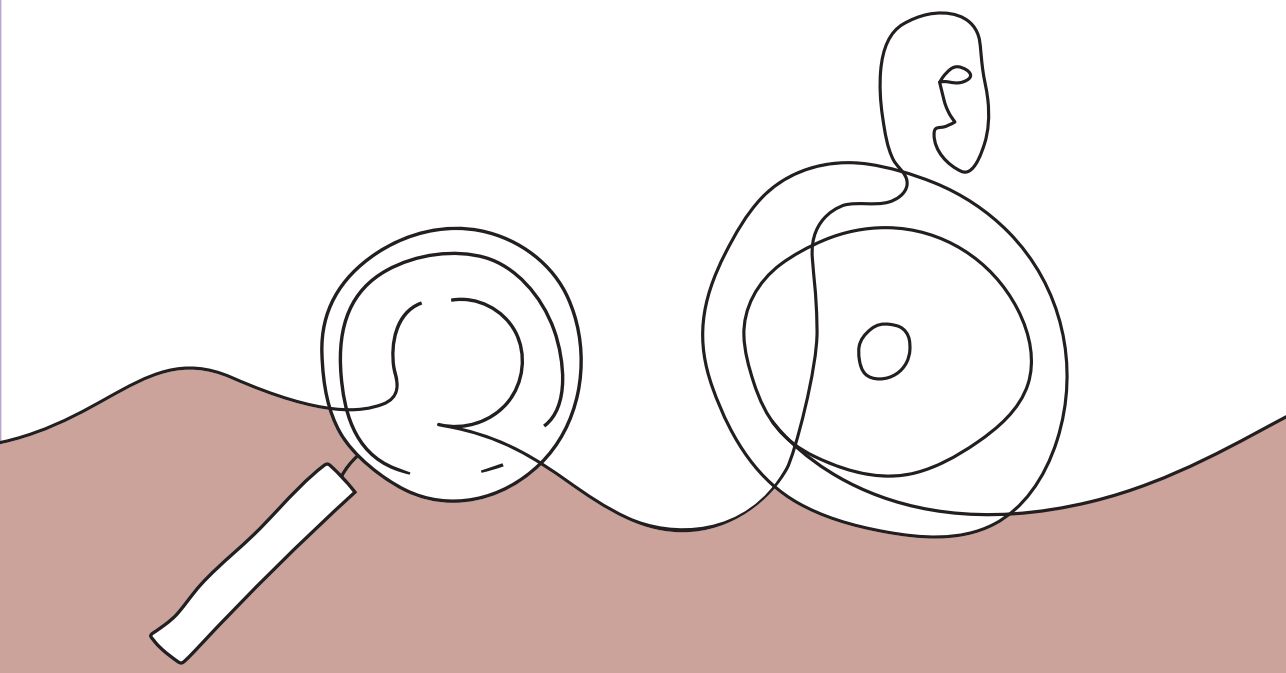
prime DX®

PRECISION INDIVIDUALIZED MEDICINE

Physician's Booklet

Genekor

Committed to Biotechnological Innovation



SHAPING SCIENCE
IMPROVING LIVES

prime DX®

PRECISION INDIVIDUALIZED MEDICINE

prime DX® is an advanced assay for **comprehensive molecular tumor profiling,** compatible with both **tumor tissue (FFPE)** and **blood based liquid biopsy (plasma).**

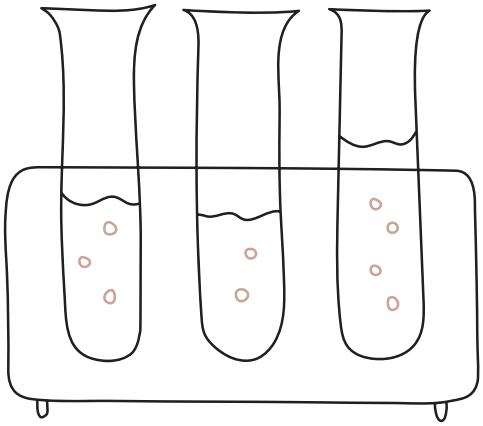
In today's era of **precision medicine**, understanding the genetic alterations that drive cancer is essential for selecting the most appropriate treatment strategy. **prime DX® testing provides clinically actionable insights** that help physicians identify potential therapeutic options tailored to each patient's tumor biology, including:

» **Targeted therapies**

» **Immunotherapy**

» **Chemotherapy**

By delivering a broad molecular profile from a single test, **prime DX® supports informed, individualized treatment decisions across multiple therapeutic pathways.**



prime DX® provides broad molecular profiling via a **1021 gene NGS panel** combined with **exome RNA sequencing**, enabling comprehensive tumor characterization.

prime DX® enables simultaneous assessment of multiple clinically relevant biomarkers:

Immunotherapy Biomarkers

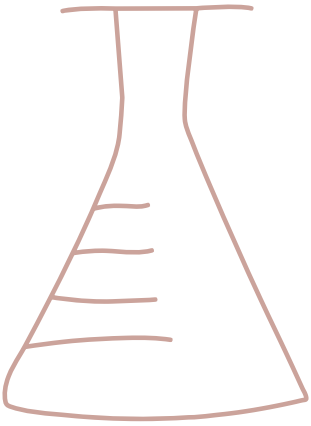
» Tumor Mutational Burden **(TMB)**
» Microsatellite Instability **(MSI)**
» HLA zygosity

PARP inhibitor–relevant biomarkers

» Genomic instability analysis (GIS)

Immunohistochemistry (IHC) biomarkers

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



Tumor agnostic biomarkers

» ***NTRK1/2/3*** **fusions**
» ***RET*** **fusions**
» ***BRAF V600E*** **mutation**
» ***HER2*** **amplification**

prime DX® now combines comprehensive DNA analysis (1021 genes) with exome RNA sequencing targeted capture, enabling a more complete and clinically meaningful characterization of tumor profiles.

DNA sequencing identifies single nucleotide variants (SNVs), insertions/deletions (indels), copy number variations (CNVs), and selected structural rearrangements, while RNA sequencing enables the direct detection of expressed gene fusions and splicing events. This integrated approach significantly enhances the sensitivity and specificity of fusion detection, particularly in cases where genomic breakpoints are complex, intronic, or not covered by DNA-based methods.

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, to predict if an immunotherapy plan would be a suitable plan or/and to create an efficient immunotherapy plan.

DNA-based analysis:

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

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

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

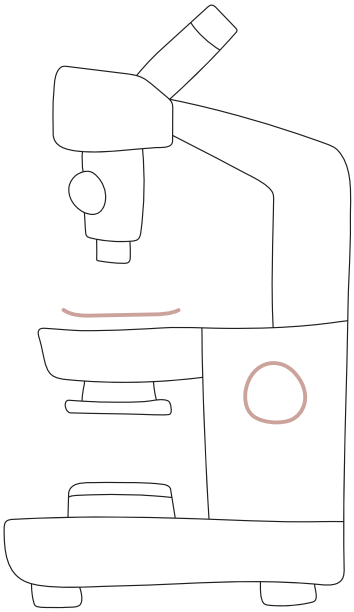
- **Target regions:**
  - Whole exons
    4847 exons of 312 genes
  - Promoter region or other non-coding region
    TERT, PMS2, BCL2L11
  - Coding regions
    1778 coding regions of 709 genes
  - Intronic regions, promoters and fusion breakpoints
    DNA-based fusion analysis in 38 genes

- **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.

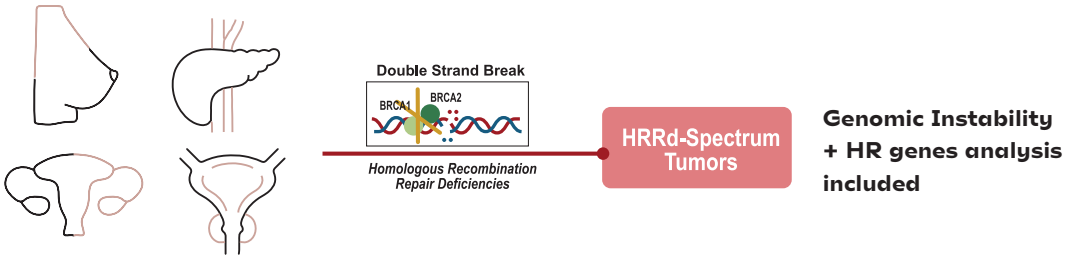


RNA based analysis:

- **Transcriptome coding regions**
  Essentially All **(20,000+)** genes

Incorporation of IHC Biomarkers into the Prime DX Panel		
Clinical value	**Biomarker**	**Tumor type**
Targeted therapy	**HER2**	Pan-cancer
	FRα	Ovarian
	CLDN18.2	Gastric
	C-MET	Lung
Immunotherapy	**PD-L1**	

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.

