Access
Immunoassay Systems

hFSH
REF 33520

Intended Use

The Access hFSH assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of follicle stimulating hormone (FSH) levels in human serum and plasma using the Access Immunoassay Systems.

Summary and Explanation

Human follicle stimulating hormone (hFSH, follitropin) is made up of two non-identical, covalently-associated glycoprotein subunits, denoted alpha and beta. It has been reported that the beta subunit of the 30,000 dalton molecular weight hFSH contains two asparagine-linked carbohydrate chains. The alpha subunit is similar in structure for the glycoproteins hFSH, hCG, hLH, and hTSH. It is differences in the beta subunit of these glycoproteins which contributes to immunological and physiological specificity.[1,2,3]

In the female, hFSH stimulates follicular growth and, in conjunction with hLH, stimulates estrogen secretion and ovulation. Following ovulation, hFSH and hLH are believed to be responsible for the transformation of the ruptured follicle into a corpus luteum and to influence the secretion of progesterone by the luteal cells.[4] Human FSH is secreted by the gonadotropic cells of the anterior lobe of the pituitary gland in response to gonadotropin releasing hormone (GnRH) from the medial basal hypothalamus. Both hFSH and hLH are secreted in a pulsatile nature, however, this is less noticeable for hFSH perhaps due to the longer half life of hFSH in circulation.[3] Levels of circulating hFSH vary in response to estradiol and progesterone. In a normal menstrual cycle, a slight peak of hFSH is observed toward the end of the luteal phase (most likely triggered by a fall in estradiol and progesterone which eliminates the negative feedback effect.) This begins the growth and maturation of ovarian follicles. The levels of hFSH then fall and remain low through the follicular phase (due to negative feedback from estradiol and progesterone produced by the developing follicle.) At mid-cycle GnRH triggers a rise in hFSH. The function of this mid-cycle peak of hFSH is unknown. Following this rise, hFSH is suppressed during the luteal phase by negative feedback from estradiol. Near the end of the menstrual cycle the small hFSH rise then begins the follicular maturation of the next cycle.[3,4,5]

Variation in cycle lengths observed in the normally menstruating female are due to variations in the length of the follicular phase. In the menopausal female, hFSH levels are elevated in response to decreased production of ovarian estrogens and progesterones which eliminates the negative feedback mechanism on the pituitary gland. As a result, ovulation and menstrual cycles decrease and eventually cease.[6]

In the male, hFSH stimulates spermatogenesis through receptors on the Sertoli cells which are present in the seminiferous tubules of the testes. While both hLH and hFSH are required for normal maturation of spermatozoa, hFSH is less sensitive to feedback inhibition by testosterone. Human FSH is thought to be regulated in part by the peptide inhibin which is produced by the Sertoli cells in males and by granulosa cells in females.[7]

Human LH and FSH levels are commonly determined in investigations of menstrual, fertility, and pubertal developmental disorders such as premature ovarian failure, menopause, ovulatory disorders and pituitary failure.[8] The ratio of hLH/hFSH has been used to assist in the diagnosis of polycystic ovary disease. Low levels of hLH and hFSH may indicate pituitary failure while elevated hLH and hFSH levels along with decreased levels of gonadal steroids may indicate gonadal failure (menopause, ovariectomy, premature ovarian syndrome, Turner's Syndrome).[9] Low gonadotropin levels are usually observed in females taking oral steroid-based contraceptives.[10] In the male, elevated hFSH and hLH with low levels of gonadal

steroids may indicate testicular failure or anorchia. In Klinefelter's syndrome hFSH may be elevated due to Sertoli cell failure.[11]

Principles of the Procedure

The Access hFSH assay is a sequential two-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel with paramagnetic particles coated with goat anti-mouse: mouse anti-hFSH complexes and TRIS buffered saline with protein. The hFSH binds to the immobilized mouse anti-hFSH on the solid phase. Materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Alkaline phosphatase conjugated goat anti-hFSH is then added and binds to the previously bound hFSH on the particles. A second separation and wash step removes unbound conjugate. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of hFSH in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

Product Information

Access hFSH Reagent Pack

Cat. No. 33520: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 28 days after initial use.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the reagent is damaged (i.e. broken elastomer), discard the pack.
- All antisera are polyclonal unless otherwise indicated.

R1a:	Paramagnetic particles coated with goat anti-mouse IgG: mouse monoclonal anti-hFSH complexes suspended in TRIS buffered saline with bovine serum albumin (BSA), surfactant, < 0.1% sodium azide, and 0.1% ProClin** 300.
R1b:	Goat anti-hFSH-alkaline phosphatase (bovine) conjugate in TRIS buffered saline, with protein (bovine, murine, goat), surfactant, < 0.1% sodium azide, and 0.1% ProClin 300.
R1c:	TRIS buffered saline with protein (bovine, murine, goat), surfactant, < 0.1% sodium azide, 0.1% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[12]
- Xi. Irritant: 0.1% ProClin 300.

