

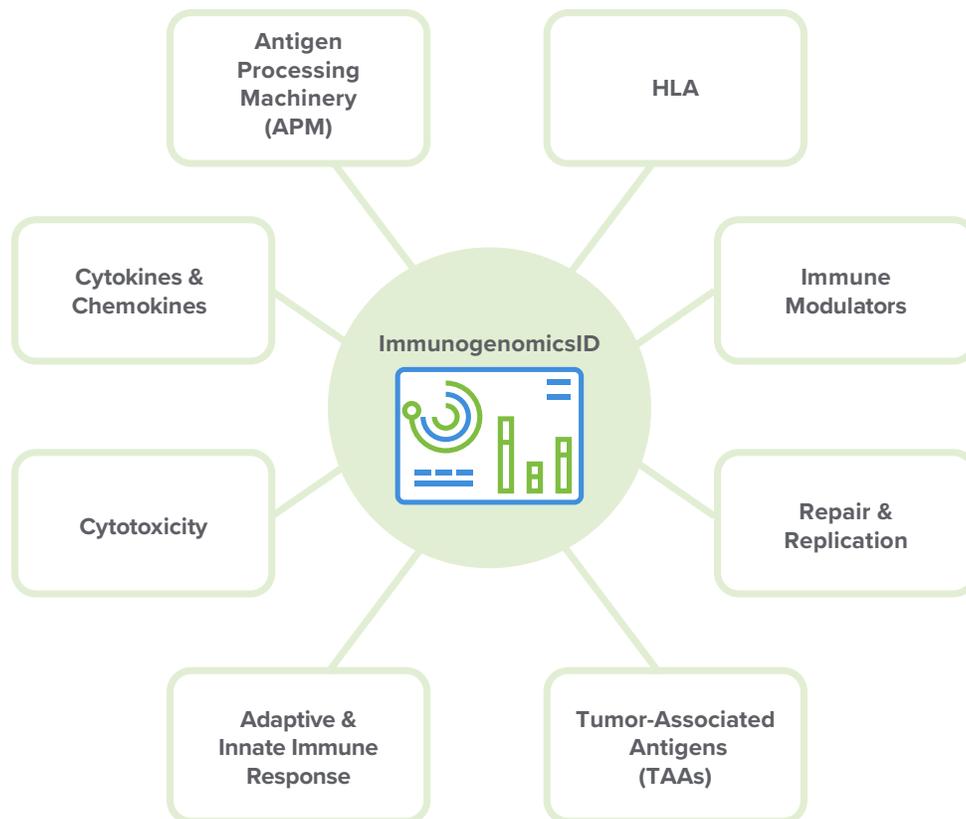
ImmunogenomicsID™

Comprehensive immunogenomic characterization

ImmunogenomicsID™, the latest analytics component of the ACE ImmunoID platform, summarizes critical areas of tumor biology such as the antigen processing machinery (APM), human leukocyte antigens (HLA), checkpoint modulation, and tumor escape.

ImmunogenomicsID combines exome and transcriptome sequencing data from a paired tumor and normal sample to generate a

comprehensive immunogenomic profile of the tumor and its microenvironment. This includes tumor mutational burden (TMB) and reporting on gene-level expression (TPM), variant type (SNVs, indels, fusions), variant expression, DNA and RNA allelic fraction (>5%), HLA Class I somatic mutation variant calls, as well as population database searches.



Antigen processing machinery (APM)

Antigenic peptides are promising targets for personalized vaccines and adoptive cell therapies. However, before these proteins are presented on the surface of tumors, they first undergo a complex journey through APM. Comprehensively characterizing the genes associated with this functional area can help to determine if somatic mutations occurring in the tumor cells will impede the cells' ability to correctly present antigens on the cell surface. Additionally, resistance to checkpoint inhibitors may be linked to defects in APM component expression. Our analytics paint the full picture of APM by capturing variant and expression data on APM genes including B2M, TAP, Proteasome, ERAP1 as well as HLA.

Human leukocyte antigen (HLA)

HLA are highly-polymorphic molecules that help the immune system distinguish self from non-self by presenting antigenic peptides to T-cells. ImmunogenomicsID identifies somatic mutations occurring in HLA Class I genes. Personalis also provides HLA typing for both HLA Class I and Class II as part of ACE Immunoid through our NeoantigenID™ analytics.