HR Genes analyzed									
ATM	*ATR*	*ATRX*	*BAP1*	*BARD1*	*BLM*	*BRCA1*	*BRCA2*	*BRIP1*	*CDK12*
CHEK1	*CHEK2*	*C11orf30*	*ERCC1*	*FAM175A*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*
FANCG	*FANCL*	*FANCM*	*MRE11*	*NBN*	*PALB2*	*RAD50*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RECQL*	*RECQL4*	*WRN*				

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

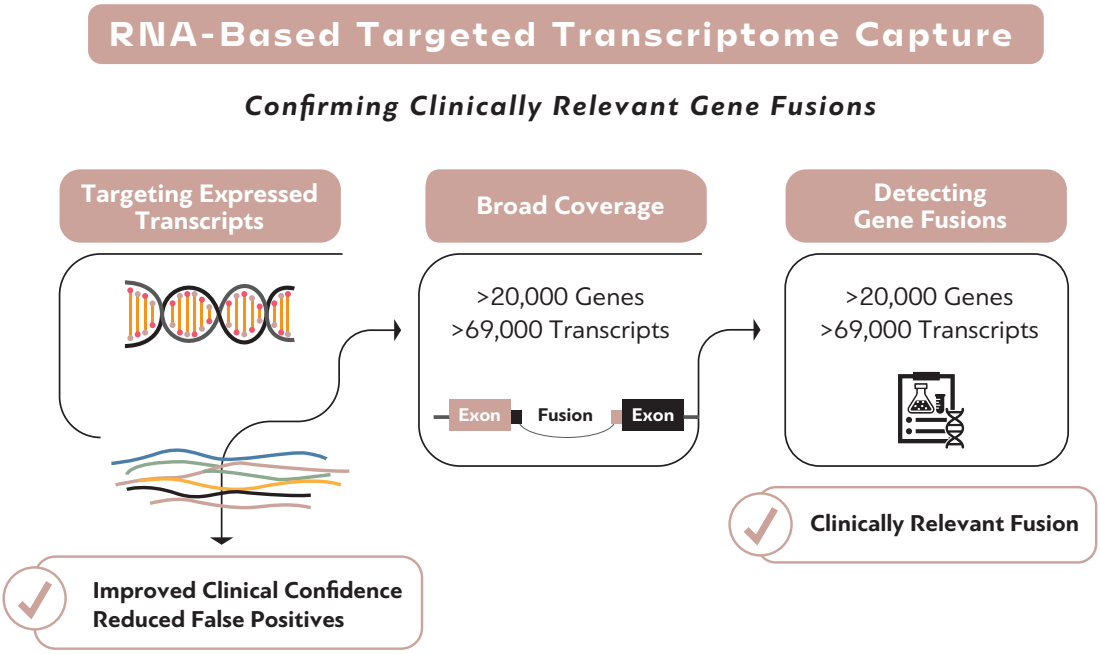
Note:

Other tumor types: With Initial Request

The advantage of combined DNA/RNA analysis

By focusing on expressed transcripts, RNA sequencing confirms the functional relevance of detected alterations, reducing false positives and increasing confidence in clinical interpretation.

The assay targets coding regions across more than 20,000 genes and over 69,000 transcripts, including partial UTR coverage, ensuring broad detection of clinically relevant fusion events.



