

**GENETIC DIAGNOSTIC LABORATORY**  
**UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE**  
**DEPARTMENT OF GENETICS**  
Tel: (215) 573-9161 • Fax: (215) 573-5940  
CLIA ID: 39D0893887

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**Li-Fraumeni Syndrome (TP53)**

**Background:** This is an autosomal dominant cancer predisposition syndrome that predisposes an affected individual to multiple forms of cancer (breast cancer, soft tissue sarcoma, leukemia, melanoma, osteosarcoma, colon cancer, pancreatic cancer, esophageal cancer, brain tumors, and other malignancies). The syndrome is due to germline mutations in the *TP53* gene.

A *TP53* germline mutation is suspected to be present in an individual for the following family history:

- a proband with a sarcoma under 45 years of age, and
- a first degree relative with any cancer under 45 years of age, and
- a third family member who is a first- or second-degree relative with cancer under 45 years or a sarcoma at any age.

More than 50% of individuals meeting the above criteria will have an identifiable mutation in the *TP53* gene.

**Assay:** Direct mutation analysis by full sequencing of exons 3-9 where 95% of mutations have been recorded to date. Sequencing is available for exons 2, 10 and 11, if requested.

**Eligibility:** Patients who have one of the index cancers and whose family history meets the Li-Fraumeni criteria are eligible for screening. At-risk individuals from families where a mutation has already been identified are eligible for site-specific mutation testing.

**Utility:** Diagnostic confirmation, carrier detection, and prenatal diagnosis

**Sensitivity:** If the patient's mutation is in the coding sequencing of the *TP53* gene, the testing will detect the mutation ~98% of the time. Mutations in non-coding sequences, insertions, deletions or other rearrangements will not be detected by full sequencing.

**Turn around:** 5-6 weeks for full sequencing; 2-3 weeks for a known familial mutation, and 1-3 weeks for prenatal diagnosis.

**Fees:** \$560-full sequencing analysis of exons 3-9  
\$320-full sequence analysis exons 2,10 and 11  
\$340-known familial mutation  
\$340-prenatal diagnosis for a known familial mutation

**CPT Codes:** Full sequencing of exons 3-9: 83891, 83894x5, 83898x8, 83904x8, 83909x2, 83912  
Full sequencing of exons 2,10 & 11: 83894x2, 83898x5, 83904x5, 83909x2, 83912  
Known familial mutation-83891, 83898x6, 83904x6, 83912  
Prenatal diagnosis- 83891x2, 83898x4, 80904x5, 83912

## LI-FRAUMENI (TP53) Testing INSTRUCTIONS FOR SAMPLE SUBMISSION

**Documentation:** Each sample must be accompanied by:

1. A requisition for DNA analysis completed by the physician, nurse or genetic counselor requesting screening. **Please note: ICD-9 code is required for billing purposes. If ICD-9 code is unknown, please provide patient's clinical symptom(s) or family history that prompted testing.**
2. The patient's pedigree to include three generations, if possible.
3. An informed consent signed by the patient (if under 18 years of age, the parent or guardian should sign) and the professional obtaining the consent. Please have the patient initial at the top of each page and send **all** pages of the consent.
4. A verification of blood tubes form signed by the patient, parent or guardian. The form should be signed at the time of the blood draw.
5. A completed registration form with check, money order, credit card authorization or information for billing the referring institution.

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**IN THE EVENT THAT ALL PROPERLY COMPLETED FORMS DO NOT ACCOMPANY THE SPECIMEN, YOU WILL BE NOTIFIED, AND TESTING WILL BE HELD UNTIL PAPERWORK IS COMPLETE.**

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### Preparing Sample:

- Obtain 2 EDTA tubes (lavender top) of blood - approx. 4 mL per tube
- Label each tube with the patient's name and date sample was obtained
- We accept banked or recently extracted DNA; please include the concentration.
  
- For prenatal testing: cultured amniotic fluid or CVS cells, 2 confluent T-25 flasks. Please call the lab prior to sending a prenatal sample. We are often able to offer testing on a direct villi or amnio sample, and we can discuss the requirements with you. 5mL of whole blood from each parent should accompany the prenatal sample.

**Shipping Sample:** Ship at room temperature via Federal Express or other overnight courier that guarantees AM delivery to arrive Monday-Friday. There is no one in the laboratory evenings and weekends to receive samples. If sample is drawn on a Friday, please refrigerate it until shipment on the following business day.

