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Reply: Pleuropulmonary blastoma-like peritoneal sarcoma and *DICER1*-associated sarcomas: Towards a unified nomenclature

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We appreciate the thoughtful commentary by Drs. McCluggage and Foulkes in response to our manuscript "Pleuropulmonary blastoma-like peritoneal sarcoma" focusing on a new manifestation of *DICER1* pathogenic variation.

DICER1-related cancers are hardly the first set of molecularly linked cancers seen within the context of tumor predisposition. The spectrum of cancers seen in the context of Li-Fraumeni syndrome, familial retinoblastoma and familial adenomatous polyposis are just three of countless of other examples.[1] A previously undefined neoplasm of the lung in children less than 10 years old with a unique age-associated progression from a circumscribed multilocular cyst, initially thought to be a type of congenital pulmonary airway malformation, to a high grade, multi-patterned sarcoma, became the entity known today as pleuropulmonary blastoma (PPB).[2,3] The cystic variant of PPB had been reported in the literature prior to the report of the highly malignant solid PPB as embryonal rhabdomyosarcoma (eRMS) arising in congenital lung cysts.[4,5] From this evolution of a "cystic eRMS," the collage of undifferentiated blastema accompanied by neoplastic cartilage, spindle cell sarcoma, RMS and anaplastic cells emerged as the morphologic template of PPB.

As McCluggage and Foulkes point out in their correspondence and as recognized through a series of studies through the International Pleuropulmonary Blastoma/*DICER1* Registry and others beginning in the 1990s, there is more to the story than simply PPB.[6] However, the clinical phenotype of *DICER1* pathogenic variation is not simply confined to a group of sarcomas arising in a number of extrapulmonary sites, but also non-sarcomas such pituitary blastoma, pineoblastoma, ciliary body medulloepithelioma (CBME), chondromesenchymal hamartoma, multinodular goiter harboring papillary thyroid carcinoma, pediatric poorly differentiated thyroid carcinoma, multicystic hepatic lesions and cystic nephroma (CN). It

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is within the setting of CBME, CN and moderately/poorly differentiated Sertoli-Leydig cell tumor that the sarcomatous motif of the archetypical PPB first manifested itself.

In the ideal world, one could hope for a consensus in terminology for these *DICER1*-related neoplasms. Indeed, our group is very interested in issues of nomenclature within *DICER1* with considerations including impact on clinical care and research, equity, accessibility and importantly, patient perspective. Consideration of impact on clinical care must include issues of availability and timing of molecular testing. Consideration of patient perspectives ensures that terms such as “mutant” are not part of the new diagnosis experience of children, adolescents, adults and their family members.

Regardless of the name, however, in most cases these tumors will be recognized by their histologic features ranging from a primitive small cell neoplasm or high grade sarcoma of the CNS in a child to a Sertoli-Leydig cell tumor (SLCT) of the ovary.[7,8] The sarcoma in the CNS may only demonstrate a single pattern in a biopsy or several in a tumor whose features are indistinguishable from metastatic PPB to the brain. The SLCT with cystic ERMS and nodules of cartilage is a *DICER1*-related neoplasm but it remains a heterologous SLCT.

The suspicion or recognition of these tumors is based on the histopathologic features and as such, the pathologist must be aware of the morphologic spectrum of *DICER1*-related tumors. If the pathologist does not appreciate the potential implications of a CN, peritoneal sarcoma or RMS of the uterus, focus on terminology and classification is beside the point. An index of suspicion with an awareness of the existence of the various *DICER1*-related tumors should be set in motion for those neoplasms with cysts in the lung, kidney, liver and peritoneum whose histologic features include RMS, nodules of cartilage and anaplasia. A delicate layer of rhabdomyoblasts in the septum beneath the peritoneum or the ciliated epithelium of the fallopian tube or a polyp of cervix should serve as an important prompt to the pathologist to suggest to the clinician that the tumor may be *DICER1*-related and the patient may have a germline *DICER1* mutation.[9–12] After that important juncture in patient care, then we can then proceed with classification – PPB-like sarcoma or *DICER1* sarcoma. We would argue that the pathologist who is familiar with the cystic and solid patterns of PPB has a visual framework from which to suggest that the “PPB-like” sarcoma should be followed up by tumor molecular testing and appropriate genetic counseling and testing.[13]

We appreciate the thoughtful response to our study and our continued shared interest in *DICER1*-related research.

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