Weill Cornell Medicine

MR-Detect: Genome-wide Mutation Integration for Ultra-Sensitive Detection of ctDNA

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Background & Unmet Need

- Circulating tumor DNA (ctDNA) in plasma cell-free DNA (cfDNA) enables non-invasive cancer detection through routine blood draws
- ctDNA levels correlate with tumor burden and reflect responses to treatment, serving as a valuable biomarker for early detection and disease monitoring
- While late-stage cancers show tumor fractions (TFs) up to 20% in cfDNA, early-stage disease exhibits dramatically lower TFs
- A conventional blood draw (5mL) yields only 2,000-5,000 genomic equivalents of cfDNA, limiting sequencing depth
- The combination of low TF and limited genomic equivalents creates a fundamental barrier to early cancer detection through conventional mutation sequencing
- **Unmet Need:** Development of ultra-sensitive methods capable of detecting plasma tumor fraction <0.1% to enable early cancer detection

Technology Overview

- **The Technology:** MRDetect, a tumor-informed method for ultra-sensitive ctDNA detection using genome-wide mutational integration and an advanced error suppression framework
- MRDetect is available via **non-exclusive license**
- MRDetect uses average depth whole genome sequencing (WGS) to pool information across multiple sites in the genome, increasing the effective ceiling of sequencing depth
- Read-level error suppression frameworks address noise associated with lower quality sequencing metrics and read depth in single nucleotide variants (SNVs) and copy number variants (CNVs)
- **PoC Data:** MRDetect enables ctDNA detection in fractions as low as 10^{-5} with a modest sequencing depth (35x), with assay-level specificity of 95%
- PoC data has been generated in clinical plasma samples from patients with lung adenocarcinoma, colorectal cancer, and metastatic melanoma

Inventors:
Dan Landau
Steven Kothen-Hill
Asaf Zviran
Viktor Adalsteinsson

Patents:
US Application
EP Application
US Application
EP Application
Issued patents in SG, AU, CN, JP
Additional Applications in CA, JP, IN, IL, KR, HK, SG, CN, AU, US

Publications:
Zviran et al. *Nat Med.* 2020.

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Cornell Reference:
D-7874, D-8206

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CNV: Copy number variant; **cfDNA:** cell-free DNA; **ctDNA:** Circulating tumor DNA; **MRD:** Minimal residual disease
SNV: single nucleotive variant; **TF:** Tumor fraction; **WGS:** Whole genome sequencing

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Technology Applications

- Early detection of cancer in high-risk populations
- Detection of minimal residual disease following cancer treatment
- Patient stratification for adjuvants to reduce unnecessary treatments
- Treatment selection based on patient-specific molecular features and response monitoring

Technology Advantages

- Simple WGS workflow does not require custom panel creation or molecular barcodes and can work with limited input material
- Enables dynamic treatment optimization through ongoing monitoring of patient response and outcomes

Supporting Data / Figures

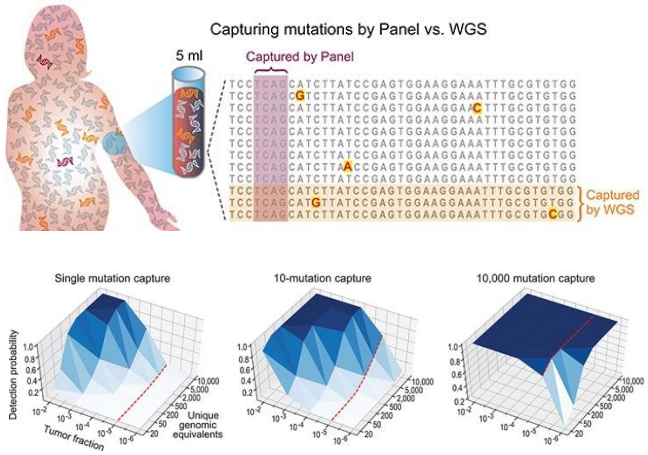

Figure 1: Top: Illustrative schematic showing that mutations captured by targeted panel deep sequencing represent only a small fraction of genome-wide somatic tumor mutations **Bottom:** Predicted probability of detecting at least one mutated read as a function of the number of coverage and the fraction of ctDNA in cfDNA.

