Risk Mitigation in Breast Predictive Factor Testing

Elizabeth H Hammond MD

Risk Defintion

Risk is the opportunity for error, and risk of an inaccurate test result for the patient.

Goal is the right test on the right patient with the right result delivered at the right time.

Pathologist Responsibility

- Scope of risks in the laboratory is broad and complex
- Pathologists are responsible as directors for the quality of all testing in the laboratory
- Pathologists are responsible for risk mitigation even if they do not perform every step of the process
- Pathologist must lead the investigation of risks and mitigate them using appropriate tools and processes

Biomarker Testing Risks

- Preanalytic
  - Specimen misidentification
  - Cold ischemic time too long
  - Type of fixative (non-NBF)
  - Length of fixation too short/too long
  - Delay in grossing of fixed specimen
  - Failure to consider specimen exclusion and inclusion criteria

Biomarker Testing Risks

- Analytic
  - Specimen misidentification
  - Failure to properly validate or verify the assay
  - Failure to consider assay exclusion criteria
  - Improper antigen retrieval or antibody dilution
  - Improper use of internal or external controls
  - Improper detection system
  - Lack of ongoing monitoring

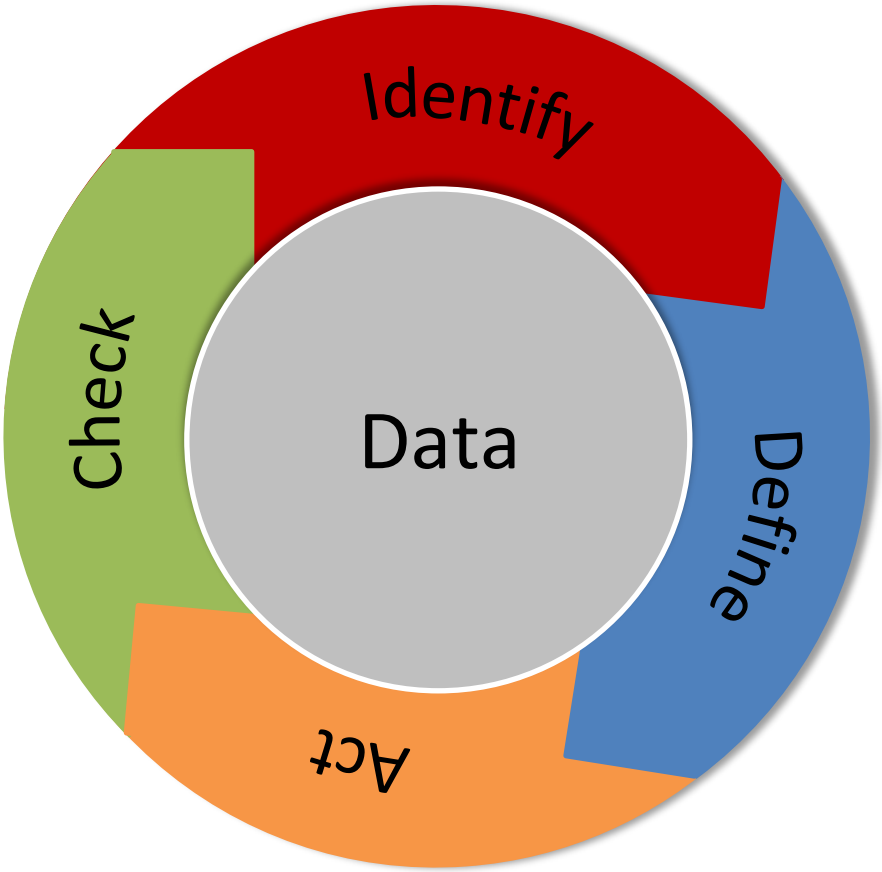
Biomarker Testing Risks

- Post analytic
  - Specimen misidentification
  - Improper threshold for assay interpretation
  - Variation in diagnostic criteria among pathologists
  - Confusion in reporting requirements
  - Reports missing critical information
  - Failure to investigate suspicious test results

Biomarker Testing Risks

- System Factors
  - Limited QA resources
  - Limited staff
  - Lack of standard SOPs
  - Lack of training and/or accountability for staff
  - Remote locations
- Human Factors

Risk Mitigation Process



Risk Mitigation Data

- Data is the best way to identify and define a problem specifically and convincingly
- Data will point the way to the most likely cause
- Data evaluated over time is valuable
  - Is the problem at one point in time or a persistent threat?
- Data will show you if the problem was solved by your intervention

Risk Mitigation Data

- Sources of BPFT Data
  - Pathology reports
  - Reports generated from pathology reports
  - Test results across populations
  - Data in the laboratory/QA monitors

Risk Mitigation Data

- Where/how do you get the data?
  - Data needs to be generated/created from existing sources.
  - Start by figuring out what you need to know and where that information is located.
  - Sometimes information you need is not available because it's not being recorded. Information needs to be recorded first.

