COLLEGE of AMERICAN PATHOLOGISTS

A Pathologist's Toolbox for Predictive Marker Quality Improvement

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- Involvement with the College of American Pathologists (CAP)
  - Member of CAP Immunohistochemistry Committee

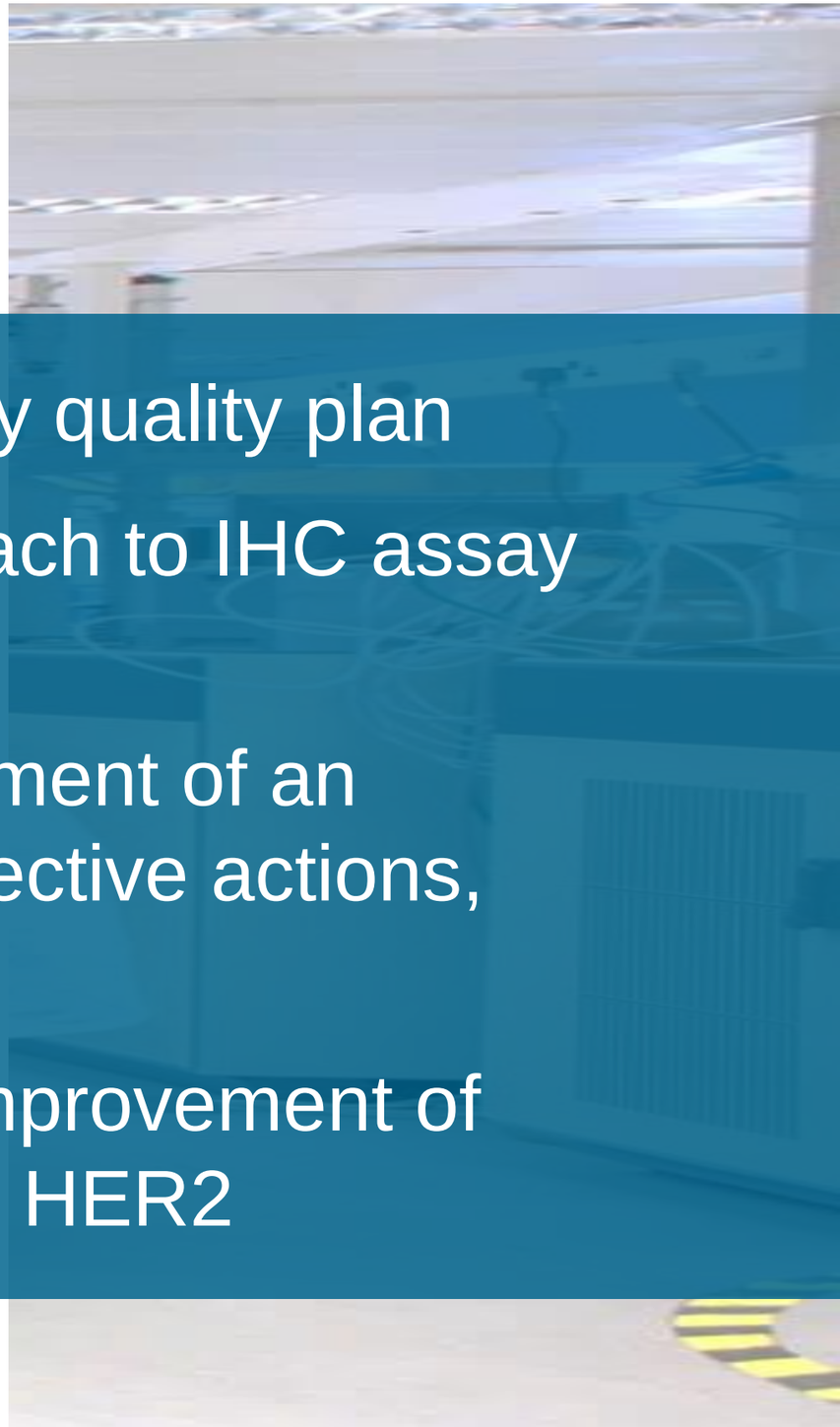
Agenda

- 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

Image Source: https://stock.adobe.com/ee/search?k=open+toolbox&asset_id=222573388

Image Source: https://dieseltech.ca/15-toolbox-organization-ideas/

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

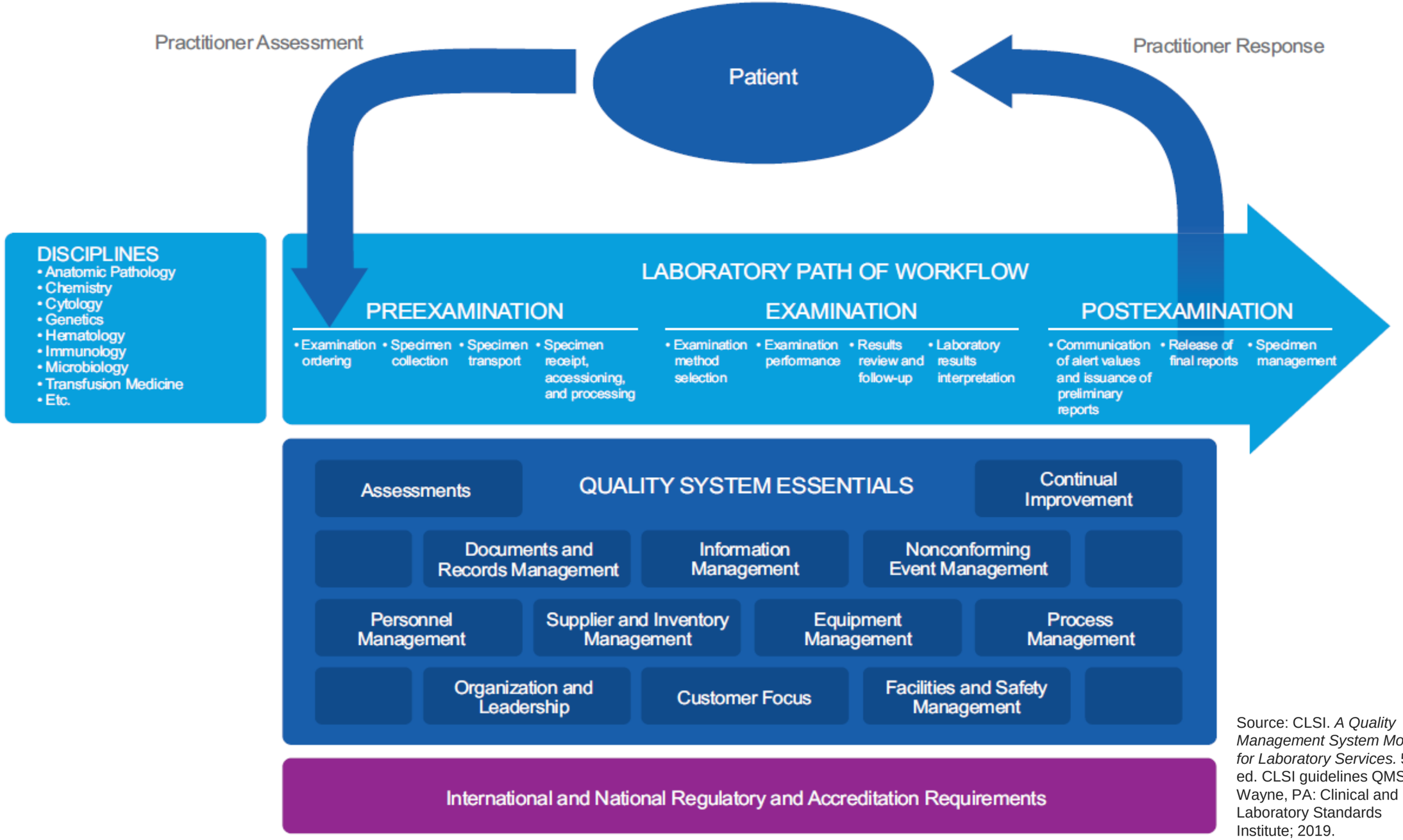
Source: https://www.whatissixsigma.net/jurans-quality-trilogy/

