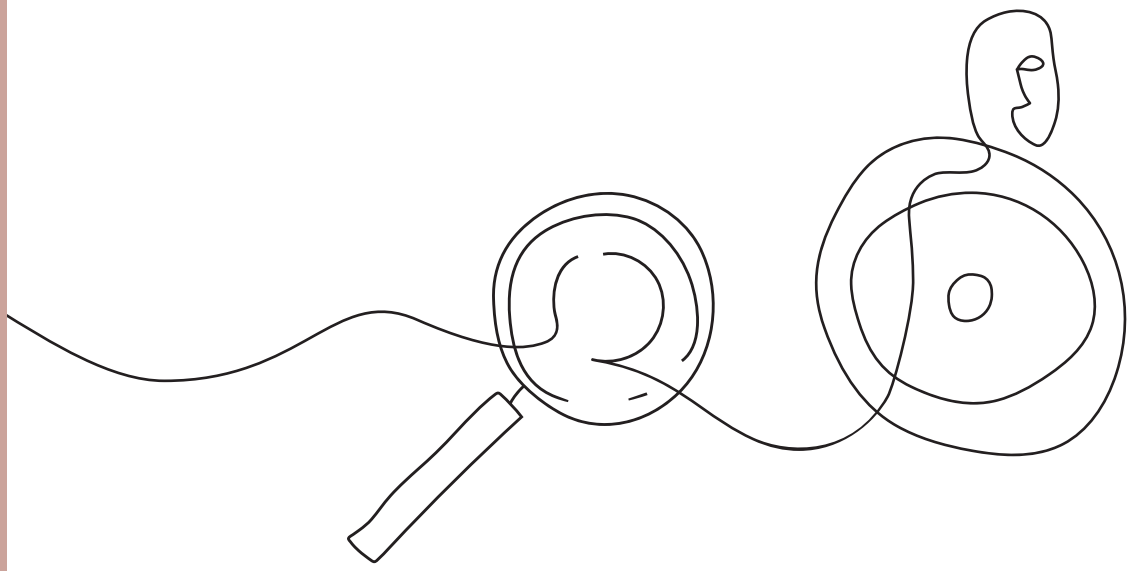
prime DX

PRECISION INDIVIDUALIZED MEDICINE

Physician's Booklet



Genekor

Committed to Biotechnological Innovation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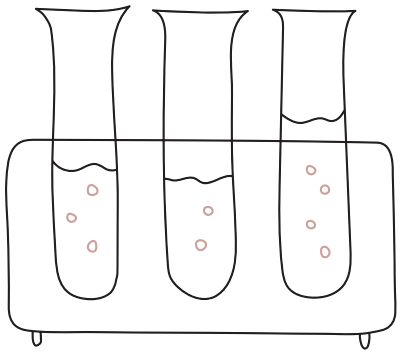
The prime DX new technology for tumor molecular profiling is compatible with FFPET, as well as PLASMA.

In the modern landscape of precision medicine, identifying the genetic mutations that drive disease is critical to providing effective, targeted therapies. Prime DX tests are designed to give the physician a comprehensive outlook on treatment options related to

» Targeted therapy
» Immunotherapy
» Chemotherapy



Clinical Application	Type of Drugs	Indicator	Indicator Dimension
1. Prediction for **Targeted Treatments**	**171 different treatments**	Target point mutation (Tissue/blood) (eg: *EGFR L858R, EGFR* exon 19 Del, etc.)	Somatic variation ---------- Germline variation (liquid)
2. Prediction for **Immunotherapy**	**11 different treatments**	TMB/MSI/PD-L1 amplification/PBRM1 negative mutation	Somatic variation
3. Prediction for **Chemotherapy**	**23 different treatments**	Pharmacogenomics site (eg: rs8175347 of UGT1A1 relating to Irinotecan)	Germline variation

Prime DX is a 1021-gene NGS panel, where 36 of these are HR genes.

