A Pan-Cancer Characterization of Both the Tumor and Micro Environment Highlights the Importance of an Integrated Approach for Immuno-Oncology

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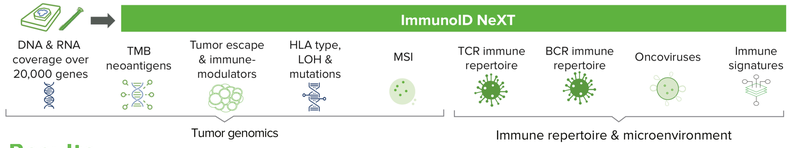
Background

A better understanding of the characteristics of cancer across different indications is required to drive the development of personalized treatments, inform therapy decisions, and improve outcomes. Integrating data from the tumor and the immune system can enable the identification of comprehensive biological signatures and composite biomarkers for the improved stratification of responders/progressors. Here, we describe a pan-cancer study, including an enhanced whole-exome and transcriptome sequencing approach, across over 700 samples representing 14 tumor types, analyzed at high depth using the ImmunoID NeXT Platform®.

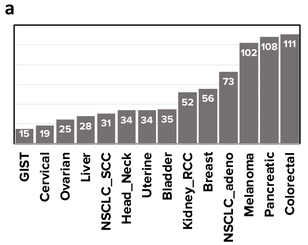
Methods

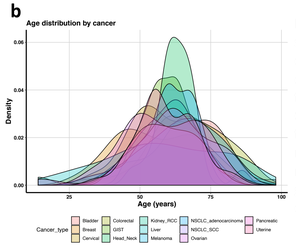
We sequenced paired tumor-normal samples on the ImmunoID NeXT Platform, an enhanced exome/transcriptome-based platform that can simultaneously profile the tumor and immune microenvironment from a single FFPE sample, across all of the approximately 20,000 genes. For each sample, we analyzed a broad set of features focused on both the tumor and immune system. From DNA, we profiled small variants, CNAs, MSI status, oncoviruses, HLA LOH, and neoantigens. From RNA, we profiled gene expression, small variants, fusions, TILs, TCR, BCR, and immune signatures. Integrated analyses assessing the impact of each feature, both within and across tumor types, were performed across the cohort.



Results

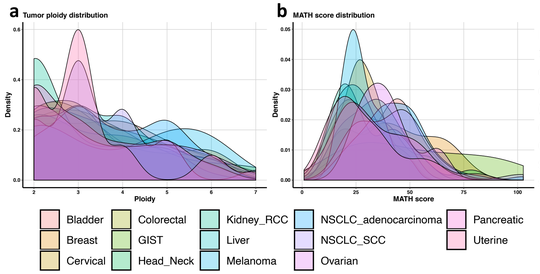
Cohort demographics





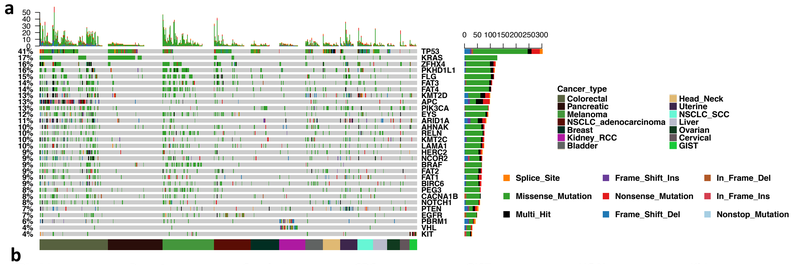
Matched tumor and normal specimen representing 14 different cancer types were collected. Patient age ranged from 14-98, with a median of 62. 56% of patients were female and 44% were male. A broad and balanced range of cancer stages and grades were collected for all cancers under investigation

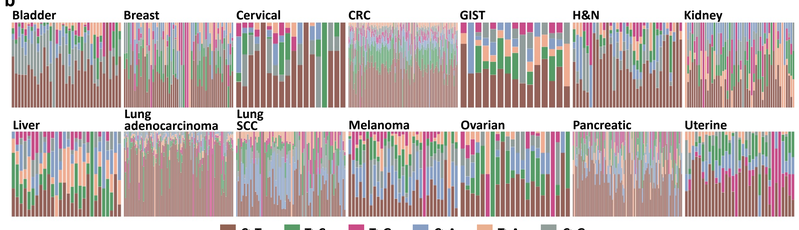
Tumor characteristics



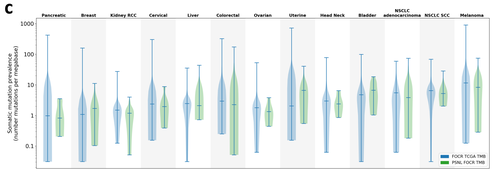
Basic tumor characteristics including tumor purity, ploidy, copy number changes and heterogeneity were calculated for all samples. The left panel (**a**) shows slight variations in the distributions of tumor ploidy across different primary tumor types. **b,** MATH score distribution, which captures a simplified score of tumor heterogeneity.

