ARCHITECT SYSTEM

en

Anti-HBc II

REF 8L44

84-6378/R1

B8L440

Anti-HBc II

Customer Service

For additional product information, please contact your local customer service organization.

This package insert must be read carefully prior to use. Package insert instructions must be followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Key to symbols used

REF	List Number	ASSAY CD-ROM	Assay CD-ROM
IVD	*In Vitro* Diagnostic Medical Device	SN	Serial Number
LOT	Lot Number	CONTROL NO.	Control Number
	Expiration Date	REAGENT LOT	Reagent Lot
2°C 8°C	Store at 2-8°C	REACTION VESSELS	Reaction Vessels
	Consult instructions for use	SAMPLE CUPS	Sample Cups
		SEPTUM	Septum
	Manufacturer	REPLACEMENT CAPS	Replacement Caps

See **REAGENTS** section for a full explanation of symbols used in reagent component naming.

ABBOTT
Diagnostics Division

NAME

ARCHITECT Anti-HBc II

INTENDED USE

The ARCHITECT Anti-HBc II assay is a chemiluminescent microparticle immunoassay (CMIA) for the qualitative detection of antibody to hepatitis B core antigen (anti-HBc) in human serum and plasma. The ARCHITECT Anti-HBc II assay is intended to be used as a screen for blood and plasma to prevent transmission of hepatitis B virus (HBV) to recipients of blood and blood components and as an aid in the diagnosis of HBV infection.

SUMMARY AND EXPLANATION OF TEST

The ARCHITECT Anti-HBc II assay utilizes microparticles coated with recombinant hepatitis B virus core antigen (rHBcAg) for the detection of anti-HBc. Anti-HBc determinations can be used as an indicator of current or past HBV infection. Anti-HBc is found in serum shortly after the appearance of hepatitis B surface antigen (HBsAg) in acute HBV infections. It will persist after the disappearance of HBsAg and before the appearance of detectable antibody to HBsAg (anti-HBs).[1-7] In the absence of information about any other HBV markers, it must be considered that an individual with detectable levels of anti-HBc may be actively infected with HBV or that the infection may have resolved, leaving the person immune.[8] Anti-HBc may be the only serological marker of HBV infection and potentially infectious blood.[9-15]

The presence of anti-HBc does not differentiate between acute or chronic hepatitis B infection.

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT Anti-HBc II assay is a two-step immunoassay for the qualitative determination of anti-HBc in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

In the first step, sample, assay diluent, specimen diluent, and rHBcAg coated paramagnetic microparticles are combined. Anti-HBc present in the sample binds to the rHBcAg coated microparticles and the reaction mixture is washed. In the second step, anti-human acridinium-labeled conjugate is added. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of anti-HBc in the sample and the RLUs detected by the ARCHITECT *i* System optics.

The presence or absence of anti-HBc in the sample is determined by comparing the chemiluminescent signal in the reaction to the cutoff signal determined from an active ARCHITECT Anti-HBc II calibration. If the chemiluminescent signal in the specimen is greater than or equal to the cutoff signal, then the sample is considered reactive for anti-HBc.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

REAGENTS

Reagent Kit, 100 Tests/500 Tests/4x500 Tests

NOTE: Some kit sizes are not available in all countries or for use on all ARCHITECT *i* Systems. Please contact you local distributor.

ARCHITECT Anti-HBc II Reagent Kit (8L44)

- **MICROPARTICLES** 1 or 4 Bottle(s) (6.6 mL per 100-test bottle/ 27.0 mL per 500-test bottle) hepatitis B core (*E. coli*, recombinant) antigen coated microparticles in TRIS buffer. Minimum concentration: 0.08% solids. Preservatives: ProClin 950 and sodium azide.
- **CONJUGATE** 1 or 4 Bottle(s) (11.0 mL per 100-test bottle/28.8 mL per 500-test bottle) murine acridinium-labeled anti-human conjugate in MES buffer with protein stabilizers. Minimum concentration: 0.04 µg/mL. Preservatives: sodium alkyl paraben and sodium azide.
- **ASSAY DILUENT** 1 or 4 Bottle(s) (5.36 mL per 100-test bottle/ 23.72 mL per 500-test bottle) assay diluent containing murine protein stabilizers in MOPSO buffer. Preservatives: ProClin 950 and sodium azide.
- **SPECIMEN DILUENT** 1 or 4 Bottle(s) (5.36 mL per 100-test bottle/23.72 mL per 500-test bottle) specimen diluent containing reductant in MOPSO buffer.

