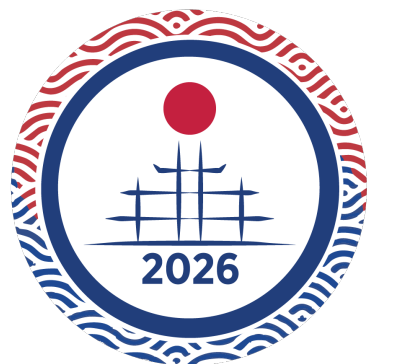




P3.110: Cloud-Based Platform for Cancer Monitoring Using Standard Whole Genome Sequencing

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INTRODUCTION

Cancer is one of the leading causes of mortality worldwide. After initial cancer treatments, patient deaths frequently result from cancer recurrence due to the presence and progression of minimal residual disease (MRD). When cells undergo apoptosis or necrosis, they release cell-free DNA (cfDNA) into the bloodstream. In cancer patients harboring MRD, circulating tumor DNA (ctDNA) originating directly from residual cancer cells is detectable within this cfDNA fraction. The presence of ctDNA in the blood is strongly associated with poor prognosis and increased risk of relapse.

Currently, tumor-informed panel sequencing, which typically has a detection limit ranging from 0.1% to 0.01%, is widely used for ctDNA detection. However, this method requires complex pre-processing steps, including individual tumor-specific panel design, target capture, and barcoding, as well as individualized bioinformatics analyses to interpret panel sequencing results. Additionally, a relatively large volume of blood (typically 20 mL) is required for such analyses.

In this study, we have developed a novel MRD detection method utilizing individual-specific genomic features derived from whole genome sequencing (WGS) data of patient-derived cfDNA samples. Notably, this approach enables MRD detection with a small volume of blood (approximately 5 mL), making it more practical for routine clinical monitoring. Furthermore, we have implemented this method into an accessible cloud-based platform, allowing clinicians and researchers to conveniently and rapidly assess MRD status.

METHODS

Our approach integrates three complementary algorithms to overcome next-generation sequencing noise in standard WGS. Consensus single nucleotide variants (cSNVs) were identified from tumor and control sample, and their supporting fragments were quantified in plasma cfDNA. The aggregated cSNV signal was statistically evaluated against an intra-sample background error distribution derived from common single nucleotide polymorphism sites, enabling sample-specific noise calibration without normal panels (**Figure 1a**). [1] If the allele frequency of supporting cSNV reads yields a p-value ≤ 0.01 against this distribution, the presence of minimal residual disease (MRD) is indicated. Patient-specific structural variant (SV) breakpoints, including gene fusions, were identified, and their unique junction sequences were queried in plasma cfDNA (**Figure 1b**). [2] In addition, neighboring cSNVs observed together on the same tumor-derived read were selected as cis-SNV markers, requiring both alterations to be detected on the same plasma cfDNA fragment (**Figure 1c**). [3] Because exact SV junctions and cis-SNV pairs are highly unlikely to arise from random sequencing errors, they were used as zero-background markers to minimize false-positive MRD detection.

We validated this method using both cancer cell-line mixing experiments (**Figure 2**) and clinical samples derived from various cancer types, including lung cancer, melanoma, breast cancer, and liver cancer (**Figure 3**). The algorithm has been integrated into a user-friendly cloud-based platform hosted on the AWS Cloud infrastructure (<https://mrdid.inha.com>) (**Figure 4**). This system leverages cloud computing to provide a scalable, efficient, and secure environment for genomic data processing and analysis, enabling users to conveniently upload and analyze their sequencing data. The platform also supports serial data uploads, facilitating longitudinal monitoring and tracking of MRD status over time.