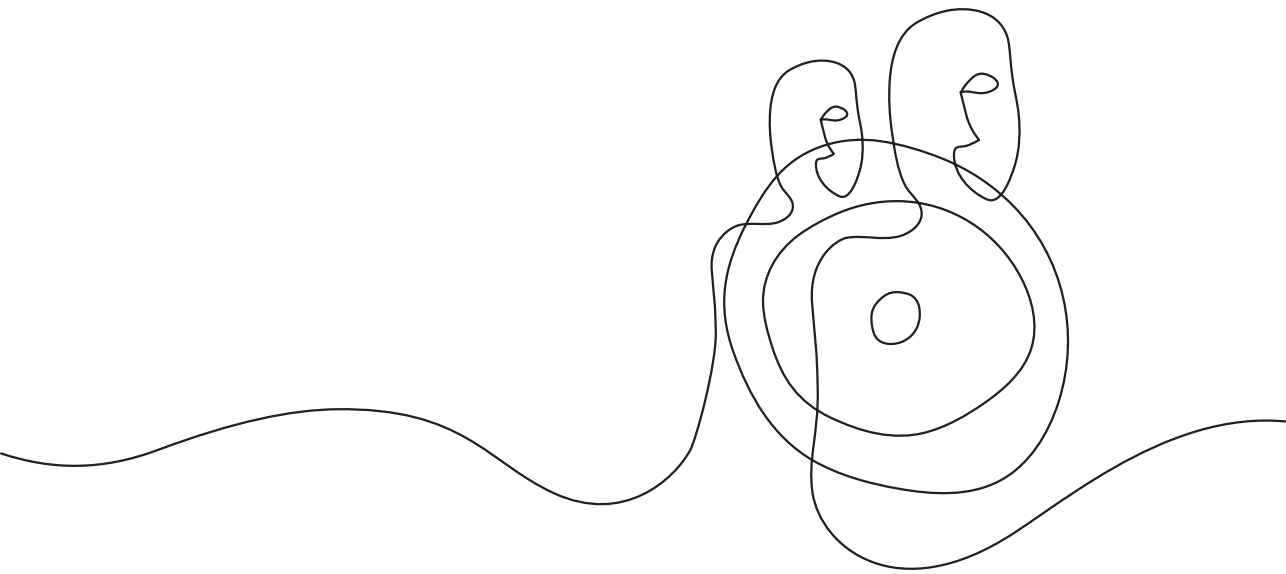
The RNA component is specifically optimized for challenging clinical samples such as FFPE-derived material. This ensures robust performance in routine diagnostic settings where sample quality is often limited.

It maintains high performance even with low-input or degraded RNA, ensuring reliable and consistent results in routine diagnostic settings where sample quality is often limited.

prime DX RNA analysis enables high-sensitivity detection of gene fusions and transcript alterations, supporting both therapeutic decision-making and accurate diagnosis.

The addition of RNA sequencing provides important advantages for patient management:

- Enables detection of known and novel or rare fusion transcripts that may have diagnostic or therapeutic relevance
- Enhances sensitivity for clinically relevant alterations that guide targeted therapy selection, including ALK, NTRK, RET, ROS1, FGFR2/3, and others
- Supports precise classification of tumors driven by gene rearrangements, particularly in sarcomas
- Identifies RNA-level events such as alternative splicing and exon skipping variants, including EGFRvIII in brain tumors and MET exon 14 skipping in NSCLC



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 utilizes a **1021 gene Next Generation Sequencing (NGS) analysis**,—and leverages an advanced platform that analyzes both **cell free DNA (cfDNA) and DNA extracted from whole peripheral blood.**

This approach enables germline testing for 64 genes 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 genetic predisposition to cancer, giving information to the physician about the probability of hereditary cancer syndrome.

64 genes analyzed for germline mutations									
APC	*ATM*	*ATR*	*ATRX*	*AXIN2*	*BAP1*	*BARD1*	*BLM*	*BMPR1A*	*BRCA1*
BRCA2	*BRIP1*	*CDH1*	*CDK4*	*CDKN2A*	*CHEK2*	*EPCAM*	*FAM175A*	*FANCA*	*FANCL*
FANCM	*FH*	*GALNT12*	*HOXB13*	*MEN1*	*MITF*	*MLH1*	*MRE11*	*MSH2*	*MSH3*
MSH6	*MUTYH*	*NBN*	*NF1*	*NF2*	*NTHL1*	*PALB2*	*PMS2*	*POLD1*	*POLE*
PTEN	*RAD50*	*RAD51B*	*RAD51C*	*RAD51D*	*RB1*	*RECQL*	*RECQL4*	*RET*	*RNF43*
SDHA	*SDHB*	*SDHC*	*SDHD*	*SMAD4*	*SMARCA4*	*STK11*	*TP53*	*TSC1*	*TSC2*
VHL	*WRN*	*WT1*	*XRCC2*						

