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Online: **cap.org (preferred method)**
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Survey of Immunohistochemistry (IHC) Validation Practices and Procedures

The College of American Pathologists (CAP) Pathology Laboratory Quality Center: Cooperative Agreement with Centers for Disease Control and Prevention (CDC)
Post Survey from CAP Proficiency Testing Mailing HER2B-2010 and "Principles of Analytic Validation of Immunohistochemical Assays" Evidence-Based Guideline 2014

Introduction

The CAP is collaborating with the CDC on a cooperative agreement, "Improving the Impact of Laboratory Practice Guidelines: A New Paradigm for Metrics." We invite your laboratory to assist our goal of examining the current state of IHC validation practices and procedures by completing this important follow-up survey to the original one sent in the 2010 HER2-B mailing. Your participation is completely voluntary and we appreciate your time which is estimated to take 20 minutes for completion. We recommend that you have your current laboratory procedures available. Your responses will remain anonymous. All information collected in this survey will be kept in a secure manner. No individual answers will be shared with the CDC. Your CAP number will connect your survey answers to demographic data on file and will ensure that only one response per laboratory is received. The CAP and the CDC will publish the post-survey overall results as part of the cooperative agreement. If you have any questions, please email center@cap.org.
Validation of nonwaived test systems is mandated by Clinical Laboratory Improvement Amendments of 1988 (CLIA 88). Since the introduction of immunohistochemistry, this test has been used as an adjunct to morphologic diagnosis and has not been subject to rigorous quality control and quality assurance measures.
Recently, with the introduction of prognostic and therapeutic Food and Drug Administration (FDA)-approved IHC tests (eg, HER2) and the 2013 publication, "Principles of Analytic Validation of IHC Assays,"[1] the field is being provided with more precise and consistent test procedures in validation.

Please note that this survey does not apply to HER2 or the ER and PgR assays as separate guidelines for those markers have already been established. A list of terms and definitions are included below:

TERM	DEFINITION
Analytic Validity	A test's ability to accurately measure the analyte of interest.
Clinical Validity	A test's ability to detect or predict a disorder, a prognostic risk, or likelihood of treatment response.
Predictive Marker	A stand-alone test that provides information on likely response to a given therapy and may directly determine therapy (eg, CD20, CD117).
Non-Predictive Marker	A test usually done as part of a panel and interpreted only in the context of other morphologic and clinical data.
Laboratory developed test (LDT)	A test developed within a clinical laboratory that is performed by the laboratory in which the test was developed and is neither FDA-cleared nor approved.
Laboratory modified test (LMT)	An FDA-cleared or approved test that is modified by a clinical laboratory. Modified means any change to the assay that could affect its performance specifications for sensitivity, specificity, accuracy, or precision, etc. Such modifications include but are not limited to: • Changes in specimen handling; • Changes in incubation times or temperatures; • Changes in specimen or reagent dilution; • Change in antibody; • Change or elimination of a procedural step; • Change in antigen detection system; • Change in scoring for semi-quantitative assays.
Validation	A defined process by which a laboratory confirms that a laboratory-developed or modified test performs as intended or claimed.
Verification	The process by which a laboratory determines that a FDA-cleared or approved assay performs according to the recommendations set forth by the manufacturer.

[1] Fitzgibbons PL, Bradley LA, Fatheree LA, et al. Principles of analytic validation of immunohistochemical assays: Guideline from the College of American Pathologists Pathology and Laboratory Quality Center. Arch Pathol Lab Med. 2014;138(11):1432-1443.

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Section I: IHC Validation Procedures

The following questions pertain to all IHC assays other than HER2, ER and PgR.

1. Does your laboratory perform IHC staining?

010
- ◯ 129 Yes
- ◯ 130 No, we only do interpretation (STOP HERE. Thank you for your response.)

2. Does your laboratory have separate written procedures for validation of IHC predictive and non-predictive markers?

020
- ◯ 129 Yes
- ◯ 130 No
- ◯ 503 Unsure

3. Does your laboratory have a written procedure that outlines the steps needed for analytic validation of new IHC assays?

030
- ◯ 657 Yes, for predictive markers only (other than HER2, ER, and PgR)
- ◯ 658 Yes, for non-predictive markers only
- ◯ 659 Yes, for both predictive and non-predictive markers
- ◯ 130 No (Skip to question 10.)
- ◯ 503 Unsure (Skip to question 10.)