RESULTS

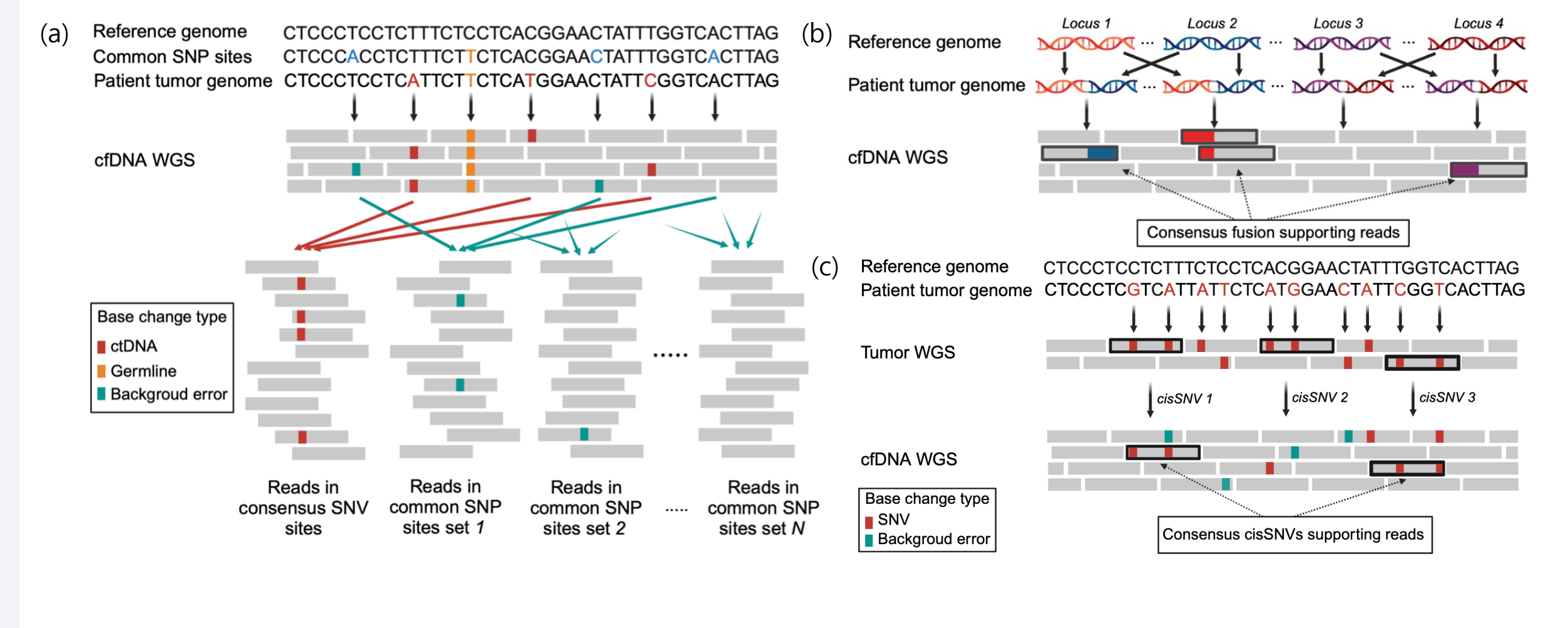


Figure 1. Whole genome sequencing(WGS)-based minimal residual disease (MRD) detection using individual-specific features. Three complementary algorithms are applied to standard WGS data to overcome sequencing noise without the need for a normal control panel. **(a)** Consensus single nucleotide variants (cSNVs) are defined from paired tumor and control WGS, and reads supporting the ctDNA (circulating tumor DNA)-type base change are quantified at these sites in cell-free DNA (cfDNA). The aggregated cSNV signal is statistically evaluated against an intra-sample background error distribution derived from common SNP loci, which enables sample-specific noise calibration; an allele frequency yielding $p \leq 0.01$ against this distribution indicates the presence of MRD. **(b)** Patient-specific structural variants (SVs) generate junction sequences that are absent from the reference genome. Because these breakpoints are unique to the individual tumor, consensus fusion (cFusion) supporting reads identified in cfDNA serve as essentially zero-background markers of ctDNA. **(c)** Neighboring cSNVs co-occurring on the same tumor-derived read in tumor WGS are selected as cis-SNV markers. Detection requires both tumor-specific alternative alleles to be observed on the same cfDNA fragment; since two random sequencing errors are highly unlikely to arise in cis, this requirement markedly improves specificity and minimizes false-positive MRD detection.