Quality Planning in Anatomic Pathology

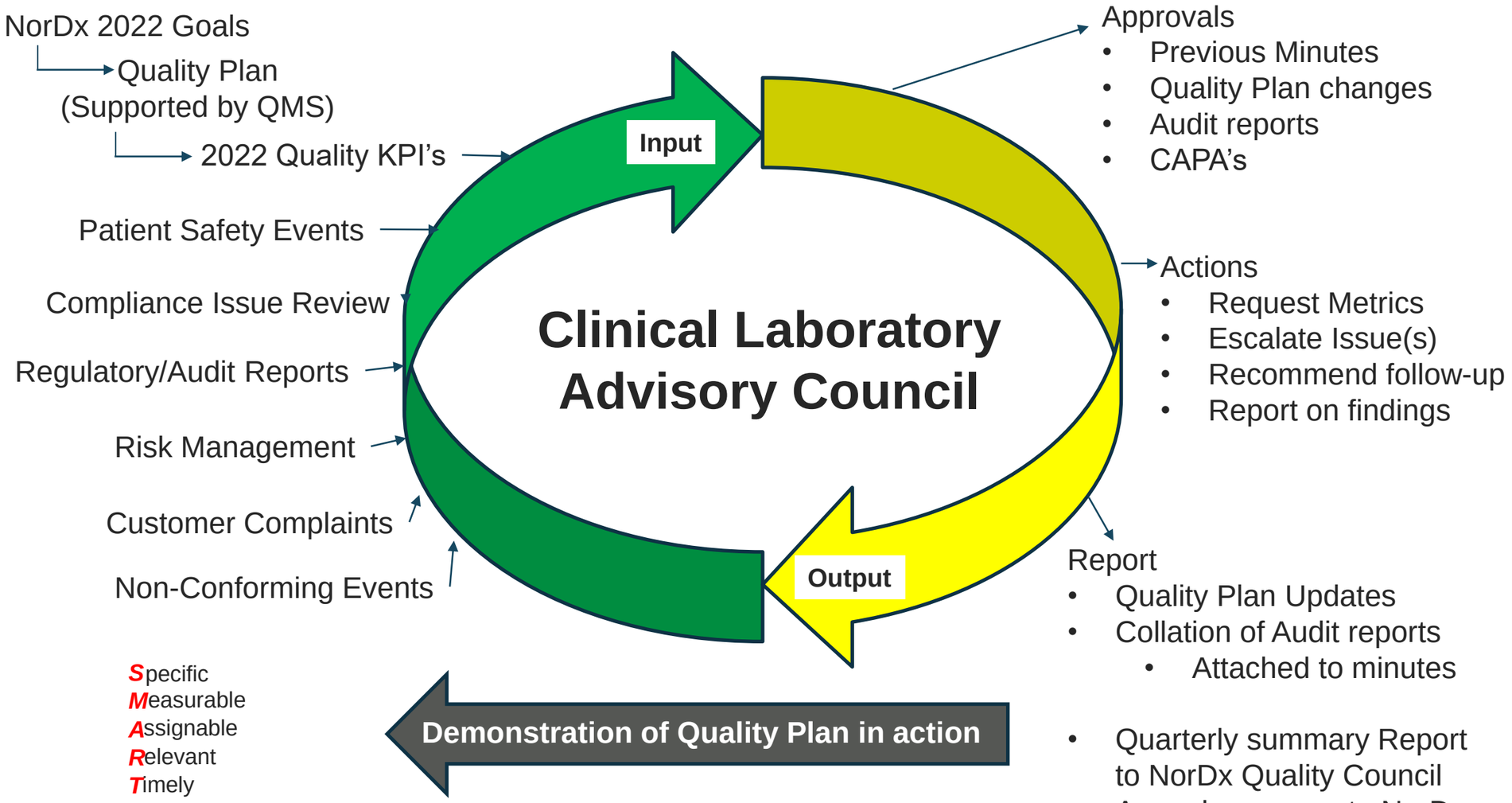
- Written plan required of AP laboratories by most inspection agencies
  - CAP, WHO, CDC
- No single best way to prepare a quality plan (CLSI QMS)
- GOAL: detect problems and identify improvement opportunities across the laboratory
- Consider the accreditors and requirements of each lab subsection
  - Comprehensive plan with appendix
  - Aggregate of many complete plans by subsection

Quality Planning in Anatomic Pathology

References:
Deborah Sesok-Pizzini, MD, MBA, editor. *Patient Safety In Anatomic and Clinical Pathology Laboratories*. Northfield, IL; 2017. CAP PUB316.
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.



Source: CLSI. *A Quality Management System Model for Laboratory Services.* 5th ed. CLSI guidelines QMS01. Wayne, PA: Clinical and Laboratory Standards Institute; 2019.



Source: NorDx Laboratories. Bob Carlson, MD; Laboratory Director.

