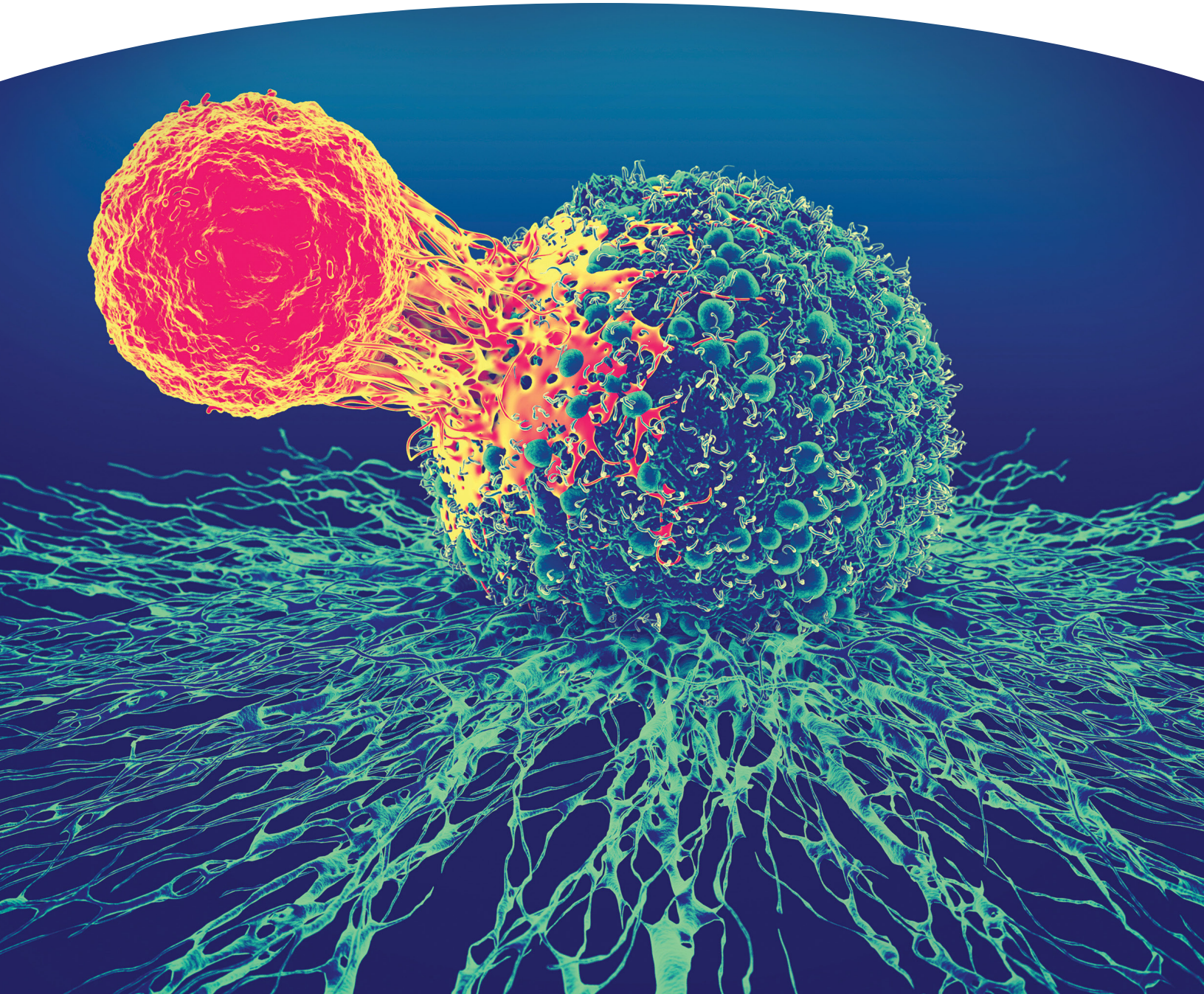
Personalis®
Precision Genomics for Immuno-Oncology

