Living with Risk

Understanding Risk
Risk-analysis, -containment & -communication

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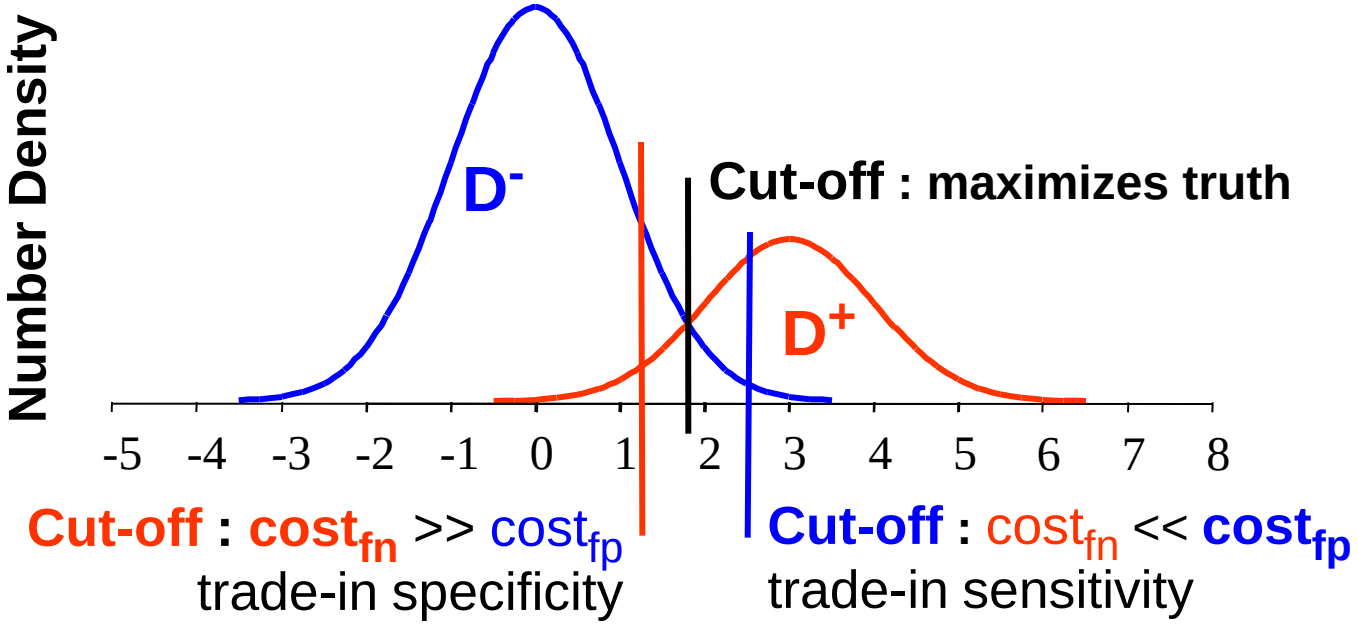
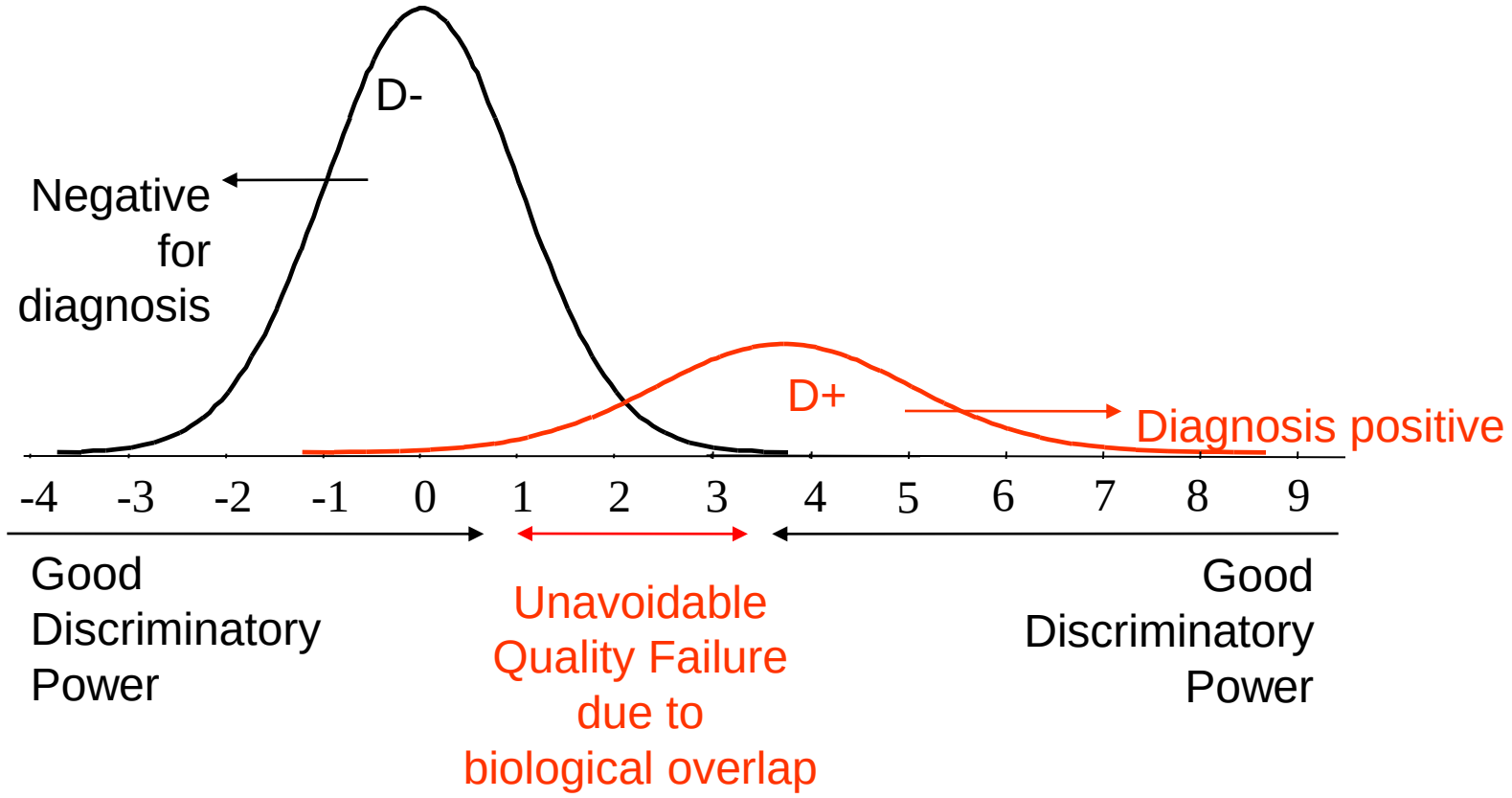
Intuitive Introduction

