Clinical UM Guideline

Subject:	Genetic Testing for TP53 Mutations		
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Description

This document addresses genetic testing for TP53 mutations.

The TP53 gene (also known as p53) located on chromosome 17 is a tumor suppressor gene. The protein product of the TP53 gene binds to cellular DNA and is involved in the control of the cell cycle and apoptosis (programmed cell death).

Note: For additional information on genetic testing for malignant conditions, please refer to:

- CG-GENE-13 Genetic Testing for Inherited Diseases
- CG-GENE-14 Gene Mutation Testing for Cancer Susceptibility and Management
- CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
- CG-GENE-16 BRCA Genetic Testing
- GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling

Clinical Indications

Medically Necessary:

Germline testing for cancer susceptibility

I. TP53 gene mutation testing for Li-Fraumeni syndrome (LFS) is considered **medically necessary** when **any** one of criteria A through *G* and **all** of criteria H are met:
   A. The individual has a family history of known TP53 mutation; **or**
   B. The individual was diagnosed with sarcoma prior to age 45 years; **and**
      1. Has a first-degree relative who was diagnosed with cancer prior to age 45 years; **and**
      2. Has an additional first- or second-degree relative on the same side of the family who was diagnosed with cancer prior to age 45 years, or sarcoma at any age; **or**
   C. The individual was diagnosed with a tumor from the LFS tumor spectrum (for example, soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) prior to age 46 years; **and**

1. Has at least one first-or second-degree relative with any of the above LFS spectrum tumors (other than breast cancer, if the proband has breast cancer) diagnosed prior to the age of 56 years or with multiple primaries at any age; **or**

D. The individual was diagnosed with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum, with the initial cancer occurring prior to age 46 years; **or**
E. The individual was diagnosed with adrenocortical carcinoma, choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype at any age, regardless of family history; **or**
F. The individual was diagnosed with early onset breast cancer at age 30 years or younger; **or**
G. The individual's somatic tumor testing has identified a TP53 variant and both of the following criteria are met:
   1. Personal and family history suggest a germline mutation; **and**
   2. The results of germline testing are likely to be used to guide further medical management of the individual;

and

H. Genetic counseling, which encompasses **all** of the following components, has been performed:
   1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   2. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   4. Counseling for the psychological aspects of genetic testing.

II. Prenatal or preimplantation genetic testing is considered **medically necessary** to establish a diagnosis of LFS in the offspring of individuals with known TP53 genetic mutation, and genetic counseling, which encompasses **all** of the following components, has been performed:
   A. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   B. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   C. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   D. Counseling for the psychological aspects of genetic testing.

Somatic tumor testing

TP53 gene mutation testing is considered **medically necessary** for individuals diagnosed with chronic lymphocytic leukemia or hypodiploid acute lymphocytic leukemia to identify those who would benefit from treatment with chemotherapy.

Not Medically Necessary:

TP53 gene mutation testing is considered **not medically necessary** in individuals not meeting the criteria above.

Coding

The following codes for treatments and procedures applicable to this guideline are included below 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.

When services may be Medically Necessary when criteria are met:

CPT	
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

ICD-10 Diagnosis	
C00.0-C96.9	Malignant neoplasms
Z15.01-Z15.09	Genetic susceptibility to malignant neoplasm
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z36.8A	Encounter for antenatal screening for other genetic defects
Z80.0-Z80.9	Family history of primary malignant neoplasm
Z84.81	Family history of carrier of genetic disease
Z85.00-Z85.9	Personal history of malignant neoplasm

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Discussion/General Information

Genetic testing for TP53 mutations may be carried out using a variety of technologies, including but not limited to direct sequencing and analysis as well as multiplex ligation-dependent probe amplification (MLPA). TP53 gene testing may be performed for the purpose of diagnosis, risk assessment, and/or disease management.

Li-Fraumeni syndrome (LFS)

LFS is a rare, autosomal dominant cancer predisposition syndrome which often manifests at a young age. Individuals with LFS have an estimated 60% chance of malignancy by age 45 and a 95% chance by age 70. LFS is diagnosed in individuals meeting established clinical criteria or in those who have a germline mutation in TP53

regardless of family cancer history. At least 70% of individuals diagnosed clinically have an identifiable germline mutation in TP53, and somatic mutations of the TP53 gene are found in approximately 50% of all tumors. Acquired TP53 mutations are observed in numerous tumors; however, no other inherited phenotypes are associated specifically with germline mutations involving TP53.

