Alinity i Prolactin-20

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BIENNIAL REVIEW:

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SUPERSEDES: Procedure titled _____

INTENDED USE

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

SUMMARY AND EXPLANATION OF THE TEST

Human prolactin (hPRL) is a single chain polypeptide of 199 amino acids and a molecular weight of approximately 23 000 daltons. Its existence as a distinct chemical entity, separate

from growth hormone, was established through a series of studies between 1965 and 1971.[1], [2] Prolactin is produced by the anterior pituitary and its secretion is regulated physiologically by inhibitory[3] and releasing[4] factors of the hypothalamus. Prolactin appears in the blood promptly after administration of thyrotropin-releasing hormone (TRH).[4], [5] The major physiologic action of prolactin is the initiation and maintenance of lactation in women.

Hyperprolactinemia has been established as a common cause of infertility and gonadal disorders in men and women. Prolactin has been shown to inhibit the secretion of ovarian steroids[6], [7] and to interfere with follicle maturation[7] and the secretion of LH and FSH[8] in the human female. Measurement of elevated serum prolactin levels may provide the first quantitative evidence of pituitary dysfunction.[9] Quantitation of prolactin levels is also of interest in the evaluation and management of patients with amenorrhea and galactorrhea.[10]

Various factors other than disease states have been found to influence prolactin levels. Factors which increase prolactin concentrations include: pregnancy, breast stimulation, stress, coitus, administration of estrogens, progesterone, androgens, some psychotropic and antihypertensive drugs, and TRH.[10], [11] Factors which decrease prolactin concentrations include the administration of L-dopa and bromocriptine.[10], [11]

The Alinity i Prolactin assay is to be used as an aid in the diagnosis of male and female infertility and pituitary dysfunction, monitoring of male and female gonadal disorders and management of amenorrhea and galactorrhea.

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

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

Sample and anti-prolactin (mouse, monoclonal) coated paramagnetic microparticles are combined and incubated. The prolactin present in the sample binds to the anti-prolactin (mouse, monoclonal) coated microparticles. The mixture is washed. Anti-prolactin (mouse, monoclonal) 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 prolactin 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 Prolactin Reagent Kit 07P66

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

REF	07P6620	07P6630
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-prolactin (mouse, monoclonal) coated microparticles in TRIS buffer with protein (bovine and murine) stabilizers. Minimum concentration: 0.1% solids. Preservative: antimicrobial agent.

CONJUGATE Anti-prolactin (mouse, monoclonal) acridinium-labeled conjugate in phosphate buffer with protein (piscine and bovine) stabilizers. Minimum concentration: 0.05 µg/mL. Preservative: ProClin.

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.[12], [13], [14], [15]

The following warnings and precautions apply to: CONJUGATE

WARNING	Contains methylisothiazolones.
H317	May cause an allergic skin reaction.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.

P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
P333+P313	If skin irritation or rash occurs: Get medical advice / attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

Safety Data Sheets are available at www.abbottdiagnostics.com or/and 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 1 hour 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 1 hour 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 the potential to compromise reagent 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 Prolactin 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.**

Alternate Result Units

Edit assay parameter "Result Units" to select an alternate unit.

Conversion formula:

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

Default Result Unit	Conversion Factor	Alternate Result Unit
ng/mL	21	mIU/L

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	Sodium heparin Lithium heparin Potassium EDTA

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 vortexing or by gently 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
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 differences.

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

07P66 Alinity i Prolactin Reagent Kit

Materials Required but not Provided

- Alinity i Prolactin assay file
- 07P6601 Alinity i Prolactin Calibrators
- 07P6610 Alinity i Prolactin 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: 80 µL
- Sample volume for each additional test from same sample cup: 30 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: 30 µL

> 3 hours on the reagent and sample manager:

    - Replace with a fresh aliquot of sample.

- Refer to the Alinity i Prolactin calibrator package insert and/or Alinity i Prolactin 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 prolactin value exceeding 200.00 ng/mL (4200.00 mIU/L) are flagged with the code "> 200.00 ng/mL" ("> 4200.00 mIU/L") and may be diluted with the Automated Dilution Protocol.

Automated Dilution Protocol

The system performs a **1:10** dilution of the sample and automatically calculates the concentration by multiplying the result by the dilution factor.

If a sample run using the Automated Dilution Protocol is flagged for less than the low linearity, it needs to be retested at a lower dilution or undiluted. The result and interpretation should not be reported.

After the automatic dilution is performed, if the sample concentration is > 2000.00 ng/mL (42 000.00 mIU/L), dilute the sample **1:40** and run using the Manual Dilution Procedure.

Manual Dilution Procedure

Suggested dilution: 1:40

Add 25 µL of the sample to 975 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 result should be > 5.00 ng/mL (> 105.00 mIU/L) 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 5 ng/mL (105 mIU/L), 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 Prolactin 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.*16*

- 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.

