Presenter: Emily Meserve, MD, MPH

- Practicing pathologist with Spectrum Healthcare Partners Maine, US
- US board certified in both anatomic and clinical pathology
- Technical Consultant, NorDx Laboratories
- Involvement with the College of American Pathologists (CAP)
  - Member of CAP Immunohistochemistry Committee
Agenda

• Your toolbox: Quality Plan
• Your tools:
  ○ Defined monitoring/reporting of non-conforming events
  ○ Defined risk assessment method/tool
  ○ Defined standard approach to non-conforming event investigation
  ○ Templates and checklists based on standard approach to non-conforming event investigation
  ○ Tools to use during an event investigation
• Practical Example
• Summary
Objectives

• Describe the elements of an IHC laboratory quality plan
• Understand the value of a standard approach to IHC assay improvement
• Review components of a thorough assessment of an underperforming assay, how to select corrective actions, and effectiveness checking
• Examine case-based studies of process improvement of selected IHC markers, especially including HER2
Quality in Health Care & the Laboratory

Source: https://www.whatissixsigma.net/jurans-quality-trilogy/
Quality Planning in Anatomic Pathology

• Written plan required of AP laboratories by most inspection agencies
  – CAP, WHO, CDC

• No single best way to prepare a quality plan (CLSI QMS)

• GOAL: detect problems and identify improvement opportunities across the laboratory

• Consider the accreditors and requirements of each lab subsection
  – Comprehensive plan with appendix
  – Aggregate of many complete plans by subsection
Quality Planning in Anatomic Pathology

References:
Qihui “Jim” Zhai, MD, FCAP; Gene P. Siegal, MD, PhD, FCAP; editors. Quality Management in Anatomic Pathology - Strategies for Assessment, Improvement, and Assurance. Northfield, IL; 2017. CAP PUB125.
Quality Plan for the IHC Lab

• 12 QSE:
  - Documents and records management
  - Organization and Leadership
  - Personnel management
  - Equipment management
  - Supplier and inventory management
  - Facilities and safety management
  - Information management
  - Non-conforming event management
  - Assessments
  - Continual improvements
  - Process management
  - Customer focus
Quality Plan for the IHC Lab

• 12 QSE:
  - Documents and records management
  - Organization and Leadership
  - Personnel management
  - Equipment management
  - Supplier and inventory management
  - Facilities and safety management
  - Information management
  - Non-conforming event management
  - Assessments
  - Continual improvements
  - Process management
  - Customer focus
Quality Planning for the IHC Lab: Non-conforming event management

- Processes to:
  - Detect
  - Document
  - Classify (risk assessment)
  - Correct
Quality Planning for the IHC Lab: Non-conforming event management

• Processes to:
  − Detect
  − Document
  − Classify (risk assessment)
  − Correct
Quality Planning for the IHC Lab: Non-conforming event management

• **Processes to:**
  - Detect
  - Document
  - Classify (risk assessment)
  - Correct

![3x3 Risk Matrix](https://www.smartsheet.com/all-risk-assessment-matrix-templates-you-need)

References:
Quality Planning for the IHC Lab: Non-conforming event management

• **Processes to:**
  - Detect
  - Document
  - Classify (risk assessment)
  - **Correct** (see *Continual Improvements*)
Quality Planning for the IHC Lab: Assessments

- External assessments and inspections
- Internal assessments and audits
  - Monitoring quality indicators

Quality Planning for the IHC Lab: Continual improvements

• Use a defined **strategy** for continual improvement - ensures consistency and increases likelihood improvements are sustained
  – Ways to identify opportunities
  – How you will choose, prioritize opportunities, if many
  – **How you will generate solutions**
  – How you will implement solutions
  – How you will evaluate the effectiveness of solutions
  – How you will sustain the improvement
Quality Planning for the IHC Lab: Continual improvements

• Ways to identify opportunities:
  – Assigned/determined by organization
  – Customer satisfaction/suggestion
  – Non-conforming events
  – Assessments
Quality Planning for the IHC Lab: Continual improvements

• How you will generate solutions
  – Set a risk assessment threshold that will trigger investigation (eg, RCA) with deadline for implementing corrective action
  – If investigation is warranted, have a defined process for conducting the investigation (ensures consistency and increased likelihood of success)
  – Learn about or have staff with knowledge necessary to implement quality tools to assist in data collection and decision-making
Quality Planning Summary

• A quality plan is the container within which to document and store tools available for Quality work.
  – Predictive  – Prognostic  – Diagnostic

• Have defined processes for
  – Non-conforming event management
  – Assessments
  – Continual improvements