R 43: May cause sensitization by skin contact.

S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Specimen Collection and Preparation

1. Serum and plasma (heparin) are the recommended samples.
2. Observe the following recommendations for handling, processing, and storing blood samples:[13]
   - Collect all blood samples observing routine precautions for venipuncture.
   - Allow serum samples to clot completely before centrifugation.
   - Keep tubes stoppered at all times.
   - Within two hours after centrifugation, transfer at least 500 µL of cell-free sample to a storage tube. Tightly stopper the tube immediately.
   - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than eight hours.
   - If the assay will not be completed within eight hours, refrigerate the samples at 2 to 8°C.
   - If the assay will not be completed within 48 hours, or for shipment of samples, freeze at -20°C or colder.
   - Thaw samples only once.
3. Use the following guidelines when preparing specimens:
   - Ensure residual fibrin and cellular matter has been removed prior to analysis.
   - Follow blood collection tube manufacturer's recommendations for centrifugation.
4. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variations in these products may exist between manufacturers and, at times, from lot-to-lot.
5. Beckman Coulter, Inc., recommends that frozen specimens can be stored up to three months before testing.

Materials Provided

R1 Access hFSH Reagent Packs

Materials Required But Not Provided

1. Access hFSH Calibrators
   Provided at zero and approximately 1, 10, 50, 100 and 200 mIU/mL (IU/L).
   Cat. No. 33525
2. Quality Control (QC) materials: commercial control material
3. Access Sample Diluent A
   Vial Cat. No. 81908
   Diluent Pack Cat. No. A79783 (For use with the UniCel DxI system onboard dilution feature.)
4. Access Substrate
   Cat. No. 81906
5. **Access, Access 2, SYNCHRON LXi:**
   Access Wash Buffer II, Cat. No. A16792
   UniCel DxI:
   UniCel DxI Wash Buffer II, Cat. No. A16793

Procedural Comments

1. Refer to the appropriate system manuals and/or Help system for a specific description of installation, start-up, principles of operation, system performance characteristics, operating instructions, calibration procedures, operational limitations and precautions, hazards, maintenance, and troubleshooting.
2. Mix contents of new (unpunctured) reagent packs by gently inverting pack several times before loading on the instrument. Do not invert open (punctured) packs.
3. Use twenty-five (25) µL of sample for each determination in addition to the sample container and system dead volumes. Use one hundred fifty-five (155) µL of sample in addition to the sample container and system dead volumes for each determination run with the DxI system

onboard dilution feature. Refer to the appropriate system manuals and/or Help system for the minimum sample volume required.

4. The system default unit of measure for sample results is mIU/mL. To change sample reporting units to the International System of Units (SI units), IU/L, refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System, multiply mIU/mL by multiplication factor 1.

Procedure

Refer to the appropriate system manuals and/or Help system for information on managing samples, configuring tests, requesting tests, and reviewing test results.

Calibration Details

An active calibration curve is required for all tests. For the Access hFSH assay, calibration is required every 28 days. Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Quality Control

Quality control materials simulate the characteristics of patient samples and are essential for monitoring the system performance of immunochemical assays. Because samples can be processed at any time in a "random access" format rather than a "batch" format, quality control materials should be included in each 24-hour time period.[14] Include commercially available quality control materials that cover at least two levels of analyte. More frequent use of controls or the use of additional controls is left to the discretion of the user based on good laboratory practices or laboratory accreditation requirements and applicable laws. Follow manufacturer's instructions for reconstitution and storage. Each laboratory should establish mean values and acceptable ranges to assure proper performance. Quality control results that do not fall within acceptable ranges may indicate invalid test results. Examine all test results generated since obtaining the last acceptable quality control test point for this analyte. Refer to the appropriate system manuals and/or Help system for information about reviewing quality control results.

Results

Patient test results are determined automatically by the system software using a smoothing spline math model. The amount of analyte in the sample is determined from the measured light production by means of the stored calibration data. Patient test results can be reviewed using the appropriate screen. Refer to the appropriate system manuals and/or Help system for complete instructions on reviewing sample results.

