NeXT Liquid Biopsy™

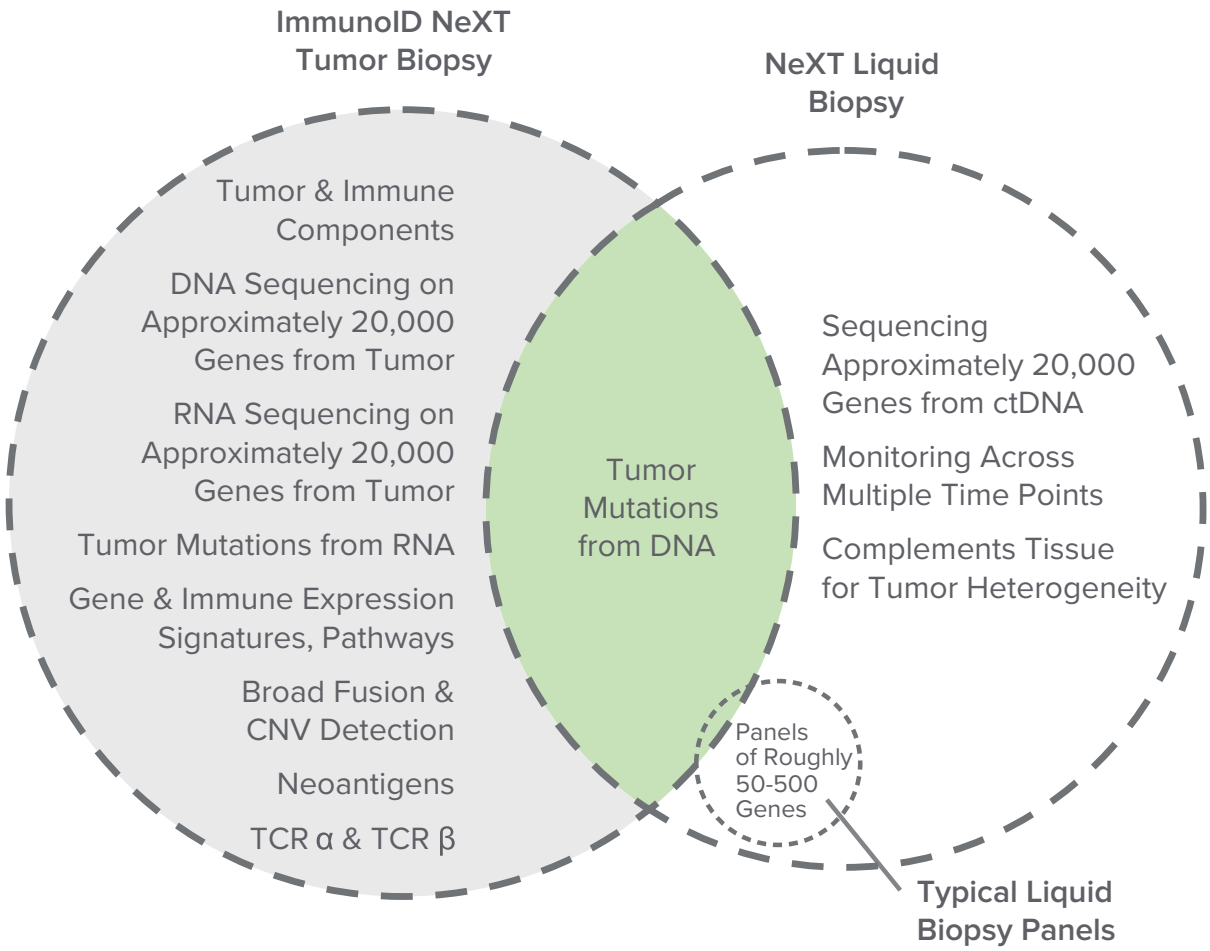
It's Time to Think About More. High-Performance Whole Exome Sequencing from Plasma.