ImmunoID NeXT™

The Universal Cancer Immunogenomics Platform



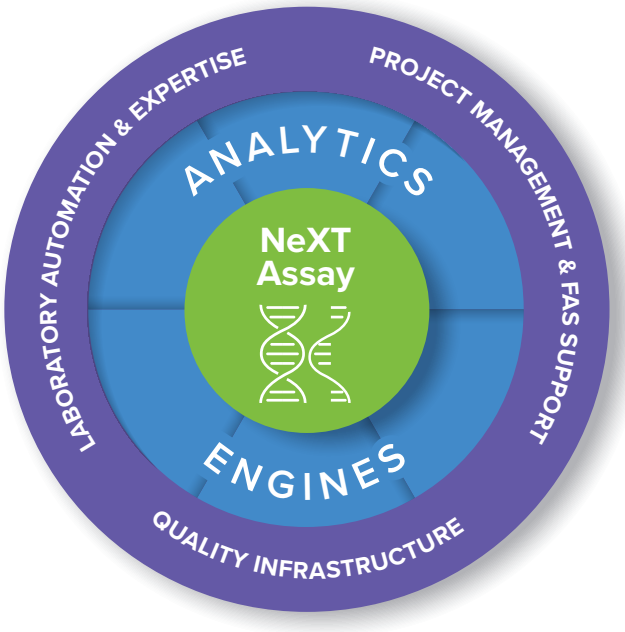
Advancing Modern Precision Oncology

The Universal Cancer Immunogenomics Platform

ImmunoID NeXT is designed specifically to enable the development of more efficacious cancer immunotherapies and the next-generation of composite biomarkers to better predict patient response. While the success of checkpoint blockade has been hugely promising, it's increasingly apparent that predicting response to immunotherapies and developing new ones requires a more comprehensive approach to tumor immunogenomics. By combining highly-sensitive, exome-scale DNA and RNA sequencing with advanced analytics, ImmunoID NeXT provides a multidimensional view of the tumor and the tumor microenvironment (TME) from a single sample.

For the first time, oncology translational and clinical researchers can comprehensively characterize both the tumor- and immune-related components of the TME using a single platform. ImmunoID NeXT enables customers to maximize the data generated from precious tumor samples, while simultaneously decreasing the complexity of data interpretation by eliminating the need to integrate multiple assay technologies and reporting formats from several sources.

ImmunoID NeXT provides an end-to-end solution for immuno-oncology and all precision oncology applications. It combines the pioneering NeXT™ Assay's sophisticated analytics engines, and quality support to provide researchers with the comprehensive immunogenomic data they need to drive their programs.



