Alinity i Ferritin-09

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BIENNIAL REVIEW:

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SUPERSEDES: Procedure titled _____

INTENDED USE

The Alinity i Ferritin assay is a chemiluminescent microparticle immunoassay (CMIA) used for the quantitative determination of ferritin in human serum and plasma on the Alinity i analyzer.

SUMMARY AND EXPLANATION OF THE TEST

Ferritin is a high-molecular weight iron-containing protein that functions in the body as an iron storage compound. Each ferritin molecule is thought to consist of a spherical protein shell of molecular weight about 460 000 daltons made up of 24 subunits with a variable amount of iron as a core of ferricoxide-phosphate.[1, 2] It has been demonstrated that the ferritin molecule, when fully saturated, may consist of over 20% iron by weight.[2]

Approximately 25% of the iron in a normal adult is present in various storage forms.[3] About two-thirds of the iron stores in the human body exist in the form of ferritin. The remaining iron stores are contained in insoluble hemosiderin, which most likely represents a form of denatured ferritin.[4]

The availability of sensitive methods for measuring serum ferritin have significantly advanced the ability to detect iron deficiency and overload. Since iron deficiency is present before the onset of anemia, detection of an iron depleted state is important for the control of nutritional anemia. The clinical assessment of iron stores has historically relied on the determination of serum iron, total iron-binding capacity (TIBC) and percent transferrin (ratio of serum iron and TIBC) or direct examination of bone marrow.

The estimation of stainable iron in the bone marrow is the traditional method for assessing body iron stores. This biopsy method provides a sensitive index of iron deficiency but has the disadvantage of being subjective and semiquantitative. Low hemoglobin concentration is the most readily available sign of anemia, but a significant fall in circulating hemoglobin cannot be detected until the final stage of iron deficiency anemia. Serum iron, TIBC and percent transferrin saturation do not distinguish iron deficiency as a progressive disease. Also, these measurements are affected by diurnal variation and may not discriminate between depleted iron stores and conditions associated with defective reticuloendothelial release of iron (e.g., anemia of chronic disease).[3] Recent literature suggests that ferritin provides a more sensitive, specific and reliable measurement for determining iron deficiency at an early stage.[9] In patients being given iron orally, serum ferritin measurements have been shown to be useful for monitoring the reaccumulation of iron stores and determining when therapy can be discontinued.[10] In chronic inflammatory disorders, infections, and in chronic renal failure, there is a disproportionate increase in serum ferritin levels in relation to iron stores. The correlation of serum ferritin to body iron stores[10] still exists, however, it is set at a higher level of serum ferritin.[7, 8] Numerous studies in the literature demonstrate the usefulness and necessity of serum ferritin measurements in combination with other parameters in determining the rate and degree of body iron overload in such disorders as thalassemia, sideroblastic anemia and in determining the response of patients treated with iron chelating agents.[5, 6] Specifically, the combined use of serum ferritin levels and mean corpuscular volume (MCV) has made differentiation between iron deficiency, beta-thalassemia trait and normal subjects possible at a very high level of accuracy.[11, 12]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

This assay is a two-step immunoassay for the quantitative determination of ferritin in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

Sample and anti-ferritin coated paramagnetic microparticles are combined and incubated. The ferritin present in the sample binds to the anti-ferritin coated microparticles. The mixture is washed. Anti-ferritin acridinium-labeled conjugate is added to create a reaction mixture and incubated. Following a wash cycle, Pre-Trigger and Trigger Solutions are added.

The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of ferritin in the sample and the RLUs detected by the system optics.

For additional information on system and assay technology**, refer to the Alinity ci-series Operations Manual, Section 3.**

REAGENTS

Kit Contents

Alinity i Ferritin Reagent Kit 07P65

Volumes (mL) listed in the table below indicate the volume per cartridge.

REF	07P6520	07P6530
Tests per cartridge	100	600
Number of cartridges per kit	2	2
Tests per kit	200	1200
MICROPARTICLES	6.6 mL	32.1 mL
CONJUGATE	6.1 mL	31.6 mL
MICROPARTICLES Anti-Ferritin (mouse, monoclonal) coated microparticles in TRIS buffer with protein (mouse and bovine) stabilizers. Minimum concentration: 0.125% solids. Preservative: antimicrobial agent.		
CONJUGATE Anti-Ferritin (rabbit, polyclonal) acridinium-labeled conjugate in MES buffer with protein (bovine) stabilizers. Minimum concentration: 75 ng/mL. Preservative: antimicrobial agent.		