Personalis®

Complementing Tumor Tissue Profiling with Plasma-based Global Resolution

NeXT Liquid Biopsy™, a high-performance, exome-wide liquid biopsy assay, is designed to complement Personalis' flagship tissue-based immunogenomics platform, ImmunoID NeXT™, to further enhance the development of more efficacious cancer therapies in advanced solid tumor indications. While solid tumor biopsies remain the gold-standard for the interrogation of the cancer genome, the advent of liquid biopsies and multi-region tissue sampling has demonstrated that there can be more to a cancer's genomic profile than that found in a single tissue biopsy.[1] However, the liquid biopsy alone may not capture all tumor variants if healthy cancer cells do not shed their contents into blood circulation. Thus, the combination of NeXT Liquid Biopsy and ImmunoID NeXT delivers the most comprehensive view of a cancer's mutational landscape by evaluating both the tissue and the blood (Figure 1).

Figure 1



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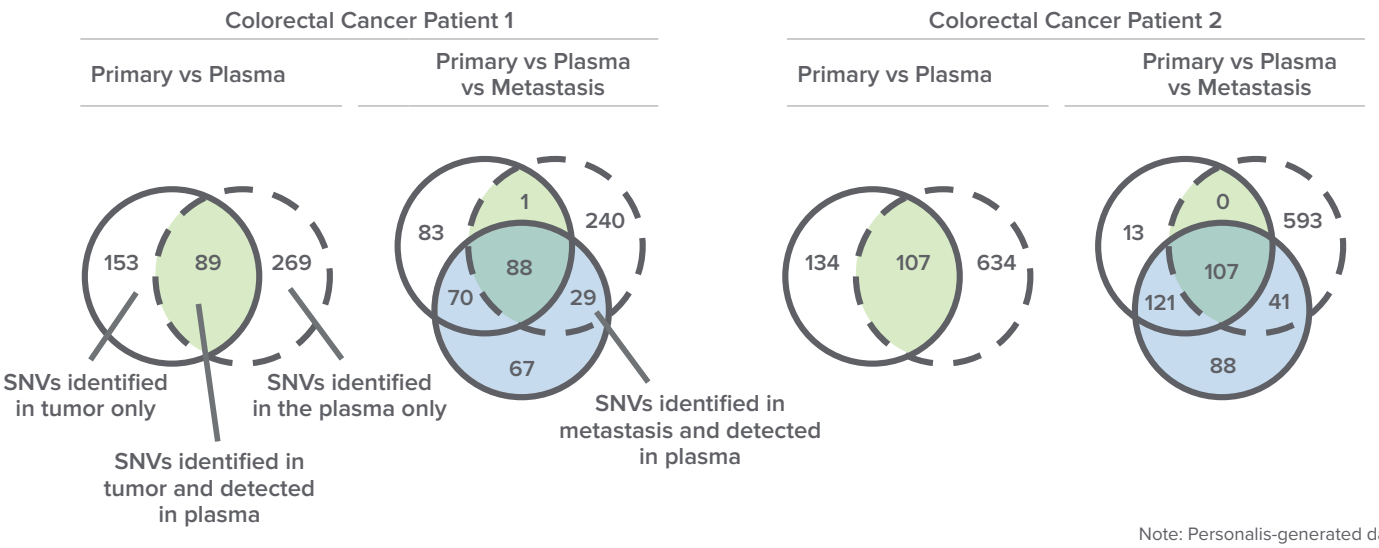
Assess Tumor Heterogeneity

A predominant hallmark of cancer is heterogeneity, which can occur both across and within disease sites (spatial) as well as during the course of its evolution (temporal). As a result, tumors (and their metastases) are composed of a diverse collection of cells that may harbor distinct molecular signatures, differing driver and passenger mutations, and biomarker statuses, all of which can contribute to the development of therapy resistance. Therefore, an accurate assessment of tumor heterogeneity can prove essential to the development of effective therapies.

