

**Subject:** Genetic Testing for TP53 Mutations  
**Guideline #:** CG-GENE-18  
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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**

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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**

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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.

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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***

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*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

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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.

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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

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- (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.

**References**

**Peer Reviewed Publications:**

1. Asdahl PH, Ojha RP, Hasle H. Cancer screening in Li-Fraumeni syndrome. *JAMA Oncol.* 2017; 3(12):1645-1646.
2. Avigad S, Peleg D, Barel D, et al. Prenatal diagnosis in Li-Fraumeni syndrome. *J Pediatr Hematol Oncol.* 2004; 26(9):541-545.
3. Baliakas P, Hadzidimitriou A, Sutton LA, et al. Recurrent mutations refine prognosis in chronic lymphocytic leukemia. *Leukemia.* 2015; 29(2):329-336.
4. Ballinger ML, Mitchell G, Thomas DM. Surveillance recommendations for patients with germline TP53 mutations. *Curr Opin Oncol.* 2015; 27(4):332-337.
5. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. *Oncogene.* 2001; 20(34):4621-4628.

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6. Birch JM, Hartley AL, Tricker KJ, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. *Cancer Res.* 1994; 54(5):1298-1304.
7. Bloom M, Maciaszek JL, Clark ME, et al. Recent advances in genetic predisposition to pediatric acute lymphoblastic leukemia. *Expert Rev Hematol.* 2020; 13(1):55-70.
8. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni Syndrome from TP53 mutation carriers. *J Clin Oncol.* 2015; 33(21):2345-2352.
9. Bougeard G, Sesboue R, Baert-Desurmont S, et al. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. *J Med Genet.* 2008; 45(8):535-538.
10. Brooks GA, Stopfer JE, Erlichman J, et al. Childhood cancer in families with and without BRCA1 or BRCA2 mutations ascertained at a high-risk breast cancer clinic. *Cancer Biol Ther.* 2006; 5(9):1098-1102.
11. Chauffaille MLLF, Zalberg I, Barreto WG, Bendit I. Detection of somatic TP53 mutations and 17p deletions in patients with chronic lymphocytic leukemia: a review of the current methods. *Hematol Transfus Cell Ther.* 2020; 42(3):261-268.
12. Chompret A, Brugieres L, Ronsin M, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. *Br J Cancer.* 2000; 82(12):1932-1937.
13. Comeaux EQ, Mullighan CG. TP53 Mutations in hypodiploid acute lymphoblastic leukemia. *Cold Spring Harb Perspect Med.* 2017; 7(3).
14. Custodio G, Parise GA, Kiesel Filho N, et al. Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. *J Clin Oncol.* 2013; 31(20):2619-2626.
15. Dite GS, Jenkins MA, Southey MC, et al. Familial risks, early-onset breast cancer, and BRCA1 and BRCA2 germline mutations. *J Natl Cancer Inst.* 2003; 95(6):448-457.
16. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* 2000; 343(26):1910-1916.
17. Eeles RA. Germline mutations in the TP53 gene. *Cancer Surv.* 1995; 25:101-124.
18. Evans DG, Wu CL, Birch JM. BRCA2: a cause of Li-Fraumeni-like syndrome. *J Med Genet.* 2008; 45(1):62-63.
19. Gonzalez D, Martinez P, Wade R, et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. *J Clin Oncol.* 2011; 29(16):2223-2229.
20. Gonzalez KD, Buzin CH, Noltner KA, et al. High frequency of de novo mutations in Li-Fraumeni syndrome. *J Med Genet.* 2009; 46(10):689-693.
21. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: Clinical characteristics of families with p53 germline mutations. *J Clin Oncol.* 2009; 27(8):1250-1256.
22. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet.* 2010; 376(9747):1164-1174.
23. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. *J Natl Cancer Inst.* 1998; 90(8):606-611.
24. Hof J, Krentz S, van Schewick C, et al. Mutations and deletions of the TP53 gene predict nonresponse to treatment and poor outcome in first relapse of childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2011; 29(23):3185-3193.

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Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

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25. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet.* 2013; 45(3):242-252.
26. Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. *Am J Hum Genet.* 2003; 72(4):975-983.
27. Kast K, Rhiem K, Wappenschmidt B, et al.; German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC). Prevalence of BRCA1/2 germline mutations in 21 401 families with breast and ovarian cancer. *J Med Genet.* 2016; 53(7):465-471.
28. Kratz CP, Achatz MI, Brugières L, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. *Clin Cancer Res.* 2017; 23(11):e38-e45.
29. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res.* 1988; 48(18):5358-5362.
30. Lin PH, Kuo WH, Huang AC, et al. Multiple gene sequencing for risk assessment in patients with early-onset or familial breast cancer. *Oncotarget.* 2016; 7(7):8310-8320.
31. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer.* 2016; 122(23):3673-3681.
32. Masciari S, Van den Abbeele AD, Diller LR, et al. F18-fluorodeoxyglucose-positron emission tomography/computed tomography screening in Li-Fraumeni syndrome. *JAMA.* 2008; 299(11):1315-1319.
33. Mouchawar J, Korch C, Byers T, et al. Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast cancer: Australian Breast Cancer Family Study. *Cancer Res.* 2010; 70(12):4795-4800.
34. Prochazkova K, Foretova L, Sedlacek Z. A rare tumor and an ethical dilemma in a family with a germline TP53 mutation. *Cancer Genet Cytogenet.* 2008; 180(1):65-69.
35. Schneider K, Zelle K, Nichols KE, et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*<sup>®</sup> [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: [https://www.ncbi.nlm.nih.gov/books/NBK1311/pdf/Bookshelf\\_NBK1311.pdf](https://www.ncbi.nlm.nih.gov/books/NBK1311/pdf/Bookshelf_NBK1311.pdf). Accessed on September 6, 2022.
36. Sorrell AD, Espenschied CR, Culver JO, Weitzel JN. Tumor protein p53 (TP53) testing and Li-Fraumeni syndrome: current status of clinical applications and future directions. *Mol Diagn Ther.* 2013; 17(1):31-47.
37. Stengel A, Schnittger S, Weissmann S, et al. TP53 mutations occur in 15.7% of ALL and are associated with MYC-rearrangement, low hypodiploidy, and a poor prognosis. *Blood.* 2014; 124(2):251-258.
38. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood.* 2014; 123(21):3247-3254.
39. Swaminathan M, Bannon SA, Routbort M, et al. Hematologic malignancies and Li-Fraumeni syndrome. *Cold Spring Harb Mol Case Stud.* 2019; 5(1):a003210.
40. Tinat J, Bougeard G, Baert-Desurmont S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. *J Clin Oncol.* 2009; 27(26):e108-109.
41. Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol.* 2011; 12(6):559-567.
42. Yamamoto Y, Kanai M, Kou T, et al. Clinical significance of TP53 variants as possible secondary findings in tumor-only next-generation sequencing. *J Hum Genet.* 2020; 65(2):125-132.
43. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. *J Clin Oncol.* 2010; 28(29):4473-4479.

