# Doğa C. Gülhan, PhD

**Gülhan Laboratory**
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In **the Gulhan laboratory**, we develop computational methods to advance personalized oncology by employing statistical and machine learning models to dissect the complexity of cancer genomes. Leveraging signature analysis techniques, we detect mutational patterns representative of genomic instability mechanisms, such as dysfunctional DNA repair or cell-cycle checkpoint pathways, based on which we produce a refined map of their subtypes. In collaboration with clinical researchers, we study the differences in targeted therapy outcomes for tumors displaying these mechanisms and their specific evolutionary trajectories leading to resistance. Genomic instability may also trigger anti-tumor immune responses or promote immune evasion. We analyze these connections to maximize the efficacy of treatments, in particular that of immunotherapies. Our goal is to develop computational methods that can achieve a more accurate interpretation of cancer genomes and use these advancements to tailor tools with clinical applications.

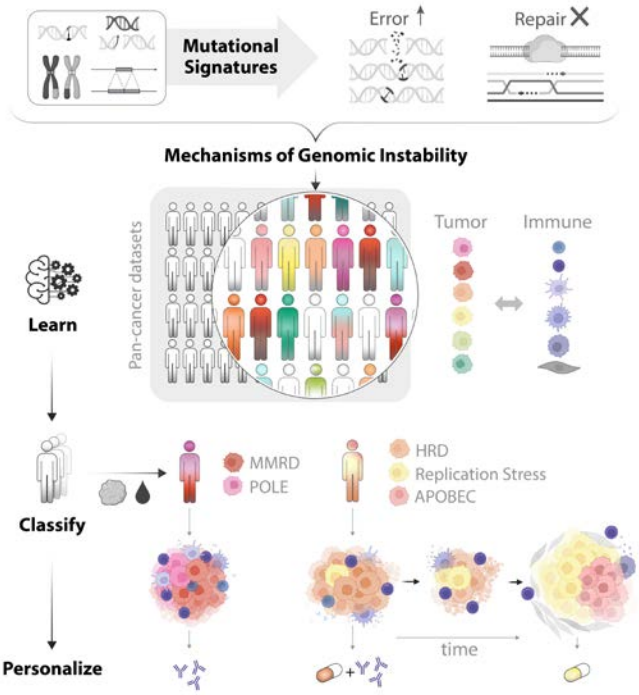
While cancer genomics offers deep insights into tumor landscapes, its full clinical potential remains untapped. Currently, personalized treatments cater to only a fraction of patients. Expanding the clinical interpretation of cancer genomes is essential to bridge this gap.

## Genomic instability to guide treatments

Cancer cells have elevated mutation rates arising from a blend of factors like exogenous mutagens and intrinsic genomic instability. The latter, resulting from events such as DNA repair deficiencies, cell cycle dysregulation, polymerase errors, and editing by APOBEC cytidine deaminases, provides cancer cells with growth advantages and evolutionary flexibility. This trait is a defining hallmark of cancer. However, genomic instability can also be a vulnerability for cancer cells. For instance, tumors with homologous recombination deficiency (HRD) are sensitive to PARP inhibitors that exacerbate DNA damage to an unsustainable level. Genomic instability also interacts intricately with the immune system. Mismatch repair deficiency (MMRD), which causes hypermutations, makes tumors susceptible to anti-PD-1 therapy. Similarly, the cGAS/STING pathway, activated by cytosolic DNA in tumors with genomic instability, can initiate immune responses. The clinical relevance of genomic instability, as exemplified by MMRD and HRD, underscores the need to assess tumors for such mechanisms. This is particularly important given that the clinical implications of several other types of genomic instabilities, including replication stress and APOBEC mutations, remain unclear.