**Shipping Address:** Genetic Diagnostic Laboratory  
University of Pennsylvania  
415 Anatomy-Chemistry Building  
3620 Hamilton Walk  
Philadelphia, PA 19104

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**REQUEST FOR LI-FRAUMENI (TP53) TESTING**

PATIENT FIRST NAME \_\_\_\_\_ PATIENT LAST NAME \_\_\_\_\_  
BIRTH DATE \_\_\_\_\_ SEX \_\_\_\_\_ RACE \_\_\_\_\_ ETHNICITY \_\_\_\_\_  
STREET ADDRESS \_\_\_\_\_  
CITY \_\_\_\_\_ STATE \_\_\_\_\_ ZIP \_\_\_\_\_ HOME PHONE \_\_\_\_\_

Please describe the patient's cancer history and/or family cancer history; include a three generation pedigree

\_\_\_\_\_

\_\_\_\_ Patient is at-risk for Li-Fraumeni but is currently asymptomatic

Has anyone in the family had DNA testing for Li-Fraumeni? \_\_\_\_ No \_\_\_\_ Yes

If yes, who and where was testing done? \_\_\_\_\_

What was the result? \_\_\_\_\_

REFERRING PHYSICIAN \_\_\_\_\_ PHONE \_\_\_\_\_ FAX \_\_\_\_\_

GENETIC COUNSELOR \_\_\_\_\_ PHONE \_\_\_\_\_ FAX \_\_\_\_\_

EMAIL ADDRESS FOR COUNSELOR OR PHYSICIAN \_\_\_\_\_  
INSTITUTION and  
DEPARTMENT \_\_\_\_\_

STREET ADDRESS \_\_\_\_\_

CITY \_\_\_\_\_ STATE \_\_\_\_\_ ZIP \_\_\_\_\_ COUNTRY \_\_\_\_\_

**ICD-9 CODE (or patient's clinical symptoms)** \_\_\_\_\_

**TEST REQUESTED**

- \_\_\_\_ Full Sequencing of exons 3-9 of the *TP53* gene
- \_\_\_\_ Full Sequencing of exons 2, 10, and 11 of the *TP53* gene
- \_\_\_\_ Screening for known familial sequencing mutation
- \_\_\_\_ Prenatal diagnosis of known familial sequencing mutation

Please include a copy of genetic result for affected family member for any familial or prenatal test requests  
For all prenatal requests, please call the laboratory to discuss requirements; 5mL of whole blood from both parents should accompany any prenatal sample for MCC studies.



***Verification of Correctly Identified Blood Tubes***

I am a participant in genetic DNA testing.

I have been shown the tubes containing my blood for this genetic testing and my name has been correctly placed on each one of these tubes.

I have signed a copy of the consent form regarding this genetic testing to be sent along with my blood samples. I have been given a copy of the consent form to keep.

Participant Name: \_\_\_\_\_

Participant/Parent Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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### **Informed Consent: Genetic Testing for Li-Fraumeni Syndrome**

**BACKGROUND:**

Li-Fraumeni Syndrome is a cancer predisposition syndrome associated with soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex and brain. Individuals with Li-Fraumeni syndrome are at increased risk to develop multiple primary cancers. About 70% of patients diagnosed clinically have an alteration in the *TP53* gene.

**PURPOSE:**

I or my child, will be tested for alterations in the *TP53* gene. I understand that the testing will take approximately 5-6 weeks to complete. The purpose of this genetic testing is to determine whether I have an altered *TP53* gene that is involved in the development of multiple cancers that run in families. Individuals who inherit an altered *TP53* gene are at greatly increased risk of developing multiple cancers when compared to individuals who do not have an altered gene. Both men and women with an alteration in the *TP53* gene are at a highly increased risk of developing one or more of the cancers mentioned above in the "background". An individual who is found to have a *TP53* gene alteration has a 50% chance to pass the mutation on to each of their children. No information pertaining to my genetic test results will be provided to any of my relatives without my consent.

**TESTING PROCEDURE:**

Genetic testing requires several teaspoons (2 tubes) of blood. Before my blood is drawn, I will watch as my name is written correctly on empty blood tubes, and after my blood is drawn I will sign a form indicating that I have positively identified the tubes containing my blood. The blood sent to the laboratory will be divided into two separate samples. The first sample will be used to complete the genetic testing. The second sample will be tested to confirm the diagnosis if the first sample indicates an alteration. There will be no additional charge for the confirmation testing.