• IHC lab quality planning should revolve around predictive markers.
  – ER, breast HER2
Defined Strategy: Non-conforming Event Management & Continual Improvements
Detection of Non-Conforming Events

IHC Dashboard (reviewed bi-monthly)
- Assay utilization
- Laboratory QC events
- Pathologist concerns

CAP Proficiency Testing
- Participant summary report (PSR)

Quality Monitoring
- ER
- PR
- Breast HER2
- Non-breast HER2
Risk Classification

• Any issue identified in PT/EQA of a predictive marker prompts at least a basic investigation
Quality Planning for the IHC Lab: Non-conforming event management

<table>
<thead>
<tr>
<th>Level</th>
<th>RL Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Unsafe Condition (Non Event)</td>
</tr>
<tr>
<td>B1</td>
<td>Near Miss - No Harm - Didn’t Reach Person - Caught by Chance</td>
</tr>
<tr>
<td>B2</td>
<td>Near Miss - No Harm - Didn’t Reach Person b/c of Active recovery by Caregivers</td>
</tr>
<tr>
<td>C</td>
<td>No Harm - Reached Person - No Monitoring Required</td>
</tr>
<tr>
<td>D</td>
<td>No Harm - Reached Person - Monitoring Required</td>
</tr>
<tr>
<td>E</td>
<td>Harm - Temporary - Intervention Needed</td>
</tr>
<tr>
<td>F</td>
<td>Harm - Temporary - Hospitalization Needed</td>
</tr>
<tr>
<td>G</td>
<td>Harm - Permanent</td>
</tr>
<tr>
<td>H</td>
<td>Harm - Permanent - Intervention Required to Sustain Life</td>
</tr>
<tr>
<td>I</td>
<td>Death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>RL Risk</th>
<th>I</th>
<th>H</th>
<th>G</th>
<th>F</th>
<th>E</th>
<th>D</th>
<th>C</th>
<th>B</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Weekly</td>
<td></td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td>18</td>
<td>21</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Once/Year</td>
<td></td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
<td>28</td>
<td>32</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority</th>
<th>Score</th>
<th>CAPA TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>1 to 8</td>
<td>10 Days</td>
</tr>
<tr>
<td>Active</td>
<td>9 to 15</td>
<td>30 Days</td>
</tr>
<tr>
<td>Tracked</td>
<td>16 to 24</td>
<td>30 Days</td>
</tr>
<tr>
<td>Noted</td>
<td>25 to 36</td>
<td>30 Days</td>
</tr>
</tbody>
</table>

Updated 2.22.21
Continual Improvements: Generate Solutions

• Several options for a standard approach to investigation
  – DMAIC from Six Sigma
  – Plan-Do-Study-Act (PDSA)
  – 8Ds problem solving method

• Familiarize yourself with one (but may need others for different situations)
Continual Improvements: Generate Solutions

- DMAIC

For more information regarding training programs, visit sixsigmacouncil.org.
Continual Improvements: Generate Solutions

- PDSA
Continual Improvements: Generate Solutions

• D0: Prepare and plan for the 8D process
• D1: Form a team
• D2: Describe the problem
• D3: Interim containment action
• D4: Root cause analysis
• D5: Determine permanent corrective action
• D6: Implement and validate the permanent corrective action
• D7: Prevent recurrence and effectiveness checking
• D8: Closure and team celebration
Continual Improvements: Generate Solutions

• Prepare templates and checklists
  − Based on defined strategies
  − Non-conforming events or issues in assessments

PT/EQA Results
Review Template

Nordix Laboratories - Immunohistochemistry Laboratory
Proficiency Testing Results Review Form

Survey: ____________________________

Date results received by Medical Director: ____________________________
Date results reviewed by Medical Director: ____________________________

Overall Survey Results:

Problems/Errors identified & initial containment/mitigation strategies (as needed):

Brief root cause analysis:
- Pre-analytic: Specimen mix-up/clinical error
- Analytic:
- Post-analytic: Clinical error

Corrective action planned/taken:

Patient results reviewed or re-tested, if applicable:

Preventive actions or ongoing surveillance: Ongoing periodic monitoring of the below metrics will continue and repeat testing will be performed as needed or requested based on clinical concerns.
- Monitoring:
  - Divisional policy changes (if any)?

Resolution/additional comments:

Reviewed by:
Technical Medical Director: ___________________________________ Date: __________
Corrective Action Template

Corrective Action Plan: Response to __________

Team:

Definition of the problem:

Initial containment/mitigation strategies:

Analyze the root causes:

Pre-analytic:

Analytic:

Post-analytic:

Determine the corrective action:

Implement the corrective action:

Define preventive actions: Ongoing periodic monitoring of the below metrics will continue and repeat testing will be performed as needed or requested based on clinical concerns.

