DiaSorin S.p.A. - Via Crescentino snc - 13040 Saluggia (VC) - Italy
DiaSorin Inc. - Stillwater, Minnesota 55082-0285, U.S.A.
www.diasorin.com
Tel. +39.0161.4871

The symbols glossary is provided electronically and can be found in the Dialog section at www.diasorin.com using the part and lot numbers associated with the corresponding IVD product.

LIAISON® QuantiFERON®-TB Gold Plus ([REF] 311020)

Caution: U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner.
For *in vitro* diagnostic use only

1. INTENDED USE

The LIAISON® QuantiFERON®-TB Gold Plus assay is an *in vitro* diagnostic test for the detection of interferon-γ (IFN-γ) in human lithium heparin plasma by chemiluminescence immunoassay (CLIA) using the LIAISON® XL Analyzer. QIAGEN QuantiFERON®-TB Gold Plus Blood Collection Tubes, containing a peptide cocktail simulating ESAT-6 and CFP-10 proteins, are used in conjunction with the LIAISON® QuantiFERON®-TB Gold Plus assay to stimulate cells in heparinized whole blood. Detection of IFN-γ is used to identify *in vitro* responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection.

The assay is a qualitative indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations to assist the clinician in making individual patient management decisions. The LIAISON® QuantiFERON®-TB Gold Plus assay must be performed using the LIAISON® XL Analyzer.

2. SUMMARY AND EXPLANATION OF THE TEST

Tuberculosis (TB) is a communicable disease, transmitted almost exclusively by cough aerosols carrying pathogens of the *M. tuberculosis* complex. TB continues to be a major public health threat, causing an estimated 10.4 million new cases and 1.3 million deaths from TB in 2016 (1). Pathogenesis is characterized by a period of asymptomatic subclinical infection, defined broadly as latent tuberculosis infection (LTBI), which might last for weeks or decades. However, there is no diagnostic gold standard for LTBI. Two tests are available for the identification of LTBI: the tuberculin skin test (TST) and the interferon gamma release assay (IGRA). They represent indirect markers of *M. tuberculosis* exposure and indicate a cellular immune response to *M. tuberculosis*.

From an operational point of view, LTBI may best be defined as a state of persistent immune response to *M. tuberculosis* antigens detected either by the TST or by IGRA without evidence of clinically symptomatic TB. Based on this definition, individuals with LTBI carry an increased risk of progression to active TB disease. However, an unknown but large number of those with LTBI will not develop active TB disease, either because their immune system persistently controls mycobacterial replication or because the mycobacteria are no longer viable. (2)

In most individuals, initial *M. tuberculosis* infection is eliminated or contained by the host's defenses, and infection remains latent. However, latent TB bacilli may remain viable and "reactivate" later to cause active TB disease. Identification and treatment of LTBI can substantially reduce the risk of developing active disease.

The goal of testing for LTBI is to identify individuals who are at increased risk of developing active TB; these individuals would benefit most from treatment of LTBI (also termed preventive therapy or prophylaxis).

In general, testing for LTBI is indicated when the risk of developing disease from latent infection (if present) is increased; examples include likely recent infection (e.g., close contact of a person with TB) or a decreased capacity to contain latent infection (e.g., because of immunosuppression, as in the case of young children in contact with those with active TB, people living with human immunodeficiency virus [HIV] infection, or otherwise immunosuppressed persons because of medications or conditions such as uncontrolled diabetes).

There are currently two accepted tests for the detection of LTBI: the Tuberculin Skin Test (TST) and IGRA.

The TST, performed using the Mantoux technique (3), consists of an intradermal injection of purified protein derivative (PPD). In a person who has cell-mediated immunity to these tuberculin antigens, a delayed-type hypersensitivity reaction will occur within 48 to 72 h. The reaction will cause localized induration of the skin at the injection site, and the transverse diameter should be measured (as millimeters of induration) by a trained individual and interpreted using risk-stratified cutoffs (4). It is important to note that cell-mediated immunity to tuberculin antigens can sometimes reflect exposure to similar antigens from environmental mycobacteria or *Mycobacterium bovis bacillus Calmette-Guérin* (BCG) vaccination or a previous infection that has been cleared (through immunological mechanisms or treatment). The TST has several known limitations. Completing the TST requires two health care visits, for tuberculin injection and induration measurement, which results in loss of approximately 10% of cases (5). In addition, measurement of reaction size is subject to inter-observer variability, although this is greatly reduced with adequate training (6). False-positive and false-negative results may occur. There are two important causes of false-positive results: nontuberculous mycobacterium (NTM) infection and prior BCG vaccination (7). NTMs are not a clinically important cause of false-positive TST results, except in populations with a high prevalence of NTM sensitization and a very low prevalence of TB infection (7). The impact of BCG on TST specificity depends on when BCG is given and on how many doses are administered (7). If BCG is administered at birth (or during infancy) and not repeated, then its impact on TST specificity is minimal and can be ignored while interpreting the results. In contrast, if BCG is given after infancy (e.g., school entry) and/or given multiple times (i.e., booster shots), then TST specificity is compromised (7).

False-negative TST results may occur because of limited sensitivity in particular patient subgroups (e.g., immunosuppressed individuals, due to medical conditions such as HIV infection or malnutrition, or those taking immunosuppressive medications), due to severe tuberculosis disease or because of pre-analytical or analytical sources of test variability (e.g., improper tuberculin handling or placement or incorrect interpretation of test results) (8, 9).

IGRAs are *in vitro* blood tests of cell-mediated immune response; they measure T-cell release of IFN-γ following stimulation by antigens specific to the *M. tuberculosis* complex (with the exception of BCG substrains), i.e., early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These antigens are encoded by genes located within the region of difference 1 (RD1) locus of the *M. tuberculosis* genome (10, 11). They are more specific than PPD for *M. tuberculosis* because they are not encoded in the genomes of any BCG vaccine strains or most species of NTM, other than *M. marinum, M. kansasii, M. szulgai, and M. flavescens* (12). However, not all NTMs have been studied for cross-reactivity.

There is some evidence of cross-reactivity between ESAT-6 and CFP-10 of *M. tuberculosis* and *M. leprae* (13,14), but the clinical significance of this in settings where leprosy and TB are endemic (e.g., India and Brazil) is poorly characterized. IGRAs appear to be unaffected by most infections with NTMs, which can cause false positive TSTs (12).

Since there is no gold standard for LTBI, sensitivity and specificity are typically estimated using surrogate patient cohorts. Sensitivity is estimated by testing a cohort of culture-confirmed active TB cases, while specificity is estimated by testing a cohort of low-risk individuals with no known TB exposure in low-incidence settings (15).

The TST and IGRA tests are based on immunological sensitization to mycobacterial antigens; a practical benefit of IGRA tests is that they require only a single laboratory test with negative and positive controls, and only one visit (16). By nature, functional T-cell assays are highly susceptible to variability by numerous factors at multiple levels, including assay manufacturing, pre-analytical processing, analytical testing and immunomodulation, therefore cases of conversion and reversion in individuals undergoing serial testing should not be excluded.

The LIAISON® QuantiFERON®-TB Gold Plus assay is an IGRA technology assessing cell-mediated immune (CMI) response through measurement of IFN-γ in a whole blood sample. The use of the QIAGEN QuantiFERON®-TB Gold Plus Blood Collection Tubes in conjunction with the LIAISON® QuantiFERON®-TB Gold Plus assay for detection and subsequent quantification of IFN-γ forms the basis of this test.

The QIAGEN QuantiFERON®-TB Gold Plus Blood Collection Tubes include two distinct TB antigen tubes: TB Antigen Tube 1 (TB1) and TB Antigen Tube 2 (TB2). Both tubes contain peptide antigens from the MTB-complex-associated antigens, ESAT-6 and CFP-10 that are designed to elicit CMI responses from CD4+ T-helper lymphocytes; the TB2 tube contains an additional set of peptides targeted to the induction of CMI responses from CD8+ cytotoxic T lymphocytes.

3. PRINCIPLE OF THE PROCEDURE

The LIAISON® QuantiFERON®-TB Gold Plus detects the analyte IFN-γ by direct, sandwich chemiluminescence immunoassay (CLIA). Anti IFN-γ monoclonal (mouse) antibodies are used for coating magnetic particles (solid phase) and anti IFN-γ monoclonal (mouse) antibodies are linked to an isoluminol derivative forming an isoluminol-antibody conjugate. Binding between the monoclonal antibodies and isoluminol in the conjugate is mediated by a Biotin-Streptavidin immunocomplex.

During the first incubation, analyte IFN-γ present in calibrators, samples or controls will bind to the solid phase and conjugated monoclonal antibodies and form a sandwich. Any unbound material in the test sample is removed with a wash cycle. During the second incubation, Assay Buffer W is added to reduce non-specific binding, followed by a second wash cycle.
Next, the starter reagents are added and a flash chemiluminescence reaction is induced. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) and is indicative of the amount of analyte IFN-γ present in calibrators, samples or controls.

4. MATERIALS PROVIDED

Reagent Integral

Magnetic Particles (2.5 mL)	**[SORB]**	Magnetic particles coated with antibody to human IFN-γ (mouse monoclonal), BSA, phosphate buffer, < 0.1% sodium azide.
Diluent (18 mL)	**[DIL]**	BSA, casein, phosphate buffer, EDTA, 0.2% ProClin® 300, Non-specific IgG (mouse polyclonal), gentamycin sulphate 0.1 g/L, detergents.
Assay Buffer W (2 x 23 mL)	**[BUF|W]**	BSA, casein, phosphate buffer, EDTA, 0.2% ProClin® 300, detergents, SDS and an inert blue dye.
Total Number of Tests		200

The order of reagents listed above reflects the layout of containers in the Reagent Integral.