Warnings and Precautions

- IVD
- For *In Vitro* Diagnostic Use
- Rx ONLY

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[13], [14], [15], [16]

Follow local chemical disposal regulations based on your location along with recommendations and content in the Safety Data Sheet to determine the safe disposal of this product.

For the most current hazard information, see the product Safety Data Sheet.

Safety Data Sheets are available at www.corelaboratory.abbott or/SDS folder.

For a detailed discussion of safety precautions during system operation, **refer to the Alinity ci-series Operations Manual, Section 8.**

Reagent Handling

- Upon receipt, gently invert the unopened reagent kit by rotating it over and back for a full 180 degrees, 5 times with green label stripe facing up and then 5 times with green label stripe facing down. This ensures that liquid covers all sides of the bottles within the cartridges. During reagent shipment, microparticles can settle on the reagent septum.
    - Place a check in the square on the reagent kit to indicate to others that the inversions have been completed.
- After mixing, place reagent cartridges in an upright position for 2 hours before use to allow bubbles that may have formed to dissipate.
- If a reagent cartridge is dropped, place in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- Reagents are susceptible to the formation of foam and bubbles. Bubbles may interfere with the detection of the reagent level in the cartridge and cause insufficient reagent aspiration that may adversely affect results.

For a detailed discussion of reagent handling precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 7.

Reagent Storage

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened	2 to 8°C	Until expiration date	Store in upright position. If cartridge does not remain upright, gently invert the cartridge 10 times and place in an upright position for 2 hours before use.
Onboard	System Temperature	30 days	
Opened	2 to 8°C	Until expiration date	Store in upright position. If cartridge does not remain upright during storage, discard the cartridge. Do not reuse original reagent caps or replacement caps due to the risk of contamination and potential to compromise reagent

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
			performance.

Reagents may be stored on or off the system. If removed from the system, store reagents with new replacement caps in an upright position at 2 to 8°C. For reagents stored off the system, it is recommended that they be stored in their original trays or boxes to ensure they remain upright.

For information on unloading reagents, refer to the Alinity ci-series Operations Manual, Section 5.

Indications of Reagent Deterioration

Deterioration of the reagents may be indicated when:

- a calibration error occurs
- a control value is out of the specified range

Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary.

For troubleshooting information, **refer to the Alinity ci-series Operations Manual, Section 10.**

INSTRUMENT PROCEDURE

The Alinity i Ferritin assay file must be installed on the Alinity i analyzer prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, **refer to the Alinity ci-series Operations Manual, Section 2.**

For information on printing assay parameters, **refer to the Alinity ci-series Operations Manual, Section 5.**

For a detailed description of system procedures, **refer to the Alinity ci-series Operations Manual.**

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

The specimen types listed below were verified for use with this assay.

Specimen Types	Collection Tubes
Serum	Serum Serum separator
Plasma	Tripotassium EDTA Lithium heparin

- Individual plasma concentration values may differ from serum by more than 10%.
- Samples in tripotassium EDTA may give values below those of serum, while samples collected in lithium heparin may give values greater than serum values.
- When serial specimens are being evaluated, the same type of specimen should be used throughout the study.

Specimen Conditions

- For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter. Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
- Specimens should be free of bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

To ensure consistency in results, recentrifuge specimens prior to testing if

- they contain fibrin, red blood cells, or other particulate matter.

NOTE: If fibrin, red blood cells, or other particulate matter are observed, mix by low speed vortex or by inverting 10 times prior to recentrifugation.

Prepare frozen specimens as follows:

- Frozen specimens must be completely thawed before mixing.
- Mix thawed specimens thoroughly by low speed vortex or by inverting 10 times.
- Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous.
- If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Recentrifuge specimens.

Recentrifugation of Specimens

- Transfer specimens to a centrifuge tube and centrifuge.
- Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.

Specimen Storage

Specimen Type	Temperature	Maximum Storage Time	Special Instructions

Specimen Type	Temperature	Maximum Storage Time	Special Instructions
Serum/Plasma	2 to 8°C	7 days	If testing will be delayed more than 7 days, specimens should be frozen at -10°C or colder.
	-10°C or colder	12 months	Specimens stored frozen at -10°C or colder for 12 months showed no performance difference.

If testing will be delayed more than 24 hours, remove serum or plasma from the clot, serum separator or red blood cells.

Avoid multiple freeze/thaw cycles.

Specimen Shipping

Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.