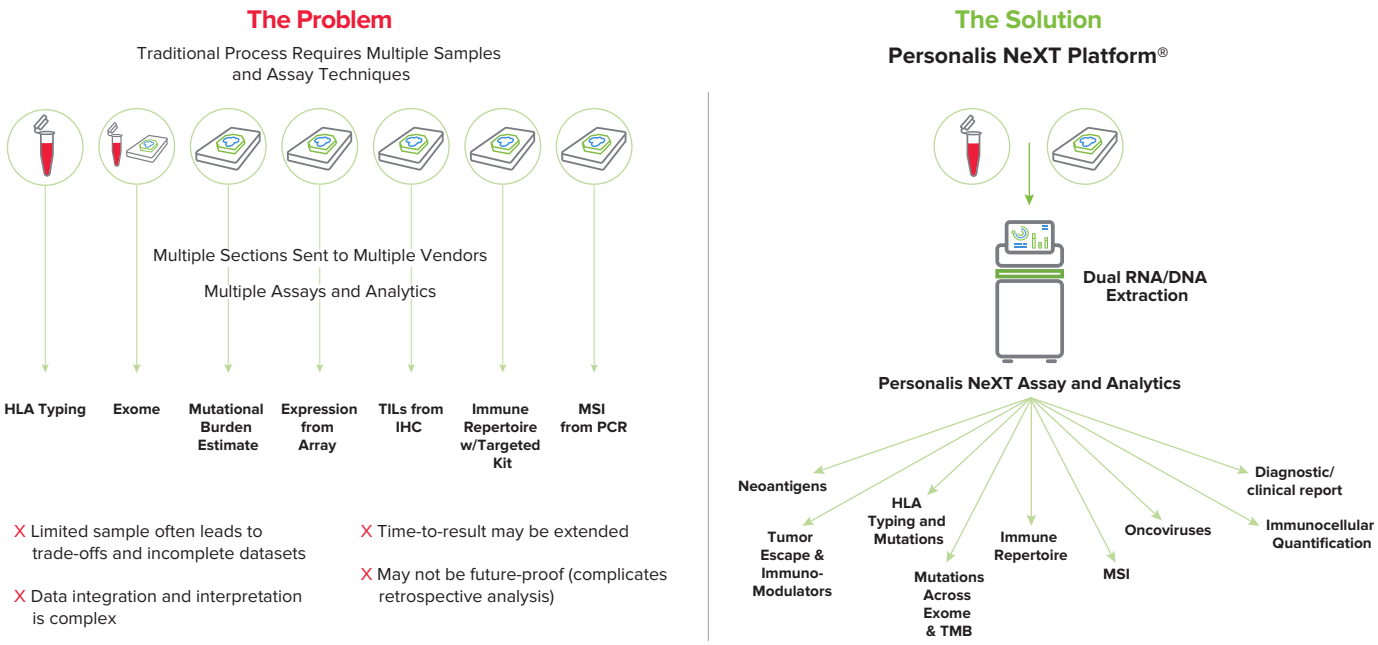
ImmunoID NeXT

Figure 1: ImmunoID NeXT: The Universal Cancer Immunogenomics Platform.

A Single Platform. A Single Sample. Multiple Biomarkers.

Purpose-built for precision oncology, ImmunoID NeXT can be used to investigate key areas of tumor biology; from elucidating mechanisms of tumor escape and detecting neoantigens, to identifying novel gene expression signatures and characterizing the immune repertoire. With these extensive capabilities, ImmunoID NeXT provides a complete picture of the cancer ecosystem and enables the consolidation of multiple biomarker assays into one.

Figure 2



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Ultra-High Sensitivity. The Scale of an Exome.

Unlike other commercial genomics platforms which make trade-offs between breadth and sequencing depth, ImmunoID NeXT optimizes both footprint and limits of detection to generate accurate and comprehensive genomic data, providing ultra-sensitive detection of single nucleotide variants (SNVs), insertions/deletions (indels), copy number alterations (CNAs), and gene fusions across ~20,000 genes.

ImmunoID NeXT also leverages Personalis' proprietary Accuracy and Content Enhanced (ACE) Technology to augment coverage of more complex and difficult-to-sequence regions (e.g. areas of high-GC content) across all ~20,000 genes that are not sufficiently covered by conventional approaches. The incorporation of ACE Technology® into the design of ImmunoID NeXT, therefore, reduces the likelihood of the non-detection of potentially important somatic variants present in patients' tumor(s).

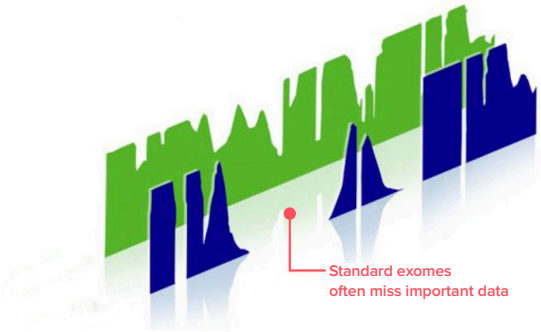


Figure 3: The sequencing coverage provided by standard exome-scale assays is shown in blue. The ACE-enabled, augmented sequencing coverage provided by ImmunoID NeXT is shown in green.

