

MATRIX plasma-in-plasma contrived samples assessment and detection of MRD using the Personalis NeXT Personal assay.

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Background: Detection of circulating tumor DNA (ctDNA) has been shown to correlate with clinical outcome of oncology patients. Molecular residual disease (MRD) profiling by ctDNA is being rapidly deployed. Current tumor-informed MRD tests assess a relatively small number of personalised variants, placing limits on their detection sensitivity and ultimately leading to false-negative results due to insufficient assay limit of detection (LOD). Here we report a performance evaluation of the Personalis NeXT Personal tumor-informed MRD assay, using a novel design for contrived samples that are highly commutable to clinical samples, enabling robust assessment of these emerging MRD assays. **Methods:** Our novel samples were built from commercially acquired matched tumor and plasma samples, across different indications. The cancer plasma was diluted into a background of healthy donor plasma to create the 72 *plasma-in-plasma* samples in each study (total of 144). Personalis performed WGS on the matched solid tumor and normal samples from each patient. ~1800 somatic variants were selected for each patient. A personalized panel was designed and used to enrich for the selected targets in the individual plasma samples. An aggregated positive variant score was evaluated to determine the presence of ctDNA in each plasma sample. **Results:** MATRIX 1 panels averaged 1863 variants (range: 1818 to 1888) selected for MRD tracking. With 152 clinically relevant variants and additional assay components, an average of 2206 variants were assessed per patient. MATRIX 2 panels averaged 1836 variants (range: 1819 to 1867) selected for MRD tracking. With 2130 clinically relevant variants they averaged 4094 variants assessed per patient. In the MATRIX 1 study, tumor signal was detected in all analyzed samples, including 9 samples at 0.002% tumor plasma dilution, with an assay sensitivity of 100%. The MATRIX 2 study showed tumor signal detected in 14 of 16 samples at 0.001% tumor plasma dilution. The 2 false negatives were reported at the 0.001% tumor plasma dilution. Thus, the assay sensitivity was 87.5% at the lowest dilution (0.001%) and 96.8% overall. **Conclusions:** The MATRIX *plasma-in-plasma approach* is a robust option for assessing the sensitivity of MRD assays to low levels of ctDNA. This approach addresses all parts of an MRD assay for both the plasma and tumor/normal tissues, and is the closest thing to real clinical samples while allowing direct interrogation of sensitivity. Additionally, it allows assessment of any genomic or epigenomic biological feature. The Personalis NeXT Personal assay shows ultra-high sensitivity with reproducible data down to the 1-3 PPM range, and expansion of the personalized panel fixed clinical content allows tracking of more driver and resistance mutations with no impact to the MRD sensitivity. Research Sponsor: AstraZeneca.