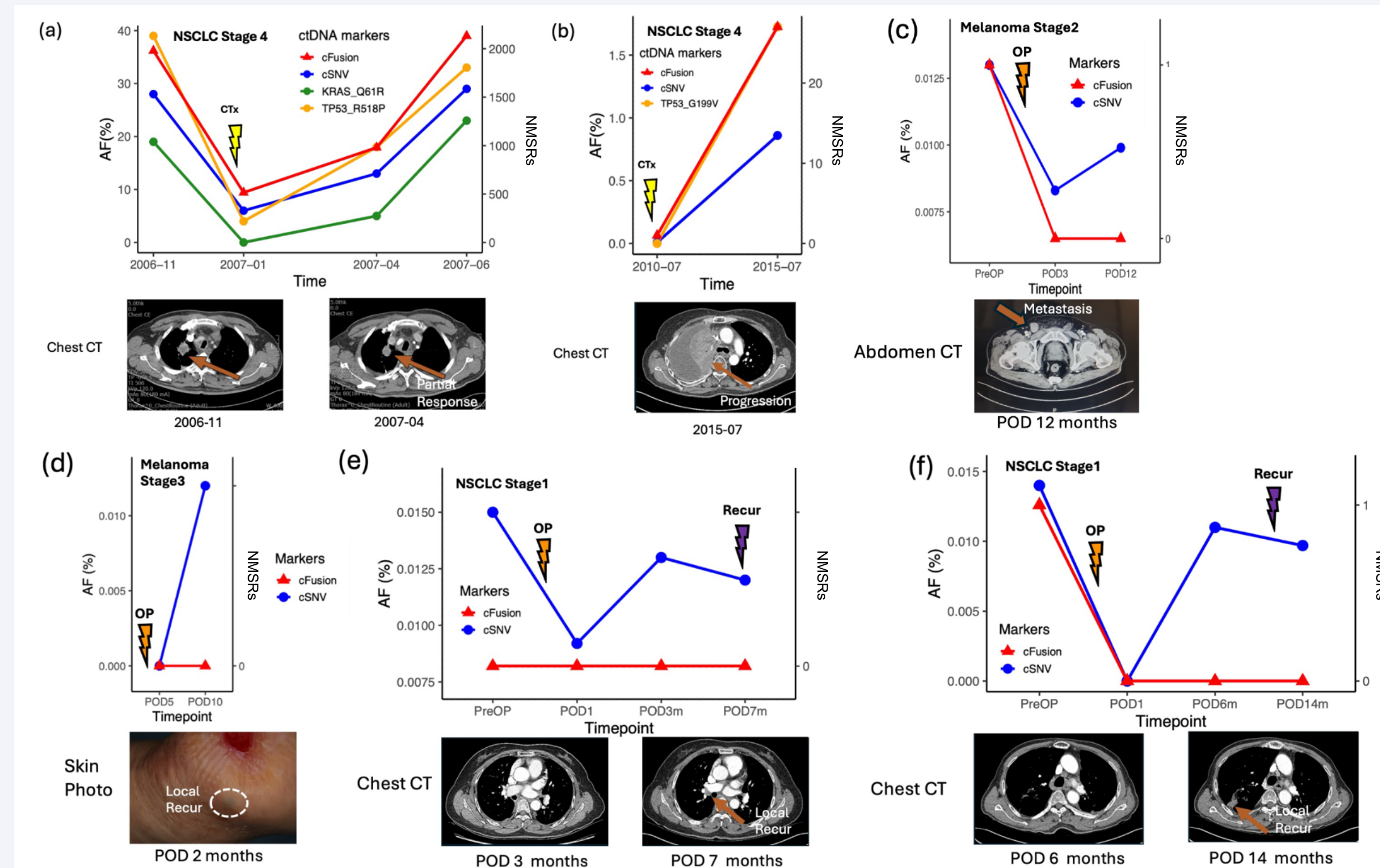


Figure 3. Clinical validation using cancer patient samples. **(a,b)** Monitoring of treatment response in stage IV NSCLC patients. Changes in cSNV AF and NMSRs (Normalized MRD Supporting Reads) were observed in accordance with chemotherapy(CTx) response, paralleling the AF of somatic mutations. **(c,d)** MRD detection in melanoma surgery patients. Detection of ctDNA in the early post-operative period led to the identification of recurrence in the following months. **(e,f)** MRD detection in early-stage NSCLC surgery patients. ctDNA was detected several months prior to recurrence confirmation by CT imaging. Additional data from breast and liver cancer patients were collected, but are not shown here.

