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ORIGINAL ARTICLE

Evaluating Random-Access CLIA for Anti-TNF Drug Monitoring: a Comparison with Traditional ELISA

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SUMMARY

Background: **Accurate therapeutic drug monitoring of anti-TNF biologics such as infliximab and adalimumab and their corresponding antibodies is essential for optimizing treatment in inflammatory conditions. This study aimed to evaluate the analytical and clinical performance of a novel chemiluminescence immunoassay-based system, the i-TRACK10 and compare it to the established LISA Tracker ELISA kits.**
Methods: **A total of 200 clinical serum samples were analyzed for infliximab, adalimumab, and their respective antibodies using both platforms. Positive and negative agreements and precision were calculated using sample sets and controls. Method agreement was assessed via Deming regression, Bland-Altman analysis, and Lin's concordance correlation, following CLSI EP09-A3 guidelines with MedCalc software.**
Results: **The iTrack10 demonstrated strong association with ELISA across analytes (Pearson's r: 0.91-0.95), but concordance varied (Lin's CCC: 0.75 - 0.93) due to biases. Deming regression slopes (0.58 to 1.52), and Bland-Altman mean biases (-3.52 to 12.58), confirmed proportional differences with moderate variability between methods. Positive and negative agreement values were above 95% across all assays. Precision analysis confirmed low intra- and inter-assay variability, with coefficient of variations generally below 5%. The chemiluminescence immunoassay system offered rapid turnaround, expanded measurement ranges, and random-access operation.**
Conclusions: **The i-TRACK10 analyzer provides a reliable, accurate, and efficient alternative to traditional ELISA kits for therapeutic drug monitoring of anti-TNF agents. Its enhanced automation and performance characteristics support its integration into routine clinical laboratory workflows.**
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INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) is a multifunctional pro-inflammatory cytokine that plays a pivotal role in the pathogenesis of various immune-mediated inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease (IBD), psoriasis, and ankylosing spondylitis [1,2]. Acting through its receptors TNFR1 and TNFR2, TNF-α promotes inflammatory signaling cascades and cellular apoptosis [3]. The introduction of monoclonal antibodies targeting TNF-α, such

as infliximab (a chimeric IgG1) and adalimumab (a fully human IgG1), has significantly improved clinical outcomes for patients with chronic inflammatory conditions who are unresponsive to conventional immunosuppressive therapies [4]. Despite their clinical benefits, these biologics are not universally effective; approximately one-third of patients exhibit primary nonresponse, and many others experience secondary loss of response over time [5]. These therapeutic failures are often linked to immunogenicity [6], the development of anti-drug antibodies (ADAs) that neutralize drug activity or enhance drug clearance, resulting in subtherapeutic serum levels and diminished treatment efficacy [6].

The presence of ADAs has also been associated with infusion-related reactions and increased treatment discontinuation rates [6]. Monitoring drug trough concentrations and ADA levels, an approach known as therapeutic drug monitoring (TDM), has therefore become an integral component of personalized treatment strategies [7,8]. TDM not only facilitates early identification of inadequate drug exposure but also supports decisions regarding dose adjustment, treatment intensification, or therapeutic switching [8-10]. Current guidelines support both reactive TDM (in cases of nonresponse or relapse) and proactive TDM (during induction or maintenance phases) to sustain optimal drug levels and reduce immunogenic risk [10-12]. The utility of TDM has also been reinforced by pharmacokinetic models, such as target-mediated drug disposition, which provide insight into drug-target interactions and guide dosing strategies [10-12].

Several assay platforms have been developed for TDM, including enzyme-linked immunosorbent assays (ELISA), radioimmune-assays, homogeneous mobility shift assays, and chemiluminescence immunoassays (CLIA). ELISA-based tests are the most widely used in clinical laboratories due to their affordability and simplicity. However, their long turnaround times, batch processing limitations, and drug-sensitive formats, particularly for ADA detection, pose practical challenges [13].

Approximately five years ago, following a comprehensive evaluation of the Lisa-Tracker ELISA assays (LISA) (Theradiag, France), our laboratory was designated as the national center for measuring drug and antibody levels of Adalimumab (ADM and ADMab, respectively) and Infliximab (IFX and IFXab respectively) for Clalit Health Services (CHS), the largest healthcare provider in Israel. As demand steadily increased, manual testing, while accurate and clinically aligned, became increasingly labor-intensive. This growing workload necessitated the adoption of a more efficient solution, leading to the implementation of a random-access analyzer system.