PROCEDURE

Materials Provided

07P65 Alinity i Ferritin Reagent Kit

Materials Required but not Provided

- Alinity i Ferritin assay file
- 07P6501 Alinity i Ferritin Calibrators
- 07P6510 Alinity i Ferritin Controls or other commercially available controls
- 09P1540 Alinity i Multi-Assay Manual Diluent
- Alinity Trigger Solution
- Alinity Pre-Trigger Solution
- Alinity i-series Concentrated Wash Buffer

For information on materials required for operation of the instrument, **refer to the Alinity ci-series Operations Manual, Section 1.**

For information on materials required for maintenance procedures, **refer to the Alinity ci-series Operations Manual, Section 9.**

Assay Procedure

For a detailed description of how to run an assay, **refer to the Alinity ci-series Operations Manual, Section 5.**

- If using primary or aliquot tubes, **refer to the Alinity ci-series Operations Manual, Section 4 to ensure sufficient specimen is present.**

- To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.

Maximum number of replicates sampled from the same sample cup: 10

Priority:

  - Sample volume for first test: 70 µL
  - Sample volume for each additional test from same sample cup: 20 µL

≤ 3 hours on the reagent and sample manager:

  - Sample volume for first test: 150 µL
  - Sample volume for each additional test from same sample cup: 20 µL

> 3 hours on the reagent and sample manager:

  - Replace with a fresh aliquot of sample.

- Refer to the Alinity i Ferritin calibrator package insert and/or Alinity i Ferritin control package insert for preparation and usage.
- For general operating procedures, refer to the Alinity ci-series Operations Manual, Section 5.
- For optimal performance, it is important to perform routine maintenance as described in the Alinity ci-series Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Sample Dilution Procedures

Samples with a ferritin value exceeding 1675.56 ng/mL are flagged with the code "> 1675.56 ng/mL" and may be diluted with either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a **1:20** dilution of the sample and automatically calculates the concentration by multiplying the result by the dilution factor.

Manual Dilution Procedure

Suggested dilution: 1:20

Add 20 µL of the sample to 380 µL of Alinity i Multi-Assay Manual Diluent.

The operator must enter the dilution factor in the Specimen or Control tab of the Create Order screen. The system will use this dilution factor to automatically calculate the concentration of the sample and report the result. The results should be > 67 ng/mL before the dilution factor is applied.

If the operator does not enter the dilution factor, the result must be manually multiplied by the appropriate dilution factor before reporting the result. If a diluted sample result is less than 67 ng/mL, do not report the result. Rerun using an appropriate dilution.

For detailed information on ordering dilutions, **refer to the Alinity ci-series Operations Manual, Section 5.**

Calibration

For instructions on performing a calibration, **refer to the Alinity ci-series Operations Manual, Section 5.**

Each assay control must be tested to evaluate the assay calibration.

Once a calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:

- A reagent kit with a new lot number is used.

Daily quality control results are outside of statistically-based quality control limits used to monitor and control system performance, as described in the Quality Control Procedures section of this package insert.

- If statistically-based quality control limits are not available, then the calibration should **not exceed a 30-day limit for recalibration frequency**.

This assay may require recalibration after maintenance to critical parts or subsystems or after service procedures have been performed.

Quality Control Procedures

The recommended control requirement for the Alinity i Ferritin assay is that a single sample of each control level be tested once every day testing performed.

To establish statistically-based control limits, each laboratory should establish its own concentration target and ranges for new control lots at each clinically relevant control level. This can be accomplished by assaying **a minimum of 20 replicates over several (3-5) days** and using the reported results to establish the expected average (target) and variability about this average (range) for the laboratory. Sources of variation that should be included in this study in order to be representative of future system performance include:

- Multiple stored calibrations
- Multiple reagent lots
- Multiple calibrator lots
- Multiple processing modules (if applicable)
- Data points collected at different times of the day

Refer to published guidelines for information or general control recommendation, for example Clinical and Laboratory Standards Institute (CLSI) Document C24-A3 or other published guidelines, for general quality control recommendations.[17]

- If quality control results do not meet the acceptance criteria defined by laboratory QC procedure, sample results may be suspect. Follow the established quality control procedures to troubleshoot. Recalibration may be necessary. For troubleshooting information, **refer to the Alinity ci-series Operations Manual, Section 10.**
- Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

Commercial controls should be used according to the guidelines and recommendations of the control manufacturer. Concentration ranges provided in the control package insert should be used only for guidance.

For any control material in use, the laboratory should ensure that the matrix of the control material is suitable for use in the assay per the assay package insert.

Quality Control Guidance

Refer to "Basic QC Practices" by James O Westgard, Ph.D. for guidance on laboratory quality control practices.[18]

Verification of Assay Claims

For protocols to verify package insert claims, refer to Verification of Assay Claims in the Alinity ci-series Operations Manual.