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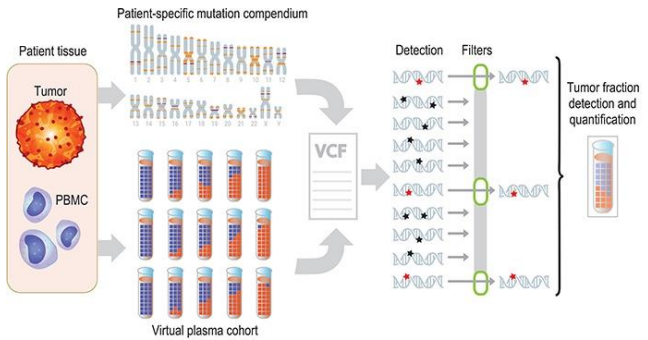

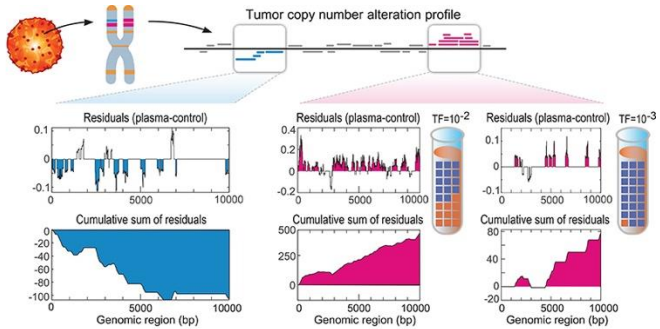

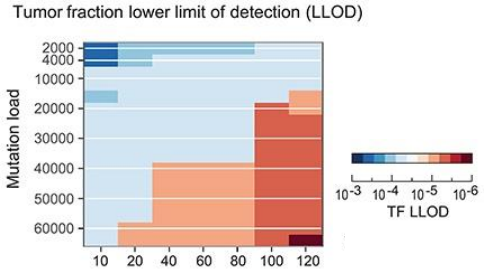

Figure 2: Top Left: Illustration of genome-wide SNV integration for inference of plasma TF, and analytical validation scheme **Top Right:** Illustration of the genome-wide copy number alteration (CNA) integration for the inference of plasma TF **Bottom:** Lower limit of detection for MRDetect-SNV measured as a function of input mutational load and WGS coverage from 21,420 in silico admixtures.

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Supporting Data / Figures

Melanoma | **CRC (n=19)** | **LUAD (n=19)**

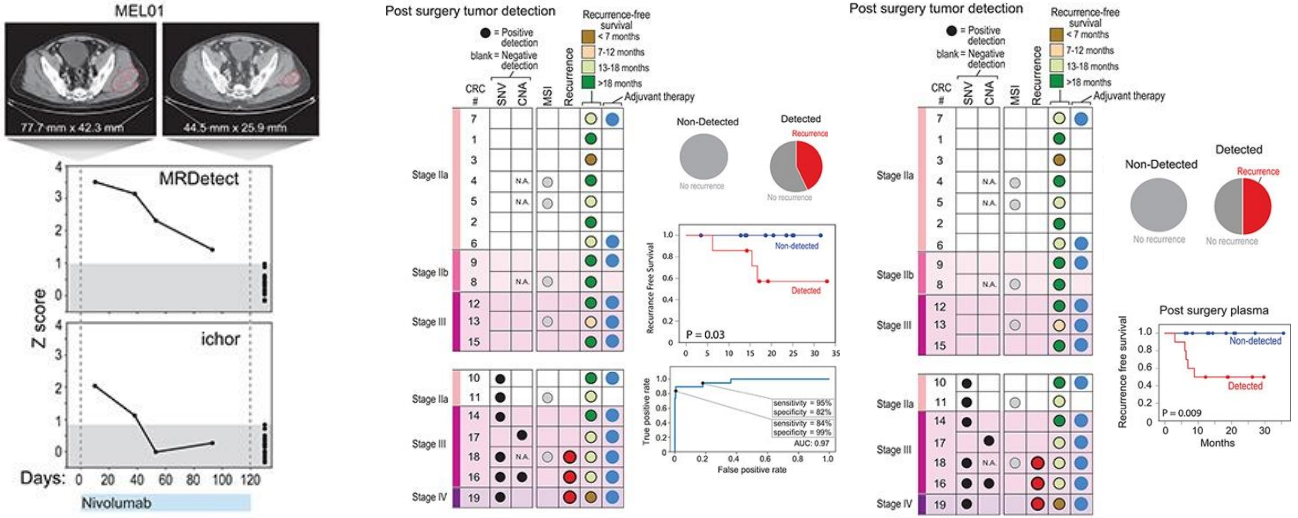

Figure 3: Left: MRDetect dynamically monitors response to immunotherapy (Nivolumab) in melanoma, matching radiographic changes **Middle:** MRDetect enables detection of post-operative residual disease in a cohort of 19 CRC patients **Right:** MRDetect enables post-operative detection in a cohort of 19 lung adenocarcinoma (LUAD) patients, a low-tumor burden cancer type.

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CRC: Colorectal cancer; **LUAD:** Lung adenocarcinoma

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