In this study we aimed to evaluate a new CLIA-based analyzer: the i-TRACK10 (iT10) (Theradiag, FR) which offers random-access functionality and short turnaround time and expanded measurement ranges for drug and antibody levels. Our study was performed in a head-to-head manner between our gold standard LISA kits and the iT10 kits.

MATERIALS AND METHODS

Patients and samples

From the total number of weekly incoming samples, 200 were selected and evenly allocated into four groups: 50 for ADM drug levels, 50 for ADMab levels, 50 for IFX drug levels, and 50 for IFXab levels. An additional 12 samples were collected for precision analysis, following the same group distribution as the initial set. Precision was evaluated through five replicate measurements per sample and further supported by the use of the kit's internal controls, as well as external controls (C+, H, and L). All samples were collected at trough level, just prior to the administration of the next dose, at designated CHS community clinics. Following collection, samples were centrifuged at 2,400 RCF for 15 minutes, and the resulting serum was isolated and stored at -20°C until analysis.

The present retrospective study was carried out in adherence to the ethical principles set forth in the Declaration of Helsinki and Good Clinical Practice guidelines. Approval for conducting the study was obtained from the Human Subjects Protection Program of the Rabin Medical Center, Petah Tikva, Israel (#0525-25-RMC). The study participants exhibited no active involvement in the FC evaluation process, with no pertinent information procured from them.

Immunoassays

As previously noted, we conducted a comparative analysis between the currently established gold standard LISA kits and the iT10 system (both: Theradiag, FR), following the manufacturer's instructions and recommended protocols. All serum samples were analyzed in parallel using both platforms under identical pre-analytical conditions, including consistent handling procedures and a single freeze-thaw cycle to preserve sample integrity.

Statistical analysis

Thresholds for drug levels and antibody levels were established in accordance with the manufacturer's guidelines and range of detection of both systems. For ADM and IFX, drug levels were deemed positive if they exceeded the cutoff limit of detection of 0.5 µg/mL (according to range of detection of 0.5 - 20 µg/mL in the LISA kits and 0.5 - 24 µg/mL in the iT10 system). For ADMab and IFXab antibody levels of < 10 ng/mL were classified as negative, while levels above this threshold were considered intermediate and positive, specifically 10 - 200 ng/mL and > 200 ng/mL, respectively. Positive agreement and negative agreement were calculated based on the established cutoff values, using the LISA kits as the reference standard. These metrics were determined with the aid of a web-based calculator [14], and

the 200-sample dataset was classified into four categories: true positives, true negatives, false positives, and false negatives. Precision was evaluated using the 12-sample set, along with internal and external controls, by calculating the coefficient of variation (CV) across five consecutive runs. Agreement between the two methods was assessed using regression models that account for measurement error in both methods. For each analyte, Deming regression with a variance ratio of 1 (due to the absence of replicate precision estimates) was performed. Bland-Altman analysis was conducted to evaluate mean bias and 95% limits of agreement (LoA) between methods. Proportional bias was assessed by regressing the differences on the mean values. Lin's concordance correlation coefficient (CCC) was used to quantify overall agreement between methods, while Pearson's correlation coefficient (r) was reported only as a measure of association. Method comparison analyses (Deming regression, Bland-Altman plots, and Lin's CCC) were performed in accordance with CLSI EP09-A3 guidelines using MedCalc Statistical Software [15].