Other Reagents

ARCHITECT *i* Pre-Trigger Solution

- **PRE-TRIGGER SOLUTION** Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

ARCHITECT *i* Trigger Solution

- **TRIGGER SOLUTION** Trigger Solution containing 0.35 N sodium hydroxide.

ARCHITECT *i* Wash Buffer

- **WASH BUFFER** Wash Buffer containing phosphate buffered saline solution. Preservatives: antimicrobial agents.

WARNINGS AND PRECAUTIONS

- **IVD**

Safety Precautions

- This product requires the handling of human specimens. It is recommended that all human sourced materials be considered potentially infectious and handled with appropriate biosafety practices.
- Microparticles contain methylisothiazolones, which are components of ProClin. These components are classified per applicable European Community (EC) Directives as: Irritant (Xi). The following are the appropriate Risk (R) and Safety (S) phrases:

R43 May cause sensitization by skin contact.
S24 Avoid contact with skin.
S35 This material and its container must be disposed of in a safe way.
S37 Wear suitable gloves.
S46 If swallowed, seek medical advice immediately and show this container or label.

- The ARCHITECT Anti-HBc II Assay Diluent contains methylisothiazolones, which are components of ProClin, and Triton X 405. These components are classified per applicable European Community (EC) Directives as: Irritant (Xi). The following are the appropriate Risk (R) and Safety (S) phrases.

R36 Irritating to eyes.
R43 May cause sensitization by skin contact.
S24 Avoid contact with skin.
S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S35 This material and its container must be disposed of in a safe way.
S37 Wear suitable gloves.
S46 If swallowed, seek medical advice immediately and show this container or label.

- Some components contain sodium azide. For a specific listing, refer to the **REAGENTS** section of this package insert. Contact with acids liberates very toxic gas. This material and its container must be disposed of in a safe way.
- For product not classified as dangerous per European Directive 1999/45/EC as amended - Safety data sheet available for professional user on request.
- For information on the safe disposal of sodium azide and a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

Handling Precautions

- Do not use reagent kits beyond the expiration date.
- **Do not pool reagents within a kit or between reagent kits.**
- Before loading the ARCHITECT Anti-HBc II Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.

- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
- To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.
  - When handling conjugate vials, change gloves that have contacted human serum or plasma, since introduction of human IgG or IgM will result in a neutralized conjugate.
  - Once a septum has been placed on the reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts, which have no effect on assay efficacy.
- For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

Storage Instructions

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The ARCHITECT Anti-HBc II Reagent Kit must be stored at 2-8°C in an upright position and may be used immediately after removal from 2-8°C storage.
- When stored and handled as directed, reagents are stable until the expiration date.
- The ARCHITECT Anti-HBc II Reagent Kit may be stored on board the ARCHITECT *i* System for a maximum of 30 days. After 30 days, the reagent kit must be discarded. For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5.
- Reagents may be stored on or off the ARCHITECT *i* System. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** For information on unloading reagents, refer to the ARCHITECT System Operations Manual, Section 5.

Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

INSTRUMENT PROCEDURE

- The ARCHITECT Anti-HBc II assay file must be installed on the ARCHITECT *i* System from the ARCHITECT *i* Assay CD-ROM before performing the assay. For detailed information on assay file installation and on viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.
- For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.
- For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

The specimen collection tubes listed below were verified to be used with the ARCHITECT Anti-HBc II assay. Other specimen collection tubes have not been tested with this assay.

- Human serum (including serum collected in serum separator tubes)
- Human plasma collected in:
  - Sodium heparin
  - Lithium heparin (PST)
  - Dipotassium-EDTA
  - Sodium citrate
  - Potassium oxalate
  - CPD
  - CPDA-1
  - ACD
- ACD tubes may show a positive bias up to 20 % relative to serum.
- Liquid anticoagulants may have a dilution effect resulting in lower concentrations for individual patient specimens.
- The ARCHITECT *i* System does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the ARCHITECT Anti-HBc II assay.

