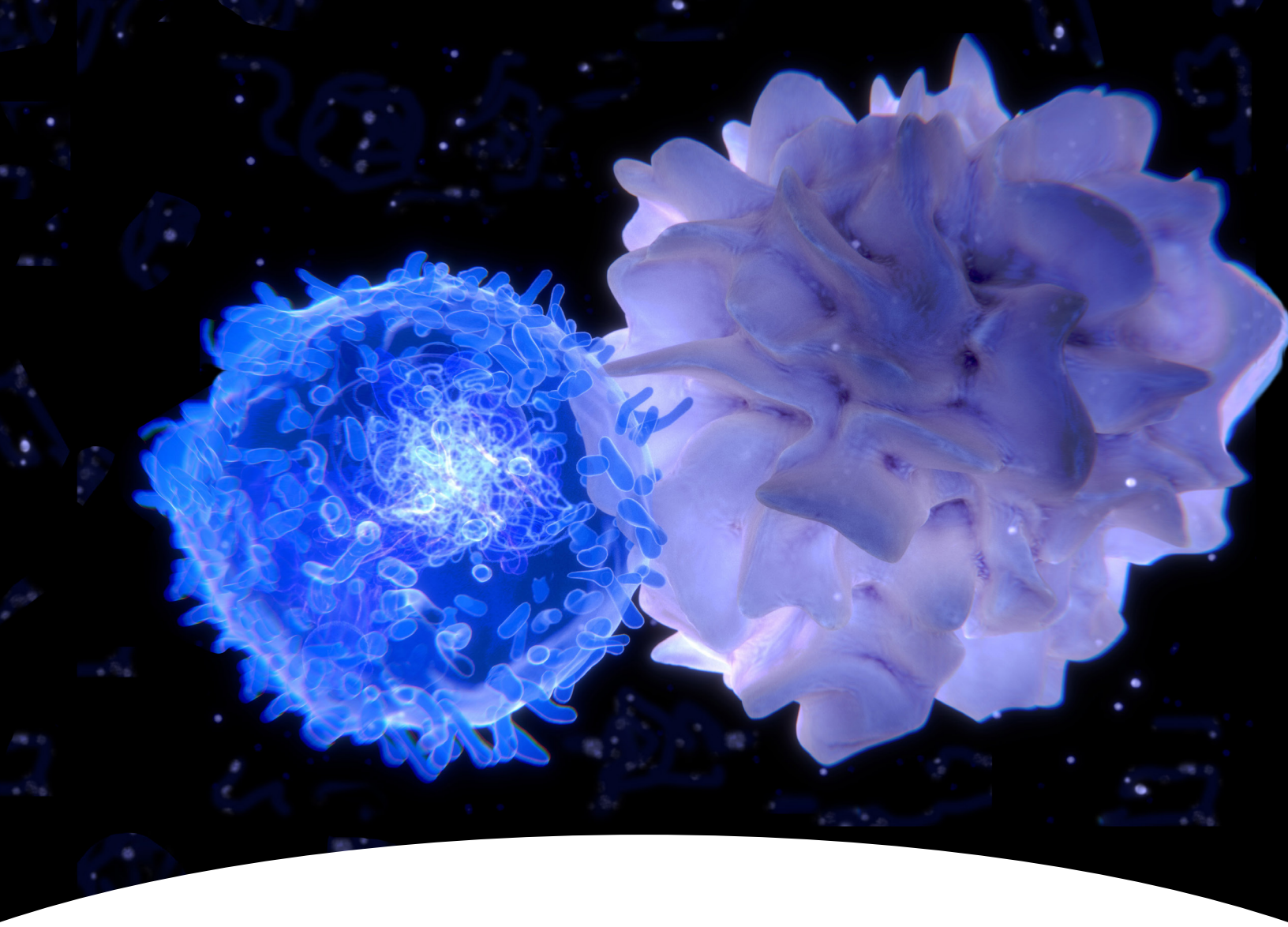


Biomarker Discovery Solutions

ImmunoID NeXT™ for Tumor Immunogenomics

Personalis®

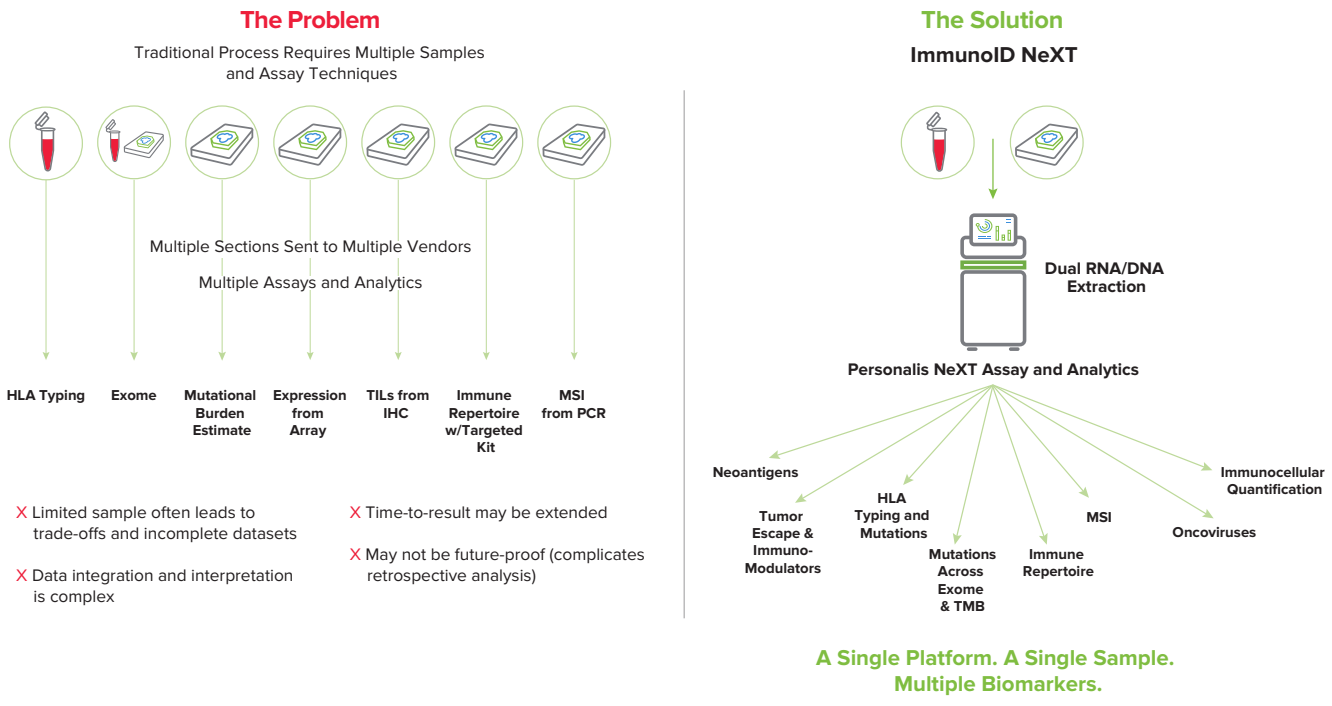
Precision Genomics for Immuno-Oncology

Personalis®

Elucidate Tumor-Immune Interactions from a Single Sample

In the immuno-oncology era, it's becoming clear that understanding and improving response to cancer immunotherapies relies on the study of the interactions between tumor cells and immune cells in the Tumor Microenvironment (TME). Traditionally, gaining molecular insights into both the tumor and the immune system has required the analysis of data derived from multiple sources, packaged in various formats. When samples are both precious and limited, researchers need a way to both simplify this process and to maximize the data generated from each individual tumor sample. This is where ImmunoID NeXT™, built on the Personalis NeXT Platform®, is designed to address these challenges.