NeXT Liquid Biopsy exploits the inherent biology associated with cellular turnover in the tumor by capturing circulating cell-free DNA (cfDNA) molecules shed into the blood. This DNA is potentially representative of multiple regions of the primary tumor and/or distant metastases, thus complementing results from ImmunoID NeXT (Figure 2).

Figure 2

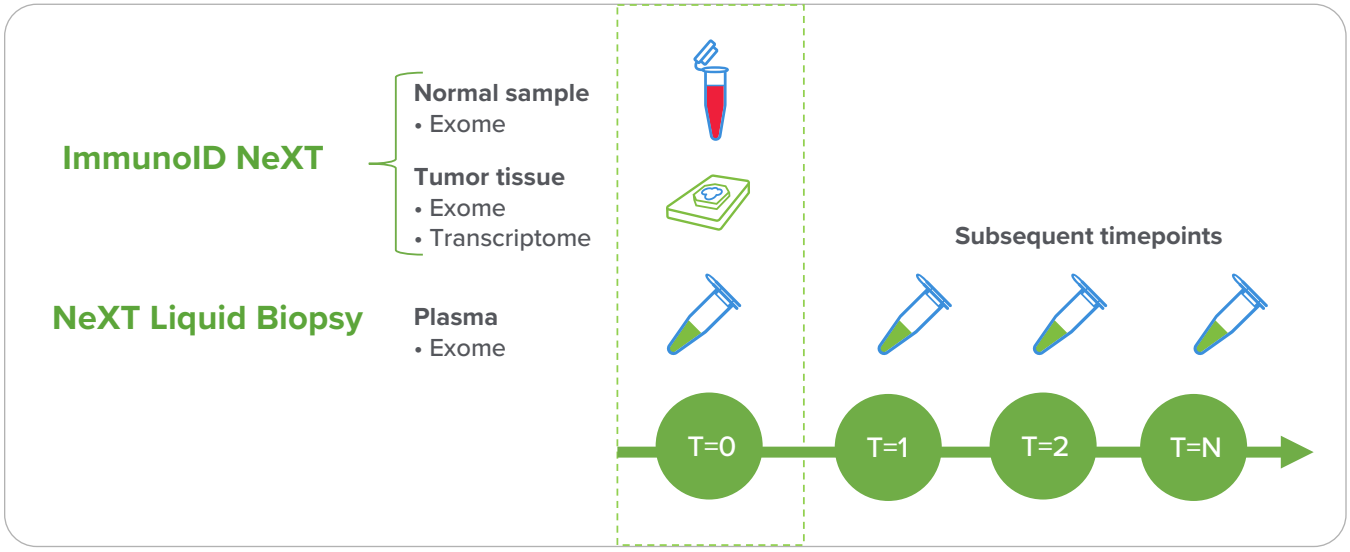


Note: Personalis-generated data

Monitor Clonal Evolution & Tumor Dynamics in Response to Therapy

Serial sampling of the tumor genome is required to determine why certain patients respond well to therapy, while others do not.[2] However, serial tissue biopsies are invasive and often unattainable, and even if serial tissue biopsies are obtained, these are limited both spatially and temporally. Following a comprehensive assessment of the mutational landscape with ImmunoID NeXT at baseline, NeXT Liquid Biopsy enables the exome-wide monitoring of both clonal and sub-clonal variants so that investigators have an extensive view of how the cancer evolves in response to therapy (Figure 3).