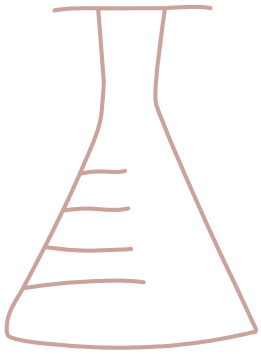
The test also includes:

Immunotherapy Biomarkers

- TMB
- MSI
- HLA

PARP Inhibitors Biomarkers

- Genomic instability analysis



IHC Biomarkers

- PD-L1
- HER2
- FRα
- CLDN18.2
- c-MET

Agnostic Markers

- NTRK1,2,3
- RET Fusions
- BRAFV600E Mutation
- HER2 Amplification

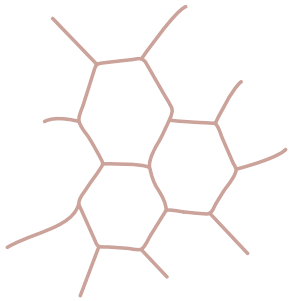
Targeted Therapies

- TMB
- MSI

Immunotherapies

It is one of the most detailed, sensitive and specific tests for tumor biology configuration, enabling physicians to **plan an efficient treatment strategy for the patient, including immunotherapy, chemotherapy, PARP inhibitors and clinical trial participation compatibility.**

Prime DX test is recommended in the following cases:



» Tumors with no standard treatment available

» Patients with advanced solid tumors

» Second-line or post-line treatment

» Rare Tumors

» Tumors of unknown primary origin

» Tumors with many available treatment options, where the physician must clarify the most effective one based on the individual tumor profile of each patient.

Also,

» For the identification of immune response biomarkers, in order to predict if an immunotherapy plan would be a suitable plan or/and in order to create an efficient immunotherapy plan.

The selection basis of the 1021 gene list is based on:

✓ NCCN guidelines + FDA + EMA
✓ Authoritative international public database

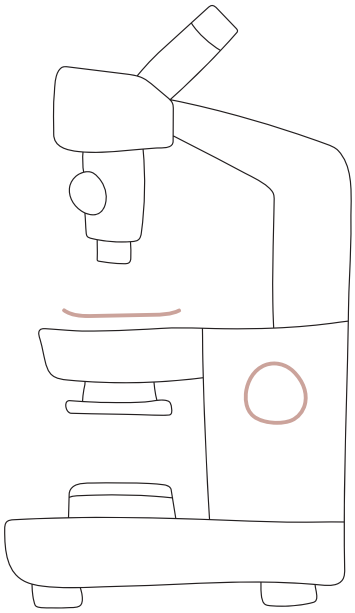
- No. of genes: **1021 genes**
- Target size: **1.6 Mb**
- Target regions:

✓ **Whole exons**
- 4847 exons of **312 genes**

✓ **The region of introns, promoters and fusion breakpoints**
- **38 genes:** 54 intronic regions of 26 genes + breakpoint regions of 12 genes

✓ **Promoter region or other non-coding region**
- *TERT, PMS2, BCL2L11*

✓ **Coding regions**
- 1778 coding regions of **709 genes**



prime DX Liquid
PRECISION INDIVIDUALIZED MEDICINE

Molecular Profiling of the tumor using liquid biopsy

Having the option of performing prime DX on liquid biopsy samples, provides a more rapid and clinically actionable tool to the treating physician to assess the tumors' molecular profile and to identify the most effective treatment.

Genekor's **prime DX® Liquid**, encompasses the same biomarkers tested in FFPET (except PD-L1 and LOH) and utilizing our advanced platform, analyzes both cell-free DNA and DNA extracted from whole peripheral blood.

This approach enables germline testing for 49 genes (Table 1) and effectively filters out CHIP (clonal hematopoiesis of indeterminate potential) mutations from the analysis, ensuring more accurate and comprehensive results.

Germline Gene Analysis

prime DX Liquid, also, analyzes genes involved in the genetic predisposition to cancer, giving information to the physician about the probability of a hereditary cancer syndrome.