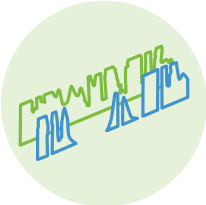
The unique, innovative design of the assay and analytical algorithms enables the delivery of critical tumor and microenvironment-related information including, but not limited to:

- T-cell receptor (TCR) repertoire composition
- B-cell receptor (BCR) repertoire and BCR isotype composition
- Neoantigen detection and neoantigen load
- Tumor mutational burden (TMB)
- Microsatellite instability (MSI) characterization
- Quantification of the immunocellular content in the tumor microenvironment (TME)
- Human leukocyte antigens (HLA) typing, HLA and beta-2 microglobulin (B2M) somatic mutations, and HLA loss of heterozygosity (LOH)
- Tumor escape and resistance mechanisms
- Oncoviral detection

Optimized for Oncology Applications

Deep Sequencing

~300X mean exome coverage, 200M total RNA reads, ultra-deep coverage of immune repertoire gene regions, as well as >1,000X coverage across 247 cancer-related genes.



Augmented Coverage

ImmunoID NeXT utilizes our proprietary ACE Technology to provide augmented coverage of difficult-to-sequence gene regions across the entire ~20,000-gene footprint.

Specific Targeting

Enhanced targeting of HLA genes, MSI-related loci, as well as oncoviral genomes to enable the accurate characterization of investigational and predictive precision oncology biomarkers.

Ultra-High Sensitivity

Accurate detection of somatic SNVs, indels, CNAs, and gene fusions, including low-abundance mutations, which is critical for the analysis of low-purity and/or highly-heterogeneous tumor samples.

Optimized Algorithms

The Personalis framework of analytical pipelines integrates both proprietary and advanced, publicly-available *in silico* tools to generate the most informative and usable insights from the comprehensive raw DNA and RNA data.

Mastering Challenging Samples

Personalis' protocols optimize nucleic acid extraction from difficult formalin-fixed paraffin-embedded (FFPE) samples. This approach enables dual extraction of both DNA and RNA from the same, precious tumor sample.