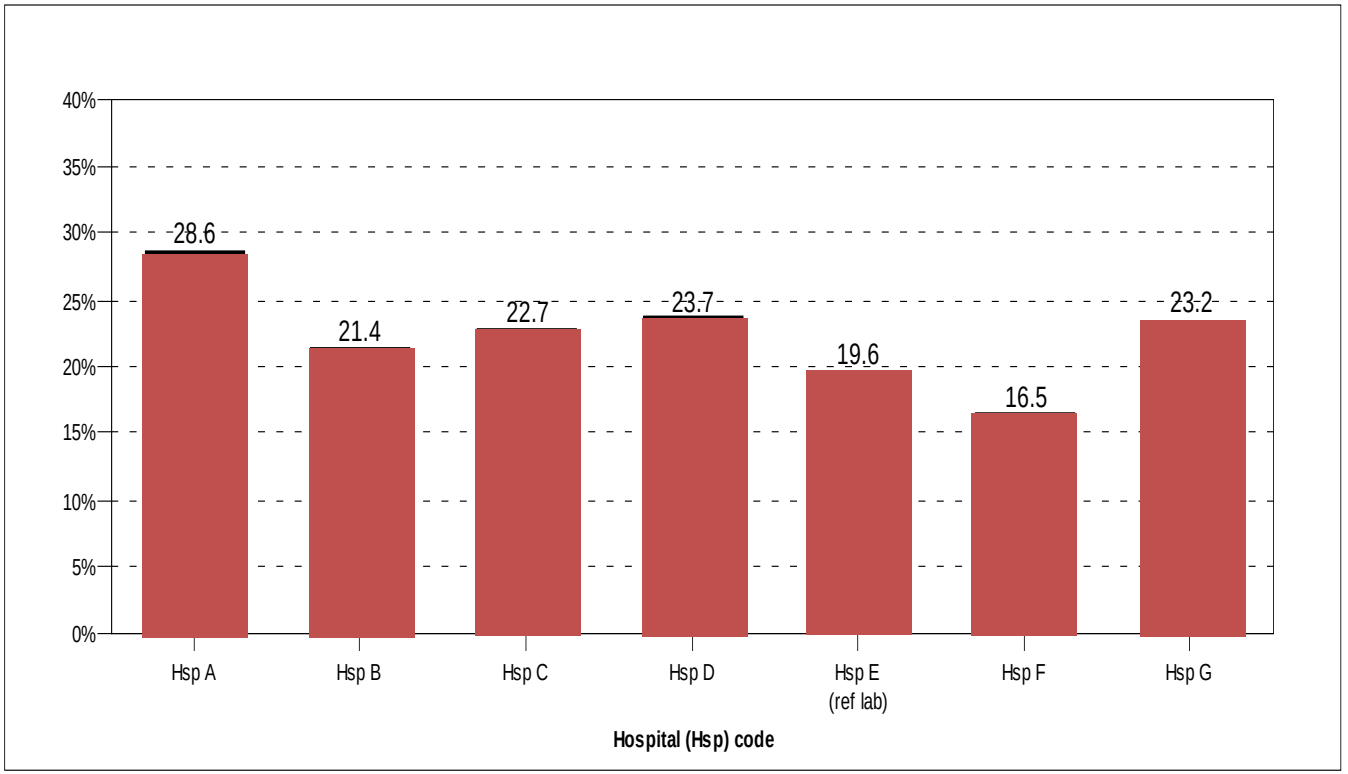
Example

- Surgeon presents case of metastatic carcinoma in the liver in 58 year-old woman with IDC 2 years before called ER negative
- Repeat ER on liver is ER positive
- Patient was never treated with Tam or AI
- Repeat on original resection still negative, but so are intrinsic controls
- Why?
- How can this be avoided in the future?