RESULTS

Of the 200 clinical samples analyzed across all assays (ADM, ADMab, IFX, IFXab), 100 samples yielded measurable concentrations above the limit of detection using the reference LISA method. These were similarly identified by the iT10 system, indicating strong analytical agreement between the two platforms. Ninety-three samples were determined to be below the detection limit, confirming accurate detection of negative cases. However, four samples were detected only by the iT10 system (positive only by iT10), while three samples were detected only by the reference LISA method (positive only by LISA). This yielded a positive agreement of 96.15%, a negative agreement of 96.88%, and an overall agreement of 96.5%, respectively. When stratifying the cohort into categories, the diagnostic positive agreement of the iT10 system was calculated to be 100% for ADM and 96.30% for IFX at trough serum levels. For anti-drug antibodies, the positive agreement was 92.31% for ADMab and 96.30% for IFXab. Negative agreement was 100% for both ADM and IFX, while ADMab and IFXab demonstrated negative agreements of 94.52% and 91.30%, respectively (Table 1). Overall diagnostic agreement at trough levels was determined to be 100% for ADM, 98% for IFX, and 94% for both ADMab and IFXab. Here, analytical agreement (positive, negative and overall) denotes concordance between numerical measurement results, without reference to clinical or therapeutic interpretation. For the quantitative drug assays (ADM and IFX), this comparison strictly reflects analytical equivalence and does not infer whether values fall within or outside the therapeutic ranges typically used for clinical decision-making (ADM: 5 - 8 µg/mL; IFX: 3 - 7 µg/mL). For ADM, Deming regression showed a slope of 0.58 (95% CI 0.49 - 0.66) and an intercept of 0.56 (0.02 - 1.10), indicating systematic underestimation by iT10 compared with LISA kits (Figure 1A, Table 2). Lin's CCC was 0.75, and Pearson's r was 0.95, reflecting strong association but reduced concordance due to bias (Table 2). Bland-Altman analysis showed a mean bias of -3.52 with 95% limits of agreement (LoA) from -11.93 to 4.90, confirming both systematic and proportional differences between methods (Figure 2A, Table 2). For ADM_ab, Deming regression yielded a slope of 1.52 (1.22 - 1.82) and an intercept of -4.00 (-7.65 to -0.35), indicating proportional bias with slightly higher values from iT10 (Figure 1B, Table 2). Lin's CCC was 0.86, and Pearson's r was 0.95, suggesting strong agreement but with consistent bias (Table 2). Bland-Altman analysis showed a mean bias of 12.58 with LoA -57.09 to 82.25, reflecting moderate variability between methods (Figure 2B, Table 2). For IFX, Deming regression showed a slope of 0.80 (0.64 - 0.97) and an intercept of 0.97 (0.32 - 1.63) (Figure 1C, Table 2). Lin's CCC was 0.93, and Pearson's r was 0.95 (Table 2). Bland-Altman analysis demonstrated a mean bias of -0.22 with LoA -5.84 to 5.39, indicating excellent concordance and clinically acceptable agreement between the methods (Figure 2C, Table 2). For IFX_ab, Deming regression showed a slope of 1.15 (0.96 - 1.34) and an intercept of -5.28 (-15.07 to 4.51) (Figure 1D, Table 2). Lin's CCC was 0.90, and Pearson's r was 0.91 (Table 2). Bland-Altman analysis demonstrated a mean bias of 6.53 with LoA -94.80 to 107.86, indicating good overall concordance but wider variability compared with IFX (Figure 2D, Table 2). The combined use of Deming regression, Bland-Altman plots, and Lin's CCC allowed detailed characterization of both statistical and clinical agreement between methods. As demonstrated by the Deming regression and Bland-Altman analyses (Figure 1 A - D, Figure 2 A - D), the iT10 system shows systematic but predictable bias relative to ELISA, particularly for ADM, which may warrant assay-specific interpretation or calibration adjustments in future validation studies. To evaluate precision and reproducibility of the iT10 system, five replicates were performed for 12 positive samples (as determined in a previous run using ELISA kits), with three samples tested per kit. In addition, five replicates were conducted for each of the three controls in every kit (C+, H = high, L = low), resulting in a total of four control sets. The coefficient of variation (CV) was calculated across five consecutive runs to evaluate the consistency of the measurements (Table 3). For the ADM assay, CVs ranged from 1.39% to 1.86%, indicating excellent reproducibility across samples 1 – 3. The ADMab assay demonstrated similarly high precision, with CVs between 1.88% and 4.77%; the highest variability was observed in sample 4 (CV = 4.77%) yet remained within acceptable analytical limits. Control samples for ADM and ADMab displayed consistent performance, with CVs ranging from 1.12% to 5.50%. The ADMab C^+ control showed the highest CV in this group (CV = 5.50%), though still indicative of good

Table 1. Qualitative comparison summary performance of iT10 versus LISA kits for ADM, ADMab, IFX, and IFXab.

	n	Samples detected by both systems	Samples undetected by both systems	Detected only by iT10	Detected only by LISA	Positive agreement	Negative agreement
ADM	50	36	14	0	0	100%	100%
ADMab	50	12	35	2	1	92.31%	94.52%
IFX	50	26	23	0	1	96.30%	100%
IFXab	50	26	21	2	1	96.30%	91.30%

Table 2. Method comparison between two systems (LISA and iT10) for IFX, ADM, and their corresponding antibodies (IFX_ab, ADM_ab).