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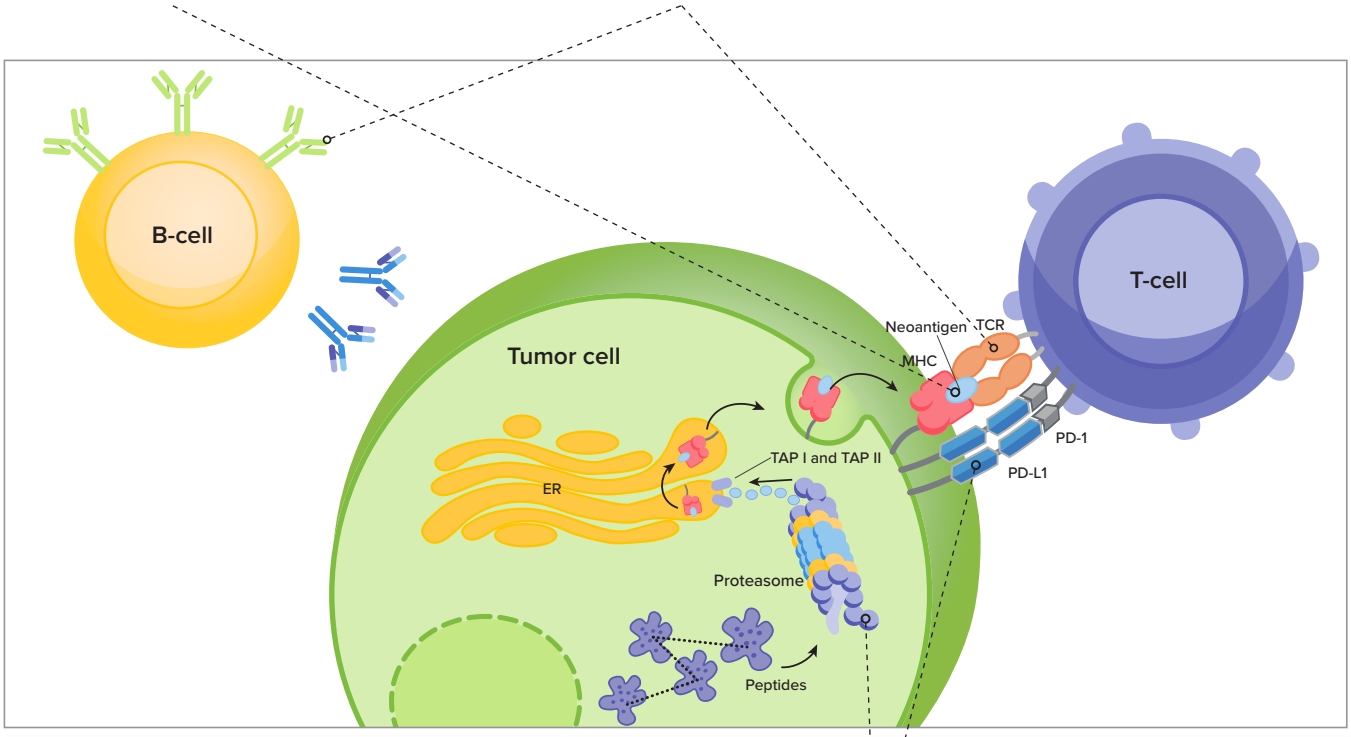
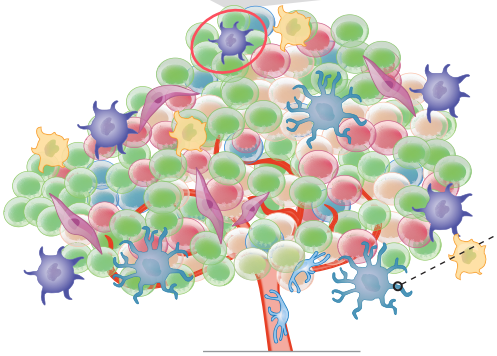
Evaluate the Entire Cancer Ecosystem

ImmunoID NeXT analytics leverage the accurate, raw data to evaluate the status of the most relevant oncology biomarkers, as have been identified and investigated in the literature. **Figure 4** below illustrates how the analytics modules elucidate the complex interplay between tumor cells and the immune cells of the TME.

NeoantigenID™ informs candidate neoantigen selection through MHC-binding prediction and presentation rank utilizing our proprietary machine-learning algorithm, SHERPA™.

RepertoireID™ enables the characterization of both the TCR and BCR repertoire from the same sample, along with determining the underlying isotype composition of BCRs within the TME.





Tumor Microenvironment

ImmunogenomicsID™ provides an overview of the TME and critical areas of tumor and immune biology such as the adaptive and innate immune response, immune checkpoint modulation, antigen processing machinery (APM), tumor associated antigens (TAAs), DNA repair and replication, MSI characterization, oncoviruses, among others.

InfiltrateID™ utilizes the single-sample gene set enrichment analysis (ssGSEA) approach to compute transcriptome-based enrichment scores for eight distinct immune cell types from a single tumor sample, quantifying the abundance of those populations within the TME of that sample.

Figure 4: ImmunoID NeXT analytics modules provide insights into the complex and dynamic interactions between the tumor cells and immune cells of the microenvironment.

ImmunoID NeXT Analytics Modules

Once the raw, augmented genomic and transcriptomic data is generated by the NeXT Exome and NeXT Transcriptome, respectively, this data is then injected into our framework of advanced analytical pipelines to provide researchers with informative and actionable insights and reporting outputs. The ImmunoID NeXT analytical modules include:

RepertoireID

RepertoireID enables the detection of TCRα, TCRβ clonotypes and BCR heavy chain (BCRh) clonotypes, along with determining the isotype make-up of BCRs present within the TME of tumor samples. Ultra-deep RNA sequencing data derived from the NeXT Transcriptome™ facilitates the detailed profiling of the top BCR and TCR clonotypes present within a tumor sample. This analytics module generates a report with key metrics relating to TCR and BCR repertoire characteristics, such as clonality, CDR3 nucleotide and amino acid sequences, CDR3 nucleotide and amino acid sequences, clonotype quantitation, distribution, and frequency, V, D, and J gene segments usage and overlap, CDR3 nucleotide sequence length, isotype composition of BCRs, and Isotype-specific CDR3 clonal frequencies for BCRs.