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

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  - Personnel management
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  - 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

Image Source: https://www.ivymarketing.com/2018/07/discover-truly-unique-brand/penguins/

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Image Source: https://www.ivymarketing.com/2018/07/discover-truly-unique-brand/penguins/

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

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  - Detect
  - Document
  - Classify (risk assessment)
  - Correct

3x3 RISK MATRIX

LIKELIHOOD ↓ / SEVERITY →	1	2	3
1	LOW – 1 –	LOW – 2 –	MEDIUM – 3 –
2	LOW – 2 –	MEDIUM – 4 –	HIGH – 6 –
3	MEDIUM – 3 –	HIGH – 6 –	HIGH – 9 –

Source: https://www.smartsheet.com/all-risk-assessment-matrix-templates-you-need

References:
Zarbo RJ et al. Error detection in anatomic pathology. *Arch Pathol Lab Med*. 2005;129:1237-1245.
Raab SS et al. Effectiveness of random and focused review in detecting surgical pathology error. *Am J Clin Pathol*. 2008;130:905-912.
Foucar E. Classification of error in anatomic pathology: a proposal for an evidence-based standard. *Semin Diagn Pathol*. 2005;22:139-146.

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

Image source: https://elearningindustry.com/how-educators-connect-teaching-and-learning-with-end-to-end-assessment

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

Image source:
https://www.seekpng.com/ima/u2w7w7t4r5a9q8e6/

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

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

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

Priority	Score	CAPA TAT
Critical	1 to 8	10 Days
Active	9 to 15	30 Days
Tracked	16 to 24	
Noted	25 to 36	