Analyte	n	Pearson's r	Lin's CCC	Deming Slope	Slope 95% CI (low)	Slope 95% CI (high)	Deming Intercept	Intercept 95% CI (low)	Intercept 95% CI (high)	BA mean Bias	BA LoA low	BA LoA high
ADM	50	0.948	0.746	0.576	0.488	0.664	0.559	0.019	1.099	-3.517	-11.933	4.899
ADMab	50	0.946	0.864	1.517	1.218	1.816	-4.0	-7.648	-0.353	12.58	-57.093	82.252
IFX	50	0.952	0.931	0.802	0.636	0.969	0.974	0.319	1.629	-0.221	-5.835	5.392
IFXab	50	0.905	0.896	1.146	0.956	1.336	-5.281	-15.068	4.505	6.528	-94.801	107.858

BA Bland-Altman, BA units - absolute, LoA limit of agreement, CCC Lin's concordance correlation coefficient.

Table 3. Precision analysis of iT10 for quantification of ADM, ADMab, IFX, and IFXab.

ADM	Mean (µg/mL)	STDEV	CV %	Range	ADMab	Mean (ng/mL)	STDEV	CV %	Range
1	10.52	0.17	1.64	-	4	125.50	5.98	4.77	-
2	12.48	0.23	1.86	-	5	554.60	15.36	2.77	-
3	14.72	0.20	1.39	-	6	221.75	4.17	1.88	-
C+	4.12	0.12	2.83	5.0 ± 25%	C+	187.80	10.32	5.50	172.6 ± 25%
H	10.30	0.28	2.68	7.2 - 17.8	H	425.60	4.76	1.12	283 - 701
L	3.12	0.04	1.28	2.0 - 5.0	L	45.80	1.47	3.21	27 - 67
IFX	**Mean (µg/mL)**	**STDEV**	**CV %**	**Range**	**IFXab**	**Mean (ng/mL)**	**STDEV**	**CV %**	**Range**
7	9.38	0.47	5.02	-	10	127.40	4.50	3.53	-
8	6.60	0.23	3.46	-	11	669.00	13.61	2.03	-
9	15.90	0.68	4.27	-	12	661.00	10.08	1.52	-
C+	3.82	0.17	4.50	4.2 ± 25%	C+	184.40	2.04	1.10	195.6 ± 25%
H	9.26	0.81	8.71	5.5 - 13.5	H	585.80	12.29	2.10	330 - 819
L	1.82	0.04	2.20	1.0 - 2.5	L	66.60	2.24	3.37	29 - 71

Values represent mean concentrations, standard deviations (STDEV), coefficients of variation (CV%), and expected ranges for positive controls and (C+), high (H), and low (L) quality control levels.