Table 1

49 genes analyzed for germline mutations									
APC	*ATM*[1]	*ATR*[1]	*AXIN2*	*BAP1*[1]	*BARD1*[1]	*BLM*[1]	*BMPR1A*	*BRCA1*[1,2]	*BRCA2*[1,2]
BRIP1[1]	*CDH1*	*CDK4*	*CDKN2A*	*CHEK2*[1,2]	*EPCAM*[2]	*FAM175A*[1]	*FANCA*[1]	*FANCL*[1]	*FANCM*[1]
GALNT12	*HOXB13*	*MEN1*	*MITF*	*MLH1*	*MRE11*[1]	*MSH2*[2]	*MSH3*	*MSH6*[2]	*MUTYH*[2]
NBN[1]	*NF1*	*NTHL1*	*PALB2*[1,2]	*PMS2*	*POLD1*	*POLE*	*PTEN*	*RAD50*[1,2]	*RAD51B*[1]
RAD51C[1,2]	*RAD51D*[1,2]	*RET*	*RNF43*	*SMAD4*	*SMARCA4*	*STK11*	*TP53*[2]	*VHL*	

Note:

1. *Genes of the homologous recombination (HR) complex*
2. *Unless otherwise noted analysis of large rearrangement was performed on the following genes: BRCA1, BRCA2, CHEK2, EPCAM (Exons 8, 9), MLH1, MSH2, MSH6, MUTYH, PALB2, RAD50 (Exons 1, 2, 4, 10, 14, 21, 23 and 25), RAD51C, RAD51D, and TP53*

Prime DX Liquid is recommended in the following cases:

- When there is not enough FFPE tissue or recent biopsy
- When the quality of the tissue is poor (ex. bone biopsy)
- When there is a metastatic and / or multifocal disease
- To evaluate patient's response / resistance to treatment
- When the patient relapses and there is a need to analyze the molecular profile with no recent biopsy available

Several studies in solid tumors support that the concurrent use of both methods (tissue + liquid biopsy) represents the optimal approach in clinical practice.

prime DX
PRECISION INDIVIDUALIZED MEDICINE
COMBO

"Revolutionizing Precision Medicine: Dual Testing for Comprehensive Molecular Profiling"

GeneKor's prime DX® Combo enables the simultaneous testing of FFPE tissue and liquid biopsy samples, providing a comprehensive molecular profile by exploiting the advantages of both procedures.

Why Choose Simultaneous Tissue and Liquid Biopsy Testing?

By integrating both approaches, clinicians gain a more comprehensive understanding of a patient's tumor biology resulting in better-informed treatment decisions. Concurrent testing can lead to :

- **faster turnaround time, enabling patients to receive timely the preferred treatment**
- **increased diagnostic accuracy by enhanced sensitivity of mutation detection, hence reducing false negative results.**

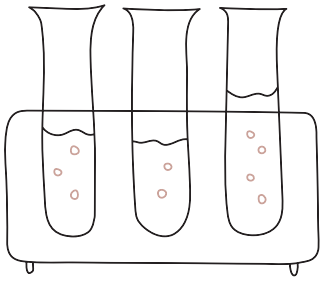
Our Technology & Expertise

State-of-the-Art Testing Platforms: Utilizing cutting-edge Next Generation Sequencing and both commercially available and proprietary bioinformatics tools, our simultaneous testing approach ensures precise, reliable, and comprehensive data.

Experienced Scientific Team: Our team of molecular scientists are experts in translating genomic data into actionable insights that guide and optimize personalized treatment approaches.

"Two Perspectives, One Powerful Profile: Uniting Tissue and Liquid Biopsy for Precision Care."

primeDX Gene Panel



Why is the NGS analysis of multiple genes necessary?

