ITCR Monthly Meeting

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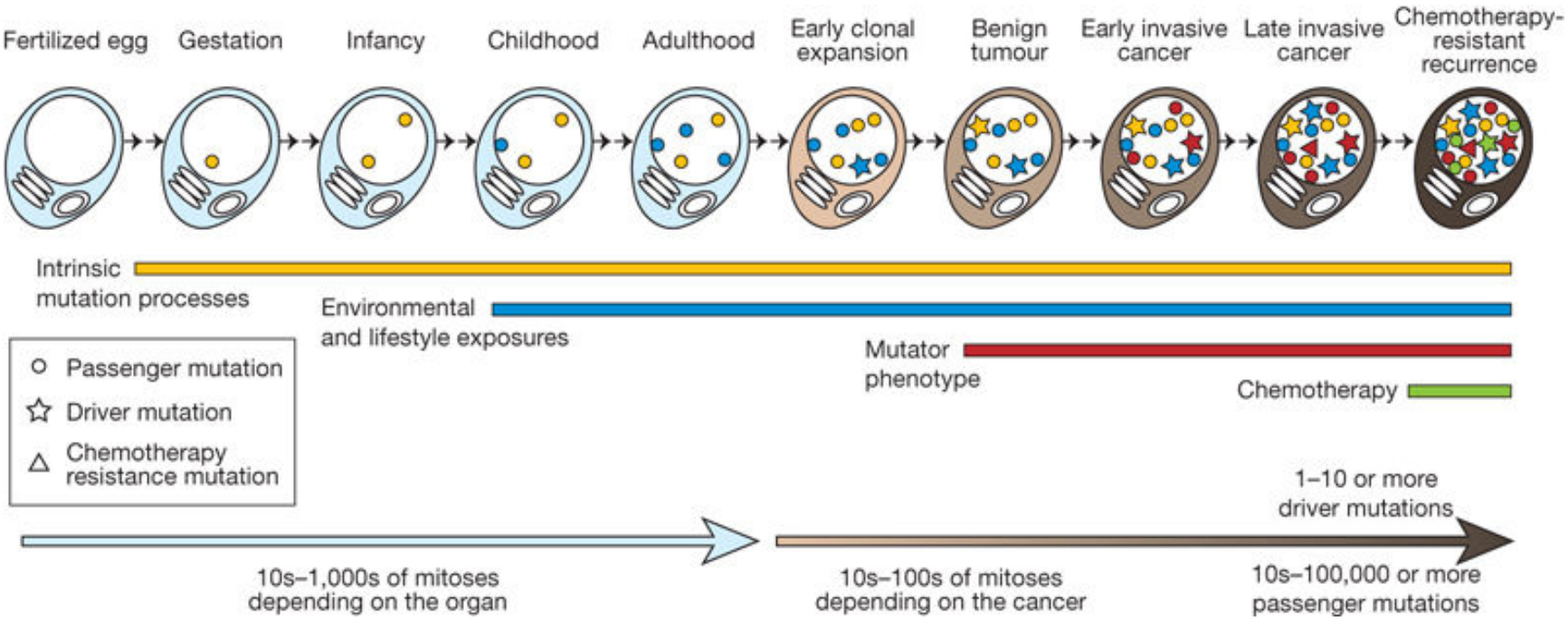
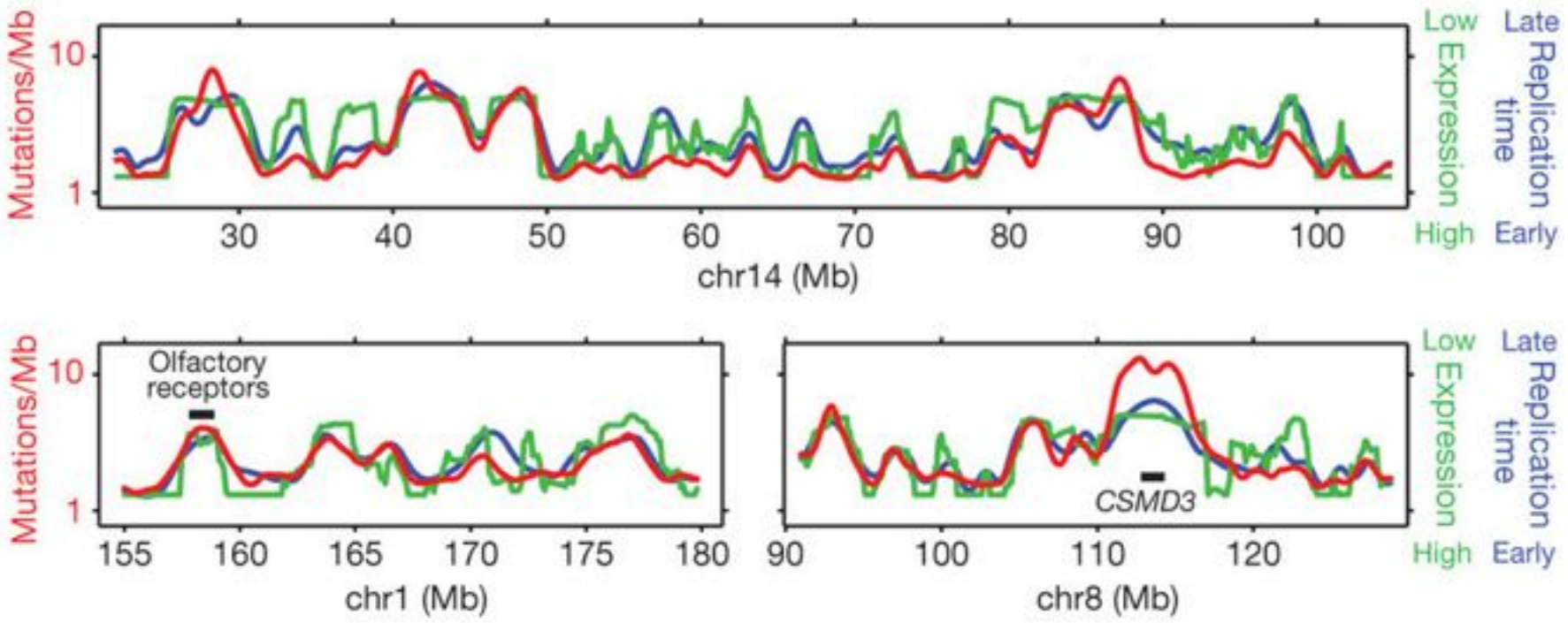
Passenger and driver mutations in cancer