Mutational landscape of driver genes varies across cancer



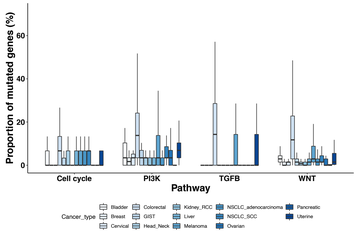


a, Waterfall plot of the top 30 most frequently mutated driver genes. Further analysis of these mutational patterns may help identify novel dual-role cancer driver genes such as NOTCH, which can exhibit oncogene or tumor-suppressor behavior depending on the biological context. **b**, Stacked bar plots showing proportion of SNV conversions across 460 predicted driver genes. Shifts were



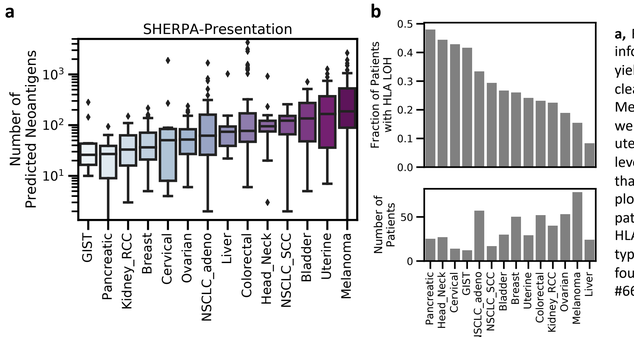
observed in the ratios of transitions and transversions when comparing to signatures generated using all detected nonsynonymous mutations. **c**, Tumor mutational burden was calculated following FOCR guidelines, and present a general concordance between the cohorts in the present study, and those found in TCGA.

Oncogenic pathways are differentially mutated between cancer types



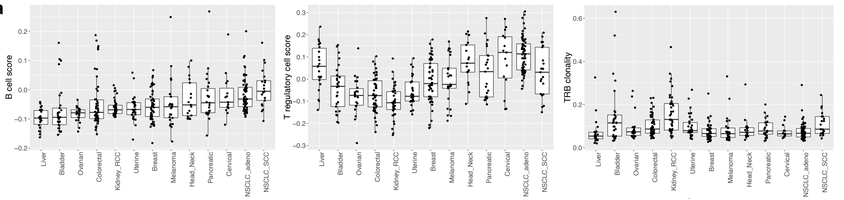
We evaluated frequently mutated canonical oncogenic signaling pathways that have been previously described, focusing primarily on those with therapeutically targetable and cancer driving mutations. Four example pathways with varying proportions of mutations are shown at left. Cancers with the highest mutational burden exhibited the highest frequency of oncogenic pathway alterations. Cancer specific variation in frequency and combination of alterations, suggests complex interaction between pathways, that likely underlie malignancy-specific response and resistance mechanisms.

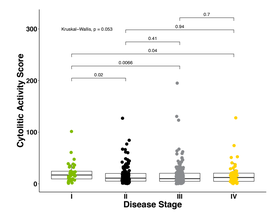
Number of predicted neoantigens and allele-specific HLA LOH frequency vary with cancer type



a, Refinement of tumor mutational information into neoantigen burden yielded a biomarker that more clearly differentiates cancer types. Median predicted neoantigen levels were higher in melanoma and uterine malignancies reaching levels approximately 7 fold higher than those observed in GIST **b,** Bar plots showing total number of patients, as well as allele-specific HLA LOH frequency for each tumor type. Additional information can be found at our companion poster, #6678

Transcriptome-based measures of the TME and immune activity vary by malignancy and disease stage





Immune cell infiltration may be a useful prognostic factor in a number of cancers - TILs are associated with increased levels of tumor neoantigens, and likely influence therapeutic response and overall survival. **a**, B cell scores are shown for a subset of cancers profiled in this study. The highest median levels were detected in squamous cell carcinomas of the lung, a malignancy where infiltration of intratumoral B cells may may be important in determining both responsiveness to, and toxicity of, ICB. Regulatory T cells (TREGs), which can induce an immunosuppressive TME were detected at high levels in cervical cancer, which may influence the low TRB clonality observed. Additional information can be found at our companion poster, #4430. **b**, Cytolytic activity score, which is indicative of anti-cancer immunity is significantly higher at earlier disease stages, when compared across all cancer types, possibly suggesting evolution of additional immune escape mechanisms as cancer progresses.

Conclusion

We performed a broad integrated analysis of the tumor and immune microenvironment for over 700 samples across 14 different tumor types using the ImmunoID NeXT Platform. This comprehensive profiling revealed significant differences between cancer types beyond mutational burden, including neoantigen burden, immune microenvironment differences, and incidence of putative tumor escape mechanisms

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