BECKMAN COULTER

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ACCESS
Immunoassay Systems

Instructions For Use

Access AMH
anti-Müllerian hormone (AMH)

REF B13127

ANNUAL REVIEW

Reviewed by	Date	Reviewed by	Date

PRINCIPLE

INTENDED USE

The Access AMH assay is a paramagnetic particle chemiluminescent immunoassay for the quantitative determination of anti-Müllerian hormone (AMH) levels in human serum and plasma using the Access Immunoassay Systems as an aid in the assessment of ovarian reserve.

SUMMARY AND EXPLANATION

Anti-Müllerian hormone (AMH) is a glycoprotein, which circulates as a dimer composed of two identical 72 kDa monomers that are linked by disulfide bridges. AMH belongs to the transforming growth factor-β family.[1,2]

AMH is named for its first described function in fetal sexual differentiation: a regression of the Müllerian ducts in males during early fetal life. In males, AMH is secreted by Sertoli cells of the testes. AMH concentrations are high until puberty, and then decrease slowly to residual post-puberty levels.[3] This decline of AMH production during puberty is related to the pubertal development stage. The most significant decrease in AMH concentrations occurs between Tanner stages II and III, and is concurrent with the increase of testosterone concentrations within the testes – an event that occurs earlier than blood testosterone concentrations increase.[4]

In the early development of the female fetus, the absence of AMH allows the Müllerian ducts to further develop, resulting in the internal female anatomy.[5] In females, AMH expression has been observed at approximately 36 weeks gestation in granulosa cells of preantral ovarian follicles and is produced by these cells until menopause.[6,7]

AMH concentrations in adult women reflect the number of small follicles entering the growth phase of their life cycle, which is proportional to the number of primordial follicles that still remain in the ovary, or the ovarian reserve.[5,8,9] AMH decreases throughout a woman's reproductive life, which reflects the continuous decline of the oocyte/follicle pool with age and, accordingly, ovarian aging.[10] Although AMH concentrations decrease with age, studies have shown that the day-to-day variability of AMH concentrations in menstruating women is so low that AMH can be measured at any day during the menstrual cycle.[11]

AMH has been used in the evaluation of ovarian reserve primarily to predict an infertile woman's response to controlled ovarian stimulation.[12] Research studies have also demonstrated that AMH may be used to estimate the time to menopause for an individual woman, as AMH has been found to be a good indicator of reproductive aging.[10] Additionally, studies have shown that AMH can be used to diagnose and monitor women with polycystic ovary syndrome (PCOS), and that AMH concentrations are elevated in normogonadotropic anovulatory women with PCOS.[13,14]

Studies reveal that AMH concentrations increase in granulosa cell tumors of the ovary and AMH may serve as a sensitive and specific marker in the follow-up of ovariectomized patients. Early detection of AMH is of great importance, as granulosa cell tumors are characterized by a high incidence of recurrence.[15,16]

In prepubertal girls, research studies have shown that AMH determination helps differentiate between gonadal and non-gonadal causes of mild virilization.[17] Undetectable AMH levels are found in 46,XX prepubertal virilized girls while higher than average female AMH concentrations are found in children with disorders of testosterone secretion, androgen insensitivity, dysgenetic testes, and ovotestes. Extremely high AMH concentrations are found in girls with virilizing Sertoli-Leydig cell ovarian tumors.[18]

The incidence of cryptorchidism is 3-6% in full-term newborn boys, which declines to 1-2% by three months of age due to spontaneous testicular descent. Studies reveal that AMH concentrations can distinguish undescended testes, which have normal male AMH concentrations, from anorchia, which have extremely low or undetectable concentrations.[18] Studies evaluating the intersex conditions in children demonstrate that AMH concentrations reflect the function of Sertoli cells, and are often determined in conjunction with testosterone measurement. Testicular dysgenesis is characterized by low concentrations of both AMH and testosterone compared to normal males. AMH has also been studied in conjunction with the measurement of FSH, LH, and testosterone for precocious and delayed puberty in boys.[19]

METHODOLOGY

The Access AMH assay is a simultaneous one-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel, along with a mouse monoclonal anti-AMH antibody conjugated to alkaline phosphatase in MES buffer, TRIS buffered saline with proteins, and paramagnetic particles coated with a mouse monoclonal anti-AMH antibody in TRIS buffer. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos* 530 is added to the vessel and light generated by this reaction is measured with a luminometer. The light production is directly proportional to the concentration of AMH in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