Stratton et al. Nature 2009

Searching for a needle in the haystack

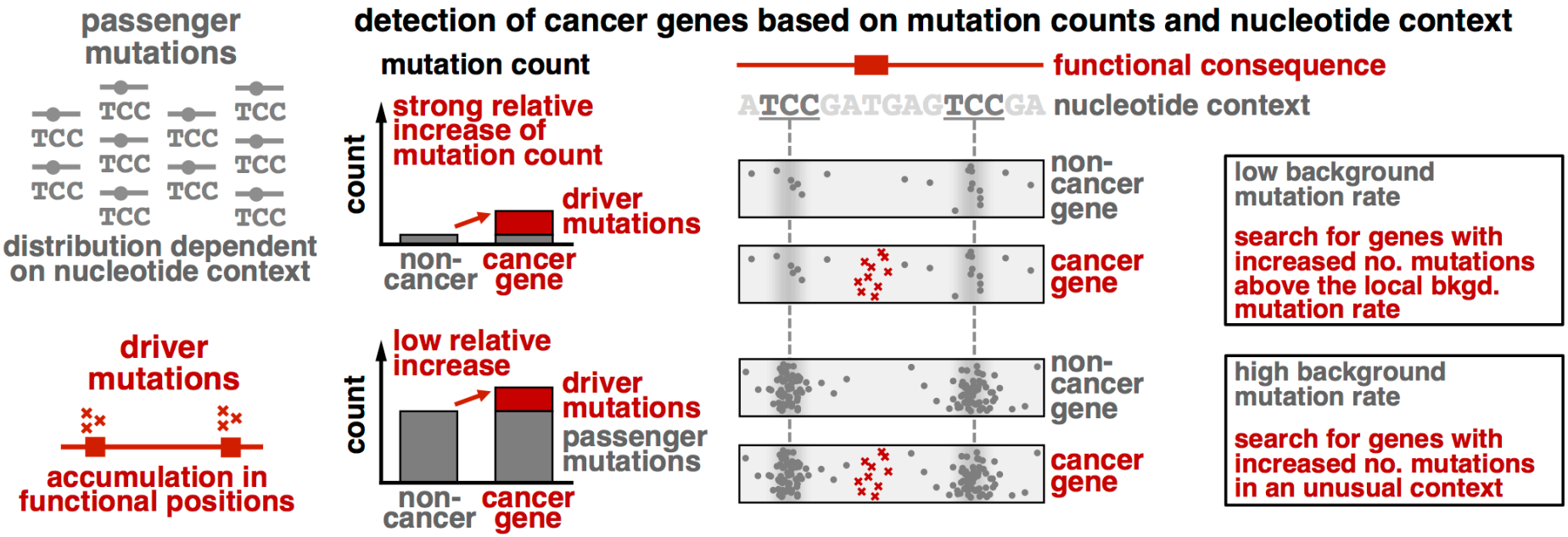
The background mutation rate varies across the human genome