When the testing has been completed, I understand that I will be contacted by the center where I am being counseled and offered an appointment to receive the results of the test in person. No information will be provided to me by phone or mail from the University of Pennsylvania, regardless of the outcome.

I understand that there are laboratory fees for the genetic testing, and I have discussed the payment options with my physician. I understand the arrangements that have been made for payment, and I am responsible for payment regardless of the outcome of the genetic analysis.

**RISKS AND DISCOMFORTS:**

I understand that there is usually a minimal amount of risk involved in drawing a blood sample. These include pain at the blood drawing site, bleeding, bruising and infection.

The risks of disclosure of information regarding my genetic susceptibility to Li-Fraumeni syndrome include depression, anxiety, anger, and fear of the future. This result could affect my relationships with family members and loved ones. I understand that if I learn that I, or my child, have an altered *TP53* gene, my ability to obtain disability or life insurance could be affected. Certain health, disability and life insurance companies may consider an inherited *TP53* alteration to be a "pre-existing condition," and I may be responsible for disclosing this prior to obtaining new health or life insurance.

Initials \_\_\_\_\_

PROBAND SEQUENCING

I may learn that the results are inconclusive at the present time and that the laboratory was unable to determine whether I, or my child, have a clinically significant alteration. Therefore, I may have gone through the testing process and not have any genetic information that could determine my, or my child's, personal risk to develop cancer in the future.

**ALTERNATIVE TO GENETIC TESTING:**

I understand that my participation in this testing is completely voluntary and will not affect my medical treatment now or in the future. The alternative is not to undergo testing, in which case I will not learn whether I have an altered form of the *TP53* gene. This decision is perfectly acceptable.

**RESULTS:**

When results of the laboratory testing are available, I will be given the option of postponing or declining disclosure of these results. If I choose to learn the results, I will be given this information as part of a counseling session.

I understand that there are three possible results to this testing:

I may learn that I have a clinically significant alteration in the *TP53* gene. I understand that this means that I have an 80-85% lifetime chance of developing one or more cancers.

I may learn that the testing did not detect an alteration in the *TP53* gene. I know that the methods currently in use are unable to detect all mutations and I may still have a mutation that was not detected by the assays available at the Genetic Diagnostic Laboratory.

The laboratory may detect an alteration in my *TP53* gene of currently unknown significance, called a "variant of unknown significance (VUS)". Our laboratory will work with your physician to help determine if the VUS can be further classified as to whether it is disease-causing for Li-Fraumeni syndrome.

**BENEFITS OF RECEIVING INFORMATION:**

This study may provide information about whether my relatives, including my children, are at 50% risk of inheriting an alteration of the *TP53* gene mutation and are at high risk for developing multiple cancers. If I am found to have a clinically significant alteration, I may choose to advise my relatives of this finding. They can have counseling and decide whether or not they wish to be tested to see if they inherited the same alteration.

This study may also provide me with the information currently available regarding my genetic predisposition and may enable me to make better choices about planning my career, my family and children, and my health care needs. If I do have an altered gene, I will be able to initiate a surveillance plan for the early detection of cancers. This plan could include an annual complete physical including skin, nervous system, and rectal examination (and Pap smear for women), twice yearly clinical breast examination (for women) and annual mammogram (for women). It is the opinion of acknowledged experts in the field that enhanced surveillance may be of benefit in early detection and treatment.

**LIMITATIONS OF DNA TESTING FOR *TP53*:**

In addition, I understand that there are limitations as to what these test results can tell me. This testing is intended to provide me with an accurate estimate about my lifetime chance of developing one or more cancers. I understand that this test will not provide me with any new information about the current status of my health. This DNA testing is highly accurate for detection of the majority of disease causing mutations; however, a small fraction of mutations may be missed by the current technology. Occasionally, there may be a result that can not be interpreted.

Initials \_\_\_\_\_

*PROBAND SEQUENCING*

**USE OF SPECIMENS:**

I understand that any blood or tissue specimens obtained for the purposes of this genetic testing become the exclusive property of the Genetic Diagnostic Laboratory. After the specific tests requested have been completed and reported, the Laboratory may dispose of, retain, or preserve these specimens and may use these specimens for research. I understand that my identity will be protected and that research results will not be provided to me or to any other party. If there are new developments in the field, my physician/genetic counselor may be contacted by the Genetic Diagnostic Laboratory staff to offer me the opportunity to have additional clinical testing.