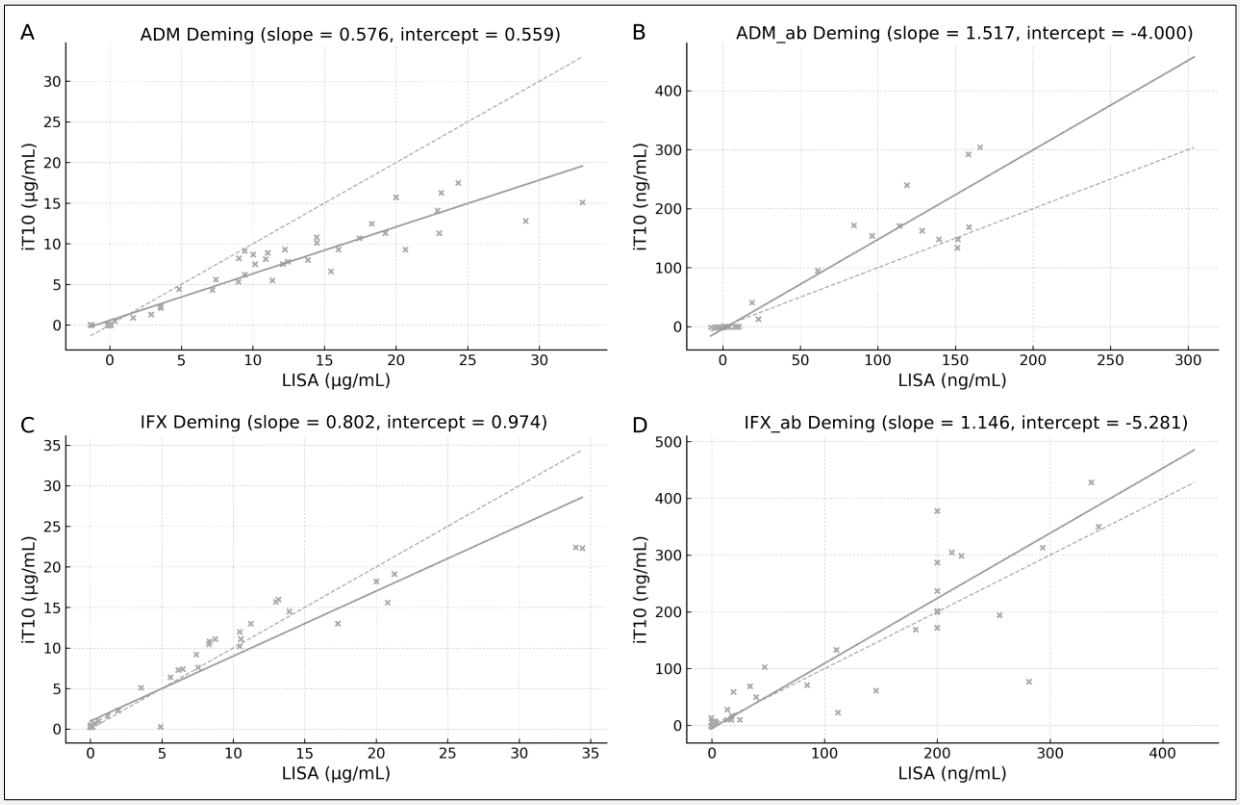

Figure 1. Deming regression plots comparing LISA and iT10 measurements for IFX, ADM, IFX_ab, and ADM_ab.

Panels (A - D) show Deming regression analyses for IFX and ADM (µg/mL) and their antibodies IFX_ab and ADM_ab (ng/mL). Solid lines indicate Deming regression fits, dashed lines represent the line of identity. Axes are labeled LISA (x) and iT10 (y).

precision. In the IFX assay, samples 7 - 9 exhibited CVs between 3.46% and 5.02%, with sample 7 at the upper threshold of acceptability. IFXab assay precision was notably high, with CVs ranging from 1.52% to 3.53% across samples 10-12. All control samples for IFX were within their predefined acceptable ranges. The H control yielded the highest variability (CV = 8.71%), while the L control showed strong precision (CV = 2.20%). IFXab control samples demonstrated excellent reproducibility, with CVs between 1.10% and 3.37%, supporting the reliability and robustness of the assay system (Table 3).

DISCUSSION

The current study evaluated the analytical performance of the iT10 CLIA-based analyzer in comparison with the established ELISA-based LISA kits for quantifying trough levels of IFX and ADM, as well as their respective anti-drug antibodies. Overall, the iT10 system demonstrated high concordance with the LISA platform, supporting its utility as a viable alternative for routine TDM in clinical practice.

Our findings indicate excellent qualitative performance of the iT10 system, with an overall positive agreement of 96.15%, negative agreement of 96.88%, and overall diagnostic agreement of 96.5% when benchmarked against the LISA kits. These metrics are consistent with previous validation studies of automated CLIA platforms, which have demonstrated similarly robust diagnostic metrics [16,17]. Notably, drug-level assessments showed higher qualitative agreement than anti-drug antibody detection. Specifically, the iT10 system achieved 100% positive and negative agreements for ADM, and 96.3% positive agreement with 100% negative agreement for IFX. These results underscore the reliability of the iT10 analyzer in detecting therapeutic drug concentrations at trough levels, a critical factor in guiding dosing adjustments and assessing treatment adequacy [18]. It is important to note that for ADM and IFX, drug levels were deemed positive if they exceeded