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

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**Government Agency, Medical Society, and Other Authoritative Publications:**

1. American Board of Genetic Counselors. Practice-Based Competencies for Genetic Counselors. Available at: [https://www.gceducation.org/wp-content/uploads/2019/06/ACGC-Core-Competencies-Brochure\\_15\\_Web\\_REV-6-2019.pdf](https://www.gceducation.org/wp-content/uploads/2019/06/ACGC-Core-Competencies-Brochure_15_Web_REV-6-2019.pdf). Accessed on September 6, 2022.
2. American College of Obstetricians and Gynecologists (ACOG). Hereditary cancer syndromes and risk assessment. Committee Opinion No. 793. December 2019. Available at: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/12/hereditary-cancer-syndromes-and-risk-assessment>. Accessed on September 6, 2022.
3. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015; 26 Suppl 5:v78-84.
4. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008; 111(12):5446-556.
5. Hampel H, Bennett RL, Buchanan A, et al; Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015; 17(1):70-87. Available at: <https://www.acmg.net/PDFLibrary/Cancer-Predisposition-Assessment-Referral-Indications.pdf>. Accessed on September 6, 2022.
6. Lancaster JM, Powell CB, Chen LM, Richardson DL; SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer women with germline mutations in the cancer susceptibility genes, BRCA1 or BRCA2, associated with hereditary predispositions. *Gynecol Oncol*. 2015; 136(1):3-7.
7. National Library of Medicine (NLM). Genetics Home Reference: Li-Fraumeni syndrome. Reviewed June 1, 2020. Available at: <http://ghr.nlm.nih.gov/condition/li-fraumeni-syndrome>. Accessed on September 6, 2022.
8. National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns*. 2006; 5(2):77-83.
9. NCCN Clinical Practice Guidelines in Oncology™. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on September 6, 2022:
  - Acute Lymphoblastic Leukemia. V1.2022. Revised April 4, 2022.
  - Acute Myeloid Leukemia. V2.2022. Revised June 14, 2022.
  - Breast Cancer Risk Reduction. V1.2022. Revised January 31, 2022.
  - Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma. V1.2023. Revised August 30, 2022.
  - Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V2.2022. Revised March 9, 2022.
  - Genetic/Familial High-Risk Assessment: Colorectal. V1.2022. Revised June 8, 2022.
  - Myelodysplastic Syndromes. V3.2022. Revised January 13, 2022.

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10. SEER Cancer Statistics Factsheets: Chronic Lymphocytic Leukemia. National Cancer Institute. Bethesda, MD. Available at: <http://seer.cancer.gov/statfacts/html/clyl.html>. Accessed on September 6, 2022.

**Websites for Additional Information**

1. American Cancer Society. What is chronic lymphocytic leukemia? Last revised: May 10, 2018. Available at: <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-what-is-cll>. Accessed on September 6, 2022.
2. Li-Fraumeni Syndrome (LFS) Association. Criteria for LFS - Li-Fraumeni Syndrome Association. Available at: <https://www.lfsassociation.org/what-is-lfs/lfs-criteria/>.
3. National Cancer Institute. Cancer Statistics. Available at: <https://seer.cancer.gov/statfacts/>. Accessed on September 6, 2022.
4. National Cancer Institute. Chronic Lymphocytic Leukemia Treatment. Updated August 26, 2022. Available at: <https://www.cancer.gov/types/leukemia/patient/cll-treatment-pdq>. Accessed on September 6, 2022.
5. U.S. National Library of Medicine. Medline Plus. TP53 Gene. Last reviewed: February 1, 2020. Available at: <https://medlineplus.gov/genetics/gene/tp53/#conditions>. Accessed on September 6, 2022.

**Index**

Li-Fraumeni  
 Low-hypodiploid Acute Lymphocytic (Lymphoblastic) Leukemia  
 TP53 (tp53)

**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

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Testing for TP53 Mutations not related to gene panels to new clinical utilization management guideline document with the same title.

Historical

Federal and State law, as well as contract language including definitions and specific coverage provisions/exclusions, and Medical Policy take precedence over Clinical UM Guidelines and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Clinical UM Guidelines, which address medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Clinical UM Guidelines periodically. Clinical UM guidelines are used when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether or not to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the back of the member's card.

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