Monitoring:

Donational policy changes (if any):

Reviewed by:

________________________ [Technical Medical Director], Date: __________
Effectiveness Checking

• Part of CAPA includes definition of monitoring:
  – Follow implemented change
  – Prove that improvements are happening
  – Haven’t over-corrected

• Define a period of monitoring and mechanism to evaluate implemented change

• Determine whether to investigate further if improvement isn’t sufficient, continue monitoring, or stop monitoring
Steps of an 8D investigation

cap.org Reference: https://copatholo.gy/3taBYah
Eight Disciplines Problem Solving Method (8Ds)

- D0: Prepare and plan for the 8D process
- D1: Form a team
- D2: Describe the problem
- D3: Interim containment action
- D4: Root cause analysis
- D5: Determine permanent corrective action
- D6: Implement and validate the permanent corrective action
- D7: Prevent recurrence and effectiveness checking
- D8: Closure and team celebration
8Ds: Quick Hypothetical: No coffee!

• D0: Prepare and plan for the 8D process
  – Prioritize this investigation relative to other commitments: Is this a calendar-clearing problem?
  – How much time should I and my staff budget for the 8D process?
  – Define the process involving the non-conforming event (Tools: Fishbone, Process map)

• D1: Form a team
  – Who are the stakeholders? (Tool: Brainstorm)

• D2: Describe the problem
  – As succinctly as possible – 1-2 sentences (Tools: Fishbone, 5 Whys)
  – Include consequence of the problem if helpful to motivate
8Ds: Quick Hypothetical: No coffee!

- **D3: Interim containment action**
  - Stop or emergent resupply
  - Replace with acceptable/equivalent alternative

- **D4: Root cause analysis**
  - How/why did our problem come to occur
  - *(Many tools)*

- **D5: Determine permanent corrective action**
  - What/which improvements can we put in place to correct the problem and prevent reoccurrence in the future *(Tools: Pareto diagram, Solutions matrix)*
8Ds: Quick Hypothetical: No coffee!

- **D6**: Implement and validate the permanent corrective action
  - Validate
  - Implementation can be tricky
- **D7**: Prevent recurrence and effectiveness checking
  - Create a monitoring plan, venue for feedback
- **D8**: Closure and team celebration
  - Formally end the investigation
  - Opportunity to celebrate and recognize team members efforts to improve patient care
Tools

- thinkreliability.com
- CAP IHC Committee’s FAQ page (https://capathology.gy/3taBYah)
- For RCA:
  - Describe: Fishbone, Process map
  - Investigate: 5 Whys, Cause map
- For decision making:
  - Solutions matrix
  - Pareto diagram
Practical Example: Breast HER2
Breast Predictive Markers

• Have the best established benchmarks around which internal quality monitoring is based
  – Participation in PT required for CAP accredited laboratories

• Non-conforming events often classified as moderate to high risk
  – Prompt timely investigation
  – Implementation of corrective action
Breast HER2 Scenario

• Issues with the breast HER2 IHC stain
• Occasionally see unacceptable 2+ scores (in intended negative cases) in PT/EQA
• Internal quality monitoring indicates an upward trend in 3+ scores (now at 25%)
• FISH amplification rates have remained stable
D0: Prepare and Plan for the 8D Process

- **Measurement**
  - Responses incorrectly recorded in submission form
  - TMA cores were interpreted out of order
  - Error in pathologist read-out
  - Improper slide handling/storage
  - Extreme temperatures during shipping
  - Shifts in tested population

- **Material**
  - Heterogeneous antigen expression in tissue
  - Suboptimal antibody clone
  - Unaware of better clone(s)
  - Suboptimal assay conditions

- **Man**
  - Significant intraobserver variation
  - Undetected QC failure
  - Suboptimal autostaining platform

- **Environment**

- **Method**

- **Machine**

- Increased percentage of Her2 equivocal (2+) and positive (3+) results
D1: Form a Team

• Major stakeholders
  - Lab staff/supervisor
  - Technical/lab director
  - Pathologists interpreting breast HER2
  - Breast oncologists
D2: Describe the Problem

- Unacceptable responses in HER2 PT/EQA
- A trend toward over-calling in PT/EQA and possibly in internal quality monitoring data
- Opportunity for improvement will be designated as high priority
  - High clinical importance of this result for patient treatment planning
D3: Interim Containment Action

- Temporarily suspend in-house testing and prioritize time and resources to investigation so that timely conclusion is reached.
- Alternatively, in-house with confirmatory send-out for HER2 3+ cases.
D4: Root Cause Analysis (RCA): PT/EQA