Where do you put your cut-off ?



Bayesian Model = maximize Utility
= minimize Adverse Effects
= min (fpr x $cost_{fp}$ + fnr x $cost_{fn}$)

You dislike gambling ?



What do you do when confronted with a " Grey Zone " result ?

- o You do not decide = Certain harm
- o You take a cut-off based decision = On average your patients benefit
- o You request additional tests = **Heuristic Model**

You comply with a " Minimal Requirement "

How the Doctor Thinks

After J Groopman

Medical diagnosis
is " Deciding in the face of Incomplete Knowledge "

Medical diagnosis 
is not " to confirm your suspicions "
but is " to reduce your doubts "
and " not to miss the unexpected "

Recipe :
Reduce risk by systematic application
of a differential diagnostic algoritm

How to negotiate Risk =
How to minimize avoidable harm ?
Summary

You (have to) accept the Risk & you minimize Adversity by a more or less Educated Gamble.

Bayesian Model

You don't accept the Risk & you minimize Risk by a more or less successful Problem-Solving Strategy.

Heuristics

These are complementary & simultaneous processes

Educational Goals

Educational Goals

Understanding Risk

Operational Definition : Risk = Deciding in the face of Uncertainty

Fault Trees, Cause-Effect- & Root-Cause-Analysis
as a first step in Failure Control

Robust Designs
as a means of Failure Prevention

Understand Method Validation as Risk Management

Contain Diagnostic Uncertainty by selection of appropriate tests

Optimize Robustness of your Method

Provide for Efficient Problem Solving Measures

Understand Laboratory Diagnosis as Communicating Risk

How to communicate how certain you are about the usefulness of a result

How to report Risk in a manner understood by the physician & the patient

Facilitate Fail-proof & Effective Communication

Requirements of Standards

Definitions

Hazard = potential source of harm

(ISO-1590 3.12)

Risk = combination of the probability of occurrence of harm and the severity of that harm

(ISO-1590 3.20)

= chance that an incident will occur (during the execution of a task)

Incident = the occurrence of a situation with harm (damage)

Harm = the unwanted consequences of an incident

Incidents of our own doing – An act of God / Nature / Labour relationships / …

Catastrophic Failure

↓ Main Focus of this Unit

↓ Disaster Preparedness

CITED FROM ISO15189:2007

4.9 Identification and control of nonconformities

4.9.1 Laboratory management shall have a policy and procedure to be implemented when it detects that any aspect of its examinations does not conform with … the agreed upon requirements of … the requesting clinician. These shall ensure that:

a) personnel responsible for problem resolution are designated

b) the actions to be taken are defined

Requirements of Standards

The external auditor

certifies whether your system is credible

Can you defend your interpretation of the standard ?

The discussion will focus on

“ Risk appreciation,
preparedness & appropriateness of actions ”
as an explicit element of

- **test validation**
- **preventive actions**

Cited from ISO 15189:2007

5.6 Assuring quality of examination procedures

5.6.1 The laboratory shall design internal quality control systems that verify the attainment of the intended quality of results. It is important that the control system provide staff members with clear and easily understood information on which to base technical and medical decisions. Special attention should be paid to the elimination of mistakes in the process of handling samples, requests, examinations, reports, etc.

5.6.2 The laboratory shall determine the uncertainty of results, where relevant and possible. Uncertainty components which are of importance shall be taken into account. Sources that contribute to uncertainty may include sampling, sample preparation, sample portion selection, calibrators, reference materials, input quantities, equipment used, environmental conditions, condition of the sample and changes of operator.

4.10 Corrective action

4.10.1 Procedures for corrective action shall include an investigative process to determine the underlying cause or causes of the problem. These shall, where appropriate, lead to preventive actions. Corrective action shall be appropriate to the magnitude of the problem and commensurate with the risks encountered.

Cited from ISO 15189:2003

4.11 Preventive action

4.11.1 Needed improvements and potential sources of nonconformities, either technical or concerning the quality system, shall be identified. If preventive action is required, action plans shall be developed, implemented and monitored to reduce the likelihood of the occurrence of such nonconformities and to take advantage of the opportunities for improvement.

4.11.2 Procedures for preventive action shall include the initiation of such actions and application of controls to ensure that they are effective. Apart from the review of the operational procedures, preventive action might involve analysis of data, including trend- and risk-analyses and external quality assurance.

NOTE **Preventive action is a pro-active process** for identifying opportunities for improvement rather than a reaction to the identification of problems or complaints.

Primary versus
Secondary Prevention

Presentation

1. Understanding Risk = Uncertain Decisions

2. Method Validation = Risk Management

3. Laboratory Diagnosis = Risk Communication

Understanding Risk

Risk = Deciding* in the face of Uncertainty°

Fault Trees, Cause-Effect- & Root-Cause-Analysis as a first step in Failure Control

Robust Designs as a means of Failure Prevention

*** In the unit The Diagnostic Process** 
we define " Diagnosis = Consequential Decision in the face of Uncertainty "

° In the unit Measurement Uncertainty 
we define " Certainty = Evidence deemed Consequential "