Data Example

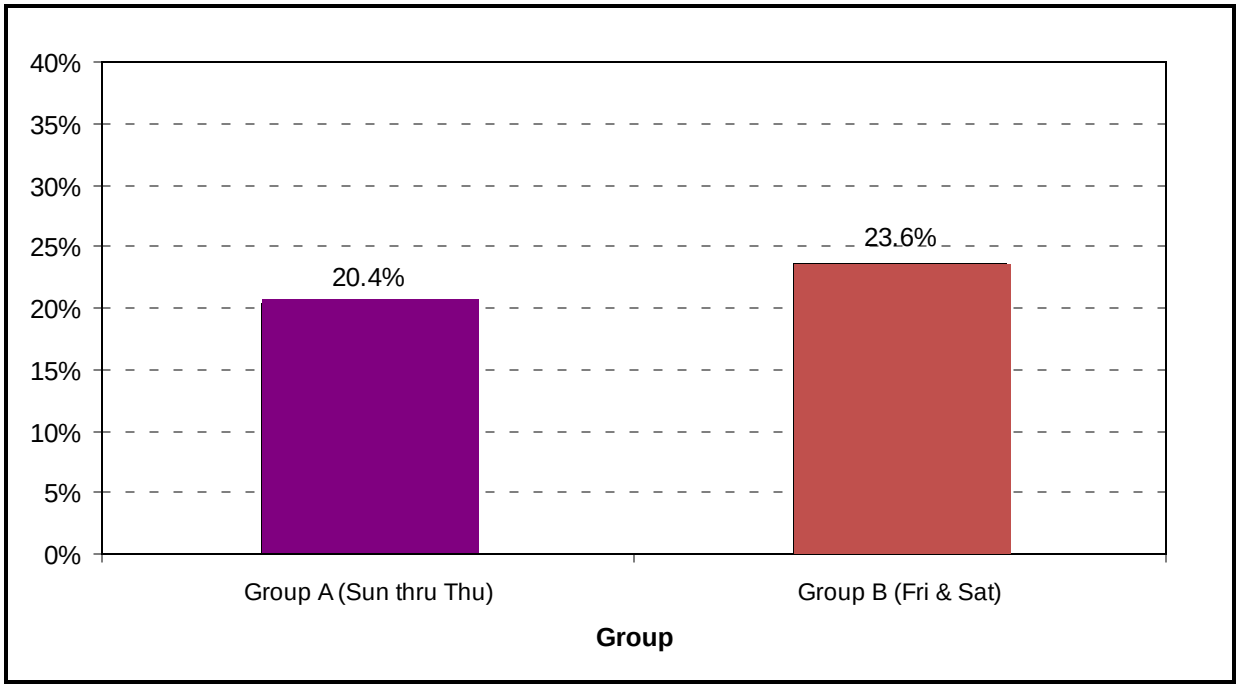
- How common is the risk mitigation issue?
  - We conducted retrospective study of all ER negative cases by day of week and processing site.
  - All ER testing done in one place by one staff.
  - Only variation was specimen handling.
- What are potential causes?
- What should be done to mitigate the issue?

ER Negative Rate by Hospital of Origin



Mean value=20.9% Age adjusted MH p value=0.05

ER Neg Rate by Day of Surgery



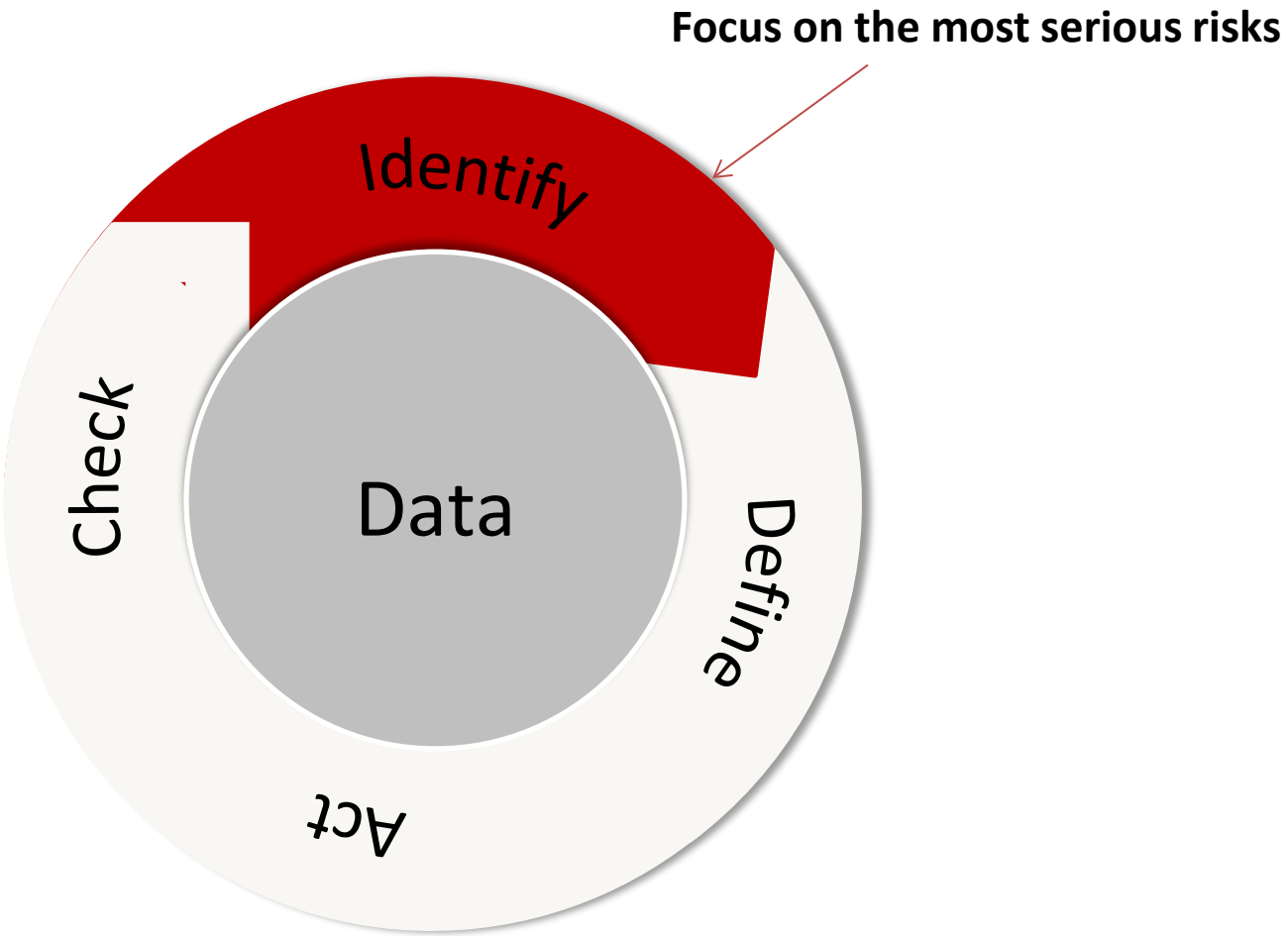
Group A: Surgery Sunday thru Thursday, any hospital
Group B: Surgery Friday thru Saturday, any hospital
Age adjusted MH test p value= 0.038