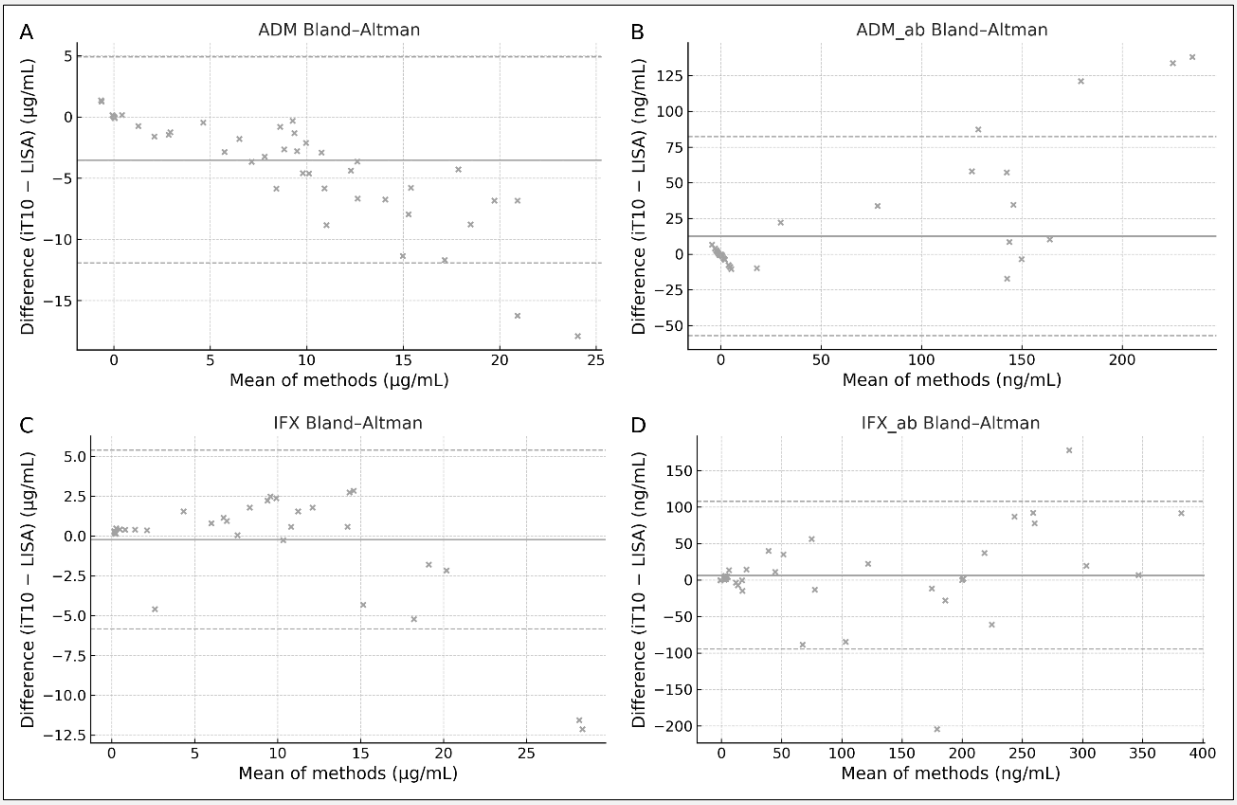

Figure 2. Bland-Altman plots comparing LISA and iT10 measurements for IFX, ADM, IFX_ab, and ADM_ab.

Panels (A - D) display differences between iT10 and LISA against their mean for each analyte. Solid lines indicate mean bias, dashed lines show 95% limits of agreement (LoA). Axes are labeled using LISA and iT10.

the cutoff limit of detection (0.5 µg/ml), which varies significantly when assessing therapeutic value positivity. For instance, while a drug level of < 5 µg/ml is regarded as low to nearly absent for certain patients, it may be adequate for achieving clinical remission in others.

In contrast, slightly reduced positive and negative agreements were observed for antibody detection - 92.31% and 94.52% for ADMab, and 96.3% and 91.3% for IFXab, respectively. This observation aligns with previous reports highlighting the inherent analytical complexity of ADA detection, particularly in the presence of circulating drug [7,13,19]. The reduced agreement in ADA assays may also reflect the biological variability of immunogenic responses and the differential sensitivity of assay formats (bridging ELISA vs. CLIA) to low-affinity or low-titer antibodies [8,18,19]. Despite these limitations, the diagnostic performance remained within acceptable clinical thresholds, affirming the feasibility of iT10 for ADA surveillance in routine care.