ImmunoID NeXT is the first commercial platform that enables the comprehensive characterization of the immune repertoire using data derived from an augmented, broad-content platform, designed specifically to explore multidimensional oncology biomarkers.

ImmunogenomicsID

ImmunogenomicsID provides an overview of the TME and critical genes that are involved in key cancer-related functional groups including antigen processing machinery (APM), DNA repair and replication, immune checkpoint modulation, tumor associated antigens (TAAs), adaptive and innate immune response, cytokines and chemokines, and cytotoxicity. Analytics include tumor mutational burden (TMB), gene-level expression (transcripts per million or TPM), variant type, variant expression, DNA/RNA allelic fraction, and variant effect impact.

A key component of ImmunogenomicsID is the ability to identify somatic mutations occurring in the HLA and B2M genes, as well as the detection of HLA LOH; events which have emerged as potential mechanisms utilized by tumors to resist immunotherapy and combination treatment regimens.

Leveraging an advanced algorithm, ImmunogenomicsID also assesses the MSI status of a tumor

sample, highlighting the stability status of five canonical loci, as well as the exome-wide analysis of the proportion of all microsatellite loci that are found to be unstable.

Via the specific targeting of viral genomes in both DNA and RNA, this module also reports out on the presence (or absence) of viruses that are known to contribute to oncogenesis in a broad variety of cancer types. These oncoviruses include HPV, HBV, HCV, EBV, KSHV, MCV, HTLV, and CMV, and their associated genotypes and subtypes.

NeoantigenID

Neoantigens are non-self (or foreign) peptide fragments that can arise as a result of somatic alterations arising anywhere across the genome. Therefore, deep and uniform coverage (of both DNA and RNA) is critical for both comprehensive neoantigen identification and the accurate assessment of neoantigen load. ImmunoID NeXT ensures highly-sensitive variant detection via both the depth of sequencing and the augmented coverage of difficult-to-sequence regions across the entire ~20,000 gene footprint. Combined, these features reduce the chances of neoantigen-producing variants (SNVs, indels, and/or fusions) going undetected.

Personalis has developed a Systematic HLA Epitope Ranking Pan Algorithm (SHERPA™) using proprietary mass spectrometry-based immunopeptidomics data to enhance neoantigen presentation prediction based on MHC-binding potential, gene expression levels, and other key parameters. The scale and scope of SHERPA was further expanded by using a large, systematically reprocessed and curated repository of publicly available mono- and multi-allelic immunopeptidomics datasets, as well as publicly available binding affinity data. This combined approach resulted in one of the largest training datasets consisting of 180 unique human alleles. The combined approach resulted in one of the largest training datasets consisting of 180 unique human alleles. The integration of additional data from diverse cell lines and tissue types improved the generalizability of SHERPA, a critically important aspect when applying it to patient samples.

SHERPA is integrated into the NeoantigenID analytics engine for comprehensive characterization of putative neoantigens to inform the development of personalized cancer therapies and neoantigen-based composite biomarkers.

