Tumor monitoring in a drop of blood

PRECISION MEDICINE STARTS WITH A FINGER STICK
The updated EURTAC study demonstrates that mutations detected in cfDNA are prognostic and consistent with data obtained from tumor biopsies,” the editorialists wrote. “More broadly, the potential benefits of liquid biopsies include a better evaluation of the tumor genome landscape with the identification of a comprehensive set of targetable mutations and the serial noninvasive monitoring, which may allow the detection of additional mutations from emerging subclones, including those involved in the development of acquired resistance.”

Circulogene Theranostics’ solution to liquid biopsy

Novel cell-free DNA enrichment method for high-quantity and high-quality starting materials:

Circulating, cell-free DNA is highly fragmented and presented at very low concentrations; therefore, its isolation is challenging. It requires high-volume input, costs, and labor intensity. Circulogene’s proprietary, cell-free DNA enrichment process possesses novel characteristics of low input (as low as 50 uL of blood) and high output (>300 ng/mL), allowing ultra-high recovery and detection of tumor DNA directly from a droplet volume of unprocessed plasma.

Advanced NGS technology for sensitive longitudinal mutation detection:

Detection of multiple, low-frequency mutations through periodic cell-free DNA analysis could predict tumor progression before the lesions are large enough to be detected by imaging. Analysis beyond a single mutation could also be used to identify and quantify tumor heterogeneity for effective treatment decision making. Liquid biopsies are not as spatially limited as tissue biopsies and can show a global spectrum of mutations that occur throughout tumor development. The sensitivity of conventional analytical methods such as Sanger sequencing is not sufficient to detect low-frequency variants. Targeted deep sequencing by next-generation sequencing (NGS) provides a cost-effective alternative for high-throughput analysis of multiple mutations with high sensitivity.

Validated sample processing and analysis procedure in clinical practice:

The utility of cell-free DNA for clinical application demands the implementation of stringent pre-analytical validation of our laboratory-developed tests to ensure consistent quality data acquisition in our CLIA-certified laboratory.
Through our patented, liquid biopsy process, Circulogene Theranostics delivers tumor monitoring from droplets of blood.

**Noninvasive Precision Medicine**
Because Circulogene’s patented technique enriches the sample, analysis only requires 50 microliters of blood from a finger stick, which is more convenient for healthcare professionals and patients.

**Accurate Identification of Tumor Mutations**
Circulogene’s tests analyze for the presence of cell-free DNA, identifying and quantifying any tumor mutations for accurate reporting and monitoring.

**Tumor Mutations Matched with Treatment**
In our personalized gene reports, Circulogene further provides information on current FDA-approved treatment options proven effective for the tumor DNA mutations identified.

**Track Responsiveness Frequently**
The efficiency of Circulogene’s process empowers physicians to closely monitor tumor responsiveness and adjust treatment protocols. Turnaround time is five to seven days, much faster than tissue biopsy results and other liquid biopsies.

**Tumor Burden and Recurrence**
The Circulogene process uses precise baseline data from which to measure cell turnover and progression.

**A Yield of 100x with 1/10 of the Sample**
We compared the sensitivity of our proprietary cell-free DNA enrichment method to the standard DNA extraction kit used industry-wide today. Results demonstrated 100x more cell-free tumor DNA in the original sample using a single drop of blood.

“The CORRECT trial was the first large clinical trial to compare liquid versus conventional tissue biopsy data, and the results show that liquid biopsy obtains more data on tumor mutations throughout the course of the disease, enabling us to better target therapy to the specificities of a patient’s tumor,” Josep Tabernero, M.D., Ph.D., M.Sc., head of the medical oncology department of Hospital Universitario Vall d’Hebron and author of the CORRECT study.
Gene Tumor Mutation References

Circulogene’s gene panels are based on extensive studies and references that show correlation between specific gene mutations and various tumor types in diagnosed cancer patients.

<table>
<thead>
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Genes below have no FDA-approved drugs at this time.

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Sources: cancer.gov and fda.gov

Precision Medicine

Circulogene Circulogene’s patented technology utilizes next-generation sequencing (NGS) to identify cancer-associated genes linked in the following ten Circulo panels.

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Cancer targeted therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules that are involved in the growth, progression, and spread of cancer. Each personalized gene profile provides information on current FDA-approved treatment options proven effective for the tumor DNA mutations identified.
Circulo Gist

With a simple finger stick, Circulogene's patented technology utilizes next-generation sequencing (NGS) to monitor known tumor mutations for individual patients. Final recommendations are the responsibility of the clinician.

Circulo Breast

Circulo Colorectal

Circulo Hematological

Circulo Lung

Circulo Melanoma

Circulo Ovarian

Circulo Pancreatic

Circulo Thyroid

Note: Circulogene does not mandate or advise treatment for individual patients. Final recommendations are the responsibility of the clinician.

Gene Tumor Mutation References

Circulogene's gene panels are based on extensive studies and references that show correlation between specific gene mutations and various tumor types in diagnosed cancer patients.

Sources: cancer.gov and fda.gov

FDA-Approved Targeted Therapies

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules that are involved in the growth, progression, and spread of cancer. Each personalized gene profile provides information on current FDA-approved treatment options proven effective for the tumor DNA mutations identified.