In comparing iTrack10 with ELISA, our analyses revealed varying degrees of agreement across analytes. For ADM, the Deming regression slope of 0.58 and intercept of 0.56 indicating a consistent underestimation by iTrack10. Although Pearson's r was high (0.95), Lin's CCC was lower (0.75), suggesting strong correlation but reduced concordance due to bias. The Bland-Altman mean bias of -3.52 and wide limits of agreement further supported the presence of both systematic and proportional differences. ADM_ab showed a different pattern, with a Deming slope of 1.52 and intercept of -4.00, pointing to proportional bias with elevated readings from iTrack10. Lin's CCC (0.86) and Pearson's r (0.95) again reflected strong association, though the Bland-Altman bias of 12.58 and LoA highlighted moderate variability. In contrast, IFX demonstrated excellent agreement between platforms. The Deming slope of 0.80, intercept of 0.97, and Lin's CCC of 0.93 all supported high concordance, with a minimal Bland-Altman bias of -0.22 and narrow LoA, suggesting clinical interchangeability. IFX_ab also showed good agreement, with a Deming slope of 1.15 and intercept of -5.28. Lin's CCC was 0.90 and Pearson's r 0.91, though the Bland-Altman bias of 6.53 and broader LoA indicated

greater variability compared to IFX. Overall, these findings underscore excellent concordance for IFX, acceptable agreement for IFX_ab, and quantifiable biases for ADM and ADM_ab**.** These results are in line with the expected variability in ADM measurements across assay types [10,20,21] and primarily reflect calibration and proportional bias**,** rather than random error. These differences are consistent and quantifiable, suggesting that method-specific reference ranges or conversion factors could allow iTrack10 results to be interpreted reliably**.**

It is important to emphasize that this study assessed analytical agreement between the iT10 and ELISA platforms rather than therapeutic or clinical agreement. Analytical agreement evaluates the quantitative relationship between two assays, while therapeutic interpretation requires determining whether a given concentration lies within, below, or above an established clinical range. The systematic underestimation observed for adalimumab (Deming slope = 0.58) therefore reflects a calibration bias rather than analytical inaccuracy. Consequently, direct substitution of iT10 results for ELISA-derived therapeutic ranges (e.g., 5 - 8 µg/mL) is not appropriate without further harmonization. To address this, future studies should establish assay-specific reference intervals or apply regression-based conversion equations to allow consistent clinical interpretation across methods.

The precision analysis reinforced the analytical robustness of the iT10 platform. Across five replicate runs of 12 clinical samples and four control sets, the coefficient of variation (CV) remained below 5.5% for all analytes and controls, with most values well under 3%. These findings are consistent with the performance criteria recommended by regulatory and laboratory standard bodies for immunoassays [11,12,22,23]. Importantly, even samples at the upper and lower ends of the concentration spectrum demonstrated acceptable precision, underscoring the platform's suitability for detecting a wide range of clinically relevant values.

From an operational perspective, the implementation of a random-access CLIA system offers significant workflow advantages. Compared to traditional ELISA platforms, the iT10 provides shorter turnaround times, minimal hands-on time, and the flexibility to run individual samples without batch constraints. These features are particularly valuable in high-throughput settings such as national reference laboratories, where rapid reporting and efficient sample handling are essential for timely clinical decision-making [24].

Nevertheless, several limitations merit consideration. First, while our study used LISA as the gold standard, no absolute reference method exists for TDM in anti-TNF therapy. Thus, observed discrepancies may partly reflect inter-assay variability rather than analytical inaccuracy. Second, our sample size, though adequate for initial validation, may not capture rare cases or borderline results that could challenge assay positive agreement. Future studies involving external proficiency panels or real-world clinical outcomes could further elucidate the clinical implications of platform-specific differences.

In conclusion, the iT10 CLIA analyzer demonstrates high positive and negative agreements and reproducibility in measuring both drug and ADA levels of ADM and IFX. Its strong concordance with established ELISA-based assays, combined with operational advantages such as automation and random access, supports its integration into routine TDM workflows. Broader adoption of such automated systems may facilitate more timely and individualized treatment adjustments, ultimately enhancing therapeutic outcomes for patients receiving anti-TNF agents.

Declaration of Generative AI in Scientific Writing:
In the course of preparing this work, the authors utilized AI to assess the accuracy of the images generated in relation to the original raw data. Following the use of this service, the authors meticulously reviewed and modified the content as necessary, thereby assuming complete responsibility for the publication's content.

Declaration of Interest:
The LISA Tracker and i-TRACK10 kits used in this evaluation study were supplied by Theradiag (Beaubourg, France). The authors maintained full independence in the study's design, conduct, data analysis and interpretation, as well as in the decision to publish and the preparation of the manuscript. Except as disclosed above, the authors declare no conflicts of interest. All authors have reviewed and approved the final version of the manuscript.

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