Reviewer Report

Title: CNVpytor: a tool for CNV detection and analysis from read depth and allele imbalance in whole genome sequencing

Version: Revision 1 **Date:** 8/29/2021

Reviewer name: Whitney Whitford, PhD

Reviewer Comments to Author:

The reviewed manuscript from Suvakov et al., and associated response letters addresses the concerns of the reviewers from the first round of submission. The major concern raised by reviewer 2 regarding comparing the performance and computational usage of CNVpytor to previously available tools, I feel was adequately addressed by the authors. Another major concern raised by reviewer 2 was the claim that CNVpytor is appropriate for use with single cell sequencing data and cancer data. The authors demonstrated that some single cell sequencing techniques generate sufficient depth for CNVpytor to accurately call CNVs. Regarding CNV calling from cancer sequence data, the authors added the following to the manuscript: "Method is suitable for segmentation of RD data in the case of mosaicism or cancer samples and such CNAs will be called if cell frequency is high enough (Fig. S6)". Can they at least hypothesise as to what cell frequency may be high enough as this is not interpretable from Fig. S6?My main piece of feedback responds to a part of the review that Suvakov et al. did not address in their response. That is again from reviewer 2 who started their major comments with: "My main concern about this manuscript is that it does not have any scientific merit. It does not introduce any novel methodology in CNV calling or technical implementation. It introduces a new implementation based on already developed technologies and methodologies. To me it is more an extended version of CNVnator rather than a novel tool." I do not completely agree with this as the reduced storage usage and decreased runtime will pose of great utility for the bioinformatics community. However, the authors also refer in the manuscript and their response letter to additional functionality for cancer and mosaic cases, and incorporating B allele frequency in calling which are currently in the development process. The manuscript would be strengthened by CNVpytor with these functionalities being included as a single publication.

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