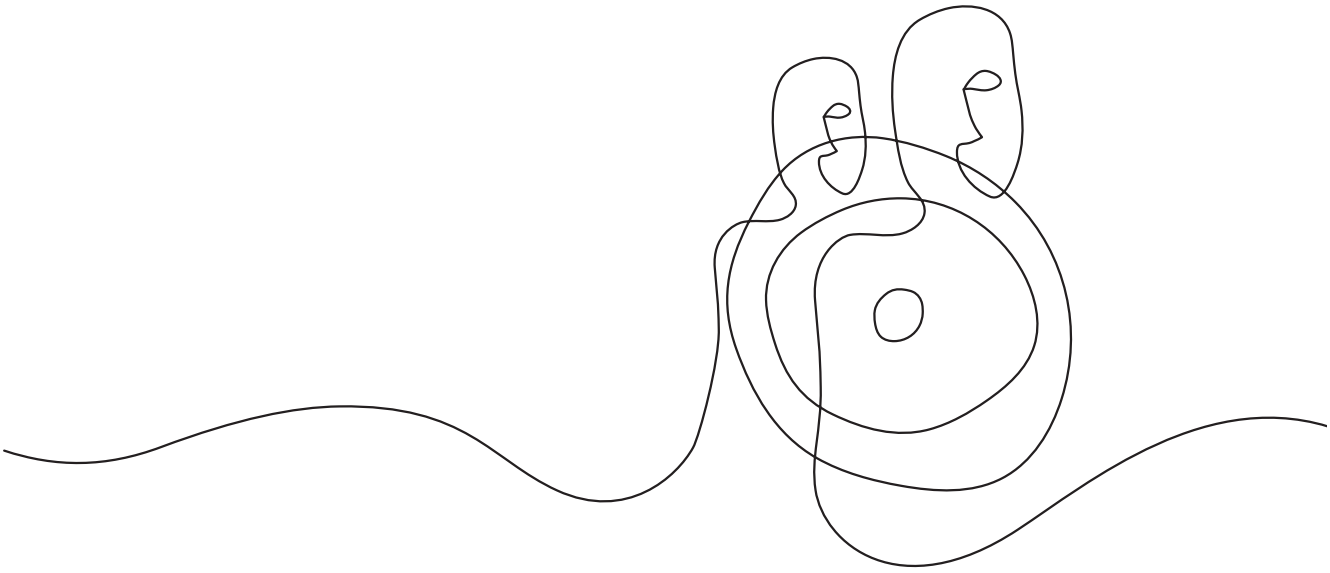
- Quantity and quality of information
- Reduced time
- Reduced cost

A multi-gene panel results in the production of a large volume of multilevel information useful for individualized treatment of patients. Thus, it increases the likelihood of finding a therapeutic target for a patient with on-label treatment, off-label treatment and/or participation in clinical trials, using minimum amount of tissue or a liquid biopsy sample and analyzing several genes simultaneously, faster and at lower cost.

The Technology

The **PrimeDX assay** holds CAP accreditation and is accredited under the terms of **ELOT EN ISO 15189:2022**, ensuring the highest standards of quality and reliability in comprehensive biomarker testing across key approved biomarkers, including BRCA1/2, EGFR, KRAS, KIT, PDGFRA, FGFR2, and more.

Sequencing is performed using the MGI DNBSEQ-T7 and MGI DNBSEQ-G400 NGS platforms, both CE-IVD certified systems that enable the simultaneous processing of multiple samples with high sensitivity and specificity, delivering faster and more reliable results at a lower cost.



Clinical value	Biomarker	1021 Panel	Level of Evidence	Source of evidence
Targeted therapies	"EGFR, ROS1 , MET, ALK , RAS, BRCA1/2 , FGFR2/3 , RET, NTRK1/2/3, IDH1 , ERBB2, BRAF, KIT, PDGFRA, PIK3CA, HRR gene ESR1, PTEN, AKT1"	YES	Strong	FDA / NCCN
	Genomic Instability Analysis *FFPE samples only	"YES, Results include LOH, LST, TAI for ovarian cancer patients"		
Chemotherapy drugs	19 polymorphism variants related to chemotherapy drugs	YES	Moderate	"J Clin Oncol. 2020 Feb 20;38 (6): 548-557"
Immunotherapy	TMB / MSI (Pan - cancer)	YES	Strong	FDA / NCCN
	HLA type (Pan - cancer)	YES	Moderate	"Science. 2018 Feb 2;359 (6375): 582-587"
	Biomarkers affecting the immunotherapy treatment response (reporting on positive & negative correlations).	46 genes with positive and negative correlation	Moderate	"Ferdinandos Skoulidis 2019 ASCO Abstract 102, ESMO 2017 Abstract # 1138"