Updated 2.22.21

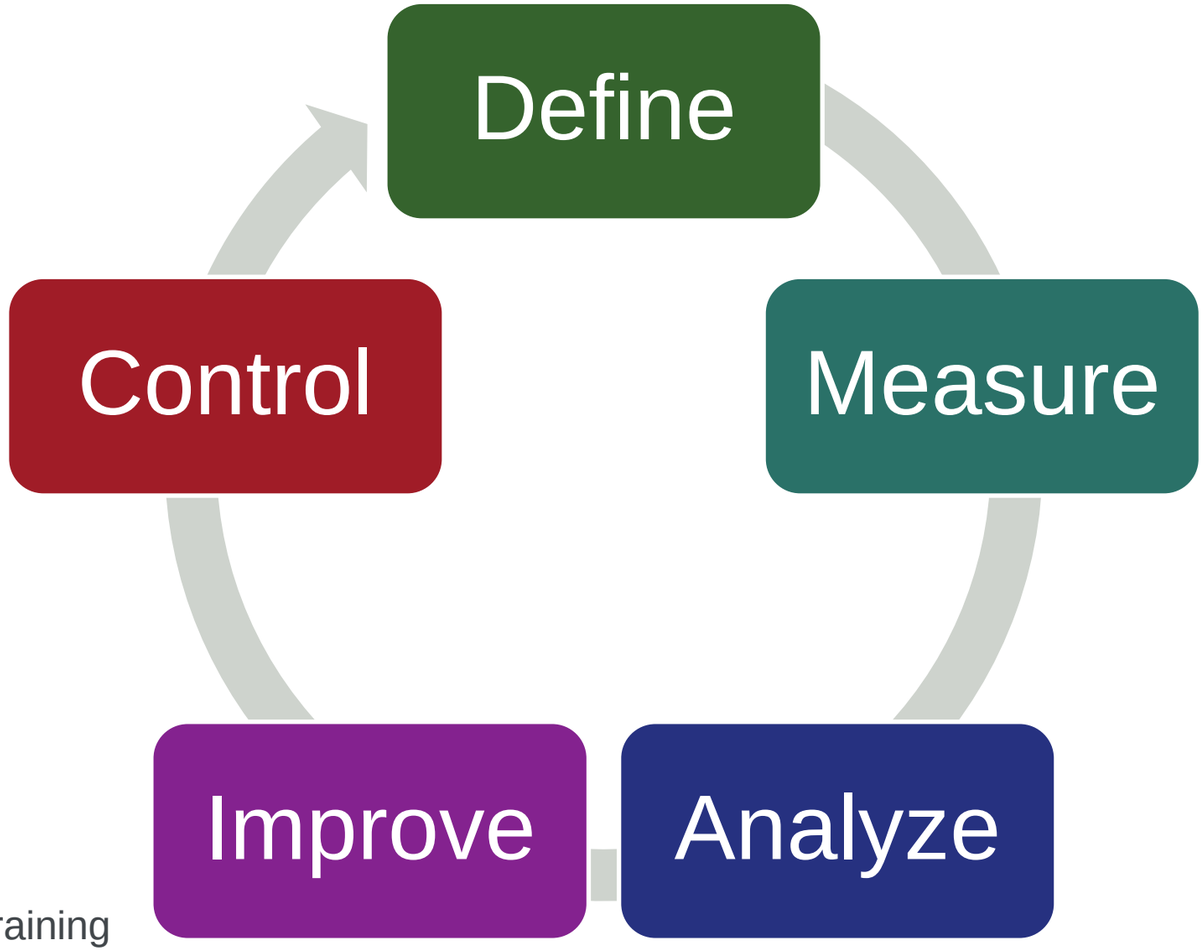
NorDx MaineHealth

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

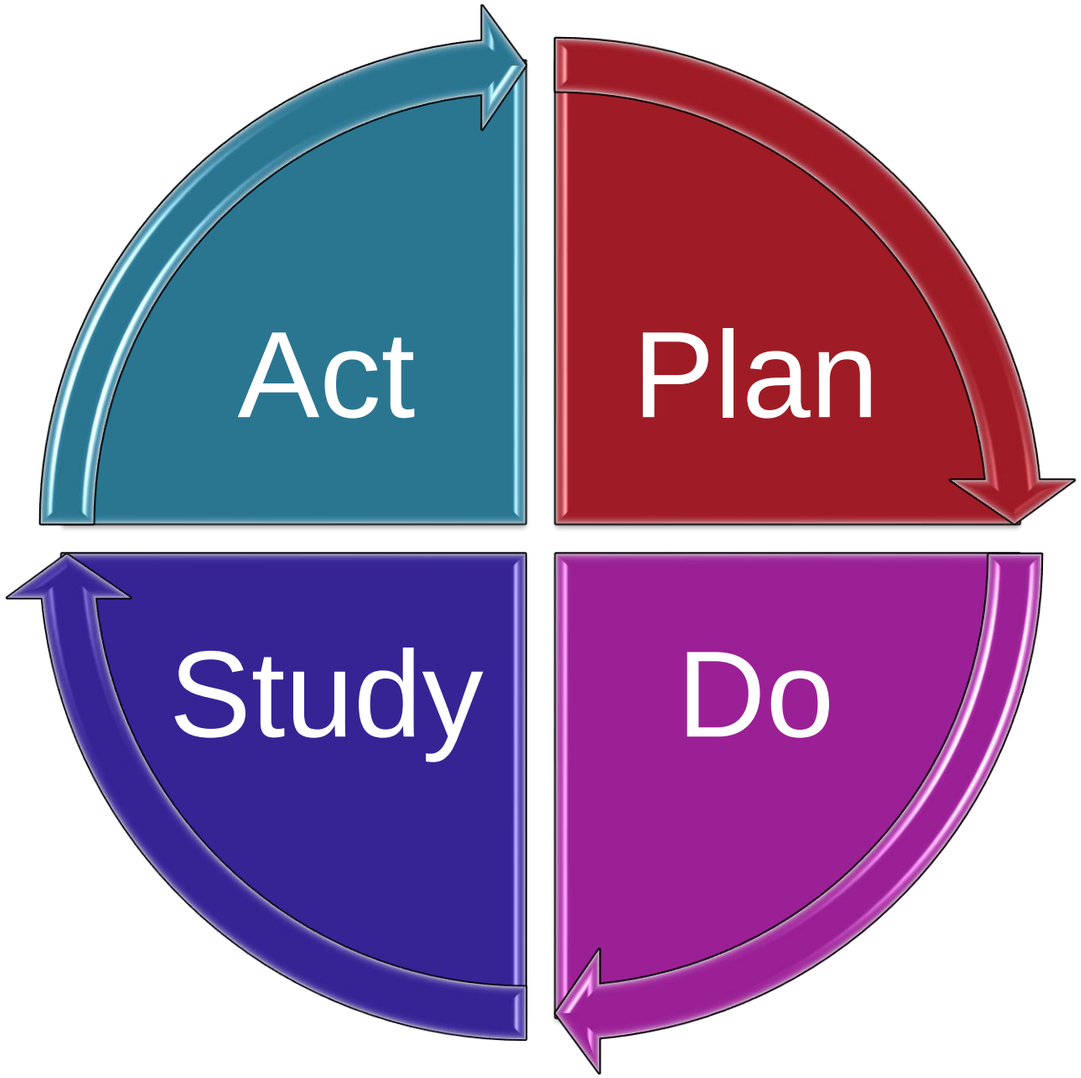
- DMAIC



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

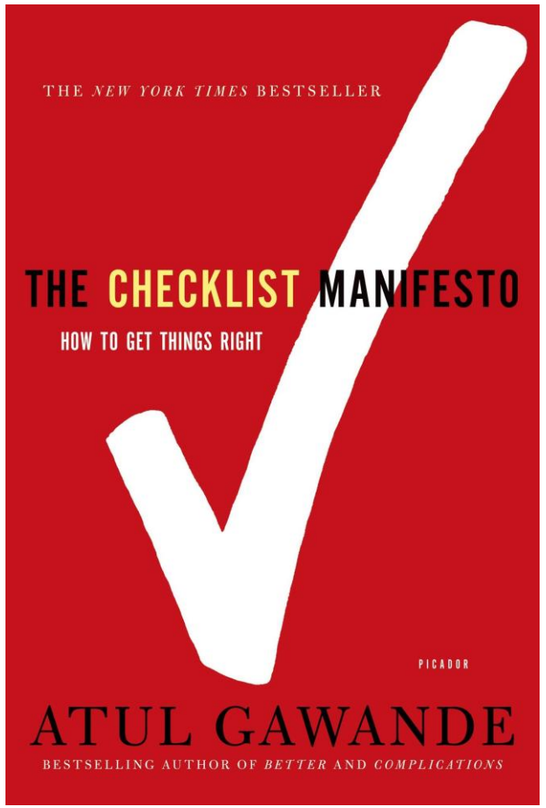


Image source: http://atulgawande.com/book/the-checklist-manifesto/

PT/EQA Results Review Template

Nordx 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/clerical error

Analytic:

Post-analytic: Clerical 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

Nordx Laboratories - Immunohistochemistry Laboratory

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:

Embed 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:

Divisional 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://capatholo.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://capatholo.gy/3taBYah)
- For RCA:
  - Describe: Fishbone, Process map
  - Investigate: 5 Whys, Cause map
- For decision making:
  - Solutions matrix
  - Pareto diagram