- **Pre-analytic**
  - Materials handled according to instructions
  - No pre-analytic issues suspected

- **Analytic**
  - Majority of discordance with intended response trend in one direction, indicating assay re-optimization may help
  - Review of PSR indicates difference between my lab’s assay conditions and majority of labs using same clone/platform

- **Post-analytic**
  - PT/EQA TMA slides blindly re-reviewed by alternative pathologist
  - Concurred with submitted results for cases in questions
D5: Determine Permanent Corrective Action

- **High Payback**
  - **High Benefit**
    - 1. Revalidate assay
    - 2. Mandatory peer review
  - **Medium Benefit**
    - 3. Education re: Her2 IHC interpretation
    - 4. Provide focused pathologist performance data
  - **Low Benefit**
    - 5. Further pursue shift in patient population hypothesis

- **High Effort/Cost**
  - Implement DIA

---

© 2022 College of American Pathologists. All rights reserved.
D5: Determine Permanent Corrective Action

Pareto Diagram

- Non-specific assay
- Intraobserver variability
- Shift in patient population
- Tumor heterogeneity
- Instrument QC failure
- Pre-analytic issue
- TMA read incorrectly
- Suboptimal clone
- Suboptimal platform

Count of Errors

Count

Cumulative %

0.0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0 100.0
D5: Determine Permanent Corrective Action

Pareto Diagram

- Non-specific assay
- Intraobserver variability
- Shift in patient population
- Tumor heterogeneity
- Instrument QC failure
- Pre-analytic issue
- TMA read incorrectly
- Suboptimal clone
- Suboptimal platform

Count of Errors vs. Cumulative %
D6: Implement and Validate the Corrective Action

• The assay will be revalidated following best practice recommendations and implemented.
• Based on timing of when upward trend exceeded benchmarks, will repeat testing on all previous 3+ cases with re-validated assay.
D7: Prevent Recurrence and Effectiveness Checking

• Will continue participation in PT/EQA

• Based on lab volumes
  – Will collect internal HER2 quality monitoring data more frequently for next 6 months (monthly instead of quarterly)
  – If at 6 months, trend is acceptable and next PT/EQA also shows improvement, will return to baseline monitoring.

• To familiarize pathologists will re-validated assay, will show examples of HER2 (1+), HER2 (2+)/FISH, and HER2 (3+) cases for education
D8: Closure and Team Celebration

• Give gratitude!

Summary

• Your toolbox: Quality Plan

• Your tools:
  ○ Defined monitoring/reporting of non-conforming events
  ○ Defined risk assessment method/tool
  ○ Defined standard approach to non-conforming event investigation
  ○ Templates and checklists based on standard approach to non-conforming event investigation
  ○ Tools to use during an event investigation
Thank you!

Contact us:

✉️ international@cap.org

📞 (847) 832-7000 Country Code: 1
Appendix – 8D Method Example for Estrogen Receptor (ER)

cap.org Reference: https://capatholo.gy/3taBYah
My lab had intermittent unacceptable responses on our Estrogen Receptor (ER) proficiency testing/external quality assessment (PT/EQA) survey, usually in cases near the 1% positive quantitative threshold.
D0: Prepare and Plan for the 8D Process

- Intermittent unacceptable responses on ER proficiency testing, usually in cases near the 1% positive quantitative threshold.
- ER is resulted as negative when the intended response is low positive, but occasionally, ER is resulted as low positive when the intended response is negative.
- Daily, there is often intraobserver variability among pathologists regarding ER interpretation.
- Based on annual monitoring data, the percent of ER negative breast cancers observed in the laboratory is within published benchmarks (<25-30%).
- It is anticipated that the issue is possibly multi-factorial, including pathologist read-out error and/or suboptimal assay conditions (either over- or under-staining).
D1: Form a team

- Representatives from stakeholder groups including
  - Lab staff/supervisor
  - Medical director
  - Breast pathologists
  - Other pathologists resulting ER IHC, breast oncologists
D2: Describe the Problem

• The lab is experiencing unacceptable responses in ER proficiency testing.

• In most instances, a clear trend in the unacceptable responses is not appreciated.
  – Pathologists routinely disagree on quantitation.
D3: Interim Containment Action

- Due to ER’s status as a highly utilized predictive marker with significant impact on patient care, it would seem prudent to:
  - Temporarily suspend in-house testing
  - Prioritize time and resources for this process improvement assessment
  - Reach a conclusion in less than 10 business days

- However, if the delay in TAT due to send-out is unacceptable:
  - In-house testing could be performed with temporary send-out confirmatory testing for any ER low positive or ER negative case.
  - Billing charges removed for the in-house test if send-out is needed.
D4: Root Cause Analysis (RCA)

**Pre-analytic**
- PT/EQA slides handled according to directions upon arrival.
- No pre-analytic variables were felt to contribute to the problem.