Limitations of the Procedure

1. Samples can be accurately measured within the analytic range of the lower limit of detection and the highest calibrator value [approximately 0.2–200 mIU/mL (IU/L)].
   - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value [i.e., < 0.2 mIU/mL (IU/L)]. When the DxI system onboard dilution feature is used, the system will report results as less than 170 mIU/mL (IU/L).
   - If a sample contains more than the stated value of the highest Access hFSH Calibrator (S5), report the result as greater than that value [i.e., > 200 mIU/mL (IU/L)]. Alternatively, dilute one volume of sample with equal volumes of Access hFSH Calibrator S0 (zero) or Access Sample Diluent A. Refer to the appropriate system manuals and/or Help system for instructions on entering a sample dilution in a test request. The system reports the results adjusted for the dilution.
     The DxI system onboard dilution feature automates the dilution process, using one volume of sample with one volume of Access Sample Diluent A, allowing samples to be quantitated up to approximately 400 mIU/mL (IU/L). The system reports the results adjusted for the dilution.
2. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with

immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples.[15,16]
Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.

3. The Access hFSH results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from addirional tests and other appropriate information.

Expected Values

1. Each laboratory should establish its own reference ranges to assure proper representation of specific populations.
2. FSH levels were measured in human serum samples from 65 adult males, 50 postmenopausal females, and 26 normal cycling females. The cycles were synchronized to the mid-cycle LH peak. The range of hFSH levels are summarized below:

	Males hFSH (mIU/mL)	Females hFSH (mIU/mL)			
		Mid-Follicular Phase	Mid-Cycle Peak	Mid-Luteal Phase	Postmenopausal
Number	65	29	26	27	50
Mean	5.88	6.43	12.27	3.45	60.76
Range	1.27–19.26	3.85–8.78	4.54–22.51	1.79–5.12	16.74–113.59

Specific Performance Characteristics

Methods of Comparison

A comparison of serum hFSH values using the Access hFSH assay on the Access Immunoassay system and a commercially available enzyme immunoassay kit gave the following statistical data:

n	Range of Observations (mIU/mL)	Intercept (mIU/mL)	Slope	Correlation Coefficient (r)
161	1.18–187.12	0.73	0.98	0.98

A comparison of hFSH values obtained by assaying paired serum and plasma samples using the Access hFSH assay on the Access Immunoassay System gave the following statistical data:

n	Range of Observations (mIU/mL)	Intercept (mIU/mL)	Slope	Correlation Coefficient (r)
186	0.63–119.94	-0.12	1.08	1.00

Linearity

Based on CLSI EP6-A[17], one high sample (≥ 200 mIU/mL) and one low sample (≤ 0.2 mIU/mL) were mixed to make seven evenly distributed sample concentrations. Four replicates of the seven mixed samples, eight replicates of the low sample, and two replicates of the high sample were run on a single Access 2 system. Using weighted quadratic regression, the Access hFSH assay was linear with a maximum deviation from linearity of 3.43%.

Imprecision

This assay exhibits total imprecision of less than 10% across the assay range. One study, using commercially available human serum based control material generating a total of 2 assays, 2 replicates per assay, over 10 days provided the following data, analyzed via analysis of variance (ANOVA).[18,19]

Sample	Grand Mean (n=40) (mIU/mL)	Within Run (%CV)	Total Imprecision (%CV)
Low	9.95	3.5	5.6
Medium	15.45	3.1	5.4
High	36.40	4.3	4.3

Analytical Specificity / Interferences

Samples containing up to 10 mg/dL (171 µmol/L) bilirubin, lipemic samples containing the equivalent of 1800 mg/dL (20.32 mmol/L) triglycerides, and hemolyzed samples containing up to 1 g/dL (10 g/L) hemoglobin do not affect the concentration of hFSH assayed. The addition of 3 g/dL (30 g/L) human serum albumin to the endogenous albumin in samples does not affect the concentration of hFSH assayed.

No significant cross-reactivity was observed when hCG, hLH, hTSH or βFSH were added to the Access hFSH Calibrator S0 (zero) at 500,000 mIU/mL, 1000 mIU/mL, 2000 µIU/mL and 22.65 ng/mL respectively.

Analytical Sensitivity

The lowest detectable level of hFSH distinguishable from zero (Access hFSH Calibrator S0) with 95% confidence is 0.2 mIU/mL (IU/L). This value is determined by processing a complete six point calibration curve, controls, and 10 replicates of the zero calibrator in multiple assays. The analytical sensitivity value is interpolated from the curve at the point that is two standard deviations from the fitted zero calibrator signal.

Access
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hFSH CALIBRATORS
REF 33525

Intended Use

The Access hFSH Calibrators are intended to calibrate the Access hFSH assay for the quantitative determination of follicle stimulating hormone (FSH) levels in human serum and plasma using the Access Immunoassay Systems.