Lawrence et al. Nature 2013

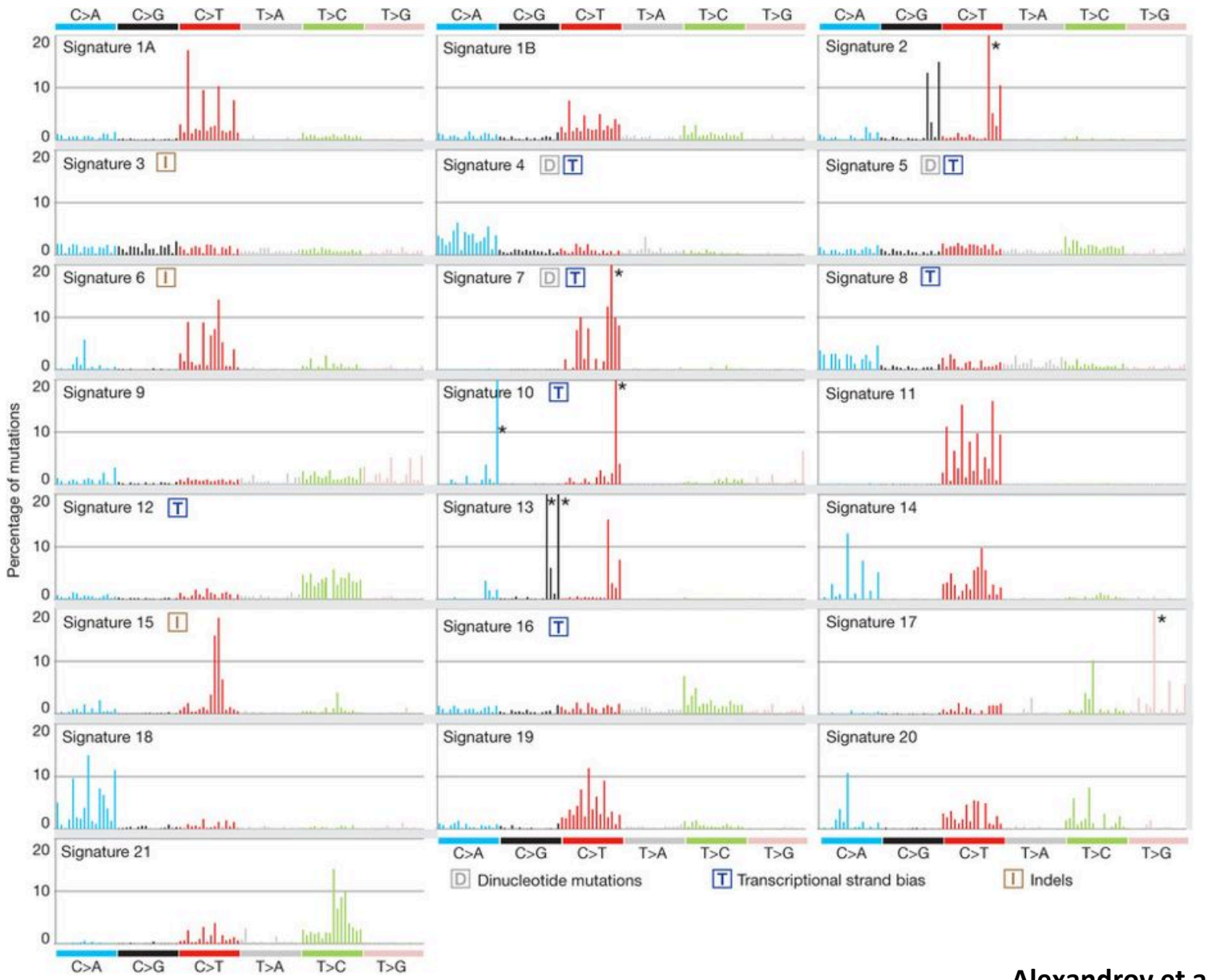
synonymous mutations provide a way to account for the variation of the regional background mutation rate in the coding space