Practical Example: Breast HER2

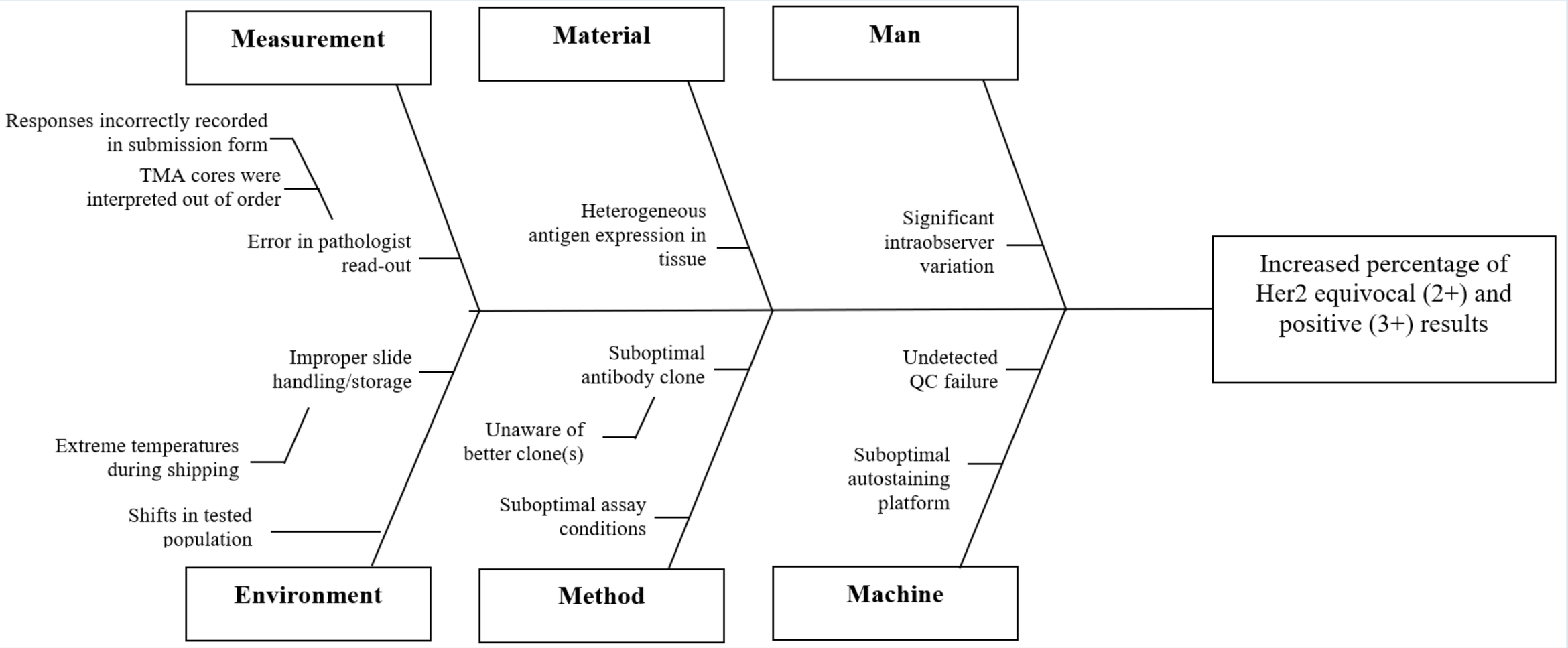
Breast Predictive Markers

- 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



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

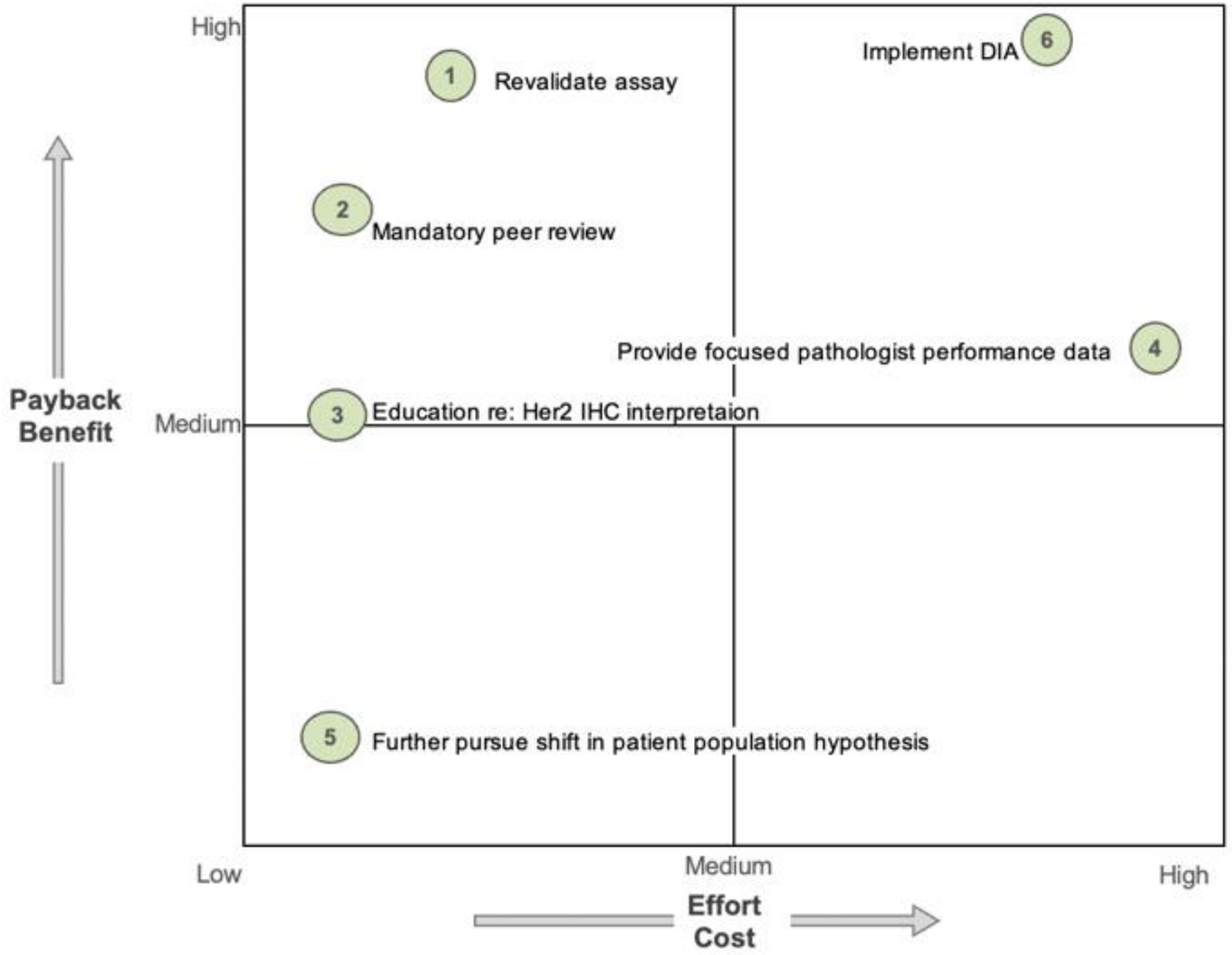
Analytic

- 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

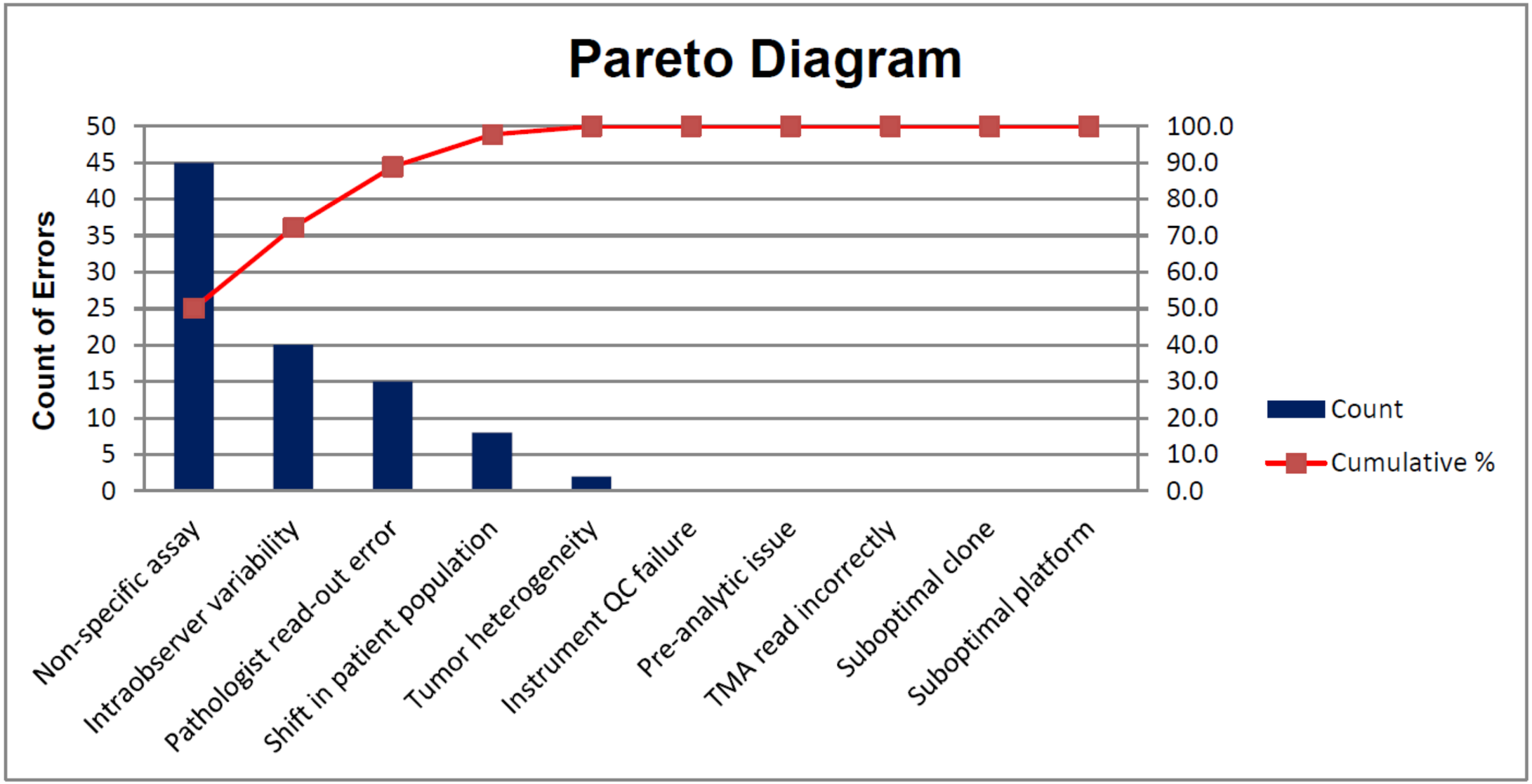
Post-analytic

- PT/EQA TMA slides blindly re-reviewed by alternative pathologist
- Concurred with submitted results for cases in questions

D5: Determine Permanent Corrective Action



D5: Determine Permanent Corrective Action



