinical practice guideline for the management of major depressive disorder. This guideline states that "Additional research is required in the use of genetic testing to aid in the selection of the most appropriate medication for a specific patient. Currently, there is insufficient evidence to support the routine use of genetic testing for the selection of one antidepressant over another (VA/DoD, 2016)."

VI. State and Federal Regulations, as applicable

A. Food and Drug Administration (FDA)

No FDA-approved tests were found for the genetic assessment of mood disorders, bipolar disorder, ADHD, schizophrenia, anxiety disorders, or other psychotic disorders as of March 09, 2020 (FDA, 2019). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

B. Centers for Medicare & Medicaid Services (CMS)

N/A

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
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)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
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)
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)
81479	Unlisted molecular pathology procedure

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

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