The Risk Matrix has Multiple Dimensions

Incidents of our own doing – an act of God / Nature / …

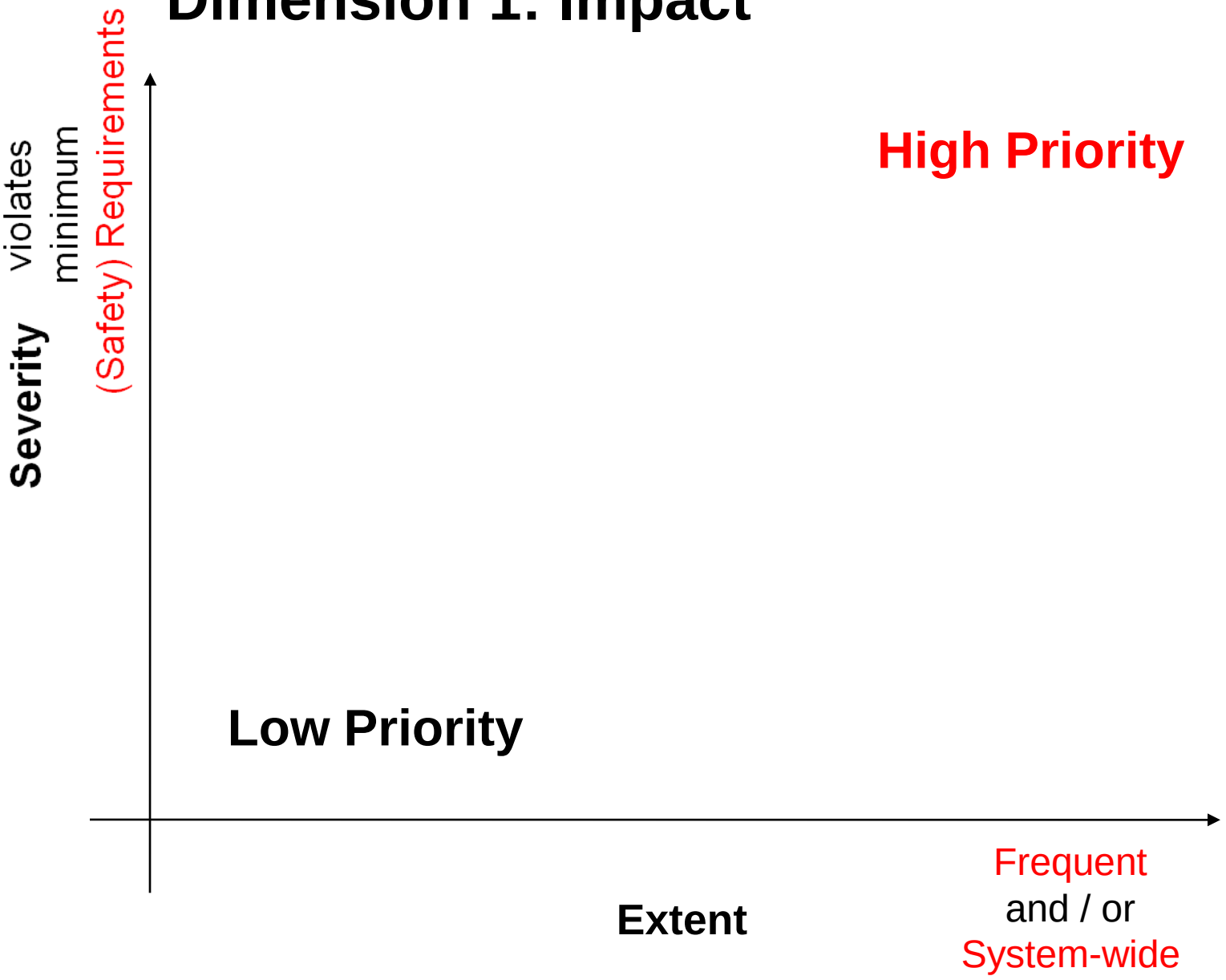
System-wide Impact of a Failure
Timeliness / Urgency of Detection & Intervention

Uncertain Incidence of Failure
Uncertain Gravity of an Adversity
- Clinical Risk / Patient Safety
- Public Health / Environmental
- Financial Risk
- Public Security

