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Serum microRNA screening for DICER1-associated pleuropulmonary blastoma

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We thank Bailey et al for highlighting this additional aspect of surveillance in individuals with *DICER1* mutations.[1] We read with interest the report by Murray et al in which a 2-year-old patient with type III PPB of the hemithorax was found to have elevated levels of specific miRNAs with early treatment-related reductions.[2]

We were pleased to see that the highest circulating miRNAs reported by Murray et al were miR-125-3p family miRNAs.[2] A recent report by our group showed that mature 5p-miRNAs produced in cells with biallelic loss of function and RNase IIIb mutations retain precursor miRNA hairpin loop sequence while 3p mature miRNAs (processed by the RNase IIIa domain) are cut normally.[3] The 3p strand bias noted by us and others[2,4] likely reflects rapid degradation of the extended 5p miRNAs.[3] A likely application for serum

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measurements of miR-125a-3p and miR-125b-3p would be monitoring therapy response and detecting recurrence.

Identification of PPB in its earliest, cystic form provides the best opportunity for cure with lowest risk of therapy related side effects.[5] The cystic stage, however, is characterized by a microscopic population of primitive mesenchymal cells. It is unknown whether such a small population of cells would elaborate sufficient miR-125-3p family miRNAs to allow early detection. The goal remains detection in the paucicellular, cystic phase with resection prior to progression to Type II or III PPB.

The incidence of PPB in *DICER1* mutation carriers appears low but this has not been systematically studied. On the other hand, preliminary data from our NCI phenotyping cohort suggests that lung cysts are the second most common manifestation of the *DICER1* syndrome after thyroid disease. Approximately 25% of mutation positive relatives of children with PPB have lung cysts detectable by CT scan (unpublished data; <http://dceg.cancer.gov/research/clinical-studies/dicer1-ppb-study>). When found in very young children, there is no reliable method to determine which cysts are destined for regression. Although pathologic examination can differentiate between Type I PPB and Type I-regressed (Ir) PPB, it has been shown that patients with Type Ir can progress to Type II or Type III PPB.[6] In addition to sarcomatous progression, these cysts can be large, compress vital structures, and have a risk for pneumothorax and cerebral air embolism with air travel or deep sea diving.[7,8] Is it beneficial to diagnose these? If yes, then CT scans are likely to remain a mainstay for detecting lung pathology in *DICER1* mutation carriers. CT scan currently provides the highest resolution for detection of pulmonary lesions. Principles to reduce radiation exposure to young children should be followed while ensuring that resolution is sufficient to detect cystic lesions. Our case report and a recent GeneReviews, [9,10] convey the most recent recommendations from the International PPB Registry.

Although it remains to be seen whether cystic PPB is associated with detectable alterations in the serum miRNA profile, we agree that a prospective trial of the use of miRNAs in conjunction with radiographic imaging in monitoring response and detecting recurrence of advanced PPB is indicated.

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