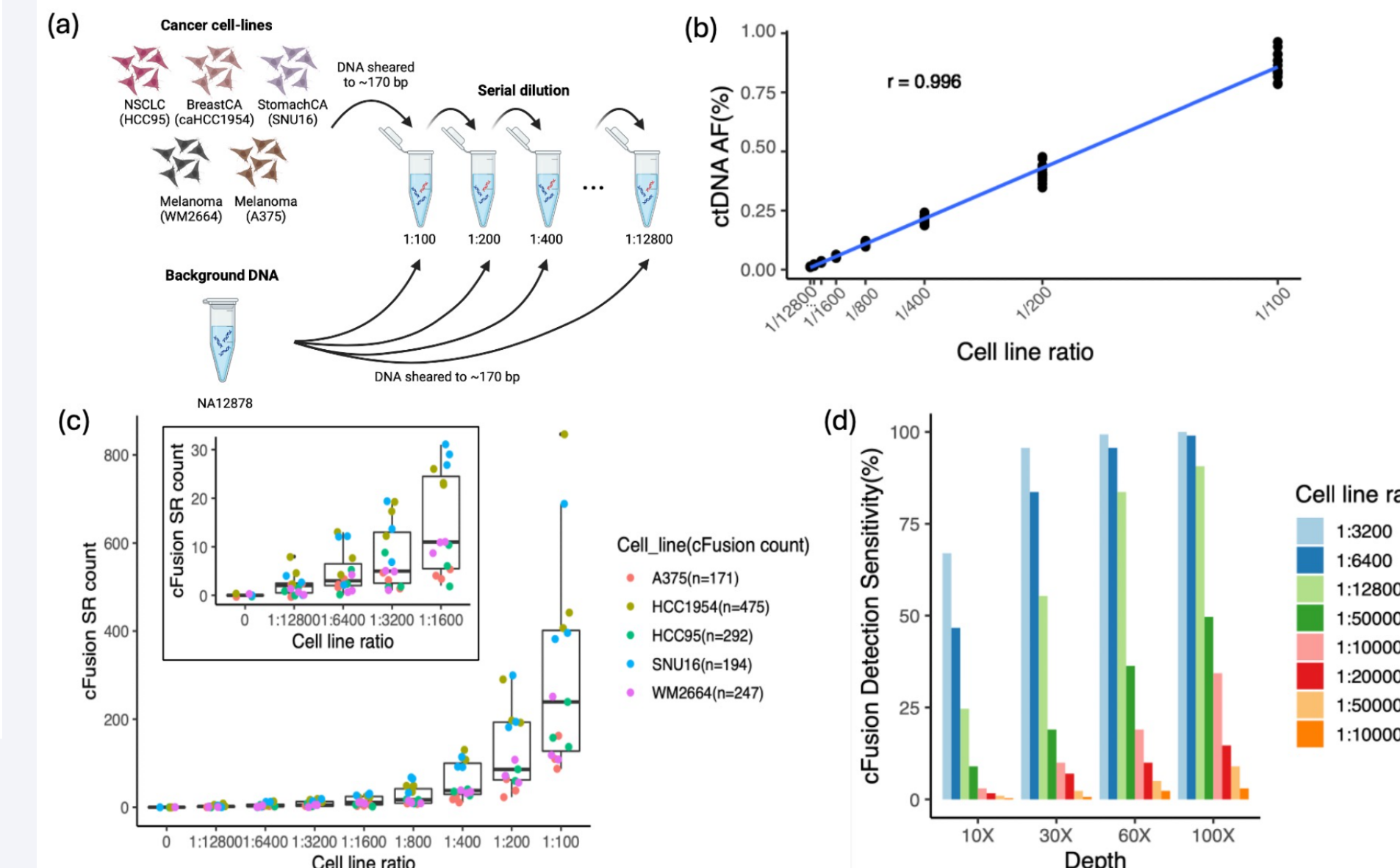


Figure 2. Analytical validation using cell line mixture experiments. **(a)** Five cancer cell lines (NSCLC, breast cancer, stomach cancer, and two melanomas) were manually mixed with background DNA (NA12878) at various ratios, with dilution levels up to 1:12,800. Each mixture was subjected to whole genome sequencing (WGS, ~60X) three times per dilution level. **(b)** All diluted cell lines were detected at each mixing ratio using the cSNV-based method, showing a strong correlation with the expected ratios ($r = 0.996$). **(c)** cFusion SRs from the cancer cell lines were detected in proportion to the mixing ratio. However, at lower dilution levels, some events were missed (1 miss at 1:6,400 [14/15 detected]; 4 misses at 1:12,800 [11/15 detected]). **(d)** Due to the unique sequences at fusion breakpoints, the limit of blank (LoB) for the cFusion-based method is effectively zero. In in silico dilution experiments up to 1:1,000,000, the sensitivity increased progressively with WGS depth.

