LETTER

# Reply to Parsons: Many tumor types follow the monoclonal model of tumor initiation

We agree that some cancers may primarily have a polyclonal origin that results in genetically heterogeneous tumors. Retracing the Evolutionary Steps in Cancer (RESIC), as currently implemented (1), is not applicable to these cases. Depending on the source of heterogeneity, we are considering several refinements to our algorithm. Should this heterogeneity arise from interactions between separate cell populations, as in the polyclonal colorectal cancer example by Parsons (2), we will remove the independence assumption of cell niches. However, such modification requires information on the mechanisms, frequency, and strength of interniche interactions, which is not currently available. Without this knowledge, any implemented modifications might not accurately represent biology. For tumor types with heterogeneity driven by the coexistence of independent (epi)genetic alterations rather than cooperation of separate niches, we will take a different approach. We are currently developing techniques to accommodate the readouts of tumors with a large extent of heterogeneity that sequencing technologies are beginning to provide; thus, we can incorporate increased levels of heterogeneity into the assumptions of RESIC and consider copy number gains and losses arising in distinct subpopulations during tumorigenesis.

However, we believe that the cancer types featured in our paper (1) do not require modifications for polyclonal tumor origins. Recent evidence suggests that many tumor types, especially colorectal cancers, have primarily monoclonal origins. For example, through microdissection, Goranova et al. (3) determined that only the combinations of alterations consistent with a monoclonal origin followed by a sequential gain of changes were detected in colorectal tumors. Indeed, Parsons (4) shows polyclonal origins for some tumor samples; however, for many samples discussed in her review, the monoclonal sequential mutation model applies (4). Similarly, for a variety of other cancer types, tumor cells were found to stem from a single lineage that sequentially accumulated alterations (5). Thus, the current implementation of RESIC represents an accurate approach to addressing the temporal sequence of mutation accumulation for these cancer types. Also, note that a polyclonal origin leading to a tumor containing cells primarily from a single lineage does not significantly alter the predictions made by the RESIC algorithm, because our methodology delineates the trajectory of alterations arising in the majority of cells. For this reason, we have considered the accumulation of alterations to occur predominantly in a single lineage (1).

Parsons (2) also expresses concern that the sensitivity of current cancer genome profiling methods is not sufficient to detect alterations in small subpopulations of cells. Given our interest in the evolutionary trajectory of the majority of cells in a tumor, the 95% sensitivity provided by copy number alteration detection using the Agilent 244A array comparative genomic hybridization platform (6) is sufficient. Additionally, because the power of mutation detection is evenly distributed across mutational states in our framework, the results are robust. Our paper is a first attempt to leverage the potential of applied mathematics and evolutionary theory to answer this important question in cancer research. We will further develop our approach as more quantitative data emerge from ongoing cancer genome projects and as we learn more about the interactions between cancer cells and microenvironmental niches.

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