Nkoy et al, SABC, 2005 and Archives, 2010

Conclusion

- The study led them to realize that what really happened in each place or on each day could not be defined because there was no data.
- Conducted prospective study to define the potential causes by asking sites to record:
  - Time of tumor removal
  - Time of tumor to grossing station
  - Length of Time in fixative
  - Fixation duration
- 2 of 5 sites were willing to conduct the study

Risk Mitigation Process



Risk Process: Identify

- In our example, a risk was identified via the patient with a metastatic carcinoma in her liver that was ER positive.
- Preferred methods for identifying risks include:
  - Monitoring your lab's test results and data using established benchmarks.
  - Evaluating your lab's SOPs against external standards such as ASCO-CAP Guidelines and inspection checklists.
  - Monitoring test results by pathologist.

Risk Process: Identify

Steps	Tools & Resources
1. Analyze current data and trends	• Trend analysis • PT data
2. Evaluate current processes	• Flow-charting • Inspection reports • Checklists (LAP) • Guidelines
3. Locate gaps between current state and desired state	• Established Benchmarks • Checklists (LAP) • PT data • Guidelines

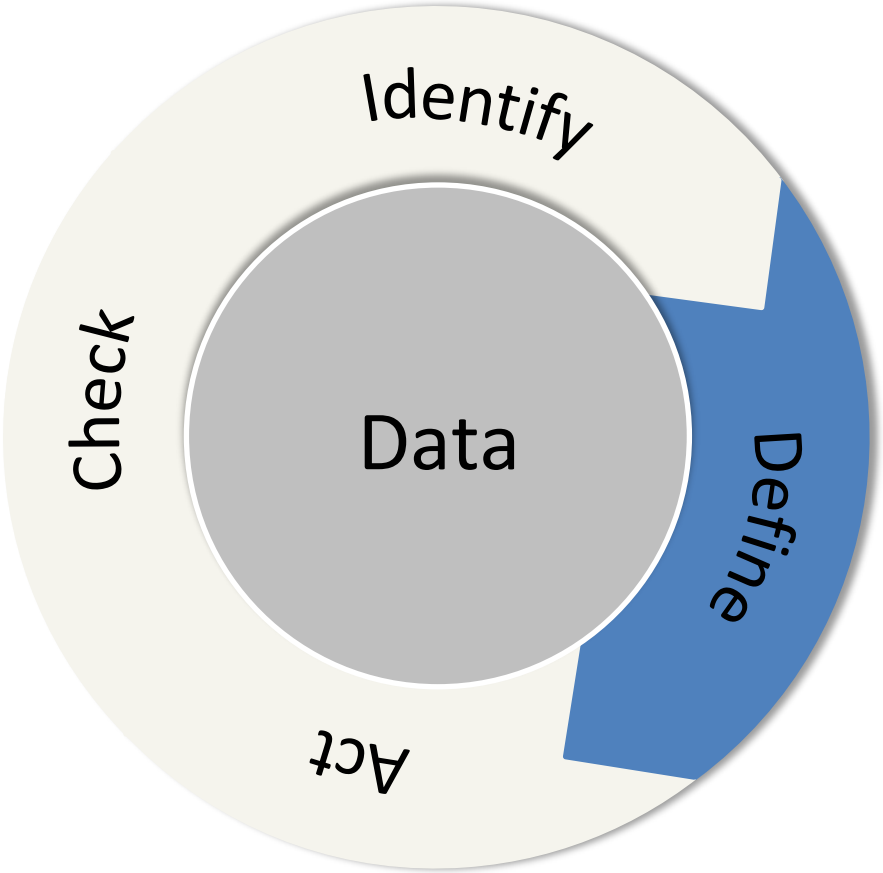
Risk Process: Identify Using ER/ PgR Benchmarks

