# Assessment of intratumoral genetic heterogeneity scores (ITGH) and its association with clinical parameters across several cancer types

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**Abstract**

In the age of precision medicine, the use of molecular data has become increasingly common in clinical oncology routine, especially with the advent of Cancer Gene Panels (CGPs). Given the relevant influence of intratumoral genetic heterogeneity (ITGH) on the prognosis and treatment of patients, its better understanding is vital. Recent advances in sequencing technologies and computational algorithms allowed the development of tools that estimate ITGH based on mutant allele frequencies (MAFs). However, several practical and methodological limitations make it difficult to get into the routine of clinical oncology. MATH score is a method capable of estimating ITGH from single biopsies taking into account parameters that are known to disrupt MAF estimates such as sample purity. This study aimed to measure the ITGH of all 33 cancer types from exome (WXS) data of the TCGA project and the MSK-IMPACT 410 cancer gene panel with MATH score in order to evaluate its association with several clinical parameters. Univariate survival analysis was done with stratified 5-Fold cross-validation strategy and ROC curves. For multivariate analysis, a modified cox regression model was used, joining the Monte-Carlo cross-validation strategy and the Bootstrap resampling method. ITGH varied significantly among patients and cancer types, where generally more aggressive tumors have higher levels of ITGH such as OV. In addition, MATH is a good prognostic marker of OS for UCEC, UCS and LGG and PFI for UCEC and LGG with WXS data. Similarly, significant results were obtained for OS in LUSC and for PFI in LUAD from CGP data. Additionally, higher MATH was associated with high TNM (stages III and IV) staging for UCEC (clinical), COAD, SKCM, KIRP, and ESCA (pathological) with WXS data and for colorectal cancer with CGP data. In addition, higher MATH was also related to the presence of metastasis in UCEC, ESCA, COAD, KIRP, and KIRC with WXS data. With MSK-IMPACT 410, higher ITGH was associated not only with presence, but also with a higher risk of metastasis in patients with colorectal cancer. On the other hand, MATH was not significantly different between responders and non-responders to immunotherapy in both the WXS and CGP data. Therefore, MATH presents itself as a promising tool for oncologists due to its simple use and easily interpreted results, in addition to the aforementioned associations with survival, staging and metastasis. In conclusion, MATH may have several applications in the near future regarding patient prognosis and therapeutic decision making.

Funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Código de Financiamento 001, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) - processo n$^{o}$ 2017/17974-9