Figure 3:
Typical Study Configuration



Interrogate Mechanisms of Intrinsic and Acquired Resistance

Insights into the genomic landscape of some cancers have fueled a shift in the treatment paradigm towards the use of personalized (genotype and/or tumor microenvironment-guided) approaches. Yet, in the cases where these therapeutic modalities produce dramatic initial responses, the majority of these tumors develop resistance and ultimately progress.[3]

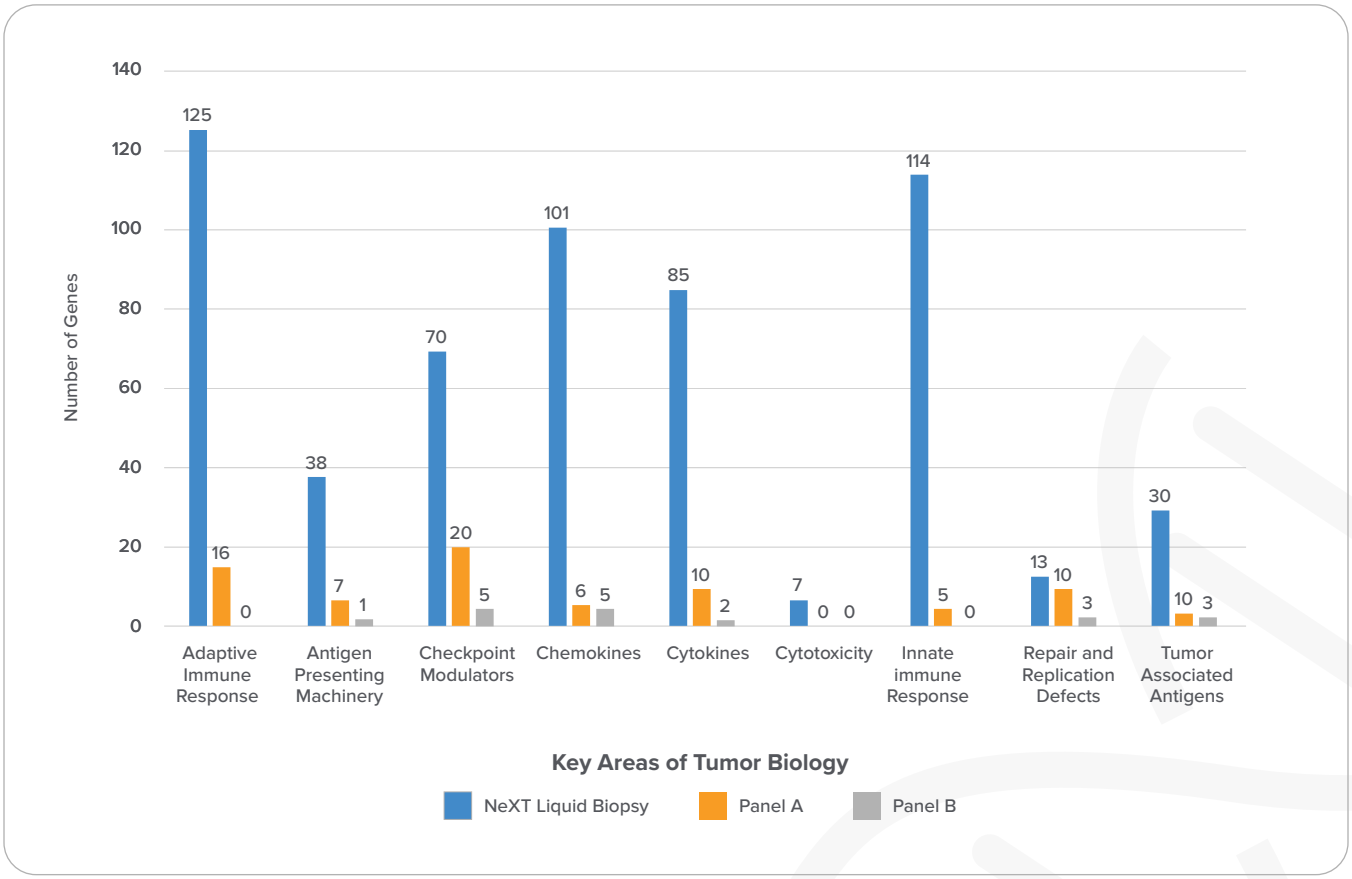
Interrogating resistance mechanisms at cancer progression with a cell-free WES (cfWES) approach has led to the discovery of novel resistance pathways, with profound implications for new therapeutic strategies.[4] NeXT Liquid Biopsy provides a non-invasive approach which can be used before, at, and after progression to comprehensively analyze the landscape of alterations that can lead to resistance.