- Overall Benchmark ER negative rate <30%
  - **Age 65+ benchmark: ER negative rate <20%**
  - **Low-grade carcinoma benchmark: ER positive rate >95%**
- Concordance with PR benchmark: PR rate typically 10-15% lower than ER.
- Follow PgR positive, ER negative results. Should be 1-3%.

Risk Process: Identify Using HER2 Benchmark

- Overall Benchmark HER2 positive rate: 12-18%
  - If ≥20% positive: correlate with histologic type, demographic factors, ER/PR status
  - If less than 10% positive: correlate with histologic type, demographic factors, ER/PR status
- No good benchmark for HER2 equivocal results
- Concordance with FISH benchmark: ≥95% for positive and negative results

Risk Mitigation Process



Define Risks

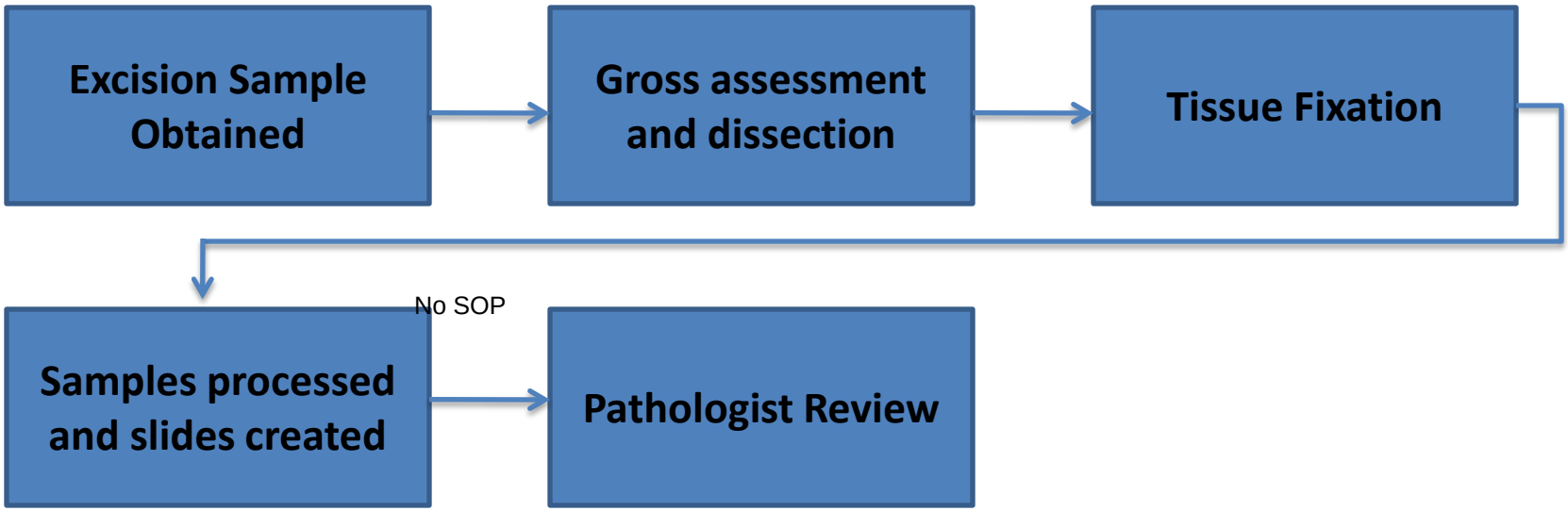
- In the example, the risk of false ER negative results was further defined by analyzing past data of all ER negative cases by day of week and processing site.
- Important data points included:
  - Facility
  - ER result
  - Patient Population (analyze for stage and grade of the disease and age of the patient)
  - Grossing protocols (different at each location)
  - Day tissue was removed from patient

Note: Time to fixation and length of fixation data was not available but are important considerations

