NEO GENOMICS

Pharma Services

Molecular Overview

Innovative solutions for
drug development programs

Innovative solutions for drug development programs

NeoGenomics' broad molecular capabilities provide our pharma and research partners with innovative oncology solutions.

NeoGenomics Pharma Services offers our clients the most informative and state-of-the-art molecular technology platforms and services to enhance any oncology drug development program or research project. Our comprehensive molecular menu combined with our flexible, rapid assay development cycles allow us to consistently meet the demands of our customers.

Our team of expert pathologists and scientists are involved in every step of the assay development process to help ensure that each biomarker on our menu is developed to the highest standards. With a wide array of offerings spanning somatic, germline and solid tumor liquid biopsy testing, clients no longer have to worry about using multiple labs to fulfill their testing requirements. If you are looking for an actionable or fully-customizable solution, NeoGenomics Pharma Services is ready to help.

Pharma Services

Genomic Center of Excellence

The most comprehensive combination of single-gene and multi-parameter tumor profiling methodologies available

Full range of molecular diagnostic technologies including next-generation sequencing, quantitative PCR, ddPCR, NanoString™, Sanger sequencing, fragment analysis, and SNP arrays

Biomarker Discovery Applications including exome sequencing and RNA-Seq

Cell-free DNA/RNA solid tumor liquid biopsy testing capabilities useful for diagnostic screening and monitoring

LDT and FDA approved assays available for qPCR, RT-qPCR, NGS and NanoString

All complementary testing methods including central pathology review, cytogenetics, FISH, flow cytometry, IHC are conducted in one lab to conserve tissue from small specimens and minimize TAT

Pharma Services supporting IVD manufacturers, pharmaceutical companies, and the biotechnology industry

Partner in every phase of the development pipeline using our experience with proof of concept studies, assay development and optimization, as well as Phase I - III clinical trials and companion diagnostics

Geonomic Services at NeoGenomics

Benefits & Highlights:

- **Clinically optimized profiles** for actionable and wide-spectrum analysis
- **Broadest selection of NGS gene panels for heme and solid tumor variant discovery available in the U.S.**
- **Comprehensive bioinformatics services:** IT professional services, data analysis services, bioinformatics consulting, systems pathology (imaging and genomics data) and data storage
- **Can be combined with industry leading pathology services** like histology and tumor enrichment by macrodissection
- **Fast and secured** NGS data transfers
- **Industry-leading TATs**.

Testing Services:

- Clinical and exploratory genomics assays
- 275 gene NGS for solid tumors and blood cancer
- 322 gene NGS for solid tumors
- Tumor Mutational Burden (TMB)
- Whole exome sequencing – tumor and germline (normal)
- Whole genome sequencing
- Solid tumor liquid biopsy by NGS
- Single and multi-sample analysis
- Nucleic acid extraction
- NGS library prep and QC
- Custom analysis
- Sanger confirmation
- Oncomine™Dx
- RNAseq - Whole transcriptome and Exome
- NanoString gene expression panels
- T-Cell receptor sequencing
- NeoAntigens
- Microbiome Analysis

Specimen Types:

- Fresh tissue, blood, bone marrow, plasma
- FFPE
  Sample Type:
- DNA/cDNA
- RNA
- Total nucleic acid

Platforms:

- MiSeq, NextSeq 500, HiSeq 4000, NovaSeq 6000
- Ion Torrent® PGMDx
- Ion S5™ and Ion Chef™
- ddPCR
- NanoString nCounter®
- ABI 3730xl
- Rotorgene Q MDx
- Cobas Z480
- QuantStudio™ 7

Enterprise Level Computing Environment:

- Easy and powerful bioinformatics
  - — Complimentary access to high performance computing cluster and advanced suite NGS tools
  - — Enables customer and project specific requirements
  - — Custom filters: e.g., artifact scrubbing filters, clinically relevant variants
- Increased Annotation: Annotation from custom database of 1000s of targeted mutations
- Simultaneous reporting of indels and CNVs
- Advanced quality control reporting available for each sample

Enriched Bioinformatics Services:

- Application-specific data analysis, including exome, whole-genome, and whole transcriptome RNA sequencing
- Custom data analysis tailored to your needs with clinical-style reporting available
- Advanced statistical analysis of variants available
- Experimental design
- Custom panel design
- Variant caller optimization
- Tumor/normal tissue comparison
- Time based analysis
- Differential expression analysis
- Insertion site ID
- Bioinformatic tools

Data Storage Solutions:

- Custom lab data storage consultation and hardware integration
- Data transfer and security consultations

Data Delivery:

- BAM files
- FASTQ files
- VCF files
- Mutation summary documents
- QC reports
- Data transfers through a secured FTP portal or password protected hard drive
- Custom data delivery also available

NeoLAB®
Solid Tumor Liquid Biopsy

NeoGenomics offers solid tumor liquid biopsy testing with the NeoLAB® Solid Tumor Liquid Biopsy Cell-Free Assay. This comprises a panel of 44 clinically relevant genes for SNVs and indels.

Target Information

Assay	Target	Unique Genes	DNA	RNA
Oncomine Pan-Cancer Cell-Free Assay	TNA (DNA + RNA)	52	50	12

Hotspot Genes		Tumor Suppressor Genes	Copy Number Genes	Gene Fusions
AKT1	HRAS	APC	CCND1	ALK
ALK	IDH1	FBXW7	CCND2	BRAF
AR	IDH2	PTEN	CCND3	ERG
ARAF	KIT	TP53	CDK4	ETV1
BRAF	KRAS		CDK6	FGFR1
CHEK2	MAP2K1		EGFR	FGFR2
CTNNB1	MAP2K2		ERBB2	FGFR3
DDR2	MET		FGFR1	MET
EGFR	MTOR		FGFR2	NTRK1
ERBB2	NRAS		FGFR3	NTRK3
ERBB3	NTRK1		MET	RET
ESR1	NTRK3		MYC	ROS1
FGFR1	PDGFRA			
FGFR2	PIK3CA			
FGFR3	RAF1			
FGFR4	RET			
FLT3	ROS1			
GNA11	SF3B1			
GNAQ	SMAD4			
GNAS	SMO			

Note: Testing is provided for solid tumor profiling only. Please do not submit samples from patients with hematological disorders.

Assay requires whole blood collected in 2 x 10mL Streck Cell-Free DNA BCT tubes. NGS results in 7 days from specimen receipt at NeoGenomics. 2 x 10mL Streck Cell-Free DNA BCT tubes. Please reach out to a NeoGenomics' Pharma Services representative for more details as well as assay performance data.

Molecular Applications

1 **Whole exome sequencing** of the tumor as well as matched normal from peripheral blood. Non-synonymous mutations, or those that translate into a non-native protein sequence are identified. Those that are present in normal tissue, are filtered out as they are not recognized to be foreign.

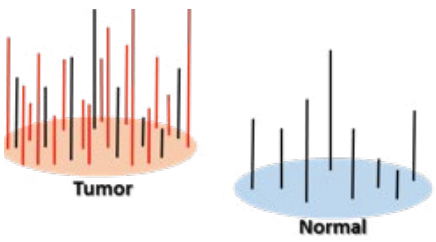
2 **Whole transcriptome sequencing** of the tumor tissue. The non-synonymous tumor specific mutations that are transcribed at high levels are identified by RNA-Seq. They are most likely to be presented on the cell surface for immune system recognition.

3 **HLA typing** – Four digit resolution obtained from whole exome and/or transcriptome data.

1

Whole Exome Sequencing

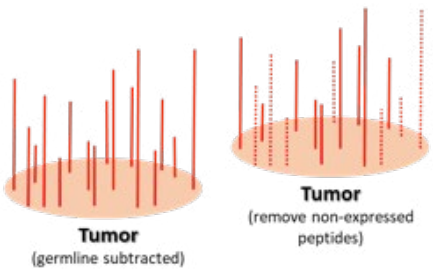
of tumor and matched normal specimens allows for identification of tumor specific somatic mutations in protein coding regions of the genome (red bars). The products of tumor specific somatic mutations are candidate neoantigens that can be potentially recognized by the host immune system.