Individual Reagent Vials

Calibrator A (lyophilized, 2 mL)	**[CAL|A]**	Recombinant human IFN-γ (produced in *E. coli*), HEPES buffer, BSA, bovine serum, 0.4% ProClin® 300, 0.2 g/L gentamycin sulfate, detergents.
Calibrator B (lyophilized, 2 mL)	**[CAL|B]**	Recombinant human IFN-γ (produced in *E. coli*), HEPES buffer, BSA, bovine serum, 0.4% ProClin® 300, 0.2 g/L gentamycin sulfate, detergents.
Buffer R (2 x 4.5 mL)	**[BUF|R]**	Streptavidin conjugated with isoluminol derivative, BSA, casein, phosphate buffer, 0.2% ProClin® 300, gentamycin sulphate 0.1 g/L, Non-specific IgG (mouse polyclonal), detergents.
Conjugate (lyophilized 2 x 4 mL)	**[CONJ]**	Biotinylated Antibody to human IFN-γ (mouse monoclonal), HEPES buffer, BSA, casein, Non-specific IgG (mouse polyclonal), 0.2% ProClin® 300, gentamycin sulphate 0.1 g/L, detergents, anti-proteases.

Buffer R, Diluent, Assay Buffer W and Magnetic Particles are provided ready-to-use. Calibrator A, Calibrator B and Conjugate are provided lyophilized.

ProClin® is a trademark of the Dow Chemical Company (Dow) or an affiliated company of Dow.

Materials Required but Not Provided

LIAISON® XL Analyzer

LIAISON® XL Cuvettes ([REF] X0016).
LIAISON® XL Disposable Tips ([REF] X0015).
LIAISON® XL Starter Kit ([REF] 319200).
LIAISON® Wash/System Liquid ([REF] 319100).
LIAISON® XL Waste Bags ([REF] X0025).

Additional Required Materials

LIAISON® Control QuantiFERON®-TB Gold Plus ([REF] 311021).

Additional Required Materials from other Suppliers

QIAGEN QuantiFERON®-TB Gold Plus Blood Collection Tubes (QFT®-Plus collection tubes ref. 622433, 622536, 623433, 622536). For orders and information contact QIAGEN local representative or visit www.qiagen.com.

QIAGEN QFT®-Plus collection tubes	**Catalog Number**
QuantiFERON®-TB Gold Plus Collection Tubes 200 QFT-Plus Blood Collection Tubes (50 each: Nil, TB1, TB2, and Mitogen tube)	622536
QuantiFERON®-TB Gold Plus Dispenser Pack Dispenser pack of QFT-Plus Blood Collection Tubes in 25 packs per carton, each pack including: 1 Nil, 1 TB1, 1 TB2, and 1 Mitogen tube. 1 Package Insert is included per carton.	622433
QuantiFERON®-TB Gold Plus HA Blood Collection Tubes 200 QFT-Plus HA Blood Collection Tubes (50 each: Nil, TB1, TB2 and Mitogen tubes)	623536
QuantiFERON®-TB Gold Plus HA Dispenser Pack Dispenser pack of QFT-Plus HA Blood Collection Tubes in 25 packs per carton, each pack including: 1 Nil HA tube, 1 TB1 Antigen HA tube, 1 TB2 Antigen HA tube and 1 Mitogen HA tube. 1 Package Insert is included per carton.	623433

5. WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use only.
- Observe the normal precautions required for handling all laboratory reagents.
- Do not eat, drink, smoke or apply cosmetics in the assay laboratory.
- Do not pipette by mouth.
- Strict adherence to the LIAISON® QuantiFERON®-TB Gold Plus assay instructions and QuantiFERON®-TB Gold Plus Blood Collection Tube instructions are necessary to obtain accurate results.
- Avoid direct contact with potentially infectious substances by wearing appropriate personal protective equipment such as laboratory coats, goggles, and disposable gloves. Wash hands thoroughly after removal of gloves.
- Avoid splashing or aerosolization of samples or reagents. All drops and spills must be wiped up with an appropriate disinfectant such as a sodium hypochlorite solution with 0.5% active chlorine, and all soiled materials must be disposed of as infected waste.
- All waste associated with biological samples, biological reagents and disposable materials used for the assay must be considered potentially infectious and therefore should be disposed of in accordance with the national, state or local regulations and guidelines of the agencies holding jurisdiction over the laboratory.
- The LIAISON® XL Analyzer should be cleaned and decontaminated on a routine basis. See the LIAISON® XL Analyzer Operator's Manual for the cleaning and decontamination procedures.
- Do not pool the contents of different vials of the same reagent (even if the reagents are from the same lot).
- Components from the same reagent kit lot may be used interchangeably. However components from different reagent kit lots must not be used interchangeably.
- Do not use kits or components beyond the expiration date indicated on the label.
- Previously frozen test samples, once thawed, must be thoroughly mixed prior to testing.

Chemical Hazard and Safety Information

- Reagents in this kit are classified in accordance with the US OSHA Hazard Communication Standard; individual US State Right-to-Know laws; Canadian Centre for Occupational Health and Safety Controlled Products Regulations; and European Union EC Regulation 1272/2008 (CLP) (for additional information see Safety Data Sheet available on www.diasorin.com).

• Hazardous reagents are classified and labelled as follows:

REAGENTS:	**[BUF|W]**, **[BUF|R]**, **[DIL]**	[CAL|A] (lyophilized), [CAL|B] (lyophilized), [CONJ] (lyophilized)
CLASSIFICATION:	Skin sens. 1 H317	Eye irrit. 2 H319 Skin irrit. 2 H315 Skin sens. 1 H317 Aquatic Chronic 3 H412
SIGNAL WORD:	Warning	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction.	H315 Causes skin irritation. H317 May cause an allergic skin reaction. H319 Causes serious eye irritation. H412 Harmful to aquatic life with long lasting effects.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/ vapours/spray. P280 Wear protective gloves/protective clothing/ eye protection/face protection. P363 Wash contaminated clothing before reuse.	P261 Avoid breathing dust/fume/gas/mist/ vapours/spray. P280 Wear protective gloves/protective clothing/ eye protection/face protection. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P273 Avoid release to the environment.
CONTAINS: (only substances prescribed pursuant to Article 18 of EC Regulation 1272/2008).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin® 300); gentamycin sulfate salt.

Note: after reconstitution [CAL|A], [CAL|B], [CONJ] are classified as reported here below:

REAGENTS:	[CAL|A] (reconstituted), [CAL|B] (reconstituted), [CONJ] (reconstituted)
CLASSIFICATION:	Skin sens. 1 H317
SIGNAL WORD:	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P363 Wash contaminated clothing before reuse.
CONTAINS: (only substances prescribed pursuant to Article 18 of EC Regulation 1272/2008).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin® 300).

Reagent containing sodium azide (Magnetic Particles [SORB])

Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after disposal, flush with a large volume of water to prevent azide build-up. For further information, refer to "Decontamination of Laboratory Sink Drains to Remove Azide Salts", in the Manual Guide-Safety Management No. CDC-22 issued by the Centers for Disease Control and Preventions, Atlanta, GA, 1976.

Pursuant to EC Regulation 1272/2008 (CLP), [SORB] is labeled as EUH210, safety data sheets available on request.

For additional information, see Safety Data Sheets available on www.diasorin.com.

6. PREPARATION OF REAGENTS

Please note the following important reagent handling precautions.

REAGENT INTEGRAL

Resuspension of Magnetic Particles

Magnetic particles must be completely resuspended before the reagent integral is placed on the LIAISON® XL Analyzer instrument. Follow the steps below to ensure complete resuspension:

– Before the seal is removed, rotate the small wheel at the magnetic particle vial compartment until the colour of the suspension has changed to brown.
– Gentle and careful side-to-side mixing may assist in the resuspension of the magnetic particles (avoid foam formation).
– Visually check the bottom of the magnetic particle vial to confirm that all settled magnetic particles have been resuspended.
– Carefully wipe the surface of each septum to remove residual liquid.
– Repeat all steps as necessary until the magnetic particles are completely resuspended.

Foaming of Reagents

In order to ensure optimal performance of the reagent integral, foaming of all reagents should be avoided. Follow the steps below to prevent foaming of reagents:

– Visually inspect the reagents, calibrators in particular (located in position two and three following the magnetic particle vial), to ensure there is no foaming present before using the reagent integral.
– If foam is present after resuspension of the magnetic particles, place the integral on the LIAISON® XL Analyzer instrument and allow the foam to dissipate.
– The reagent integral is ready for use once the foam of all reagents has dissipated and the integral is positioned onboard the LIAISON® XL Analyzer instrument and mixing.

Loading of Reagent Integral into the Reagent Area

– The LIAISON® XL Analyzer instrument is equipped with a built-in solid-state magnetic device which aids in complete resuspension of microparticles prior to placement of the reagent integral into the reagent area of the instrument. Refer to the LIAISON® XL Analyzer operator's manual for details.
  a. Insert the reagent integral into the dedicated slot.
  b. Allow the reagent integral to remain in the solid-state magnetic device for at least 30 seconds (up to several minutes). Repeat as necessary.
– Place the reagent integral into the reagent area of the LIAISON® XL Analyzer with the label facing left and let it stand for 15 minutes before using. The analyzer automatically stirs and completely resuspends the magnetic particles.

CONJUGATE

Conjugate for LIAISON® QuantiFERON®-TB Gold Plus assay is supplied lyophilized. Buffer R is provided in liquid format. Conjugate and Buffer R are kit lot specific and must be used only with the associated reagent integral lot. Correct lot matching between the reagent integral and Conjugate is automatically checked by the LIAISON® XL Analyzer. Each vial of the Conjugate reagent allows 200 tests to be performed.

One Buffer R vial must be used to reconstitute one vial of lyophilized Conjugate.

Do not pool the contents of different Buffer R vials, even if they belong to the same lot. Discard the remaining volume of a vial of Buffer R after using it for Conjugate reconstitution.

Do not pool the contents of different Conjugate vials, even if they belong to the same lot.

Proper reconstitution of Conjugate is essential.

– Reconstitute the Conjugate vial contents with 4 mL of Buffer R.
– Seal the Conjugate vial with the stopper cap and mix thoroughly by gentle inversion 5 times. Avoid foaming.
– Allow the Conjugate vial to stand at 18°-25°C for at least 15 minutes to achieve complete dissolution.
– Affix the provided label to the Conjugate vial.
– Once reconstituted, refer to Section 7 for storage guidelines.
– The reconstituted Conjugate solution must be loaded onto the LIAISON® XL Analyzer in the ancillary reagent area, immediately before use.
– For details on the reagent use in the ancillary reagent area on board the instrument, refer to the LIAISON® XL Analyzer operator's manual.