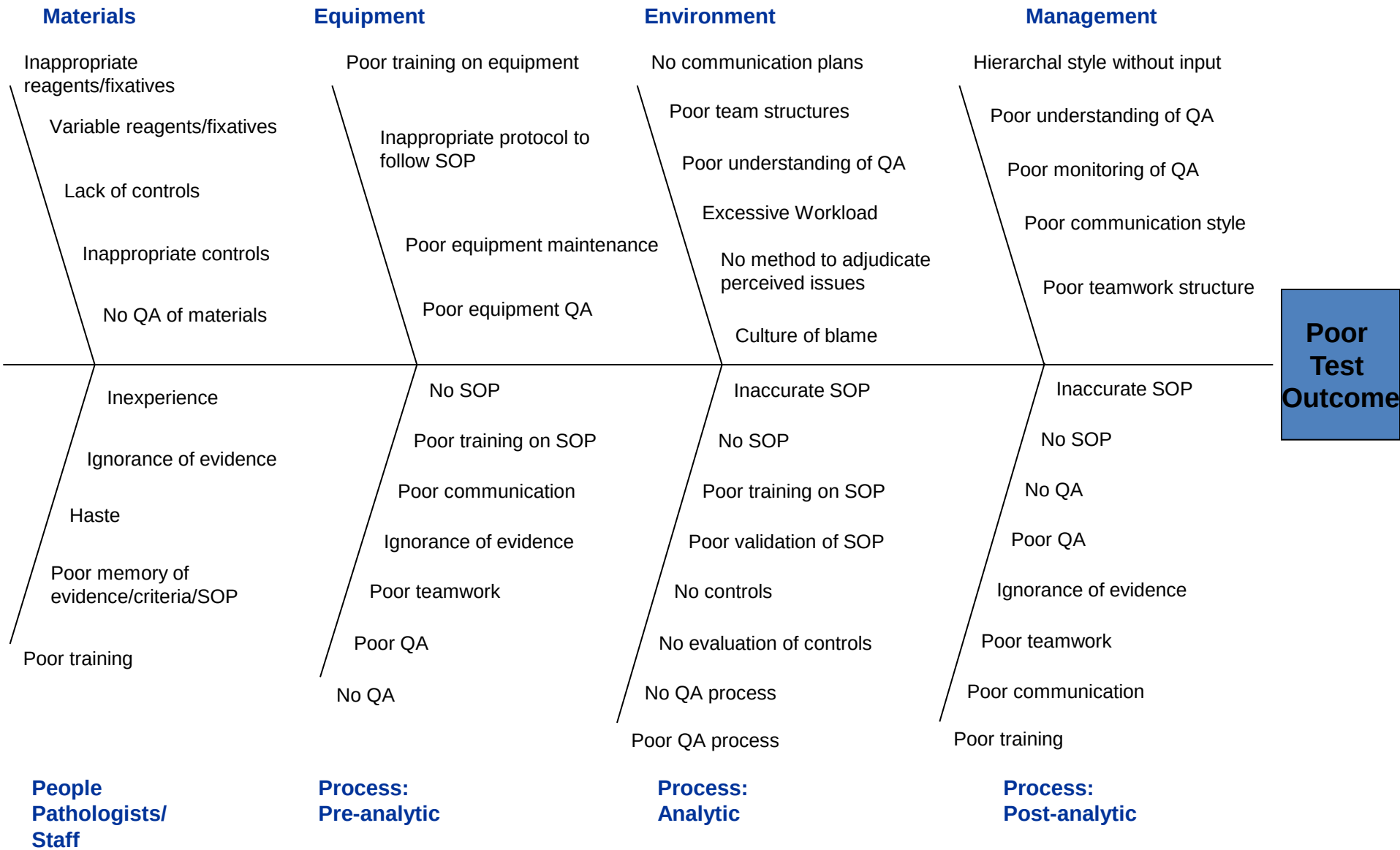
Risk Mitigation Process: Define

Steps	Tools & Resources
1. Brainstorm potential causes of identified risks	• Affinity diagram • Cause and Effect/Fishbone diagram • Flow-charting
2. Define nature and scope of the risk or problem	• Data analysis
3. Determine source (root cause) of the risk or problem	• Data analysis