Specimen Conditions

- Do not use specimens with the following conditions:
  - heat-inactivated
  - pooled
  - grossly hemolyzed (> 500 mg/dL)
  - obvious microbial contamination
  - cadaver specimens or any other body fluids
- 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.
- Use caution when handling patient specimens to prevent cross contamination. Use of disposable pipettes or pipette tips is recommended.
- For optimal results, inspect all specimens for bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.
- Patient specimens should be tested within 3 hours of being placed on board the ARCHITECT *i* System.
- No interference was observed between experimental controls and nonreactive or reactive specimens tested with elevated levels of bilirubin (20 mg/dL), triglycerides (3000 mg/dL), protein (4.5 - 12 g/dL), red blood cells (0.4% v/v), or hemoglobin (500 mg/dL).

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for serum and plasma collection tubes. Gravity separation is not sufficient for specimen preparation.
- Mix thawed specimens thoroughly by low speed vortexing or by inverting 10 times. Visually inspect the specimens. If layering or stratification is observed, continue mixing until specimens are visibly homogeneous.
- To ensure consistency in results, specimens must be transferred to a centrifuge tube and centrifuged at ≥ 10000 RCF (Relative Centrifugal Force) for 10 minutes before testing if
  - they contain fibrin, red blood cells, or other particulate matter, or
  - they were frozen and thawed.

  Transfer clarified specimen to a sample cup or secondary tube for testing.

- Centrifuged specimens with a lipid layer on the top must be transferred to a sample cup or secondary tube. Care must be taken to transfer only the clarified specimen without the lipemic material.

Storage

- Specimens may be stored on or off the clot, red blood cells, or separator gel for up to 3 days at 15-30°C or 14 days refrigerated at 2-8°C.
- If specimens are stored at 15-30°C and testing will be delayed more than 3 days, remove serum or plasma from the clot, red blood cells, or separator gel and store frozen at -20°C or colder.
- If specimens are stored at 2-8°C and testing will be delayed more than 14 days, remove serum or plasma from the clot, red blood cells, or separator gel and store frozen at -20°C or colder.
- No qualitative performance differences were observed between experimental controls and nonreactive or spiked reactive specimens subjected to 6 freeze/thaw cycles; however, multiple freeze/thaw cycles should be avoided.

Shipping

- Before shipping specimens, it is recommended that specimens be removed from the clot, red blood cells, or separator gel.
- When shipping specimens, package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Specimens may be shipped on wet ice or dry ice. Do not exceed the storage time limitations listed above.

PROCEDURE

Materials Provided

- 8L44 ARCHITECT Anti-HBc II Reagent Kit

Materials Required but not Provided

- ARCHITECT *i* System
- ARCHITECT *i* **ASSAY CD-ROM**
- 8L44-01 ARCHITECT Anti-HBc II Calibrator
- 8L44-10 ARCHITECT Anti-HBc II Controls
- ARCHITECT *i* **PRE-TRIGGER SOLUTION**
- ARCHITECT *i* **TRIGGER SOLUTION**
- ARCHITECT *i* **WASH BUFFER**
- ARCHITECT *i* **REACTION VESSELS**
- ARCHITECT *i* **SAMPLE CUPS**
- ARCHITECT *i* **SEPTUM**
- ARCHITECT *i* **REPLACEMENT CAPS**
- Pipettes or pipette tips (optional)