Nucleotide contexts provide an additional signal in favor of driver mutations



Dietlein et al. submitted

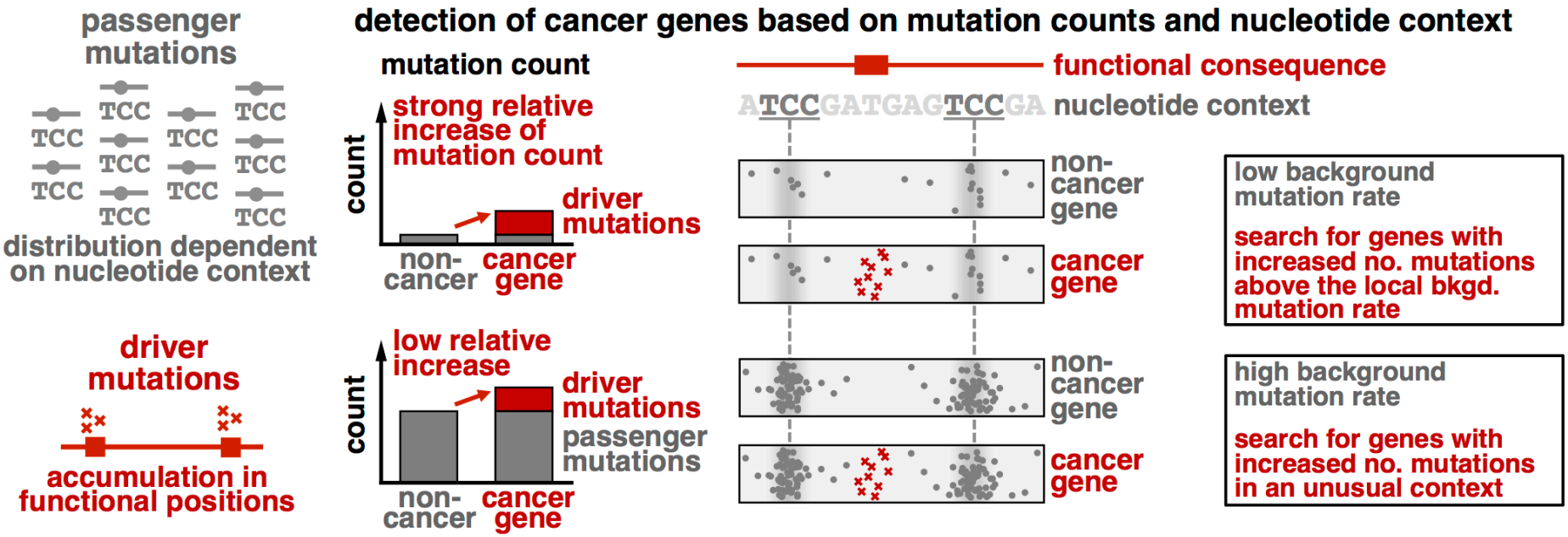
Mutational signatures in cancer