The original vial label refers only to the lyophilized Conjugate. Once reconstituted, pursuant to EC Regulation 1272/2008 (CLP), the Conjugate is classified as Skin sens. 1 H317. For more details, refer to Section 5.

CALIBRATORS

Calibrators for LIAISON® QuantiFERON®-TB Gold Plus assay are supplied lyophilized. Calibrators are kit lot specific and must be used only with the reagent integral lot they are matched with. Correct lot matching between the reagent integral and Calibrators is reported on the integral label.

Do not pool the contents of different Calibrator vials, even if they belong to the same lot.

Proper reconstitution of Calibrators is essential.

– LIAISON® QuantiFERON®-TB Gold Plus Calibrators are supplied lyophilized.
– Reconstitute the vial contents with 2.0 mL of deionized or distilled water.
– Allow the vials to stand for at least 15 minutes at 18°-25°C to achieve complete dissolution.
– Affix the provided barcode label to the vial.
– Mix vials thoroughly by gentle inversion; avoid foaming.
– Once reconstituted, refer to Section 7 for storage guidelines.
– The reconstituted solution of each calibrator can be stored in original vials and loaded on the instrument on a suitable rack. For details on the use of the Calibrators on board the instrument, refer to the LIAISON® XL Analyzer Operator's Manual.

Original vial labels refer only to lyophilized Calibrators. Once reconstituted, pursuant to EC Regulation 1272/2008 (CLP), calibrators are classified Skin sens. 1 H317. For more details, refer to Section 5.

CONTROLS

Refer to the LIAISON® Control QuantiFERON®-TB Gold Plus instructions for use section for proper preparation and handling instructions for assay controls.

7. REAGENT STORAGE AND STABILITY

REAGENT INTEGRAL

Upon receipt, the Reagent Integral must be stored in an upright position to facilitate resuspension of the Magnetic Particles. Refer to Reagent Integral Preparation (Section 6) for resuspension instructions.

– Unopened Reagent Integral is stable until the expiry date when stored at 2°-8°C.
– Open Reagent Integral is stable for four (4) weeks stored at 2°-8°C or onboard the LIAISON® XL Analyzer. Always use the same LIAISON® XL Analyzer for testing when using a reagent integral that has already been opened.
– Use the storage rack provided with the LIAISON® XL Analyzer for upright storage of the reagent integral.
– Do not freeze the reagent integral.
– Keep away from direct light.

CONJUGATE

– Unopened lyophilized Conjugate is stable until the expiry date when stored at 2°-8°C. Upon receipt, the Conjugate must be stored at 2°-8°C in an upright position to prevent adherence of the lyophilizate to the vial cap.
– Opened and reconstituted Conjugate is stable for 14 days when stored in capped vials at 2°-8°C between successive uses. After reconstitution, the conjugate must be stored in an upright position to prevent adherence of the solution to the vial cap.

Do not leave the reconstituted Conjugate at room temperature longer than the time required to process it on the Analyzer. Do not freeze.

During handling, use appropriate precautions to prevent bacterial contamination of the Conjugate.

BUFFER R

– Unopened Buffer R is stable until the expiry date when stored at 2°-8°C. Buffer R must be stored in an upright position to prevent adherence of the solution to the vial cap.
– Opened Buffer R must be used immediately to reconstitute the lyophilized Conjugate. Any remaining buffer after use for Conjugate reconstitution must be discarded.

Do not leave the Buffer R at room temperature longer than the time required to process it. Do not freeze.

During handling, use appropriate precautions to prevent bacterial contamination of Buffer R.

CALIBRATORS

– Unopened lyophilized Calibrators are stable until the expiry date when stored at 2°-8°C. Upon receipt, the calibrators must be stored at 2-8°C in an upright position to prevent adherence of the lyophilized material to the vial cap.
– Open and reconstituted Calibrators are stable for four (4) weeks when stored at 2°-8°C between successive uses, in their capped vials. After reconstitution, the calibrators must be stored at 2°-8°C in an upright position to prevent adherence of the solution to the vial cap.
– Each Calibrator vial contains sufficient volume for the performance of at least 4 calibrations.

Do not leave the reconstituted calibrators at room temperature longer than the time required to process them on the Analyzer. Do not freeze.

During handling, use appropriate precautions to prevent bacterial contamination of Calibrators.

8. SPECIMEN COLLECTION AND PREPARATION

LIAISON® QuantiFERON®-TB Gold Plus assay must be performed using lithium heparin plasma from whole blood samples collected, handled and processed with QIAGEN QuantiFERON®-TB Gold Plus (QFT-Plus) Blood Collection Tubes.

Whole blood samples must be collected and processed in accordance with the QIAGEN QuantiFERON®-TB Gold Plus Blood Collection Tubes instructions for use.

- Before loading on the LIAISON® XL Analyzer for IFN-γ detection, plasma samples must be visually inspected; samples having particulate matter, turbidity, or erythrocyte debris may require transfer to a secondary storage tube and additional centrifugation before testing. Lipemic samples as well as samples exhibiting obvious microbial contamination should not be tested. After incubation and centrifugation of the primary tube some hemolysis may occur. Assay interference due to hemoglobin was not observed at concentrations up to 1000 mg/dL. Check for and remove air bubbles from samples before testing.
- In order to avoid errors on the LIAISON® XL Analyzer due to clots, it is recommended thawed aliquots or samples with particulate matters to be centrifuged for 10 minutes at 10,000 RCF (g) prior to placement on the LIAISON® XL Analyzer.
- Test can be performed on samples processed and centrifuged directly in QIAGEN QFT-Plus Blood Collection Tubes, or on plasma samples processed and centrifuged in QFT-Plus Blood Collection Tubes, then transferred to secondary tubes after centrifugation. Tubes are loaded in appropriate sample racks onto the LIAISON® XL Analyzer (refer to LIAISON® XL Analyzer Operator's Manual for further details).
- Proper sample handling and storage is crucial to ensuring the integrity of the sample. For testing performed directly from centrifuged QIAGEN QFT-Plus Blood Collection Tubes, plasma samples can be stored in the centrifuged blood collection tubes for up to 28 days at 2°-8°C prior to testing. Plasma samples transferred from QFT-Plus Blood Collection Tubes to secondary storage tubes can be stored at 2°-8°C for up to 28 days prior to testing, or stored frozen at –20°C for up to six months prior to testing. Frozen plasma samples, once thawed should be mixed well before testing Frozen plasma samples remain stable for up to 4 freeze/thaw cycles.
- The minimum plasma sample volume required for LIAISON® QuantiFERON®-TB Gold Plus assay testing is 210 µL specimen (60 µL specimen + 150 µL dead volume).

9. ASSAY PROCEDURE

Strict adherence to the LIAISON® XL Analyzer Operator's Manual is required to ensure proper LIAISON® QuantiFERON®-TB Gold Plus assay performance.

Each test parameter is identified via information encoded in the Reagent Integral Radio Frequency Identification transponder (RFID Tag). If the RFID Tag cannot be read by the LIAISON® XL Analyzer, the Reagent Integral cannot be used. If this occurs do not discard the Reagent Integral; contact your local DiaSorin technical support for assistance.

The LIAISON® XL Analyzer operational steps are as follows:

1. Diluent and Magnetic Particles are dispensed into the LIAISON® XL Cuvette.
2. Conjugate is dispensed into the LIAISON® XL Cuvette.
3. Calibrators, Controls or samples are dispensed into the LIAISON® XL Cuvette.
4. Incubation at 37°C.
5. Wash is conducted using LIAISON® Wash/System Liquid.
6. Assay Buffer W is dispensed.
7. Incubation at 37°C.
8. Wash is conducted using LIAISON® Wash/System Liquid.
9. LIAISON® XL Analyzer Starter Kit reagents are added followed by measurement of emitted light.

10. CALIBRATION

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the assigned master curve. Each Calibration vial contains sufficient volume for the performance of at least 4 calibrations.

Calibrators must be used only with the Reagent Integral lot they are matched with. Do not use calibrators matched with a different Reagent Integral lot together in the same assay. To ensure correct lot matching, the calibrator lot number is printed also on the Reagent Integral Label.

Recalibration performed in triplicate is mandatory whenever at least one of the following conditions occurs:

– A new lot of Reagent Integral or Starter Kit is used.
– The previous calibration was performed more than four (4) weeks prior.
– The LIAISON® XL Analyzer has been serviced.
– The values of the controls lie outside the expected ranges.

Refer to the LIAISON® XL Analyzer Operator's Manual or Quick Guide for calibration instructions.

Calibrator values are stored in the Radio Frequency Identification transponder (RFID Tag).

11. QUALITY CONTROL

LIAISON® QuantiFERON® -TB Gold Plus assay quality control must be performed by using LIAISON® Control QuantiFERON®-TB Gold Plus controls.

LIAISON® Control QuantiFERON®-TB Gold Plus controls are recommended for internal quality control and they should be run in singlicate.

Assay quality control should be performed at least once per day of use or in accordance with local, state and/or federal regulations or accreditation requirements and your laboratory's quality control procedures. It is recommended that the user refer to CLSI document, C24-A3 and 42 CFR 493.1256(c) for guidance on appropriate quality control practices.

LIAISON® Control QuantiFERON®-TB Gold Plus controls (level 1 and level 2) are intended to monitor for substantial reagent failure. If the control results fall outside the expected ranges (control failure) all test results are invalid and must not be reported and should be repeated. If a control failure is observed, assay calibration should be performed followed by repeat testing of controls and samples.

The performance of other controls should be evaluated for compatibility with the LIAISON® QuantiFERON®-TB Gold Plus assay before they are used. It is the responsibility of the user to validate the use of other controls and to establish appropriate control ranges.

