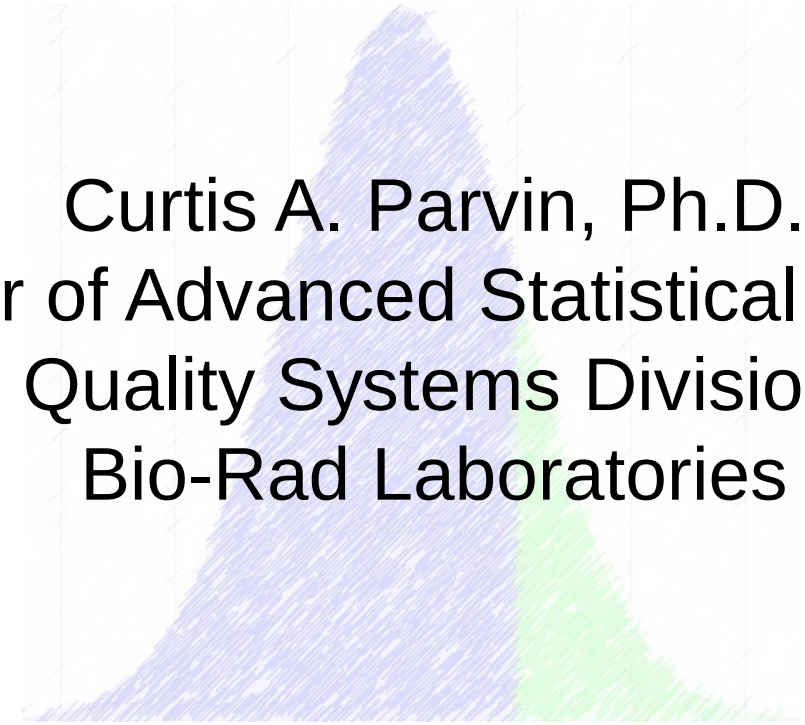
Linking QC Performance to Patient Risk



Curtis A. Parvin, Ph.D.
Manager of Advanced Statistical Research
Quality Systems Division
Bio-Rad Laboratories

Learning Objectives

- Discuss the importance of a “patient risk” approach to QC planning
- Describe the elements of a QC system that impact patient risk
- Identify the ways in which labs can reduce patient risk with QC
- Analyze the relationship between QC performance and patient risk

Laboratory Medicine

- Goal: To improve patient health
- Tools: Laboratory tests
- Mechanism: Support medical decisions
  - Produce accurate results
  - Minimize patient risk

Risk Management Principles

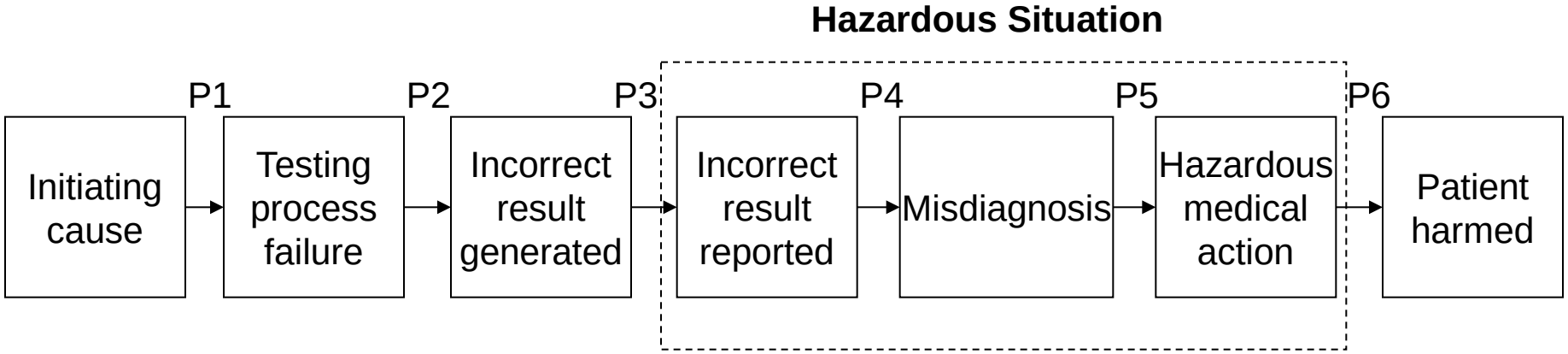
- Risk management guidelines for the laboratory
  - ISO 15189: Medical laboratories – Requirements for quality and competence
  - ISO 14971: Medical devices – Application of risk management to medical devices
  - CLSI EP23: Laboratory quality control based on risk management

Risk Management Principles

- Risk management provides a formal approach to
  - Identify potential failure modes in the lab
  - Rank identified failure modes in terms of their patient risk
  - Establish policies and procedures to prevent or reduce (mitigate) the risks
  - Focus on the highest ranked risks
- Patient risk is defined as the combination of
  - The probability of occurrence of patient harm
  - The severity of patient harm

EP23-A: Probability of Patient Harm

Sequence of Events Creating Risk of Harm for a Patient (Example)



CLSI EP23, Figure 6

Probability of Patient Harm

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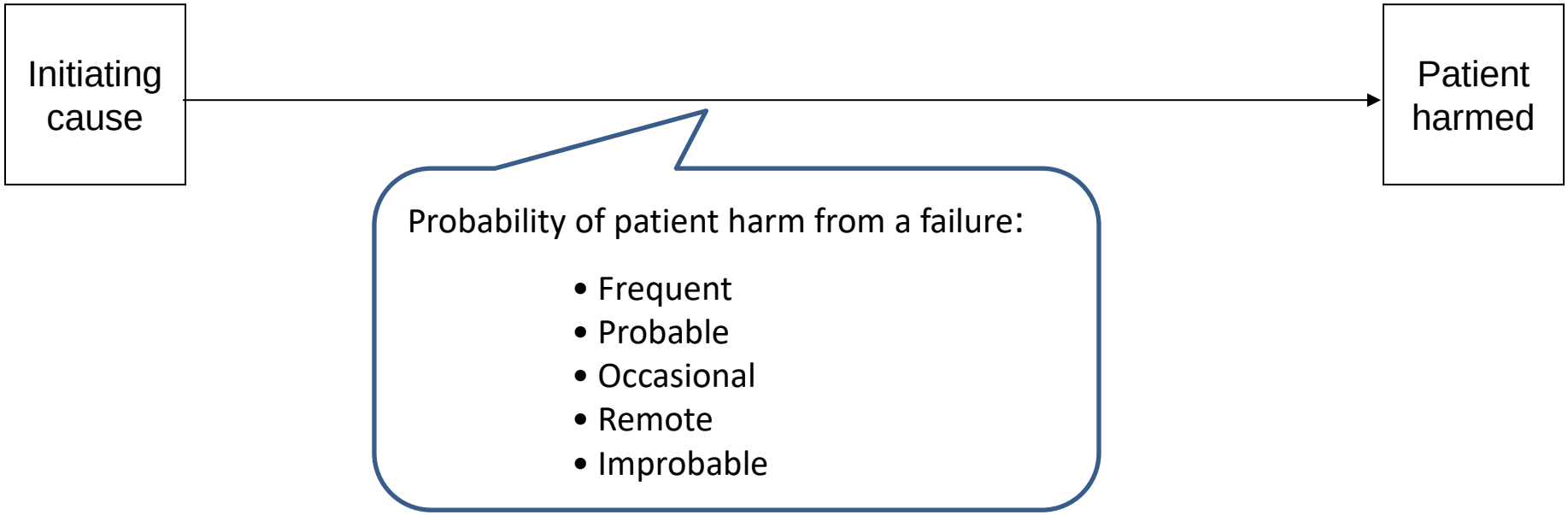

Probability of Harm Categories

Category Level	CLSI EP23 Example	ISO 14971 Example
Frequent	Once/week	≥1/1,000
Probable	Once/month	<1/1,000 and ≥1/10,000
Occasional	Once/year	<1/10,000 and ≥1/100,000
Remote	Once/few years	<1/100,000 and ≥1/1,000,000
Improbable	Once/life of measuring system	<1/1,000,000

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If lab averages 100 analyte results per day

1/(100*365) = 1/36,500

Probability of Harm Categories

Category Level	CLSI EP23 Example	ISO 14971 Example
Frequent	Once/week	≥1/1,000
Probable	Once/month	<1/1,000 and ≥1/10,000
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Remote	Once/few years	<1/100,000 and ≥1/1,000,000
Improbable	Once/life of measuring system	<1/1,000,000

If lab averages 20 analyte results per day

1/(20*365) = 1/7,300

Severity of Harm

- Severity of harm is described in terms of the severity of the consequence to the patient
- Severity of harm depends on
  - Analyte
  - Patient care situation

Severity of Harm Categories

- Both ISO 14971 and CLSI EP23 give the same example severity of harm categories
  - Negligible = inconvenience or temporary discomfort
  - Minor = temporary injury or impairment not requiring professional medical intervention
  - Serious = injury or impairment requiring professional medical intervention
  - Critical = permanent impairment or life-threatening injury
  - Catastrophic = patient death

EP23-A Risk Acceptability Matrix

	Severity of Harm				
Probability of Harm	**Negligible**	**Minor**	**Serious**	**Critical**	**Catastrophic**
Frequent	Unacceptable	Unacceptable	Unacceptable	Unacceptable	Unacceptable
Probable	Acceptable	Unacceptable	Unacceptable	Unacceptable	Unacceptable
Occasional	Acceptable	Acceptable	Acceptable	Unacceptable	Unacceptable
Remote	Acceptable	Acceptable	Acceptable	Acceptable	Unacceptable
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ISO 14971 - Risk Acceptability Matrix

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Probability of Harm	**Negligible**	**Minor**	**Serious**	**Critical**	**Catastrophic**
Frequent	Unacceptable	Unacceptable	Unacceptable	Unacceptable	Unacceptable
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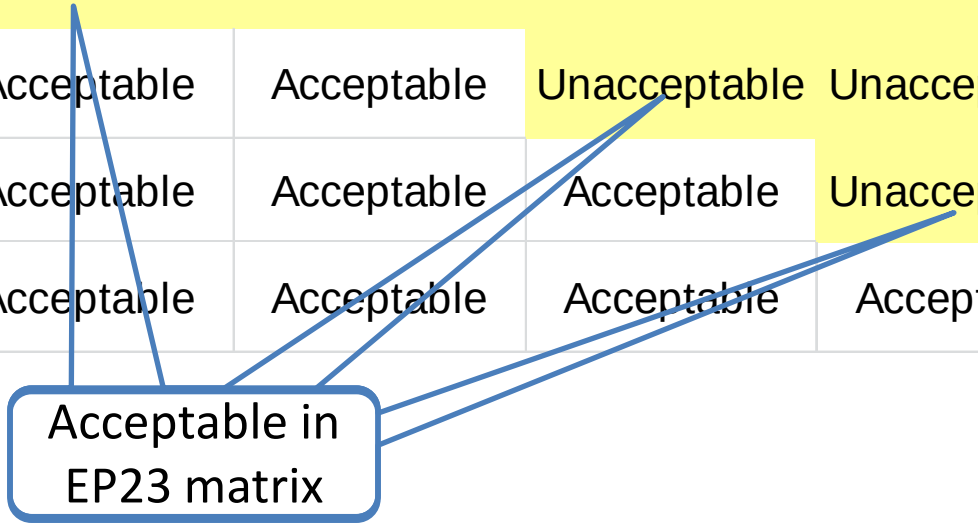

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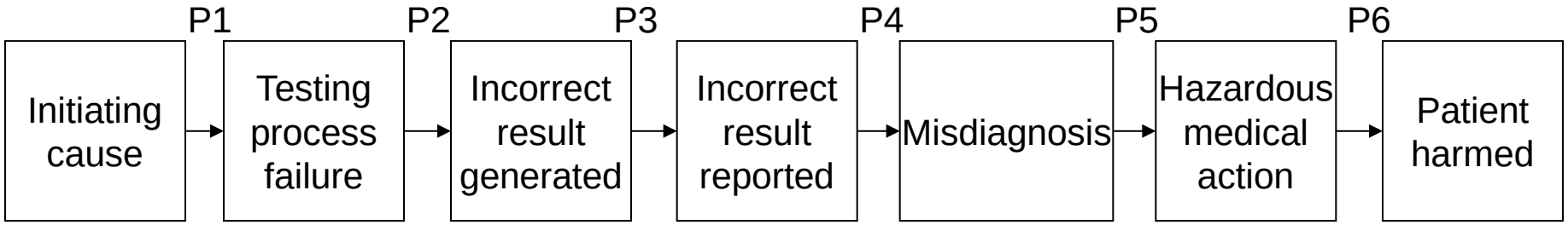
Probability of Patient Harm

Sequence of Events Creating Risk of Harm for a Patient



Probability of Patient Harm

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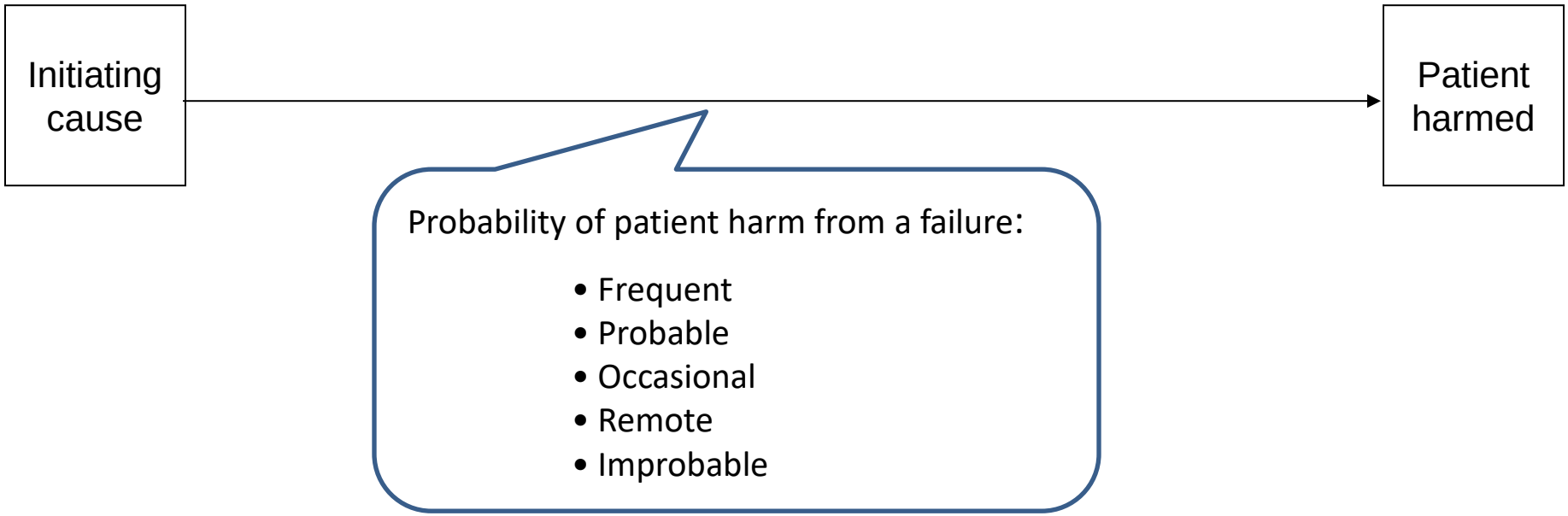
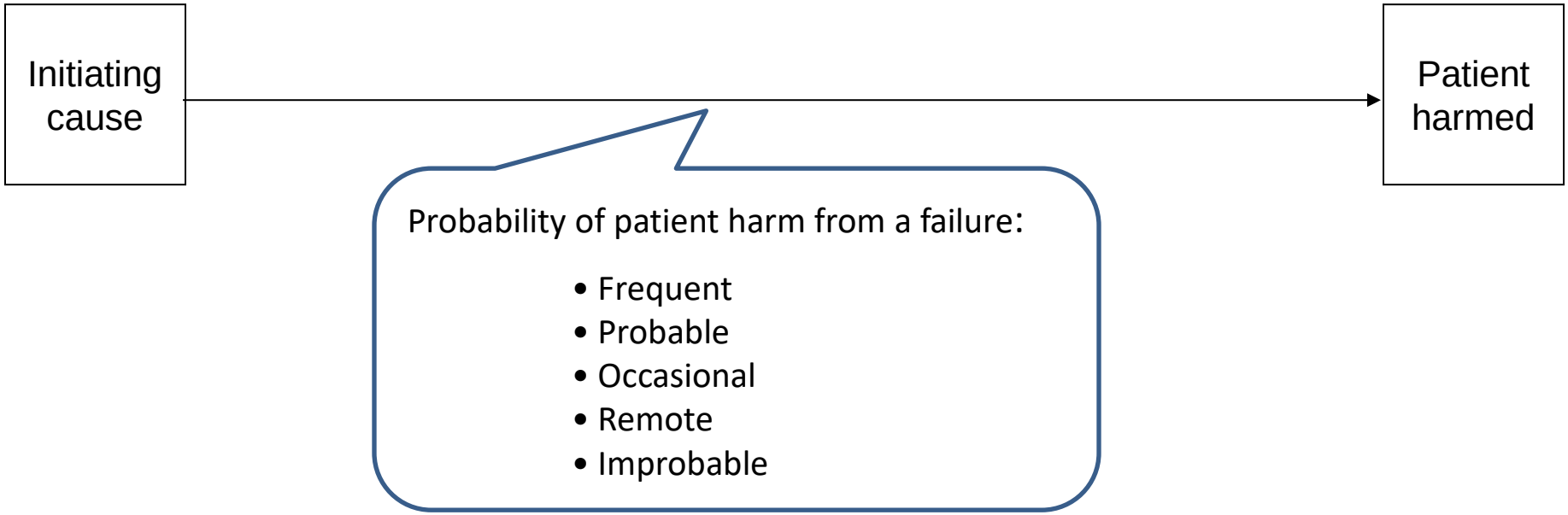


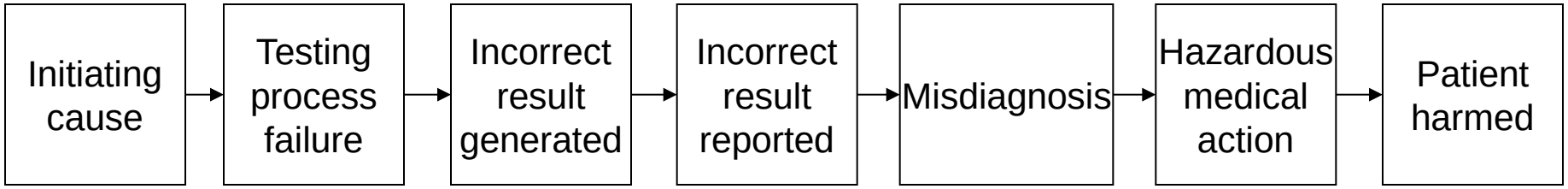
Probability of Patient Harm

Sequence of Events Creating Risk of Harm for a Patient

We should be able to do better than this!



Predicting Probability of Patient Harm



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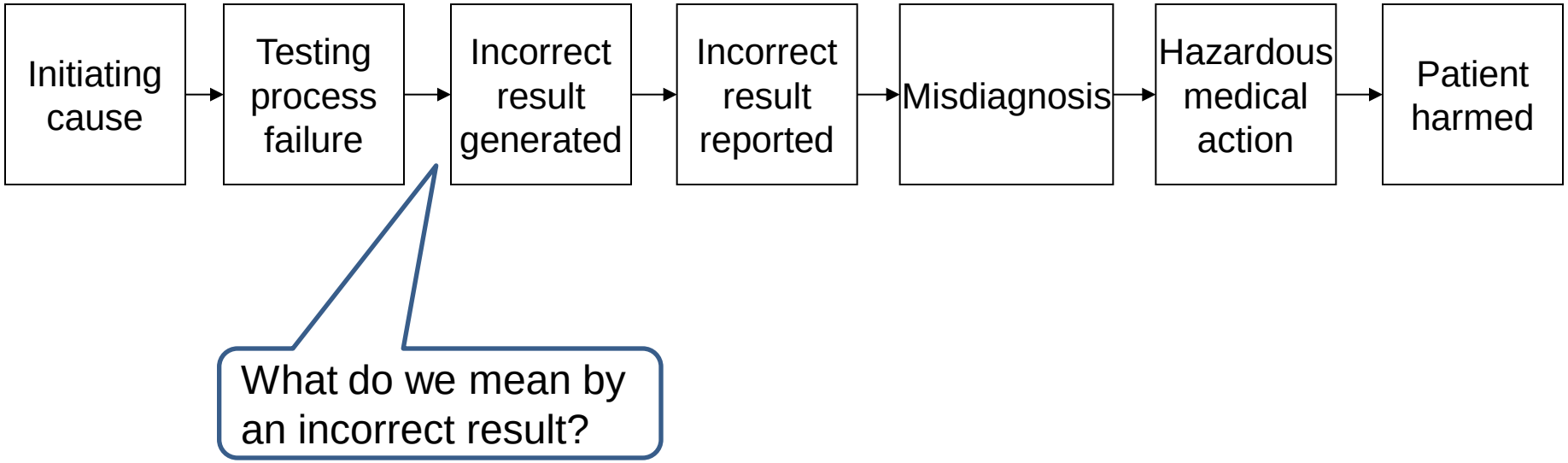
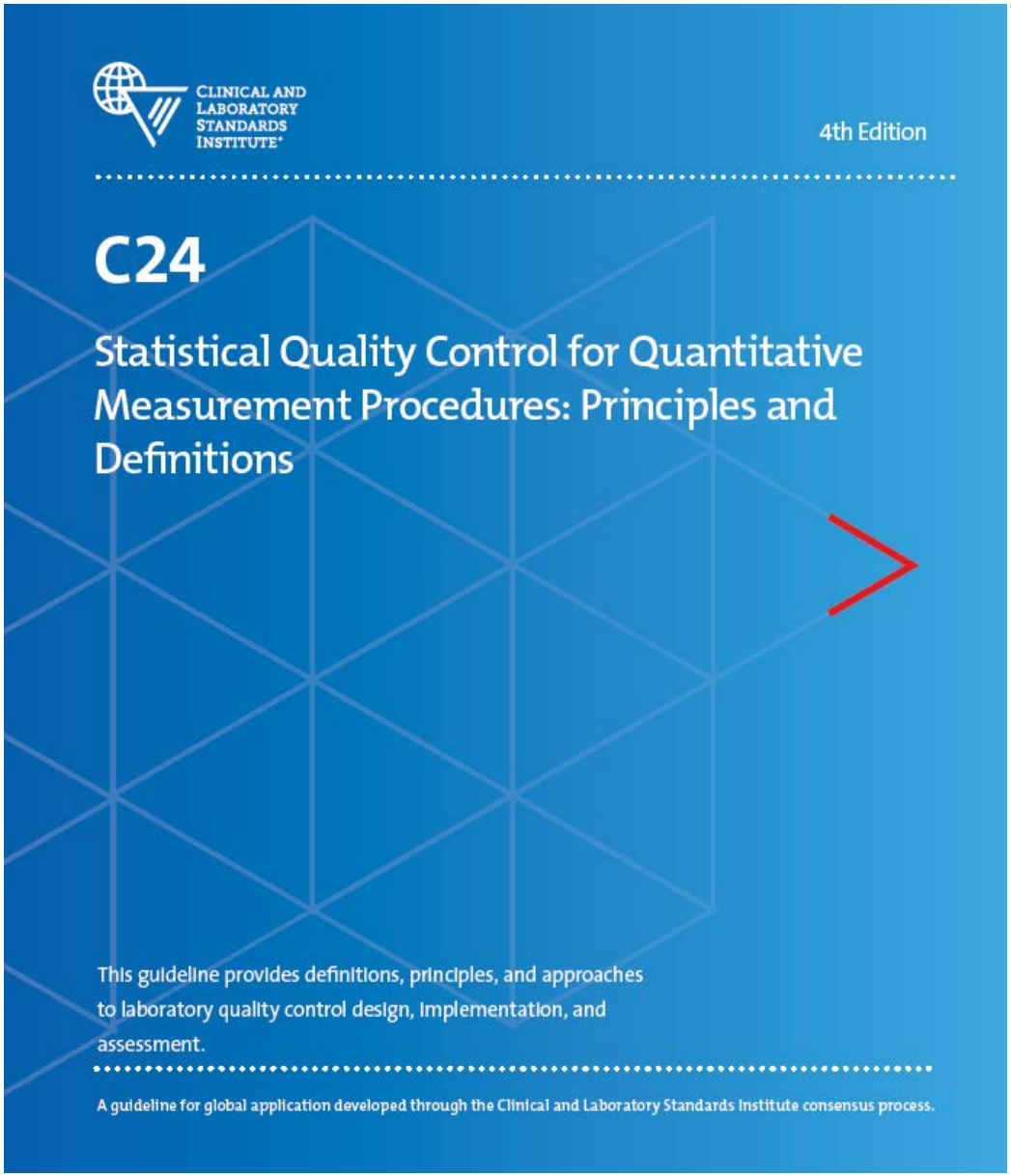


The Quality Required of Patient Results

- ISO 15189 Clause 5.6.1: *Laboratory QC should assure that patient results meet the quality required for their intended use*
- The quality of a patient result depends on the difference between the correct value and the value reported.
- If the error in a patient's result exceeds the allowable total error (TE_a) the result is considered **erroneous** (incorrect, unacceptable) and creates a hazardous situation for the patient.

CLSI C24, 4th Edition



CLSI C24, 4th Edition

C24, 4th ed.
September 2016
Replaces C24-A3

Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions

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Abstract

Clinical and Laboratory Standards Institute guideline C24—*Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions* discusses the principles of statistical QC, with particular attention to the planning of a QC strategy and the application of statistical QC in a medical laboratory. Although these principles are of interest to manufacturers, this guideline is intended for use by medical laboratory personnel in order to provide a QC strategy that uses control materials that are external to a reagent kit, instrument, or measuring system and that are intended to simulate the measurement of a patient specimen.

CLSI C24, 4th Edition: Definitions

analyte – constituent of a sample with a measurable property[13]; **NOTE:** In "mass of protein in 24-hour urine," "protein" is the analyte and "mass" is the property. In "concentration of glucose in plasma," "glucose" is the analyte and "concentration" is the property. In both cases, the full phrase represents the measurand.[13]

bias (of measurement) – estimate of a systematic measurement error[12]; difference between the expectation of a test result or measurement result and a true value[14]; **NOTE 1:** In practice, the accepted reference value is substituted for the true value[14]; **NOTE 2:** Bias represents the quantitative expression of trueness.

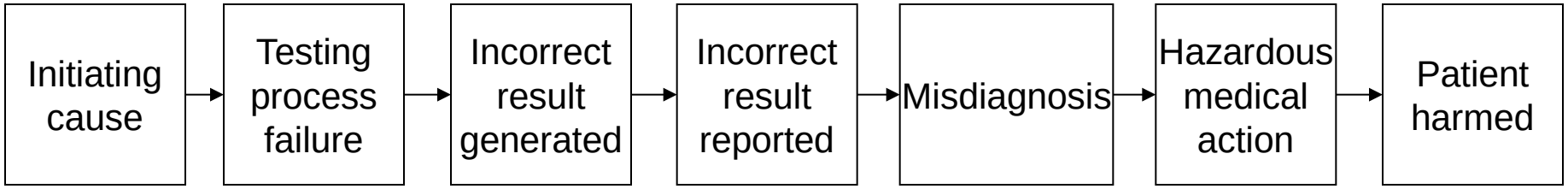
coefficient of variation (CV) – (positive random variable) standard deviation (SD) divided by the mean[15]; **NOTE 1:** The CV is commonly reported as a percentage[15]; **NOTE 2:** The predecessor term "relative SD" is deprecated by the term CV.[15]

control limit – the most extreme value of a quality control material that is still considered to be acceptable.