**REQUEST FOR MORE INFORMATION:**

I have been assured that my results will not be released to any relative or any other third party without my express written consent. I understand that I may ask more questions about this testing and my results at any time. At the Genetic Diagnostic Laboratory, Susan Walther, MS, CGC (215-573-9161) and Arupa Ganguly, PhD, FACMG (215-898-3122) will be available to answer questions as they arise. I will be given a copy of this consent form to keep.

I have explained to \_\_\_\_\_ the purpose of this genetic testing, the procedures required and the possible risks and benefits to the best of my ability.

\_\_\_\_\_  
Printed Name of Professional Obtaining Consent

\_\_\_\_\_  
Signature of Professional Obtaining Consent

\_\_\_\_\_  
Date

**CONSENT OF PATIENT:**

I have read and received a copy of this consent form. I agree to have genetic testing and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

\_\_\_\_\_  
Printed Name of Patient

\_\_\_\_\_  
Patient's DOB

\_\_\_\_\_  
Signature of Patient

\_\_\_\_\_  
Date

**CONSENT OF PARENT OR GUARDIAN:**

I have read and received a copy of this consent form. I agree to have genetic testing performed for my child and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

\_\_\_\_\_  
Printed Name of Parent/Guardian

\_\_\_\_\_  
Relationship to Child

\_\_\_\_\_  
Signature of Parent/Guardian

\_\_\_\_\_  
Child's Name

\_\_\_\_\_  
Child's DOB

Initials \_\_\_\_\_

FAMILIAL MUTATION

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**Informed Consent: Genetic Testing for Li-Fraumeni Syndrome of a Known Familial Mutation**

**BACKGROUND:**

Li-Fraumeni Syndrome is a cancer predisposition syndrome associated with soft-tissue sarcoma, breast cancer, leukemia, osteosarcoma, melanoma, and cancer of the colon, pancreas, adrenal cortex and brain. Individuals with Li-Fraumeni syndrome are at increased risk to develop multiple primary cancers. About 70% of patients diagnosed clinically have an alteration in the *TP53* gene.

**PURPOSE:**

I, or my child or fetus, will be tested for the alteration in the *TP53* gene which has been identified in one of my family members. I understand that the testing will take approximately 2-3 weeks to complete. The purpose of this genetic testing is to determine whether I, or my child, have an altered *TP53* gene that is involved in the development of multiple cancers that run in families. Individuals who inherit an altered *TP53* gene are at greatly increased risk of cancers when compared to individuals who do not have an altered gene. Both men and women with an alteration in a *TP53* gene are at a highly increased risk of developing one or more of the cancers mentioned in the "background". An individual who inherits an alteration in the *TP53* gene has a 50% chance to pass the mutation on to each of their children.

I have had the opportunity to discuss the benefits and drawbacks of *TP53* testing for myself or for my child. No information pertaining to my genetic test results will be provided to any of my relatives without my consent.

**TESTING PROCEDURE:** Genetic testing requires several teaspoons (2 tubes) of blood. Before my blood is drawn, I will watch as my name is written correctly on empty blood tubes and after my blood is drawn I will sign a form indicating that I have positively identified the tubes containing my blood. The blood sent to the laboratory will be divided into two separate samples. The first sample will be used to complete the genetic testing. The second sample will be tested to confirm the diagnosis if the first sample indicates an alteration. There will be no additional charge for the confirmation testing.

When the testing has been completed, I understand that I will be contacted by the center where I am being counseled and offered an appointment to receive the results of the test in person. No information will be provided to me by phone or mail from the University of Pennsylvania, regardless of the outcome.

If this is a prenatal sample, cells from either a CVS or amniocentesis will be used to isolate fetal DNA for analysis of the DNA mutation found in my family that causes Li-Fraumeni syndrome. In order to confirm that analysis was performed on fetal cells, studies to rule out any maternal cell contamination will also be performed.

I understand that there are laboratory fees for the genetic testing, and I have discussed the payment options with my physician. I understand the arrangements that have been made for payment, and I am responsible for payment regardless of the outcome of the genetic analysis.

**RISKS AND DISCOMFORTS:**

I understand that there is usually a minimal amount of risk involved in drawing a blood sample. These include pain at the blood drawing site, bleeding, bruising, and infection.

Initials \_\_\_\_\_

*FAMILIAL MUTATION*

The risks of disclosure of information regarding my genetic susceptibility to these cancers include depression, anxiety, anger, and fear of the future. This result could affect my relationships with family members and loved ones. I understand that if I learn that I have an altered *TP53* gene, my ability to obtain health, disability or life insurance could be affected. Certain health, disability and life insurance companies may consider a *TP53* alteration to be a “pre-existing condition,” and I may be responsible for disclosing this information prior to obtaining new health or life insurance.