SPECIMEN

SPECIMEN COLLECTION AND PREPARATION

1. Serum and plasma (lithium heparin) are the recommended samples.
2. Observe the following recommendations for handling, processing, and storing blood samples:[20]
    - Collect all blood samples observing standard precautions for venipuncture.
    - Allow serum samples to clot completely before centrifugation in a vertical, closure up position.
        - Nonanticoagulated tubes containing gel or a clot activator should be stored in an upright position as soon as the mixing is complete.
        - Precentrifugation serum/cells contact time is according to tube manufacturer’s recommendations. Clotting may be slowed at cooler temperatures or if patient is on anticoagulant therapy.
    - Keep tubes stoppered at all times.
    - Physically separate serum or plasma from contact with cells as soon as possible.
    - Store samples tightly stoppered at room temperature (15 to 30°C) for no longer than 24 hours.
    - If the assay will not be completed within 24 hours, refrigerate the samples at 2 to 8°C.
    - If the assay will not be completed within 6 days, or for shipment of samples beyond 6 days, freeze at -20°C or colder.
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. Thaw samples no more than two times.
6. Avoid assaying lipemic or hemolyzed samples.

REAGENTS

PRODUCT INFORMATION

Access AMH Reagent Pack

Cat. No. B13127: 100 determinations, 2 packs, 50 tests/pack

- Provided ready to use.
- Store upright and refrigerate at 2°C to 10°C.
- Refrigerate at 2°C to 10°C for a minimum of 2 hours before use on the instrument.
- Stable until the expiration date stated on the label when stored at 2°C to 10°C.
- Stable at 2 to 10°C for 31 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 pack is damaged (i.e., broken elastomer), discard the pack.

R1a:	Dynabeads** paramagnetic particles coated with monoclonal anti-AMH in TRIS buffer with surfactant, protein (bovine), <0.1% sodium azide, 0.1% ProClin*** 300.
R1b:	Anti-AMH alkaline phosphatase conjugate in MES buffer, surfactant, protein (bovine, recombinant), < 0.1% sodium azide, 0.1% ProClin 300.
R1c:	TRIS buffer with surfactant, protein (murine, bovine), < 0.1% sodium azide, 0.1% ProClin 300.

**Dynabeads is a registered trademark of Dynal A.S., Oslo, Norway.

***ProClin is a trademark of Rohm and Haas Company or of its subsidiaries or affiliates.

WARNING 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.[21]
- 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.

MATERIALS NEEDED BUT NOT SUPPLIED WITH REAGENT KIT

1. Access AMH Calibrators
   Provided at zero and approximately 0.16, 0.6, 4, 10, and 24 ng/mL (1.1, 4.3, 29, 71, and 171 pmol/L).
   Cat. No. B13128
2. Access AMH QC (Quality Control) or other commercially available control material.
   Provided at approximately 1, 5 and 15 ng/mL (7.1, 36 and 107 pmol/L).
   Cat. No. B13129
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 2, UniCel DxC 600i:**
   Access Wash Buffer II, Cat. No. A16792
   UniCel DxI 600, UniCel DxI 800, UniCel DxC 880i, UniCel DxC 860i, UniCel DxC 680i, UniCel DxC 660i:
   UniCel DxI Wash Buffer II, Cat. No. A16793

EQUIPMENT AND MATERIALS

R1	Access AMH Reagent Packs

CALIBRATION

CALIBRATION INFORMATION

An active calibration curve is required for all tests. For the Access AMH assay, calibration is required every 31 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.[22] Include Access AMH QC or other 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.

TESTING PROCEDURE(S)

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 (20) µL of sample for each determination in addition to the sample container and system dead volumes. Use forty-five (45) 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 ng/mL. To change the reporting units to the International System of Units (SI Units), pmol/L (pM), refer to the appropriate system manuals and/or Help system. To manually convert concentrations to the International System, multiply ng/mL by multiplication factor 7.14.

Procedure

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

RESULTS INTERPRETATION

Patient test results are determined automatically by the system software. 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.

REPORTING RESULTS

EXPECTED RESULTS

1. Each laboratory should establish its own reference ranges to assure proper representation of specific populations.
2. In one study, AMH concentrations were measured in serum samples collected from apparently healthy adult females, adult males and newborns using the Access AMH assay on the Access 2 Immunoassay System.

