Sure..... integrate immune markers into Prognosis

• It's not as easy as you think
• Consider the genomic, i.e. mutations (SNV), copy number aberrations, neoantigens, clonality, subclonality, evolution, and then how these spatially relate to each other.
Immunological/Pathological/Prognosis

• Intratumoral Heterogeneity and Chromosomal Instability

Somatic mutations, SNV and CAN measured as a percentage of the genome affected by such alterations, classified as clonal (present in all cancer cells) or subclonal (present in a subset of cancer cells)

- 30% of somatic mutations were subclonal
- 48% of CNA were subclonal
- SCC > Adeno for clonal but ND in subclonal or within Ad subtypes
- POOR PROGNOSIS: Tumors with higher proportion of subclonal CNAs, not subclonal mutations

Patients with early-stage tumors with high levels of copy-number heterogeneity may represent a high-risk group who may benefit from close monitoring and early therapeutic intervention during follow-up.

Take home: Capturing tumors prior to subclonal diversification requires earlier detection and screening.

The NEW ENGLAND JOURNAL of MEDICINE

Tracking the Evolution of Non-Small-Cell Lung Cancer

Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution

Primary NSCLC resection and multiregion sampling

Exome sequencing of tumour regions

Phylogenetic tree informs PCR assay panel construction

Mutations in tissue

Multiple patient-specific assay panels combined

Multiplex-PCR assay pool

Blood sample

Patient-specific phylogenetic tracking

Multiplex-compatible primers targeting patient-specific SNVs

cDNA extracted

Pre-surgery

PCR NGS

CRUK0045: LUAD

CRUK0065: LUSC
Immune heterogeneity in tumors is dictated by immunologic sculpting, immunoediting, and immune escape and is visible at the levels of DNA (mutation, copy number, genetic heterogeneity), RNA (expression), and the epigenome (promoter hypermethylation).

Immune infiltration and tumor mutational burden (TMB) can vary within the same tumor, with 28% of samples demonstrating immunologic heterogeneity and 21% of samples harboring TMB heterogeneity.

Neoantigen-producing mutations were more likely to be located in areas of subclonal copy number loss compared to non-neoantigen mutations.

Immunologically cold tumors
- more ubiquitously expressed clonal neoantigens,
- HLA loss of heterozygosity is present and is a mode of immune evasion.
- Epigenetic neoantigen repression, with neoantigenic mutations much more likely to have DNA promoter hypermethylation compared to the same genes lacking neoantigenic mutations.
TCR Repertoire Intratumor Heterogeneity in Localized Lung Adenocarcinomas: An Association with Predicted Neoantigen Heterogeneity and Postsurgical Recurrence

July 21, 2017; DOI: 10.1158/2159-8290.CD-17-0256

MHC I predicted neoantigens

A

D

MHC II predicted neoantigens

B

E

C

F
What about immune gene signatures?

In silico construction of immune gene risk signature using 25 immune related genes

- Cytokines, cytokine receptors, and genes related to the T-cell receptor signaling pathway, B-cell antigen receptor signaling pathway, natural killer cell cytotoxicity, and antigen processing and presentation pathways.

C-index 0.64 which isn’t that great
Geospatial immune variability illuminates differential evolution of lung adenocarcinoma

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