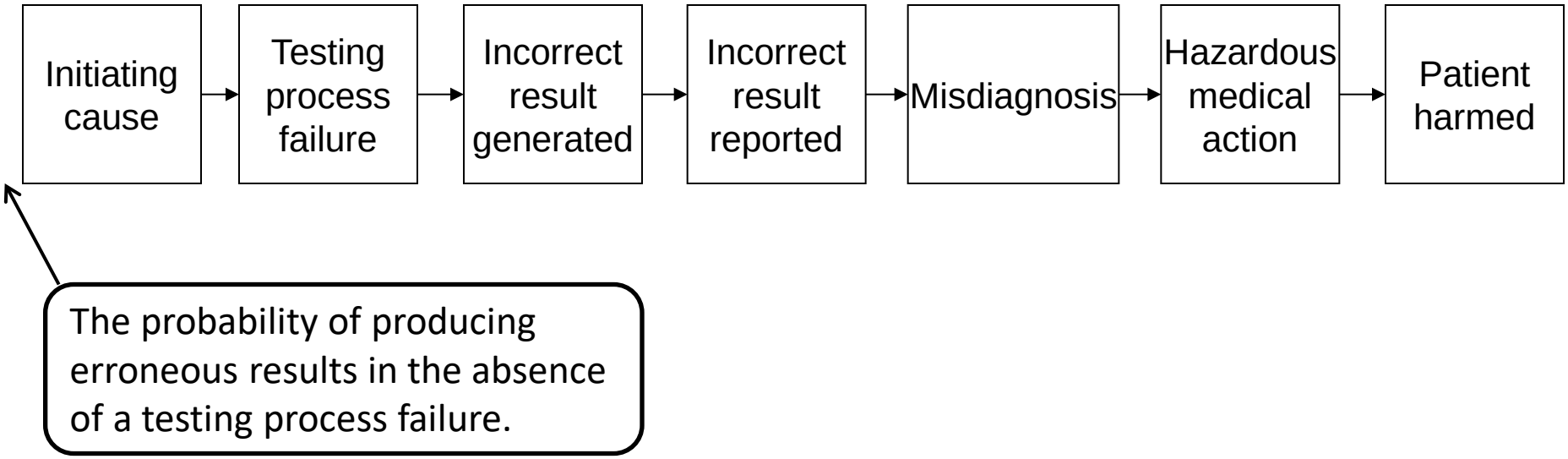
erroneous result – a patient result that fails its quality requirement; **NOTE 1:** The quality requirement is usually expressed in terms of an allowable total error (TEa) requirement. If the measurement error in a patient's result exceeds the TEa requirement, the result is erroneous; **NOTE 2:** May also be referred to as an incorrect result or an unacceptable result.

error (of measurement) – measured quantity value minus a reference quantity value[12]; **NOTE 1:** The concept of "measurement error" can be used both a) when there is a single reference quantity value to

Predicting Probability of Patient Harm



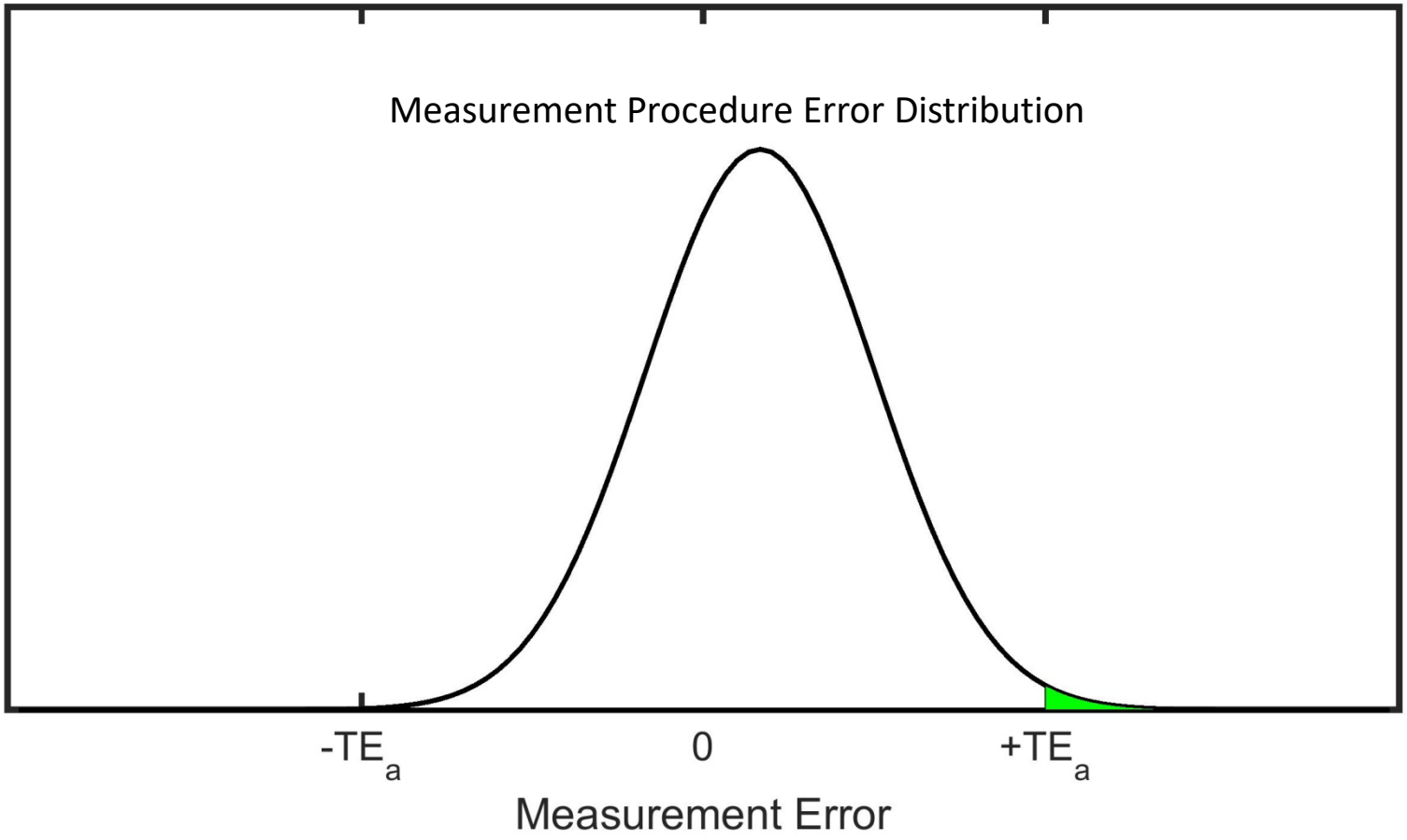
Predicting Probability of Patient Harm



Probability of Erroneous Results in the Absence of a Testing Process Failure

- The probability of producing erroneous results in the absence of a testing process failure can be computed based on;
  - a measurement procedure's bias and imprecision
  - the allowable total error requirement for an analyte.

Probability of Erroneous Results in the Absence of a Testing Process Failure



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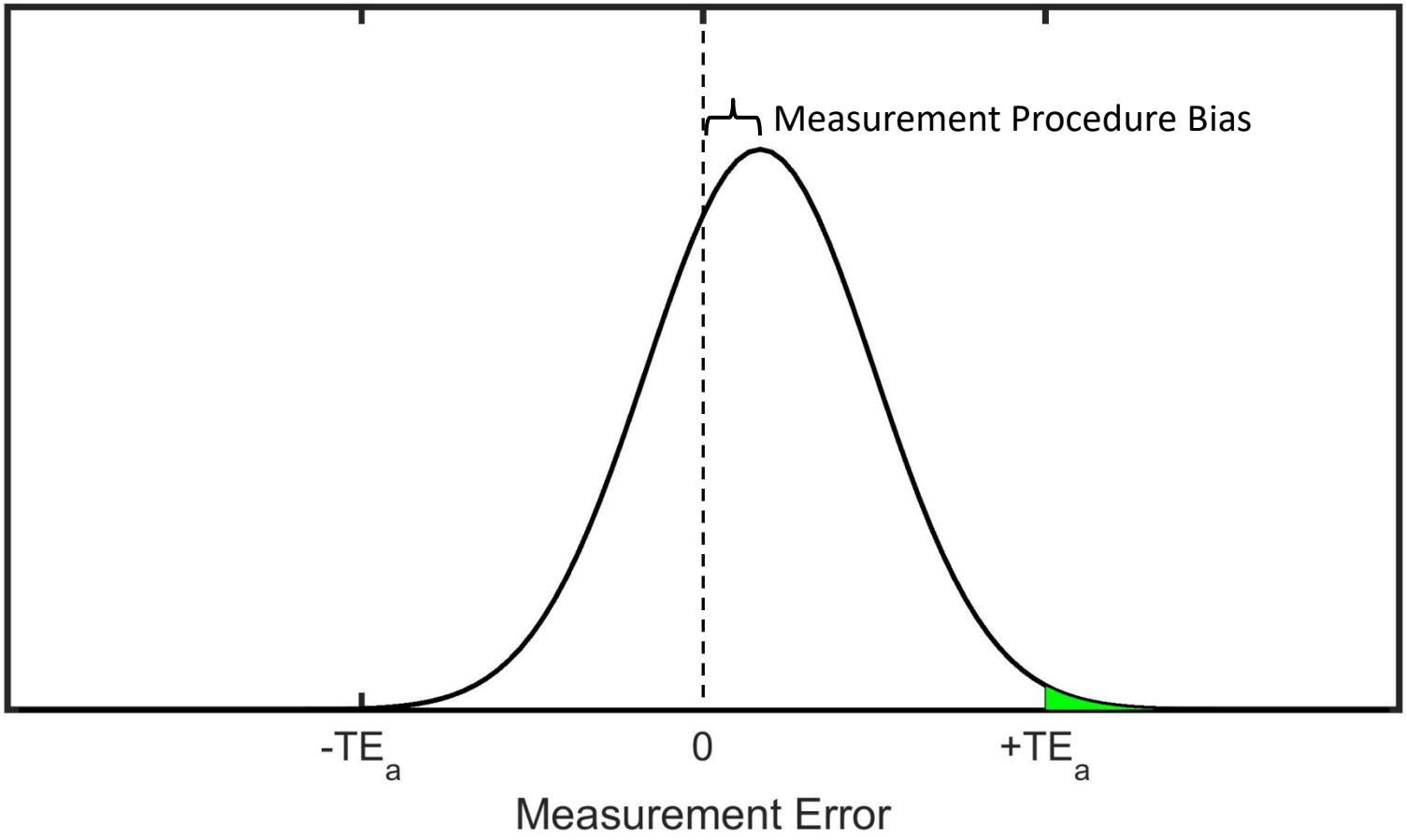

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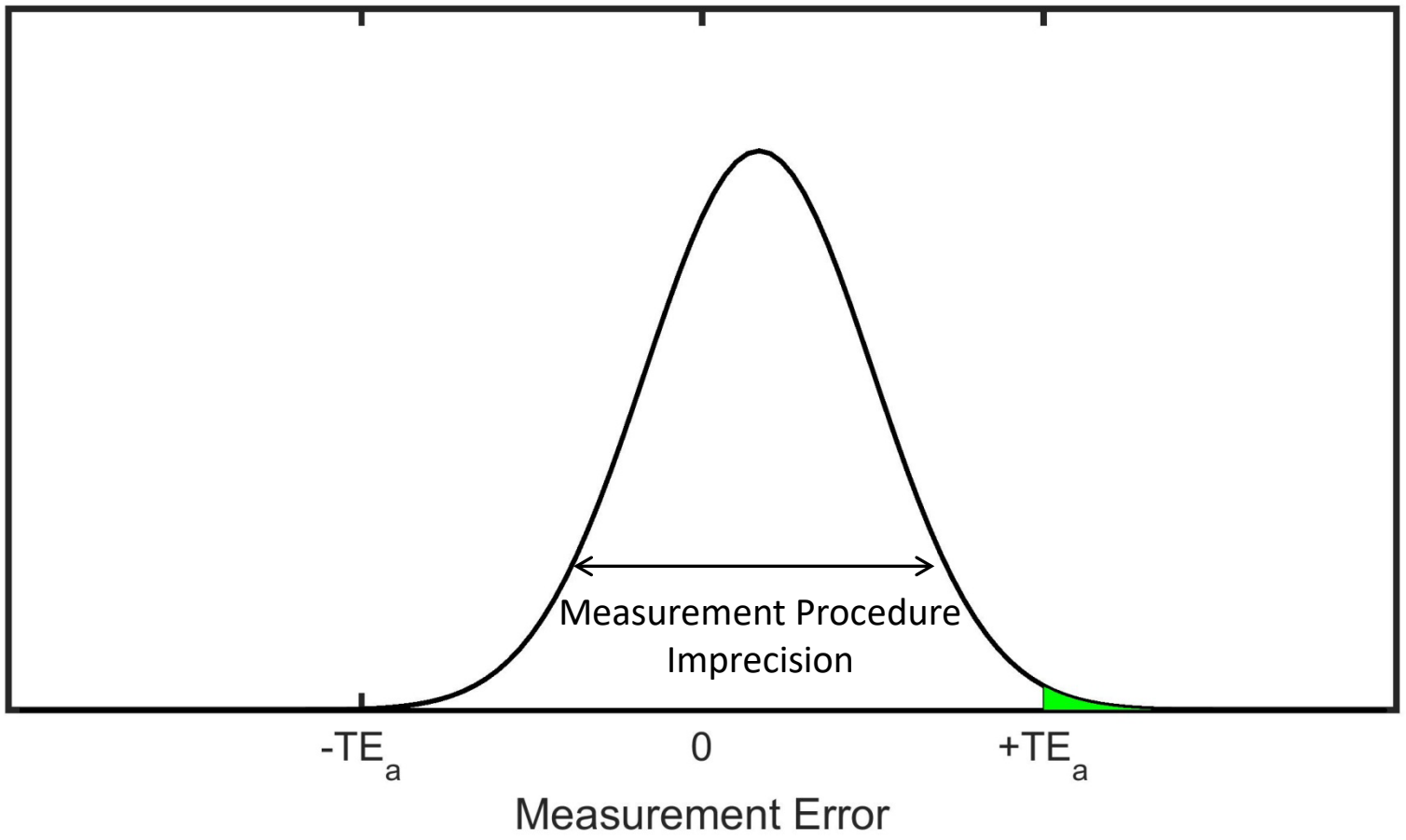

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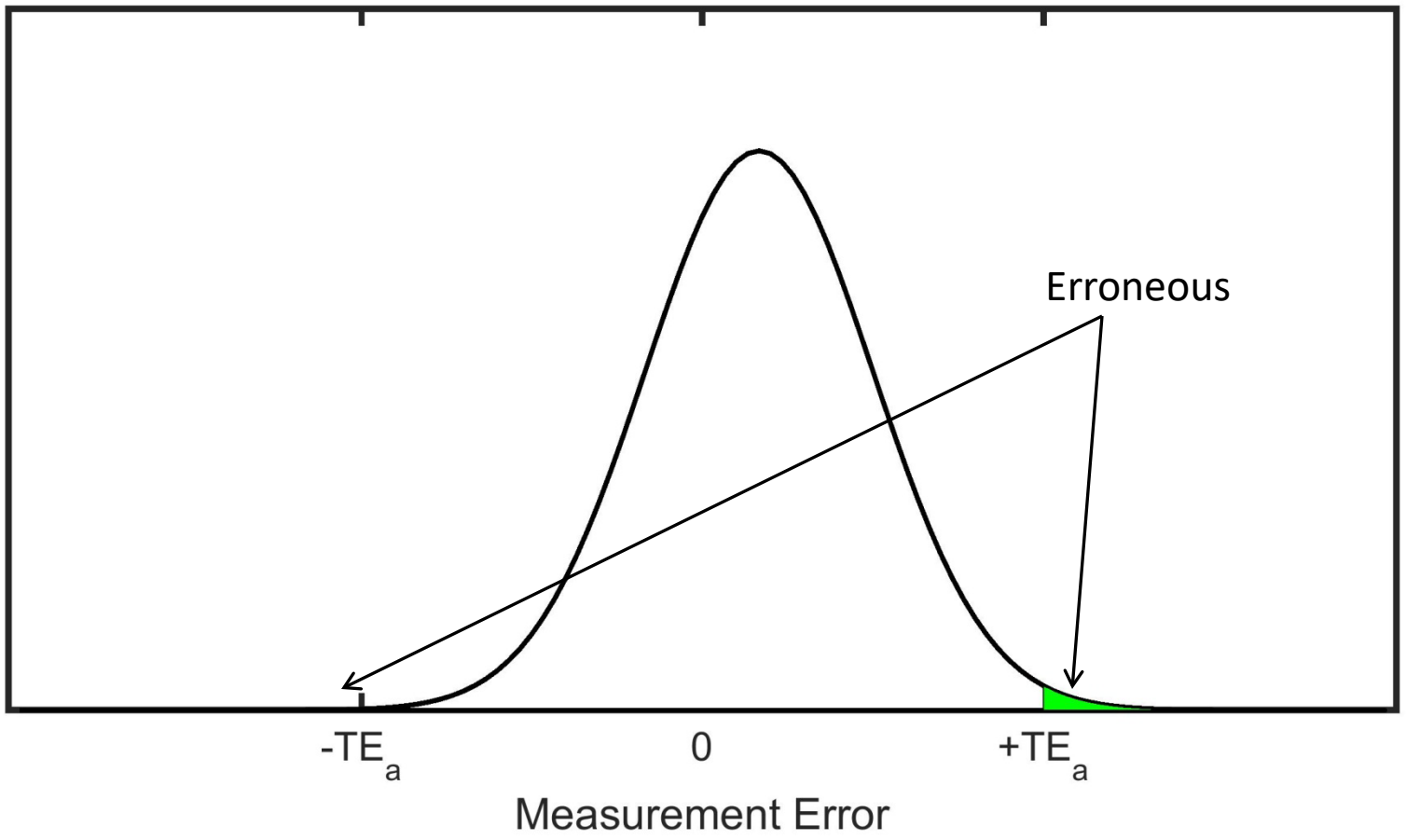
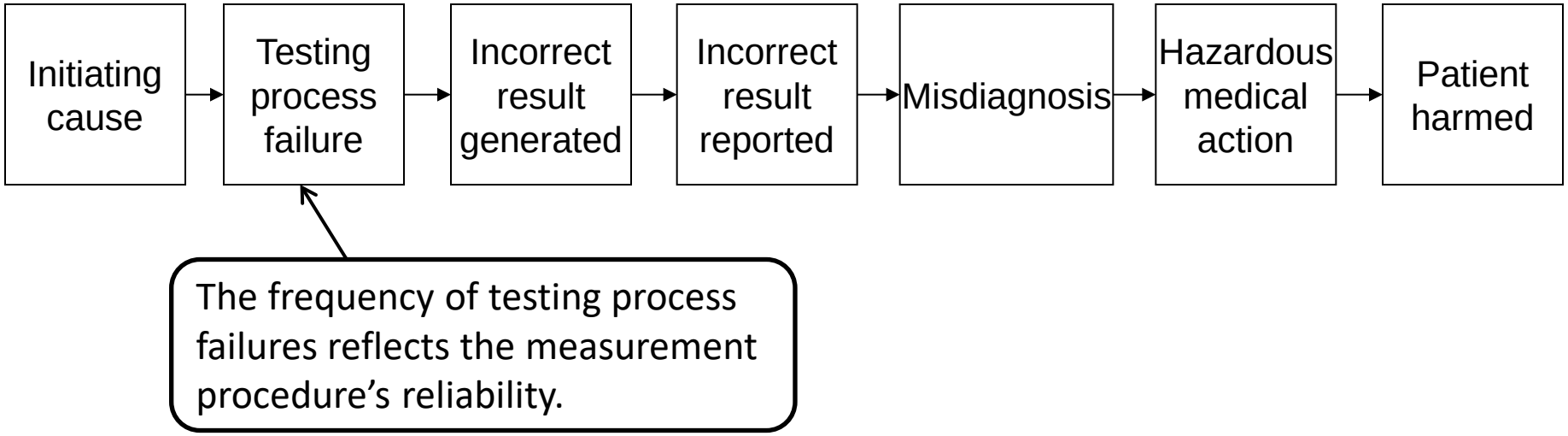


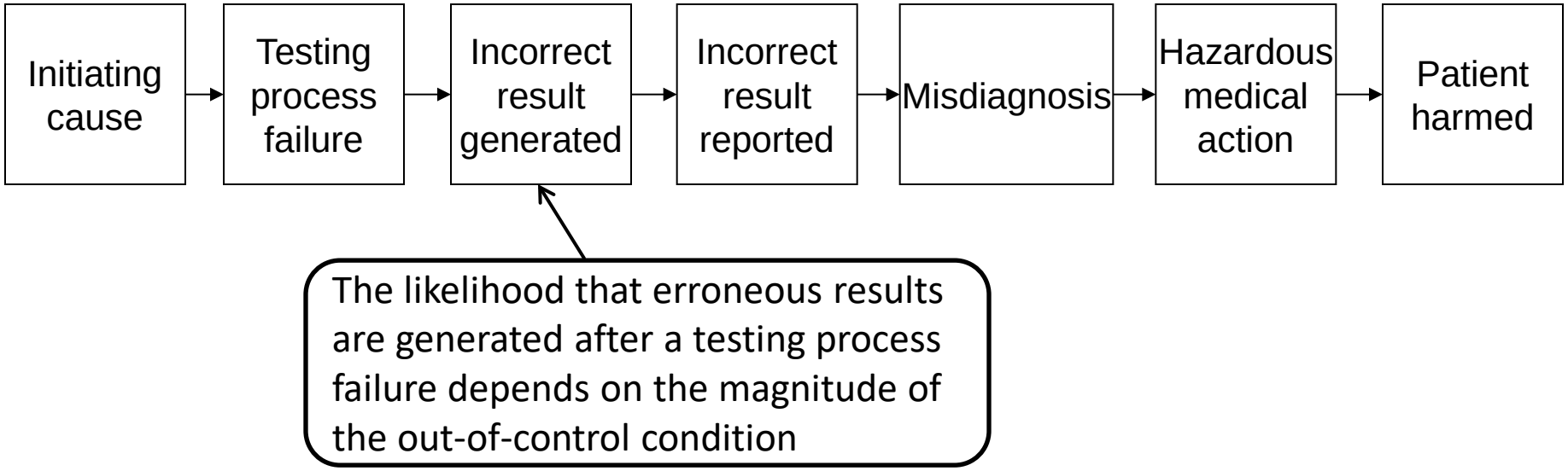
Predicting Probability of Patient Harm



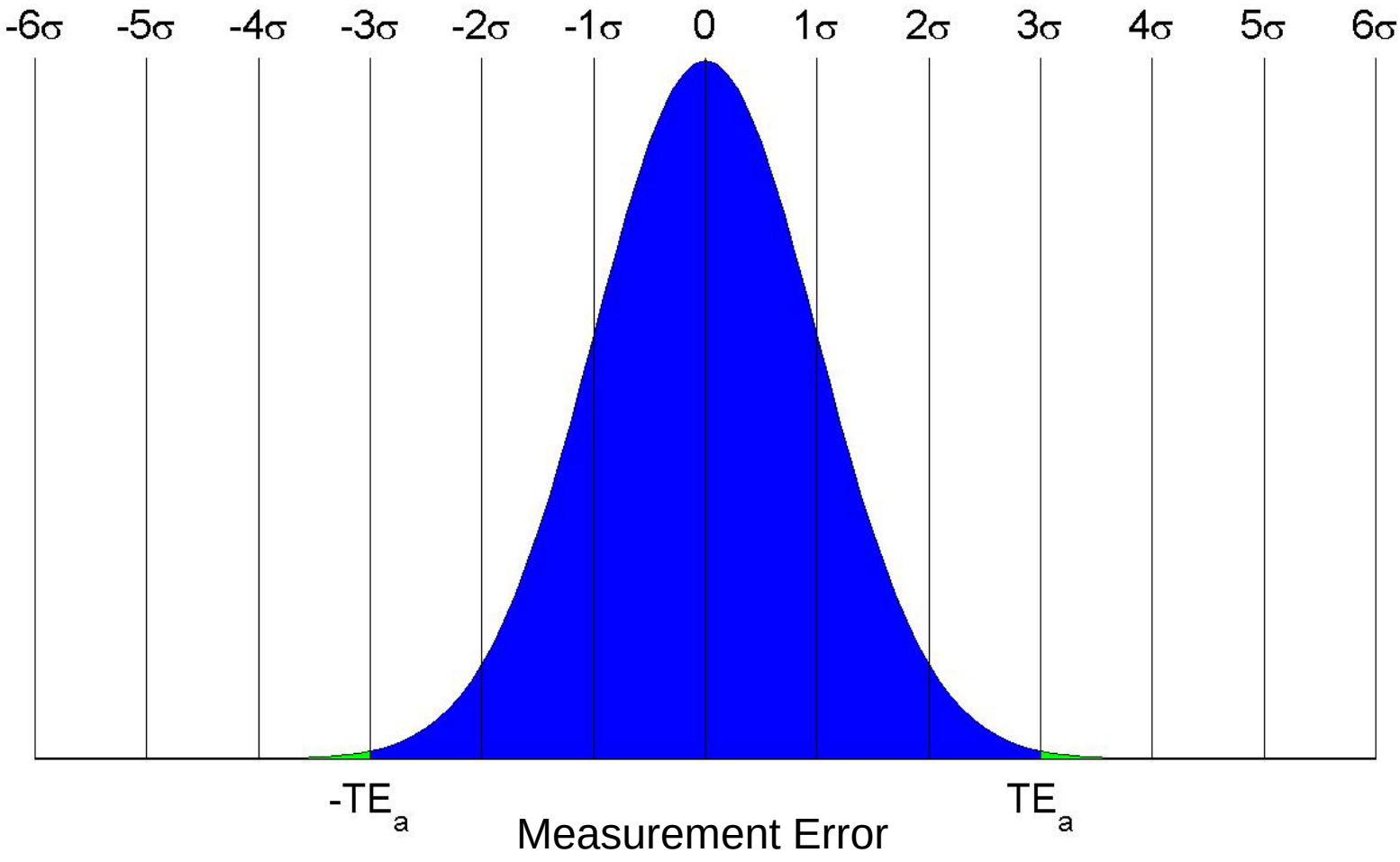
Measurement Procedure Reliability

- From a patient risk perspective, measurement procedure reliability is best expressed as the mean # of in-control patient results reported between testing process failures (MPBF)
  - MPBF can be obtained from;
    - An estimate of mean time between test system failures,
    - The average number of patient results for the analyte per day

Predicting Probability of Patient Harm



Erroneous Results when In-Control



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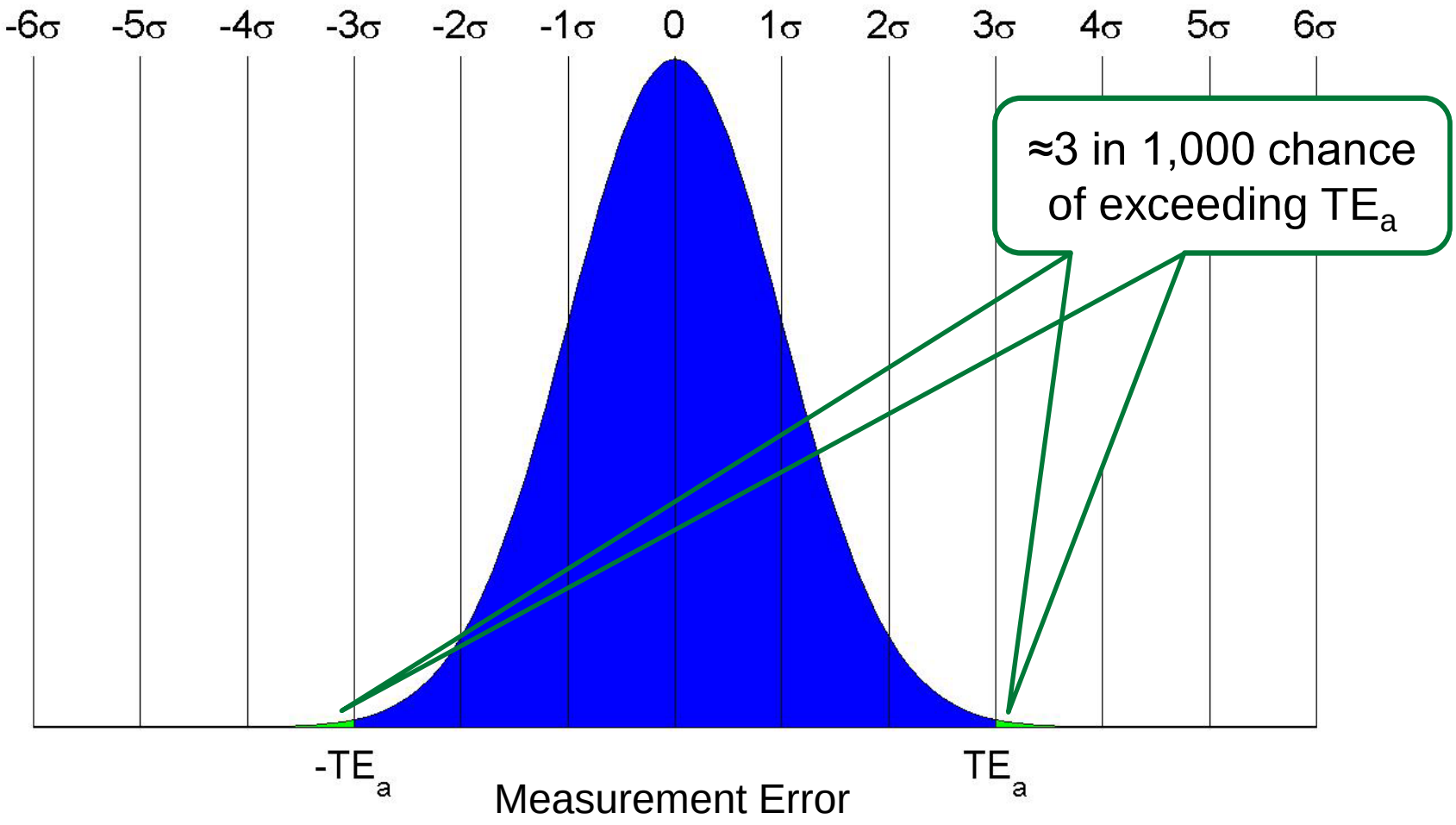
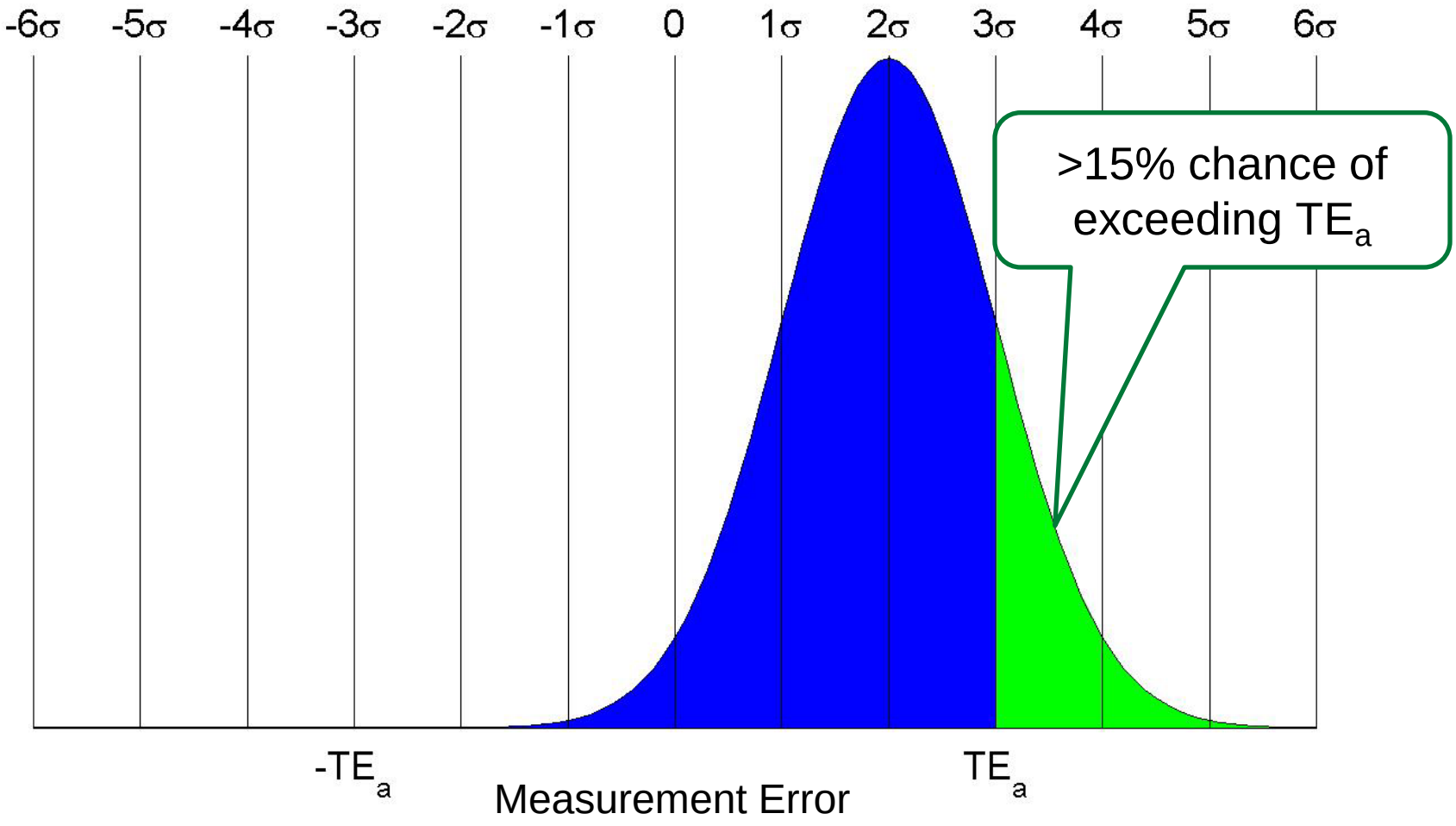