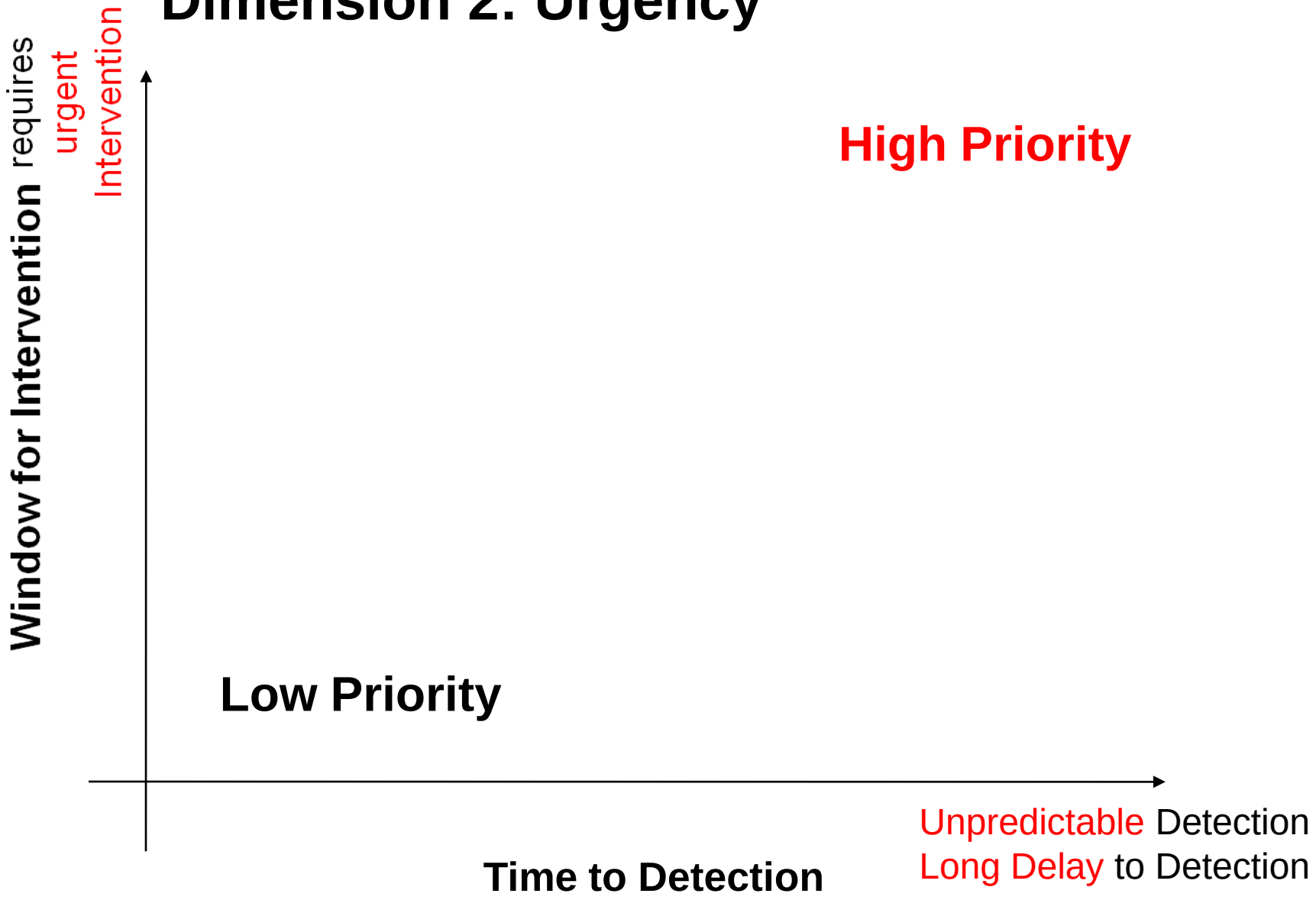
Uncertain Outcome of Remedial Actions

Bounds of the **Decision Process**
- Numeracy of Decision maker
- Weight of the Environment
- Emotional Factors…