Once a TP53 mutation has been identified in a family, testing of at-risk relatives can identify those family members who also have the familial mutation. Management for individuals with LFS may include increased surveillance for the development of cancer. For individuals with LFS, breast MRIs instead of mammograms may be recommended as a means to reduce radiation exposure. Prophylactic mastectomy rather than lumpectomy may be recommended as a preventive measure in individuals with a germline TP53 mutation. Individuals with germline TP53 mutations are cautioned to avoid known carcinogens including excessive sun exposure, tobacco use, occupational exposures and excessive alcohol use.

Germline testing for cancer susceptibility

Two forms of LFS have been identified: classic LFS and Li-Fraumeni-like syndrome (LFLS). Several criteria sets have been developed over the years to identify individuals with classic LFS or LFLS. Individuals with classic LFS meet the following criteria: a diagnosis of a sarcoma was made before age 45 years; a first-degree relative was diagnosed with any cancer prior to age 45 years; and an additional first- or second-degree relative was diagnosed with any form of cancer prior to age 45 years or diagnosed with sarcoma at any age (Li, 1988). Individuals with LFLS fulfill a portion, but not all, of the above criteria. The Birch criteria and the Eeles criteria are less stringent than the criteria for LFS and were developed to identify individuals with LFLS. The Chompret criteria was developed to update the criteria to account for different clinical presentations associated with germline TP53 mutations (Birch, 1994; Chompret, 2001; Eeles, 1995). Bougeard and colleagues (2015) noted the 3 clinical situations which might suggest the presence of LFS:

1. Familial presentation [a proband with an LFS tumor (breast cancer, STS, osteosarcoma, CNS tumor, ACC, leukemia, bronchoalveolar lung cancer) under 46 years and one first- or second-degree relative with an LFS tumor under 56 years or with multiple tumors],
2. Multiple primary tumors (two of which belong to the narrow LFS spectrum, the first being developed before 46 years) or
3. Rare cancers [ACC or choroid plexus carcinoma (CPC) irrespective of the family history].

The importance of the role of TP53 in tumor suppression is illustrated by the fact that the majority of individuals fulfilling the criteria for classic LFS (and a smaller proportion of individuals fulfilling the Chompret criteria) carry germline variants in the TP53 gene.

Multiple studies have been published demonstrating the clinical validity of genetic testing for LFS in childhood and adult cancer (Birch, 2001; Bougeard, 2008; Chompret, 2000; Hwang, 2003; Mai, 2016). At this time, the TP53 mutations are considered high penetrance and is the only gene which has unequivocally been shown to be

associated in LFS (Bougeard, 2015). LFS syndrome management involves more frequent monitoring, beginning at an earlier age compared to the general population (NCCN, V1.2023). The clinical utility of TP53 mutation testing in individuals with a high-risk personal or family history suggestive LFS has been established (Asdahl, 2017; Ballinger, 2015; Gonzalez, 2009; Kratz, 2017; Villani, 2011).

Somatic tumor testing

Hypodiploid acute lymphocytic leukemia (ALL)

ALL is a rapidly progressing type of cancer that originates in the lymphocytes of the bone marrow. Because ALL cells typically invade the blood fairly quickly, they can metastasize to other parts of the body, including but not limited to the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles. If not treated promptly, proliferation of leukemia cells can cause bone marrow failure and death due to anemia, hemorrhage, and/or infection within a few months.

Contemporary therapy for ALL generally involves the administration of various cytotoxic chemotherapeutic agents in several phases over several years. Treatment is curative in more than 90% of children. However, relapse of ALL occurs in up to 20% of children and even more frequently in adults and is often refractory to further chemotherapy. For this reason, relapsed ALL is a leading cause of childhood cancer death (Comeaux, 2017).

Although TP53 mutations are one of the most frequently observed somatic alterations in cancer, and are also common in acute myeloid leukemia, they are relatively uncommon in ALL. In cases involving ALL, TP53 is frequently mutated in two settings: (1) relapsed and (2) low-hypodiploid ALL. Hypodiploid ALL encompasses up to 5% of childhood ALL cases "and is stratified according to the severity of aneuploidy; with several stereotyped patterns of chromosomal loss identified: near haploidy (24–31 chromosomes), low hypodiploidy (32–39 chromosomes), and high hypodiploidy (40–44 chromosomes)" (Comeaux, 2017). Each of these patterns of chromosomal loss is characterized by distinct genetic mutations which are not commonly found in other forms of ALL, one of the most prominent being TP53 mutations in low-hypodiploid ALL. It has been noted that the frequency of TP53 mutations/deletions increase with age and that individuals harboring a hypodiploid ALL have a high risk of treatment failure. Research suggests the presence of TP53 mutations/deletions is a valuable prognostic parameter for individuals with ALL and may be used as a tool to identify which individuals would benefit from chemotherapy treatment (Comeaux, 2017; Holmfeldt, 2013; Stengal, 2014).

