Weill Cornell Medicine

MRD-EDGE: Ultra-Sensitive Detection of Circulating Tumor DNA for Cancer Screening and Diagnosis

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Background & Unmet Need

- Liquid biopsy is an emerging noninvasive method for cancer diagnosis and monitoring which involves sequencing blood plasma cell-free DNA (cfDNA) to identify circulating tumor DNA (ctDNA)

- ctDNA detection is of particular interest for evaluating minimal residual disease (MRD), which indicates the lingering presence of cancerous cells after an initial cancer treatment

- Current ctDNA detection methods have inadequate sensitivity in low volume cancer due to the sparsity of ctDNA in blood and usually require a matched tumor sample, which may not be feasible in many clinical settings

- **Unmet Need:** A sensitive noninvasive liquid biopsy platform to accurately detect residual tumor in blood samples at low tumor burden in the tumor-informed or tumor-naïve context

Technology Overview

- **The Technology:** MRD-EDGE is an ultra-sensitive machine learning-guided ctDNA analysis platform for MRD detection in low tumor fraction cancers

- MRD-EDGE incorporates simultaneous profiling of single nucleotide variants (SNV) and copy number variants (CNV) to enhance ctDNA detection

- The deep learning SNV classifier integrates properties of somatic mutations to distinguish ctDNA from sequencing error, enabling ctDNA detection even in the parts per million range and below

- The CNV module couples read-depth denoising with fragmentomics and an allelic imbalance classifier to detect ctDNA even at low aneuploidy levels

- **PoC Data:** MRD-EDGE enabled tracking tumor burden changes in response to immunotherapy in non-small cell lung cancer (NSCLC), ctDNA shedding in precancerous colorectal adenomas, and de novo mutation calling in melanoma, yielding clinically informative tumor fraction monitoring

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Cornell Reference:
D-9641
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Technology Applications

- Ultrasensitive MRD detection following surgical resection of cancer
- Noninvasive liquid biopsy for cancer screening
- Real-time serial monitoring of therapy response to inform therapeutic optimization
- Patient monitoring during remission for early detection of relapse
- Applicability in a wide range of solid tumors

Technology Advantages

- Ultra-sensitive SNV and CNV detection due to advanced error suppression and radical amplification of ctDNA signal
- ctDNA detection in tumor-informed or tumor-naïve context (without matched tumor tissue)
- Simple Whole Genome Sequencing (WGS) workflow does not require custom panel creation or molecular barcodes and can work with limited input material
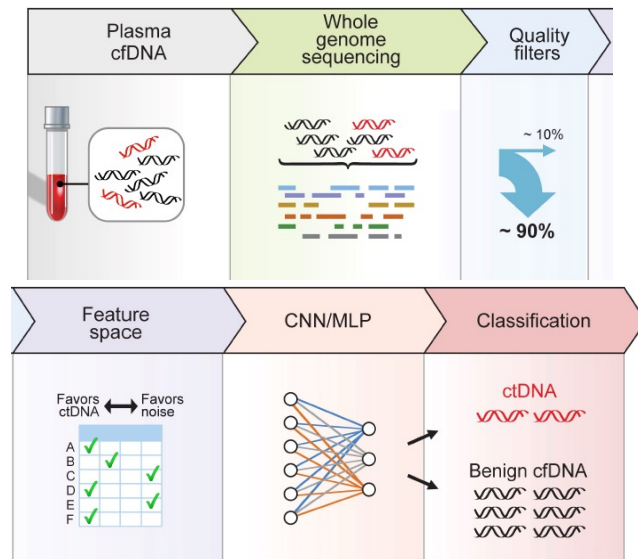
Supporting Data / Figures

Figure 1: ctDNA analysis workflow with MRD-EDGE.

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Figure 2: (A) MRD-EDGE SNV combines a novel fragment-level deep learning architecture with epigenetic features to classify fragments as ctDNA. **(B)** MRD-EDGE CNV integrates machine learning-based read-depth denoising with allelic imbalance and fragmentomics for ultrasensitive ctDNA detection.