Tumor Fraction in prime Liquid

Tumor Fraction Assessment

prime Liquid now incorporates tumor fraction (TF) estimation using a deep-learning approach based on cfDNA fragment size analysis (fragmentomics). By evaluating the distribution of DNA fragment lengths in plasma, this method provides a quantitative measure of circulating tumor DNA (ctDNA) without requiring prior knowledge of tumor-specific mutations. This additional layer of information supports more accurate interpretation of liquid biopsy results, increases confidence in negative findings, and enables non-invasive monitoring of disease dynamics over time.

What is Tumor Fraction (TF)?

Tumor Fraction (TF) represents the proportion of tumor-derived DNA within the total circulating cell-free DNA (cfDNA) in plasma.

Higher TF increases the likelihood of detecting tumor-specific variants, while low TF may reflect limited tumor shedding, early-stage disease, or treatment response. TF is influenced by tumor biology, disease burden, and therapy, and should always be interpreted in the appropriate clinical context alongside molecular and other relevant clinical findings.

Clinical Utility

Improved result interpretation

Interprets variant findings in the context of ctDNA abundance, increasing confidence in molecular results.

Detection sensitivity awareness

Identifies samples with low tumor content, helping distinguish true negative results from low tumor shedding and reducing the risk of false negatives.

Patient monitoring

Enables longitudinal tracking of tumor fraction, providing insights into treatment response and disease progression.

Deeper molecular insight

Provides an orthogonal signal beyond mutation detection, particularly valuable when no actionable variants are identified.

Revolutionizing Precision Medicine: Dual Testing for Comprehensive Molecular Profiling

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.

The prime DX 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.

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

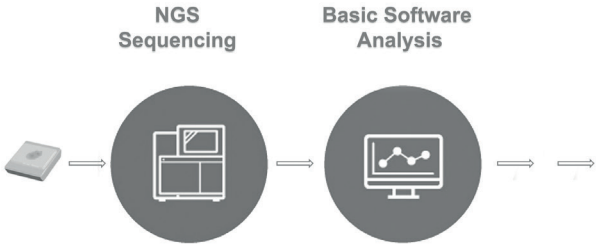
Why is the NGS analysis of multiple genes necessary?

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.

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" KRAS	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"

LAB vs LAB

Other Labs



VS

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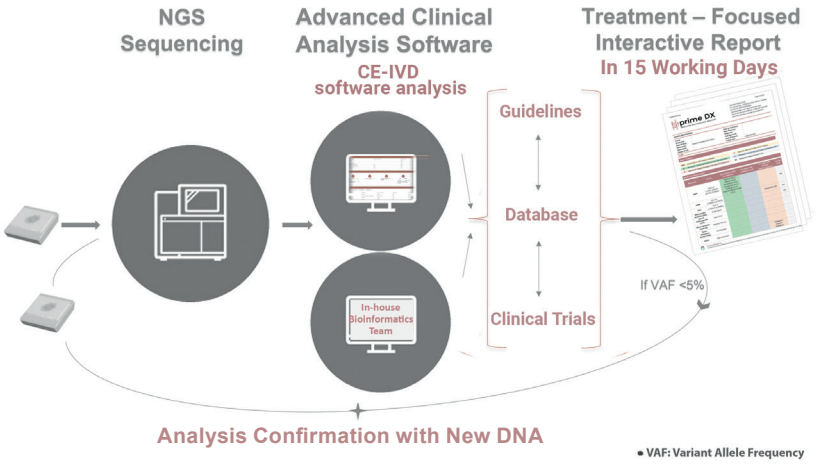

• VAF: Variant Allele Frequency

Accreditations & Certifications

Clinical Reliability: ISO 15189:2022 (Cert. No. 822)* & **CAP Accredited Laboratory.**

Data Security: Certified according to **ISO/IEC 7001:2022** for Information Security Management.

Quality Management: **ISO 9001:2015** Certified Quality Management System.

Method Reliability: prime DX® is performed using **CE-IVD** marked reagents/software, in compliance with IVDR.

** Within the official scope of accreditation.*

Genekor Medical S.A.

info@genekor.com | genekor.com

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