The TP53 alteration seems to be an essential component of the pathogenesis of low-hypodiploid ALL, with approximately 50% of tumors showing somatic TP53 mutations and many of the remaining cases acquiring other genetic or epigenetic alterations that negatively affect TP53 function (Bloom, 2020). Based on the published data and specialty consensus input, TP53 gene mutation testing may be considered appropriate for individuals diagnosed with hypodiploid acute lymphocytic leukemia in order to identify those who would benefit from treatment with chemotherapy and as a prognostic factor (Bloom, 2020; Comeaux, 2017; Hof, 2011; Swaminathan, 2019) .

Chronic Lymphocytic Leukemia (CLL)

CLL is a chronic, slowly developing form of leukemia which is characterized by the progressive accumulation of incompetent leukemic cells in the peripheral blood, lymphoid tissues and bone marrow. CLL represents approximately 1.1% of all new cancer cases in the U.S. with approximately 20,160 new cases being diagnosed and an estimated 4410 individuals dying of the disease in 2022 (NCI, 2022). In contrast to some other forms of leukemia, CLL can progress slowly causing few, if any, problems in its initial stages. While individuals can live with CLL without any symptoms for decades, others live for a shorter period. Careful analysis of an individual's blood and physical condition help to determine the stage of the disease – a crucial first step in deciding on the proper course of treatment. Some individuals with CLL do not benefit from early, aggressive treatment, but instead do better with careful long-term monitoring of the disease. Frequently CLL is diagnosed incidentally by blood tests that are performed during a routine physical exam. In other cases, it is discovered as a result of the individual seeking treatment for symptoms. There is an inherited genetic susceptibility for CLL; family members of individuals with CLL have a 6-to-9-fold increased risk of developing the disease (Eichhorst, 2015; NCCN, V1.2023; SEER, 2016).

Several factors have been identified which provide prognostic information for CLL. These factors include but are not limited serum markers such as beta-2 microglobulin, thymidine kinase, cytogenetic abnormalities detected by FISH (for example, del(13q), del(11q) and del(17p) and TP53 mutations. Del(17p) and a mutation of TP53 have been identified and evaluated in individuals with CLL and are considered useful markers to provide prognostic information beyond clinical staging. Individuals with a detectable del(17p) or a mutation of TP53 have the poorest prognosis, with a median OS of 2-5 years. These individuals also tend to experience poorer outcomes such as shorter treatment-free interval, shorter survival (32 months) and poorer response to chemotherapy (Dohner, 2000).

Several studies using fludarabine-based regimens have identified TP53 mutations as an independent predictor of shorter survival and decreased resistance to chemotherapy. Zenz and colleagues (2010) conducted a randomized controlled trial in order to define the impact of TP53 mutations in CLL. The researchers assessed TP53 mutations by denaturing high-performance liquid chromatography (exons 2 to 11) in a group of 375 individuals with a follow-up of 52.8 months (German CLL Study Group CLL4 trial; fludarabine alone and fludarabine in addition to cyclophosphamide [FC]). The authors identified TP53 mutations in 8.5% of subjects (28 of 328 participants). None of the participants with TP53 mutation demonstrated a complete response. In subjects with TP53 mutation, compared with subjects without TP53 mutation, median progression-free survival (PFS; 23.3 versus 62.2 months, respectively) and OS (29.2 versus 84.6 months, respectively) were appreciably decreased (both $p<0.001$). TP53 mutations in the absence of 17p deletions were found in 4.5% of participants. PFS and OS for subjects with 17p deletion and subjects with TP53 mutation in the absence of 17p deletion were similar. Multivariate analysis distinguished TP53 mutation as the strongest prognostic marker regarding PFS (hazard ratio [HR]=3.8; $p<0.001$) and OS (HR=7.2; $p<0.001$).

In the prospective, randomized trial comparing FC with chlorambucil or fludarabine, researchers investigated the frequency and prognostic value of TP53 abnormalities in individuals with CLL. The researchers analyzed a total of 529 CLL samples from the Leukemia Research Foundation Chronic Lymphocytic Leukemia 4 (LRF CLL4) trial for mutations in the TP53 gene. TP53 mutation status was correlated with response and survival data. Mutations of

TP53 were noted in 8.5% of participants, including 87.5% who carried the 17p deletion, and conferred a poor prognosis independent of other adverse features (Gonzalez, 2011).