Immune modulation

Checkpoint inhibitors have transformed cancer care. Immune modulation by these therapies has been accomplished by antagonizing checkpoints expressed on the surface of activated T-cells (CTLA-4 and PD-1) or by inhibiting the ligands of these receptors (PD-L1). Additionally, other methods of immune checkpoint modulation are currently being investigated such as neutralizing immune-suppressors in the tumor microenvironment (e.g. IDO), or activating immune effector cell receptors like OX40 or 4-1BB. ImmunogenomicsID provides insights into each

of these pathways, and also includes gene and expression information on other emerging immune modulatory targets including LAG-3, TIM-3, KIR, GITR, and ICOS.

DNA repair and replication

A deficient mismatch repair (dMMR) system results in the persistence of DNA mismatches in microsatellites that may then result in somatic mutations. Tumors which have microsatellite instability (MSI) due to dMMR may exhibit the MSI-high phenotype. While conventional testing requires both IHC (for dMMR proteins) as well as PCR for microsatellite markers, ImmunogenomicsID provides gene expression data which can be used as a proxy for these assays for relevant genes such as POLE, MLH1, BRCA1, BRCA2.

Tumor-associated antigens (TAAs)

Shared antigens or TAAs are common to specific tumor lineages and can be used as targets for adoptive cell therapies and non-personalized cancer vaccines. ImmunogenomicsID includes data on critical genes associated with shared antigens including PRAME, MAGE, SSX2, MUC1, and CTAG1B (NY-ESO-1).

Adaptive and innate response

Both innate and adaptive immune response modulate tumor growth by inducing inflammation that can create an immune-suppressive or pro-tumorigenic environment. The innate immune system is the body's first line of defense because it elicits a non-specific response against any foreign particle. The cells involved with innate response initiate tissue repair, and secrete factors which can enhance tumor growth. Conversely, the cells of the adaptive immune system form a response against specific antigens.

Therapies which can stimulate tumor-specific adaptive immunity can help to counter-balance immune suppression (via cells of the innate immune system) by inducing acute inflammation and driving cytotoxic T-cells into the tumor microenvironment to eliminate cancer cells. ImmunogenomicsID reports on genes associated with both types of immune response to better understand the activity profile of the immune infiltrate through genomic and transcriptomic data on genes such as AIF1, IL2, IRF1, and VCAM1.

Cytokines and chemokines

ImmunogenomicsID reports on interleukens and chemokines to further elucidate the tumor microenvironment. Chemokines such as CXCL10, CXCL9, and CXCL11 stimulate cytotoxic activity in the immune infiltrate. Additionally, there is also a

strong association between cytotoxic activity and the expression of genes involved in attracting T-helper cells to the tumor site including interleukins and CXCL1,9,10,11, and CXCR3 among others.

Cytotoxicity

Cytotoxic factors such as granzymes (GZMs), perforin 1 (PRF1) and granulysin (GNLY) are released by cells of the immune system (e.g. NK cells or cytotoxic T-lymphocytes) and are essential for their cytotoxic activity against cancer cells. Evaluating the expression of these factors can help to determine the degree of cytotoxic activity within a tumor. ImmunogenomicsID provides information on genes such as GNLY, GZMA, GZMB, and PRF1.

ImmunogenomicsID Output Example

The partial analytics output below was generated using a lung cancer sample and integrates both DNA and RNA information for tumor immunogenomic characterization.

Gene Symbol	Common Symbol	General Category	Gene Expression (TPM)	Variant Type	DNA Allelic Fraction	RNA Allelic Fraction	Variant Effect	Variant Effect Impact
CTLA4	CTLA4	Checkpoint Modulators	19.837	SNV	0.053	_	missense_variant	Moderate
GATA3	GATA3	Adaptive Immune Response	18.215	SNV	0.108	_	splice_acceptor_variant+intron_variant	High
TGFB2	TGFB2	Cytokines	22.934	SNV	0.147	0.441	missense_variant	Moderate
POLE	POLE	Repair and Replication Defects	47.000	SNV	0.095	0.395	missense_variant	Moderate
CTNNB1	CTNNB1	Tumor Associated Antigens	657.974	SNV	0.065	0.095	missense_variant	Moderate

Get in touch

To learn more about how we can help accelerate your biomarker discovery and translational research programs, contact us at info@personalis.com.



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