Adult Reference Group	Age Range (years)	N	Median ng/mL (pmol/L)	95% RI ng/mL (pmol/L)
Females	18-25	80	3.71 (26.49)	0.96-13.34 (6.82-95.22)
Females	26-30	82	2.27 (16.21)	0.17-7.37 (1.22-52.66)
Females	31-35	80	1.88 (13.43)	0.07-7.35 (0.53-52.48)
Females	36-40	80	1.62 (11.60)	0.03-7.15 (0.20-51.03)
Females	41-45	79	0.29 (2.05)	0.00-3.27 (0.00-23.35)
Females	≥ 46	82	0.01 (0.06)	0.00-1.15 (0.00-8.19)
Males	> 18	83	4.87 (34.77)	0.73-16.05 (5.20-114.60)

Pediatric Reference Group	Age Range (days)	N	Median ng/mL (pmol/L)	95% RI ng/mL (pmol/L)
Males	≤ 60	55	46.94 (335.17)	15.11-266.59 (107.92-1903.49)
Females	≤ 60	44	0.16 (1.17)	0.01-3.39 (0.04-24.19)

PROCEDURAL NOTES

LIMITATIONS

1. Samples can be accurately measured within the analytical range of the lower limit of detection and the highest calibrator value (approximately 0.02-24 ng/mL [0.14-171 pmol/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., < 0.02 ng/mL [< 0.14 pmol/L]). When the DxI system onboard dilution feature is used, the system will report results as less than 20 ng/mL (146 pmol/L).
   - If a sample contains more than the stated value of the highest Access AMH Calibrator (S5), report the result as greater than that value (i.e., > 24 ng/mL [> 171 pmol/L]). Alternatively, dilute one volume of sample with 15 volumes (1/16) of Access Sample Diluent A or dilute one volume of sample with 9 volumes (1/10) of 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 nine volumes of Access Sample Diluent A, allowing samples to be quantitated up to approximately 240 ng/mL (1714 pmol/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.[23,24]
   Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies.
3. Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor, endogenous alkaline phosphatase, fibrin, and proteins capable of binding to alkaline phosphatase.[25] Carefully evaluate the results of patients suspected of having these types of interferences.
4. The Access AMH results should be interpreted in light of the total clinical presentation of the patient, including: symptoms, clinical history, data from additional tests, and other appropriate information.
5. The Access AMH assay does not demonstrate any “hook” effect up to 1000 ng/mL.

PERFORMANCE CHARACTERISTICS

METHODS COMPARISON

Representative data for methods comparison are provided for illustration only. Performance obtained in individual laboratories may vary.

A comparison of 104 values across the range of the assay using the Access AMH assay on the Access 2 Immunoassay system and the manual AMH Gen II ELISA (Cat. No. A79765) test gave the following statistical data using Passing Bablok regression and Spearman correlation for the r calculation:

n	Range of Observations (ng/mL)	Intercept (ng/mL)	Slope (95% CI)	Correlation Coefficient (r)
104	0.16 - 21.7	0.12	0.91 (0.89-0.94)	0.99
93	0.16 - 9.88	0.09	0.95 (0.92-0.97)	0.99

Linearity

Representative data for linearity are provided for illustration only. Performance obtained in individual laboratories may vary.

Based on CLSI EP6-A,[26] one high sample (>24 ng/mL) and one low sample (<0.02 ng/mL) were mixed to make 7 evenly distributed sample concentrations. Four replicates of the 7 mixed samples, 8 replicates of the low sample and 4 replicates of the high sample were run on a single Access 2 instrument. The Access AMH assay was designed to be linear, with a maximum deviation from linearity of ≤ 5.0% for samples > 0.16 ng/mL, and ≤ 0.04 ng/mL for samples ≤ 0.16 ng/mL. One study, analyzed using a polynomial regression method demonstrated a maximum deviation from linearity of 2.45% for samples > 0.16 ng/mL and < 0.00 ng/mL for samples ≤ 0.16 ng/mL.

Imprecision

Representative data for imprecision are provided for illustration only. Performance obtained in individual laboratories may vary.

The Access AMH assay exhibits total imprecision ≤ 10.0% at concentrations ≥ 0.16 ng/mL, and total standard deviation (SD) ≤ 0.032 ng/mL, at concentrations < 0.16 ng/mL. One study, using human serum samples involved a total of 40 assays with 2 replicates per assay, over 20 days. The following data were calculated based on CLSI EP5-A2[27] guidelines.