Quality Control Guidance

Refer to “Basic QC Practices” by James O Westgard, Ph.D. for guidance on laboratory quality control practices.*17*

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

For information on alternate result units, refer to the INSTRUMENT PROCEDURE, Alternate Result Units section of this package insert.

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 (mIU/L) which meets the limits of acceptable performance for linearity, imprecision, and bias.

The measuring interval of the Alinity i Prolactin assay is **0.82 to 200.00 ng/mL** (17.22 to 4200.00 mIU/L).

LIMITATIONS OF THE PROCEDURE

- Results should be used in conjunction with other data; e.g., symptoms, results of other tests, and clinical impressions.
- If the prolactin 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 Prolactin that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.*18*, *19*
- 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.*20*
- Prolactin may exist in alternate structural forms (e.g. macroprolactin) which may exhibit variable levels of physiological activity. In patients with elevated prolactin results, additional information may be required for diagnosis. *21*, *22*, *23*, *24*, *25*

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.

Manufacturers provided reference ranges are adopted, efforts will be made to verify it.

The expected ranges for this assay were established by testing serum specimens from 100 apparently healthy males and 100 apparently healthy, nonpregnant females using the ARCHITECT i System. The expected range for males includes the entire range of values. For the female expected range, the central 90 percent interval of all values is reported in the following table.

	Prolactin Values				
	ng/mL			mIU/L	
Population	**n**	**Median**	**Range**	**Median**	**Range**
Males	100	6.99	3.46 - 19.40	146.79	72.66 - 407.40
Females	100	10.29	5.18 - 26.53	216.09	108.78 - 557.13

CALIPER Pediatrics Reference Ranges: https://caliperdatabase.org

Reference Intervals (Female and Male)

Age	Lower Limit	Upper Limit	Sample Size	Lower Confidence Intervals	Higher Confidence Intervals
0 to <1 Year	5.41	63.07	50	(4.39, 6.44)	(49.9, 76.4)
1 to <19 Years	3.39	27.82	16	(3.15, 3.58)	(18.2, 33.9)

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 Prolactin Reagent Kit, 1 lot of the Alinity i Prolactin Calibrators,

and 1 lot of the Alinity i Prolactin Controls, and 1 instrument. Three buffered protein based panels were assayed in a minimum of 2 replicates at 2 separate times per day on 20 different days.[26]

Sample	N	Mean (ng/mL)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Panel 1	120	7.54	0.124	1.6	0.194	2.6
Panel 2	119	18.38	0.275	1.5	0.393	2.1
Panel 3	119	38.75	0.653	1.7	1.079	2.8

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

Sample	N	Mean (mIU/L)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Panel 1	120	158.41	2.603	1.6	4.064	2.6
Panel 2	119	385.93	5.775	1.5	8.249	2.1
Panel 3	119	813.72	13.717	1.7	22.663	2.8

[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 Prolactin 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.[27]

	ng/mL	mIU/L
LoB[a]	0.45	9.45
LoD[b]	0.47	9.87
LoQ[c]	**0.79**	16.59

[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 the total allowable error of ≤ 1.25 ng/mL was met.

Linearity

A study was performed based on guidance from CLSI EP06-A.[28]

This assay is linear across the measuring interval of **0.82 to 200.00 ng/mL** (17.22 to 4200.00 mIU/L).

Analytical Specificity

This study was performed on the ARCHITECT i System.

Human serum specimens containing 13-16 ng/mL of prolactin were supplemented with follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG), human growth hormone (hGH), human placental lactogen (hPL), luteinizing hormone (LH), or thyroid stimulating hormone (TSH) at specific levels. The results are stated in the following table.

Potential Cross Reactant	Concentration Tested	Cross Reactivity (%)
FSH	≤ 1000 mIU/mL	0
Hcg	≤ 100 000 mIU/mL	0
hGH	≤ 1000 ng/mL	0.03
hPL	≤ 100 000 ng/mL	0
LH	≤ 5000 mIU/mL	0.001
TSH	≤ 20 000 µIU/mL	0

Interference

This study was performed on the ARCHITECT i System.

Potential interference from hemoglobin, bilirubin, triglycerides, and protein was studied in the ARCHITECT Prolactin assay. The ARCHITECT Prolactin assay demonstrated less than 10% interference for the following potentially interfering substances:

Potentially Interfering Substance	Interferent Level
Hemoglobin	≤ 500 mg/dL
Bilirubin	≤ 20 mg/dL
Triglycerides	≤ 3000 mg/dL
Protein	≤ 12.0 g/dL

Method Comparison

A study was performed based on guidance from CLSI EP09-A3 using the Passing-Bablok regression method.[29, 30]

		Units	n	Correlation Coefficient	Intercept	Slope	Concentration Range
Alinity i Prolactin vs ARCHITECT Prolactin	Serum	ng/mL	200	0.99	0.58	1.03	1.12-178.04
	Serum	mIU/L	200	0.99	12.12	1.03	23.42-3738.84

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