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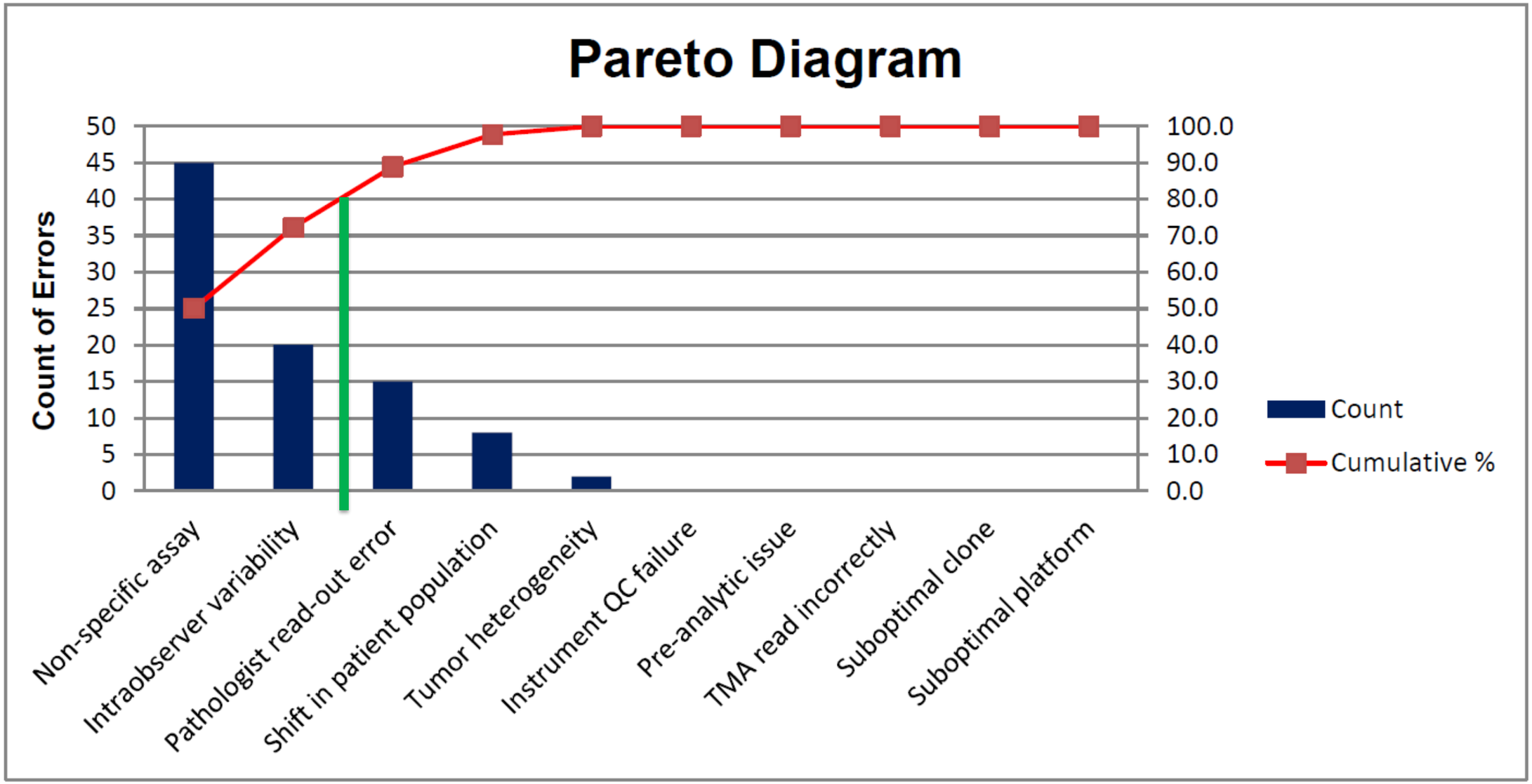

D6: Implement and Validate the Corrective Action

- 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!

Image source: https://www.istockphoto.com/vector/jumping-business-people-cheerful-company-employees-office-managers-team-event-men-gm1337421963-418312155

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
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Image Source: https://stock.adobe.com/ee/search?k=open+toolbox&asset_id=222573388

Image Source: https://dieseltech.ca/15-toolbox-organization-ideas/

Thank you!