4. Does the written procedure include specification for verifying unmodified FDA-approved assays?

040
- ◯ 129 Yes
- ◯ 130 No
- ◯ 259 Not applicable; we don't have FDA-approved or cleared IHC assays
- ◯ 503 Unsure

5. Does the written procedure include specification for validation of LDT or LMT assays?

050
- ◯ 660 Yes, for predictive LDTs or LMTs only (other than HER2, ER and PgR)
- ◯ 661 Yes, for non-predictive LDTs or LMTs only
- ◯ 662 Yes, for both predictive and non-predictive LDTs or LMTs
- ◯ 130 No
- ◯ 259 Not applicable; we do not create LDTs or LMTs
- ◯ 503 Unsure

6. Does the written procedure include any specifications for validating IHC tests performed on cytologic specimens (eg, alcohol fixed cell blocks, smears, cytospins)?

060
- ◯ 657 Yes, for predictive markers only
- ◯ 658 Yes, for non-predictive markers only
- ◯ 659 Yes, for both predictive and non-predictive markers
- ◯ 130 No
- ◯ 259 Not applicable; we do not perform IHC tests on cytology specimens
- ◯ 503 Unsure

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Section I: IHC Validation Procedures, cont'd

7. Does the written procedure include any specifications for validating IHC tests performed on decalcified specimens?

010 ◯ 657 Yes, for predictive markers only
◯ 658 Yes, for non-predictive markers only
◯ 659 Yes, for both predictive and non-predictive markers
◯ 130 No
◯ 259 Not applicable; we do not perform IHC tests on decalcifed specimens
◯ 503 Unsure

Section II: Documentation Procedures

8. Please answer the following in regards to validation of new IHC antibody assays in your laboratory.
If your laboratory does not have separate procedures, please complete Table A only.

Table A

When validating a new non-FDA approved, <u>non-predictive</u> IHC assay (eg, cytokeratin, S100, CD45), does your laboratory… <u>OR</u> complete if there is only one procedure in your laboratory for both non-predictive and predictive IHC assays.			
	Yes	**No**	**Unsure/Not applicable**
Test a specified minimum number of cases?	020 ◯ 129 **Total number:** 030 [ ][ ] .	◯ 130	◯ 663
Include specified numbers of positive and negative cases in the validation set?	040 ◯ 129 **Positive number:** 050 [ ][ ] . **Negative number:** 060 [ ][ ] .	◯ 130	◯ 663
Require minimum positive and negative concordance rates?	070 ◯ 129 **Positive rate:** 080 [ ][ ][ ] . **%** **Negative rate:** 090 [ ][ ][ ] . **%**	◯ 130	◯ 663
Require a minimum overall concordance rate?	100 ◯ 129 **Overall rate:** 110 [ ][ ][ ] . **%**	◯ 130	◯ 663

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Section II: Documentation Procedures, cont'd

8. Continued from previous page.

Table B

When validating a new non-FDA approved <u>predictive marker</u> IHC assay other than HER2, ER/PgR (eg, CD20), does your laboratory…			
	Yes	**No**	**Unsure/Not applicable**
Test a specified minimum number of cases?	010 ◯ 129 **Total number:** 020 ☐☐.	◯ 130	◯ 663
Include specified numbers of positive and negative cases in the validation set?	030 ◯ 129 **Positive number:** 040 ☐☐. **Negative number:** 050 ☐☐.	◯ 130	◯ 663
Require minimum positive and negative concordance rates?	060 ◯ 129 **Positive rate:** 070 ☐☐☐. **%** **Negative rate:** 080 ☐☐☐. **%**	◯ 130	◯ 663
Require a minimum overall concordance rate?	090 ◯ 129 **Overall rate:** 100 ☐☐☐. **%**	◯ 130	◯ 663

9. Does your laboratory document validations and verifications of IHC assays?

110 ◯ 664 Yes, always
◯ 665 Yes, sometimes
◯ 130 No
◯ 503 Unsure

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Section III: Re-Validation Procedures

10. For an existing validated IHC assay, does your laboratory have a written procedure that specifies when to reassess an assay when there are changes in the conditions of testing to ensure it performs as expected?

010 ◯ 657 Yes, for predictive markers only (other than HER2, ER and PgR)
◯ 658 Yes, for non-predictive markers only
◯ 659 Yes, for both predictive and non-predictive markers
◯ 130 No (Skip to question 12.)
◯ 503 Unsure (Skip to question 12.)

11. Please answer the following in regards to re-validation of existing IHC antibody assays in your laboratory. If your laboratory does not have separate procedures, please complete Table A only.

Table A

Are the following changes explicitly specified when re-validating non-FDA approved, non-predictive IHC assays (eg, cytokeratin, S100, CD45)? OR complete if there is only one procedure in your laboratory for non-predictive and predictive assays.