InfiltrateID

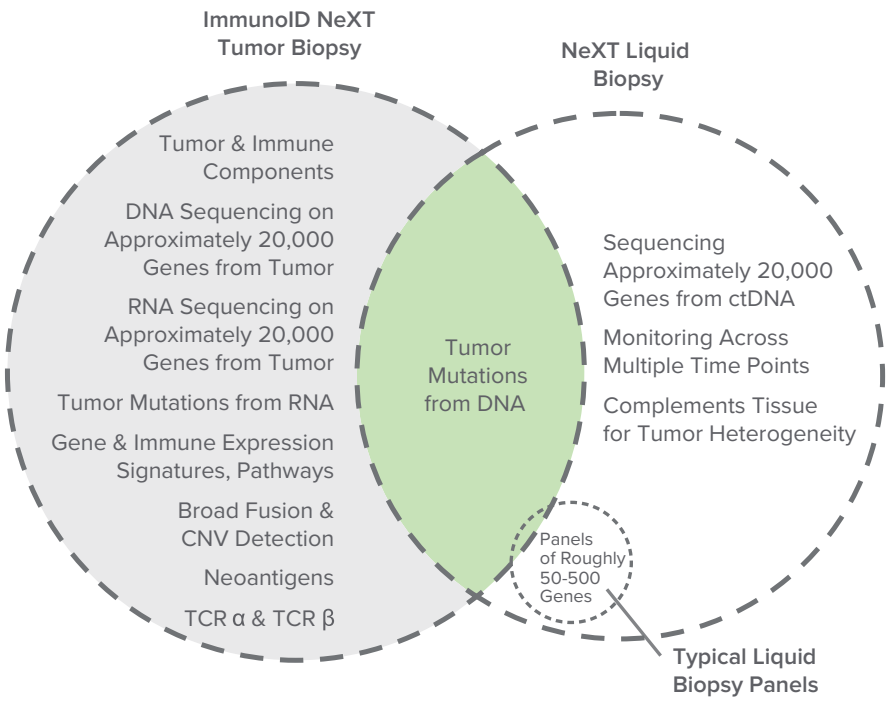
InfiltrateID leverages the augmented gene expression data derived from the NeXT Transcriptome to quantitate the presence of eight distinct immune cell populations in a single

tumor specimen. InfiltrateID utilizes the single-sample gene set enrichment analysis (ssGSEA) approach to compute transcriptome-based enrichment scores for each of the immune cell type, thereby helping to delineate the underlying Immunocellular profile within the tumor microenvironment for a given tumor sample.

NeXT Liquid Biopsy™: Complementing Tumor Tissue Profiling with Plasma-based Global Resolution

NeXT Liquid Biopsy, a first-of-its-kind, high-performance exome-wide liquid biopsy assay, is designed to complement ImmunoID NeXT, providing a unique ability to further evaluate the cancer ecosystem, and advance the development of next-generation composite biomarkers. While solid tumor biopsies remain the standard for the interrogation of the cancer genome, the advent of liquid biopsies and multi-region tissue sampling has demonstrated that there can be more to a cancer's genotypic profile than that found in a single tissue biopsy. However, the liquid biopsy alone may not capture all tumor variants if healthy cancer cells do not shed their contents into blood circulation. Therefore, the combination of NeXT Liquid Biopsy and ImmunoID NeXT delivers the most comprehensive view of a cancer's mutational landscape by evaluating both the tissue and the blood.

Figure 5



With NeXT Liquid Biopsy, researchers now have a powerful tool to: 1) Overcome challenges posed by spatial and temporal heterogeneity, 2) Monitor clonal evolution and tumor dynamics in response to personalized therapies, and 3) Interrogate mechanisms of acquired resistance at the point of progression, if they occur. NeXT Liquid Biopsy is purpose-built to navigate the inherent variability of circulating tumor DNA (ctDNA); enabling the elucidation of key areas of tumor biology not often addressed by targeted, commercially-available liquid biopsy panels.

Performance for the Present. Foundations for the Future.

Integrating a broad, exome-scale approach into your clinical and translational research will prove beneficial in the long run. ImmunoID NeXT provides comprehensive, accurate, and practically applicable genomic data at the forefront of today's immuno-oncology field, while also enabling the discovery of yet-to-be-identified biomarker signatures.

Ready to streamline your precision oncology translational and clinical programs? Contact us at info@personalis.com.

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