12. LIMITATIONS OF THE PROCEDURE

1. To obtain an accurate result interpretation for a patient, combine only the results from tubes collected from the patient in the same sampling session.
2. Inaccurate or indeterminate results may occur if strict adherence to the LIAISON® QuantiFERON®-TB Gold Plus assay and QuantiFERON®-TB Gold Plus Blood Collection Tube instructions is not exercised.
3. Grossly hemolyzed, icteric or lipemic samples, as well as samples containing particulate matter or exhibiting obvious microbial contamination should not be tested.
4. Bacterial contamination or heat inactivation of the specimens may affect the test results.
5. The four individual blood collection tube results of a patient sample can be combined to determine the final qualitative interpretation only if assay testing of subsequent tube(s) occurs within ≤18 hours of testing of the initial tube, and all tubes are maintained at 2°-8°C prior to testing.
6. In order to ensure correct correlation of the result of each assay tube and the interpretation, a conversion factor must not be set on the LIAISON® XL Analyzer.
7. A negative result does not preclude the possibility of M. tuberculosis infection or tuberculosis disease: false-negative results can be due to the stage of infection (e.g., specimen obtained prior to the development of cellular immune response), co-morbid conditions that affect immune functions, incorrect handling of the blood collection tubes following venipuncture, incorrect performance of the assay, or other immunological variables.
8. A positive result should not be the sole or definitive basis for determining infection with *M. tuberculosis*. Incorrect performance of the assay may cause false-positive responses.
9. Heterophilic antibodies in human specimens can react with reagent immunoglobulins, interfering with in vitro immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference and their results should be evaluated with care.
10. While ESAT-6 and CFP-10 are absent from all BCG strains and from most known nontuberculous mycobacteria, it is possible that a positive result may be due to infection by *M. kansasii, M. szulgai, or M. marinum*. If such infections are suspected, alternative testing should be considered.

11. The performance characteristics of the test in the following groups of individuals has not been extensively evaluated: individuals younger than age 18 years, pregnant women, individuals with impaired or altered immune functions or other clinical conditions (e.g. HIV infection, transplant recipients, hematological disorders, malignancies, diabetes, chronic renal failure).

13. INTERPRETATION OF RESULTS

LIAISON® QuantiFERON®-TB Gold Plus assay results are interpreted using following algorithm (Table 1) that combines the results from each of the four QFT-Plus Blood Collection Tubes. The result (i.e., amount of analyte IFN-γ) for each blood collection tube is reported in International Units per mL (IU/mL). Although the assay detects IFN-γ quantitatively, the interpretation of the result for a single patient is strictly qualitative. The magnitude of the amount of measured IFN-γ cannot be correlated to stage or degree of infection, level of immune responsiveness, or likelihood for progression to active disease.

Note: Diagnosing or excluding tuberculosis disease, and assessing the probability of LTBI, requires a combination of epidemiological, historical, medical, and diagnostic findings that should be taken into account when interpreting LIAISON QuantiFERON-TB Gold Plus assay results. See general guidance on the diagnosis and treatment of TB disease and LTBI https://www.cdc.gov/tb/publications/guidelines/default.htm.

Responses to the Mitogen positive control and occasionally to TB antigen can be above the assay range. Cases of undetectable response might be observed. This has no impact on test result. For calculation purposes:

IFN-γ values > 10 IU/mL should be handled as 10 IU/mL.

IFN-γ values < 0 IU/mL should be handled as 0 IU/mL.

Table 1. Interpretation of LIAISON QuantiFERON-TB Gold Plus Assay Results

<table>
<tr><th>Nil (IU/mL)</th><th>TB1 minus Nil (IU/mL)</th><th>TB2 minus Nil (IU/mL)</th><th>Mitogen minus Nil (IU/mL)</th><th>LIAISON® QuantiFERON®-TB Gold Plus result</th><th>Report/ Interpretation</th></tr>
<tr><td rowspan="4">≤ 8.0</td><td>≥ 0.35 and
≥ 25% of Nil</td><td>Any</td><td rowspan="2">Any</td><td rowspan="2">Positive†</td><td rowspan="2">M. tuberculosis infection likely</td></tr>
<tr><td>Any</td><td>≥ 0.35 and
≥ 25% of Nil</td></tr>
<tr><td>< 0.35
OR
≥ 0.35 and
< 25% of Nil</td><td>< 0.35
OR
≥ 0.35 and
< 25% of Nil</td><td>≥ 0.5</td><td>Negative</td><td>M. tuberculosis infection NOT likely</td></tr>
<tr><td>< 0.35
OR
≥ 0.35 and
< 25% of Nil</td><td>< 0.35
OR
≥ 0.35 and
< 25% of Nil</td><td>< 0.5</td><td rowspan="2">Indeterminate*</td><td rowspan="2">Likelihood of M. tuberculosis infection cannot be determined</td></tr>
<tr><td>> 8.0</td><td colspan="3">Any</td></tr>
</table>

†Where M. tuberculosis infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate. If repeat testing of one or both replicates is positive, the test result is considered positive.

*Indeterminate results are uncommon and may be related to the status of the immune system of the patient. An indeterminate result may also be related to technical factors (e.g., inappropriate storage or handling of the blood collection tubes) if the instructions for use are not followed. If technical issues are suspected with the reagent storage, blood collection or handling of the blood samples, repeat the test with new blood samples. Physicians may choose to redraw a specimen or perform other procedures as appropriate.

These calculations can be also performed by using the LIAISON® QuantiFERON® Software (LQS) which is an optional tool provided for LIAISON® QuantiFERON®-TB Gold Plus assay result interpretation. Contact your local DiaSorin Technical Support for further details.

14. SPECIFIC PERFORMANCE CHARACTERISTICS

14.1. Potential Interfering Substances

Controlled studies of potentially interfering substances performed on samples at three (3) IFN-γ levels showed no interference in the performance of the LIAISON® QuantiFERON®-TB Gold Plus assay at the concentration for each substance listed in Table 2 below. The testing was based on CLSI EP07-A2.

Table 2. Potential Interfering Substances

Substances	Tested concentration	Substances	Tested concentration
Triglycerides	3000 mg/dL	IL-2	10 ng/mL
Hemoglobin	1000 mg/dL	IL-4	5 ng/mL
Unconjugated bilirubin	20 mg/dL	IL-5	100 ng/mL
Conjugated bilirubin	20 mg/dL	IL-6	100 ng/mL
Total protein (high)	120 g/L	IL-10	100 ng/mL
Total protein (low)	38 g/L	IL-12	100 ng/mL
RF (Rheumatoid Factor)	469 IU/mL	IFN-alpha	50 ng/mL
HAMA	600 ng/mL	IFN-beta	50 ng/mL
Cholesterol	350 mg/dL	TNF-alpha	5 ng/mL
Prednisolone	0.3 mg/dL	Biotin	3500 ng/mL
Cyclosporine	5 µg/mL	Abacavir sulfate	15 µg/mL

14.2.1. 20-Day Precision Study

A within-laboratory precision study was performed using a panel of ten (10) Li-Heparinized plasma samples spiked with concentrations of native IFN-γ to span the measuring range of the assay. The sample panel and one (1) lot of kit controls were tested. Samples were tested at one location, in duplicate, in 2 runs per day, over 20 operating days, by three technicians, using two lots of LIAISON® QuantiFERON®-TB Gold Plus assay kits. CLSI document EP05-A3 was consulted in the preparation of the testing protocol. A summary of the study results is illustrated in Table 3 below.

Table 3. 20-Day Precision Study Summary Results - LIAISON® QuantiFERON®-TB Gold Plus (2 Kit Lots)

Panel Member	N	Mean	Repeatability		Between-Run		Between Day		Between Lot		Within-Lab (Total)	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
QFTB-01-P01	160	0.241	0.008	3.121	0.005	2.242	0.019	7.836	0.005	1.932	0.022	8.939
QFTB-01-P02	160	0.294	0.011	3.590	0.007	2.263	0.023	7.854	0.003	1.169	0.026	9.003
QFTB-01-P03	160	0.525	0.012	2.250	0.011	2.076	0.035	6.674	0.000	0.000	0.039	7.343
QFTB-01-P04	160	0.797	0.020	2.514	0.013	1.637	0.059	7.455	0.000	0.000	0.064	8.036
QFTB-01-P05	160	1.556	0.035	2.252	0.033	2.149	0.123	7.899	0.000	0.000	0.132	8.490
QFTB-01-P06	160	2.988	0.090	3.006	0.034	1.125	0.248	8.301	0.039	1.318	0.269	8.997
QFTB-01-P07	160	3.913	0.090	2.308	0.081	2.079	0.340	8.700	0.000	0.000	0.361	9.238
QFTB-01-P08	160	5.494	0.121	2.201	0.093	1.687	0.466	8.487	0.053	0.967	0.493	8.980
QFTB-01-P09	160	5.851	0.121	2.068	0.155	2.644	0.474	8.108	0.000	0.000	0.513	8.775
QFTB-01-P10	160	6.678	0.173	2.585	0.243	3.633	0.542	8.124	0.000	0.000	0.619	9.267
Control #7124010	160	0.074	0.009	11.943	0.009	11.554	0.013	18.207	0.022	29.419	0.028	38.381
Control #7125010	160	1.520	0.036	2.345	0.040	2.613	0.125	8.231	0.067	4.398	0.152	9.971

14.2.2. 5-Day Reproducibility Study

A 5-day reproducibility/precision study was conducted at two external laboratories and at DiaSorin Inc. Each site used two different lots of LIAISON® QuantiFERON®-TB Gold Plus assay kits. A panel of ten (10) Li-Heparin plasma samples spiked with concentrations of native IFN-γ to span the measuring range of the assay was used for testing. The sample panel and one (1) lot of kit controls were tested at all three (3) sites, using six (6) replicates per run in one (1) run per day for five (5) operating days, by multiple operators. The CLSI document EP15-A3 was consulted in the preparation of the testing protocol. A summary of the study results is illustrated in Tables 4 - 7 below.