		Within-run		Between Run		Total Imprecision	
Sample	Grand Mean ng/mL (n = 80)	SD (ng/mL)	% CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV
Sample 1	0.13	0.003	N/A	0.003	N/A	0.004	N/A
Sample 2	2.63	0.038	1.5	0.073	2.8	0.083	3.1
Sample 3	10.45	0.177	1.7	0.254	2.4	0.310	3.0
Sample 4	17.81	0.265	1.5	0.472	2.6	0.541	3.0

Analytical Specificity / Interferences

Representative data for analytical specificity/interferences are provided for illustration only. Performance obtained in individual laboratories may vary.

Serum samples with AMH concentrations of approximately 1 and 5 ng/mL (7.1 and 36 pmol/L) were spiked with multiple concentrations of the substances below and run on a single Access 2 Immunoassay System. Values were calculated as described in CLSI EP7–A2.[28] Interference was determined by testing controls (no interfering substance added) and matched test samples (with interfering substance added). There was no significant interference (exceeding 10% shift in dose) observed when the following substances were tested at the indicated concentrations.

Substance	Highest Concentration Added
Acetaminophen	20 mg/dL
Acetylsalicylic Acid	65 mg/dL
Ascorbic Acid	170 µmol/L

Substance	Highest Concentration Added
Bilirubin (conjugated)	43 mg/dL
Bilirubin (unconjugated)	40 mg/dL
Biotin	735 nmol/L
Gamma Globulin	60 mg/mL
Hemoglobin	300 mg/dL
Heparin (Low Molecular Weight)	3000 U/L
Ibuprofen	50 mg/dL
Multi-vitamin	1% (v/v)
Intralipids	37 mmol/L
Total protein (human serum albumin)	12 g/dL
Uric Acid	1.4 mmol/L

Serum samples with AMH concentrations of approximately 1 and 5 ng/mL (7.1 and 36 pmol/L) were spiked with multiple concentrations of the substances below and run on a single Access 2 Immunoassay System. Values were calculated as described in CLSI EP7-A2.[28] There was no significant cross reactivity (exceeding 5% cross reactivity) observed when the following substances were tested at the indicated concentrations.

Substance	Highest Concentration Added
Inhibin A	100 ng/mL
Activin A	16.32 µg/mL
hLH	100 mIU/mL
hFSH	115 mIU/mL
TGF β-1	65 ng/mL

Limit of Blank

Representative data for Limit of Blank is provided for illustration only. Performance obtained in individual laboratories may vary.

The Access AMH assay is designed to have a Limit of Blank (LoB) of ≤ 0.01 ng/mL (0.07 pmol/L). In one study, LoB was tested using a protocol based on CLSI EP17-A2.[29] A total of 240 replicates of a zero analyte sample, the Access AMH S0 calibrator, were measured in 12 runs using multiple reagent packs and calibrator lots on multiple Access 2 Systems. This study determined the LoB for Access AMH to be 0.0024 ng/mL (0.017 pmol/L).

Limit of Detection

Representative data for Limit of Detection is provided for illustration only. Performance obtained in individual laboratories may vary.

The Access AMH assay was designed to have a Limit of Detection (LoD) of ≤ 0.02 ng/mL (0.14 pmol/L). In one study, LoD was tested using a protocol based on CLSI EP17-A2.[29] Nine replicates each from seven low-level samples were measured using multiple reagent pack lots and one calibrator lot in ten runs on multiple Access 2 Systems. This study determined the LoD for Access AMH to be 0.0049 ng/mL (0.035 pmol/L).

Limit of Quantitation

Representative data for Limit of Quantitation is provided for illustration only. Performance obtained in individual laboratories may vary.

The Access AMH assay was designed to have a Limit of Quantitation (LoQ) of ≤ 0.08 ng/mL (0.57 pmol/L). In one study, LoQ was tested using a protocol based on CLSI EP17-A2.[29] Nine replicates of seven low-level samples were measured using multiple reagent pack lots and one calibrator lot in ten runs on multiple Access 2 Systems. This study determined the LoQ for Access AMH to be 0.010 ng/mL (0.071 pmol/L).

ADDITIONAL INFORMATION

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