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Title: Defining lineage relationships of multiple lung tumors through shared large genomic rearrangements

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Body: The ability to determine the relatedness of synchronous tumors of the lung as independent primaries or metastasis, would greatly aid in directing optimal clinical treatment strategies. While the current gold standard of predicting tumor relatedness is based on the histopathological profile of each tumor, a more definitive measure based on genomic profiles would be more robust. Recent studies have demonstrated that somatic chromosomal rearrangements are frequent and unique observations in many tumors. We therefore endeavored to utilize the genomic rearrangement profiles of multiple lung tumors of the same patient to aid in predictions of their relatedness. Through mate pair library sequencing of DNA derived from pure laser capture microdissected tumor cell populations we were able to efficiently yield the rearrangement profiles of individual tumors. Initial studies demonstrated the utility of this methodology in defining lineage between adjacent tumors of differing grade. Subsequent application of this methodology on distal synchronous tumors from the same patient enabled robust predictions of metastatic disease or independent primary lesions. While the total number of rearrangements ranged extensively between tumors, the derivation of just small numbers of shared unique rearrangements in associated tumors, not present in the germ line of that patient, were highly predictive of tumor lineage. We envisage this protocol as a powerful clinical tool in aiding physicians in the treatment of multiple tumor nodules.