2

RNA Sequencing

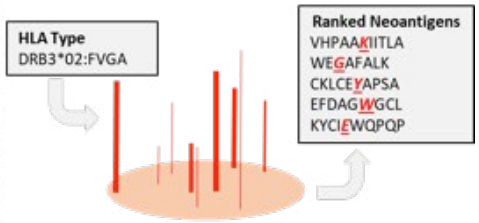
of the tumor's transcriptome allows for effective identification of expressed mRNA for candidate neoantigens (solid red bars). Non-expressed mutations are removed as they are not viable targets (dotted red bars) for the immune system.



3

HLA Typing

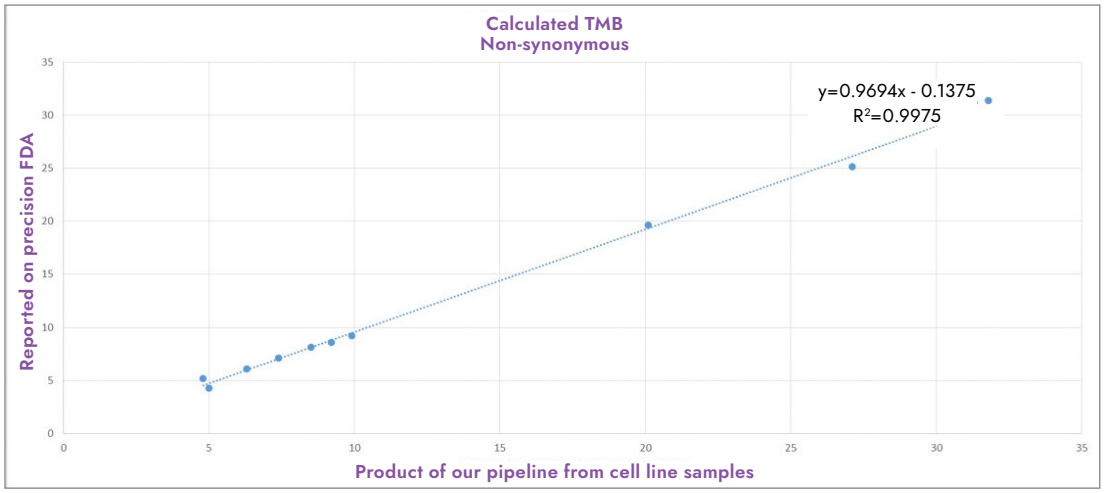
using NGS allows for identification of Class 1 and Class 2 by information recognition to 4 digit resolution. With this information, prediction algorithms are used to stack rank the highly expressed and strongest HLA binding peptides containing tumor specific mutations.



Molecular Applications

Tumor Mutational Burden (TMB)

Mutational burden is defined as the fraction of non-synonymous mutations within protein coding sequences of the genome. Studies support that tumors with high mutational burden may be predictive for patient response to immunotherapy treatments making it a clinically relevant biomarker for oncology. NeoGenomics offers both direct and indirect assessment of a tumor's mutational status using various techniques.



Direct

- **Whole exome sequencing** – offers more precise TMB quantification than large gene panels which extrapolate from sequencing a subset of genes in the genome. WES also offers the added benefit of interrogating HLA as well as other relevant loci that are not normally captured in gene panels which recently have shown to be of interest in the IO field. NeoGenomic's TMB by WES workflow consists of:
  - Tumor WES — FFPE tumor samples are enriched for tumor, DNA extracted and whole exome sequenced at 10 Gb to identify non-synonymous mutations. At this depth of sequencing, ~5% mutations can be effectively identified within all protein coding sequences.
  - Normal WES — matched patient normal FFPE tissue or peripheral blood. Whole exome sequencing at 5 Gb of normal input establishes a matched control for precise quantitation of TMB for each patient's tumor.
  - Quantitative results are # mutations (non-synonymous) per megabase (10^6 bases) of sequence.
- **Optionally, tumor RNA-Seq transcriptome and expression analysis** – provides an expressed mutational burden value which may be useful in predicting neoantigen levels.
- **Comprehensive Gene Panel** – FFPE tumor samples are processed using a CLIA/CAP validated NGS panel of 320+ genes. Results are reported as qualitative and quantitative TMB results. Quantitative results are expressed as # mutations (non- synonymous) per megabase (10^6 bases) of sequence. Sequencing of matched normal sample is not required for this assay.

