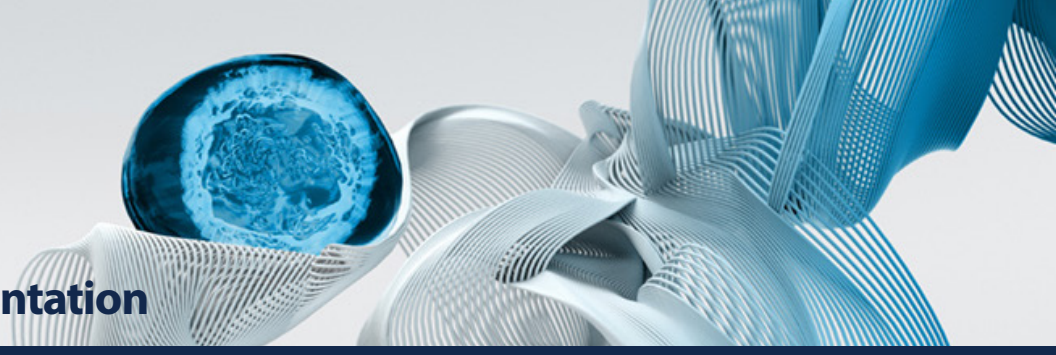
BioSkryb GENOMICS



AGBT 2021 Poster Presentation

Cells explored. Answers revealed.

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Improving the sensitivity of detection of low frequency somatic variants via Primary Template-directed Amplification of single cells.

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Technology Development Poster Session on Tuesday, March 2nd from 3:30pm-5:30pm ET

Somatic mutations occur in cells throughout development and produce variants at a range of frequencies across an organism. The frequencies of these variants depend on several factors, including cell type, developmental timing, and any increase in fitness associated with the variant either directly or indirectly through linkage to a co-occurring variant. Detecting somatic mutations is particularly important in cancer, where understanding the spectrum of somatic changes in a tumor can affect diagnosis, prognosis, and treatment. Several approaches have been developed to identify somatic mutations in bulk DNA samples, either using matched tumor-normal samples or directly from tumor samples themselves. Although these methods have been successful, they are fundamentally limited in their sensitivity of detection of low-frequency variants and are unable to directly detect cellular co-occurrence. In contrast, single-cell approaches for detecting somatic variants have sensitivity that is theoretically bounded only by the sensitivity of detection of variants within individual cells and the cellular throughput. Additionally, single-cell approaches can detect somatic variants co-occurring in the same cell and can thus be used to infer the evolutionary history of cells in a tumor. Currently, most existing methods for identifying variants from single cells have poor sensitivity due to artifacts introduced during the whole-genome amplification step. Primary template-directed amplification (PTA) is a recently developed high-fidelity method for whole genome amplification that shows increased coverage uniformity across the genome and has lower allelic dropout rates than existing single-cell amplification methods. These features enable accurate variant calling in single cells using PTA and overcome a main impediment to the detection of low-frequency somatic variants from the sequencing of single cells. Here we compare the sensitivity and precision of somatic variant calling between in silico mixed tumor-normal bulk samples and PTA-based single-cell data from numerous single cells. Using this approach, we estimate the number of single cells required to exceed the genome-wide mean sensitivity of bulk-based methods at a range of genome coverages.