Add-on Options

Immunohistochemistry assays can be ordered as an add-on with Prime DX

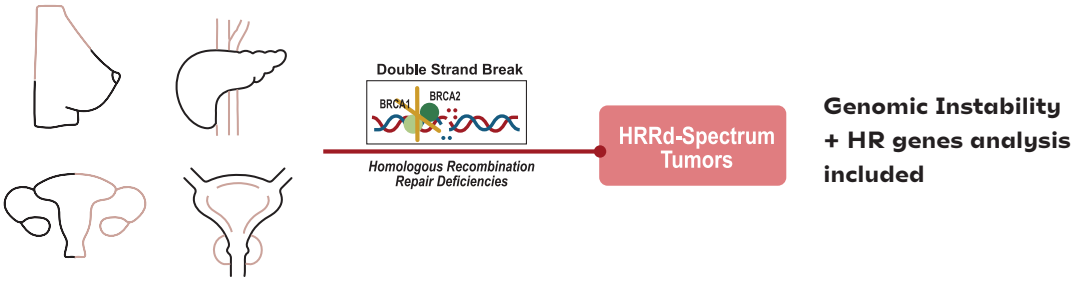
Clinical value	Biomarker	Tumor type	Level of Evidence	Source of evidence
Targeted therapy	HER2	Pan-cancer	Strong	FDA
	FRa	Ovarian	Strong	FDA, EMA
	CLDN18.2	Gastric	Strong	FDA, EMA
Immunotherapy	PD-L1	Pan-cancer	Strong/Moderate	FDA
IHC BIOMARKERS	C-MET	Lung	Strong/Moderate	FDA

Enhancing prime DX test with HRD testing

To optimize Treatment Decisions Through Comprehensive Genomic Insight

Homologous Recombination Deficiency (HRD) testing provides valuable information beyond BRCA1/2 mutation status, offering a deeper understanding of a tumor's DNA repair capacity. Incorporating Genomic Instability analysis (through Rediscore) to HRR (Homologous Recombination Repair) gene mutation analysis can identify additional patients who may benefit from PARP inhibitor treatment or platinum-based chemotherapy.

Prime DX & RediScore NGS for Ovarian, Breast, Pancreatic and Prostate Cancer



By integrating HRD status into clinical decision-making, physicians can:

- Refine treatment selection and personalize therapy beyond BRCA mutation results.
- Predict therapeutic response to DNA-damaging agents and PARP inhibitors.
- Improve patient outcomes through more precise and informed treatment strategies.
- HRD testing serves as an important add-on diagnostic tool for the above supporting precision oncology in cancer care.

The new PRIME test offers HRD analysis through both the presence of BRCA1/2 or other HRR gene mutations and the presence Genomic Instability analysis (Rediscore). This comprehensive NGS approach provides an integrative analysis of both Comprehensive Genomic Profile (CGP) and HRD status in a single assay which is an important advancement compared to the majority of available tests focusing solely on the HRD status assay and represents an essential addition to a more comprehensive tumor characterization.

Broader applications:

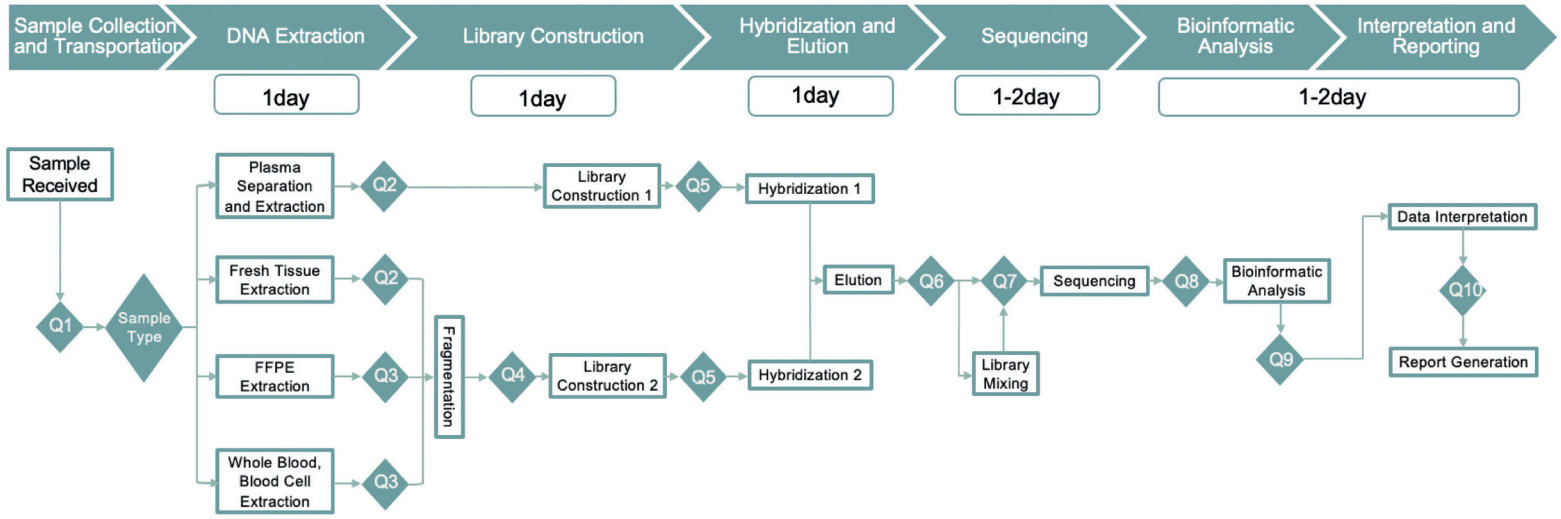
While most established for ovarian cancer, HRD as a biomarker is being used across a range of other cancer types as well, especially breast, pancreas and prostate