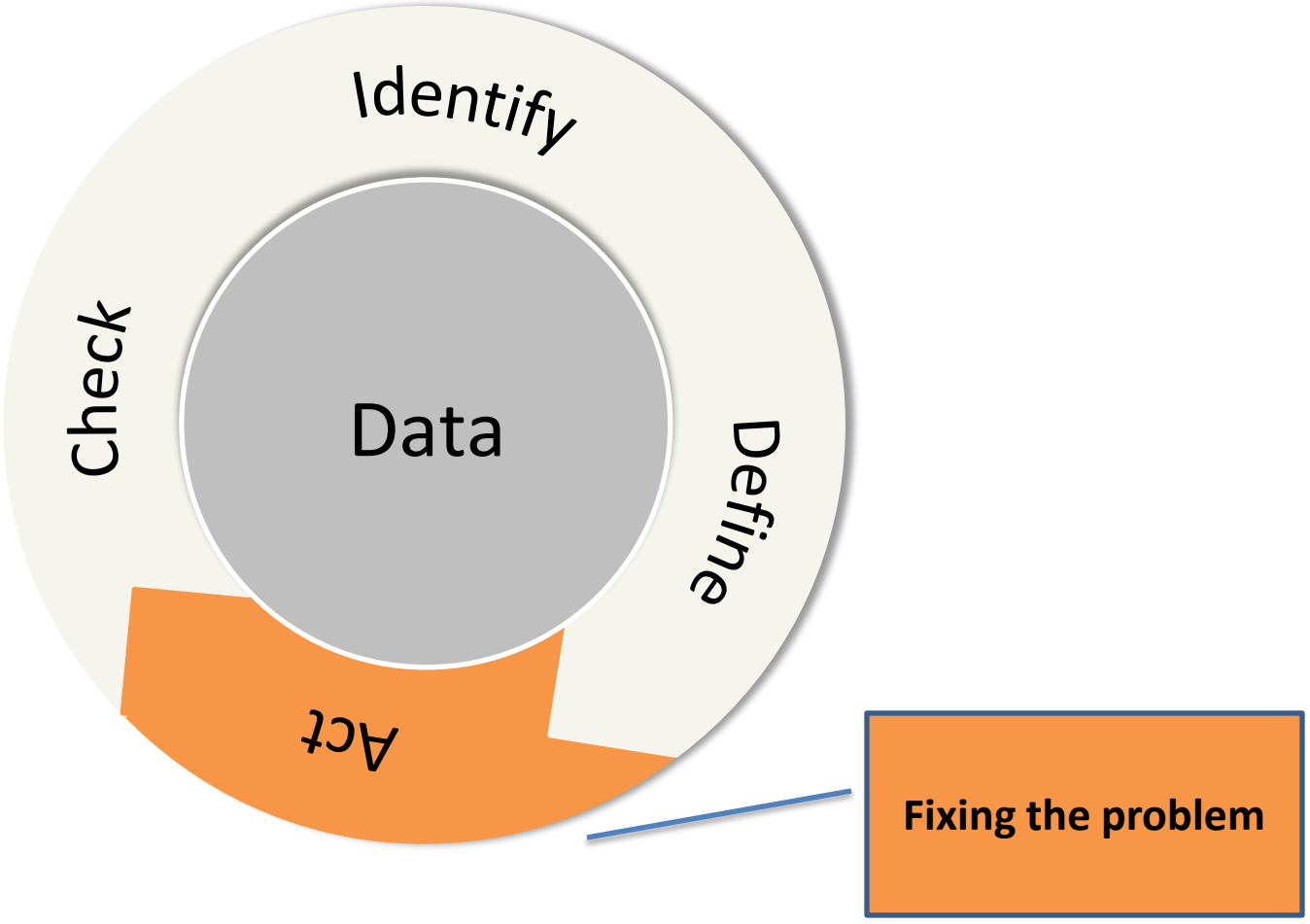
Risk Mitigation Process: Define Tool: Process Flow Charting



Tool: Cause and Effect Diagram (Fishbone)



Risk Mitigation Process



Act on Risks

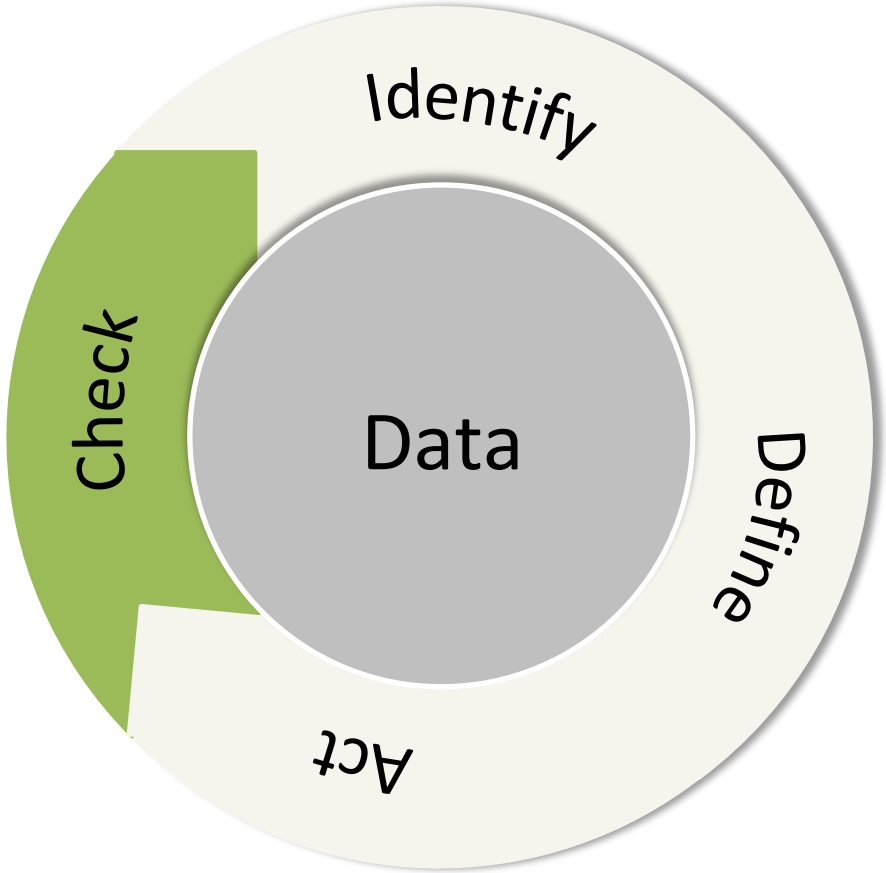
- In the example, the prospective study which asked sites to record fixation time points created an effective intervention. ER negative rate was reduced.
- Acting on risks must address the root cause of the problem and can include:
  - Process adjustments
  - Revisions to SOPs
  - Training and education of surgical staff, grossing room staff, data clerks and pathologists
- Start simple: Try to come up with the most simple intervention to start, sometimes the best solutions are simple ones.