Erroneous Results when Out-of-Control



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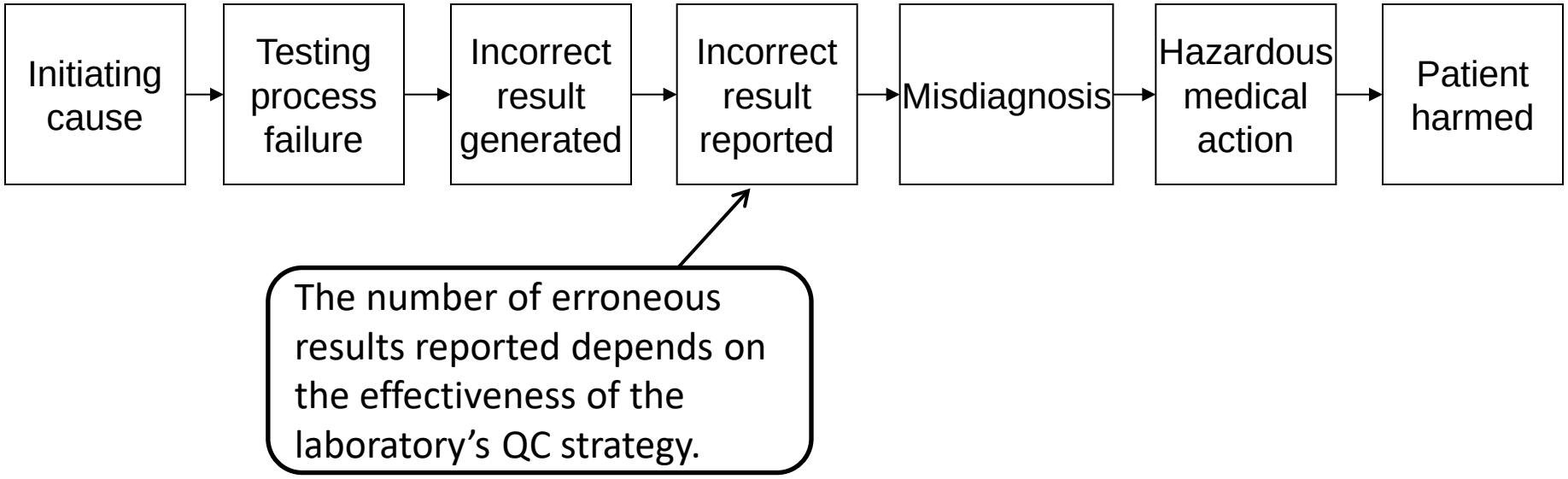
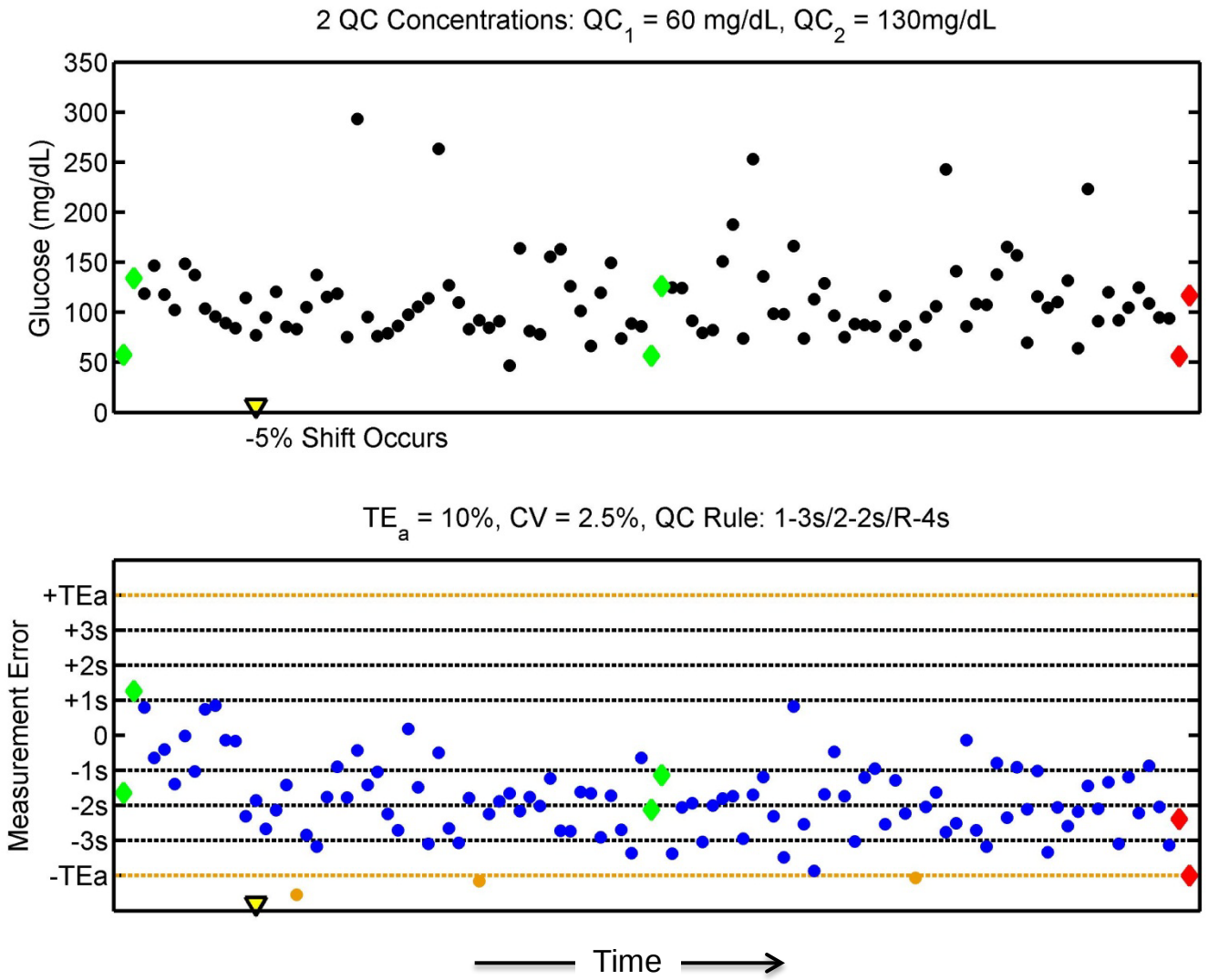


Number of Erroneous Patient Results

- The number of erroneous patient results due to an out-of-control condition in a measurement procedure depends on
  - The quality specification (allowable total error)
  - The size of the out-of-control condition
  - The frequency of QC testing
  - The power of the QC rule(s) to detect the out-of-control error condition

Erroneous Patient Results: Example 1



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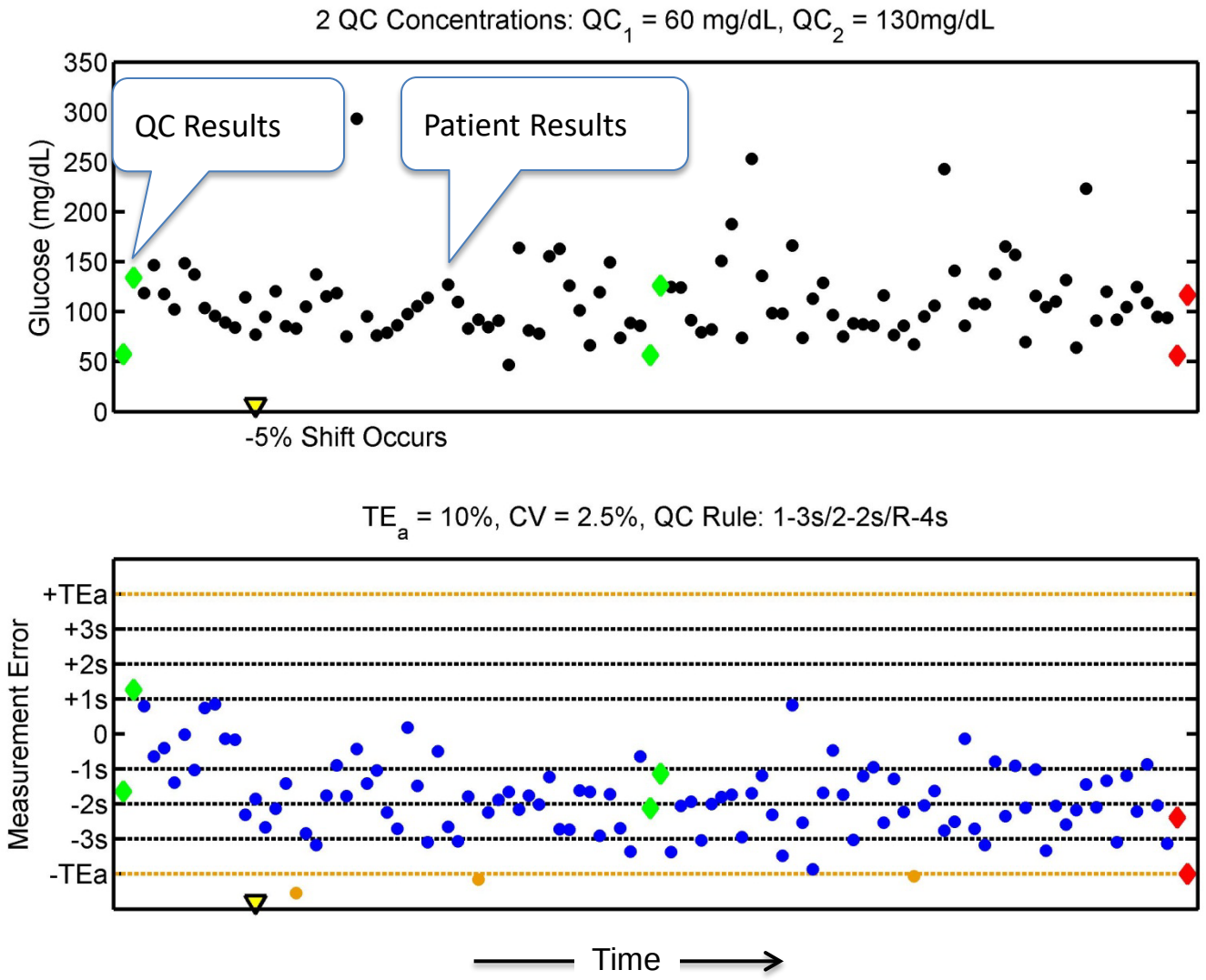

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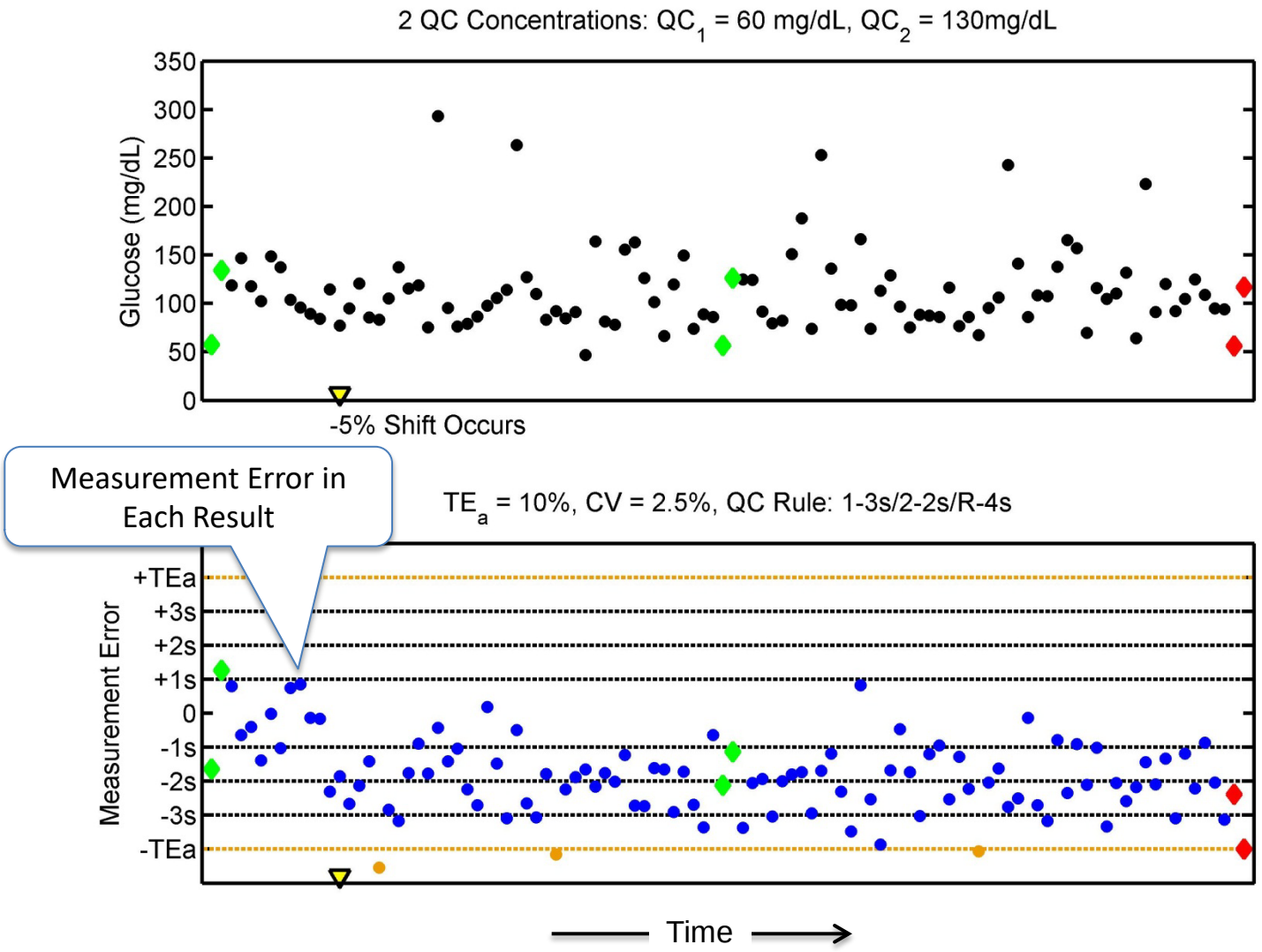

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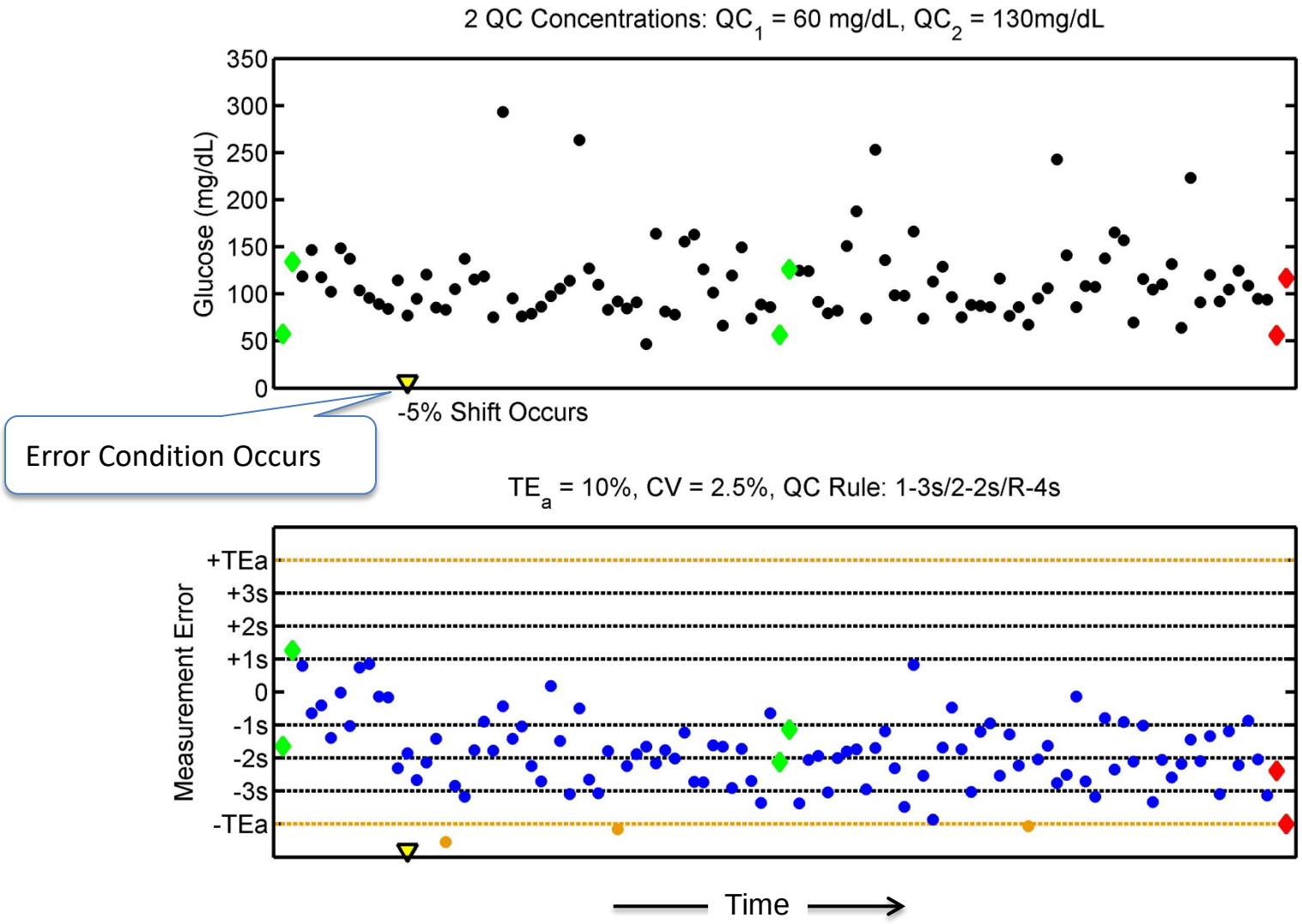

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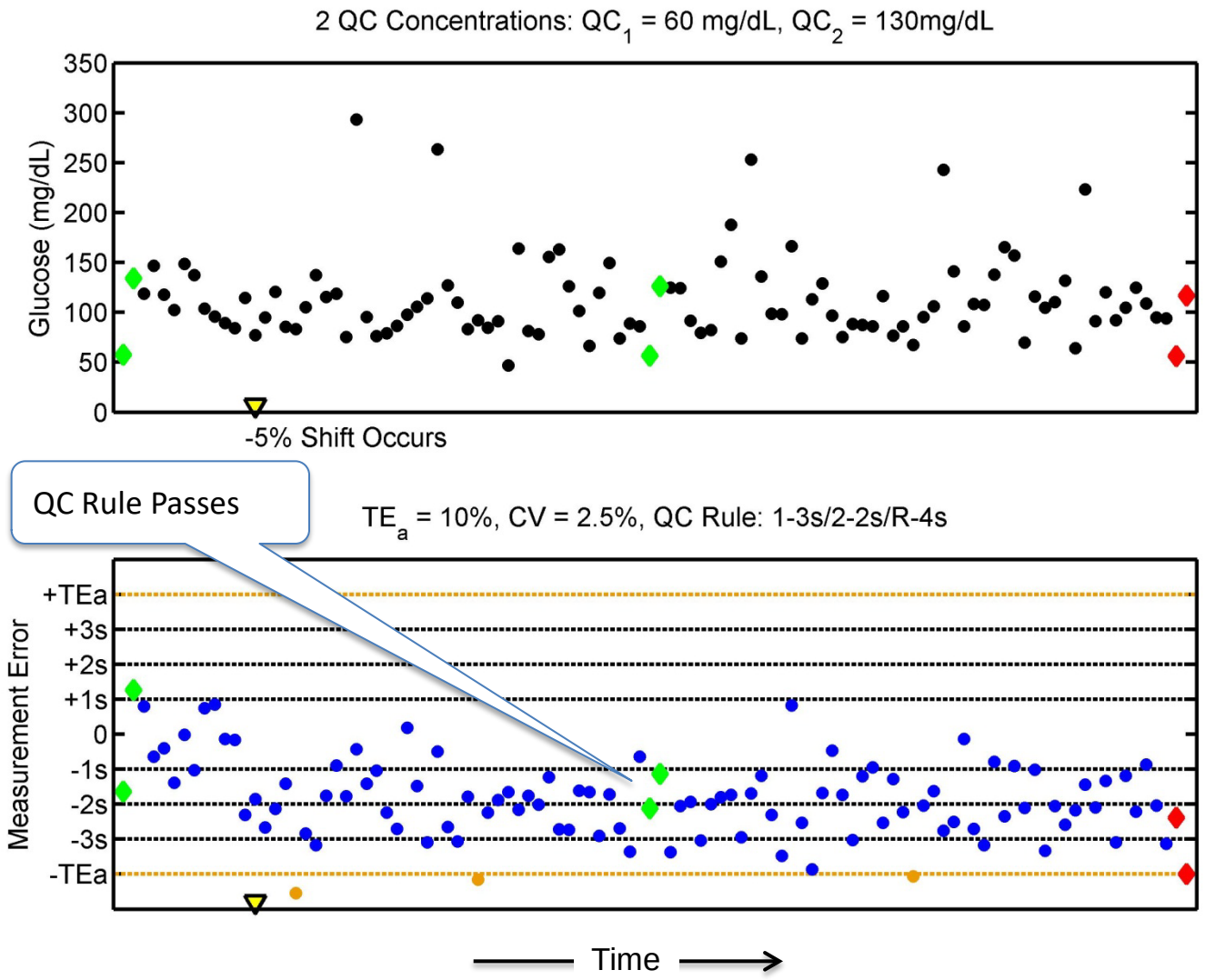

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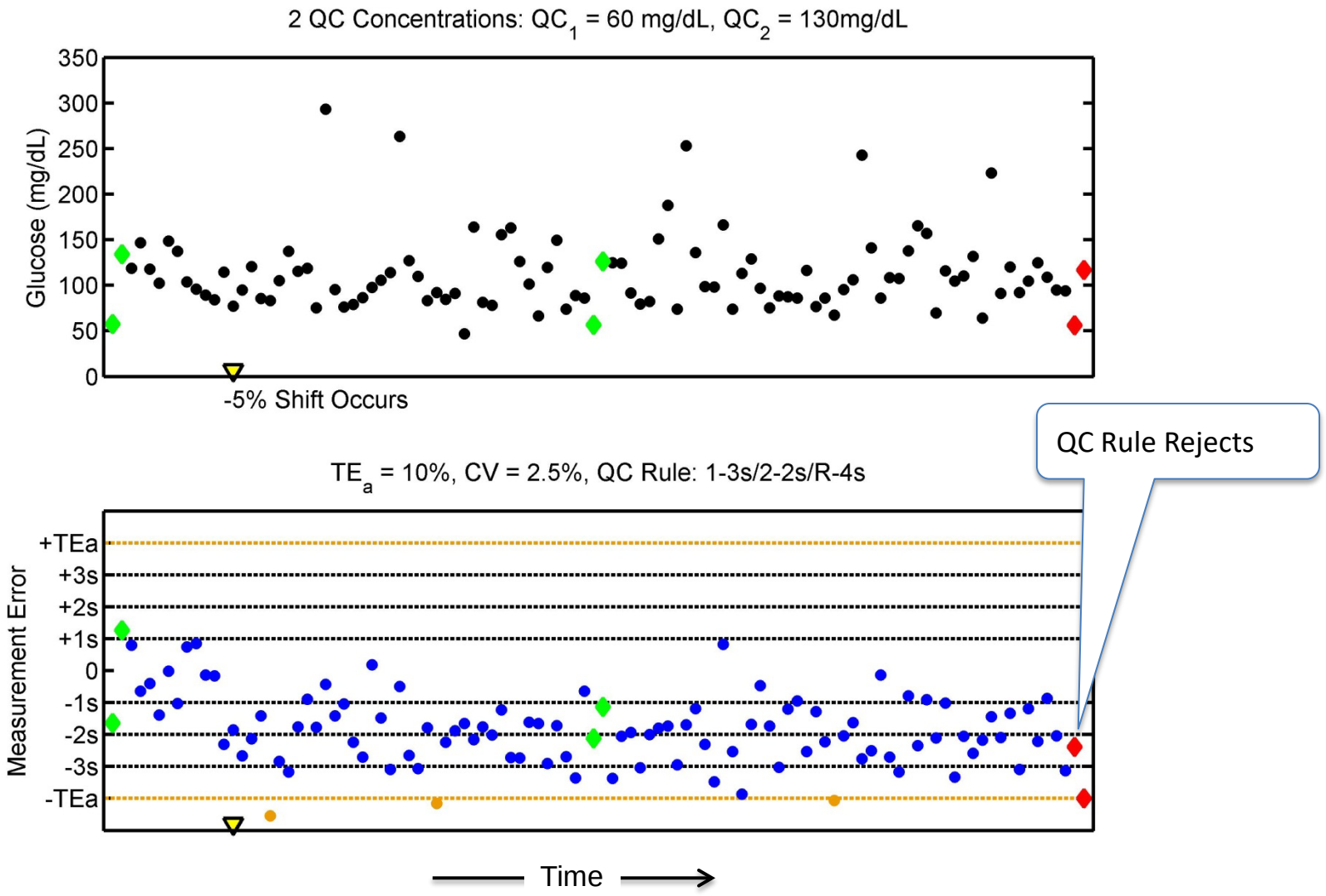

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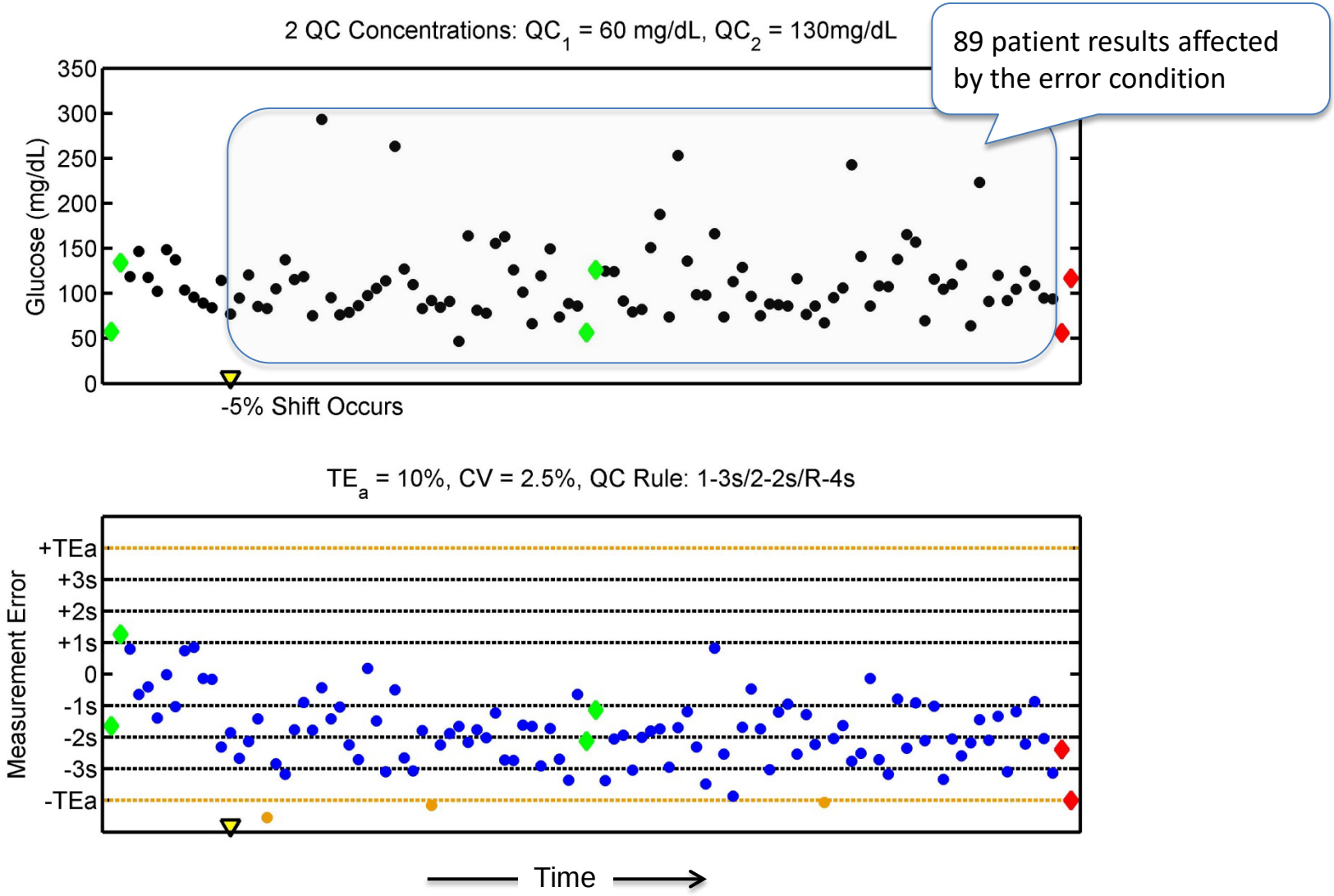

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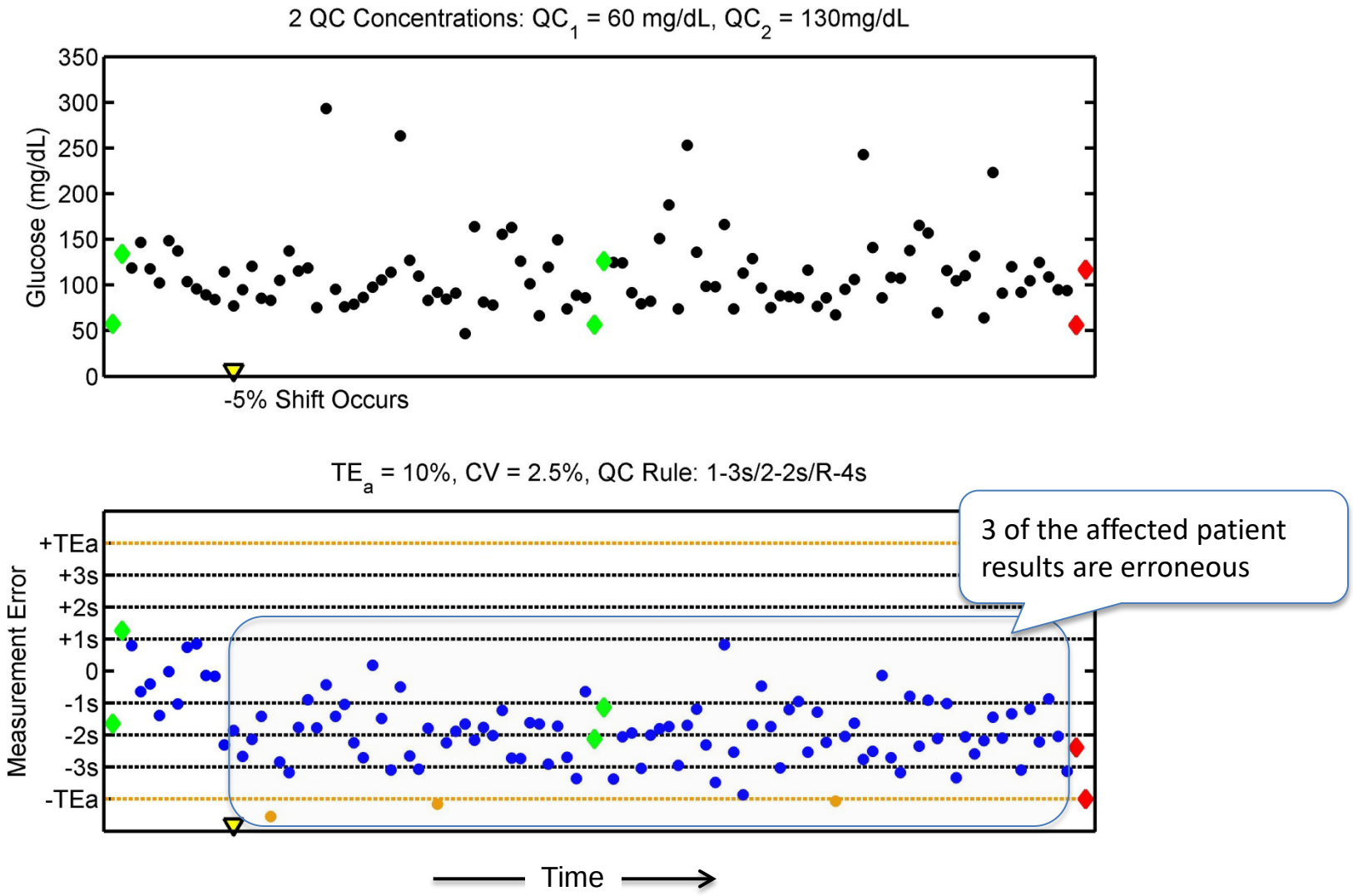