Note:

Other tumor types: With Initial Request

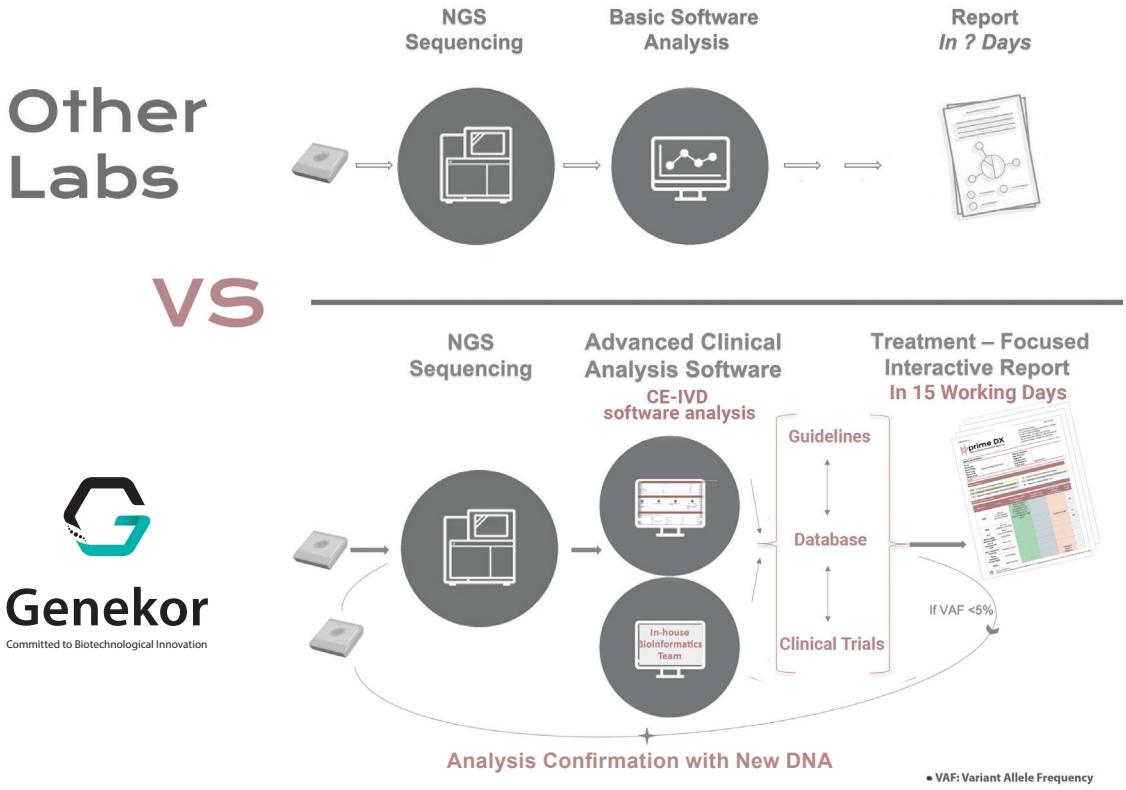
Workflow and Quality Control Points

Comprehensive in-process quality control: 10 Quality Control Points (QCP) in Testing for the entire process