**Analytic**
- If unacceptable responses fail to show a consistent trend or if there is not a known source of random variation in the laboratory, this suggests that analytic problems do not wholly explain the observed problem.
- If the majority of the intended responses trend in one direction, this may indicate that some degree of assay re-optimization would help the situation.
- After review of the PSR, assay conditions are similar, but not identical, to the majority of laboratories using the same clone/platform.

**Post-analytic**
- TMAs are re-reviewed by a blinded pathologist who did not participate in the initial proficiency test review.
- Significant disagreement is observed in cases in question.
D5: Permanent Corrective Action (PCA)

• In order to determine the PCA, a Pareto diagram was created.
After review of the Pareto diagram, it is determined that the PCA will be two-fold.

- To address analytic concerns, the assay will be re-validated according to existing recommendations for ER validations to align assay conditions more closely with those of laboratories using similar clone/platform.
- To address pathologist intraobserver variability and read-out error, the laboratory will consider digital image analysis.

All pathologists will also be reminded of the 2020 ASCO/CAP ER/PR guideline updates and the instituted laboratory policy for prospective adjudication of ER low positive and ER negative cases.

- For example, an internal policy is implemented in which any case within or approaching the 1-10% low positive category is shown to a second pathologist before reporting, with any discordance reconciled by a third pathologist.
D6: Implement and Validate the Permanent Corrective Action

- The revalidated assay will be implemented.
- Pathologists appropriately use adjudication procedure.
D7: Prevent Recurrence

- Continued participation in PT/EQA.
- Attention to ER performance monitoring reports.
  - Consider adding ER low positive data to ongoing quality monitoring to observe trends.
  - Could consider random sampling of reported ER low positive and ER negative cases for re-review for group educational purposes.
D8: Closure and Team Celebration

Appendix – 8D Method Example for Progesterone Receptor (PR)

cap.org Reference: https://capathology.org/3taBYah
Process Improvement Assessment Example for PR

My lab had had unsuccessful performance for our Progesterone Receptor (PR) proficiency testing/external quality assessment (PT/EQA) survey.
D0: Prepare and Plan for the 8D Process

- PR assay recently revalidated due to clinician concern that rate of ER negative/PR positive breast cancer was too high in the patient population.
- PR PT/EQA failure occurred in the first proficiency test event after the PR assay was re-validated.
- Initially anticipated significant time requirement from the lab medical director and laboratory staff to:
  - perform revalidation
  AND
  - perform repeat testing of patient samples tested since the re-validated protocol was launched.
D1: Form a team

• Representatives from stakeholder groups including
  − Laboratory medical director
  − Laboratory supervisor
  − Laboratory tech staff
  − Chief of pathology at sites with PT failure
  − Representative breast oncologist (who participated in the initial re-validation)
D2: Describe the Problem

- Failure to achieve acceptable (90%) concordance with intended responses on a graded proficiency test.

- Five Whys Cause Map
D3: Interim Containment Action

- Initial examination of the unacceptable responses indicated consistent trend toward false negative results.
- False negative would have insignificant impact on immediate patient care.
- Testing was allowed to continue in-house for the duration of the PIA.
  - Pathologists and breast oncologists were notified.
  - Plans were made to perform repeat testing on all PR negative cases resulted between launch of the prior re-validated assay and re-launch of the assay when the corrective action identified by the current assessment was implemented.
D4: Root Cause Analysis (RCA) – Pre-analytic

• One site observed complete tissue wash-off of 1 core.
  – Only 19 responses could be provided and the denominator for calculating concordance rate was reduced.
  – Had this tissue remained on the slide and reported result was concordant with the intended response, this site would not have achieved <90% concordance.
    • Some degree of tissue wash-off is observed in routine clinical cases in the laboratory.
    • Past PIAs to address this issue specifically have identified high humidity conditions, insufficient or loss of charge of glass slides, and extended or aggressive protocols as causes of tissue wash-off.

• It is not anticipated that these factors contributed significantly in this case due to the controlled pre-analytic conditions of PT materials and not overly aggressive assay conditions.

• Cause of this tissue wash-off remains uncertain.
D4: Root Cause Analysis (RCA) – Analytic

Assay conditions

- Due to the prior assay changes to mitigate clinician concern regarding false positive PR results, the primary antibody incubation time had been recently reduced.