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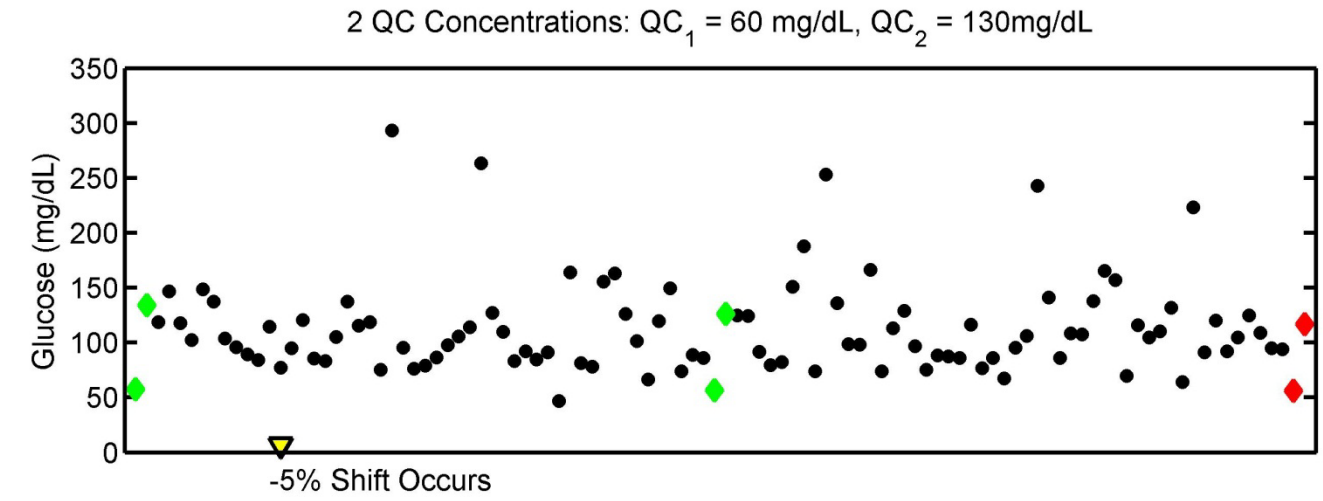

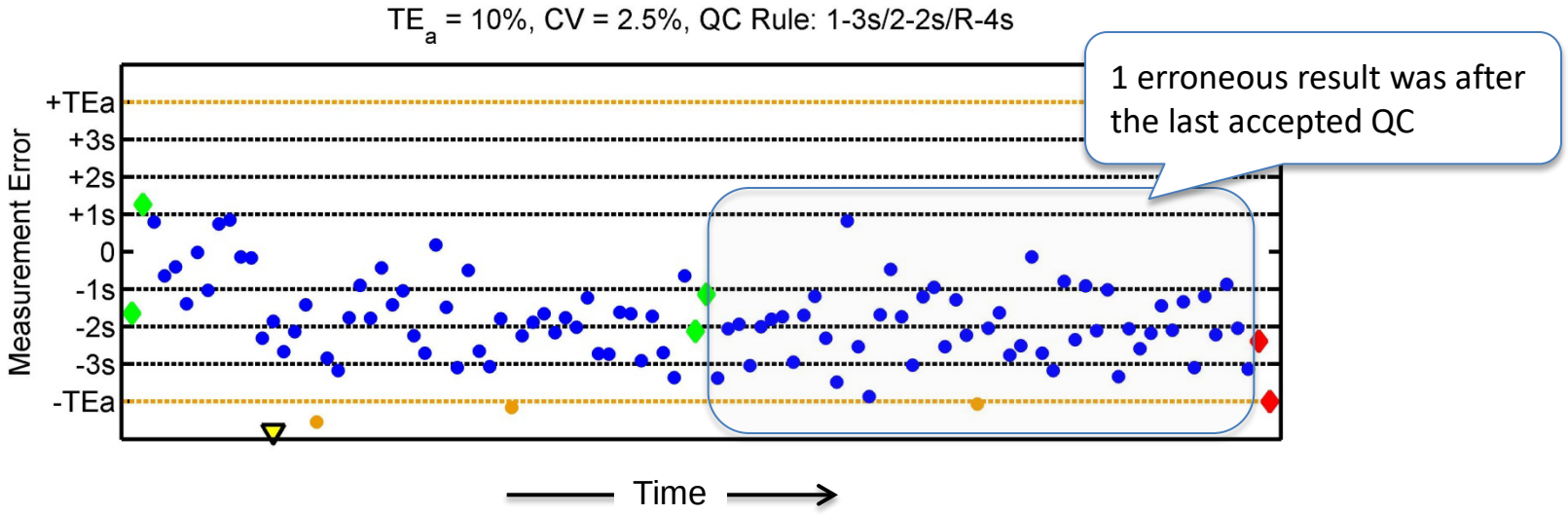

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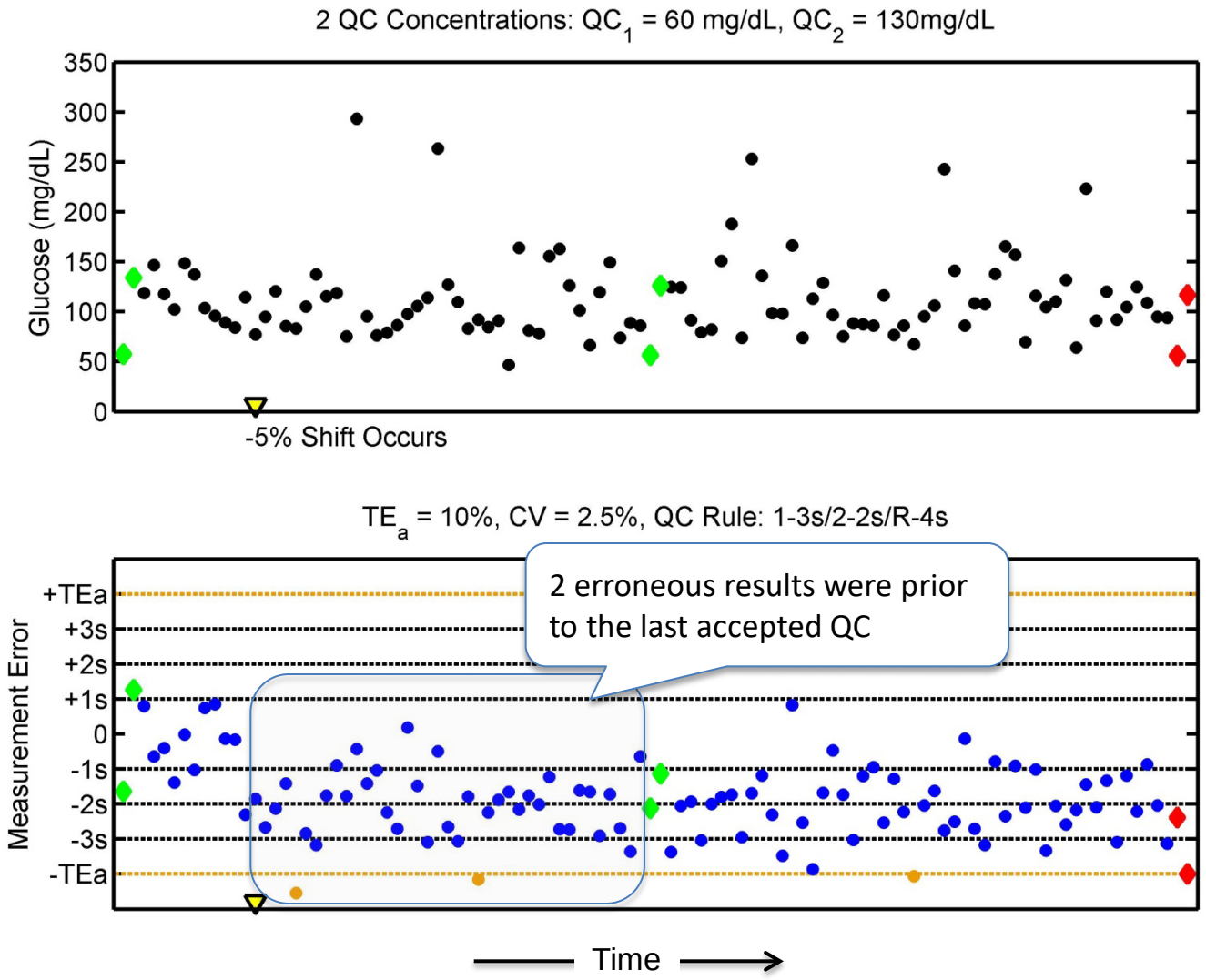
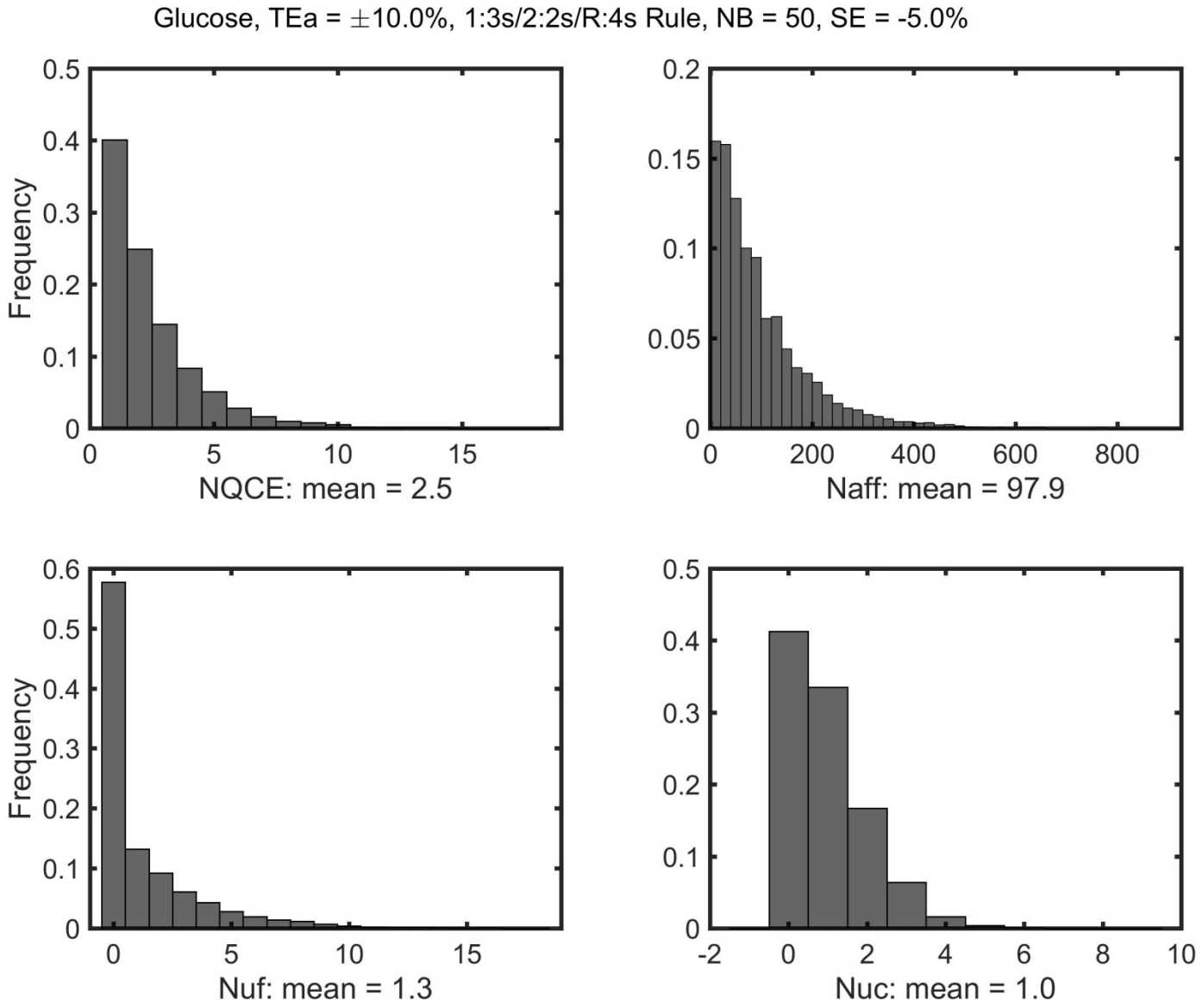


Number of Erroneous Patient Results

- Erroneous results can be divided into 2 groups:
- Those that are corrected before they are acted on
  - $E(N_{uc})$: Expected number of unacceptable correctable results
- Those that are never corrected
  - Final results that create hazardous situations
  - $E(N_{uf})$: Expected number of unacceptable final results
- If erroneous results back to the last accepted QC can be corrected before acted on;
  - $E(N_{uc})$ = # erroneous results back to last accepted QC
  - $E(N_{uf})$ = # erroneous results prior to last accepted QC

Erroneous Patient Results: Example 1



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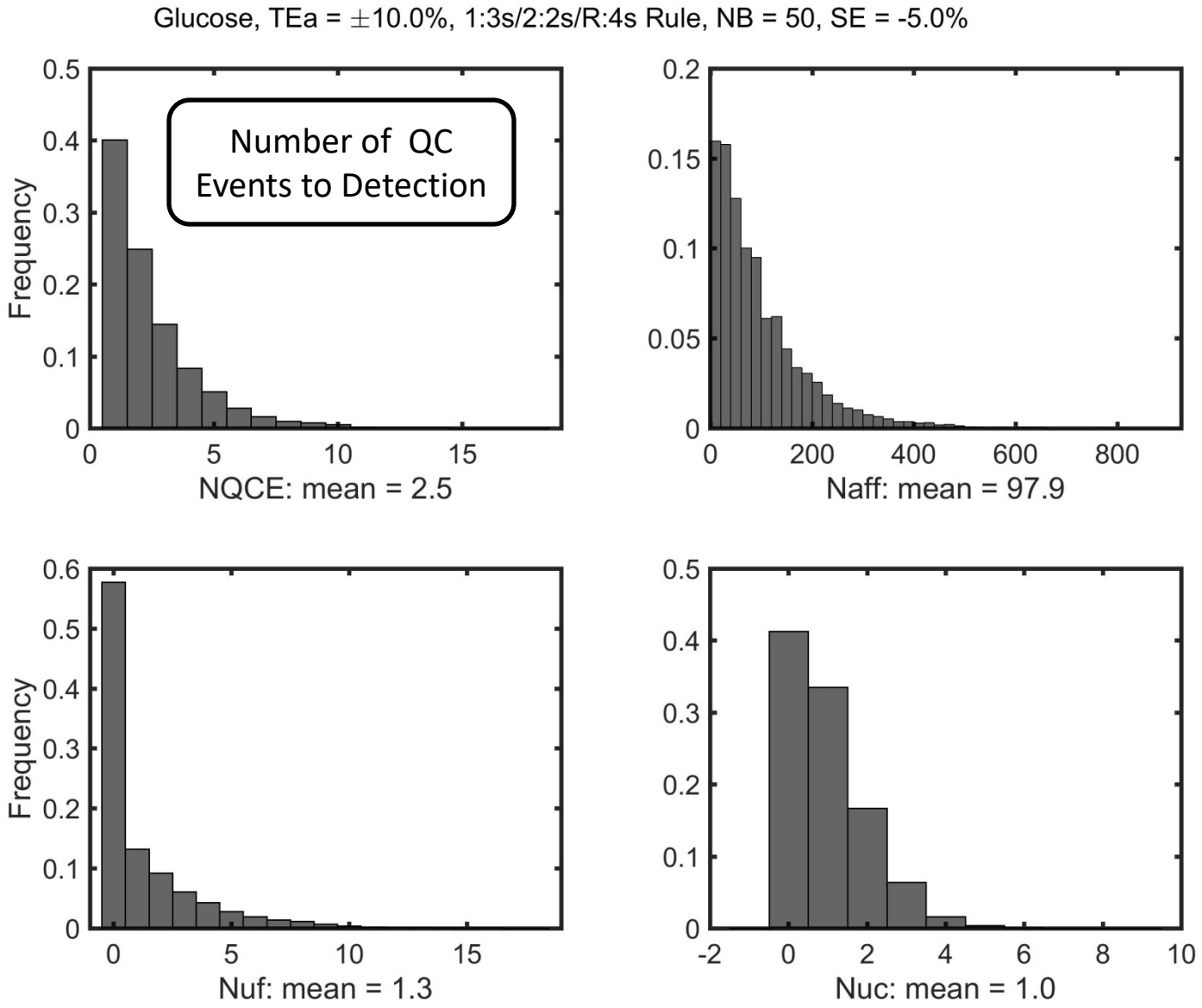

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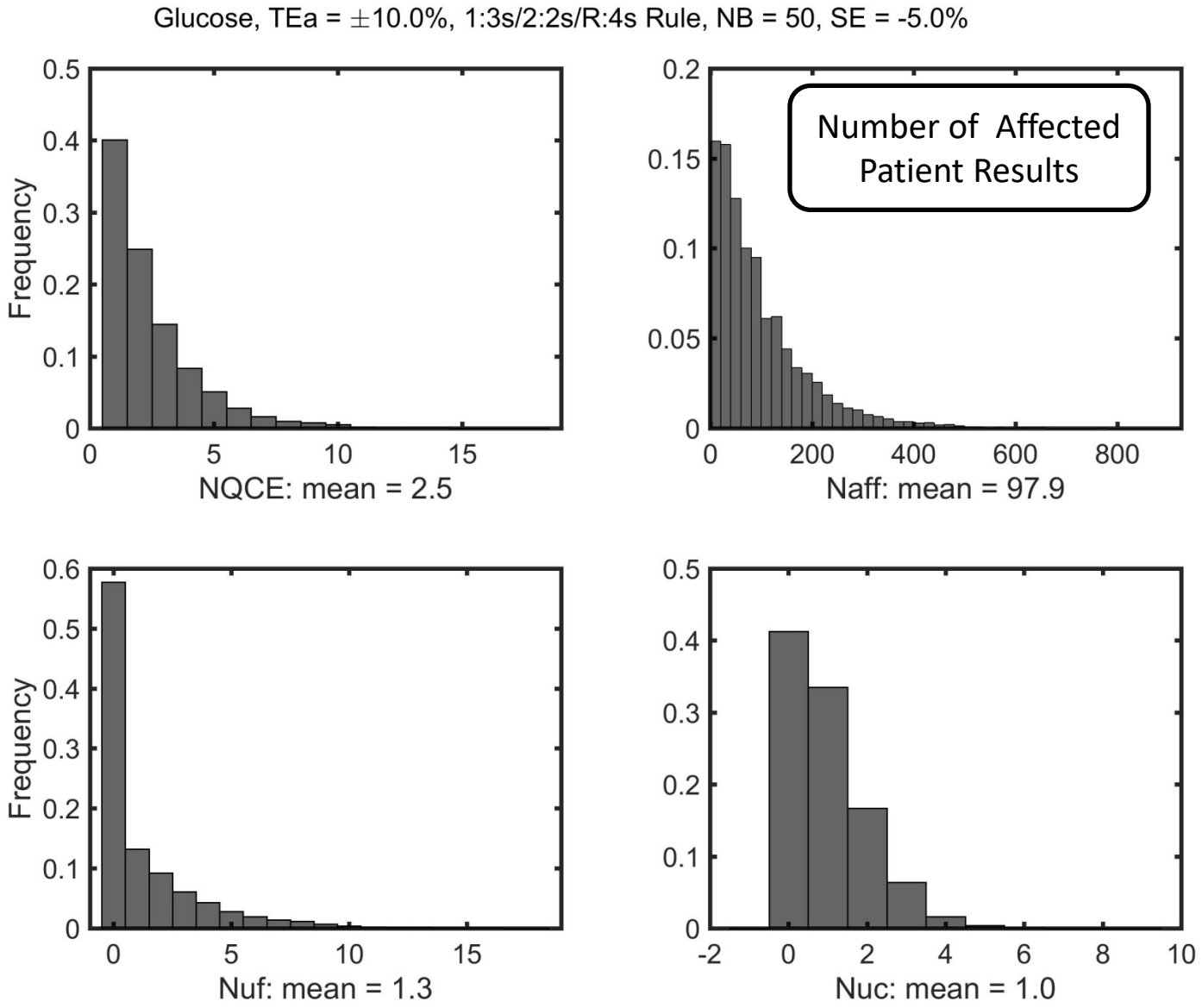

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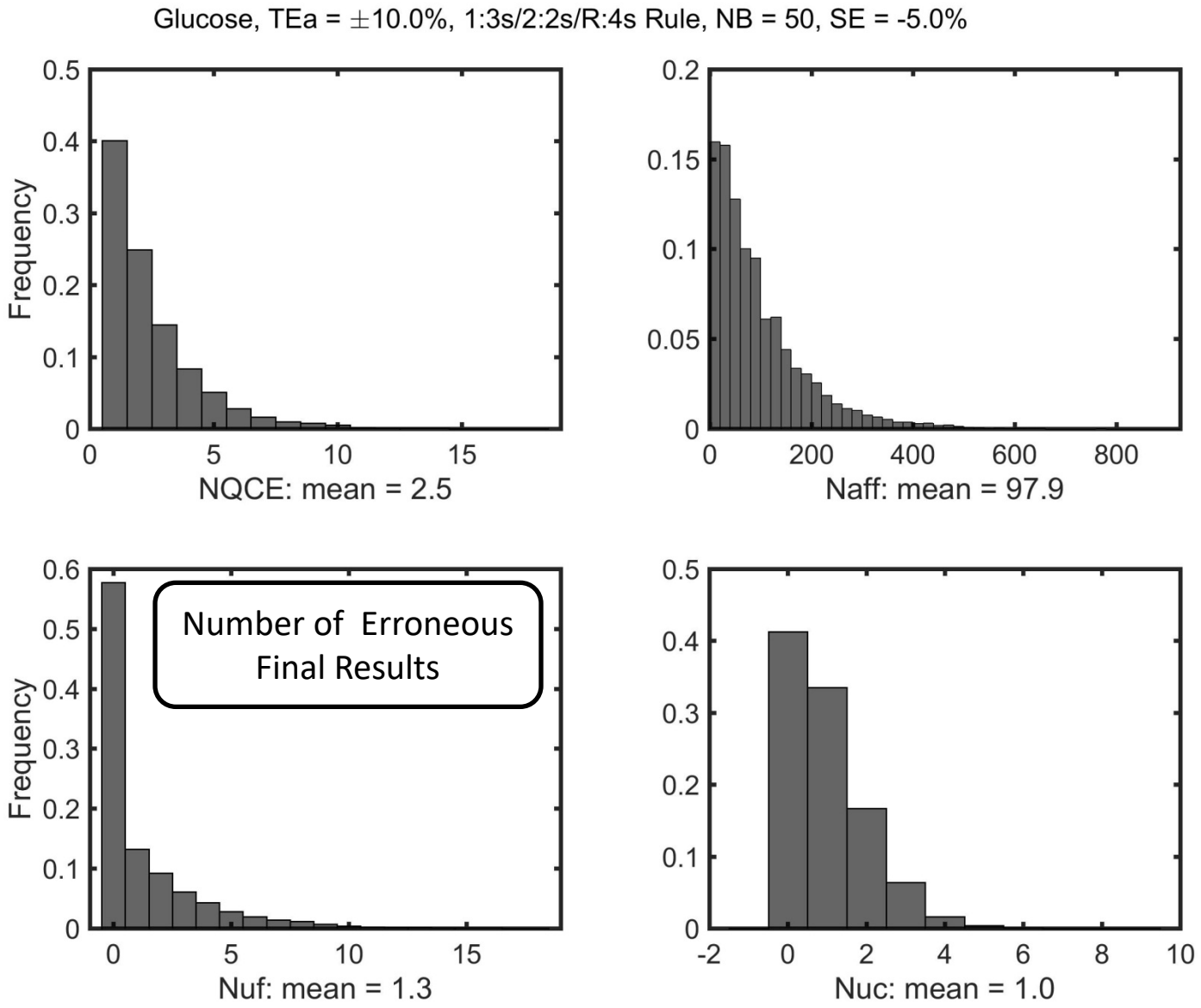