InDirect

- Microsatellite Instability (MSI) – Microsatellite instability is indicative of deficiencies in DNA repair pathways and correlate with increased TMB. NeoGenomics MSI assay evaluates mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) using fragment analysis to establish MSI status. Both tumor and matched normal samples (FFPE or peripheral blood) are required.

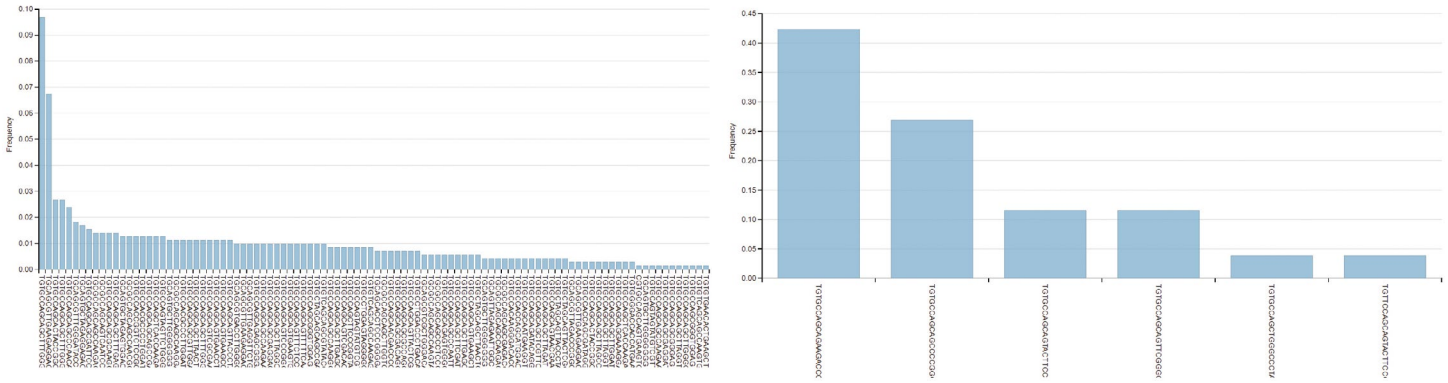
NOTE: MMR IHC is also offered at NeoGenomics. Please contact us for more information.

Molecular Applications

Tumor Microenvironment: T-Cell Receptor Sequencing — Diversity and Clonality

T-cell receptor sequencing by NGS allows for diversity and clonality characterization of a patient's T-cell population. Diversity can be understood as the number of unique T-cell clones whereas clonality is an evaluation of the relative amount of each clone in the sample. TCR sequencing has recently been utilized for profiling the T-cell landscape present within the tumor microenvironment and results support that different T-cell profiles are informative to response and survival. Especially, the presence of Tumor-infiltrating lymphocytes (TIL) is often associated with better clinical outcomes.

NeoGenomics offers RNA and DNA based TCR repertoire profiling via next generation sequencing. Diversity and Clonality of TCR Repertoire in Tumor Microenvironment:

