Evaluation of current clinical criteria in a diverse sample of TP53 mutation carriers

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Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome characterized by an excess of early-onset cancers, a high lifetime risk of cancer, and a wide range of tumor types. Although the optimal clinical management of LFS patients remains uncertain due to the wide range of associated cancer susceptibilities and marked inter- and intra-familial variation in disease penetrance, recent studies suggesting a benefit in comprehensive screening protocols for both children and adults make the timely identification of individuals with LFS increasingly important (Masciari et al., 2008; Villani et al., 2011; McBride et al., 2014).

Several criteria have been proposed to identify patients appropriate for germline genetic testing of TP53, the only gene known to cause LFS. The National Comprehensive Cancer Network (NCCN) has synthesized several of these criteria into its “Clinical Practice Guidelines for Genetic/Familial High-Risk Assessment” for LFS. Prior studies on the sensitivity of criteria included in their guidelines have shown that their cumulative sensitivity approaches 100% in populations referred for genetic testing subsequent to clinical suspicion when examining personal and family histories at the time of test requisition (Gonzales et al., 2009). However, especially in the context of rare diseases, populations referred solely on the basis of clinical suspicion may represent the most severe presentations and therefore the families most likely to meet testing criteria. Additionally, given that one of the primary goals in the identification of hereditary cancer syndromes is prevention and/or early detection of associated malignancies, and given that LFS patients often develop multiple primary cancers in their lifetimes, an assessment of clinical testing criteria not only at the time that genetic testing is actually ordered, but also at the time of a patient’s first cancer diagnosis, provides an additional important measure of utility. Lastly, although the NCCN now recommends TP53 genetic testing be offered to any individual with a diagnosis of adrenocortical carcinoma, choroid plexus tumor, or breast cancer before 35 years of age, individuals diagnosed with any other cancer included in the accepted ‘LFS spectrum’ (sarcoma, brain tumor, leukemia, or lung bronchoalveolar cancer), are not likely to be identified by current genetic testing guidelines in the absence of remarkable personal and/or family cancer history.

The TP53 Research Database at M.D. Anderson Cancer Center includes families ascertained on both a clinical basis and as part of systematic research protocols. By analyzing the cancer histories of positive and negative families within this database, we provide estimates of the sensitivity and specificity of the criteria schemes included in the NCCN guidelines both individually and as a whole. We conclude that a significant portion of TP53 mutation carriers may be missed by current testing criteria at the time of a proband’s initial cancer diagnosis and when risk assessment is made based primarily on the cancer family history. ‘De novo’ mutations and inherited mutations in families with tumor histories atypical of the accepted ‘LFS spectrum’ may be particularly likely to be missed due to variable penetrance. It may be prudent to consider TP53 genetic testing in any proband diagnosed with an LFS spectrum cancer, particularly at an early age, regardless of individual or family cancer histories.

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