RESULTS

Calculation

The Alinity i Ferritin assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, X-weighted) to generate a calibration and results.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the Alinity ci-series Operations Manual, Section 5.

Measuring Interval

Measuring interval is defined as the range of values in ng/mL which meets the limits of acceptable performance for linearity, imprecision, and bias.

The measuring interval of the Alinity i Ferritin assay is **1.98 to 1675.56 ng/mL**.

LIMITATIONS OF THE PROCEDURE

- For diagnostic purposes, results should be used in conjunction with other data; e.g., symptoms, results of other tests, clinical impressions, etc.
- If the Ferritin results are inconsistent with clinical evidence, additional testing is recommended.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits such as Alinity i Ferritin that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.[19, 20]
- Heterophilic antibodies in human serum 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 anomalous values may be observed. Additional information may be required for diagnosis.[21]

EXPECTED VALUES

This study was performed on the ARCHITECT i System.

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

Evaluation of serum specimens from 32 normal males and 60 normal females with the ARCHITECT Ferritin assay yielded the following results.

Normal Range Summary	No. of Subjects	Median (ng/mL)	Central 95% Interval (ng/mL)
Males	32	75.62	21.81 - 274.66
Females	60	39.42	4.63 - 204.00

These individuals were determined to be normal based on the AxSYM Ferritin Assay.

The manufacturers provided reference ranges adopted, effort made to verify locally.

Caliper Pediatrics suggestive refrence ranges, (https://caliperdatabase.org)

Ferritin levels below 10 ng/mL have been reported as indicative of iron deficiency anemia.[22], [23] There are patients with iron deficiency anemia who have elevated or normal ferritin levels because of other causes, such as hepatocellular disease or iron therapy.[4], [7]

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

The Alinity i analyzer and the ARCHITECT i System utilize the same reagents and sample/reagent ratios.

Unless otherwise specified, all studies were performed on the Alinity i analyzer.

Precision

Within-Laboratory Precision

A study was performed based on guidance from CLSI EP05-A2. Testing was conducted using 1 lot of the Alinity i Ferritin Reagent Kit, 1 lot of the Alinity i Ferritin Calibrators, and 1 lot of the Alinity i Ferritin Controls and 1 instrument. Three controls (Panels 1-3) and 3 human plasma panels (Panels 4-6) were assayed in a minimum of 2 replicates at 2 separate times per day on 20 different days.[24]

Sample	n	Mean (ng/mL)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Panel 1 (Low Control)	120	20.33	0.810	4.0	0.940	4.6
Panel 2 (Medium Control)	120	147.02	4.743	3.2	5.699	3.9

Sample	n	Mean (ng/mL)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Panel 3 (High Control)	120	396.16	21.431	5.4	21.626	5.5
Panel 4	120	941.15	46.171	4.9	46.733	5.0
Panel 5	120	12.56	0.394	3.1	0.475	3.8
Panel 6	120	8.17	0.335	4.1	0.338	4.1

[a] Includes within-run, between-run, and between-day variability.

Lower Limits of Measurement

A study was performed based on guidance from CLSI EP17-A2. Testing was conducted using 3 lots of the Alinity i Ferritin Reagent Kit on each of 2 instruments over a minimum of 3 days. The maximum observed Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) values are summarized below.*25*

	ng/mL
LoB[a]	0.81
LoD[b]	1.04
LoQ[c]	**1.98**

[a] The LoB represents the 95th percentile from n ≥ 60 replicates of zero-analyte samples.

[b] The LoD represents the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

[c] The LoQ was determined from n ≥ 60 replicates of low-analyte level samples and is defined as the lowest concentration at which a maximum allowable precision standard deviation of 0.87 ng/mL was met.

Linearity

A study was performed based on guidance from CLSI EP06-A.*26*

This assay is linear across the measuring interval of **1.98 to 1675.56 ng/mL**.

Interference

This study was performed on the ARCHITECT i System.

Potentially Interfering Endogenous Substances

The testing demonstrated ≤ 10% mean interference at the levels indicated below.

Potentially Interfering Substance	Interferent Level
Hemoglobin	≤ 200 mg/dL
Bilirubin	≤ 20 mg/dL
Triglycerides	≤ 3000 mg/dL
Protein	≤ 12 g/dL

Method Comparison

A study was performed based on guidance from CLSI EP09-A3 using the Passing-Bablok regression method. [27]

		Units	n	Correlation Coefficient	Intercept	Slope	Concentration Range
Alinity i Ferritin vs ARCHITECT Ferritin	Serum	ng/mL	118	1.00	-0.24	1.01	2.74 - 1560.56

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