	Yes*	No	Unsure	*If yes, please provide case information. No.** of cases specified	No.** of cases variable and set by Laboratory Director	No.** of cases not specified
Introduction of a new lot of antibody	020 ◯ 129	◯ 130	◯ 503	030 ____ .	040 ◯ 666	◯ 667
Change in antibody dilution	050 ◯ 129	◯ 130	◯ 503	060 ____ .	070 ◯ 666	◯ 667
Change in antibody vendor (same clone)	080 ◯ 129	◯ 130	◯ 503	090 ____ .	100 ◯ 666	◯ 667
Change in antibody clone	110 ◯ 129	◯ 130	◯ 503	120 ____ .	130 ◯ 666	◯ 667
Introduction or change in antigen retrieval method	140 ◯ 129	◯ 130	◯ 503	150 ____ .	160 ◯ 666	◯ 667
Change in incubation or retrieval times (same method)	170 ◯ 129	◯ 130	◯ 503	180 ____ .	190 ◯ 666	◯ 667
Change in antigen detection system	200 ◯ 129	◯ 130	◯ 503	210 ____ .	220 ◯ 666	◯ 667
Change in fixative type	230 ◯ 129	◯ 130	◯ 503	240 ____ .	250 ◯ 666	◯ 667
Change in tissue processing equipment	260 ◯ 129	◯ 130	◯ 503	270 ____ .	280 ◯ 666	◯ 667
Change in testing equipment	290 ◯ 129	◯ 130	◯ 503	300 ____ .	310 ◯ 666	◯ 667
Change in environmental conditions (eg, laboratory relocation)	320 ◯ 129	◯ 130	◯ 503	330 ____ .	340 ◯ 666	◯ 667
Change in water supply	350 ◯ 129	◯ 130	◯ 503	360 ____ .	370 ◯ 666	◯ 667

**No. of cases refers to typical minimum number cases required to test in validation set.

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Results must be received at the CAP no later than midnight, Central Time by the due date below:

Section III: Re-Validation Procedures, cont'd

11. Continued from previous page.

Table B

Are the following changes explicitly specified when re-validating non-FDA approved predictive marker IHC assays other than HER2, ER/PgR (eg, CD20)?

	Yes*	No	Unsure	*If yes, please provide case information. No.** of cases specified	No.** of cases variable and set by Laboratory Director	No.** of cases not specified
Introduction of a new lot of antibody	010 ◯ 129	◯ 130	◯ 503	020 .	030 ◯ 666	◯ 667
Change in antibody dilution	040 ◯ 129	◯ 130	◯ 503	050 .	060 ◯ 666	◯ 667
Change in antibody vendor (same clone)	070 ◯ 129	◯ 130	◯ 503	080 .	090 ◯ 666	◯ 667
Change in antibody clone	100 ◯ 129	◯ 130	◯ 503	110 .	120 ◯ 666	◯ 667
Introduction or change in antigen retrieval method	130 ◯ 129	◯ 130	◯ 503	140 .	150 ◯ 666	◯ 667
Change in incubation or retrieval times (same method)	160 ◯ 129	◯ 130	◯ 503	170 .	180 ◯ 666	◯ 667
Change in antigen detection system	190 ◯ 129	◯ 130	◯ 503	200 .	210 ◯ 666	◯ 667
Change in fixative type	220 ◯ 129	◯ 130	◯ 503	230 .	240 ◯ 666	◯ 667
Change in tissue processing equipment	250 ◯ 129	◯ 130	◯ 503	260 .	270 ◯ 666	◯ 667
Change in testing equipment	280 ◯ 129	◯ 130	◯ 503	290 .	300 ◯ 666	◯ 667
Change in environmental conditions (eg, laboratory relocation)	310 ◯ 129	◯ 130	◯ 503	320 .	330 ◯ 666	◯ 667
Change in water supply	340 ◯ 129	◯ 130	◯ 503	350 .	360 ◯ 666	◯ 667

**No. of cases refers to typical minimum number cases required to test in validation set.

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Section IV: General IHC Laboratory Data

Please answer the following questions with respect to ALL IHC assays currently in use.

12. What is the total number of antibodies in use in your IHC laboratory?

010 [ ][ ][ ] .

13. What was the total number of new antibodies introduced into your laboratory during 2014?

020 [ ][ ][ ] .

14. What was the total number of surgical pathology accessions in your laboratory during 2014?

030 [ ][ ][ ][ ][ ][ ] .

15. Please provide the following information on the *most* recent IHC assay that your laboratory newly placed into clinical service.