Explore the Unknown with Confidence

The majority of commercially-available liquid biopsy panels employ a targeted genomic footprint to interrogate a collection of known, well-established oncogenic driver and tumor suppressor genes. While monitoring these genes is important in many therapeutic strategies, these panels often do not capture key areas of tumor biology responsible for conferring survival advantages, the emergence of subclones, and ultimately the development of therapeutic resistance and relapse. Thus, a global understanding of tumor dynamics is essential for the development of effective and durable therapeutic strategies.

NeXT Liquid Biopsy overcomes these challenges by capturing all ~20,000 protein-coding genes of the human genome, providing oncology translational and clinical researchers with a unique ability to explore important areas of tumor biology not accessible through targeted panel approaches (Figure 4).

Figure 4



References

1. Tumor Heterogeneity and Resistance to Cancer Therapies. Dagogo-Jack et al. Nature Reviews, 2017.

2. The Implications of Clonal Genome Evolution for Cancer Medicine. Apraricio et al., New England Journal of Medicine, 2013.

3. Polytherapy and Targeted Cancer Drug Resistance. Chatterjee N, et al. Trends Cancer. 2019.

4. Liquid Versus Tissue Biopsy for Detecting Acquired Resistance and Tumor Heterogeneity in Gastrointestinal Cancers. Parikh et al. Nature Medicine. 2019.

Unprecedented Performance at Exome Scale

As the first of its kind, NeXT Liquid Biopsy is purpose-built to navigate the inherent variability of circulating tumor DNA by delivering a high-performance, whole-exome liquid biopsy assay. Through innovative library preparation, high depth of sequencing, and advanced error suppression techniques, NeXT Liquid Biopsy goes far beyond cfWES approaches described in the literature, profiling low-abundance, exome-wide mutations with unprecedented confidence and sensitivity. Additionally, 247 cancer-related genes are boosted with additional probes to enhance performance in these well-defined areas of the genome (Figure 5 and Table 1). Further enhancement is gained by leveraging matched normal samples to remove germline variants from somatic variant calling, an important feature not utilized in many liquid biopsy solutions.