Alexandrov et al. Nature 2013

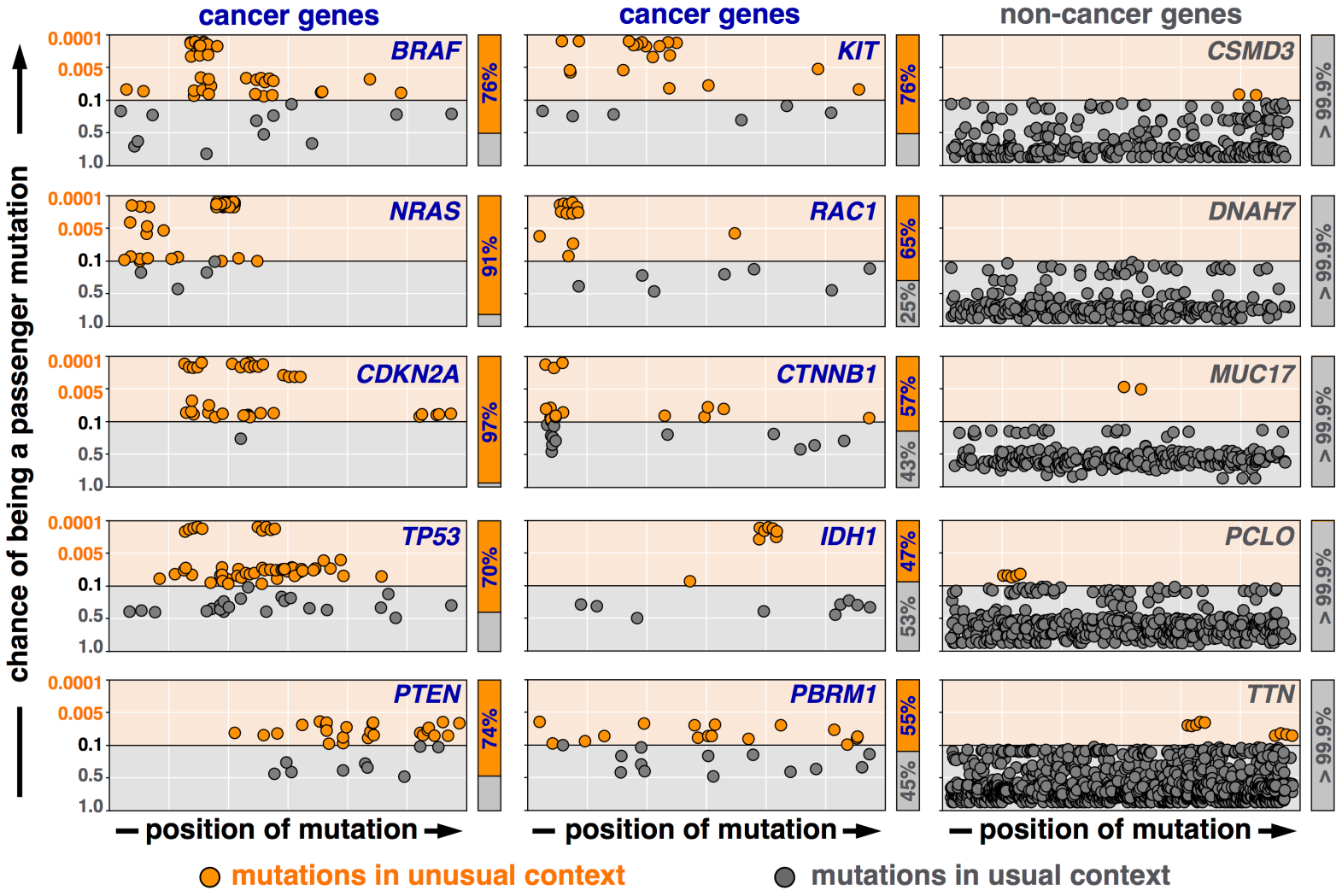
nucleotide contexts may provide a way to identify driver mutations in the non-coding space