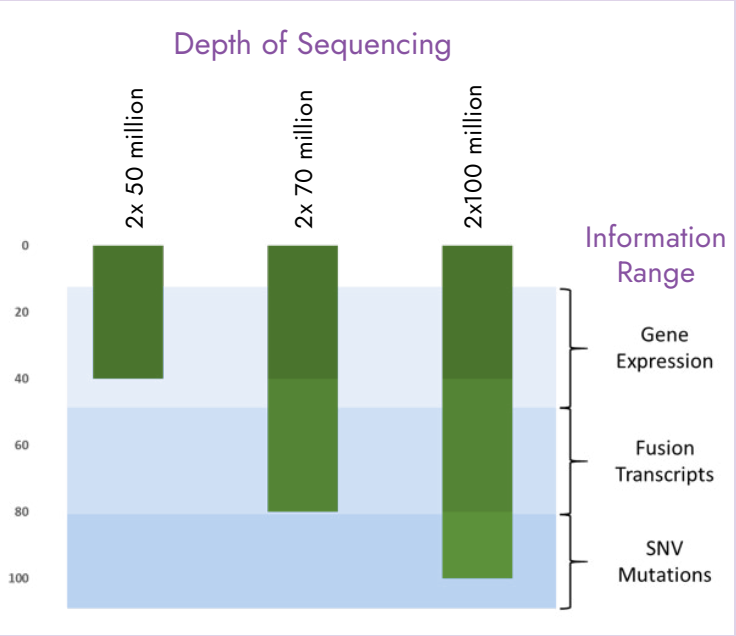


Biomarker Discovery:

Whole Transcriptome RNA-Seq

When the goal is to understand the pathways involved in a clinical phenomenon, whole transcriptome sequencing is often the first step. Being a non-hypothesis driven approach, RNA-seq is a versatile tool for unbiased characterization of the biology as well as discovering the breadth of potential biomarkers. NeoGenomics standard RNA-seq workflow, sequences samples on Illumina's HiSeq 4000 at 50 million reads (2 x100bp pair end reads) read depth to generate gene expression profiles which can be used for differential cohort expression analysis.

Sequencing deeper to 2 x 70 million (100bp length) or 2 x 100 million (100bp length) reads allows for identification of novel transcript fusions and SNV mutations. After identification of novel biomarkers by RNA-seq, the next step is to verify and create a focused clinical testing assay.



PanCancer IO 360

Gene Expression Panel

The NanoString PanCancer IO 360 Gene Expression Panel is a 770 gene CodeSet that is designed for profiling tumor biopsies and characterizing gene expression patterns associated with the tumor, the immune response, and the microenvironment which shape tumor-immune interactions.

The panel contains 48 gene signatures which describe key aspects of immuno-oncology to aid in sample characterization. Among these 48 gene signatures is the Tumor Inflammation Signature (TIS) which is an 18-gene signature that measures pre-existing, peripherally suppressed adaptive immune responses in the tumor. The TIS algorithm measures the geometric mean of a set of 10 housekeeping genes for the calculation of the TIS score.

Tumor Immunoge-nicity	Tumor Sensitivity to Immune Attack	Inhibitory Immune Mechanisms	Stromal Factors	Inhibitory Metabolism	Anti-Tumor Immune Activity	Inhibitory Immune Signaling	Immune Cell Population Abundance	
Antigen Processing Machinery	Apoptosis	IDO1 Gene Expression	Endothelial Cells	Glycolysis	Tumor Inflammation Signature (TIS)	CTLA4 Gene Expression	B Cells	NK CD56dim Cells
Antigen Presenting Machinery Expression Loss	Tumor Proliferation	PD-L1 Gene Expression	Stromal Tissue Abundance	Hypoxia	Cytotoxicity	IL10 Gene Expression	CD45+ Cells	Natural Killer Cell Abundance
Immuno-proteasome	JAK-STAT Pathway Gene Expression Loss	B7-H3 Gene Expression			Interferon Gamma Signaling	Inflammatory Chemokines	CD8 T Cell	T Cells Abundance
MAGE Genes Expression		TGF-Beta Gene Expression			Interferon Signaling Response	Myeloid-Derived Inflammatory Signaling	Cytotoxic Cells	TH1 Cell (TBX21/T-bet) Expression
Loss of Mismatch Repair Gene Expression					Lymphoid Compartment Activity	PD-1 Gene Expression	Dendritic Cells	Treg (FOXP3 Expression)
Hypermutation					MHC Class II Antigen Presentation5	PD-L2 Gene Expression	Exhausted CD8 Cell	
MSI Predictor					Myeloid Compartment Activity	TIGIT Gene Expression	Macrophage	
						ARG1 Gene Expression	Mast Cells	
						NOS2 Gene Expression	Neutrophils`	

Tumor Inflammation Signature Genes

CCL5	CD8A	STAT1	PD-L2/PDCD1LG2	HLA-DQA1	HLA-DRB1
CXCL9	CXCR6	TIGIT	PD-L1/CD274	HLA-E	CMKLR1
CD27	IDO1	LAG3	CD276	PSMB10	NKG7