Genes below have no FDA-approved drugs at this time.

Cancer.gov and FDA.gov
Circulo Breast
PIK3CA BRAF AKTI ERBB2

Circulo Colorectal
KRAS HRAS PIK3CA APC SMAD4 SRC

Circulo Gastric
APC BRAF PIK3CA CTNNB1 GNAS HRAS

Circulo Lung
EGFR KRAS ALK PIK3CA MTL HRAS NRR NRS STK11 TP53

Circulo Melanoma
BRAF PIK3CA KIT NRAS GNA11 GNAQ HRAS

Circulo Ovarian
KRAS BRAF PIK3CA PTEN

Circulo Pancreatic
SMAD4 R8I STK1B

Circulo Thyroid
KTR BRAF RET HRAS NRAS

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Gene Tumor Mutation References

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Cytosimtab Panimium
MECT Coloradobrasil Panonias
PDGFR Ablatimib Pamporini
DKD Anazahind Ntutum
AKL Centrinb Criztinbia
JAK2 Ruxolinib Rizaribb
BRAF Dilerafin Transmelb Vemurafinib

Sources: cancer.gov and fda.gov

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JAK2 Ruxolinib Rizaribb
BRAF Dilerafin Transmelb Vemurafinib
**FDA Biomarker Guidance**

**KRAS**

**Cetuximab** Colorectal Cancer  
**LABEL INFORMATION**  
Cetuximab is indicated for KRAS wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests. Cetuximab is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras.

**Panitumumab** Colorectal Cancer  
**LABEL INFORMATION**  
Panitumumab is indicated for the treatment of wild-type KRAS metastatic colorectal cancer as determined by an FDA-approved test. Panitumumab is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either KRAS or NRAS.

**Open Clinical Trials: 23**

**NCT01960023**  
**GENE** KRAS  
**INTERVENTION(S)** Drug:Cetuximab; Drug:Neratinib;  
**SUMMARY CONDITION(S)** Colorectal Cancer;  
**STATE(S)** FL; ID; IL; MI; NC; PA

**NCT02278133**  
**GENE** KRAS  
**INTERVENTION(S)** Drug:WNT974; Drug:LGX818; Biological:Cetuximab;  
**SUMMARY CONDITION(S)** Metastatic Colorectal Cancer;  
**STATE(S)** FL; SC; TX; WI; MI
Open Clinical Trials Continued

**NCT02292758**  
**GENE**: KRAS  
**PHASE**: Phase 2  
**STATUS**: Recruiting  
**INTERVENTION(S)**: Drug:Bevacizumab; Drug:Irinotecan; Drug:Cetuximab;  
**SUMMARY CONDITION(S)**: Metastatic Colorectal Cancer;  
**STATE(S)**: IA; KS; LA; MA; MN; MO; NH; NY; WI

**NCT02008383**  
**GENE**: KRAS  
**PHASE**: Phase 1  
**STATUS**: Recruiting  
**INTERVENTION(S)**: Biological:Panitumumab; Drug:Cabozantinib;  
**SUMMARY CONDITION(S)**: Colorectal Cancer;  
**STATE(S)**: NC

**NCT01312857**  
**GENE**: KRAS  
**PHASE**: Phase 2  
**STATUS**: Recruiting  
**INTERVENTION(S)**: Drug:Panitumumab; Drug:Randomization to No Panitumumab;  
**SUMMARY CONDITION(S)**: Metastatic Colorectal Cancer;  
**STATE(S)**: NJ; NY

**NCT02448810**  
**GENE**: KRAS  
**PHASE**: Phase 2  
**STATUS**: Recruiting  
**INTERVENTION(S)**: Biological:BAX69 + infusional 5-FU/LV; Biological:BAX69 + panitumumab; Biological:BAX69 + 5-FU/LV; Biological:BAX69 + panitumumab; Drug:Standard of Care; Biological:Standard of Care;  
**SUMMARY CONDITION(S)**: Metastatic Colorectal Cancer;  
**STATE(S)**: IL

**NCT01079780**  
**GENE**: KRAS  
**PHASE**: Phase 2  
**STATUS**: Recruiting  
**INTERVENTION(S)**: Biological:Cetuximab; Biological:Ramucirumab; Drug:irinotecan hydrochloride;  
**SUMMARY CONDITION(S)**: Colorectal Cancer;  
**STATE(S)**: AL; CO; CT; GA; IL; IN; IA; KS; LA; MD; MA; MI; MN; NE; NJ; NM; ND; OH; OK; PA; SD; TX; VA; WV; WI

**NCT01814501**  
**GENE**: KRAS  
**PHASE**: Phase 2  
**STATUS**: Recruiting  
**INTERVENTION(S)**: Biological:Panitumumab; Drug:irinotecan hydrochloride; Drug:fluorouracil; Drug:leucovorin calcium;  
**SUMMARY CONDITION(S)**: Mucinous Adenocarcinoma of the Colon; Mucinous Adenocarcinoma of the Rectum; Recurrent Colon Cancer; Recurrent Rectal Cancer; Signet Ring Adenocarcinoma of the Colon; Signet Ring Adenocarcinoma of the Rectum; Stage IV Colon Cancer; Stage IV Rectal Cancer;  
**STATE(S)**: OH; TN

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