- In the PIA for that re-validation, a preventive action plan stipulated that if a high rate of potential false negatives were observed, the assay conditions would be further adjusted by making a small increase in primary antibody incubation time, which would align with the manufacturers recommendations and the majority of laboratories using the same clone (per the CAP PSR).

- Antigen retrieval conditions were already aligned with those of other laboratories using the same clone/platform.

Pathologist read-out

- In review of the unacceptable cores, laboratory quarterly monitoring reports for breast predictive markers, and daily cases, it appeared that pathologists were having 2 issues:
  - Difficulty with reproducible quantification at the 1% positive threshold
  - Dismissing weak, nuclear staining as non-specific

Biology

- Heterogeneity of tumor quantity is a well-established factor that effects standardization in TMA based surveys.

- The lab in question prepares PT materials for interpretation at four CLIA-licensed sites.

- By comparing the four TMAs after the fact:
  - Reasonably consistent staining intensity observed across the interpreted TMAs
  - Significant variability in the quantity of tumor in core profiles was seen (affecting denominator and subsequently % positive calculation)
D4: Root Cause Analysis (RCA) – Post-analytic

- TMA is re-reviewed.
- Submitted responses confirmed to reflect staining on the slide.
  - No clerical errors in response submission
D4: Root Cause Analysis (RCA) – Conclusion

- The root cause is likely multifactorial including both
  - analytic assay concerns
  - pathologist read-out concerns
D5: Determine Permanent Corrective Action

- Several possible solutions exist to address the assay and pathologist read-out concerns.
- The time/cost requirements to complete assay revalidation was deemed necessary to produce an assay with acceptable performance so as to continue performing the test in-house. (PR is no longer monitored.)
- A mandatory prospective peer review was initiated for all PR negative and PR low positive cases.
  - DIA was not further pursued due to high cost and implementation requirements.
  - Pathologist education was performed due to anticipated low time/energy cost but, admittedly, of uncertain yield other than increasing awareness of the need to be conscientious at the 1% threshold and seek other opinions.
- Site-specific retrospective ER-/PR+ breast cancer data were generated and shared for focused performance evaluation; however, a formal adjudication procedure was not ever defined or implemented.
D6: Implement and Validate the Permanent Corrective Action

• Primary antibody incubation duration was increased 4 minutes to align with manufacturer recommendations and the conditions reported by the majority of laboratories using the same clone.

• A full assay revalidation was performed.

• The launch of the new assay was announced to breast oncologists.

• All patient samples with PR negative results since the last assay change were re-tested with the new assay conditions at no charge to the patient.
D7: Prevent Recurrence

• Breast predictive marker quality monitoring was expanded to include site-specific data for ER-/PR+ breast cancer.
• As a result of cumulative assay changes, a compensatory increase in triple negative and ER+/PR- breast cancer was anticipated, and these metrics were included accordingly.
• The laboratory continues to participate in PT/EQA.
• Internal process for annual pathologist competency assessment, as required for breast predictive markers, was to be re-evaluated.
D8: Closure and Team Celebration

• Monitoring of site-specific ER-/PR+ breast cancer was planned to continue for 12 months
  - If at that time, the rate of ER-/PR+ breast cancer was stable at <2% and there were no clinician concerns, the corrective action plan would be closed.
  - If not, the lab would re-evaluate.
Appendix – 8D Method Example for ALK

cap.org Reference: https://capatholo.gy/3taBYah
Process Improvement Assessment Example for hs-ELK

My lab had unsuccessful performance for our ALK proficiency testing/external quality assessment (PT/EQA) survey.
D0: Prepare and Plan for the 8D Process

• The lab achieves unacceptable concordance with intended responses on ALK proficiency testing/external quality assessment (PT/EQA).
• Initially anticipate an analytic issue with the assay
• Allocate several hours of lab tech and lab director time to troubleshoot the assay
D1: Form a team

- Representatives from stakeholder groups including
  - Lab tech/lab supervisor
  - Medical director
D2: Describe the Problem

• The lab registered unacceptable results on 4 of 10 cores. In all unacceptable cores:
  – The intended response was positive.
  – The lab’s submitted response was negative.