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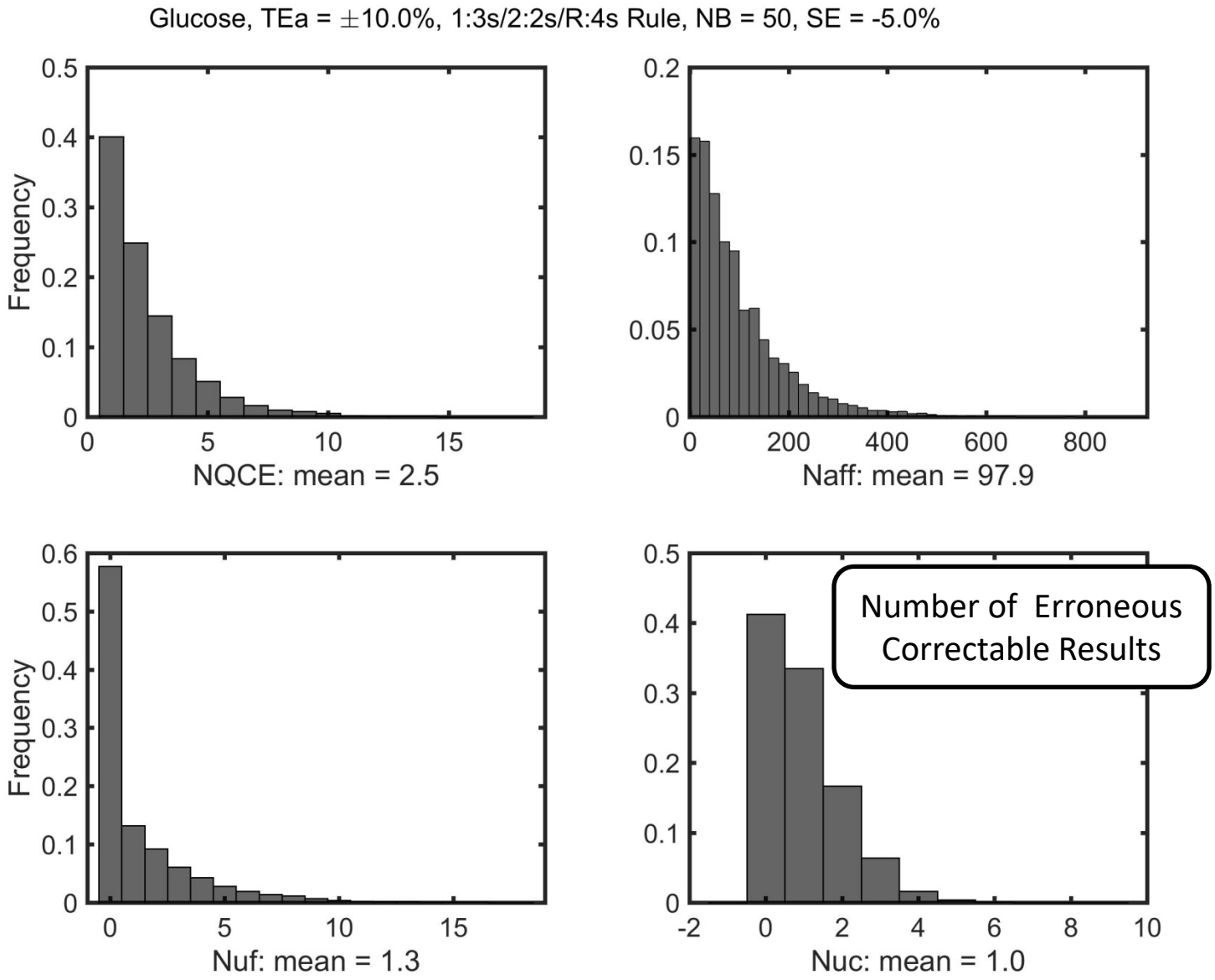
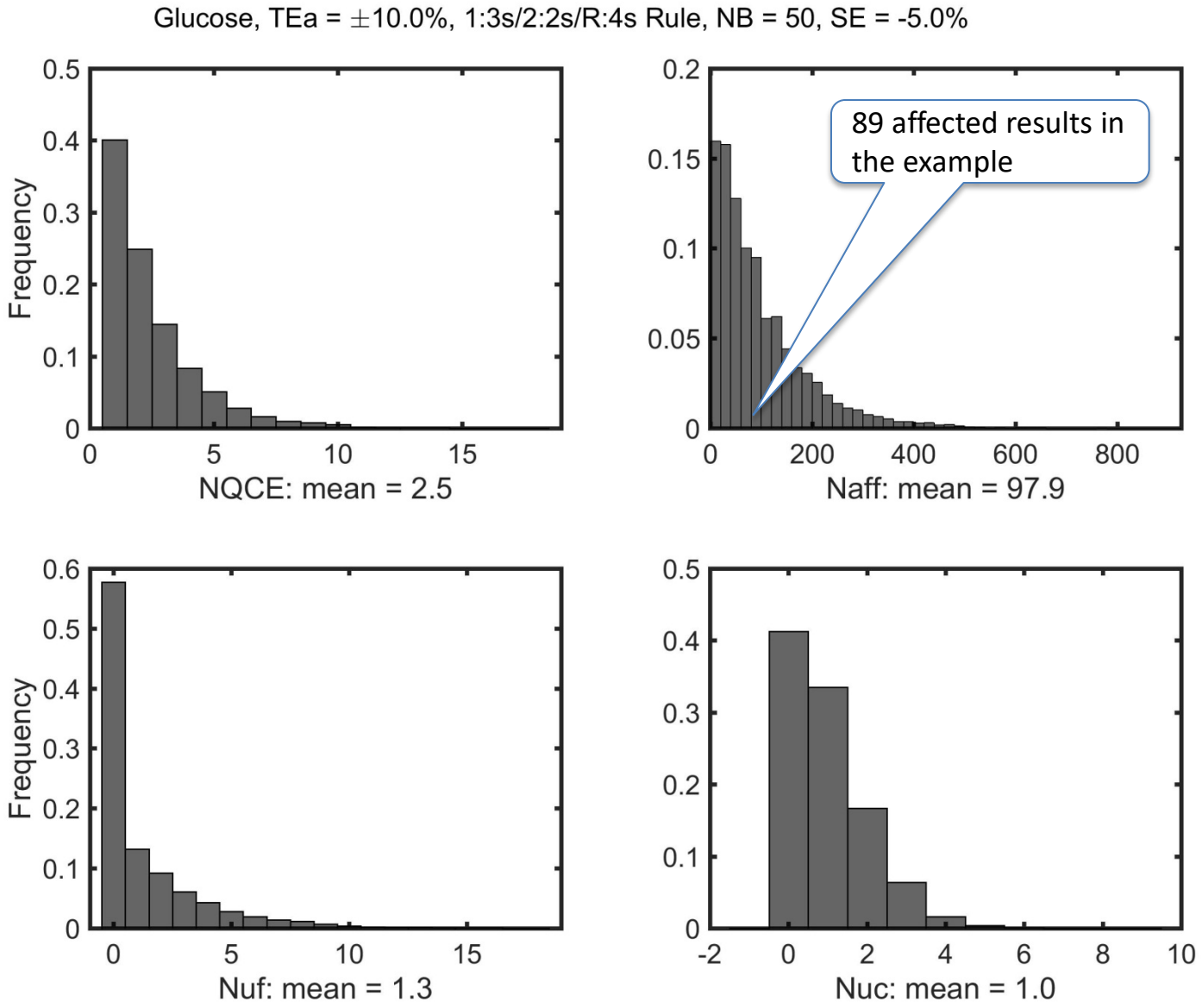
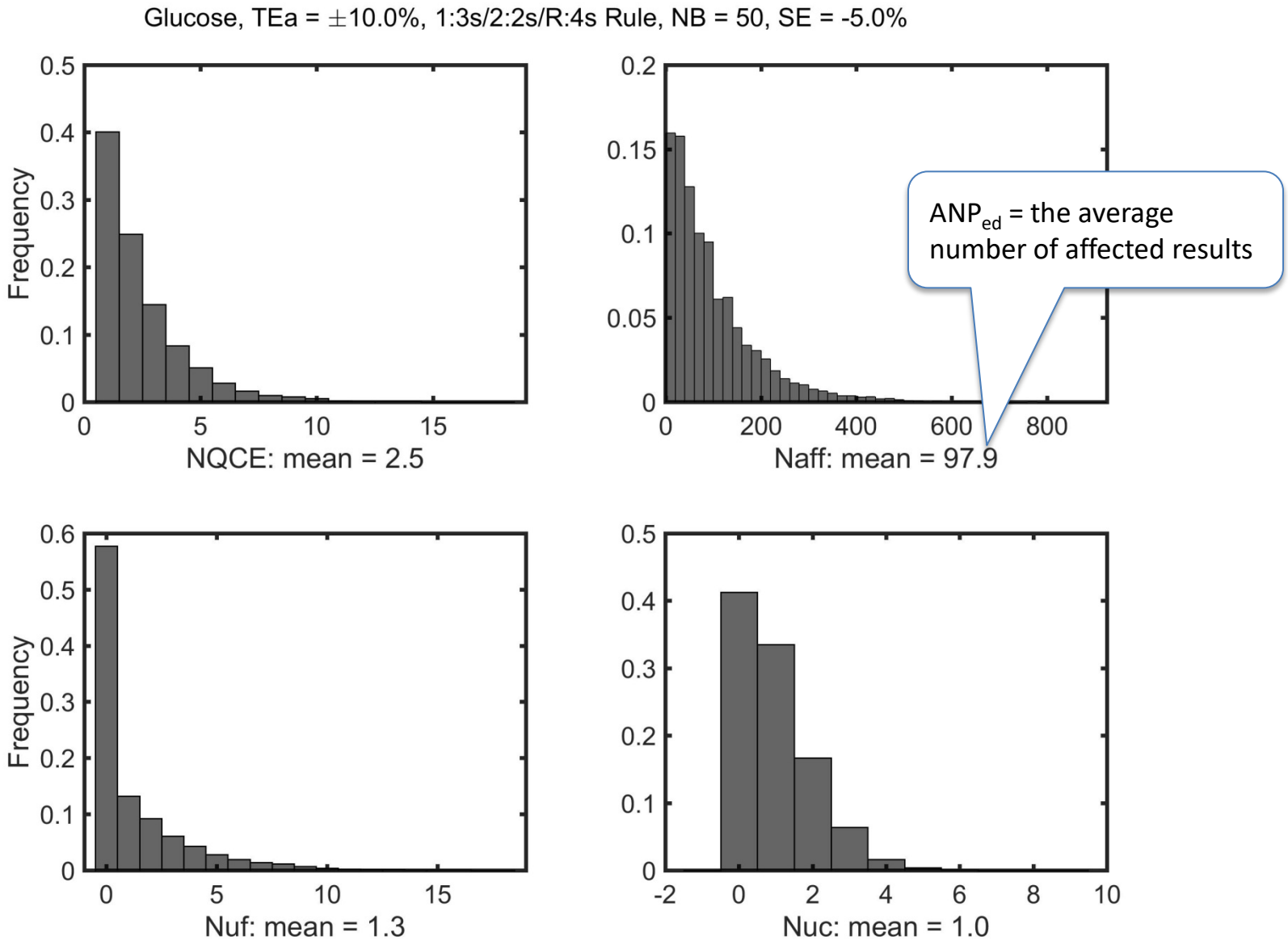


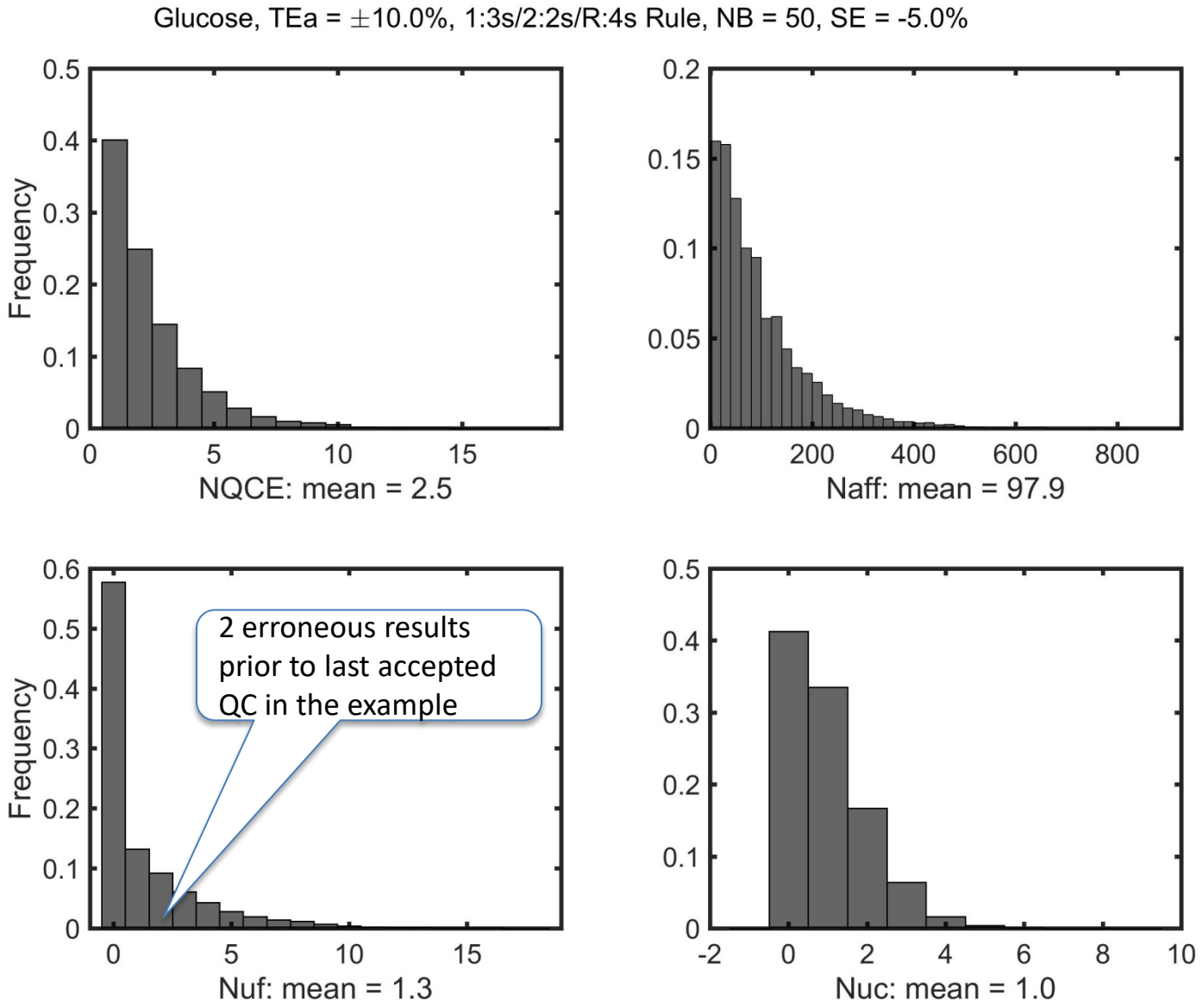
Erroneous Patient Results: Example 1



Erroneous Patient Results: Example 1



Erroneous Patient Results: Example 1



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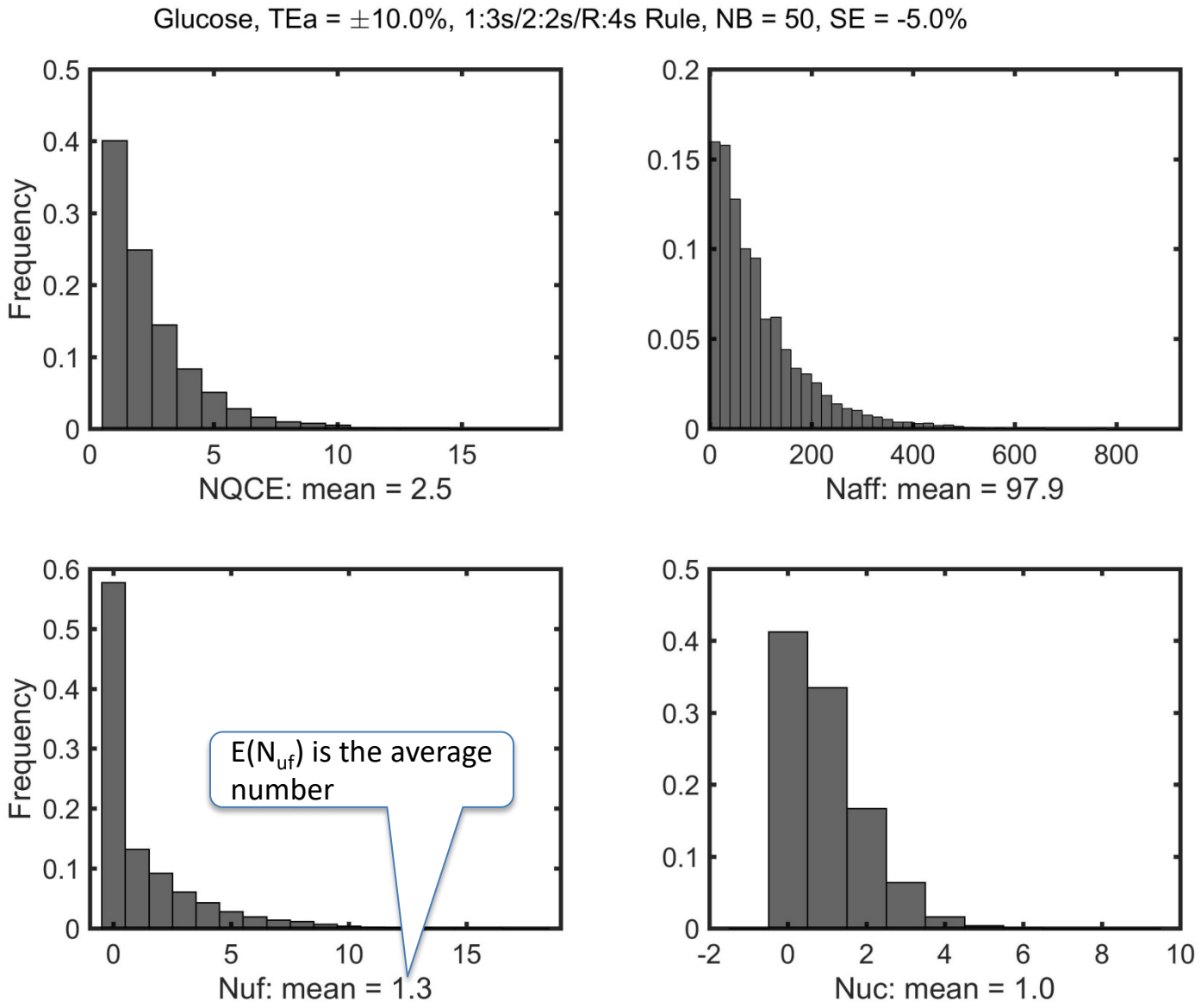
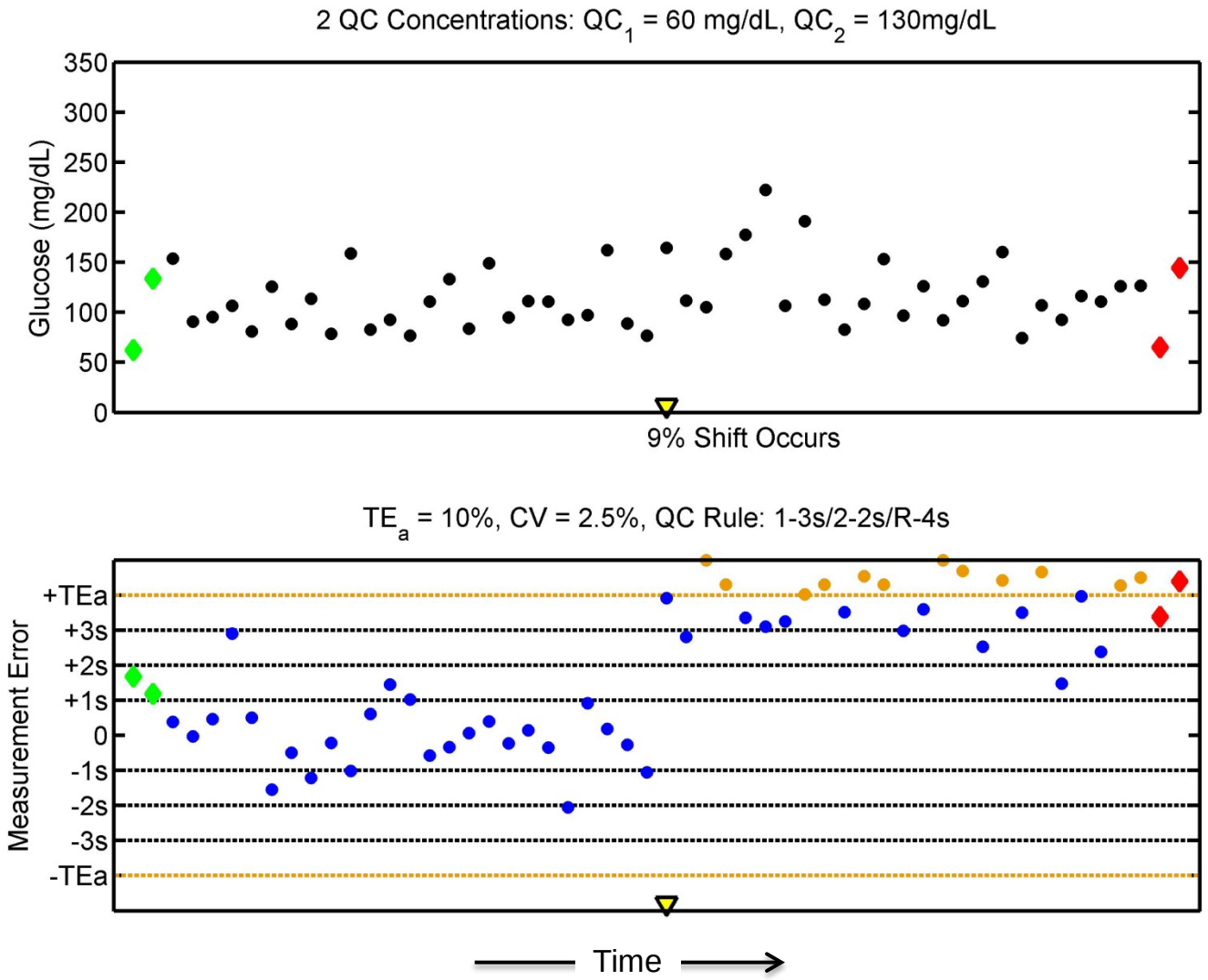
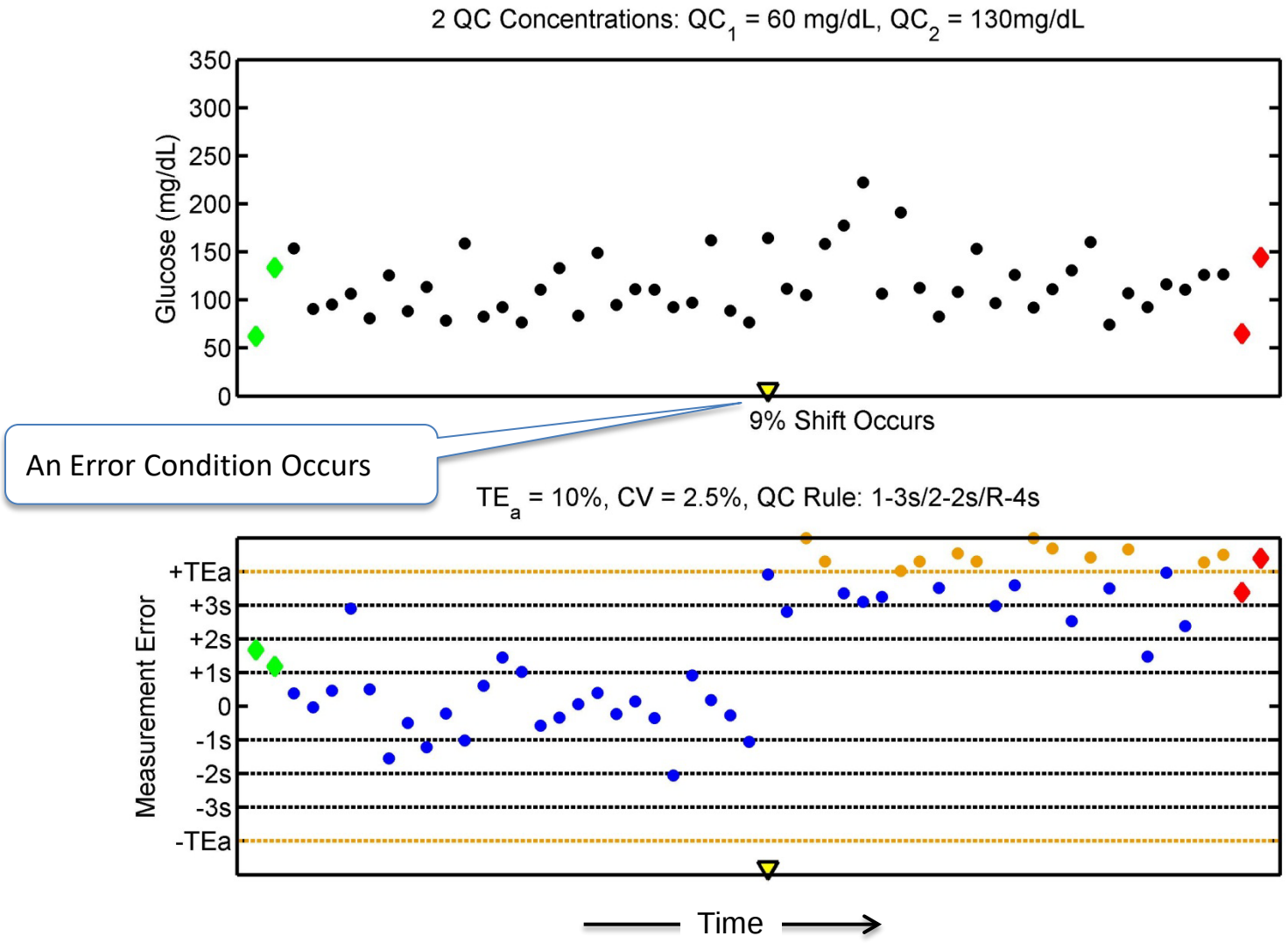