Table 4. LIAISON® QuantiFERON®-TB Gold Plus Assay Reproducibility Study Summary Results - Combined Study Sites and Assay Kit Lots

Sample ID	N	Mean (IU/mL)	Repeatability		Between Day		Between Lot		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Level 1	180	0.068	0.009	12.70	0.012	17.00	0.014	20.80	0.020	29.70
Ctrl Level 2	180	1.598	0.058	3.70	0.102	6.40	0.081	5.00	0.142	8.90
QFTB-01-P01	180	0.273	0.011	4.00	0.023	8.30	0.013	4.70	0.034	12.60
QFTB-01-P02	180	0.329	0.015	4.50	0.022	6.60	0.004	1.10	0.032	9.90
QFTB-01-P03	180	0.574	0.018	3.20	0.031	5.50	0.004	0.70	0.048	8.40
QFTB-01-P04	180	0.867	0.031	3.50	0.046	5.30	0.025	2.90	0.070	8.10
QFTB-01-P05	180	1.691	0.081	4.80	0.104	6.20	0.050	3.00	0.154	9.10
QFTB-01-P06	180	3.193	0.126	3.90	0.170	5.30	0.070	2.20	0.236	7.40
QFTB-01-P07	180	4.093	0.131	3.20	0.188	4.60	0.122	3.00	0.265	6.50
QFTB-01-P08	180	5.606	0.165	3.00	0.242	4.30	0.103	1.80	0.342	6.10
QFTB-01-P09	180	6.062	0.246	4.10	0.283	4.70	0.137	2.30	0.399	6.60
QFTB-01-P10	180	6.974	0.199	2.90	0.347	5.00	0.142	2.00	0.446	6.40

Table 5. LIAISON® QuantiFERON®-TB Gold Plus Assay Reproducibility Study Summary Results - Site 1, Combined Assay Kit Lots

Sample ID	N	Mean (IU/mL)	Repeatability		Between-Day		Between Lot		Total Within-Site	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Level 1	60	0.074	0.006	8.30	0.009	11.90	0.017	22.90	0.020	27.10
Ctrl Level 2	60	1.611	0.041	2.50	0.095	5.90	0.084	5.20	0.133	8.30
QFTB-01-P01	60	0.286	0.008	2.80	0.019	6.70	0.005	1.90	0.021	7.50
QFTB-01-P02	60	0.341	0.010	3.00	0.014	4.30	0.000	0.00	0.018	5.20
QFTB-01-P03	60	0.602	0.015	2.60	0.034	5.60	0.000	0.00	0.037	6.10
QFTB-01-P04	60	0.899	0.021	2.30	0.037	4.10	0.000	0.00	0.042	4.70
QFTB-01-P05	60	1.756	0.065	3.70	0.081	4.60	0.000	0.00	0.104	5.90
QFTB-01-P06	60	3.248	0.088	2.70	0.134	4.10	0.082	2.50	0.180	5.50
QFTB-01-P07	60	4.188	0.090	2.10	0.130	3.10	0.118	2.80	0.197	4.70
QFTB-01-P08	60	5.753	0.147	2.60	0.169	2.90	0.086	1.50	0.240	4.20
QFTB-01-P09	60	6.173	0.201	3.30	0.215	3.50	0.111	1.80	0.315	5.10
QFTB-01-P10	60	7.116	0.143	2.00	0.313	4.40	0.035	0.50	0.346	4.90

Table 6. LIAISON® QuantiFERON®-TB Gold Plus Assay Reproducibility Study Summary Results - Site 2, Combined Assay Kit Lots

Sample ID	N	Mean (IU/mL)	Repeatability		Between-Day		Between Lot		Total Within-Site	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Level 1	60	0.059	0.006	9.50	0.008	13.80	0.014	23.80	0.017	29.10
Ctrl Level 2	60	1.546	0.055	3.60	0.134	8.60	0.034	2.20	0.149	9.60
QFTB-01-P01	60	0.247	0.010	4.00	0.021	8.40	0.000	0.00	0.023	9.30
QFTB-01-P02	60	0.306	0.020	6.40	0.025	8.10	0.000	0.00	0.032	10.30
QFTB-01-P03	60	0.538	0.021	3.90	0.035	6.50	0.000	0.00	0.041	7.60
QFTB-01-P04	60	0.820	0.035	4.20	0.059	7.20	0.000	0.00	0.068	8.30
QFTB-01-P05	60	1.603	0.089	5.50	0.136	8.50	0.000	0.00	0.163	10.10
QFTB-01-P06	60	3.068	0.147	4.80	0.238	7.80	0.097	3.20	0.296	9.70
QFTB-01-P07	60	3.959	0.146	3.70	0.292	7.40	0.165	4.20	0.366	9.20
QFTB-01-P08	60	5.408	0.141	2.60	0.332	6.10	0.181	3.40	0.404	7.50
QFTB-01-P09	60	5.965	0.293	4.90	0.432	7.20	0.263	4.40	0.585	9.80
QFTB-01-P10	60	6.742	0.188	2.80	0.466	6.90	0.201	3.00	0.541	8.00

Table 7. LIAISON® QuantiFERON®-TB Gold Plus Assay Reproducibility Study Summary Results - Site 3, Combined Assay Kit Lots

Sample ID	N	Mean (IU/mL)	Repeatability		Between-Day		Between Lot		Total Within-Site	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Level 1	60	0.072	0.012	17.30	0.016	22.50	0.018	24.30	0.027	37.40
Ctrl Level 2	60	1.638	0.074	4.50	0.066	4.00	0.140	8.60	0.172	10.50
QFTB-01-P01	60	0.285	0.014	4.90	0.027	9.60	0.022	7.70	0.038	13.30
QFTB-01-P02	60	0.340	0.013	3.90	0.022	6.50	0.015	4.40	0.030	8.80
QFTB-01-P03	60	0.582	0.018	3.20	0.021	3.60	0.019	3.20	0.033	5.80
QFTB-01-P04	60	0.881	0.034	3.90	0.033	3.70	0.053	6.00	0.071	8.10
QFTB-01-P05	60	1.714	0.086	5.00	0.068	4.00	0.112	6.50	0.157	9.10
QFTB-01-P06	60	3.263	0.134	4.10	0.108	3.30	0.000	0.00	0.172	5.30
QFTB-01-P07	60	4.131	0.148	3.60	0.058	1.40	0.060	1.50	0.170	4.10
QFTB-01-P08	60	5.657	0.202	3.60	0.179	3.20	0.000	0.00	0.270	4.80
QFTB-01-P09	60	6.048	0.234	3.90	0.085	1.40	0.072	1.20	0.259	4.30
QFTB-01-P10	60	7.065	0.251	3.60	0.217	3.10	0.139	2.00	0.359	5.10

14.3. High-dose Hook Effect

No high-dose hook effect was observed for IFN-γ concentrations up to 10,000 IU/mL.

14.4. Summary of Clinical Performance

As there is not a definitive standard test for confirming or excluding the diagnosis of LTBI, sensitivity and specificity for the LIAISON® QuantiFERON®-TB Gold Plus assay cannot be determined. Specificity was approximated by evaluating persons with low risk of tuberculosis infection (Low Risk cohort), and sensitivity was approximated by evaluating subjects with culture-confirmed active TB disease (Active TB cohort). Assay performance was also evaluated in cohort of healthy study subjects with known risk factors for latent TB infection (Mixed Risk cohort).

A summary of the demographic information for each study cohort is provided in Tables 8 - 11 below.

Table 8. Demographics of Clinical Study Subjects by Gender.

	Active TB		Low Risk		Mixed Risk	
Gender	**n**	**%**	**N**	**%**	**n**	**%**
Female	45	28.1%	57	18.3%	188	33.0%
Male	115	71.9%	255	81.7%	382	67.0%
Total	**160**	**100.0%**	**312**	**100.0%**	**570**	**100.0%**

Table 9. Demographics of Clinical Study Subjects by Race

	Active TB		Low Risk		Mixed Risk	
Race	**n**	**%**	**N**	**%**	**n**	**%**
American Indian/ Alaskan Native	0	0.0%	0	0.0%	6	1.1%
Asian	7	4.4%	0	0.0%	6	1.1%
Black/African American	45	28.1%	299	95.8%	321	56.3%
Native Hawaiian or Other Pacific Islander	0	0.0%	0	0.0%	0	0.0%
White	85	53.1%	13	4.2%	225	39.5%
Unknown	14	8.8%	0	0.0%	5	0.9%
Other	9	5.6%	0	0.0%	7	1.2%
Total	**160**	**100.0%**	**312**	**100.0%**	**570**	**100.0%**

Table 10. Demographics of Clinical Study Subjects by Age

Cohort	Active TB			Low Risk			Mixed Risk		
Gender	**n**	**range (yrs)**	**average (yrs)**	**N**	**range (yrs)**	**average (yrs)**	**N**	**range (yrs)**	**average (yrs)**
Female	45	19-85 (n=2 no age)	40	57	18-62	36.8	188	19-72	44.3
Male	115	18-85 (n=2 no age)	41	255	18-65	38	382	20-79	46.8

Table 11. Mixed Risk Study Cohort - Demographics and Risk Factors

Total Subjects (570)		Number	Percentage
Gender	Male	382	67.0%
	Female	188	33.0%
Age (years)	Range	19-79	NA
	Mean	45.9	NA
Previously diagnosed with active TB (TST/Mantoux test for TB)	Yes	9	1.6%
	No	561	98.4%
Treated for Active or Latent TB	Yes	7	1.2%
	No	563	98.8%
BCG vaccinated	Yes	10	1.8%
	No	558	97.9%
	Unknown	2	< 0.4%
Resided in area with elevated active TB rate	Yes	388	68.1%
	No	182	31.9%
Lived, worked or volunteered (> 1 month) in a jail or prison, homeless shelter, healthcare worker	Yes	273	47.9%
	No	297	52.1%
Close contact of someone with or suspected of having active TB disease	Yes	12	2.1%
	No	558	97.9%
Condition resulting in weakened immune system HIV Positive, Hepatitis B or C Positive, Renal Failure	Yes	48	8.4%
	No	522	91.6%
HIV Positive	Yes	40	7.0%
	No	530	93.0%
Had a Tuberculin Skin Test (TST) / Mantoux test for TB	Yes and Pos	15	2.6%
	Yes and Neg	183	32.1%
	Yes and Unknown	18	3.2%
	No	354	62.1%
Had a previous QuantiFERON® Test	Yes and Pos	1	< 0.2%
	Yes and Neg	14	2.5%
	No	555	97.4%
Had a previous T-Spot Test	Yes and Pos	0	0.0%
	Yes and Neg	6	1.1%
	No	564	98.9%

Clinical Specificity

A multi-center study evaluating clinical specificity of the LIAISON® QuantiFERON®-TB Gold Plus assay was performed including 312 study subjects with no identified risk factors for TB infection. All samples were prospectively collected and tested with the LIAISON® QuantiFERON®-TB Gold Plus assay and the QIAGEN QFT-Plus test.

