

# Product Focus: Liquid Biopsy

## Non-invasive Cancer Monitoring with Liquid Biopsy Technology

The state of patient health is commonly perceived through the abundance of cell-free nucleic acids (cfNA), which consist of cell-free DNA (cfDNA) and cell-free RNA (cfRNA) molecules. Specific cfNAs are associated with different health conditions, and have the potential to advance the efficacy of clinical diagnosis by identifying specific diseases based on cfNA profiles. Liquid biopsy offers non-invasive and easy access to tumor biomarkers through a conventional blood draw. Circulating tumor DNA (ctDNA), released into the bloodstream by tumor cells, has the potential to account for tumor heterogeneity compared with tissue biopsy samples. Circulating tumor cells and cfDNA have complementary capabilities. Circulating tumor cells are intact, so can be used for cell-surface markers, while cfDNA addresses tumor heterogeneity and has incredible power for improving detection.

### Circulating tumor DNA analysis

Leveraging **Roche's** experience with the first IVD, plasma based cobas® EGFR Mutation Test v2 technology, the **AVENIO ctDNA Analysis Kits\*** are a portfolio of three next generation sequencing (NGS) liquid biopsy assays that provide the flexibility to match the right gene panel to the right oncology research goal. All panels include genes in the National Comprehensive Cancer Network (NCCN) Guidelines and detect four mutation classes: single nucleotide variants (SNVs), insertions and deletions (InDels), copy number variants (CNVs) and fusions in a single assay, with high specificity and sensitivity. A key feature of the AVENIO Oncology portfolio is the availability of matched panels for testing plasma (AVENIO ctDNA Analysis Kits) and tissue (AVENIO Tumor Tissue Analysis Kits). As a product family, these matching assays enable oncology researchers to profile and monitor tumors longitudinally.

- The AVENIO ctDNA Targeted Kit- 17 genes (81kb) detects biomarkers relevant for lung, colorectal cancer (CRC), and other solid tumor cancers, and is an efficient, practical, focused tumor profiling assay.
- The AVENIO ctDNA Expanded Kit- 77 genes (192kb) includes emerging cancer biomarkers and is especially suited for expanded tumor profiling.
- The AVENIO ctDNA Surveillance Kit- 197 genes (198kb) is specifically designed and optimized for longitudinal tumor burden monitoring in lung cancer and CRC.

### Roche AVENIO ctDNA Analysis Kits



Non-small cell lung carcinoma (NSCLC) dominates lung cancer diagnoses in the US. The disease is by far the leading cause of cancer death among both men and women. Using traditional tissue biopsies to diagnose and analyze the disease involves a highly invasive procedure which carries significant risks and is expensive. A liquid biopsy allows powerful genetic analysis to be carried out at lower cost than traditional tissue biopsy, and for faster time to result, which can be critical when treatment decisions are being made.

**Inivata's InVision® platform** unlocks essential genomic information from a simple blood draw to transform the care of cancer patients. The company's technology is based on pioneering research from the Cancer Research UK Cambridge Institute, University of Cambridge and is backed by multiple high calibre publications. Inivata's lead product, InVisionFirst™-Lung, provides best-in-class molecular profiling of patients with advanced NSCLC, to enable clinicians to make more informed treatment decisions. This is a qualitative laboratory developed test that uses targeted advanced sequencing technology to detect SNVs, CNVs, InDels and structural variants, from patients with advanced NSCLC.

### Cell-free DNA/RNA

**Circulogene's CLIA/CAP-certified liquid biopsy cell-free DNA/RNA tests** can provide clinically actionable information in a non-invasive, faster, and cheaper way, with real-time longitudinal surveillance for efficacy of therapeutic regimen, patient response, evolving drug resistance, and disease recurrence beyond tissue biopsy from the primary tumor. These characteristics enable the selection of best-targeted therapy specific for each patient's genetic makeup without delay, from a single tube of 4-mL blood.

Currently, the screening of clinically-actionable mutations performed on cfDNA/cfRNA liquid biopsy suffers from poor isolation and recovery efficiency of the silica-based methodology, requiring multiple tubes of blood (>10 mL). Circulogene's one-of-a-kind liquid biopsy technology ensures minimal sample loss in

the very first step, to offset additional material loss along the entire process to achieve highest possible sensitivity and accuracy. High-sensitivity single-tube blood biopsy employing cfDNA/cfRNA is well-suited to provide clinicians with the fastest way to accurately assess patients' clinical status, and to tailor targeted intervention at the earliest time point.

The main challenges in working with cfDNA in liquid biopsy samples are the low concentration (1 - 50 ng/mL) and the high degree of fragmentation of cfDNA (< 500 bp). An additional complication is that the ctDNA only accounts for up to 20% of the total cfDNA. Therefore, processing higher sample volumes – typically in the range of several milliliters – is required.

**STRATEC Molecular** has developed the **InviMag® Free Circulating DNA Kit/ IG**, which enables efficient, standardized and fully automated purification of cfDNA fragments from 4 mL of plasma samples on the InviGenius® PLUS instrument. The InviGenius® PLUS simplifies laboratory workflows by using a walk-away robotic system for a magnetic bead based isolation of nucleic acids from up to 12 samples in parallel. Using this automated method, the isolated cfDNA is concentrated in an elution volume of down to 40 µL for further detection and analysis.