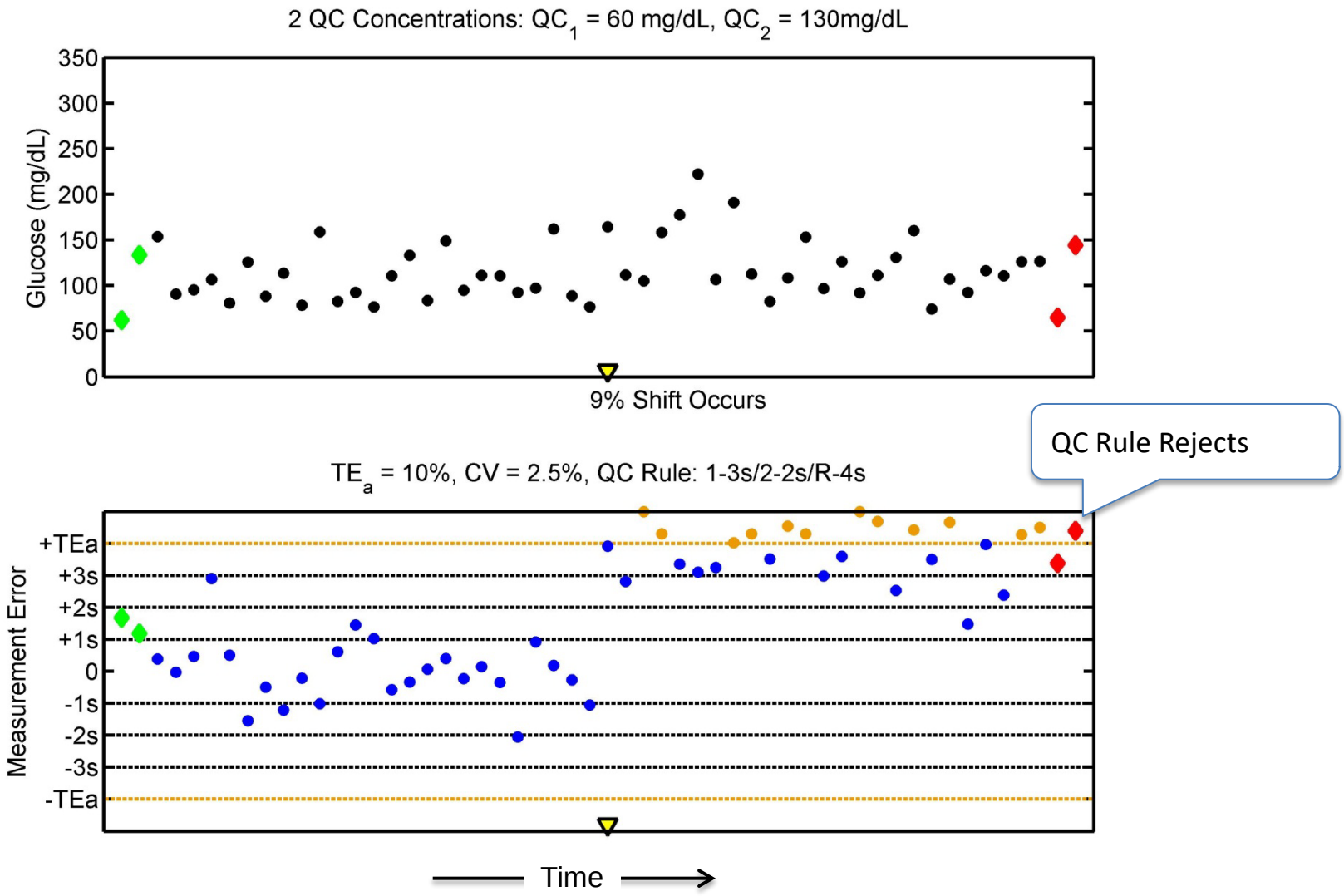
Erroneous Patient Results: Example 2



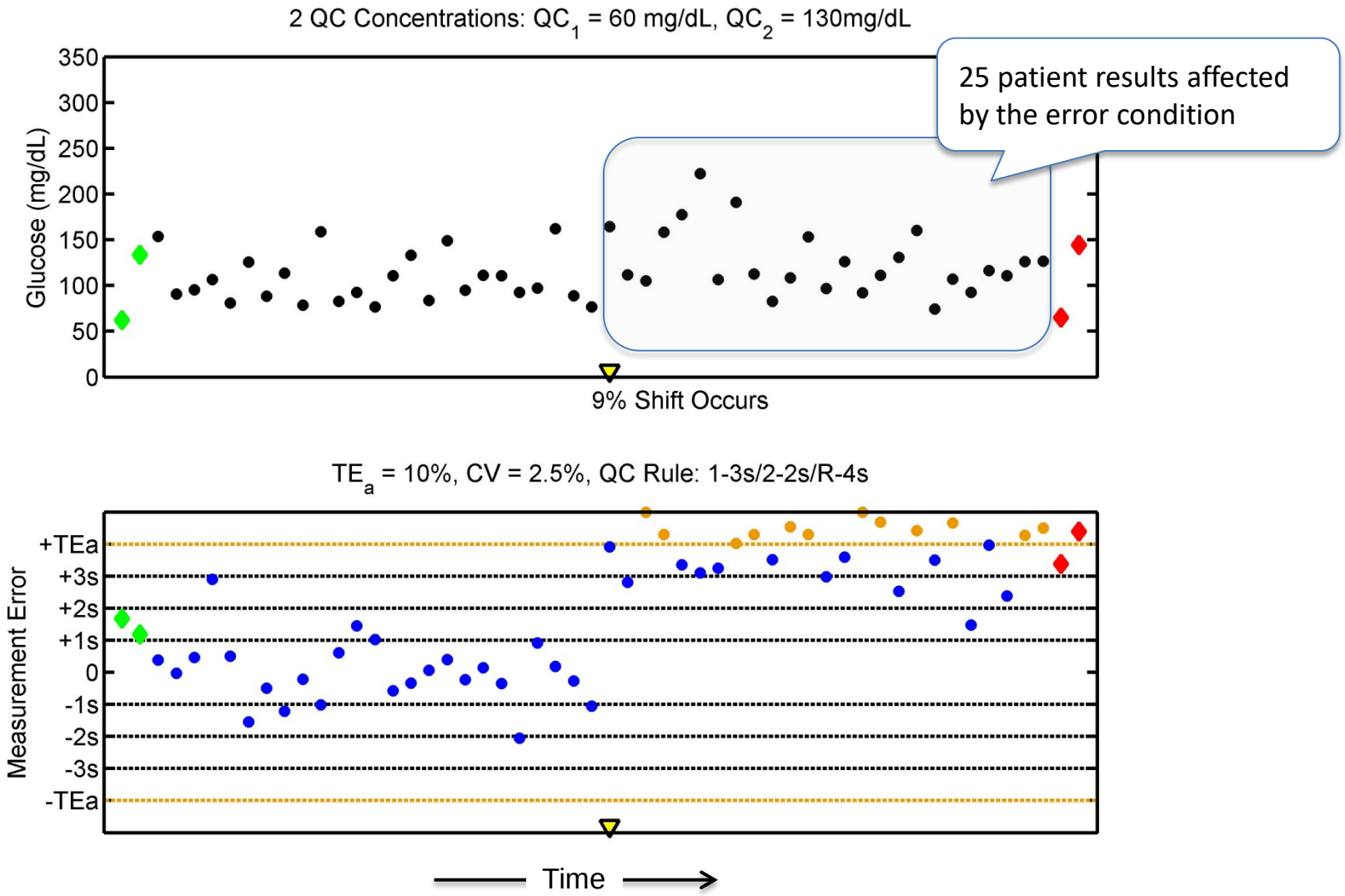
Erroneous Patient Results: Example 2



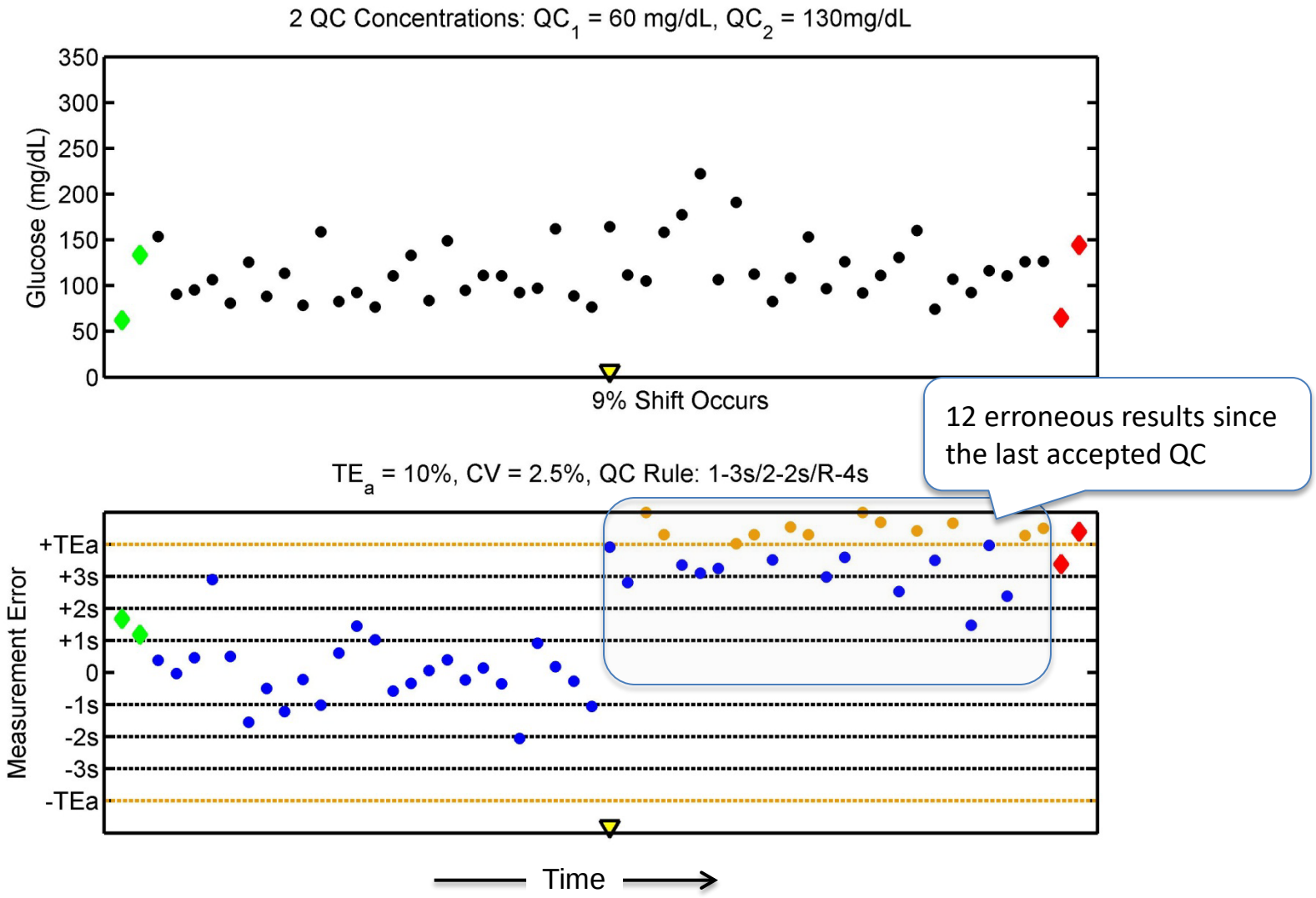
Erroneous Patient Results: Example 2



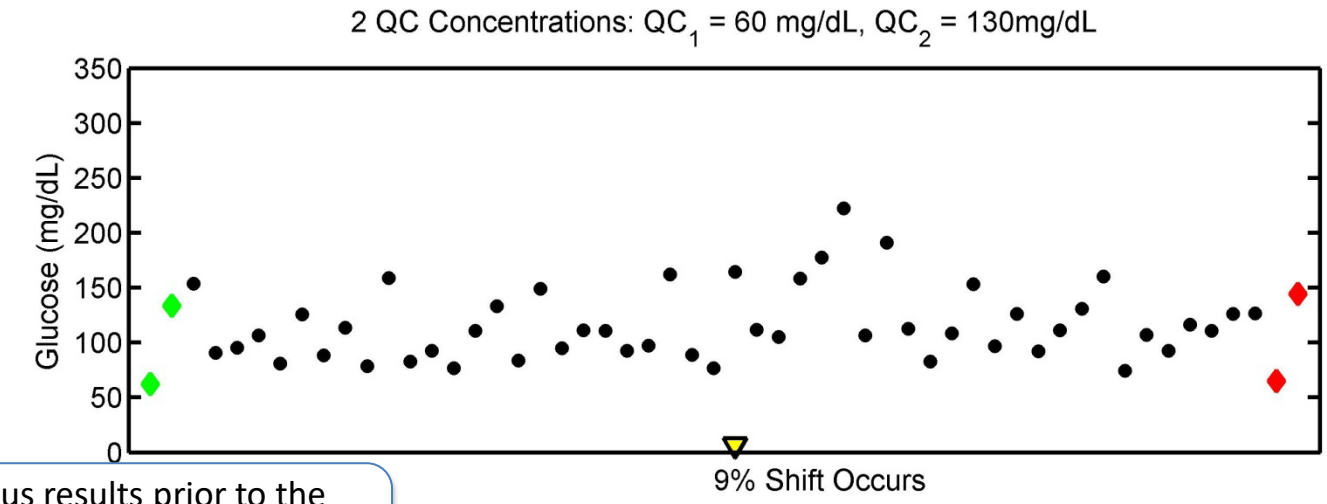
Erroneous Patient Results: Example 2



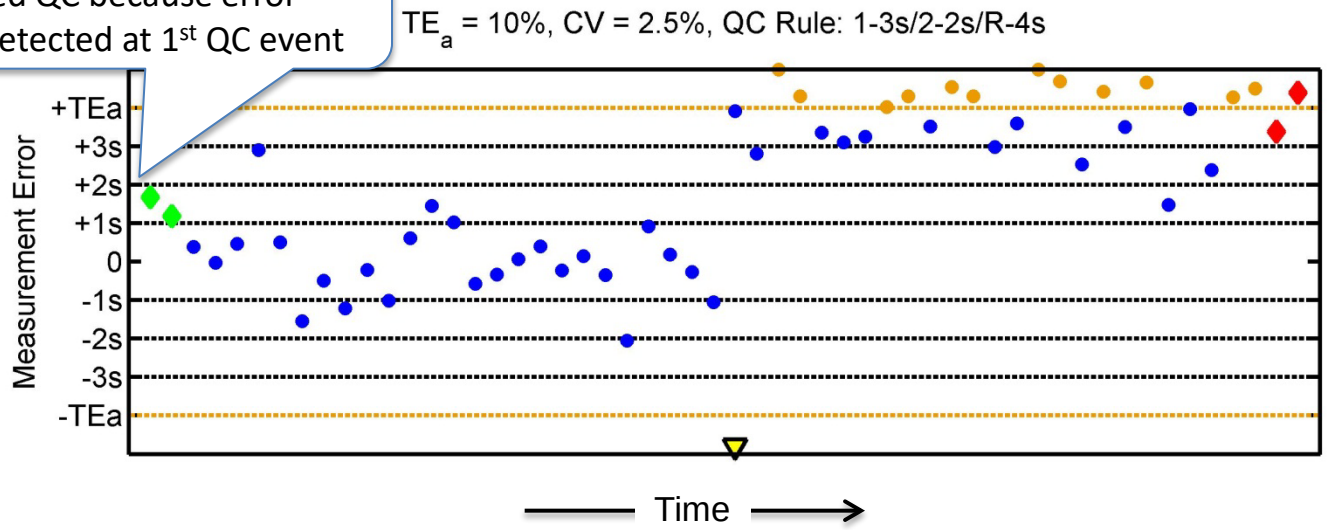
Erroneous Patient Results: Example 2



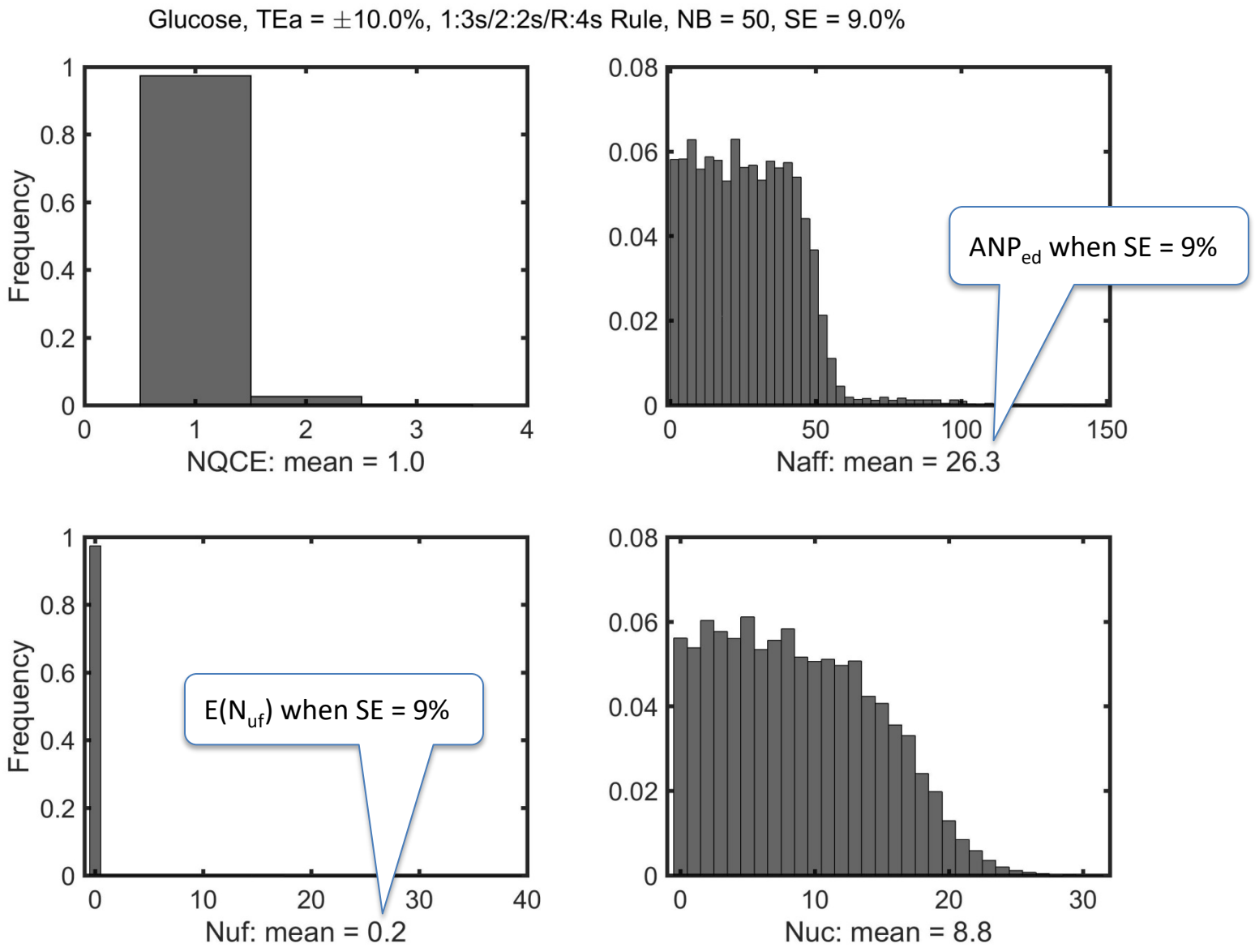
Erroneous Patient Results: Example 2



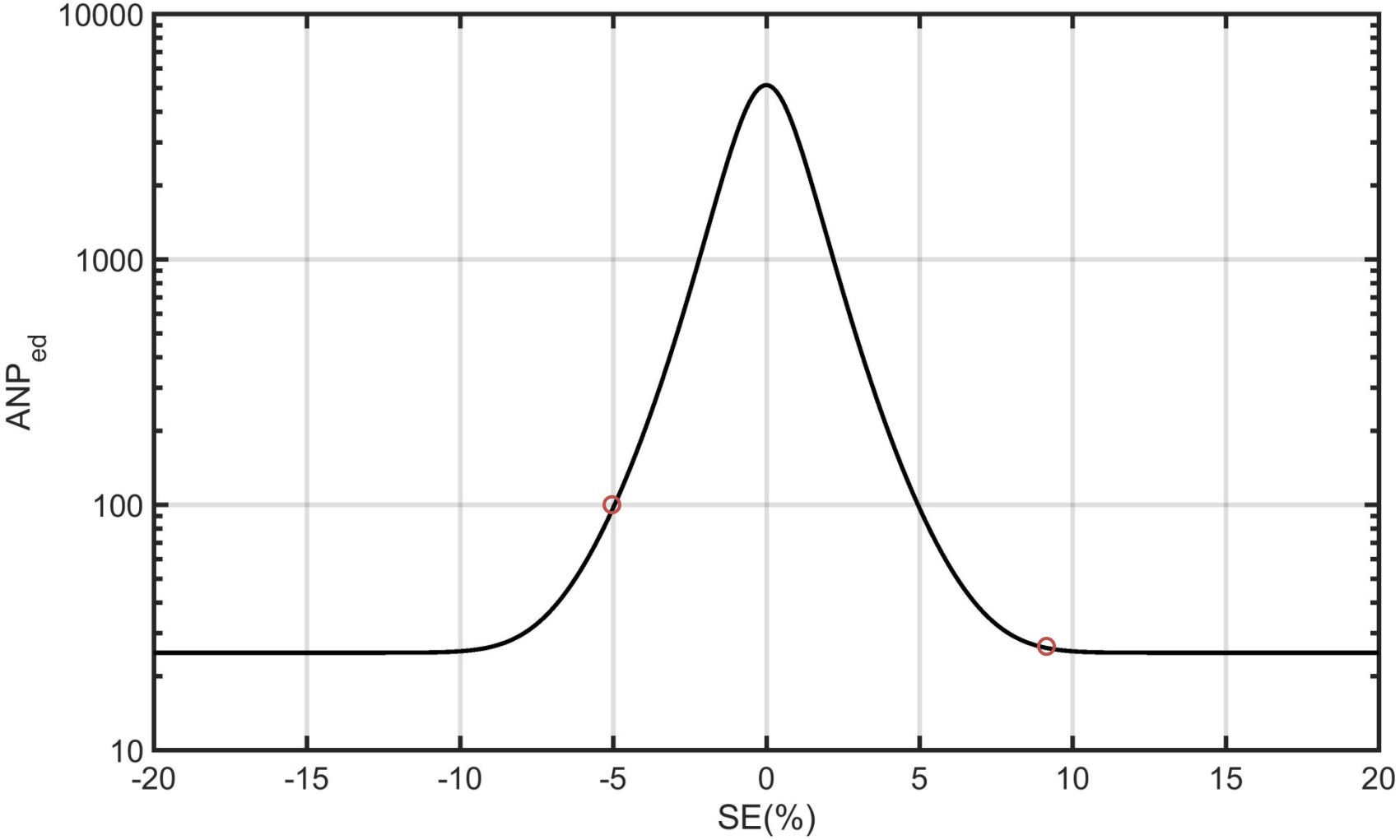
No erroneous results prior to the last accepted QC because error condition detected at 1st QC event



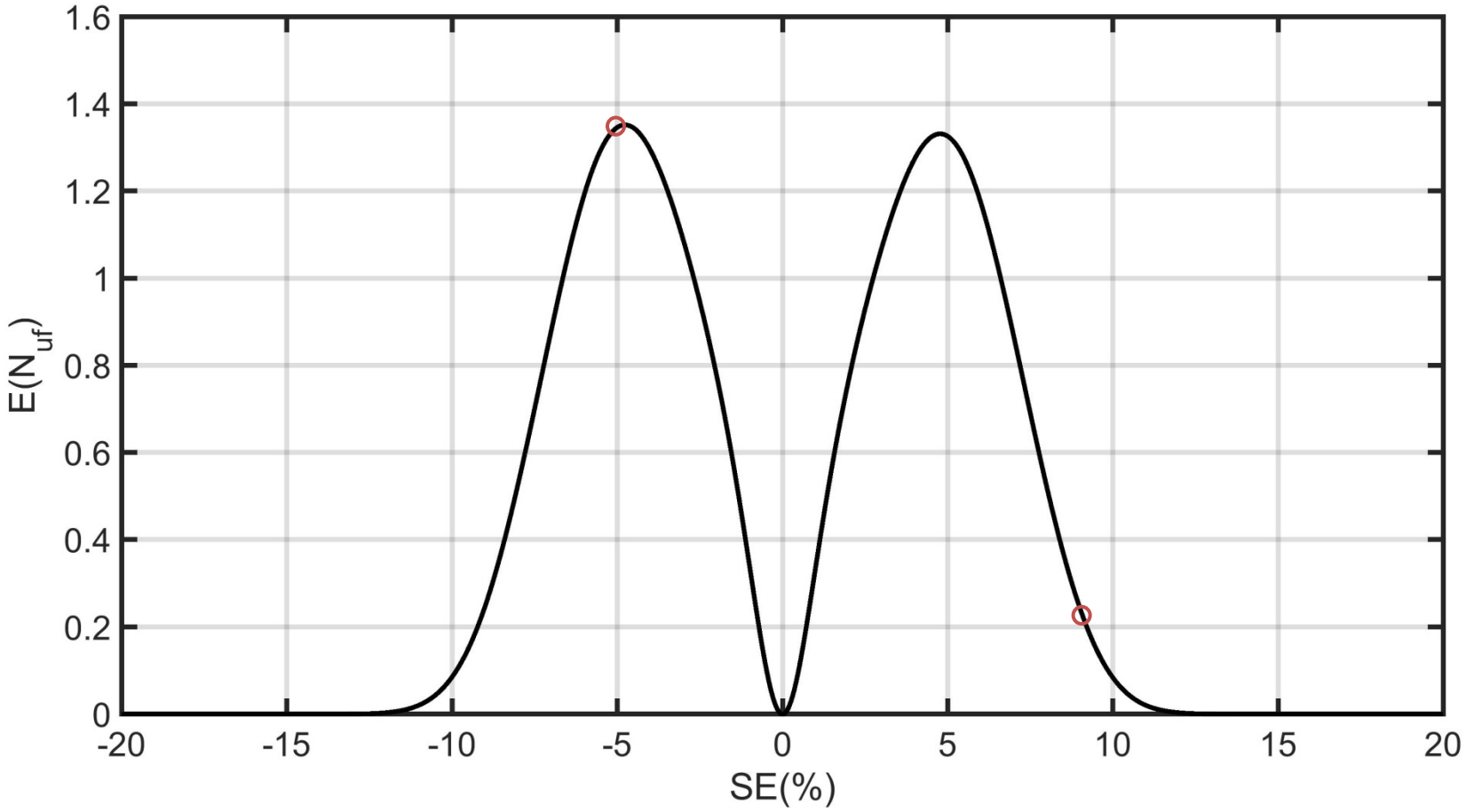
Erroneous Patient Results: Example 2



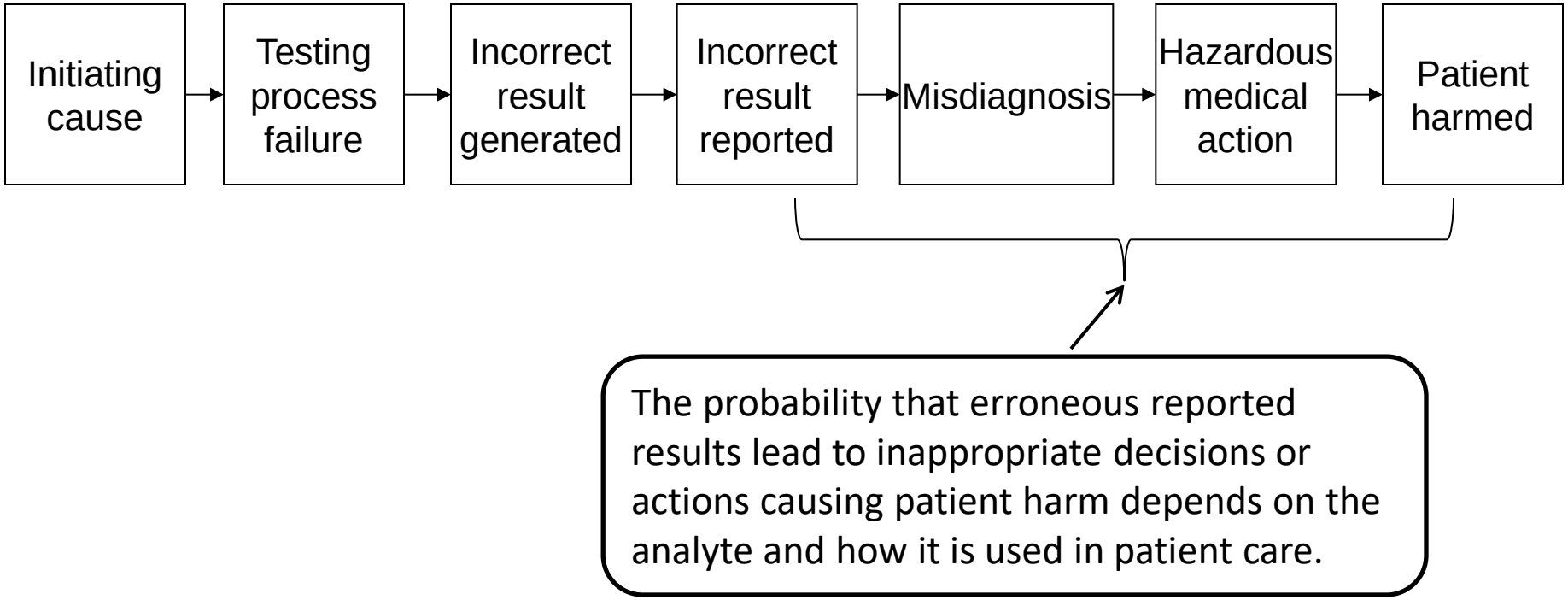
Average # of Affected Patient Results



Expected # of Erroneous Patient Results Prior to Last Accepted QC Event



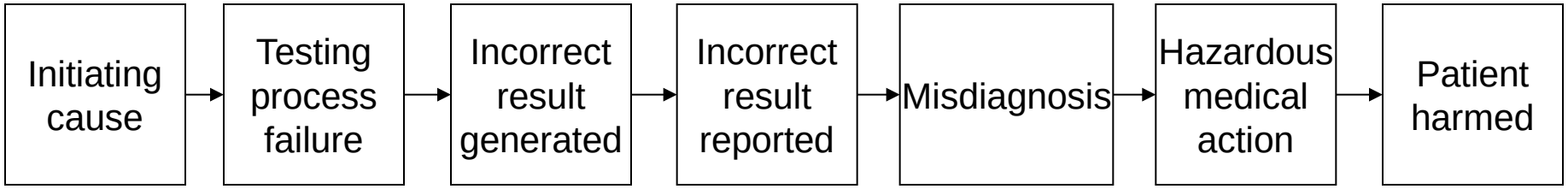
Predicting Probability of Patient Harm



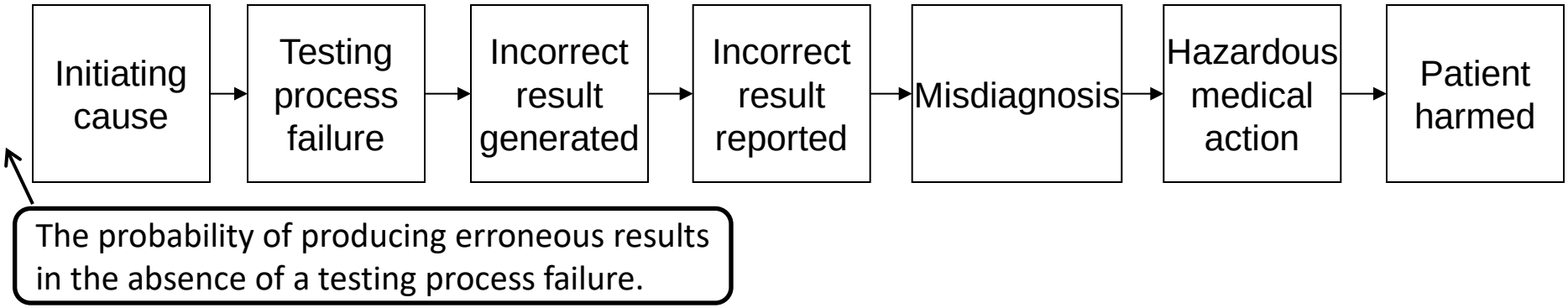
Probability Erroneous Results Lead to Harm

- The probability that erroneous reported results lead to patient harm will depend on;
  - knowledge of how test results are used to make patient care decisions.
  - may be obtained from expert opinion, the literature, or consultation with local physicians