Table 12 illustrates the clinical specificity performance data in terms of the obtained versus expected negative results, with 95% confidence intervals. Samples having indeterminate (IND) results are not included in the analysis.

Table 12. Clinical Specificity Study Performance Summary Data

Clinical Specificity Low Risk		Pos	Pos	Neg	Neg	IND	IND	Specificity 95% CI	Specificity 95% CI
Collection Site	**N**	**Qiagen**	**DiaSorin**	**Qiagen**	**DiaSorin**	**Qiagen**	**DiaSorin**	**Qiagen EIA**	**DiaSorin LIAISON**
US Mid-West	**312**	**8**	**9**	**276**	**279**	**28**	**24**	**97.2% (276/284) 94.5%-98.6%**	**96.9% (279/288) 94.2%-98.3%**

Clinical Sensitivity

A multi-center study evaluating clinical sensitivity of the LIAISON® QuantiFERON®-TB Gold Plus assay was performed including 160 study subjects with signs and symptoms of active M. tuberculosis disease confirmed by culture with positive Acid-Fast Bacilli (AFB) smear or Nucleic Acid Amplification (NAA) test. Subjects were either on no TB treatment or with ≤ 14 days of TB treatment prior to blood collection. Samples were either prospectively or retrospectively collected and tested with the LIAISON® QuantiFERON®-TB Gold Plus assay and the QIAGEN QFT-Plus test.

Table 13 illustrates the clinical sensitivity performance data in terms of obtained versus expected positive results, with 95% confidence intervals. Samples having indeterminate (IND) results are not included in the analysis.

Table 13. Clinical Sensitivity Study Performance Summary Data

Clinical Sensitivity Active TB Cohort		Pos	Pos	Neg	Neg	IND	IND	Sensitivity 95% CI	Sensitivity 95% CI
	N	**Qiagen**	**DiaSorin**	**Qiagen**	**DiaSorin**	**Qiagen**	**DiaSorin**	**Qiagen EIA**	**DiaSorin LIAISON**
Retrospective†	51	44	49	7	2	0	0	86.3% (44/51) 74.3%-93.2%	96.1% (49/51) 86.8%-98.9%
Prospective*	109	83	81	22	22	4	6	79.0% (83/105) 70.31%-85.74%	78.6% (81/103) 69.77%-85.45%
Cumulative Total	**160**	**127**	**130**	**29**	**24**	**4**	**6**	**81.4% (127/156) 74.6%-86.7%**	**84.4% (130/154) 77.9%-89.3%**

†Retrospective samples were obtained from study subjects with active culture confirmed TB; however retrospective samples were chosen for LIAISON QuantiFERON-TB Gold Plus assay testing due to a previous known positive QFT-Plus test result.

*Prospective samples were obtained from study subjects with active cultured confirmed TB; the QFT-Plus test result was unknown at the time enrollment.

Clinical Performance in Study Subjects with Identified Risk Factors for Tuberculosis Infection (Mixed Risk Cohort)

Clinical performance was evaluated in a cohort of 570 healthy study subjects with identified risk factors for tuberculosis infection (Mixed Risk). A description of demographics and risk factors for the Mixed Risk cohort are included in Tables 8-11 above. The performance of the LIAISON® QuantiFERON®-TB Gold Plus assay was compared to that of the Qiagen QFT-Plus test and is illustrated in Table 14. Samples having indeterminate results are not included in the analysis.

Table 14. Summary Performance of LIAISON® QuantiFERON®-TB Gold Plus versus QFT-Plus in Healthy Study Subjects with Known Risk Factors for LTBI

Mixed Risk Cohort		QFT-Plus		
		Positive	Negative	Total
LIAISON® QuantiFERON®-TB Gold Plus	Positive	58	3	61
	Negative	2	505	507
	Total	**60**	**508**	**568**

The positive percent agreement (PPA) and negative percent agreement (NPA) between the results of the LIAISON QuantiFERON-TB Gold Plus assay and the QFT-Plus are as follows:

PPA: 96.7% (58/60), 95%CI (88.6-99.1%)
NPA: 99.4% (505/508), 95%CI (98.3 - 99.8%)

Clinical Performance in BCG Vaccinated Study Subjects

A total of 69 study subjects in the Active TB cohort and 10 study subjects in the Mixed Risk cohort reported having received the BCG TB vaccine. Samples from these study subjects were tested with the LIAISON® QuantiFERON®-TB Gold Plus assay and the assay results were compared to QIAGEN QFT-Plus test results. A summary of comparative performance data is provided in Table 15 below. The performance data are based on the total number of valid results. Three samples with indeterminate (IND) results were not included in the performance calculations.

Table 15. Comparative Clinical Performance Data Summary – BCG Vaccinated Study Subjects

BCG Vaccinated Subjects		QFT-Plus		
		Pos (+)	Neg (-)	Total
LIAISON® QuantiFERON®-TB Gold Plus	Pos (+)	54	6	60
	Neg (-)	0	16	16
Total		**54**	**22**	**76**

The comparative performance data revealed a positive percent agreement (PPA) of 100% (54/54), 95% CI (93.4 – 100), a negative percent agreement (NPA) of 72.7% (16/22), 95% CI (51.8 – 86.8), and an overall agreement of 92.1% (70/76), 95% CI (83.8 – 96.3).

Clinical Performance in HIV+ Study Subjects

A total of 13 study subjects in the Active TB cohort and 40 study subjects in the Mixed Risk study cohort reported infection with the HIV. Samples from these study subjects were tested with the LIAISON® QuantiFERON®-TB Gold Plus assay and the assay results were compared to QIAGEN QFT-Plus test results. A summary of comparative performance data is illustrated in Table 16 below. The performance data are based on the total number of valid results.

Table 16. Comparative Clinical Performance Data Summary – HIV+ Study Subjects

HIV (+) Subjects		QFT-Plus		
		Pos (+)	Neg (-)	Total
LIAISON® QuantiFERON®-TB Gold Plus	Pos (+)	11	0	11
	Neg (-)	2	40	42
Total		**13**	**40**	**53**

The comparative performance data revealed a positive percent agreement (PPA) of 86% (11/13), 95% CI (57.8 - 95.7), a negative per-cent agreement (NPA) of 100% (40/40), 95% CI (91.2 - 100), and an overall agreement of 96.2% (51/53), 95% CI (87.2 - 99.0).

Comparative Clinical Performance Summary

Comparative performance of the LIAISON® QuantiFERON®-TB Gold Plus assay versus the QFT-Plus test for the three clinical study cohorts, is illustrated in Table 15 below as Positive percent agreement and Negative percent agreement with 95% confidence intervals. Samples having indeterminate (IND) results are not included in the analysis.

Table 17. Comparative Clinical Performance Data Summary (All Cohorts)

Cohort	N	PPA (95% CI)	NPA (95% CI)	Overall (95% CI)
Active TB	154[A]	98.4% (124/126) (94.4% - 99.6%)	78.6% (22/28) (60.5% - 89.8%)	94.8% (146/154) (90.1% - 97.3%)
Low Risk	278[B]	87.5% (7/8) (52.9% - 97.8%)	99.3% (268/270) (97.3% - 99.8%)	98.9% (275/278) (96.9% - 99.6%)
Mixed Risk	568[C]	96.7% (58/60) (88.6% - 99.1%)	99.4% (505/508) (98.3% - 99.8%)	99.1% (563/568) (98.0% - 99.6%)
Total	**1000[D]**	**97.4% (189/194) (94.1% - 98.9%)**	**98.6% (795/806) (97.6% - 99.2%)**	**98.4% (984/1000) (97.4% - 99.0%)**

[A] 6 IND
[B] 34 IND
[C] 2 IND
[D] 42 TOTAL IND not included in analysis

14.5. Expected Values

Observed response distributions – stratified by risk

A range of IFN-ɣ responses to TB1, TB2, and control tubes were observed in clinical trials and stratified by risk of *M. tuberculosis* infection. The mixed risk group consists of subjects representative of a general testing population, including subjects with and without risk factors for TB exposure, and where active TB is unlikely (i.e. LTBI).

Table 18. Expected Value Results (IU/mL) by tube for low risk, mixed risk and subjects with active TB.

Result IU/mL	Low Risk Samples				Mixed Risk Samples				Active Samples			
	Nil (LR)	TB1-Nil (LR)	TB2-Nil (LR)	Mit-Nil (LR)	Nil (MR)	TB1-Nil (MR)	TB2-Nil (MR)	Mit-Nil (MR)	Nil (Active)	TB1-Nil (Active)	TB2-Nil (Active)	Mit-Nil (Active)
<0.1	242	262	261	0	417	497	483	3	29	13	10	1
0.1 - <0.35	33	8	9	0	143	25	33	0	65	20	20	2
0.35 - <1	1	5	4	15	6	15	14	1	42	40	31	8
1 - <2	1	1	2	32	2	4	6	5	11	20	25	9
2 - <3	0	0	1	11	0	5	7	4	3	14	11	4
3 - <4	0	0	0	18	0	3	5	5	1	16	12	5
4 - <5	1	1	1	21	0	1	2	9	3	6	8	6
5 - <6	0	1	0	12	0	3	4	9	0	5	4	7
6 - <7	0	0	0	10	0	1	1	6	0	2	6	0
7 - <8	0	0	0	5	0	4	1	5	0	3	7	3
8 - <9	0	0	0	14	0	0	0	2	0	4	3	2
9 - <10	0	0	0	9	0	0	0	7	0	0	2	1
≥10	0	0	0	131	0	10	12	512	0	11	15	106

Figure1. Distribution of TB1 and TB2 (nil subtracted) values in a low risk population (n= 278)