• This suggested insufficient assay sensitivity.
  – A team member suggests creating a Fishbone diagram to consider whether there may be alternative or additional causes of the unacceptable PT performance.
D2: Describe the Problem – Fishbone

Unacceptable performance on hs-ALK proficiency testing (60% concordance)

- Measurement
  - Responses incorrectly recorded in submission form
  - TMA cores were interpreted out of order
  - Error in pathologist read-out
  - Improper slide handling/storage
  - Extreme temperatures during shipping

- Material
  - Heterogeneous antigen expression in tissue cores
  - Suboptimal antibody clone
  - Unaware of better clone(s)
  - Suboptimal assay conditions

- Man
  - Significant intraobserver variation
  - Undetected QC failure
  - Suboptimal autostaining platform

- Environment

- Method

- Machine

© 2022 College of American Pathologists. All rights reserved.
D3: Interim Containment Action

- Due to high rate of false negative results, and that a negative result has the significant effect of excluding a patient from receiving therapy, the lab will:
  - Temporarily cease in-house predictive ALK IHC
  - Perform as a send-out
D4: Root Cause Analysis (RCA)

Pre-analytic
• PT/EQA slides handled according to directions upon arrival.
• No pre-analytic variables were felt to contribute to the problem.

Analytic
• The PSR from the past ALK survey is reviewed for comparison of assay parameters with other laboratories. It is noted:
  • majority of labs use highly sensitive ALK clones
  • other laboratories observing negative results on the 4 cores in question in this analysis were predominately also using ALK1 (not a highly sensitive ALK clone)

Post-analytic
• TMA is re-reviewed
• Submitted responses confirmed to reflect staining on the slide (no clerical errors)

Conclusion
The root cause of the problem is use of an insufficiently sensitive clone.
D5: Determine Permanent Corrective Action

• The lab will change to a highly sensitive ALK clone. Based on:
  – Additional literature review
  – Comparison with other laboratories via the PSR
  – Review of recommendations to perform predictive ALK testing using highly sensitive clones

• Alternatively, re-optimization of the assay using ALK1 was considered.
  – However, available literature suggests that assay parameters have not been identified for ALK1 that produce acceptable concordance with ALK rearrangement.
D6: Implement and Validate the Permanent Corrective Action

• New clone requires full revalidation using 20 positive and 20 negative cases.

• The comparator method will be results of ALK FISH and/or molecular.

• Clinicians, especially pulmonary oncologists:
  − Notified of the RCA
  − Offered the opportunity to perform repeat testing using the highly sensitive clone at no cost to patient
D7: Prevent Recurrence

- ALK1 is felt to still be a diagnostically relevant immunostain that should be retained on the test menu.
  - Potential for confusion and inappropriate ordering if there are two “ALK stains” in the IHC menu.
  - The order for highly sensitive ALK will be specified by clone name (HSALK).
- Periodic monitoring of highly sensitive ALK results will be performed to confirm that ~5% of lung cancers are positive by highly sensitive ALK immunohistochemistry.
- Automated reminder will be set-up to prompt at least annual literature review regarding the availability and performance of new highly sensitive ALK clones.
D8: Closure and Team Celebration

Appendix – 8D Method Example for BRAF

cap.org Reference: https://capathology.org/3taBYah
My lab has intermittent unacceptable responses for our BRAF V600E proficiency testing/external quality assessment (PT/EQA) survey.
D0: Prepare and Plan for the 8D Process

• The lab has intermittent unacceptable responses on BRAF V600E proficiency testing/external quality assessment (PT/EQA).

• Unacceptable responses are usually cases where:
  – intended response was positive.
  – submitted response was negative.

• Anticipate missing low positive cases requiring assay re-optimization and revalidation.

• Anticipate allocating several hours of lab staff and medical director time for process improvement assessment and resolution.
D1: Form a team

• Representatives from stakeholder groups including
  - Lab tech/supervisor
  - Medical director
  - Possibly staff in molecular genetics who can provide confirmed V600E mutation cases
D2: Describe the Problem

- Over the last several rounds of BRAF V600E PT
  - Intermittent false negative results
  - Indicating insufficient assay sensitivity
D3: Interim Containment Action

• Although a problem requiring resolution, the frequency of false negative results seems low level.

• The interim plan will be to:
  − Continue in-house testing
  − Perform confirmatory molecular analysis for all BRAF V600E IHC negative results
D4: Root Cause Analysis (RCA)

Pre-analytic
- PT/EQA slides handled according to directions upon arrival.
- No pre-analytic variables were felt to contribute to the problem.

Analytic
- The PSR from past BRAF V600E surveys is reviewed for comparison of assay parameters with other laboratories
  - majority of labs using the same clone/platform use a longer primary antibody incubation duration and more aggressive antigen retrieval.
- Past lot-to-lot comparisons are retrieved and reviewed – no decrement in staining observed over time.
- Original BRAF V600E validation documentation is retrieved and reviewed showing strongly positive staining in all positive cases.
- On-slide positive control tissue selected from the positive validation cases is strongly positive.