## Enhanced signature analysis

Mutational signature analysis identifies patterns corresponding to distinct biological processes, revealing a tumor's mutagenic history. However, current approaches frequently oversimplify the nature of mutagenesis by presuming linear accumulation and neglecting correlations both within mutational processes and their dependencies on global and tumor-specific topographical features. Through more realistic statistical modeling of DNA damage and repair processes, we develop new algorithms. By applying these methods to




*We employ mutational signature analysis techniques to infer the origin of mutations, enabling us to categorize tumors based on their mechanisms of genomic instability. By leveraging large cancer genome datasets and using machine learning techniques, we create algorithms specifically designed for patient stratification in clinical settings to personalize their treatment. Part of this figure was created with BioRender.com.*

rapidly growing datasets of whole-genome sequenced cancers, we aim to achieve a more detailed map of processes and improve the accuracy of genomic instability classification.

## Dissecting the complexity

A significant challenge in the translation of signatures into clinical biomarkers is the pronounced diversity across the subtypes of tumors within a class of genomic instability. Consider APOBEC mutagenesis as an example: Based on the origin of single-stranded DNA, the mutations may occur on lagging strand in tumors with replication stress, the nontemplate strand in tumors with transcription stress, hairpins, DNA within micronuclei, or extrachromosomal DNA. Tumors that result from these distinct mechanisms are expected to demonstrate considerable variability in their molecular characteristics, which can limit the utility of signatures as biomarkers. Genomic diversity is not the only aspect to be considered; the relevance of genomic instability for treatments can differ based on the transcriptional profiles of tumors and the immune microenvironment, and these are highly tissue-specific. Moreover, as tumors evolve, all of these factors need to be monitored and reevaluated. Our lab aims to develop computational methods that can resolve these complexities, and tailored tools for clinical applications that can be used to guide cancer treatments.

## Leveraging circulating tumor DNA

Circulating tumor DNA (ctDNA) offers a non-invasive means to capture the clonal and spatial heterogeneity as well as the temporal evolution of tumors. Mutational signature analyses using ctDNA have numerous potential clinical applications. For instance, they can be used to distinguish mutations of tumor origin from those due to clonal hematopoiesis or amplification artifacts. Consequently, they can play a particularly crucial role in development of strategies for early cancer diagnosis and evaluating minimal residual disease. We also construct signatures analysis algorithms tailored for ctDNA that can be used to classify patients non-invasively according to their genomic instability and monitor the changes in signatures which might signal development of resistance.

## Selected Publications:


Jin H*, **Gulhan DC***, Ben-Isvy D, Geng D, Ljungstrom V, Park PJ. Accurate and sensitive mutational signature analysis with MuSiCal. *bioRxiv* 2022.04.21.489082.

Batalini F*, **Gulhan DC***, Mao V, Tran A, Polak M, Xiong N, Tayob N, Tung N, Winer EP, Mayer EL, Knappskog S, Mayer EL, Lønning PE, Matulonis UA, Konstantinopoulos PA, Solit DB, Won HH, Eikesdal HP, Park PJ, Wulf GM. Mutational signature 3 detected from clinical panel sequencing is associated with responses to olaparib in breast and ovarian cancers. *Clin. Cancer Res*. 2022 Nov 1;28(21):4714-4723.

Cortés-Ciriano, I, **Gulhan DC**, Lee JJK, Melloni GEM, Park PJ. Computational analysis of cancer genome sequencing data. *Nat Rev Genet*. 2022 May; 23(5):298-314.

Färkkilä A, **Gulhan DC**, Casado J, Jacobson CA, Nguyen H, Kochupurakkal B, Maliga Z, Yapp C, Chen YA, Schapiro D, Zhou Y, Graham JR, Dezube BJ, Munster P, Santagata S, Garcia E, Rodig S, Lako A, Chowdhury D, Shapiro GI, Matulonis UA, Park PJ, Hautaniemi S, Sorger PK, Swisher EM, D'Andrea AD, Konstantinopoulos PA. Immunogenomic profiling determines responses to combined PARP and PD-1 inhibition in ovarian cancer. *Nat. Commun*. 2020 Mar 19;11(1):1459.

**Gulhan DC**, Lee JJ, Meloni GEM, Cortes Cirano I, Park PJ. Detecting the mutational signature of homologous recombination deficiency in clinical samples, *Nat Genet*. 2019 May;51(5):912-919.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