Summary and Explanation

Quantitative assay calibration is the process by which samples with known analyte concentrations (i.e., assay calibrators) are tested like patient samples to measure the response. The mathematical relationship between the measured responses and the known analyte concentrations establishes the calibration curve. This mathematical relationship, or calibration curve, is ued to convert RLU (Relative Light Unit) measurements of patient samples to specific quantitative analyte concentrations.

Traceability

The measurand (analyte) in the Access hFSH Calibrators is traceable to the WHO 2nd International Reference Preparation for hFSH (78/549). Traceability process is based on EN ISO 17511.

The assigned values were established using representative samples from this lot of calibrator and are specific to the assay methodologies of the Access reagents. Values assigned by other methodologies may be different. Such differences, if present, may be caused by inter-method bias.

Product Information

Access hFSH Calibrators
Cat. No. 33525: S0–S5, 4.0 mL/vial

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Mix contents by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Signs of possible deterioration are control values out of range.
- Refer to calibration card for exact concentrations.

S0:	Buffered bovine serum albumin (BSA) matrix with surfactant, < 0.1% sodium azide, and 0.5% ProClin** 300. Contains 0 mIU/mL (IU/L) hFSH.
S1, S2, S3, S4, S5:	hFSH at levels of approximately 1, 10, 50, 100 and 200 mIU/mL (IU/L), respectively, in buffered BSA matrix with surfactant, < 0.1% sodium azide, and 0.5% ProClin 300.
Calibration Card:	1

Warnings and Precautions

- For *in vitro* diagnostic use.
- The antigen used in the preparation of the reagent is derived from human pituitary glands. Handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.[20]

- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[12]
- Xi. Irritant: 0.5% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Refer to the appropriate system manuals and/or Help system for information on calibration theory, configuring calibrators, calibrator test request entry, and reviewing calibration data.

Calibration Details

The Access hFSH Calibrators are provided at six levels-zero and approximately 1, 10, 50, 100 and 200 mIU/mL prepared gravimetrically from purified hFSH and buffered BSA matrix. Assay calibration data are valid up to 28 days.

Calibrators run in duplicate.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

Access
Immunoassay Systems

SAMPLE DILUENT A

REF 81908 (Vial)

REF A79783 (Diluent Pack)

Intended Use

The Access Sample Diluent A is intended for use with Access assays to dilute patient samples containing analyte concentrations greater than the analyte specific S5 calibrator.

Summary and Explanation

The analyte level in patient samples may exceed the level of the specific S5 calibrator. If a quantitative value is required, it will be necessary to dilute the samples in order to determine the analyte concentration.

Product Information

Access Sample Diluent A
Cat. No. 81908: 4 mL/vial

- Provided ready to use.
- Allow the contents to stand for 10 minutes at room temperature.
- Mix contents by gently inverting before use. Avoid bubble formation.
- Stable until the expiration date stated on the vial label when stored at 2 to 10°C.

Diluent:	Buffered BSA matrix with surfactant, < 0.1% sodium azide, 0.5% ProClin** 300.

Cat. No. A79783: 2 diluent packs, 32.9 mL/pack

- Provided ready to use.
- Store upright and refrigerate at 2 to 10°C.
- Refrigerate at 2 to 10°C for a minimum of two hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2 to 10°C.
- Stable at 2 to 10°C for 56 days after initial use of each well.
- Signs of possible deterioration are a broken elastomeric layer on the pack or control values out of range.
- If the diluent pack is damaged (i.e., broken elastomer), discard the pack.

R1a – R1e:	Buffered BSA matrix with surfactant, < 0.1% sodium azide, 0.5% ProClin 300.

Warnings and Precautions

- For *in vitro* diagnostic use.
- Patient samples and blood-derived products may be routinely processed with minimum risk using the procedure described. However, handle these products as potentially infectious according to universal precautions and good clinical laboratory practices, regardless of their origin, treatment, or prior certification. Use an appropriate disinfectant for decontamination. Store and dispose of these materials and their containers in accordance with local regulations and guidelines.
- Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.[12]

- Xi. Irritant: 0.5% ProClin 300.

R 43: May cause sensitization by skin contact.
S 28-37: After contact with skin, wash immediately with plenty of soap and water. Wear suitable gloves.

- The Material Safety Data Sheet (MSDS) is available upon request.

Procedure

Samples can be accurately measured within the analytical range of the lower limit of detection and the highest calibrator value of the specific assay. If a sample contains more analyte than the stated value of the S5 calibrator, dilute the sample following dilution instructions in the specific assay labeling under "Limitations of the Procedure" in the reagent pack section. Refer to the appropriate system manuals and/or Help system for instructions on how to enter a sample dilution in a test request.

Limitations of the Procedure

If there is evidence of microbial contamination or excessive turbidity in a reagent, discard the vial.

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