Post-analytic
- TMA is re-reviewed by pathologists most experienced at interpretation of BRAF V600E IHC in the group.
- Submitted responses confirmed to reflect staining on the slide (no clerical errors and interpreted correctly).

Conclusion
- The root cause of the problem is likely suboptimal assay conditions.
- Absence of low positive cases from the validation cohort and on-slide control tissue likely contributed to a suboptimal initial validation.
D5: Determine Permanent Corrective Action

• Re-optimize and revalidate the assay
D6: Implement and Validate the Permanent Corrective Action

• Assay to be revalidated using longer antibody incubation duration (or other parameters).

• Larger number of cases will be included in the validation cohort to characterize the spectrum of positivity in cases, including low positivity cases.
  - A low positive case will be identified and used as the on-slide positive control tissue.
D7: Prevent Recurrence

- Continued participation in PT/EQA
- Attention to fluctuations in the low positive control
- Could consider molecular testing of a random sample of IHC negative cases
  - to confirm no recurrent issue with false negatives
Additional comments:

- Review of CAP PT survey data for BRAF V600E collected in recent years indicates that most “unacceptable” results occurred in assessment of BRAF V600E status in colonic adenocarcinoma samples.
  
  - Speculated that a lower level of mutant protein expression in these tumors compared to others such as melanoma may be the underlying issue.
    - If a lab used only melanoma tissue in the assay validation process, it may select a staining condition that is optimized for detecting abundant mutant protein in melanoma, which may be insufficiently sensitive for reliable detection of mutant protein in colonic adenocarcinoma.

- Validation of the staining protocol has to be performed using all tumor types for the intended clinical applications.

- Correct interpretation of staining results may also be challenging for some colonic adenocarcinoma samples, and orthogonal testing methods should be considered in challenging cases.
Appendix – 8D Method Example for KIT

cap.org Reference: https://capatholo.gy/3taBYah
My lab has unsuccessful performance for our KIT proficiency testing/external quality assessment (PT/EQA) survey.
D0: Prepare and Plan for the 8D Process

• Intermittent unacceptable responses on KIT proficiency testing
• The majority of the unacceptable responses occurred:
  – Intended response was negative.
  – Submitted response is positive.
• Appropriate KIT staining is localized to the cytoplasm.
  – Majority of the unacceptable responses demonstrated nuclear staining.
• Based on this preliminary review of the data, the laboratory leadership anticipates:
  – Cause of nuclear staining is due to extended or overly aggressive assay conditions.
  – Allocating several hours of lab staff and medical director time for process improvement assessment and resolution.
D1: Form a team

- Representatives from stakeholder groups including
  - Lab tech/supervisor
  - Medical director
D2: Describe the Problem

• Unacceptable responses in KIT proficiency testing
• Most instances:
  – Intended result is negative.
  – Lab has submitted a result of positive.
  – Insufficient specificity
D3: Interim Containment Action

- KIT serves a limited role as a predictive marker.
  - Diagnostically useful marker in some situations
- Diagnostically, there are alternative markers to KIT testing available in the laboratory (DOG1 in GIST; CD34 or MPO in AML).
  - Limited potential for negative adverse effect on patient care.
- Notify pathologists of:
  - Concern for potential over-staining
  - Temporarily recommend against use of the in-house stain while process improvement assessment is on-going
D4: Root Cause Analysis (RCA)

**Pre-analytic**
- PT/EQA slides handled according to directions upon arrival.
- No pre-analytic variables were felt to contribute to the problem.

**Analytic**
- The PSR from the past KIT survey is reviewed for comparison of assay parameters with other laboratories.
- Noted that a majority of labs use assay parameters that are less aggressive or shorter duration than what is currently used in the laboratory.

**Post-analytic**
- TMA is re-reviewed.
- Submitted responses confirmed to reflect staining on the slide (no clerical errors).

**Conclusion**
- The root cause of the problem is likely overly aggressive or extended assay conditions.
D5: Determine Permanent Corrective Action

- Assay to be reoptimized considering changes including:
  - Shorter antibody incubation duration
  - Less aggressive antigen retrieval conditions
  - Omitting additional heat options
- Conditions will be titrated until nuclear staining is not observed.
D6: Implement and Validate the Permanent Corrective Action

• The reoptimized and revalidated protocol will be implemented.

• At that time, pathologists will be notified:
  – Change in assay parameters
  – Recommendation against performing in-house testing will end
D7: Prevent Recurrence

• Continued participation in PT/EQA
• Attention to fluctuations in control tissue
• Return of nuclear staining would require another process improvement assessment.
D8: Closure and Team Celebration