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CORRESPONDENCE

Cancer surveillance for individuals with Li-Fraumeni syndrome

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To the Editor:

With great interest, we read the guidelines authored by the European Reference Network on Genetic Tumor Risk Syndromes for individuals with Li–Fraumeni syndrome (LFS) [1]. We acknowledge that "these guidelines do not … intend to be a legal standard of care …" [1]. However, official guidelines carry significant weight and are often followed strictly by clinicians and insurance providers. Here, we—physicians and researchers working for and with individuals with LFS—respectfully articulate concerns that challenge selected statements.

The authors coin the term "heritable *TP53*-related cancer syndrome". LFS was originally defined clinically [2]. Following gene discovery and amplified through an increasing use of multigene panel testing, the LFS-phenotype has dynamically expanded and carriers of pathogenic *TP53* variants frequently do not meet the original clinical definition [3]. There are numerous examples in the field of medical genetics where syndromes kept the original name despite the fact that they were first described clinically and, after gene discovery, the phenotypic spectrum evolved. The advantage of introducing a new genetic definition of the syndrome is not apparent; furthermore, adoption of new terminology should require discussion within the international LFS patient and research community.

The recommendation that patients with "jaw osteosarcoma" should be offered testing [1] is not supported by published data.

It is stated that "testing for disease-causing *TP53* variants should be performed before starting treatment in order to avoid …, if possible, radiotherapy and genotoxic chemotherapy and to prioritize surgical treatments" [1]. Until reliable, reproducible and validated data are available on (1) outcomes of patients with LFS and cancer being treated on standard protocols, compared to sporadic counterparts; (2) the specific excess risk for second malignant neoplasms contributed by various chemo/radiation therapies; and (3) efficacy for alternative treatment regimens for LFS patients with various cancers, it would be premature and inappropriate to withhold curative genotoxic chemotherapy and radiation options from patients with LFS and cancer. One may consider surgical local control options over radiation therapy in cases where there is clinical equipoise. These are important ongoing and future research priorities.

The guideline categorizes variants as *high* vs *low cancer risk*, based on whether a specific variant has been associated with childhood cancer or whether it represents a dominant negative (DN) variant [1]. Although we believe that risk prediction for LFS individuals is an urgent scientific task, altering surveillance practices based on the type of *TP53* variant may be premature given the current lack of accurate risk prediction tools. There are several arguments against the proposed strategy: (1) >1% of children with cancer harbor a germline variant of *TP53* [4], however, only a minority of children are currently tested at diagnosis and there is no ubiquitous registration of *TP53* variants and corresponding cancer phenotypes; thus, the data needed to determine whether a specific variant occurred in a child with cancer is incomplete; (2) individual family history (e.g., a LFS pedigree without childhood cancer) does not reliably predict a *TP53* variant as not being associated with childhood cancer risk; (3) classifying DN variants as being high risk may be too simple as there are multiple examples of non-DN *TP53* variants being associated with a high cancer risk and/or

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childhood cancer; [5, 6] (4) genetic modifiers are not incorporated in the proposed risk algorithm [7].

The guideline recommends that "in children, clinical examination should be performed every 6 months, with specific attention to signs of virilization or early puberty, …" and that "In children … abdominal ultrasound for the detection of adrenocortical carcinoma should be conducted at least every 6 months" and "when abdominal ultrasound does not allow a proper imaging of the adrenal glands, measurement of urine steroids …" [1]. In our view, *any* unexplained symptom should be worked up. Given the rapid growth of childhood tumors, an interval of 6 months for exam or ultrasound appears to be too long and is not justified by data. There are no data showing that longer intervals are less stressful for families. In addition to 24 h urine cortisol analyses, we recommend blood analyses to include 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione [8–10].

The guideline states that "WBMRI without gadolinium enhancement should be conducted annually" [1]. The decision on whether Gadolinium is used is generally made by the radiologist and may depend on factors such as findings on previous images [11].

The guidelines recommend that "in female individuals, breast MRI should be conducted annually, from 20 years until 65 years" and "in adults until 50 years, brain MRI should be conducted annually" [1]. There are no data to support stopping breast and brain MRI after these age limits.

The guidelines state that "colonoscopy should be performed, from 18 years, every 5 years, only if the carrier received abdominal radiotherapy for the treatment of a previous cancer, or if there is a familial history of colorectal tumors suggestive of an increased genetic risk". The published data supporting surveillance even in absence of CRC in the family [12] are discounted as being "problematic" [1] but the authors provide no rationale for that assessment. Notably, colonoscopy is one of the rare proven measures that can prevent cancer.

In summary, the new guideline is designed in a way that may be applicable in certain health care systems across various European countries. Selected changes to the current guidelines [8, 9] are not supported by data or apply knowledge that is not yet complete. We recommend to consider modifications to the guideline following broader discussion, based on ongoing clinical and epidemiologic studies, as well as biological research, involving patient organizations, such as the Li–Fraumeni Syndrome Association, as well as multiple disciplines.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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