Nucleotide contexts provide an additional signal in favor of driver mutations



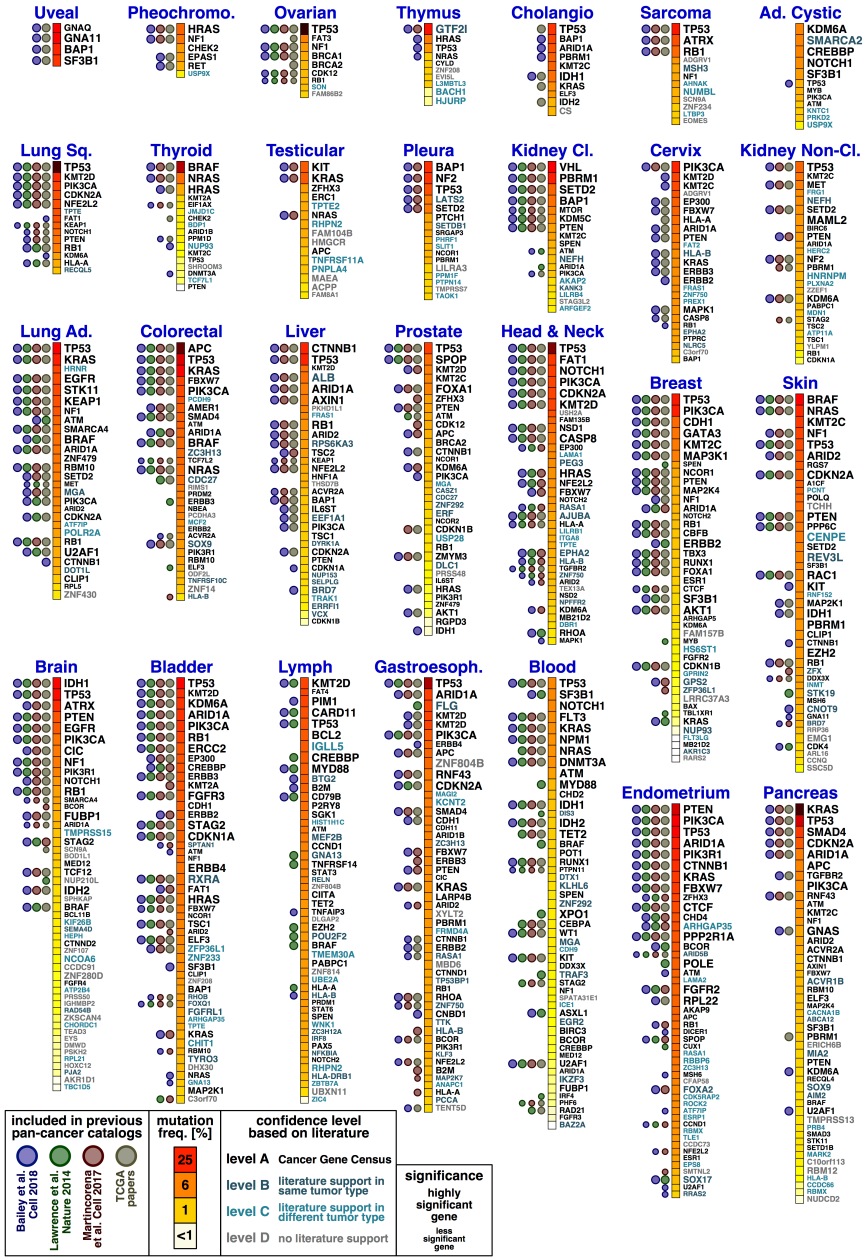
Dietlein et al. submitted

Nucleotide contexts provide an additional signal in favor of driver mutations



Dietlein et al. submitted

A catalog of driver genes in human cancer



Dietlein et al. submitted

Aim 1 To define the landscape of noncoding cancer driver mutations using nucleotide context

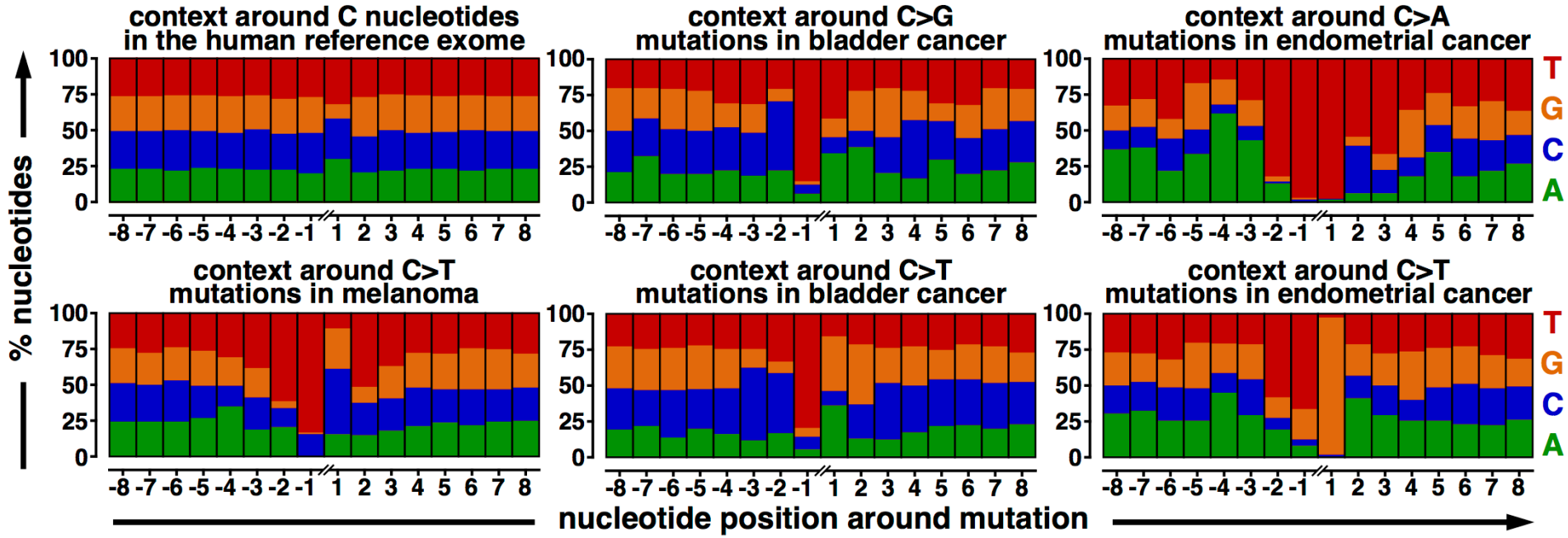
Rationale: The role of noncoding mutations in tumor formation largely remains unknown. The emerging availability of large whole-genome sequencing datasets creates an ample opportunity to develop new mutational significance algorithms