Figure 5

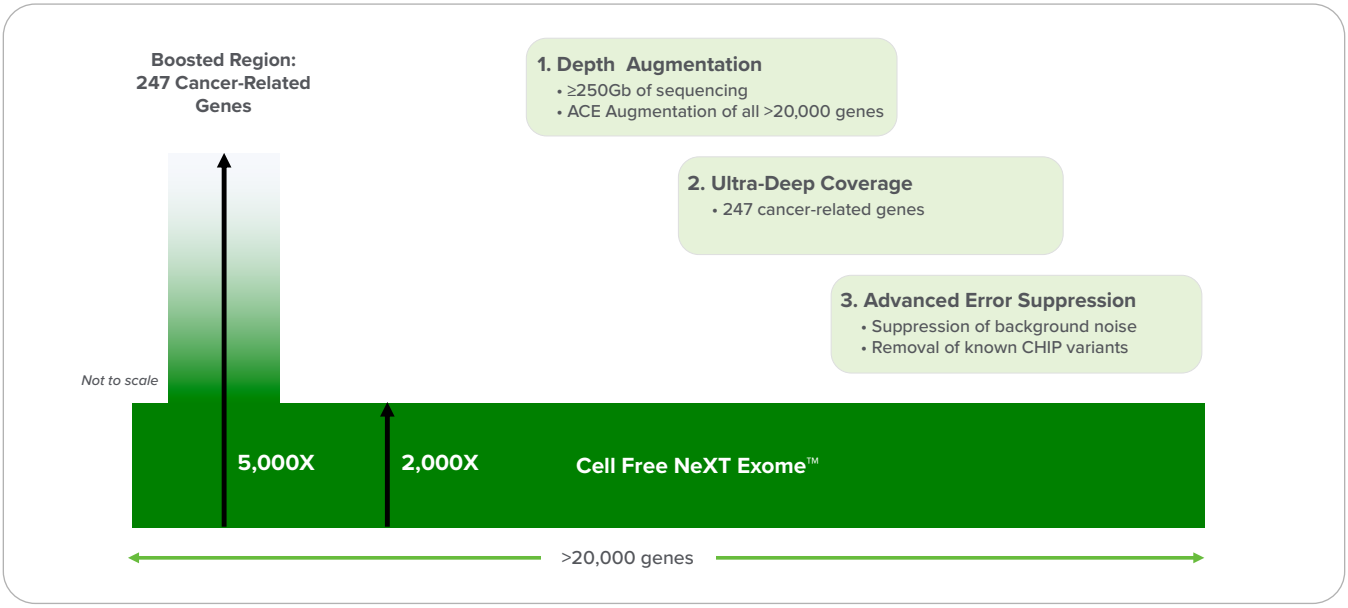


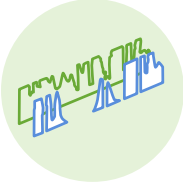
Table 1

Personalis Performance (SNVs and Indels)			
Region	**MAF**	**Background Error Rate**	**Sensitivity**
Boosted Region	≥0.5%	≤0.6 False Positives Per Mbp	≥95%
Whole Exome Region	≥1%	≤0.6 False Positives Per Mbp	≥85%
Reported in Literature			
Publication	**MAF**	**Background Error Rate**	**Sensitivity**
cfWES (Chicard et al, 2017)	≥5%	N/A	N/A
cfWES (Murtaza et al, 2013)	≥10%	N/A	N/A
cfWES (Christensen et al, 2019)	≥10%	N/A	N/A

Unique Benefits of the NeXT Liquid Biopsy Platform

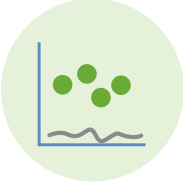
Deep Sequencing

~2,000X mean coverage across the entire ~20,000-gene DNA footprint, as well as boosted ~5,000X mean coverage across 247 cancer-related genes to deliver enhanced sensitivity.



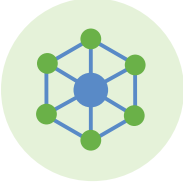
Augmented Coverage

NeXT Liquid Biopsy utilizes our proprietary ACE Technology™ to provide augmented coverage of difficult-to-sequence gene regions across the entire ~20,000-gene footprint.



Advanced Error Suppression

Our robust variant filtration process integrates both proprietary and publicly-available tools to generate high-confidence variant calls and reduce background noise attributed to normal circulating DNA.



Fully Integrated with ImmunoID NeXT

Variants detected from both the tissue and plasma, and at all timepoints, are integrated into a single report, facilitating the interrogation of the entire mutational landscape at baseline, and the longitudinal analysis of both plasma-specific and tissue-specific alterations.

De Novo and Monitoring Analysis Modes

De Novo mode reports plasma-specific variants at all time points, while Monitoring mode reports variants found in the solid tumor and/or at previous timepoints, which is important for longitudinally tracking therapy response and tumor evolution.

Compatible Sample Requirements

Personalis' protocols enable flexible sample formats – blood, plasma, or cell-free DNA – to be processed within the lab, requiring as little as 50ng cfDNA per sample.

It's time to think about more. NeXT Liquid Biopsy, combined with ImmunoID NeXT, further enhances the development of efficacious cancer therapies by assessing tumor heterogeneity, monitoring response, and providing a unique opportunity to explore both intrinsic and acquired mechanisms of resistance in later-stage solid tumor indications. As a first-of-its-kind, high-performance, exome-wide assay, NeXT Liquid Biopsy provides oncology translational and clinical researchers the ability to explore critical areas of tumor biology often not accessible in targeted gene panels.

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