If this is a prenatal sample, I have been counseled on the risks of the prenatal procedure, and I understand that the genetic analysis of the *TP53* DNA mutation found in my family will determine whether my fetus has inherited the altered gene and for the future risk to develop cancers associated with Li-Fraumeni syndrome.

Some individuals may experience feelings of guilt or other forms of anxiety if they are found not to have an altered gene, while other family members did inherit an altered gene.

**ALTERNATIVE TO GENETIC TESTING:**

I understand that my participation in this testing is completely voluntary and will not affect my medical treatment now or in the future. The alternative is not to undergo testing, in which case I will not learn whether I have an altered form of the *TP53* gene. This decision is perfectly acceptable.

**RESULTS:**

When results of the laboratory testing are available, I will be given the option of postponing or declining disclosure of these results. If I choose to learn the results, I will be given this information as part of a counseling session.

I understand that there are two possible results to this testing:

1. I may learn that I, my child or my fetus, have a clinically significant altered *TP53* gene. I understand that this result means that I have an 80-85% lifetime chance of developing one or more cancers.
2. I may learn that the testing did not detect the altered *TP53* gene that has been found in my family members.

**BENEFITS OF RECEIVING INFORMATION:**

This study may provide information about whether my relatives, including my children, are at 50% risk of inheriting an alteration of the *TP53* gene mutation and are at high risk for developing multiple cancers. If I am found to have a clinically significant alteration, I may choose to advise my relatives of this finding. They can have counseling and decide whether or not they wish to be tested to see if they inherited the same alteration.

This study may also provide me with the information currently available regarding my genetic predisposition and may enable me to make better choices about planning my career, my family and children, and my health care needs. If I do have an altered gene, I will be able to initiate a surveillance plan for the early detection of cancers. This plan could include an annual complete physical including skin, nervous system, and rectal examination (and Pap smear for women), twice yearly clinical breast examination (for women) and annual mammogram (for women). It is the opinion of acknowledged experts in the field that enhanced surveillance may be of benefit in early detection and treatment.

If I do not inherit the alteration of the *TP53* gene, I may feel relieved that I am not at increase risk of developing multiple cancers and that my children are not at risk of inheriting the *TP53* alteration from me.

**LIMITATIONS OF DNA TESTING FOR TP53:**

In addition, I understand that there are limitations as to what these test results can tell me. This testing is intended to provide me with an accurate estimate about my lifetime chance of developing one or more cancers. I understand that this test will not provide me with any new information about the current status of my health.

**USE OF SPECIMENS:**

I understand that any blood or tissue specimens obtained for the purposes of this genetic testing become the exclusive property of the Genetic Diagnostic Laboratory. After the specific tests requested have been completed and reported, the Laboratory may dispose of, retain, or preserve these specimens and may use these specimens for research. I understand that my identity will be protected and that research results will not be provided to me or to any other party. If there are new developments in the field, my physician/genetic counselor may be contacted by the Genetic Diagnostic Laboratory staff to offer me the opportunity to have additional clinical testing.

**REQUEST FOR MORE INFORMATION:** I have been assured that my results will not be released to any relative or to any other third party without my express written consent. I understand that I may ask more questions about this testing and my results at any time. At the Genetic Diagnostic Laboratory, Susan Walther, MS, CGC (215-573-9161) and Arupa Ganguly, PhD, FACMG (215-898-3122) will be available to answer questions as they arise. I will be given a copy of this consent form to keep.

I have explained to \_\_\_\_\_ the purpose of this genetic testing, the procedures required and the possible risks and benefits to the best of my ability.

\_\_\_\_\_  
Signature of Professional Obtaining Consent

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Date

**CONSENT OF PATIENT:**

I have read and received a copy of this consent form. I agree to have genetic testing and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

\_\_\_\_\_  
Printed Name of Patient

\_\_\_\_\_  
Patient's DOB

\_\_\_\_\_  
Signature of Patient

\_\_\_\_\_  
Date

**CONSENT OF PARENT OR GUARDIAN:**

I have read and received a copy of this consent form. I agree to have genetic testing performed for my child and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

\_\_\_\_\_  
Printed Name of Parent/Guardian

\_\_\_\_\_  
Relationship to Child

\_\_\_\_\_  
Signature of Parent/Guardian

\_\_\_\_\_  
Child's Name

\_\_\_\_\_  
Child's DOB