Figure 1: ImmunoID NeXT combines multiple biomarker assays into one; simultaneously solving many logistical and technical problems for clinical trial sponsors.



Personalis, Inc.

Broad Exploration of Modern Oncology Biomarkers

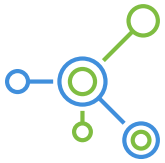
ImmunoID NeXT enables the identification of known and novel biomarkers that are predictive of resistance, response, and adverse event (AE) risk associated with modern oncology therapies.

Resistance

Response

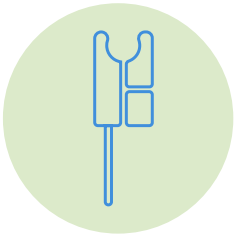
AE Risk

Composite



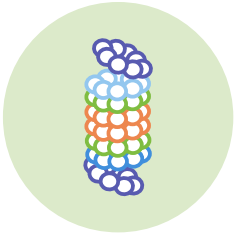
Resistance

Despite the success of Immune Checkpoint Inhibitors (ICIs), the majority of initial non-responders tend to progress at a natural rate, and a significant proportion of initial responders eventually relapse. Thus, understanding the underlying biological mechanisms of primary and acquired resistance to immunotherapy has become a major focus of the field. ImmunoID NeXT provides insight into the following known tumor escape mechanisms, while also supporting the identification of previously undefined ones.