In addition, STRATEC Molecular offers a quantitative PCR (qPCR assay) – the **InviQuant GeneCount 40** – to quantitate the extracted cfDNA, for example prior to use in NGS or other downstream applications.

### Material compiled by The Scott Partnership

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Benefits of this liquid biopsy solution include:

- Fully automated cfDNA extraction from plasma samples.
- System works for single sample volumes of 4 ml.
- Purity of cfDNA fit for qPCR, ddPCR, NGS, Pyrosequencing, mass array etc.
- Only 10 min hands-on time (manual kits about 60 min).

### STRATEC InviMag Free Circulating DNA Kit IG



Liquid biopsies are well known for their applications in patients with solid tumor cancers, but the same advantages apply to patients with hematologic cancers whose care calls for recurring bone marrow biopsy procedures. The **NeoLAB™ Liquid Biopsy** suite from **NeoGenomics** includes a set of 14 assays for the detection and measurement of critical biomarkers in the peripheral blood plasma of patients with known and suspected hematologic cancers.

The NeoLAB cell-free hematologic tumor analysis provides a sensitive assessment of therapy effectiveness and disease progression, and allows more frequent monitoring through a non-invasive collection method. This removes the potential for missing patchy disease in marrow collection, as plasma is homogenous, and spares patients from an invasive, uncomfortable and expensive procedure.

NeoLAB also provides multiplex and single-marker testing, and the Liquid Biopsy plasma-based tests are available in four multiplex profiles and 10 single-gene analyses, covering myeloid disorders and Bruton tyrosine kinase (BTK) inhibitor resistance.

The **Zymo Research Quick-cfDNA/cfRNA™ Serum & Plasma Kit** efficiently isolates both cfDNA and cfRNA from plasma and other challenging biological samples. Zymo Research partnered with SomaGenics Inc. to combine its kit with the RealSeq-Biofluids Kit to obtain higher yields from low sample volumes.

The combination of these kits provides an improved read alignment of small cfRNA by up to 100-fold, and increases the diversity of detectable species by up to 4-fold over alternative workflows.

The **Quick-cfDNA/cfRNA™ Serum & Plasma Kit** is optimized for separation of cfDNA and cfRNA from the same sample input. The 'parallel' protocol separates cfDNA and cfRNA into separate elutes, while the 'co-purification' protocol collects both cfDNA and cfRNA into the same eluate. Currently available isolation technologies (especially for cfRNA) lack efficient recovery, which is problematic when surveying for rare cell-free disease biomarkers. The kit from Zymo Research shows high yield recovery of cfRNA as well as abundant and diverse microRNA species.

### Biomarker detection with digital PCR

**Stilla Technologies** focuses on accelerating the development of next-generation genetic tests by providing an innovative method of digital PCR (dPCR), called **Crystal™ Digital PCR**. The recently launched **Naica™ System** is the only dPCR solution to offer reliable multiplexing with 3-color detection capability. By encapsulating all steps for dPCR in a single chip, the Naica System also offers a fast and user-friendly solution, rendering dPCR accessible to all.

The most promising application for Crystal Digital PCR is liquid biopsy and the detection of ctDNA. Crystal Digital PCR uniquely allows the multiplexed detection of rare tumor biomarkers directly from the patient's blood, without the need for a tissue biopsy. This technique is particularly useful for cancer monitoring and for the detection of resistance mutations in a tumor.

### Stilla Naica™ System



### Bio-Rad QXDx™ BCR-ABL %IS Kit



Chronic myeloid leukemia (CML) is marked by the presence of the **BCR-ABL** fusion gene, which serves as a biomarker of tumor burden and treatment effectiveness. Tyrosine kinase inhibitors are effective in treating CML, but therapy must remain ongoing through a patient's lifetime because current technologies are not sensitive enough to detect low levels of BCR-ABL that can cause recurrence.

The **QXDx™ BCR-ABL %IS Kit** from **Bio-Rad Laboratories** is the first CE-IVD digital PCR liquid biopsy test that can monitor the molecular response to therapy in patients with CML. The kit provides an absolute measure of BCR-ABL transcripts and is able to detect deep molecular response values of MR 4.7 or 5.0 in 2- or 4-well formats, respectively, which exceed typical limitations of RT-qPCR-based tests, which are reliable only down to MR 4.5. With its CE-IVD marking, the kit is available for diagnostic use in most of Europe and Asia. It can be used with Bio-Rad's QX200™ AutoDG™ ddPCR Dx System or with the QX200 ddPCR Dx System.

\*For Research Use Only. Not for use in diagnostic procedures.

#### Companies mentioned in this Product Focus

<b>Bio-Rad Laboratories</b>	<a href="http://www.bio-rad.com">www.bio-rad.com</a>
<b>Circulogene</b>	<a href="http://www.circulogene.com">www.circulogene.com</a>
<b>Inivata</b>	<a href="http://www.inivata.com">www.inivata.com</a>
<b>NeoGenomics</b>	<a href="http://www.neogenomics.com">www.neogenomics.com</a>
<b>Roche</b>	<a href="http://www.roche.com">www.roche.com</a>
<b>Stilla Technologies</b>	<a href="http://www.stillatechnologies.com">www.stillatechnologies.com</a>
<b>STRATEC Molecular</b>	<a href="http://www.molecular.strattec.com">www.molecular.strattec.com</a>
<b>Zymo Research</b>	<a href="http://www.zymoresearch.com">www.zymoresearch.com</a>

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