Q1 • Broken or leaking samples • Proper use of consumables • Correct sample type sent for testing • No serious hemolysis or coagulation • Temperature • Transport time is within the appropriate range • No staining of sections	Q2/3 • DNA Fragment • DNA Volume	Q4 • Fragment Length • Total Volume of Fragment	Q5 • Total Volume of Library • Library Fragment	Q6 • Concentration of Library Elution • Fragment of Library Elution	Q7 • Concentration of Sequencing Library	Q8 • Q30 • Mismatch	Q9 • Pair Check • Average Depth • GC • Capture Efficiency • 0.5X Coverage • Con Est	Q10 • Basic Information • Data Tested • Data Annotation	

LAB vs LAB


Other Labs
NGS Sequencing
Basic Software Analysis
Report
In ? Days
VS
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NGS Sequencing
Advanced Clinical Analysis Software
CE-IVD software analysis
Treatment – Focused Interactive Report
In 15 Working Days
Guidelines
Database
Clinical Trials
In-house Bioinformatics Team
If VAF <5%
Analysis Confirmation with New DNA
• VAF: Variant Allele Frequency

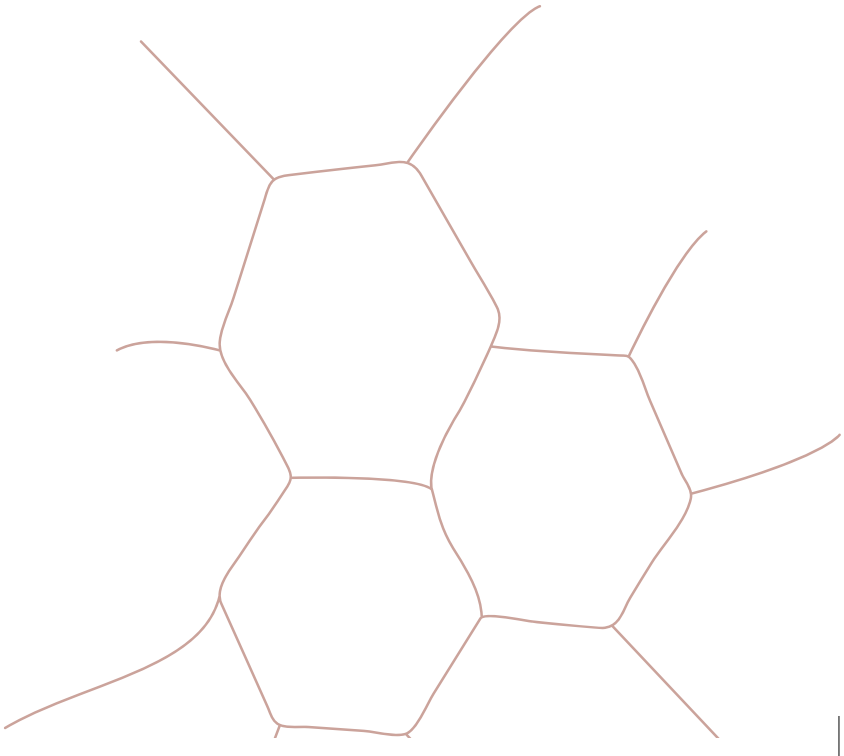
Besides the state-of-the-art technology, the scientific team of the lab plays a very important role, since it is responsible for producing thorough, fast and reliable results.

Genekor's team consists of very experienced scientists, that are dedicated in finding dependable solutions for physicians and their cancer patients, have multiyear experience in the cancer field and have participated in numerous international publications.

During the analysis there are a few very important aspects of the process that differentiate Genekor lab from the others:

- Comprehensive data analysis and management platform, with integrated high-performance hardware using CE-IVD software.
- All positive results with VAF < 5% are validated by an alternative method analysis.
- The in-house bioinformatics team enhances the analysis process by providing computational pipelines for comprehensive reporting with high clinical value
- The generated report is interactive, allowing the physician to go through all the necessary information related to gene alterations, on-label and off-label treatment options and ongoing clinical trials.

Finally, Genekor offers scientific support and genetic counselling before, throughout and after the examination process.



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