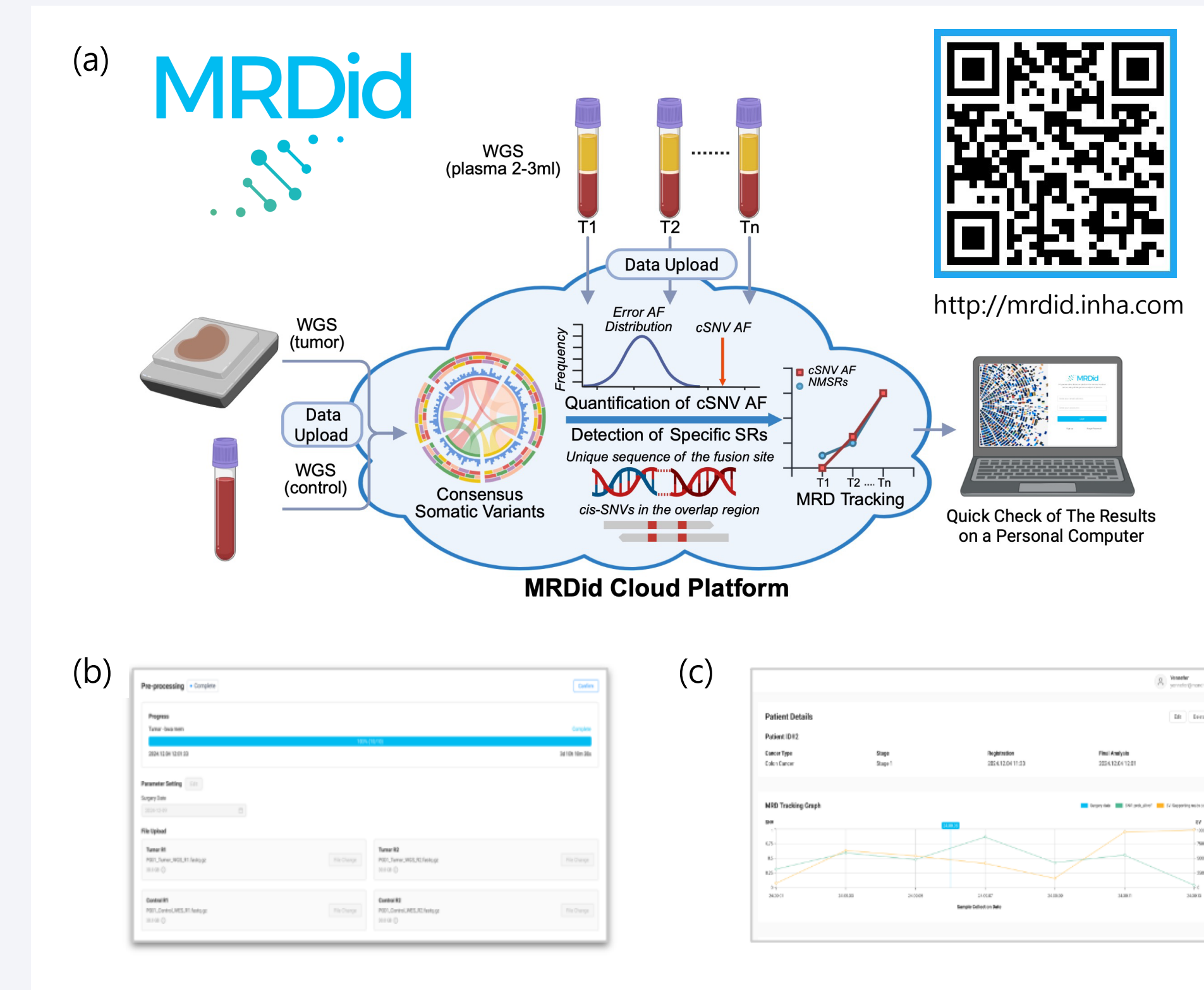


Figure 4. MRDId: Cloud platform for Minimal Residual Disease identification using individual-specific features. **(a)** QR code for accessing MRDId (<https://mrdid.inha.com>) and workflow of the cloud platform. **(b-c)** Whole genome sequencing (WGS) FASTQ files from tumor and matched normal samples are uploaded to initiate preprocessing, after which a consensus somatic variant set is generated. Upon uploading WGS data of plasma cfDNA (2–3 mL), quantification of cSNV AF, detection of cFusion SR and cis-SNVs are performed. Users can track serial MRD detection results through the website using a personal computer.

CONCLUSION

We developed algorithms to detect MRD by leveraging individual-specific genomic features from cfDNA WGS data, and validated this method using cancer cell-line experiments and clinical samples from various cancer types [1,2]. Since these algorithms relies solely on the unique genomic characteristics of individual