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(847) 832-7000 Country Code: 1

Appendix – 8D Method Example for Estrogen Receptor (ER)

cap.org Reference: https://capatholo.gy/3taBYah

Process Improvement Assessment Example for ER

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

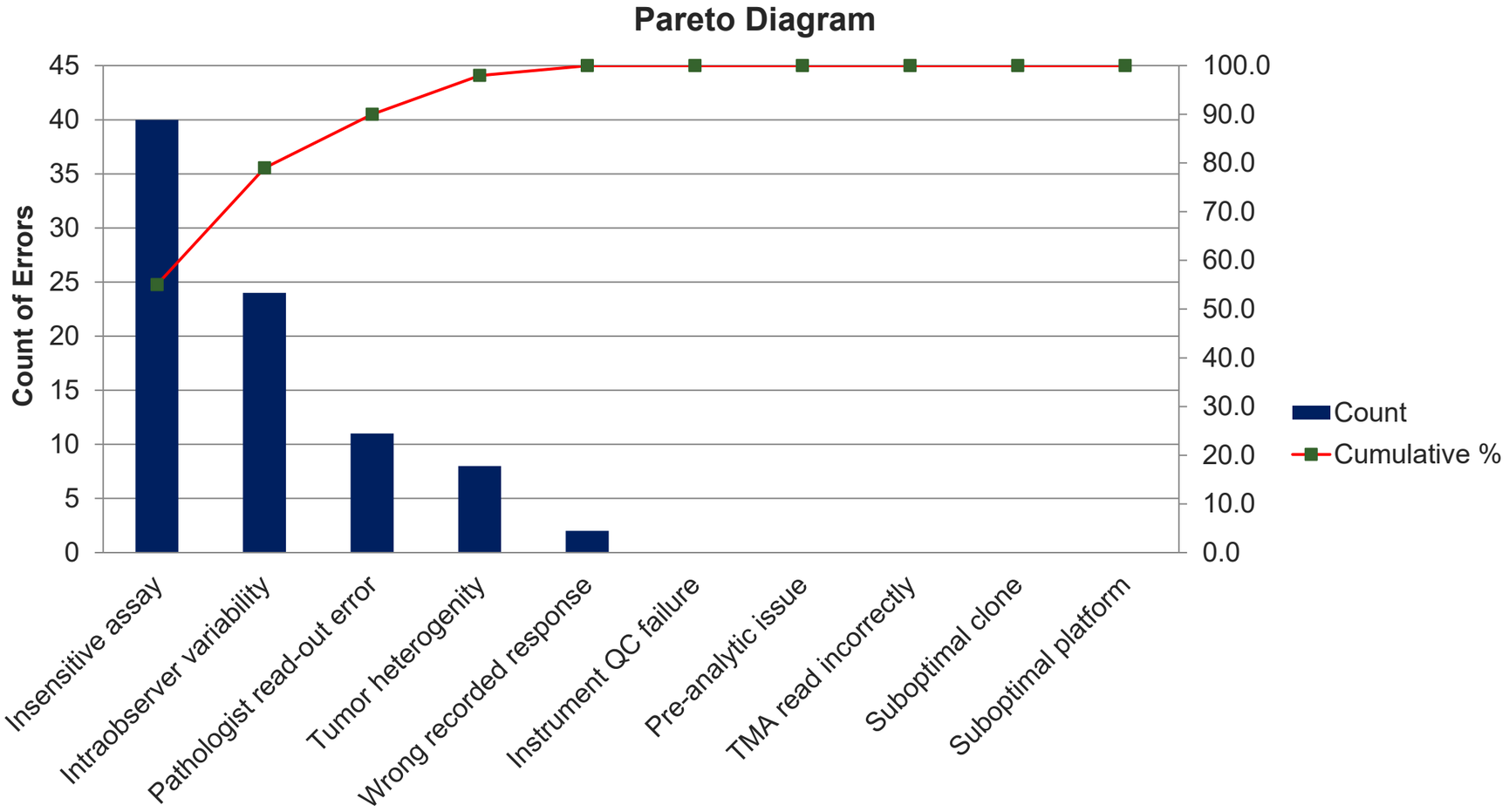
- If unacceptable responses fail to show a consistent trend or if there is not a known source of random variation in the laboratory, this suggests that analytic problems do not wholly explain the observed problem.
- If the majority of the intended responses trend in one direction, this may indicate that 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.



D5: Permanent Corrective Action (PCA)

Pareto diagram

- Visual representation of the percent of error assigned to each possible cause
- Vertical line is dropped from 80% of the cumulative percent curve to the x-axis
- Possible causes to the left of this vertical line account for 80% of the observed error and are considered most important to include in PCA.
- Possible causes to the right of this vertical line account for fewer than 20% of the observed error and are considered less important at this time.

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

Image source: https://www.istockphoto.com/vector/jumping-business-people-cheerful-company-employees-office-managers-team-event-men-gm1337421963-418312155

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

cap.org Reference: https://capatholo.gy/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

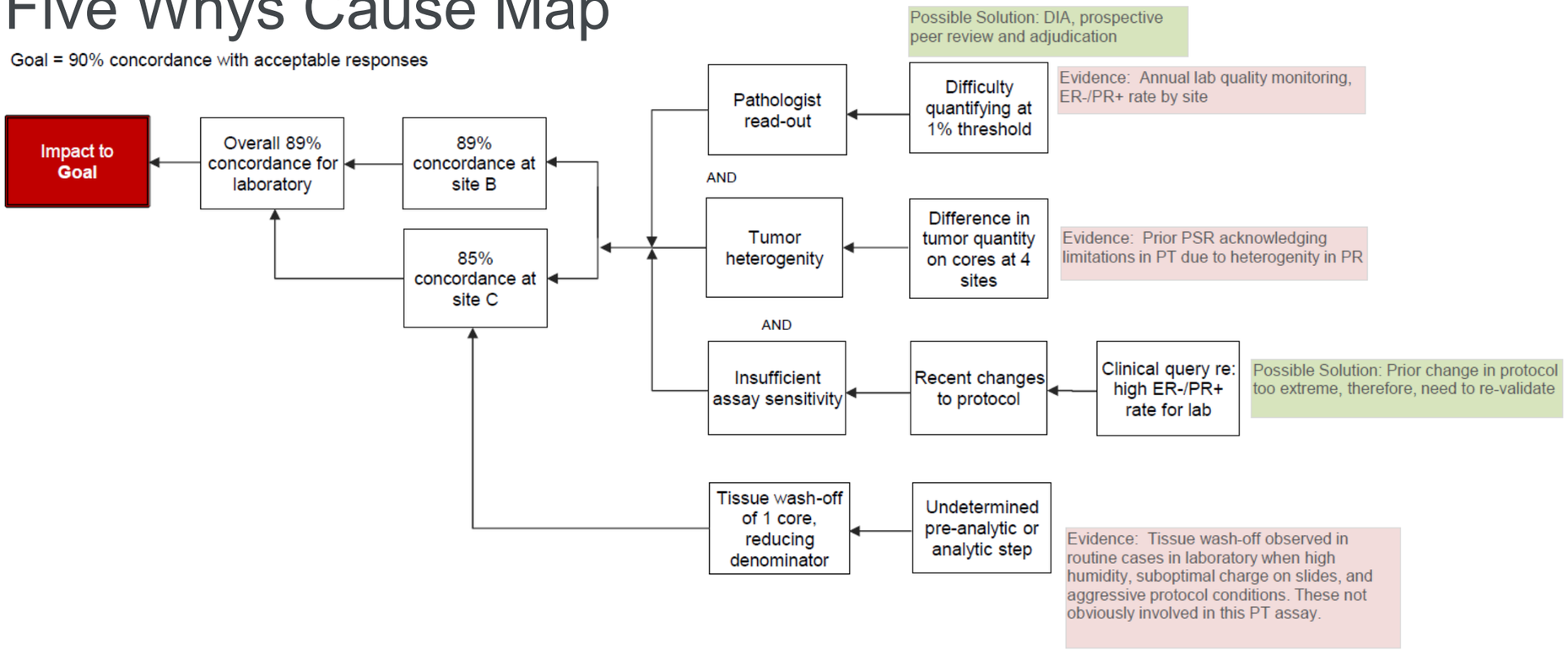
    AND
  - perform repeat testing of patient samples tested since the re-validated protocol was launched.