Human Leukocyte Antigen (HLA)

Genomic alterations affecting HLA genes are a common mechanism which tumors use to evade the host's immune response, and develop resistance to immunotherapy. At Personalis, we've been pioneers in utilizing exome data and proprietary *in silico* methods to accurately genotype HLA genes, and to reliably detect somatic mutations and loss of heterozygosity (LOH) events affecting these genes – alterations that can contribute directly to a tumor's ability to evade the host's immune system.



Antigen Processing Machinery (APM)

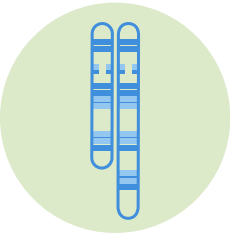
While the MHC proteins (which are encoded by HLA genes) are critical for the correct presentation of potentially-immunogenic antigens (neoantigens) on the surface of tumor cells, defects occurring in any of the upstream components of the APM can also impact a cell's ability to present such antigens for immunosurveillance.

Immune Checkpoint Modulation

Immune checkpoint inhibitors (ICIs) have transformed cancer care by blocking "checkpoint" proteins expressed on the surface of T-cells (CTLA-4 and PD-1) or by inhibiting the tumor-related ligands of these receptors (PD-L1). Based on this success, other methods of checkpoint modulation have been investigated such as targeting immunosuppressive enzymes (e.g., IDO), or activating immune effector cell receptors (e.g., OX40, 4-1BB), but these approaches have been less fruitful thus far, often due to the overexpression of immunosuppressive proteins in the TME.

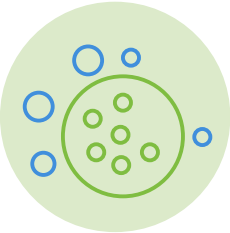
Canonical Pathways

Somatic mutations occurring in genes associated with specific cancer and/or immune-related pathways may influence the ability of tumor cells to evade the immune system. Alterations leading to the inactivation of canonical cancer pathways such as the MAPK and PI3K pathways are associated with increased resistance to ICIs, while activating mutations associated with the WNT-β-catenin and IDO1 pathways can result in the suppression of effector T-cells and Natural Killer (NK) cells in the TME (Conway et al., 2018).



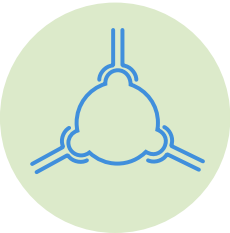
Tumor Aneuploidy

Elevated numbers of somatic copy number alterations (CNAs) are linked to tumor ICI resistance. It has been demonstrated that tumor aneuploidy can result in reduced expression of immune-related genes such as HLA, IFNγ pathway genes, chemokines, and cytolytic immune cell genes, conferring resistance in many cases (Keenan et al., 2019).



Cytokines/Chemokines

A tumor unresponsiveness to reduced expression of interferon – particularly IFNγ, which is secreted by effector T-cells – is a common mechanism of resistance to immunotherapy. Additionally, there is a strong association between cytotoxic activity and the expression of genes involved in T-cell recruitment to the tumor site including interleukins and other cytokines. ImmunoID NeXT can be used to elucidate the TME phenotype and facilitate the discovery of novel cytokine/chemokine gene expression signatures of resistance to immunotherapies and combinations.



Tumor Surface Antigen Modulation

Surface antigen modulation is a well-understood escape mechanism for immunotherapies like chimeric antigen receptor (CAR)-T-cells, monoclonal antibodies, and bispecific T-cell engagers (BiTEs) that are commonly used to treat hematologic malignancies. While it can pre-exist therapy administration owing to inherent tumor heterogeneity, therapeutic pressure can induce alternative splicing; generating antigen isoforms with disruption of the target epitope and/or reduced cell surface expression (Shah & Fry, 2019).

Mechanisms of Resistance	
Category	**ImmunoID NeXT Solutions**
Human Leukocyte Antigen	• HLA Class I and Class II germline • HLA LOH • HLA somatic mutations
Antigen Processing Machinery (Somatic mutations and gene expression)	• B2M gene • TAP1/TAP2 genes • Proteasome-related genes • Endoplasmic reticulum-related genes
Immune Checkpoint Modulation (Somatic mutations and gene expression)	• Co-inhibitory targets (e.g. PD-L1/PD-1, CTLA-4, TIGIT, LAG-3, etc.) • Co-stimulatory targets (e.g. OX40, GITR, 4-1BB, CD40, etc.) • Immunosuppressive enzymes (e.g. IDO1/IDO2, ARG1, etc.)
Canonical Pathways (Somatic mutations and gene expression)	• JAK/STAT pathway • MAPK & PI3K pathways • WNT-β-catenin pathway • IDO1 pathway • And more...
Tumor Aneuploidy	• Exome-wide CNA detection
Cytokines/Chemokines (Somatic mutations and gene expression	• Type I and type II IFN-related genes • Interleukin genes • Other cytokine/chemokine genes involved in both innate and adaptive immunity
Tumor Surface Antigen Modulation	• Transcript-specific expression (identification of alternatively-spliced variants) • Tumor surface antigen gene expression

Response

Understanding the reasons why some patients are resistant to oncology therapies is important, but, because of their potential side-effects, it is even more critical to ensure that they are only administered to patients who are expected to respond. Therefore, the identification and use of molecular markers that are predictive of response is essential in bringing the curative potential of immuno-oncology drugs to more patients.