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

Assay Procedure

- Before loading the ARCHITECT Anti-HBc II Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles remain adhered to the bottle, continue inverting the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions on placing septums on bottles refer to the **Handling Precautions** section of this package insert.
- Load the ARCHITECT Anti-HBc II Reagent Kit on the ARCHITECT *i* System.
  - Verify that all necessary assay reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order calibration, if necessary.
  - For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.
- Order tests.
  - For information on ordering patient specimens and controls and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- The minimum sample cup volume is calculated by the system and is printed on the Orderlist report. No more than 10 replicates may be sampled from the same sample cup. To minimize the effects of evaporation, verify adequate sample cup volume is present before running the test.
  - Priority: 75 µL for the first ARCHITECT Anti-HBc II test plus 25 µL for each additional ARCHITECT Anti-HBc II test from the same sample cup.
  - ≤ 3 hours on board: 150 µL for the first ARCHITECT Anti-HBc II test plus 25 µL for each additional ARCHITECT Anti-HBc II test from the same sample cup.
  - > 3 hours on board: replace with a fresh sample (patient specimens, controls, and calibrator).
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- Prepare calibrator and controls.
  - Mix ARCHITECT Anti-HBc II Calibrator and Controls by gentle inversion before use.
  - To obtain the recommended volume requirements for the ARCHITECT Anti-HBc II Calibrator and Controls, hold the bottles **vertically** and dispense 5 drops of the calibrator or 4 drops of each control into each respective sample cup.
- Load samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
- For additional information on principles of operation, refer to the ARCHITECT Operations Manual, Section 3.
- For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. When a laboratory requires more frequent maintenance, follow those procedures.

Specimen Dilution Procedures

- Specimens cannot be diluted for the ARCHITECT Anti-HBc II assay.

Calibration

- To perform an ARCHITECT Anti-HBc II calibration, test calibrator in replicates of three. A single sample of each Anti-HBc II control level must be tested to evaluate the assay calibration. Ensure that assay control values are within the concentration ranges specified in the control package insert. Calibrators should be priority loaded.
- Once an ARCHITECT Anti-HBc II 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.
  - Controls are out of range.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

QUALITY CONTROL PROCEDURES

The recommended control requirement for the ARCHITECT Anti-HBc II assay is that a single sample of each control be tested once every 24 hours each day of use. If laboratory quality control procedures require more frequent use of controls to verify test results, follow those procedures.

The ARCHITECT Anti-HBc II control values must be within the acceptable ranges specified in the control package insert. If a control is out of its specified range, the associated test results are invalid and samples must be retested. Recalibration may be indicated.

Verification of Assay Claims

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B. The ARCHITECT Anti-HBc II assay belongs to method group 5, except functional sensitivity.

RESULTS

Calculation

- The ARCHITECT *i* System calculates the cutoff RLU from the mean RLU of three replicates of Calibrator 1 and stores the result. The cutoff RLU is determined by multiplying the Anti-HBc II Calibrator 1 mean RLU by 1.0.

  Cutoff RLU = Calibrator 1 Mean RLU x 1.0

- The ARCHITECT *i* System calculates the S/CO result for each specimen and control as follows.

  S/CO = Sample RLU/Cutoff RLU

Interpretation of Results

Initial ARCHITECT Anti-HBc II Results

Initial Result (S/CO)	Instrument Flag	Interpretation	Retest Procedure
< 1.00	NONREACTIVE	Nonreactive	No retest required
≥ 1.00	REACTIVE	Reactive	Retest in duplicate

Final ARCHITECT Anti-HBc II Interpretation

Initial Interpretation	Results with Retest	Final Interpretation
Nonreactive	No retest required	**Nonreactive**
Reactive	If two of the three results are < 1.00 S/CO	**Nonreactive**
Reactive	If two of the three results are ≥ 1.00 S/CO	**Reactive**

NOTE: For details on configuring the ARCHITECT *i* System to use grayzone interpretations, refer to the ARCHITECT System Operations Manual, Section 2. The grayzone interpretation from the ARCHITECT interpretations screen is not used by the ARCHITECT *i* System unless a grayzone is configured.

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 ARCHITECT System Operations Manual, Section 5.

LIMITATIONS OF THE PROCEDURE

- If the anti-HBc results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.
- For diagnostic purposes, results should be used in conjunction with other data; e.g., symptoms, results of other tests, clinical impressions, etc.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[16] 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.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA).[17,18] Specimens containing HAMA may produce anomalous values when tested with assay kits that employ mouse monoclonal antibodies.[17]

SPECIFIC PERFORMANCE CHARACTERISTICS

Precision

The ARCHITECT Anti-HBc II assay is designed to have an imprecision of ≤10% total** CV for specimens at 1.20 S/CO and for the Positive Control. The study was performed at one internal and two external evaluation sites each using one instrument. A panel consisting of three different control lots and two human plasma specimens was tested in replicates of four across three reagent lots and three calibrator lots per site. Each combination of instruments, panel members, and reagent lots was tested in four runs. Data from this study are summarized in Table 1*.