PanCancer IO 360

Gene Expression Panel

The PanCancer IO 360 Gene Expression Panel and TIS readout has been analytically validated at NeoGenomics Laboratories for testing of solid tumor FFPE samples. Some of the tumor types included in the validation were:

- Melanoma
- Head and Neck
- Colon cancer
- Endometrial
- Non-small cell lung carcinoma (NSCLC)
- Ovarian
- Prostate, kidney, bladder

RNA extraction is validated for the RNeasy FFPE Kit (Qiagen) and AllPrep DNA/RNA FFPE Kit (Qiagen). RNA input is recommended at >=100 ng but can be as low as 50 ng.

For assay details or validation information, please inquire with a NeoGenomics Pharma Services representative.

Specimen Input Requirements

	Whole Genome Sequencing	Whole Exome Sequencing	Targeted Gene Panel Sequencing
DNA**	≥ 200ng	≥ 200ng	10ng - 250ng
RNA**	Not Applicable	Not Applicable	Not Applicable
Cell Pellets	1 million cells	1 million cells	1 million cells
Fresh/Unfexed Tissue	>0.2 cm3	>0.2 cm3	>0.2 cm3
FFPE Tissue	5-10 slides cut at 5um	5-10 slides cut at 5um	5-10 slides cut at 5um
Bone Marrow Aspirate	EDTA 2ml (Purple Top)	EDTA 2ml (Purple Top)	EDTA 2ml (Purple Top)
Peripheral Blood	EDTA 5ml (Purple Top)	EDTA 5ml (Purple Top)	EDTA 5ml (Purple Top)
PAXgene Tube	1 tube	1 tube	1 tube

	Microbiome 16s Sequencing	Whole Transcriptome Sequencing	TCR Sequencing	NanoString
DNA**	1ng - 10ng	Not Applicable	Not Applicable	Not Applicable
RNA**	Not Applicable	≥ 100ng	20ng - >400ng	50ng - 250ng
Cell Pellets	Not Applicable	1 million cells	1 million cells	1 million cells
Fresh/Unfexed Tissue	Not Applicable	>0.2 cm^3	>0.2 cm^3	>0.2 cm^3
FFPE Tissue	Not Applicable	5-10 slides cut at 5um	5-10 slides cut at 5um	5-10 slides cut at 5um
Bone Marrow Aspirate	Not Applicable	EDTA 2ml (Purple Top)	EDTA 2ml (Purple Top)	EDTA 2ml (Purple Top)
Peripheral Blood	Not Applicable	EDTA 5ml (Purple Top)	EDTA 5ml (Purple Top)	EDTA 5ml (Purple Top)
PAXgene Tube	Not Applicable	1 tube	1 tube	1 tube

**The actual sample requirement depends on the sample quality and kits to be used for particular applications.

About NeoGenomics Pharma Services

NeoGenomics' Pharma Services unifies several innovative companies' scientific and medical leadership under one leading brand, offering one of the most comprehensive laboratory services menu available for biomarker testing supporting oncology clinical trials globally. We provide our clients with an unparalleled level of expertise, service, flexibility, and scalability. Additionally, we offer alternative business models and solutions across the continuum of development from pre-clinical research and development through commercialization.

To learn more about NeoGenomics Pharma Service, visit us online at https://neogenomics.com/pharma-services.

NeoGenomics Pharma Service can be your right research partner with NGS or other innovative services. Please contact NeoGenomics Pharma Service at 800.720.4363 or email at pharmaservices@neogenomics.com.

NeoGenomics Laboratories is a specialized oncology reference laboratory providing the latest technologies, testing, partnership opportunities, and interactive education to the oncology and pathology communities. We offer the complete spectrum of diagnostic services in molecular testing, FISH, cytogenetics, flow cytometry, and immunohistochemistry through our nation-wide network of CAP-accredited, CLIA-certified laboratories.

Committed to research as the means to improve patient care, we provide Pharma Services for pharmaceutical companies, in vitro diagnostic manufacturers, and academic scientist-clinicians. We promote joint publications with our client physicians. NeoGenomics welcomes your inquiries for collaborations. Please contact us for more information.

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