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Patents:
PCT Application Filed
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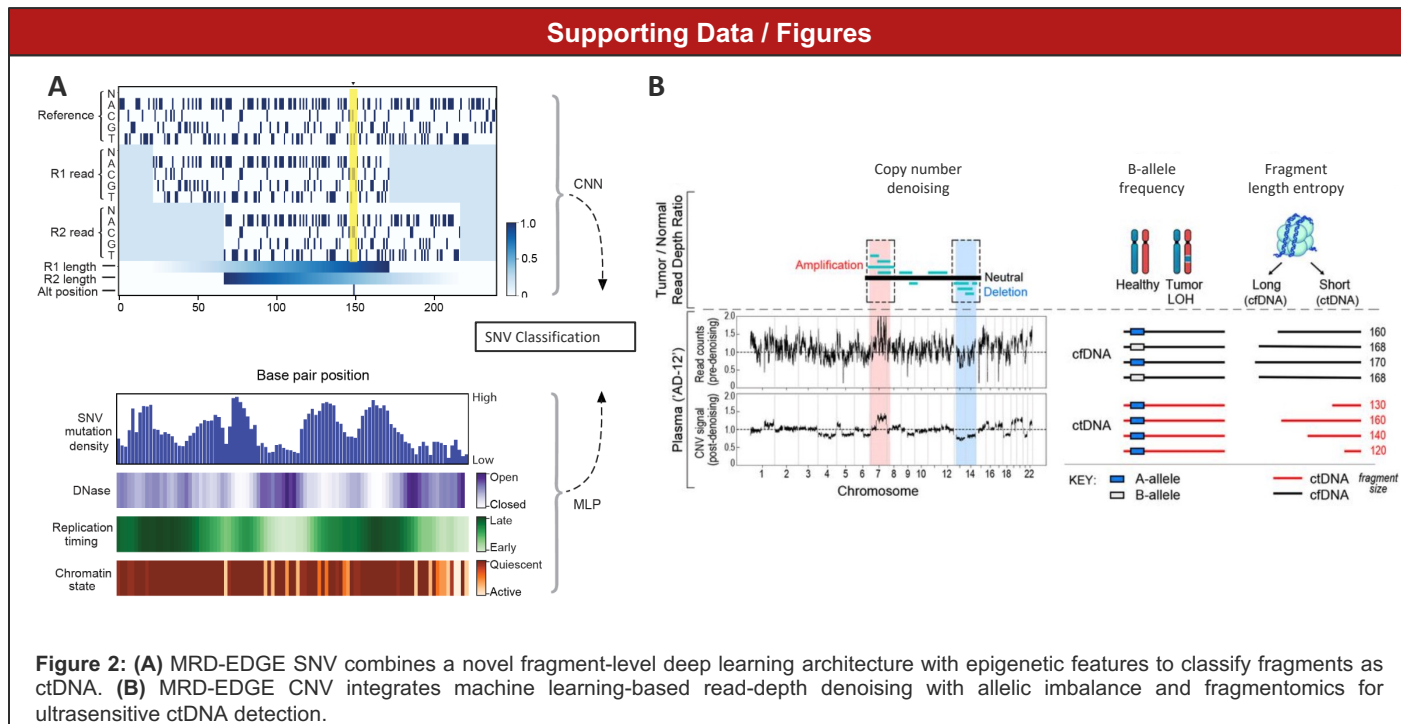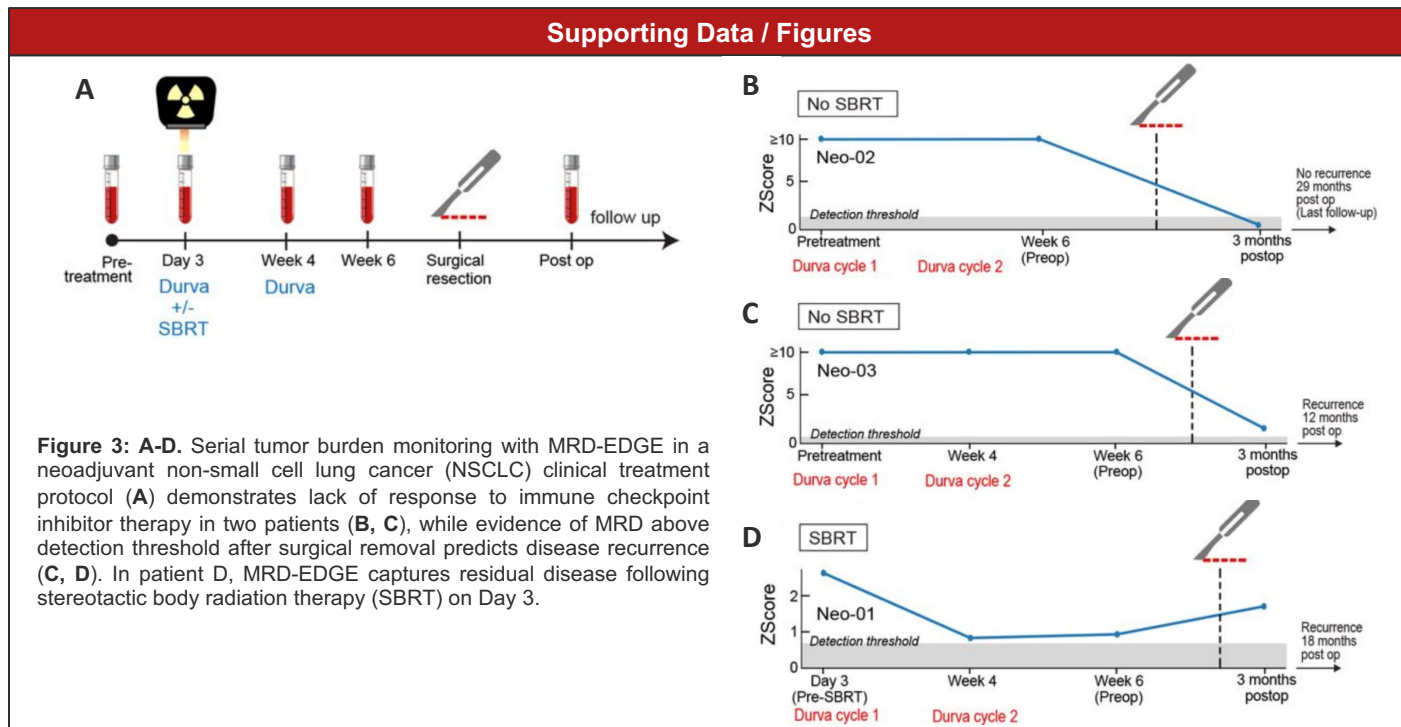**Publications:**
Widman et al. *bioRxiv* [Preprint]. 2022.