Act on Risk: Workflow Standardization

- Breast specimen workflow standardization at Intermountain Healthcare led to simplification:
  - OR staff came to a more standard way of handling breast cancer samples that made everyone's life easier and decreased cold ischemic time.
  - Grossing room changed process to the specimen being immediately cut in.
  - Specimen radiographs not sent to a separate facility.

Risk Mitigation Process

Making sure the problem was fixed and stays fixed



Check (Hold the Gain)

- After 1 year, the results were measured:
  - At measuring sites, the mean time to fixation (cold ischemic time) was 18 minutes
  - PR negative rate was significantly lower and ER negative rate was also lower at measuring sites
  - FISH testing showed decrease of 10% in specimens requiring repeat testing

Check (Hold the Gain)

- Process changes may not be durable and reminders are needed of the importance.
- New errors and risks may be discovered which require initiation of new efforts.
- Staffing, equipment or process changes may alter circumstances and promote new errors.
- Ongoing monitoring is *always needed*.

Risk Mitigation Process: Check

Steps	Tools & Resources
1. Use iterative cycles to collect feedback and make adjustments	• Regular team meetings • Trend analysis
2. Share progress and data with stakeholders	• Presentations to stakeholders
3. Look for broader applications of successful improvements	• Publish your results so others will have access to the information

Ongoing Monitoring

- Not a formal process
- ASCO/CAP recommends monitoring every 6 months
- Periodic monitoring using CAP IHC surveys and external QC

Ongoing Monitoring ER/PgR

Monitor positive and negative rates

- Overall Benchmark ER- rate: <30%
  - If ≥30%: correlate with histologic type, demographic factors
    - **Age 65+ benchmark ER- rate: <20%**
      - **If ≥20%: re-validate assay**
    - **Low-grade carcinoma benchmark ER+ rate: >95%**
      - **If ≤95%: revalidate**

Monitor concordance with PR. PR rate typically 10-15% lower than ER.

Monitor and document successful external Proficiency Testing

Monitor pathologist interpretative competence (use CAP surveys or internal validation sets)

Ongoing Monitoring for HER2

Monitor positive and negative rates

- Overall Benchmark HER2+ rate: 12-18%
  - If ≥20%: correlate with histologic type, demographic factors, ER/PR status
- No good benchmark for HER2 equivocal results

Monitor concordance with FISH (optional): benchmark ≥95% for positive and negative results

Monitor and document successful external PT

Monitor pathologist interpretative competence

Proficiency Testing

- Easier than validation - different standard
  - 90% concordance expected
- Can be based on interlaboratory testing
- Currently recommended for all prognostic/ predictive markers
- Will ultimately be required for all markers ('regulated' PT for high complexity tests)

Interpretive Competency Assessment

- ASCO/CAP Guidelines place the burden of interpretive competency assessment and documentation on the Laboratory Director
- Each pathologist who reads and reports a given prognostic/predictive marker must be objectively assessed for:
  - Knowledge and use of interpretive criteria
  - Concordance with consensus or standard interpretation - 95% (minimum 40 slide set using selection criteria for initial test verification)
  - Adherence to reporting requirements
  - Reproducibility (testing every 6 months)

Interpretive Competency Assessment

- Appropriate assessment tools:
  - Consensus standards
  - PT materials
  - Validated in-house sample sets
  - Extramural validation samples
- Appropriate scoring standards:
  - Concordance with consensus interpretation
  - Comparison with original interpretation
  - Objective outside review
- Image analysis can facilitate the competency assessment

Summary

- No prognostic or predictive marker should be used without
  - *Technical verification or validation*
  - *Ongoing monitoring*
  - *Laboratory proficiency*
  - *Interpretative competence*
- Pathology practice should be biased towards use of validated markers, unless the assay is part of a clinical trial or research study for which the patient has granted permission