Year introduced	040 [ ][ ][ ][ ] .	050 ◯ 503 Unsure
Name of antibody	060 _____	070 ◯ 503 Unsure
Was a validation study performed for this antibody assay?	080 ◯ 129 Yes ◯ 130 No	◯ 503 Unsure
*If yes, please provide the following information.		
Total number of cases included in the validation set	090 [ ][ ] .	100 ◯ 503 Unsure
Number of known positives cases tested	110 [ ][ ] .	120 ◯ 503 Unsure
Positive concordance rate	130 [ ][ ][ ] .	140 ◯ 503 Unsure
Number of known negative cases tested	150 [ ][ ] .	160 ◯ 503 Unsure
Negative concordance rate	170 [ ][ ][ ] .	180 ◯ 503 Unsure
Overall concordance rate	190 [ ][ ][ ] .	200 ◯ 503 Unsure

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Section IV: General IHC Laboratory Data, cont'd

16. For your *most* recent IHC antibody assay, what primary method of validation did your laboratory use?

010
- ◯ 668 Correlated the new test's results with the morphology and expected results
- ◯ 669 Compared the new test's results with the results of prior testing of the same tissues with a validated assay in the same laboratory
- ◯ 670 Compared the new test's results with the results of testing the same tissue validation set in another laboratory using a validated assay
- ◯ 671 Compared the new test's results with previously validated non-immunohistochemical tests
- ◯ 672 Tested previously graded tissue challenges from a formal proficiency testing program (if available) and compared the results with the graded responses

020
- ◯ 010 Other, specify: _____
- ◯ 503 Unsure

Section V: Awareness and Adoption

17. Prior to this survey, were you aware and/or familiar with the CAP "Principles of Analytic Validation of IHC Assays"[1] guideline published in 2014?

030
- ◯ 129 Yes
- ◯ 673 No, however plan to review the guideline within next 6 months (Skip to question 21.)
- ◯ 674 No, and do not plan to review the guideline (Skip to question 21.)

18. What is your current status with adopting the CAP "Principles of Analytic Validation of IHC Assays"[1] guideline recommendations that apply to your laboratory practice?

040
- ◯ 675 Currently adopted all recommendations
- ◯ 676 Adopted some, but not all, recommendations
- ◯ 677 Plan to adopt all or some within the next 6 months
- ◯ 678 Plan to adopt all or some within the next 7-12 months
- ◯ 679 Do not plan to adopt unless they become requirement from accreditation agency

19. How do you currently use (or plan to use) the CAP "Principles of Analytic Validation of IHC Assays"[1] guideline recommendations? (Fill all that apply.)

050
- ◯ 680 Prospectively for newly acquired antibodies for predictive markers
- ◯ 681 Prospectively for newly acquired antibodies for non-predictive markers
- ◯ 682 Prospectively for revalidation situations
- ◯ 683 Retrospectively to revalidate antibodies currently in use
- ◯ 684 Do not plan to use

[1] Fitzgibbons PL, Bradley LA, Fatheree LA, et al. Principles of analytic validation of immunohistochemical assays: Guideline from the College of American Pathologists Pathology and Laboratory Quality Center. Arch Pathol Lab Med. 2014;138(11):1432-1443.

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Section V: Awareness and Adoption, cont'd

20. Please indicate the *most difficult* aspect(s) about adopting the guideline recommendations into your validation process. (Choose up to three responses.)

010
- ◯ 685 Number of cases recommended for predictive assays
- ◯ 686 Number of cases recommended for non-predictive assays
- ◯ 687 Number of cases available for routine antigens
- ◯ 688 Number of cases available for rare antigens
- ◯ 689 Achieving 90% concordance
- ◯ 690 Incorporating high-low expressors
- ◯ 691 Assessing cytology specimens
- ◯ 692 Assessing decalcified specimens
- ◯ 693 Changes in testing conditions (revalidation requirements); specify: 100 _____
- ◯ 694 Documentation
- ◯ 695 Sufficient time/staff to run validations
- ◯ 696 Additional cost/expense
- ◯ 010 Other, specify: 150 _____
- ◯ 650 Not applicable; do not plan to use

Section VI: Additional Information

21. What is your primary role/job title?

170
- ◯ 697 IHC Laboratory Director – MD/DO
- ◯ 698 IHC Laboratory Director – PhD
- ◯ 699 IHC Laboratory Director – Other medical credential(s), specify: 180 _____
- ◯ 700 Department Chair/Laboratory Medical Director
- ◯ 701 Staff pathologist
- ◯ 702 IHC section/Histotechnology Supervisor/Manager
- ◯ 703 Quality Assurance Manager
- ◯ 704 Other role/title, specify: 190 _____

22. Please provide any other additional information or comments on IHC validation practices in your laboratory.

200
_____

_____

_____

Thank you for responding to this 2015 IHC Validation Practices and Procedures Survey. Your laboratory may be invited to participate in a focus group.