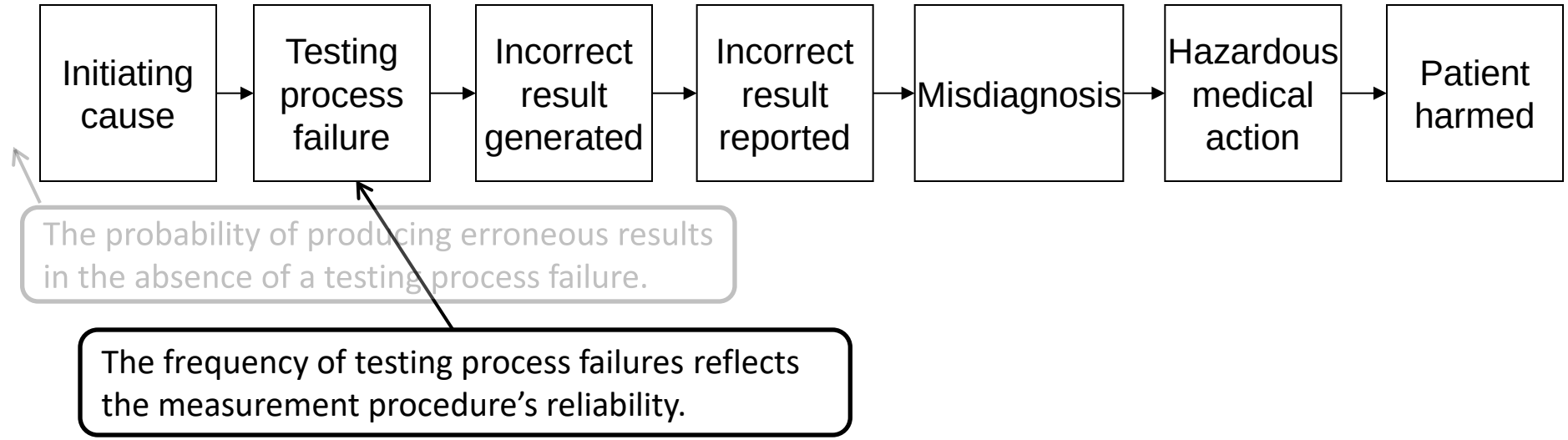
Predicting Probability of Patient Harm



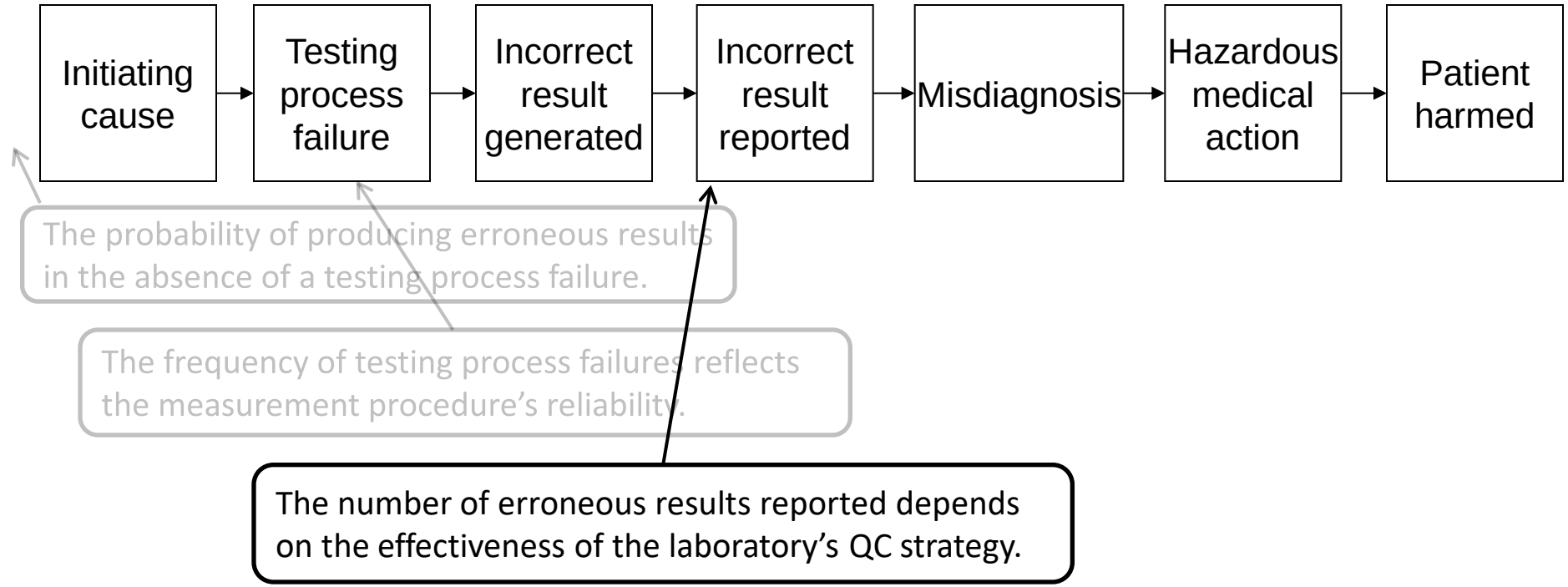
Predicting Probability of Patient Harm



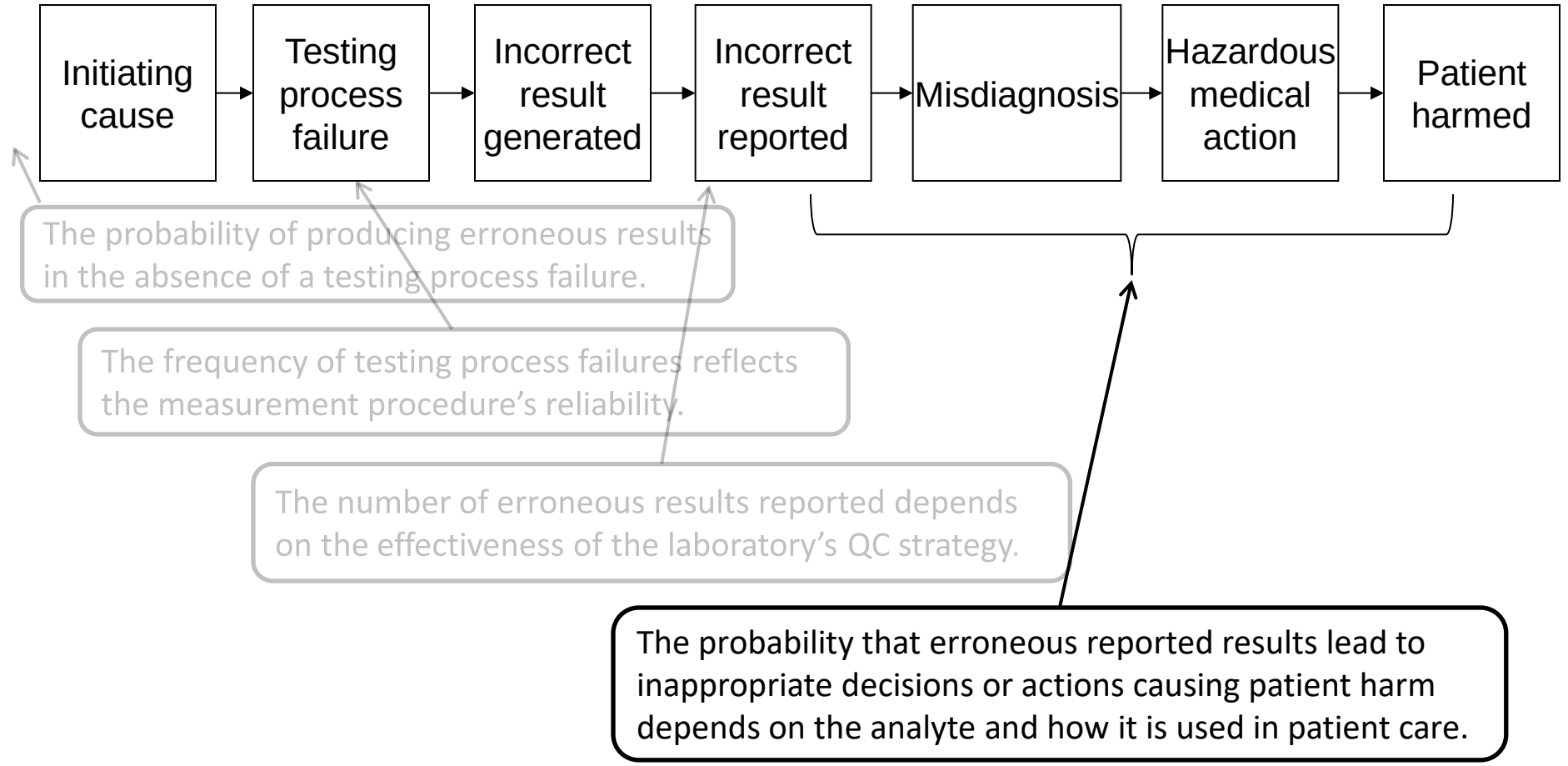
Predicting Probability of Patient Harm



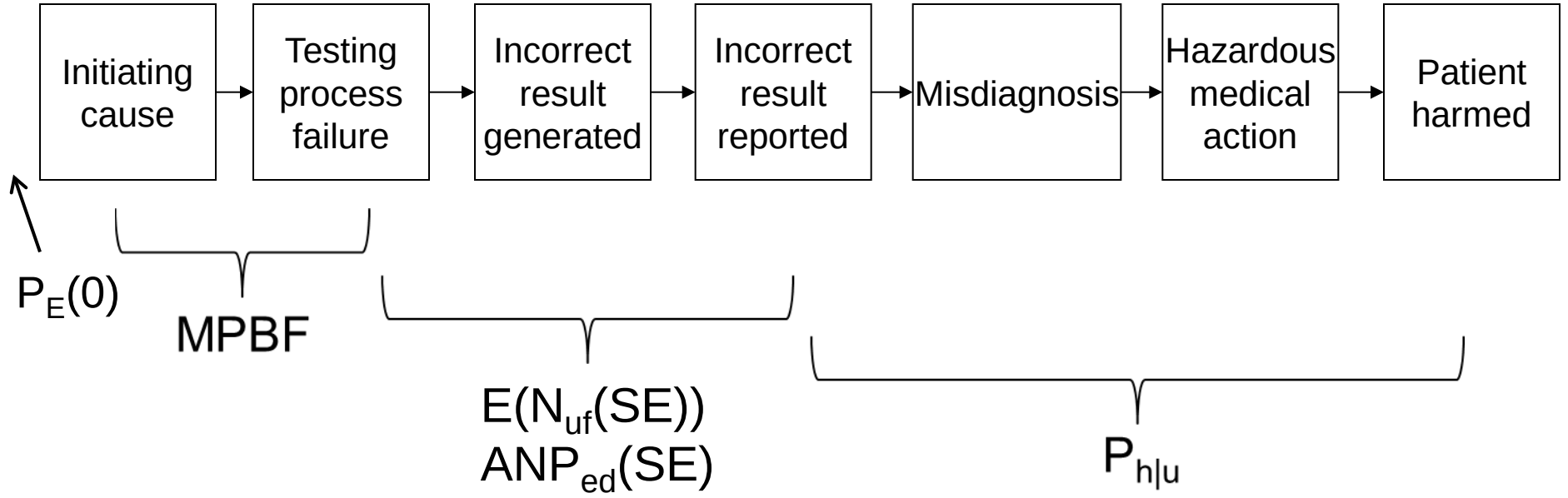
Predicting Probability of Patient Harm



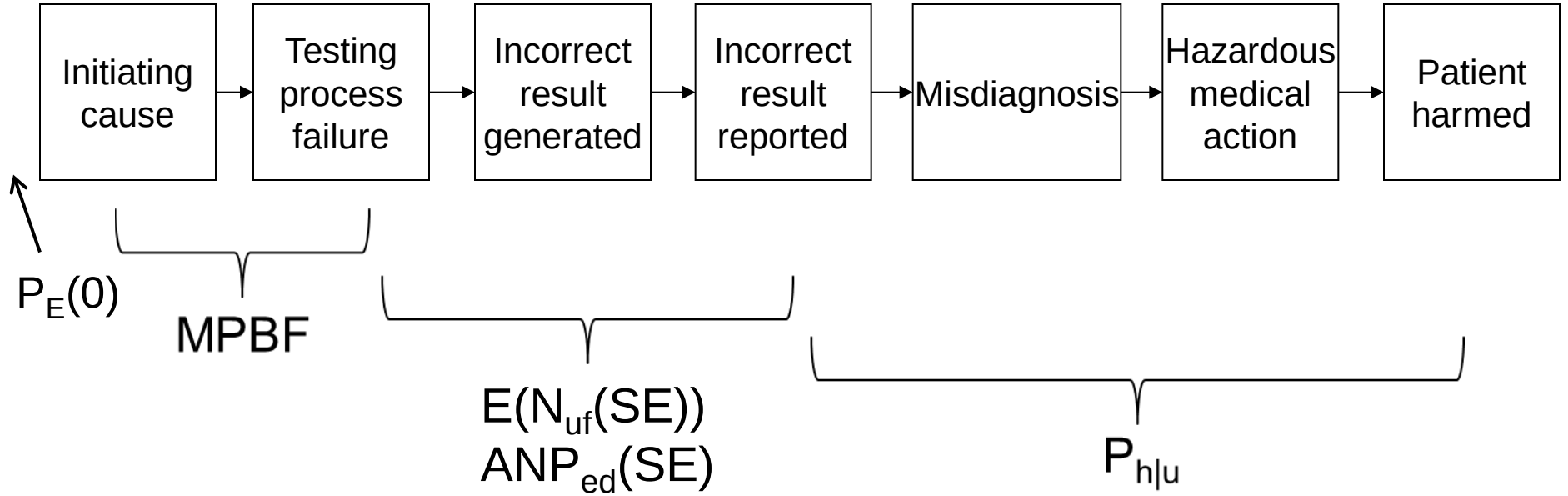
Predicting Probability of Patient Harm



Predicting Probability of Patient Harm



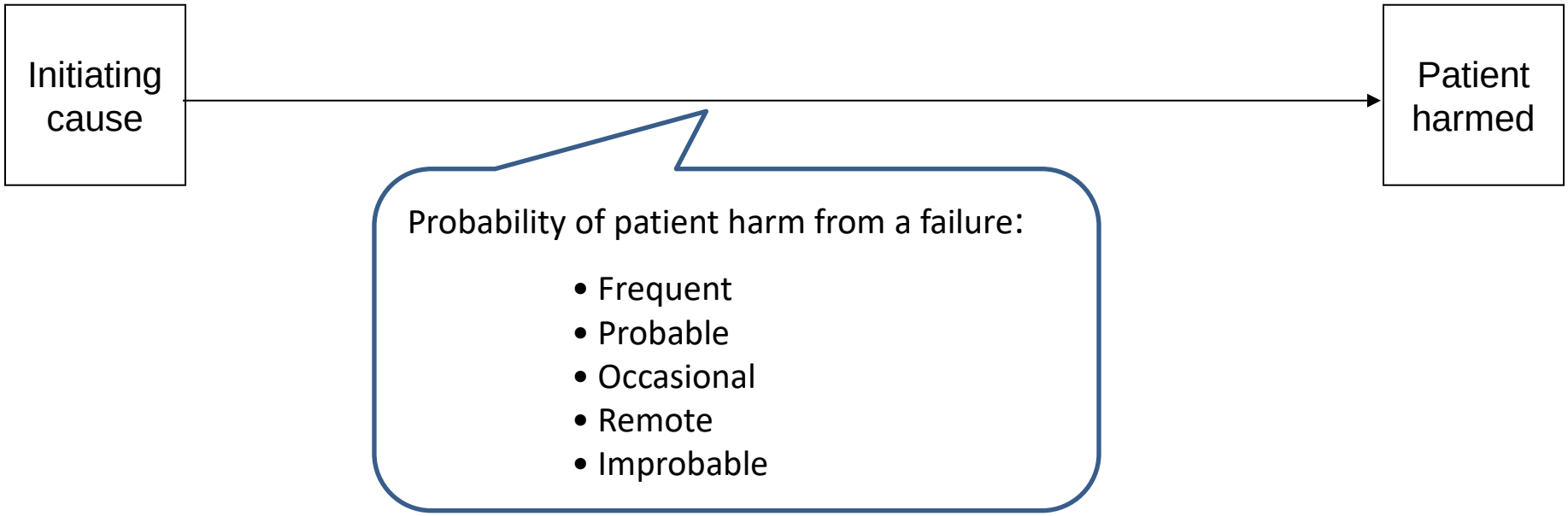
Predicting Probability of Patient Harm



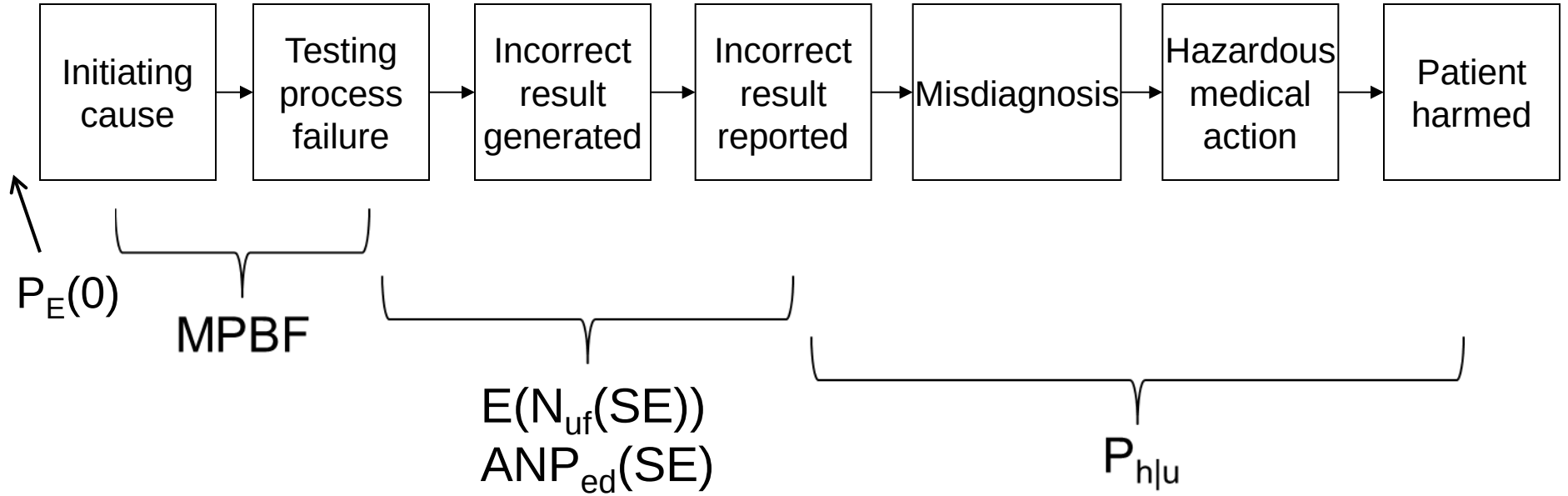
$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

Predicting Probability of Patient Harm

We should be able to do better than this!



Predicting Probability of Patient Harm



$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

Predicting Probability of Patient Harm

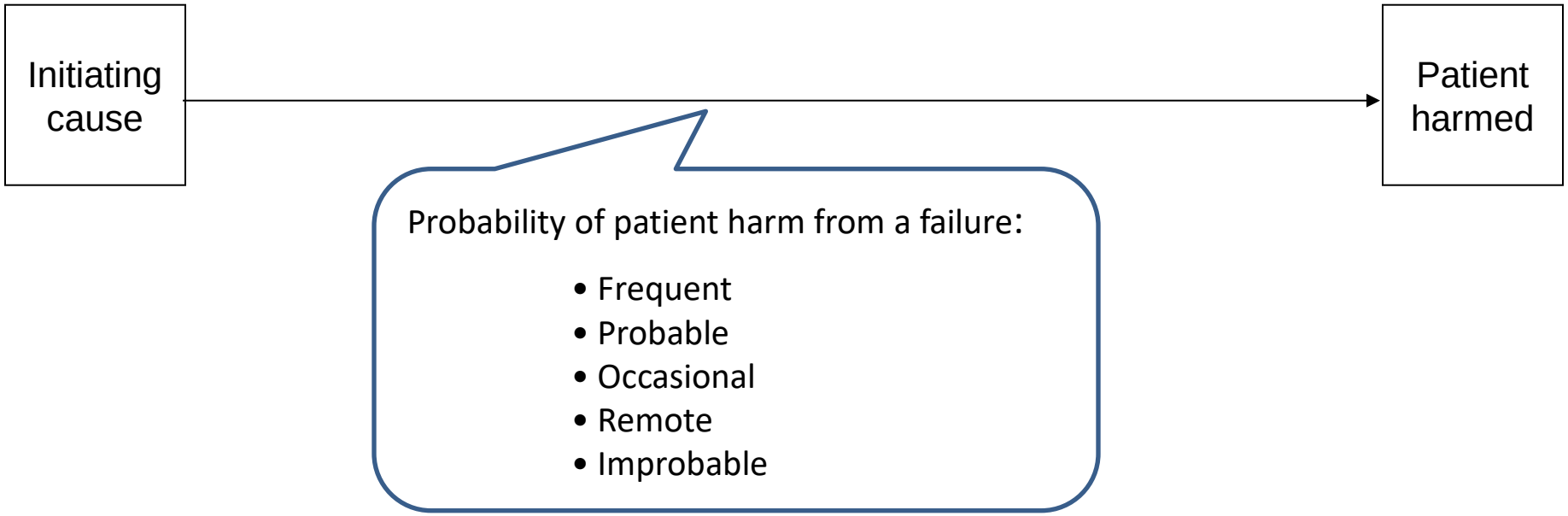
- Can be computed based on;
  - The in-control probability of producing erroneous results
  - The reliability of the measurement procedure
  - The effectiveness of the QC strategy
  - The likelihood that erroneous reported results cause harm
- Cannot be computed without computer software that performs the required computations

Predicted Probability of Harm Example

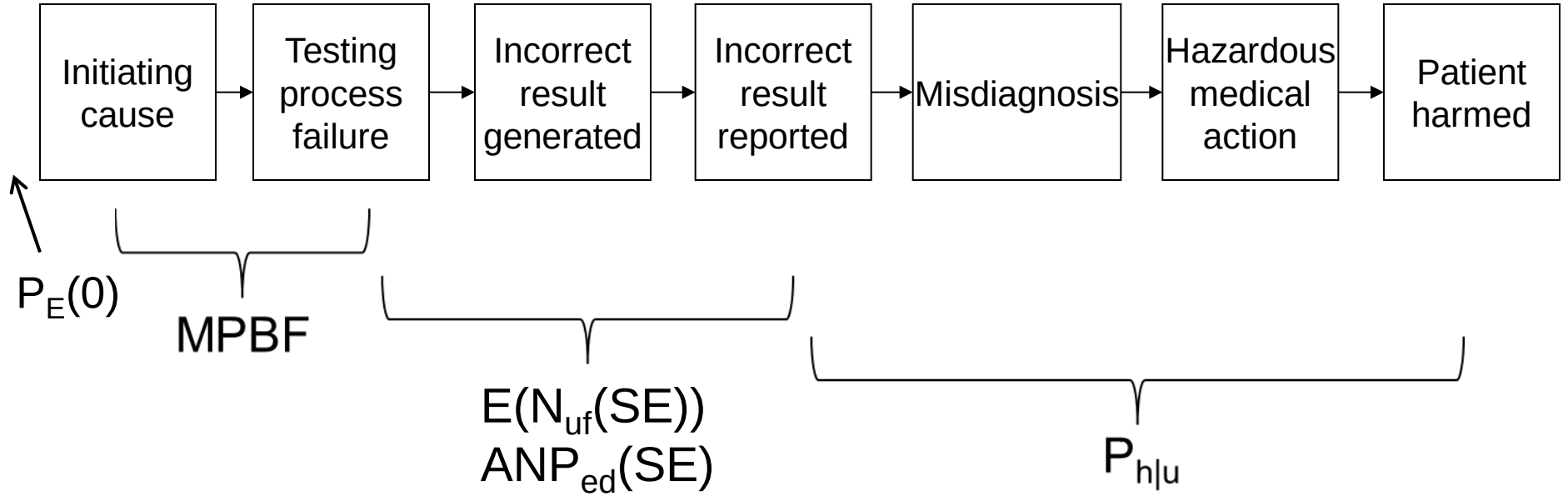
- Glucose: CV = 2.5%,TEa = ±10%
- Average # patient results / day = 100
- Mean days between test system failures = 30
  - MPBF = 100*30 = 3,000
- QC Strategy:
  - 2 QC levels,
  - QCs evaluated once per day,
  - 1:3s QC rule
- Probability of harm given incorrect result = 0.5

Predicted Probability of Harm Example

What's the predicted probability of harm?



Predicting Probability of Patient Harm



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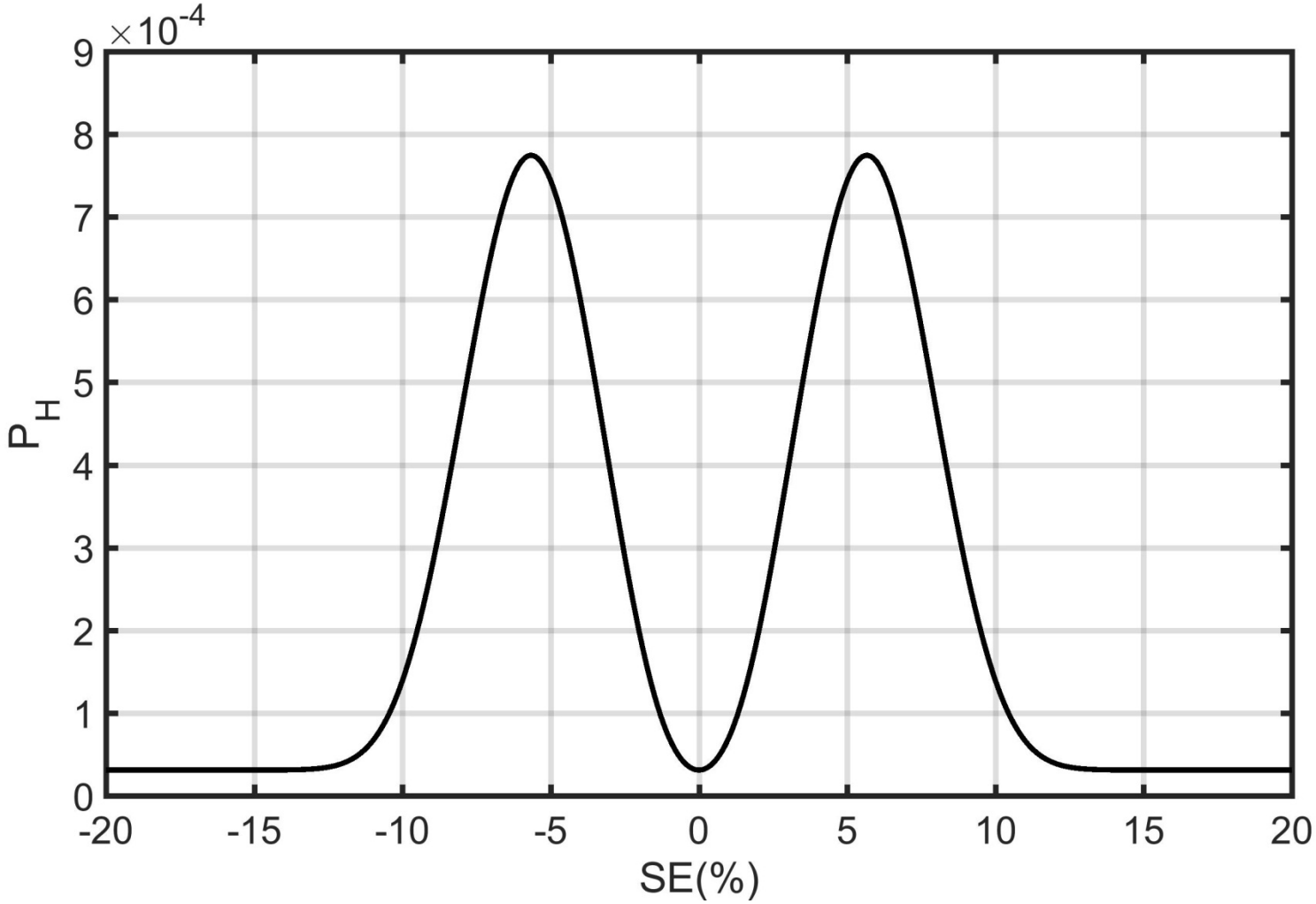
Predicted Probability of Harm Example



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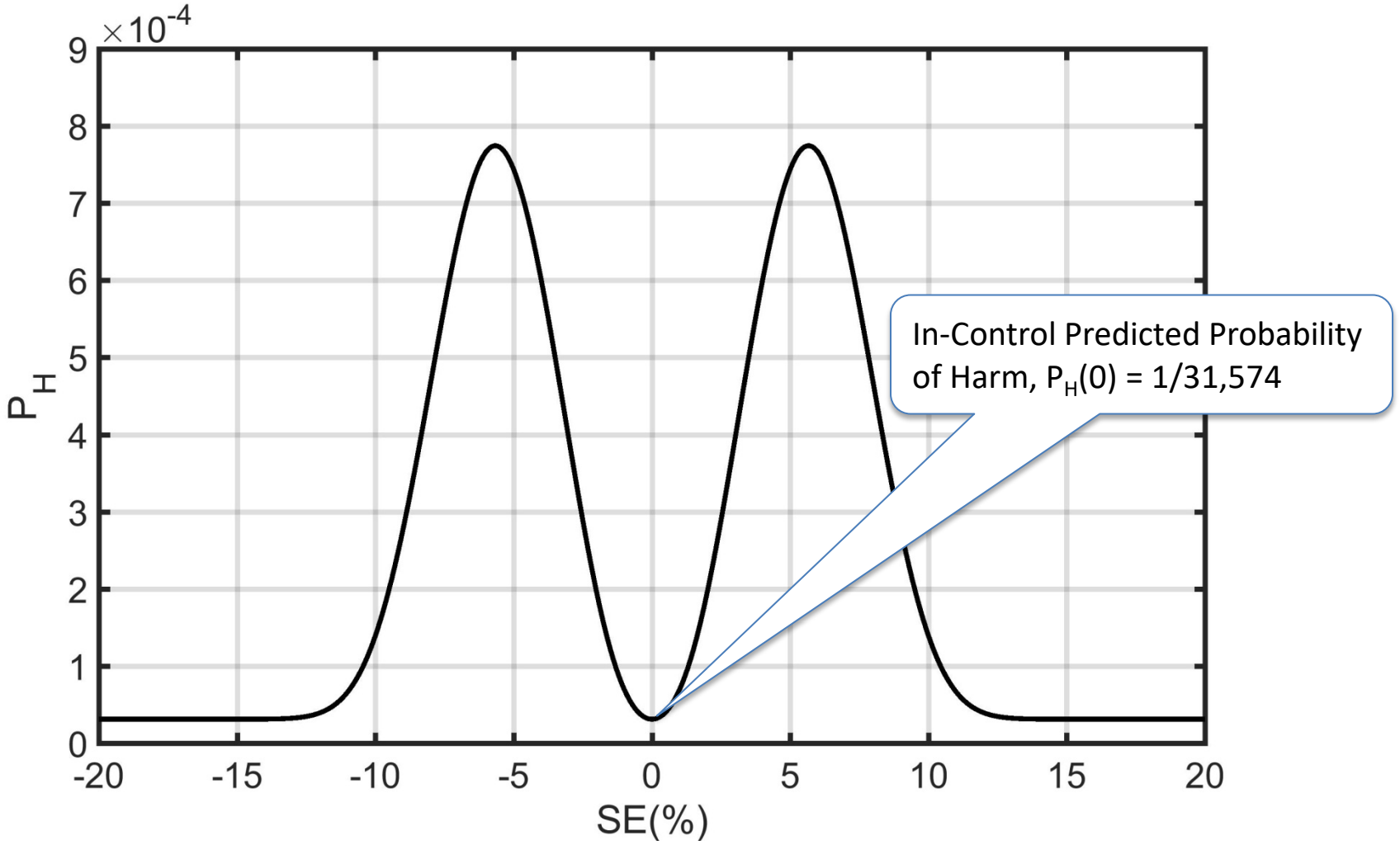
Predicted Probability of Harm Example



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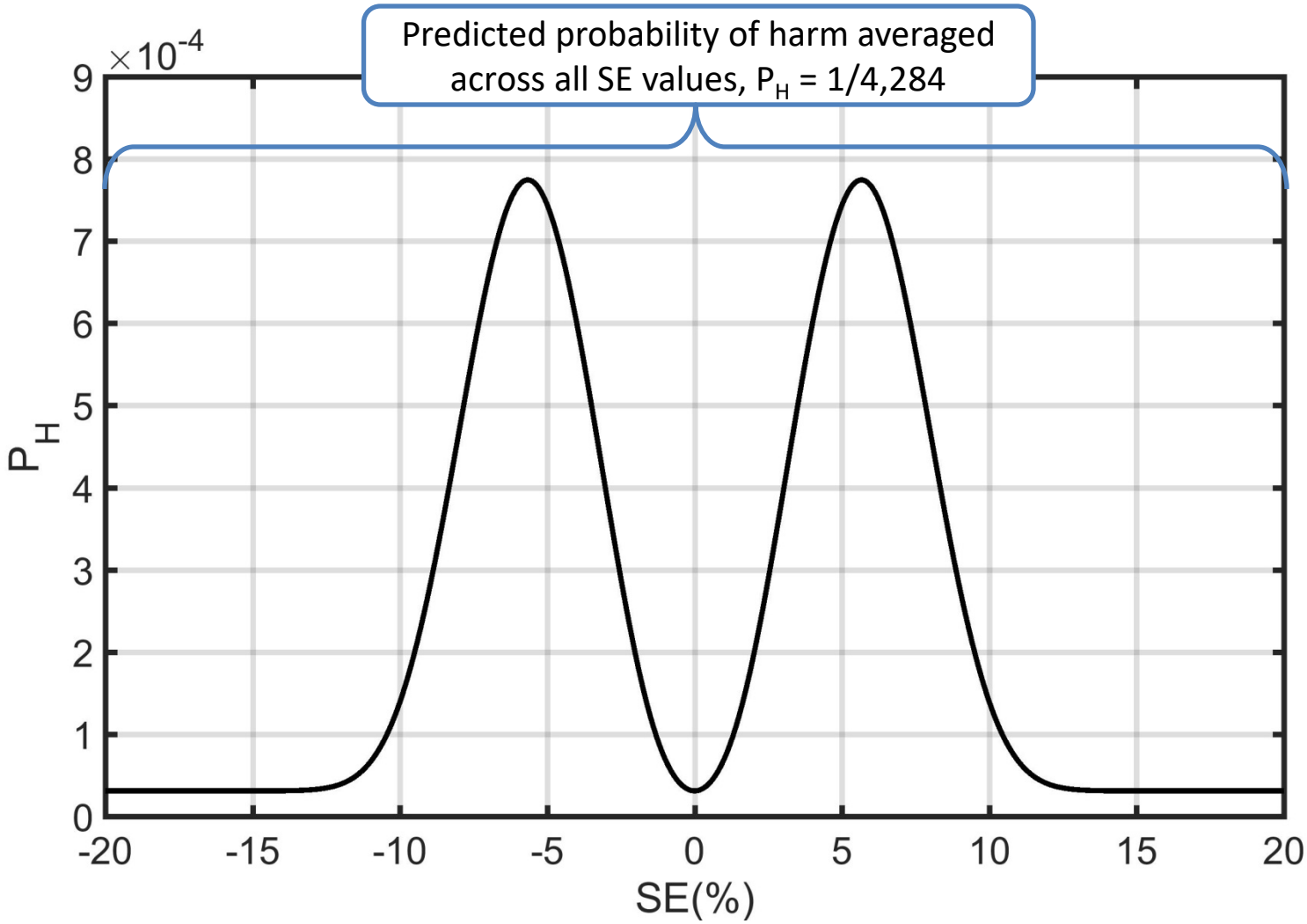
Predicted Probability of Harm Example



$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

Predicted and Acceptable Probability of Harm

- Predicted probability of harm depends on;
  - The measurement procedure's in-control performance and reliability,
  - The lab's QC strategy,
  - How analyte is used in medical decisions.

- Acceptable probability of harm is derived from;
  - Severity of harm,
  - Risk acceptability matrix.