Stilgenbauer and colleagues (2014) conducted an analysis of the CLL8 study (a prospective, international, multicenter, randomized [1:1] first-line treatment trial comparing FC or FC with rituximab [FCR]). Study results demonstrated that TP53, NOTCH1, and SF3B1 were mutated in 72 of 628 (11.5%), 62 of 622 (10%), and 114 of 621 (18.4%) CLL participants requiring front-line therapy, respectively. Individuals with a mutation in TP53 experienced significantly decreased OS and PFS outcomes regardless of treatment with FC or FCR.

The NCCN (V1. 2023) recommends that all individuals diagnosed with CLL undergo TP53 sequencing prior to the initiation of treatment to direct the selection of appropriate therapy (2A recommendation). TP53 alterations found in CLL have been shown to convey resistance to some standard chemotherapies such as fludarabine, cyclophosphamide and rituximab (Chauffaille, 2020). The ESMO guidelines provide direction regarding the role of TP53 mutation analysis in selecting appropriate treatment regimens.
Studies have demonstrated that TP53 mutation is an independent marker of poor prognosis in individuals with CLL. Genetic testing as a prognostic factor is starting to play a role in therapeutic selection. Current guidelines recommend using TP53 mutation status as a tool to identify the most appropriate regimen for symptomatic CLL individuals requiring treatment.

Germline Testing in the presence of a somatic tumor TP53 mutation

Somatic mutations in the TP53 gene are present in up to 50% of tumors, including relapsed or refractory CLL (Chauffaille, 2020; Schneider, 2019). The NCCN CPG (V1.2023) notes that somatic TP53 pathogenic/likely pathogenic mutations in the absence of germline pathogenic/likely pathogenic mutations stating:

> Somatic TP53 variants frequently confound germline testing results. Late post-zygotic aberrant clonal expansions (ACEs) containing a pathogenic TP53 variant, limited to hematologic compartment or to a tumor, may be detected in the blood or saliva through germline testing, particularly using NGS technology. The phenomenon of ACE is well described and is most often due to CHIP, which can be demonstrated in healthy populations at increasing frequency with increasing age. This finding has important clinical implications regarding the potential application of unwarranted clinical intervention.

Yamamoto and colleagues (2020) evaluated the relationship between TP53 mutations identified through next-generation sequencing (NGS) somatic tumor testing and germline testing. Individuals with advanced cancer underwent NGS somatic tumor testing. A total of 61.9% (120/194) of the population were found to have a pathogenic/likely pathogen mutation in one of several genes, including TP53, PTEN, BRCA1 and BRCA2, with TP53 mutation being the most common variant found. The results of germline testing were available for 30 individuals with somatic TP53 mutations. No cases of a TP53 germline mutation were located. The authors summarized that unless individuals have a relevant medical or family history, the significance of germline testing following positive somatic tumor testing appears to be low in daily clinical practice.

Genetic Counseling

According to the National Society of Genetic Counselors (NSGC, 2006), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

(1) Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
(2) Provides education about inheritance, genetic testing, disease management, prevention and resources; and
(3) Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
(4) Provides counseling for the psychological aspects of genetic testing

Definitions

Acute lymphocytic leukemia (also known as acute lymphoblastic leukemia; ALL): A fast growing type of cancer that originates in the lymphocytes (white blood cells) in the bone marrow.

Chronic lymphocytic leukemia: A type of cancer in which the bone marrow produces abnormal leukocytes (white blood cells).

Germ cell: An ovum or a sperm cell or one of its precursors.

Germline mutation: Any detectable and heritable change in the lineage of germ cells. Mutations in these cells are transmitted to offspring, while, on the other hand, somatic mutations are not inherited.

Leukemia: A type of cancer affecting the blood and bone marrow.

Penetrance: The probability of a clinical condition occurring when a particular genotype is present.

Proband: The affected individual who serves as the starting point for the genetic study of a family.

Somatic cells: Cells that make up the body of an organism with the exception of germ cells.

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, Discussion, References and Websites sections.
Reviewed	11/11/2021	MPTAC review. Updated Discussion and References sections.
Revised	11/05/2020	MPTAC review. Revised to add a medically necessary clinical indication for germline testing when a TP53 mutation is identified during somatic tumor testing. Updated Discussion, References and Websites sections. Reformatted Coding section and updated with 01/01/2021 CPT changes, added 81351, 81352, 81353 replacing 81404, 81405; also updated with additional ICD-10-CM codes.
New	11/07/2019	MPTAC review. Initial document development. Moved content related to genetic panel testing from GENE.00035 Genetic Testing for TP53 Mutations to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling. Moved content of GENE.00035 Genetic Testing for TP53 Mutations not related to gene panels to new clinical utilization management guideline document with the same title.