samples, it does not require the construction of control panel datasets, and its bioinformatics pipeline is straightforward, making it well suited for cloud-based implementation.

Based on this advantage, we have developed **MRDId** (Cloud Platform for **M**inimal **R**esidual **D**isease **i**dentification using individual specific features), a robust, user-friendly cloud platform for MRD detection using cfDNA WGS data and patient-specific genomic signatures. Compared to current methodologies, MRDId eliminates the need for additional wet and dry lab processes during MRD analysis (Figure 5). It provides significant improvements in sensitivity, specificity, and operational convenience, enabling efficient MRD monitoring from only a small volume of blood.

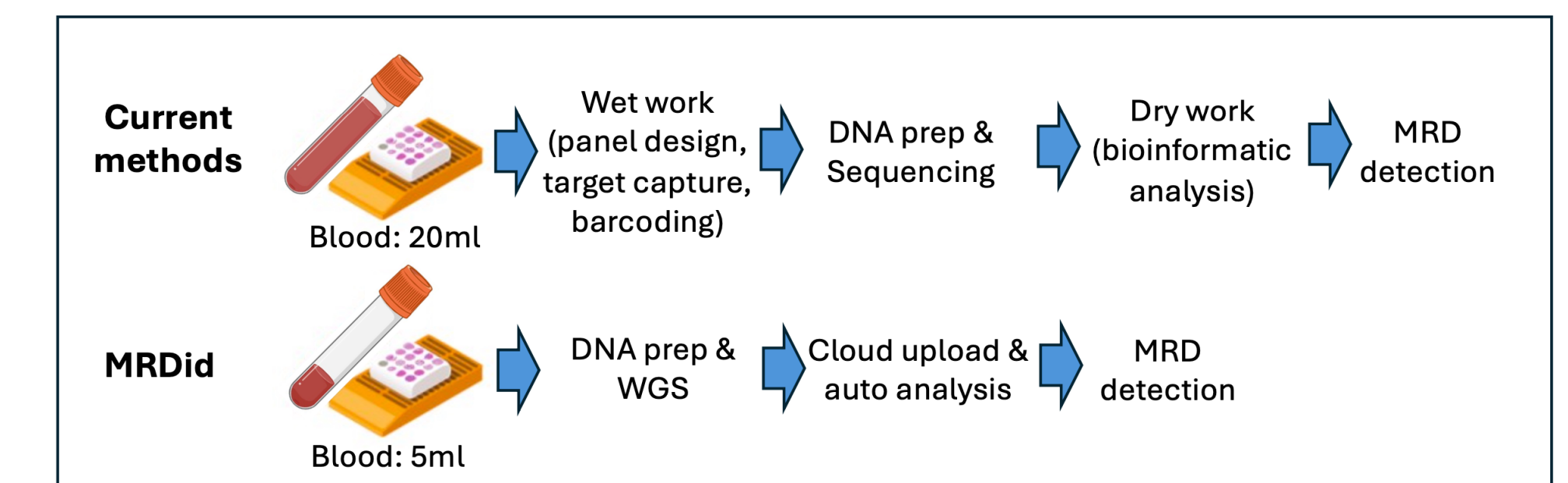


Figure 5. Comparison of current standard approaches for MRD detection with the MRDId platform in terms of workflow complexity

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