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Figure 3: A-D. Serial tumor burden monitoring with MRD-EDGE in a neoadjuvant non-small cell lung cancer (NSCLC) clinical treatment protocol (**A**) demonstrates lack of response to immune checkpoint inhibitor therapy in two patients (**B, C**), while evidence of MRD above detection threshold after surgical removal predicts disease recurrence (**C, D**). In patient D, MRD-EDGE captures residual disease following stereotactic body radiation therapy (SBRT) on Day 3.

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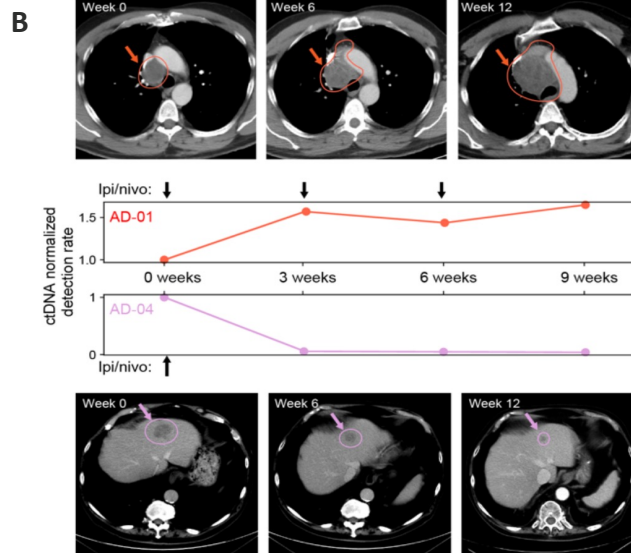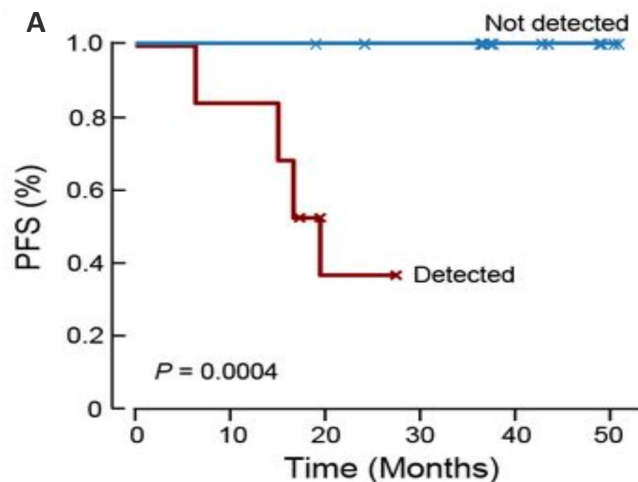
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Figure 4. (A) Tumor-informed post-operative ctDNA detection in early-stage colorectal cancer is associated with shorter progression-free survival. **(B)** Serial tumor-naïve ctDNA monitoring with MRD-EDGE reflects changes seen on imaging.

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