Patient Risk Management Index: RMI

- We define the patient risk management index as;

$$\text{RMI} = \frac{\text{Predicted PH}}{\text{Acceptable PH}}$$

- RMI ≤ 1 implies acceptable risk.
- RMI values permit easy assessment and comparison of multiple analytes
  - with different frequencies of test system failure
  - with different probabilities of harm from erroneous results
  - with different severities of patient harm

RMI Example

- Glucose severity of harm = Minor

ISO 14971 - Risk Acceptability Matrix

	Severity of Harm				
Probability of Harm	**Negligible**	**Minor**	**Serious**	**Critical**	**Catastrophic**
Frequent	Unacceptable	Unacceptable	Unacceptable	Unacceptable	Unacceptable
Probable	Unacceptable	Unacceptable	Unacceptable	Unacceptable	Unacceptable
Occasional	Acceptable	Acceptable	Unacceptable	Unacceptable	Unacceptable
Remote	Acceptable	Acceptable	Acceptable	Unacceptable	Unacceptable
Improbable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

EP23-A Risk Acceptability Matrix

	Severity of Harm				
Probability of Harm	**Negligible**	**Minor**	**Serious**	**Critical**	**Catastrophic**
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Occasional	Acceptable	Acceptable	Acceptable	Unacceptable	Unacceptable
Remote	Acceptable	Acceptable	Acceptable	Acceptable	Unacceptable
Improbable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

RMI Example

- Glucose severity of harm = Minor
- Acceptable P_H:
  - Acceptable frequency of harm level: Occasional

Probability of Harm Categories

Category Level	CLSI EP23 Example	ISO 14971 Example
Frequent	Once/week	≥1/1,000
Probable	Once/month	<1/1,000 and ≥1/10,000
Occasional	Once/year	<1/10,000 and ≥1/100,000
Remote	Once/few years	<1/100,000 and ≥1/1,000,000
Improbable	Once/life of measuring system	<1/1,000,000

RMI Example

- Glucose severity of harm = Minor
- Acceptable P_H:
  - Acceptable frequency of harm level: Occasional
  - Using ISO 14971 Risk Acceptability Matrix: $P_H < 1/10{,}000$

$$\text{RMI} = \text{Predicted } P_H \,/\, \text{Acceptable } P_H$$

RMI Example

- Glucose severity of harm = Minor
- Acceptable P_H:
  - Acceptable frequency of harm level: Occasional
  - Using ISO 14971 Risk Acceptability Matrix: $P_H < 1/10{,}000$

$$\text{RMI} = \text{Predicted } P_H \,/\, \text{Acceptable } P_H$$

$$\text{RMI} = (1/4{,}284) \,/\, (1/10{,}000)$$

$$\text{RMI} = 2.3$$

Change QC Rule

- Glucose: CV = 2.5%,TEa = ±10%
- Average # patient results / day = 100
- Mean days between test system failures = 30
  - MPBF = 100*30 = 3,000
- Probability of harm given incorrect result = 0.5
- QC Strategy:
  - 2 QC levels,
  - **1:3s QC rule**,
  - QC evaluated once per day

Change QC Rule

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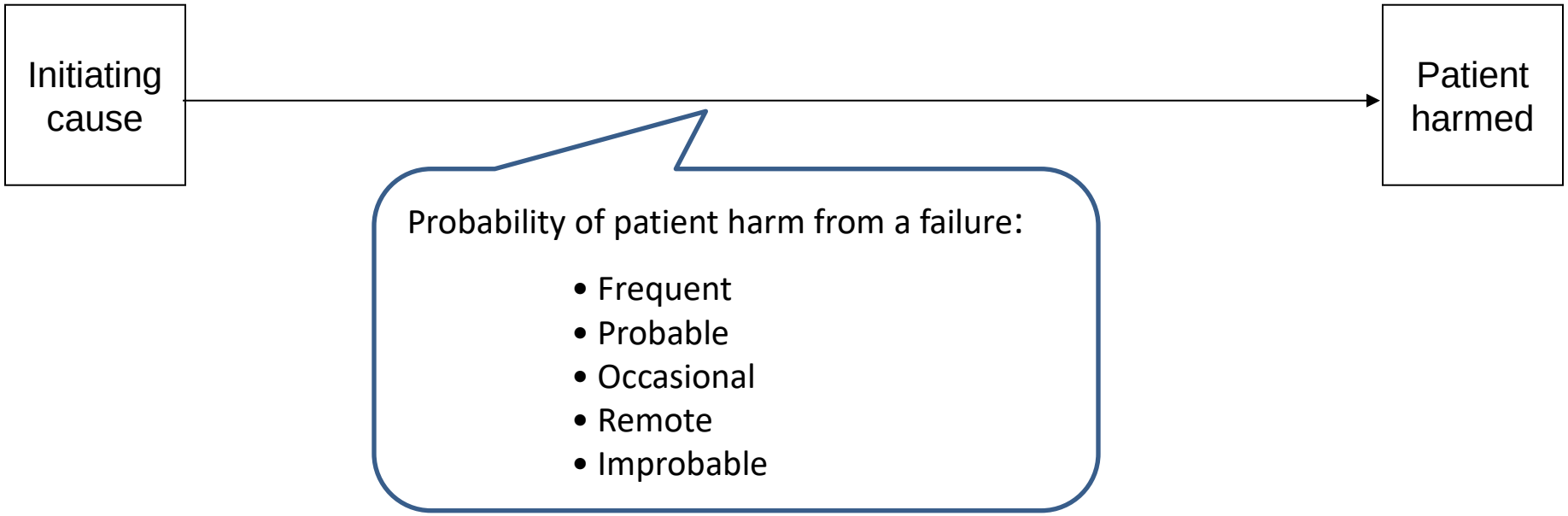
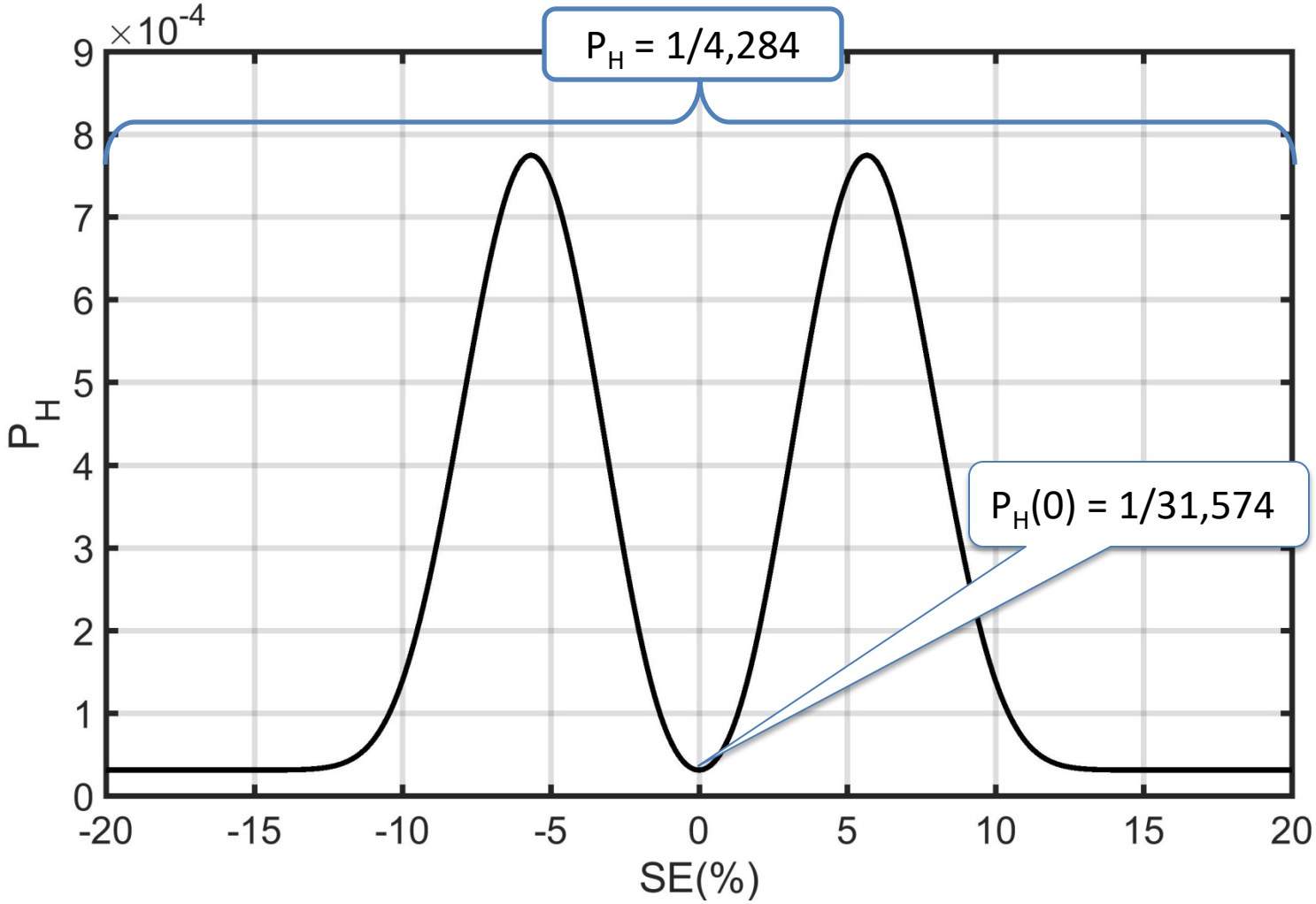
Change QC Rule

What's the predicted probability of harm?

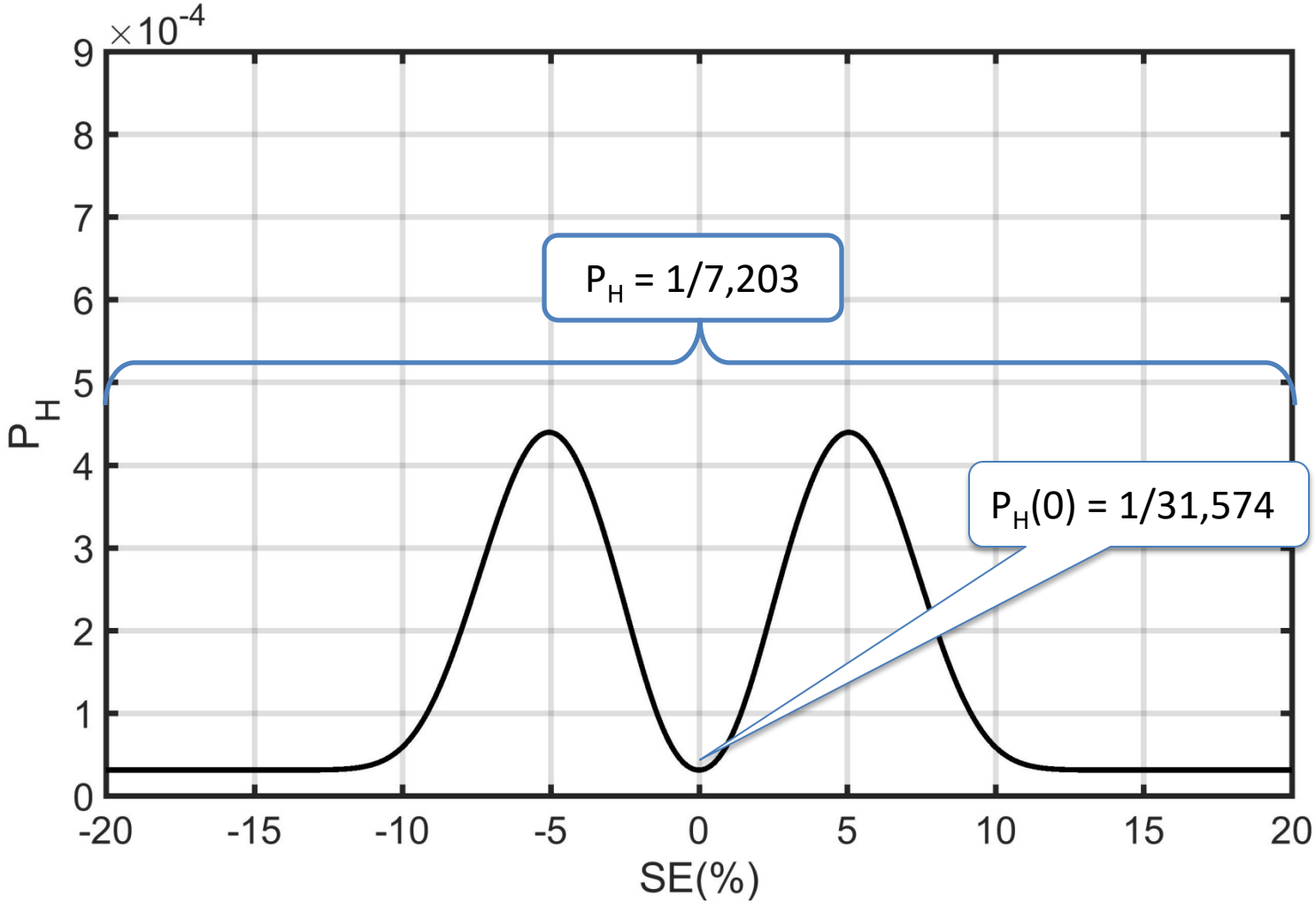


1:3s QC Rule



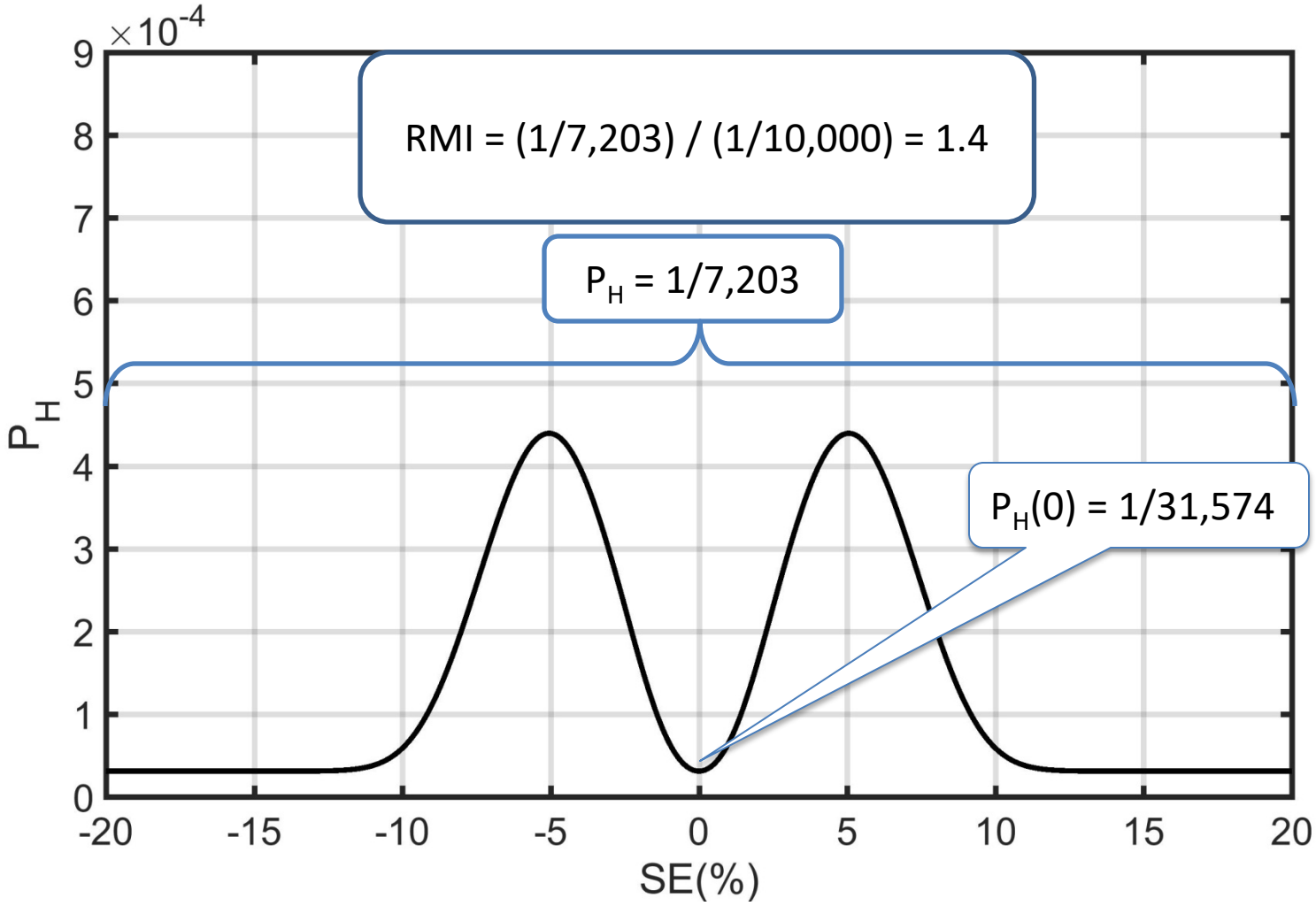
$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

1:3s/2:2s/R:4s QC Rule



$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

1:3s/2:2s/R:4s QC Rule



$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

Change QC Frequency

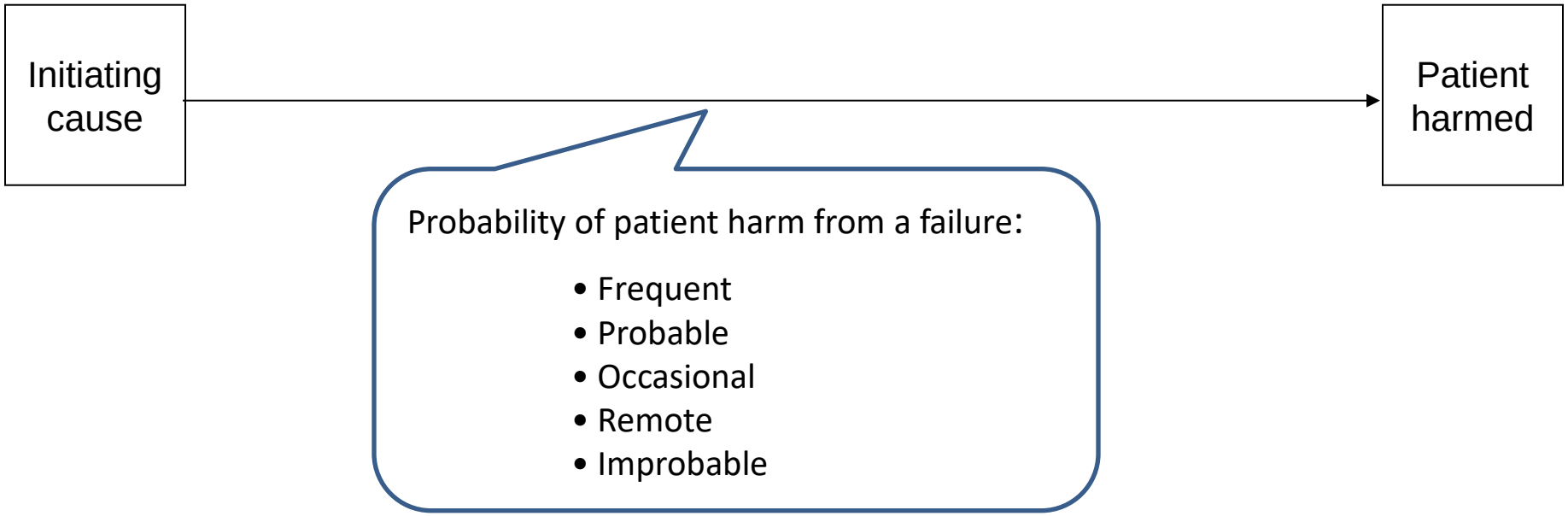
- Glucose: CV = 2.5%,TEa = ±10%
- Average # patient results / day = 100
- Mean days between test system failures = 30
  - MPBF = 100*30 = 3,000
- Probability of harm given incorrect result = 0.5
- QC Strategy:
  - 2 QC levels,
  - 1:3s/2:2s/R:4s QC rule,
  - **QC evaluated once per day**

Change QC Frequency

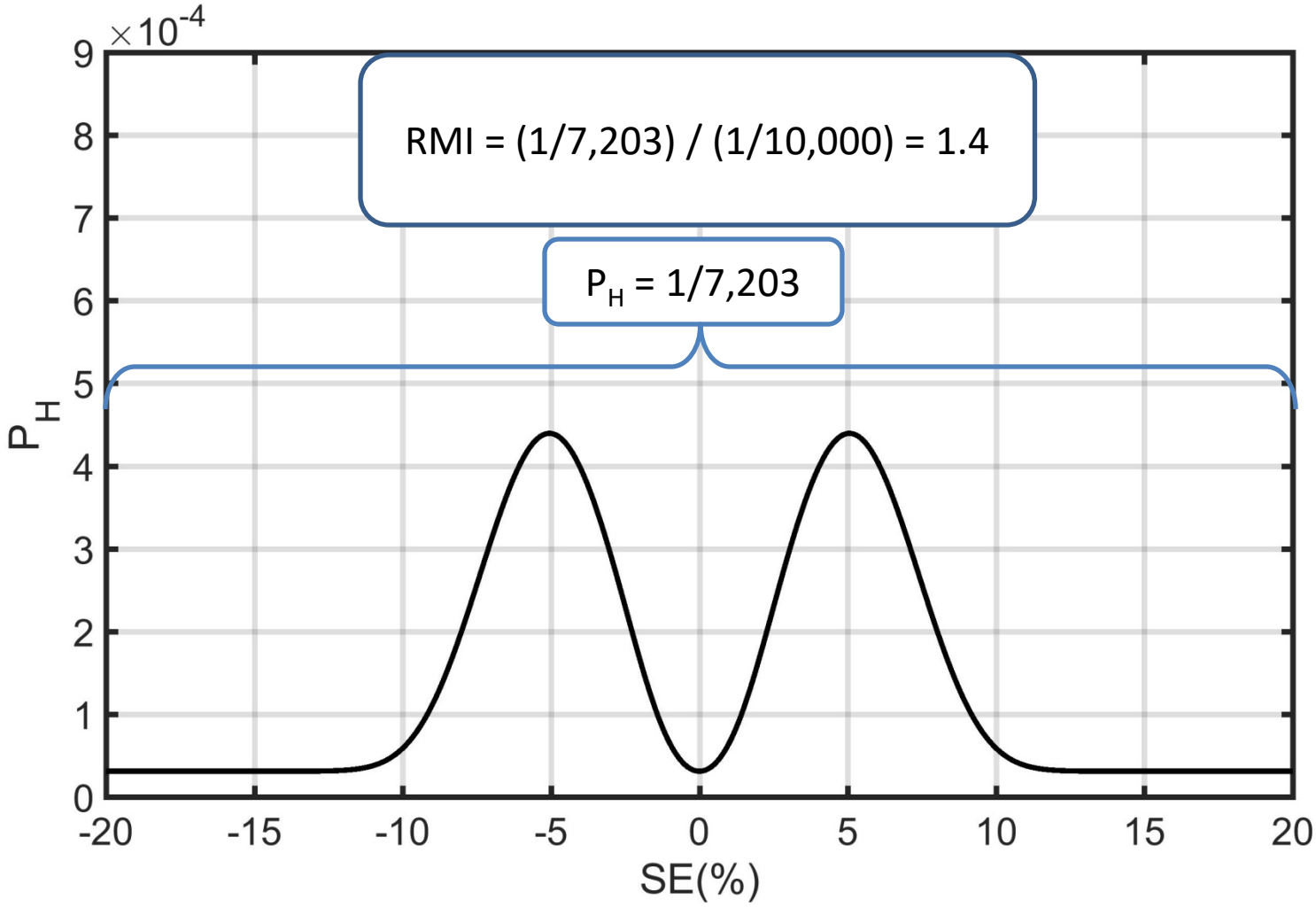
- Glucose: CV = 2.5%,TEa = ±10%
- Average # patient results / day = 100
- Mean days between test system failures = 30
  - MPBF = 100*30 = 3,000
- Probability of harm given incorrect result = 0.5
- QC Strategy:
  - 2 QC levels,
  - 1:3s/2:2s/R:4s QC rule,
  - **QC evaluated twice per day**

Change QC Frequency

What's the predicted probability of harm?



QC Evaluated Once Per Day



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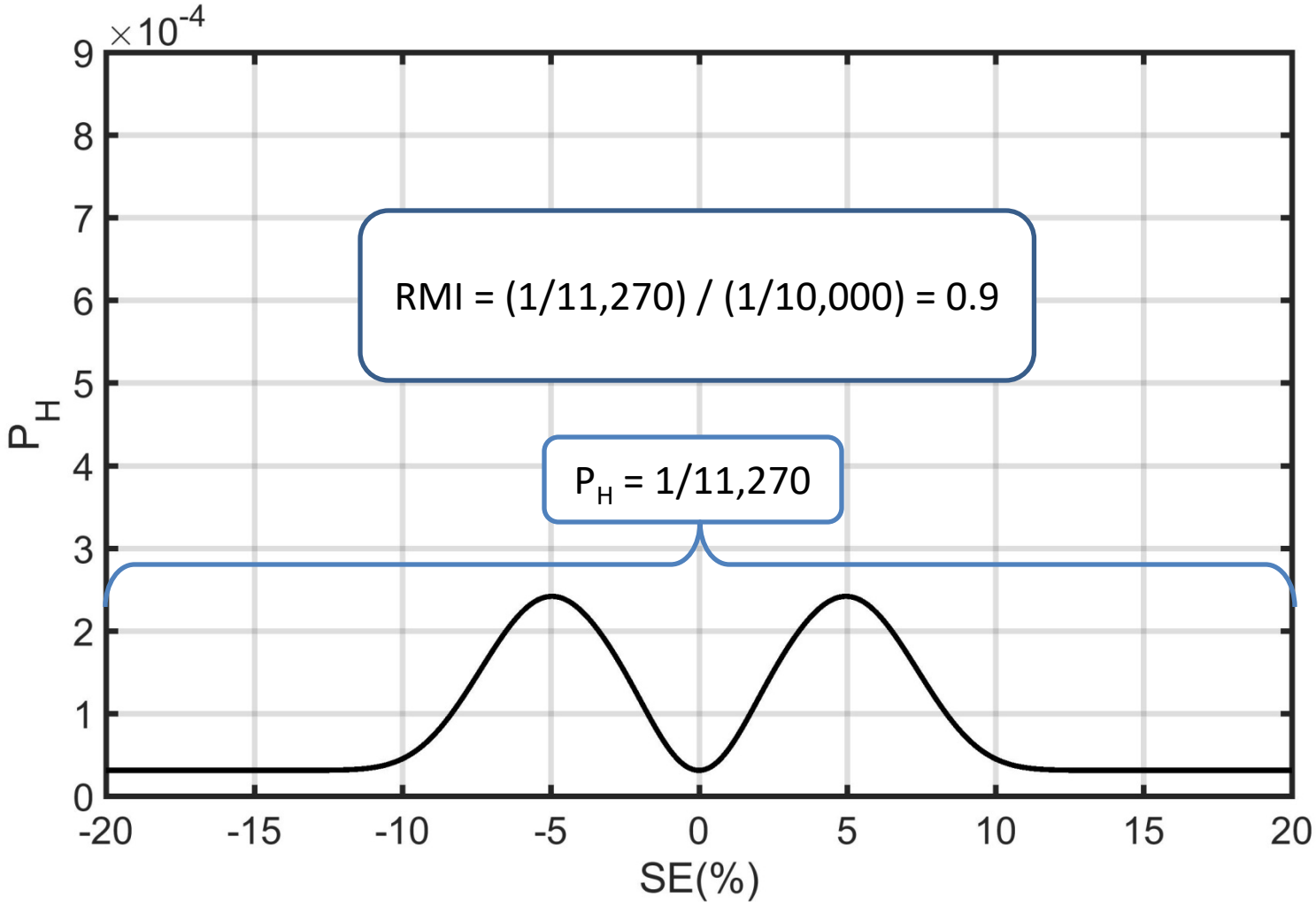
QC Evaluated Twice Per Day



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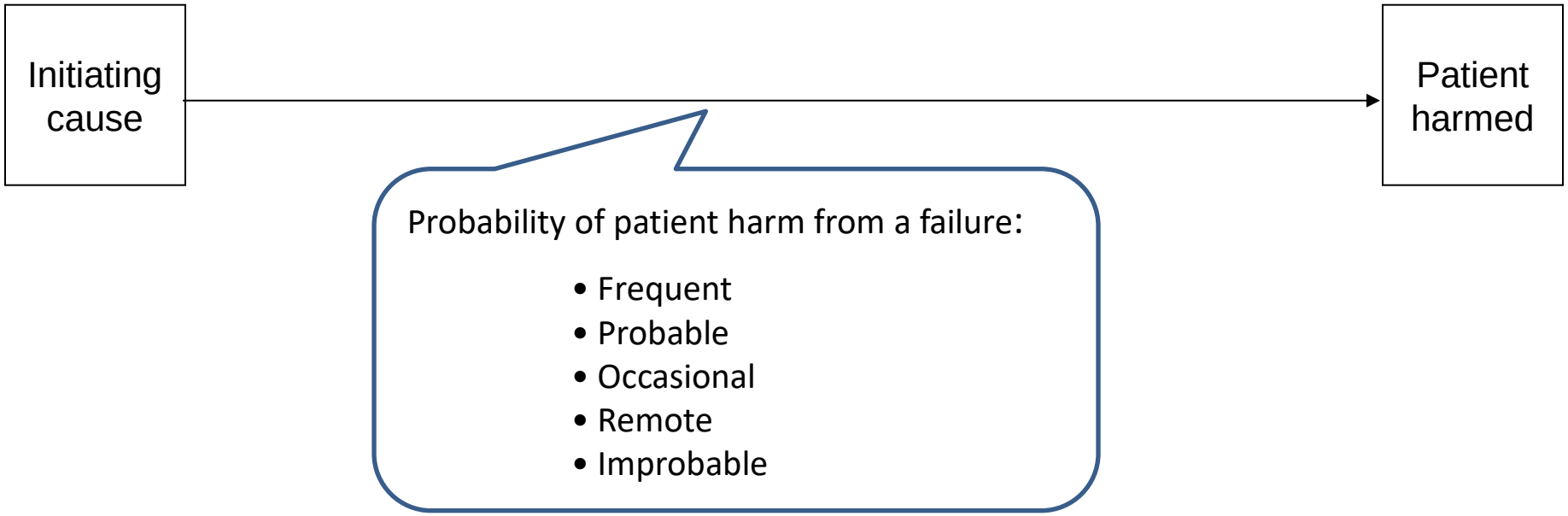
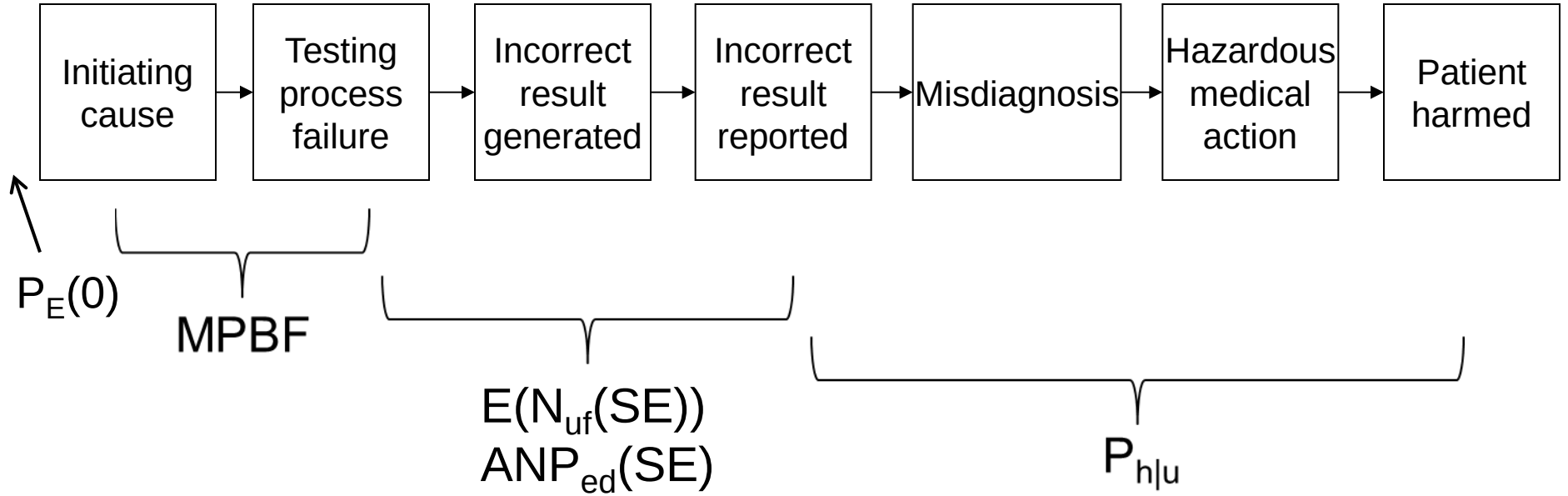
Predicted Probability of Patient Harm



Predicted Probability of Patient Harm



$$P_H(SE) = \{P_E(0) + E(N_{uf}(SE)) / (MPBF + ANP_{ed}(SE))\} * P_{h|u}$$

Summary

- A lab's tolerance for reporting erroneous patient results should depend on;
  - the likelihood that erroneous patient results lead to harm,
  - the severity of patient harm.
- The lab's impact on patient risk depends on;
  - The in-control performance of the lab's measurement procedures
  - The reliability of the lab's measurement procedures
  - The lab's QC strategy
- It's important to be able to objectively assess the impact of a lab's QC strategy on patient risk.
- One way to link QC performance to patient risk is to compute RMI and seek QC strategies with RMI < 1.

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