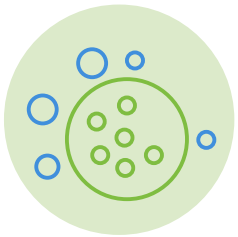
Neoantigen Load & Tumor Mutational Burden (TMB)

Despite the initial excitement surrounding the predictive potential of TMB as a biomarker of response, some setbacks have called into question whether a simple count of non-synonymous somatic mutations is biologically informative enough to help guide treatment decisions in a pan-cancer fashion. At Personalis, we believe that determining which of these mutations will be expressed as neoantigens and presented for immunosurveillance may be more suggestive of a tumor's potential sensitivity to immunotherapy.

Predictive Biomarkers of Response	
Category	**ImmunoID NeXT Solutions**
Neoantigen Load & Tumor Mutational Burden (TMB)	• Neoantigen load • TMB • NEOPS™ (Neoantigen-based composite biomarker) • Synonymous and non-synonymous SNV and indel reporting

AE Risk

For certain types of immunotherapies, the incidence of adverse events (AEs) such as cytokine release syndrome (CRS) and other immune-related AEs (irAEs) has served to temper excitement related to otherwise promising clinical outcomes. This has prompted the exploration of biomarkers that can be used to predict AE risk both before and during treatment.



Cytokine Expression Signatures

One promising approach to predicting irAE risk (particularly CRS risk in CAR-T-treated patients) is cytokine gene expression profiling. Evaluating the pattern and timing of fluctuations in cytokine gene expression prior to and over the course of therapy can help to identify at-risk patients.

Germline Genetic Variations

Germline genetic factors can influence autoimmune disease risk. Since these diseases represent common irAEs associated with ICI therapy, it's important to determine how to identify patients who are at risk of developing such complications. It has been shown that germline variants previously associated with autoimmune risk can potentially be used to evaluate susceptibility to irAEs in ICI-treated patients (Kirchhoff et al., 2017). Via germline variant reporting, ImmunoID NeXT can be leveraged to discover germline variants and variation signatures associated with AE risk.

Predictive Biomarkers of AE Risk	
Category	**ImmunoID NeXT Solutions**
Cytokine expression signatures	• Cytokine gene expression profiling • Gene and transcript-level expression to enable differential gene expression analysis
Germline genetic variations	• Germline variant analysis
Signature(s) identification	• Advanced analysis for potential signature identification

Composite Biomarkers

The use of single-analyte biomarkers (e.g. PD-L1 expression) has yielded modest results in the quest to accurately predict which patients are likely to respond (or not) to immunotherapies and their combinations with other treatment modalities. In the immunotherapy age, it's clear that more effective patient stratification techniques will require the integration of multiple biomarkers that not only molecularly profile a given patient's tumor, but that also reveal how the host's immune system is reacting to – and interacting with – that tumor.

At Personalis, we believe that such an approach will deliver the benefits of the immuno-oncology revolution to a greater proportion of patients. With the comprehensive tumor- and immune-related biomarker information that's generated by ImmunoID NeXT, we can help our biopharmaceutical partners identify composite biomarkers to improve upon the predictive power of single-analyte approaches and bring the potential of immunotherapy to more cancer patients. NEOPS™ (Neoantigen Presentation Score) is an example of how this approach is able to drive more accurate biomarkers. By accounting for tumor escape mechanisms and combining them into a composite neoantigen score, NEOPS provides a fuller representation of tumor antigen presentation to the immune system compared to simpler models. Further, NEOPS can also be clinically practical, with comprehensive tumor profiling achieved using very limited tumor tissue.

Get in Touch

To learn more about how we can help with your immuno-oncology research, contact us at info@personalis.com.

Sales Contact

United States
info@personalis.com

Europe
europe@personalis.com

Other Countries
info@personalis.com

Personalis, Inc.

1330 O'Brien Drive, Menlo Park, CA 94025
+1 855-GENOME4 (436-6634) | +1 650-752-1300
www.personalis.com

For Research Use Only. Not for use in diagnostic procedures.

Personalis®

DOC-001228(A)