TP53 Testing for Li-Fraumeni Syndrome (LFS)

INDICATIONS FOR TP53 TESTING INCLUDE (NOT LIMITED TO) THE FOLLOWING:

- Women diagnosed with breast cancer < 35 years-of-age*
- Individuals meeting revised Chompret criteria:
  - Individual with tumor belonging to LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia and/or lung bronchoalveolar cancer) before 46 years-of-age and at least one first- or second-degree relative with LFS tumor (except breast cancer, if proband has breast cancer) before 56 years-of-age or with multiple tumors;
  - OR an individual with multiple tumors (except multiple breast tumors), two belonging to the LFS tumor spectrum, with first occurring before 46 years-of-age;
  - OR an individual with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history
- Individual from a family with a known TP53 mutation

*NCCN guidelines recommend TP53 testing for women diagnosed with breast cancer < 35 years of age with previously negative BRCA1/BRCA2 testing. It has recently been suggested that for early-onset breast cancer patients without a family history concurrent analysis of BRCA1/BRCA2 and TP53 may decrease health care costs and allow faster results, to help guide medical management.

BENEFITS OF TESTING

Knowing your patient has a TP53 mutation can have a significant impact on medical management including time-sensitive surgery decisions.

- Result turn-around time of less than two weeks for stat cases (test code 2866) can provide valuable information for surgical decisions (lumpectomy vs mastectomy vs prophylactic bilateral mastectomies, etc) NCCN guidelines recommend the option of a risk-reducing mastectomy be discussed with patients who have a TP53 mutation
- Tailor treatment- NCCN guidelines advise that therapeutic radiation therapy be used with caution for TP53 mutation carriers (due to increased radiation sensitivity)
- Modify cancer surveillance and age of onset for initial screening- NCCN guidelines recommend increased breast cancer screening for TP53 mutation carriers and starting at an earlier age (more frequent clinical breast exams and breast MRIs in addition to annual mammograms, etc)
- Offer other cancer-specific preventative measures (e.g. more frequent colonoscopy and novel screening approaches) to address risks of the various LFS associated cancers
- Identify other at-risk family members

Note: In addition to single gene analysis, TP53 testing is also available as part of Ambry’s hereditary cancer panels (BreastNext, OvaNext, ColoNext and CancerNext) that frequently benefit patients with a suspected syndromic to cancer predisposition, conflicting pathology, missing family-history, and/or ambiguous diagnostic criteria.

INSURANCE

Ambry is contracted with the majority of commercial insurances and Medicare. All out-of-network patients are treated as in-network to minimize out of pocket costs. Medicaid coverage varies by state and pre-verification is recommended.

PATIENT PROTECTION PLAN

If patient out-of-pocket financial responsibility is potentially greater than $100, Ambry will contact the patient for verbal approval prior to initiating the test. We remain committed to working with you and your patients to make the genetic testing process as simple and cost effective as possible.

DISEASE CHARACTERISTICS

Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome caused by mutations in the TP53 gene with a 7-20% de novo mutation rate.

LFS is estimated to occur in approximately 1/20,000 people and is commonly (but not exclusively) associated with the following types of cancer: sarcoma (osteosarcoma or soft tissue sarcoma), pre-menopausal breast cancer, brain tumors, adrenocortical carcinoma (ACC) and leukemia, in addition to other cancers.

While breast cancer is the most commonly observed tumor type in individuals with germline TP53 mutations, choroid plexus carcinoma and childhood adrenocortical carcinoma (ACC) are also highly indicative of a germline TP53 mutation, regardless of family history. Individuals with TP53 mutations have a 50% risk of TP53 any of the associated cancers by age 30 and have up to 93% lifetime cancer risk.

Early-onset and multiple primary cancers are also observed in TP53 mutation carriers, with average age of diagnosis of 21.9 years (earlier in females than males). Studies show 5-8% of women with early-onset breast cancer and a negative family history have a TP53 mutation. The likelihood of a TP53 mutation is elevated in women with early-onset breast cancer who present with a family of LFS-associated cancers.
**SUPPLEMENTARY CASE EXAMPLES**

Early-onset breast cancer, diagnosed in mid 30’s

- Individual is heterozygous for the p.C141Y mutation in the TP53 gene
- This result is consistent with a diagnosis of Li-Fraumeni syndrome
- Cancer Risk Estimate: lifetime cancer-risk of up to 93%. Primary associated tumor types include sarcomas, pre-menopausal breast cancer, brain tumors (including astrocytomas, glioblastomas, medulloblastomas, and choroids plexus carcinomas), and adrenocortical carcinoma (ACC)
- Individuals with TP53 mutations are estimated to have a 21-49% risk of developing cancer by age 30 and a lifetime cancer risk of up to 68-93% (Hwang et al., 2003)

**Atypical LFS phenotypes**

- Impact on medical management
  - NCCN Guidelines – LFS Syndrome:
    - Discuss option of risk-reducing mastectomy (RRM)
    - Therapeutic RT should be used with caution
    - Clinical breast exam (CBE) every 6-12 months and annual mammogram and breast MRI (if patient does not elect RRM)
    - Annual comprehensive physical exam with high index of suspicion for rare cancers ad second malignancies in cancer survivors: include careful skin and neurologic examinations
    - Consider colonoscopy every 2-5 years

**IMPACT ON MEDICAL MANAGEMENT**

Walsh et al., 2011 studied 360 ovarian cancer patients unselected for family history or age of onset. Greater than 30% of the sample had no family history of breast or ovarian cancer and greater than 35% of individuals were diagnosed after the age of 60. Three TP53 mutations were identified in probands not meeting established diagnostic criteria for LFS.

“Mutations not associated with “typical phenotypes” are of particular interest. For example, the three TP53 mutations occurred in patients without a family history of Li–Fraumeni syndrome. As comprehensive genetic testing is undertaken for individuals not selected for established syndromic phenotypes, a wider range of expressivity associated with germ-line mutations of cancer susceptibility genes will become increasingly apparent” (Walsh et al. PNAS 2011).

**REFERENCES**

15. wikigenes collaborative publishing: http://www.wikigenes.org/e/gene/e/7157.html