Hypothesis: Current mutational significance algorithms have been developed for coding mutations. Applying them to noncoding regions does not exploit the full potential of whole-genome sequencing datasets

Approach: Develop a new statistical model that accounts for:

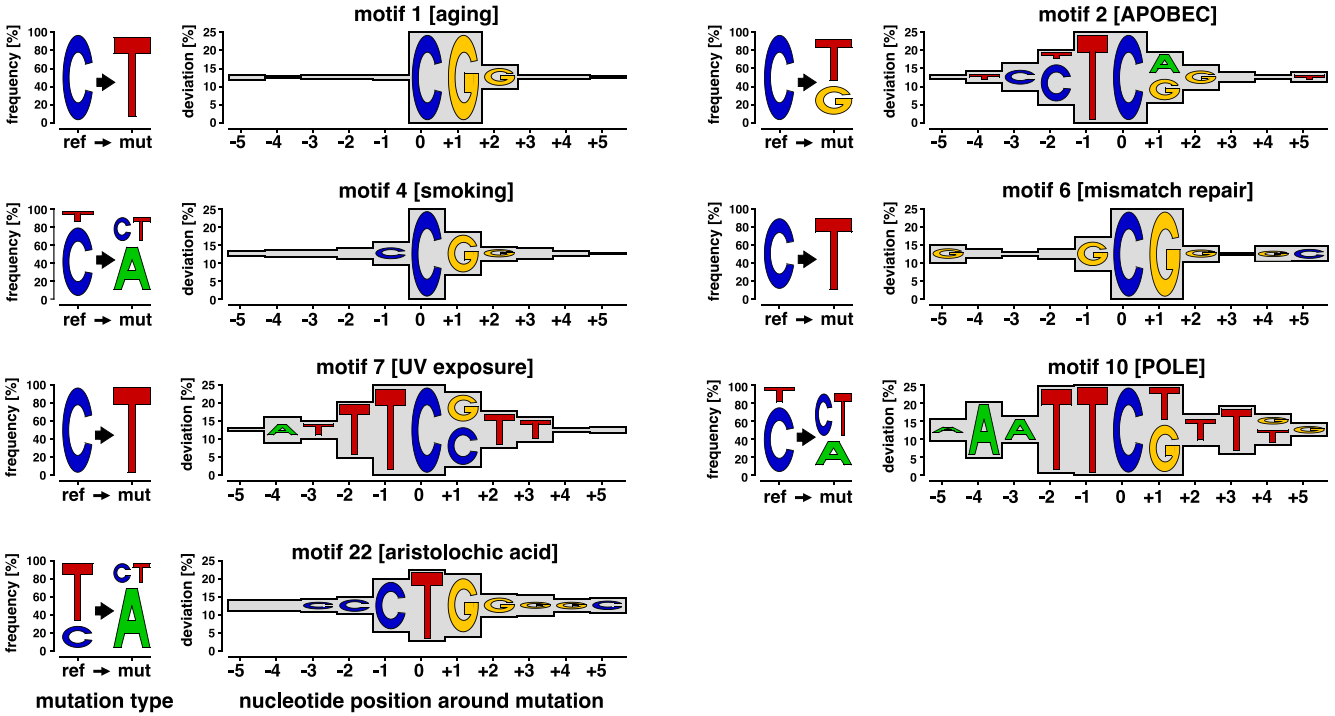
- Context-dependent distribution of passenger mutations
- Modeling of the background mutation rate
- Partitioning of the background mutation rate:
- Modeling the sequence composition of the reference genome
- Coverage fluctuation