Table 1
ARCHITECT Anti-HBc II Precision

			Within Run		Total**	
Panel Member	N	Mean S/CO	SD	%CV	SD	%CV
Negative Control	432	0.22	0.01	6.52	0.02	7.57
Positive Control	431	2.97	0.08	2.63	0.09	2.87
Human Plasma Panel 1	144	0.81	0.02	2.73	0.03	3.24
Human Plasma Panel 2	144	1.18	0.03	2.52	0.03	2.87

* Representative data; results in individual laboratories may vary from these data.

** Total is an accumulation of within run, between run and between day.

Specificity

The ARCHITECT Anti-HBc II assay is designed to have an overall specificity of ≥ 99.5% on a blood donor population and ≥ 98.0% on a hospitalized/diagnostic population. A study was performed at one internal and two external evaluation sites. A total of 5141 serum and plasma specimens collected from five blood-donation centers and 260 hospitalized/diagnostic specimens were evaluated to assess specificity.

From the blood donor population a total of 26 specimens were classified as reactive. Two additional specimens were excluded from specificity calculation as final specimen disposition could not be determined. From the hospitalized/diagnostic specimens a total of 28 specimens were classified as reactive. One additional specimen was excluded from specificity calculation as final specimen disposition could not be determined. Data from this study are summarized in Table 2*.

Table 2
ARCHITECT Anti-HBc II Specificity

		ARCHITECT Anti-HBc II			
Category	N	IR [%]	RR [%]	Clinical Specificity	95% Confidence Interval
Overall Blood Donors	5141	44 [0.86]	41 [0.80]	99.71% (5098/5113)	99.52 - 99.84%
Blood Donor Serum	3584	25 [0.70]	22 [0.61]	99.75% (3561/3570)	99.52 - 99.88%
Blood Donor Plasma	1557	19 [1.22]	19 [1.22]	99.61% (1537/1543)	99.16 - 99.86%
Hospitalized/ Diagnostic Specimens	260	28 [10.77]	28 [10.77]	100% (231/231)	98.42 - 100%

* Representative data; results in individual laboratories may vary from these data.

Sensitivity

A total of 406 anti-HBc positive specimens from patients with acute, chronic and recovered HBV infection and signs and symptoms of HBV infection were tested, resulting in a sensitivity of 100% (406/406), 95% confidence interval: 99.10% - 100%. (Representative data; results in individual laboratories may vary from these data).

Analytical Sensitivity

The ARCHITECT Anti-HBc II assay is designed to show an analytical sensitivity of less than 1.0 PEI U/mL. The sensitivity of the ARCHITECT Anti-HBc II assay was evaluated with a four-member panel that was standardized against reference serum from the Paul-Ehrlich-Institute (PEI). The panel was tested with three reagent lots. The ARCHITECT Anti-HBc II assay sensitivity ranged from 0.4 to 0.5 PEI U/mL. (Representative data; results in individual laboratories may vary from these data).

Interference

Additional studies were performed to evaluate other potential interfering disease states on the ARCHITECT Anti-HBc II assay. A total of 104 specimens were tested from the following categories: antinuclear antibodies (ANA), Epstein-Barr virus (anti-EBV positive), hepatitis A virus (anti-HAV IgM positive), hepatitis C virus (anti-HCV positive), human immunodeficiency virus (anti-HIV-1 positive), human anti-mouse antibodies (HAMA) positive, influenza vaccine recipients, non-viral liver disease, rheumatoid factor positive, syphilis, systemic lupus erythematosus (SLE), toxoplasmosis IgG positive, varicella zoster (anti-VZV positive), anti-*E. coli* positive and yeast infection. With these specimens, ARCHITECT Anti-HBc II showed the same qualitative results as the comparator method.

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