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

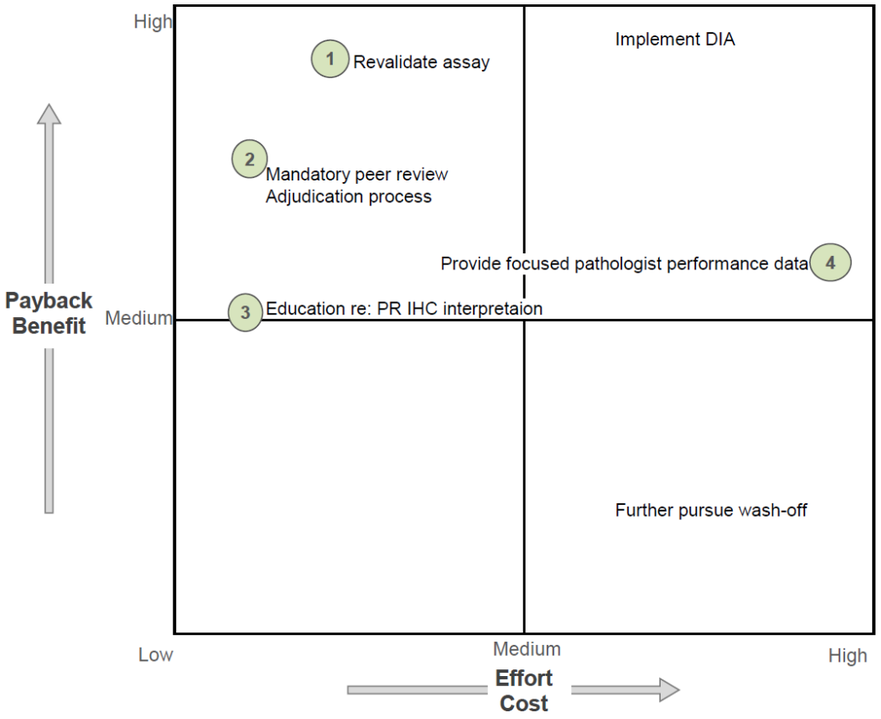
- TMA is re-reviewed.
- Submitted responses confirmed to reflect staining on the slide.
  - No clerical errors in response submission

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.

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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

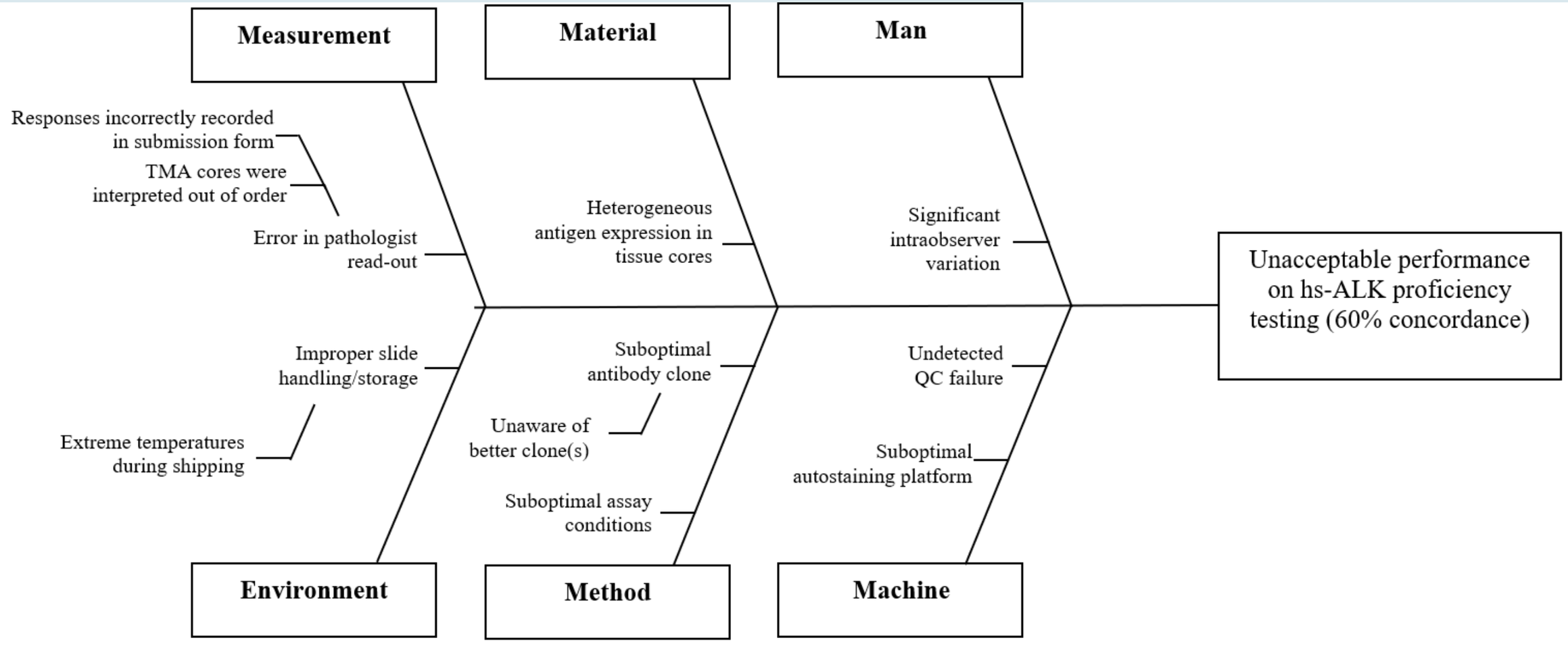
D1: Form a team

- 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



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

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Appendix – 8D Method Example for BRAF

cap.org Reference: https://capatholo.gy/3taBYah

Process Improvement Assessment Example for BRAF

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

D8: Closure and Team Celebration

- 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.

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Appendix – 8D Method Example for KIT

cap.org Reference: https://capatholo.gy/3taBYah

Process Improvement Assessment Example for KIT

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

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