Extended nucleotide contexts around passengers contain a signal



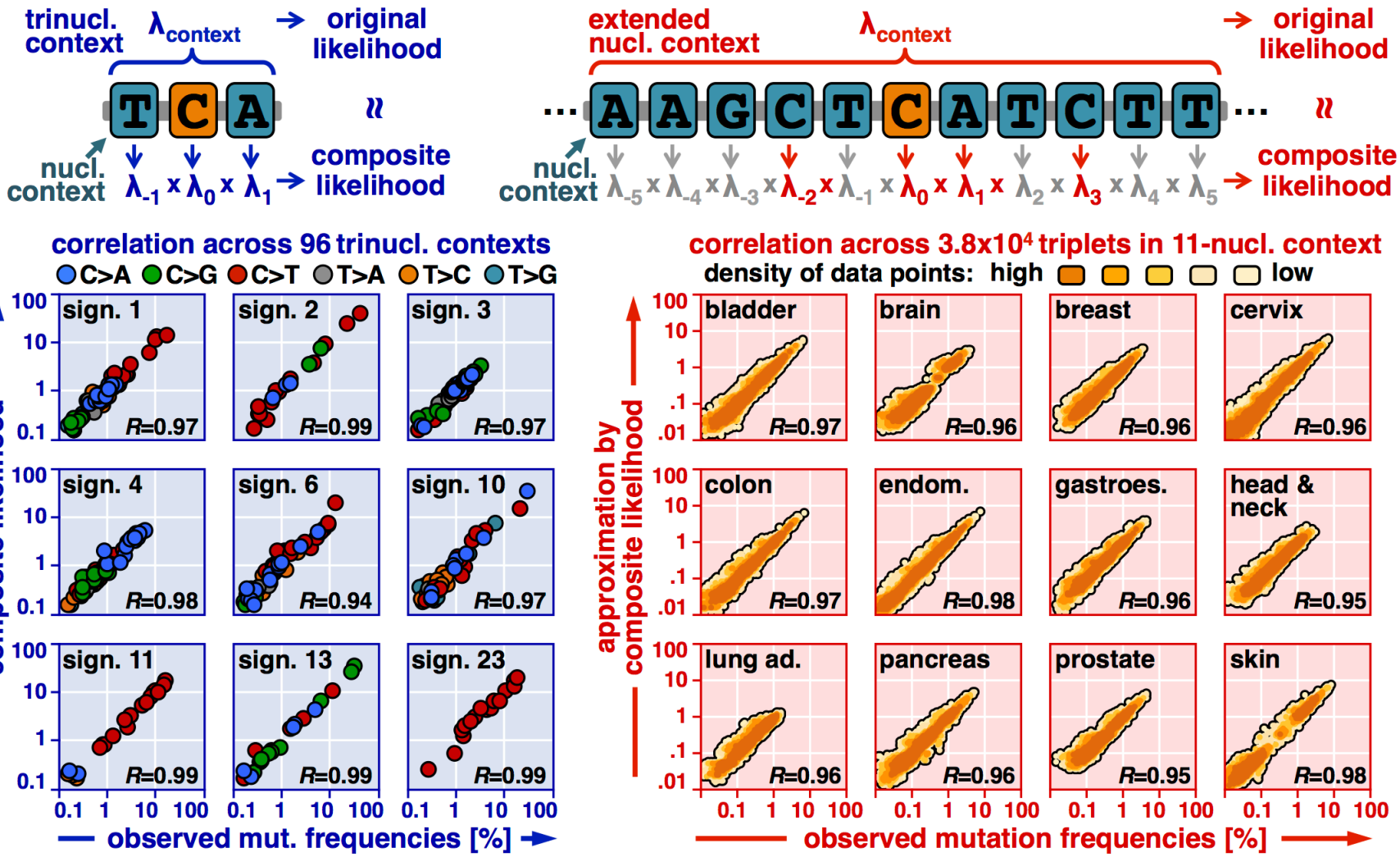
Dietlein et al. submitted

Extended nucleotide contexts around passengers contain a signal



Dietlein et al. submitted

A composite likelihood model to account for extended nucleotide contexts



Dietlein et al. submitted

Aim 2 To evaluate the clinical significance of passenger mutation distribution patterns for immunotherapies

Rationale: Despite the clinical relevance of immunotherapies, robust markers for patient stratification are currently lacking. The most common parameter to predict clinical response is the mutational burden.

Hypothesis: Recent studies have suggested that not only the total number of passenger mutations but also their underlying biology mediates clinical response to immunotherapy. We and others have shown that the underlying biology of passenger mutations is not only reflected by their surrounding trinucleotide context but that a relevant signal is in the extended nucleotide context.

Aim 2 To evaluate the clinical significance of passenger mutation distribution patterns for immunotherapies

Approach: Use extended nucleotide contexts for "improved" mutational signatures

- Apply our composite likelihood model to a sequencing dataset of 249 tumors with clinically annotated outcomes to immune checkpoint therapy
- Evaluate the immunogenicity of each individual passenger mutation by using established algorithms , such as POLYSOLVER algorithm and NetMHCpan-3.0
- Determine which passenger mutations from the whole-exome sequencing data can be rediscovered in the corresponding RNA sequencing data of the same tumor.
- Develop an integrative model to combine these aspects and predict the immunotherapy response of a tumor, based on the immunogenicity of its passenger mutations