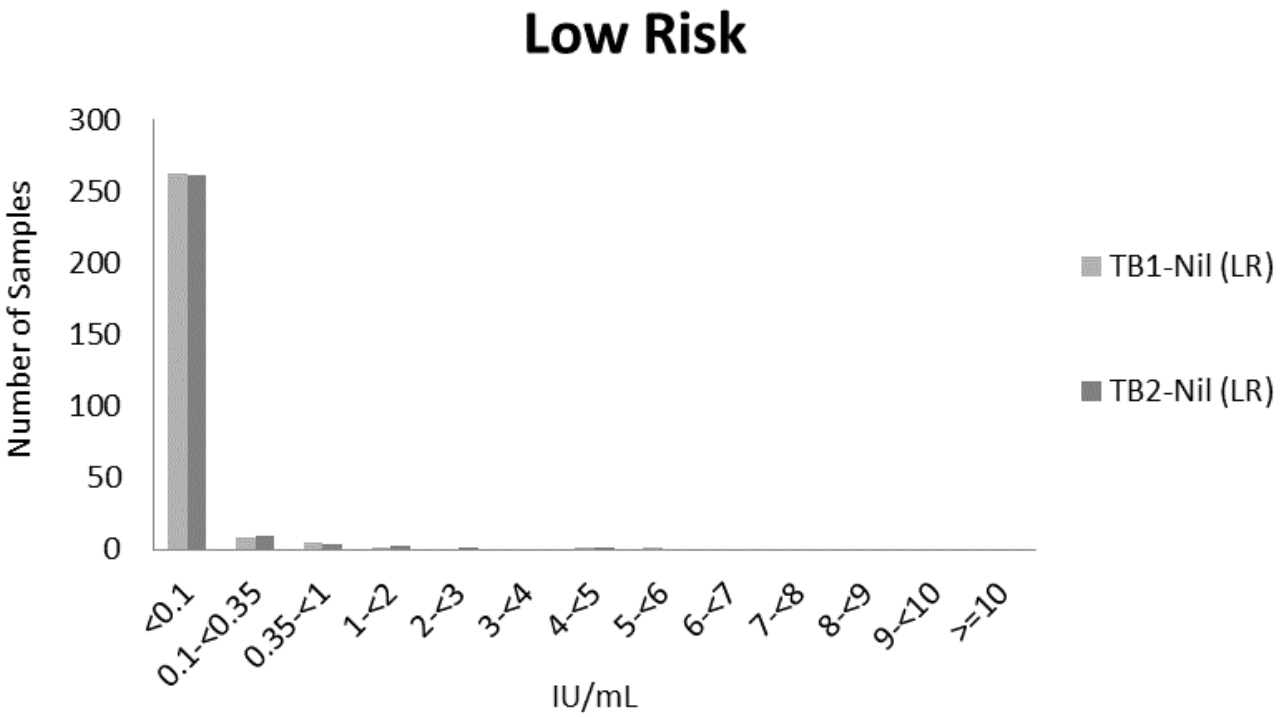


Figure 2. Distribution of TB1 and TB2 (nil subtracted) values in a mixed risk population (n= 568)

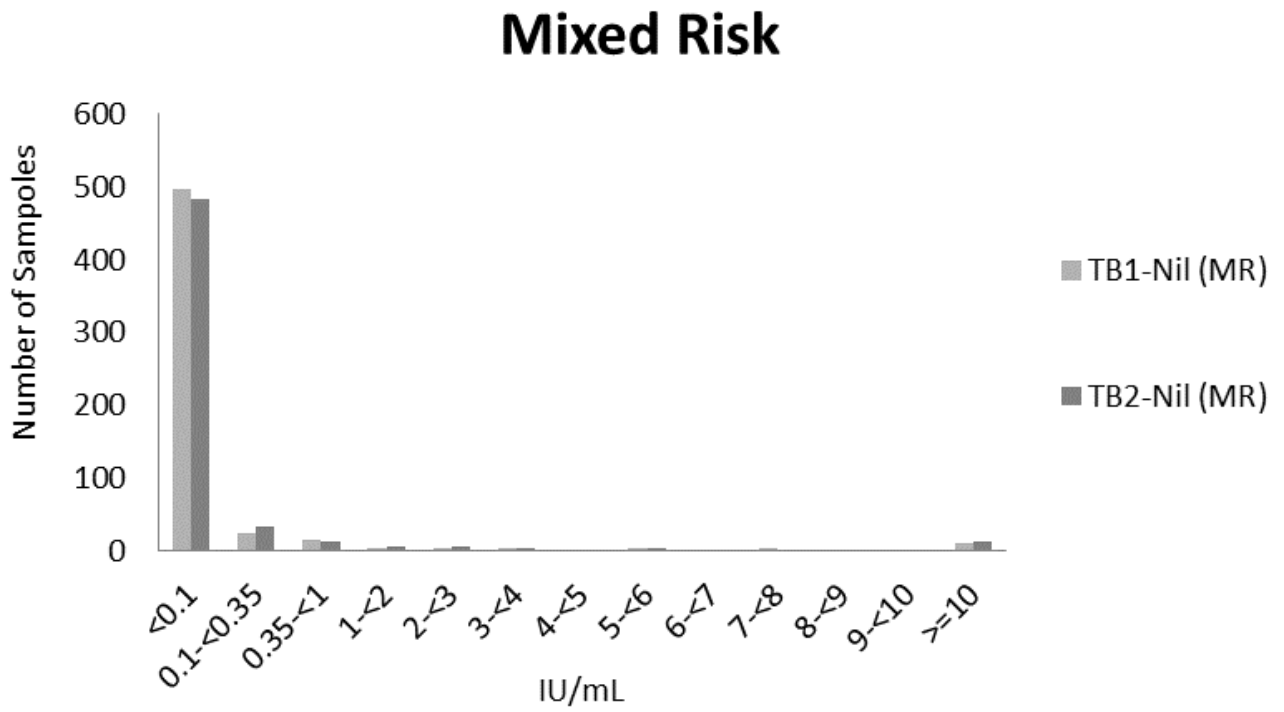
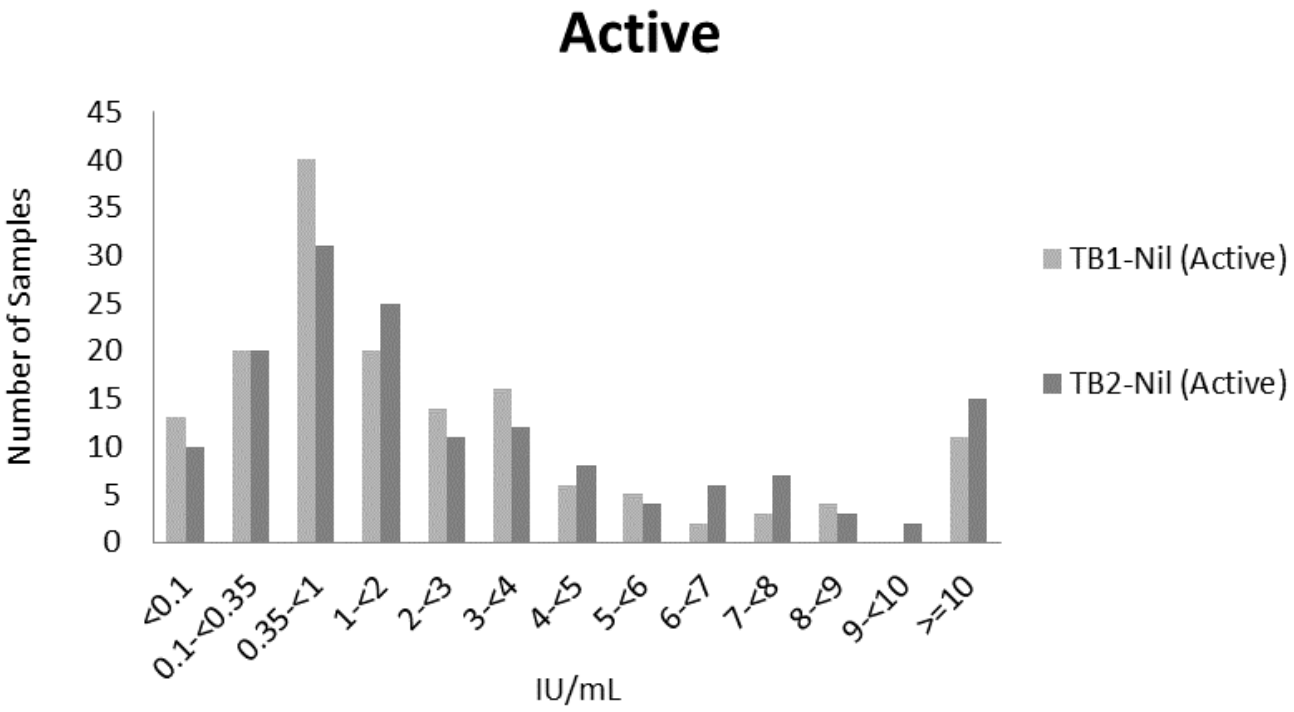


Figure 3. Distribution of TB1 and TB2 (nil subtracted) values in a population with culture confirmed M. tuberculosis infection (n= 154)



References

1. World Health Organization. 2017. Global tuberculosis report: WHO 2017. WHO, Geneva, Switzerland.
2. Elisa Petruccioli, 2016 Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis Eur Respir J 2016; 48: 1751–1763
3. Madhukar Pai, a Claudia M. Denkinger, a,b Sandra V. Kik, a Molebogeng X. Rangaka, c Alice Zwerling, d Olivia Oxlade, e John Z. Metcalfe, f Adithya Cattamanchi, f David W. Dowdy, d Keertan Dheda, g Niaz Banaeih Gamma Interferon Release Assays for Detection of Mycobacterium tuberculosis Infection Clinical Microbiology Reviews p. 3–20 January 2014 Volume 27 Number 1
4. American Thoracic Society. 2000. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am. J. Respir. Crit. Care Med. 161: S221–S247. http://dx.doi.org/10.1164/ajrccm.161.supplement_3.ats600
5. Sester M, Sotgiu G, Lange C, Giehl C, Girardi E, Migliori GB, BossinkA, Dheda K, Diel R, Dominguez J, Lipman M, Nemeth J, Ravn P, Winkler S, Huitric E, Sandgren A, Manissero D. 2011. Interferongammarelease assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. Eur. Respir. J. 37:100–111. http://dx.doi.org/10.1183/09031936.00114810.
6. S. D. Chaparas, H. M. Vandiviere, and I. Melvin, "Tuberculin test. Variability with the Mantoux procedure," American Review of Respiratory Disease, vol. 132, no. 1, pp. 175–177, 1985
7. Farhat M, Greenaway C, Pai M, Menzies D. 2006. False-positive tuberculin skin tests: what is the absolute effect of BCG and nontuberculous mycobacteria? Int. J. Tuberc. Lung Dis. 10:1192–1204
8. Cohn D.L., The Effect of BCG Vaccination on Tuberculin Skin Testing Does It Matter? American Journal of Respiratory and Critical Care Medicine vol 164 2001
9. A. Trajman et al Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence Hindawi Publishing Corporation Pulmonary Medicine Volume 2013, Article ID 601737, 11 pages http://dx.doi.org/10.1155/2013/601737
10. Mahairas GG, Sabo PJ, Hickey MJ, Singh DC, Stover CK. 1996. Molecular analysis of genetic differences between Mycobacterium bovis BCG and virulent M. bovis. J. Bacteriol. 178:1274–1282
11. Sorensen AL, Nagai S, Houen G, Andersen P, Andersen AB. 1995. Purification and characterization of a low-molecular-mass T-cell antigen secreted by Mycobacterium tuberculosis. Infect. Immun. 63:1710–1717
12. Andersen P, Munk ME, Pollock JM, Doherty TM. 2000. Specific immune-based diagnosis of tuberculosis. Lancet 356:1099–1104. http://dx.doi.org/10.1016/S014-06736(00)02742-2.V
13. Geluk A, van Meijgaarden KE, Franken KL, Subronto YW, Wieles B, Arend SM, Sampaio EP, de Boer T, Faber WR, Naafs B, Ottenhoff TH. 2002. Identification and characterization of the ESAT-6 homologue of Mycobacterium leprae and T-cell cross-reactivity with Mycobacterium tuberculosis. Infect. Immun. 70:2544–2548. http://dx.doi.org/10.1128/IAI.70.5.2544-2548.2002V
14. Geluk A, van Meijgaarden KE, Franken KL, Wieles B, Arend SM, Faber WR, Naafs B, Ottenhoff TH. 2004. Immunological crossreactivity of the Mycobacterium leprae CFP-10 with its homologue in Mycobacterium tuberculosis. Scand. J. Immunol. 59:66–70. http://dx.doi.org /10.1111/j.0300-9475.2004.01358.x
15. Pai M, Riley LW, Colford JM, Jr. 2004. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. Lancet Infect. Dis. 4:761–776. http://dx.doi.org/10.1016/S1473-3099(04)01206-X.

Petruccioli E, Chiacchio T, Pepponi I, et al. First characterization of the CD4 and CD8 T-cell responses to QuantiFERON-TB Plus. J Infect 2016; [In press DOI: 10.1016/j.jinf.2016.09.008].

For Customer Service in the U.S. and Canada call toll free: 1-800-328-1482.

The symbols glossary is provided electronically and can be found in the Dialog section at www.diasorin.com using the part and lot numbers associated with the corresponding IVD product.

LIAISON® Control QuantiFERON®-TB Gold Plus ([REF] 311021)

Caution: U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner.

For *in vitro* diagnostic use only

1. INTENDED USE

The LIAISON® Control QuantiFERON®-TB Gold Plus is intended for use as assayed quality control samples to monitor the performance of the LIAISON® QuantiFERON®-TB Gold Plus assay. The performance characteristics of LIAISON® Control QuantiFERON®-TB Gold Plus have not been established for any other assays or instrument platforms other than LIAISON® XL Analyzer.

The certificate of analysis bar codes give specific information on the lot of controls and should be read by the hand-held bar code scanner of the LIAISON® XL Analyzer prior to loading the control vials on board. For details, refer to the analyzer operator's manual.

2. MATERIALS PROVIDED

Control level 1 (lyophilized 2 x 2 mL)	**[CONTROL|1]**	Recombinant human IFN-γ (produced in *E. coli*), HEPES buffer, BSA, bovine serum, 0.4% ProClin® 300, 0.2 g/L gentamycin sulfate.
Control level 2 (lyophilized 2 x 2 mL)	**[CONTROL|2]**	Recombinant human IFN-γ (produced in *E. coli*), HEPES buffer, BSA, bovine serum, 0.4% ProClin® 300, 0.2 g/L gentamycin sulfate.

ProClin® is a trademark of the Dow Chemical Company (Dow) or an affiliated company of Dow.

The controls are provided lyophilized. The range of concentrations of each control is reported on the certificate of analysis and indicates the limits established by DiaSorin for control values that can be obtained in reliable assay runs. Each laboratory is responsible for adopting different limits to meet individual requirements.

3. WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use only.
- The LIAISON® Control QuantiFERON®-TB Gold Plus are not kit lot specific and may be safely interchanged even with different LIAISON® QuantiFERON®-TB Gold Plus assay kit Reagent Integral lots.
- Do not eat, drink, smoke or apply cosmetics in the assay laboratory.
- Do not pipette by mouth.
- Avoid direct contact with potentially infected material by wearing appropriate personal protective equipment such as laboratory coats, protective goggles, and disposable gloves. Wash hands thoroughly after removal of gloves.
- Avoid splashing or aerosolization of samples or reagents. All drops and spills must be wiped up with an appropriate disinfectant such as sodium hypochlorite solution with 0.5% active chlorine, and all soiled material must be disposed of as infected waste.
- All waste associated with biological samples, biological reagents and disposable materials used for the assay must be considered potentially infectious and therefore should be disposed of in accordance with the national, state or local regulations and guidelines of the agencies holding jurisdiction over the laboratory.
- Do not use kits or components beyond the expiration date indicated on the label.
- The LIAISON® Control QuantiFERON®-TB Gold Plus are not calibrators and should not be used for assay calibration.
- Observe the normal precautions required for handling all laboratory reagents.

Chemical Hazard and Safety Information

Reagents in this kit are classified in accordance with the US OSHA Hazard Communication Standard; individual US State Right-to-Know laws; Canadian Centre for Occupational Health and Safety Controlled Products Regulations; and European Union EC Regulation 1272/2008 (CLP) (for additional information see Safety Data Sheet available on www.diasorin.com).

Hazardous reagents are classified and labelled as follows:

REAGENTS:	[CONTROL|1] (lyophilized), [CONTROL|2] (lyophilized)
CLASSIFICATION:	Eye irrit. 2 H319 Skin irrit. 2 H315 Skin sens. 1 H317 Aquatic Chronic 3 H412
SIGNAL WORD:	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H315 Causes skin irritation. H317 May cause an allergic skin reaction. H319 Causes serious eye irritation. H412 Harmful to aquatic life with long lasting effects.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P273 Avoid release to the environment.
CONTAINS: (only substances prescribed pursuant to Article 18 of EC Regulation 1272/2008).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin® 300); gentamycin sullfate salt.

Pursuant to EC Regulation 1272/2008 (CLP), after reconstitution [CONTROL|1] and [CONTROL|2] are classified and labeled as follows:

REAGENTS:	[CONTROL|1] (reconstituted), [CONTROL|2] (reconstituted)
CLASSIFICATION:	Skin sens. 1 H317
SIGNAL WORD:	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P363 Wash contaminated clothing before reuse.
CONTAINS: (only substances prescribed pursuant to Article 18 of EC Regulation 1272/2008).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin® 300).

For additional information see Safety Data Sheets available on www.diasorin.com.

4. STORAGE AND STABILITY

Do not leave the reconstituted controls at room temperature longer than the time required to process them on the LIAISON® XL Analyzer.

– Unopened and lyophilized Controls are stable until the expiry date when stored at 2°-8°C. Upon receipt, the controls must be stored at 2-8°C in an upright position to prevent adherence of the lyophilized material to the vial cap.
– Open and reconstituted Controls are stable for four (4) weeks when stored at 2°-8°C in their sealed vials between uses. After reconstitution the controls must be stored at 2°-8°C in an upright position to prevent adherence of the solution to the vial or the tube cap.

5. PREPARATION OF REAGENTS

– Reconstitute the vial contents with 2.0 mL deionized or distilled water.
– Allow the vials to stand for 15 minutes at 18-25°C to achieve complete dissolution.
– Mix vials thoroughly by gentle inversion; avoid foaming.
– The minimum volume required for each test is 460 µL (60 µL control + 400 µL dead volume).
– Place the control vials in LIAISON® XL Analyzer suitable rack. There is sufficient volume in each control vial for the performance of at least 20 tests.
– At the time of use, equilibrate controls to room temperature (20°-25°C) before opening the vials and keep them on board the LIAISON® XL Analyzer instrument only for the amount of time required for quality control testing.
– After control testing is complete, seal each control vial with the stopper cap and promptly transfer and store at 2°-8°C in an upright position.

– During handling, use appropriate precautions to prevent bacterial contamination of controls.

Original vial labels refer only to lyophilized controls. Once reconstituted, pursuant to EC Regulation 1272/2008 (CLP), controls are classified Skin sens. 1 H317. For more details, refer to paragraph 3.

6. TARGET VALUE

The expected range of concentration of each control is reported on the certificate of analysis and indicates the limits established by DiaSorin for control values that should be obtained for reliable assay runs. If control values obtained after successful calibration lie repeatedly outside the expected ranges, the test should be repeated using an unopened control vial.

7. QUALITY CONTROL

Quality control should be performed once per day of use, or according to guidelines or requirements of local regulations or accredited organizations. It is recommended that the user refers to CLSI document, C24-A3, and 42 CFR 493.1256(c) for guidance on appropriate quality control practices.

Controls are intended to monitor for substantial reagent failure. Whenever controls fall outside of the expected ranges provided on the certificate of analysis, calibration should be repeated and controls and samples retested. **Do not report patient results until control results fall within expected ranges.**

Strict adherence to the instructions of the LIAISON® QuantiFERON®-TB Gold Plus assay is necessary to obtain reliable results.

8. LIMITATIONS

Control values for assays other than LIAISON® QuantiFERON®-TB Gold Plus assay have not been established.

For Customer Service in the U.S. and Canada call toll free: 1-800-328-1482.

200/007-002, 01 - 2019-11