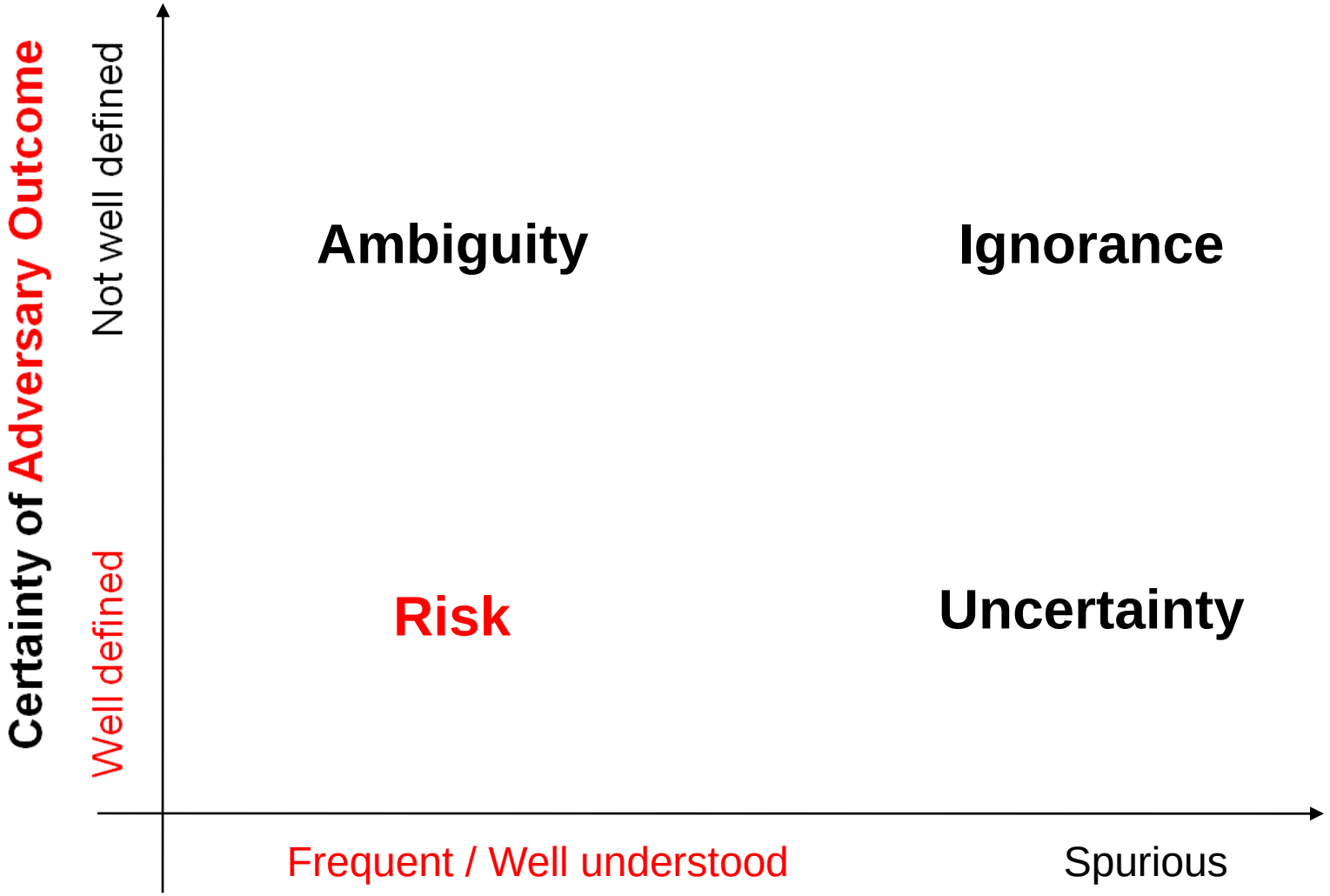
Dimension 1: Impact



Dimension 2: Urgency

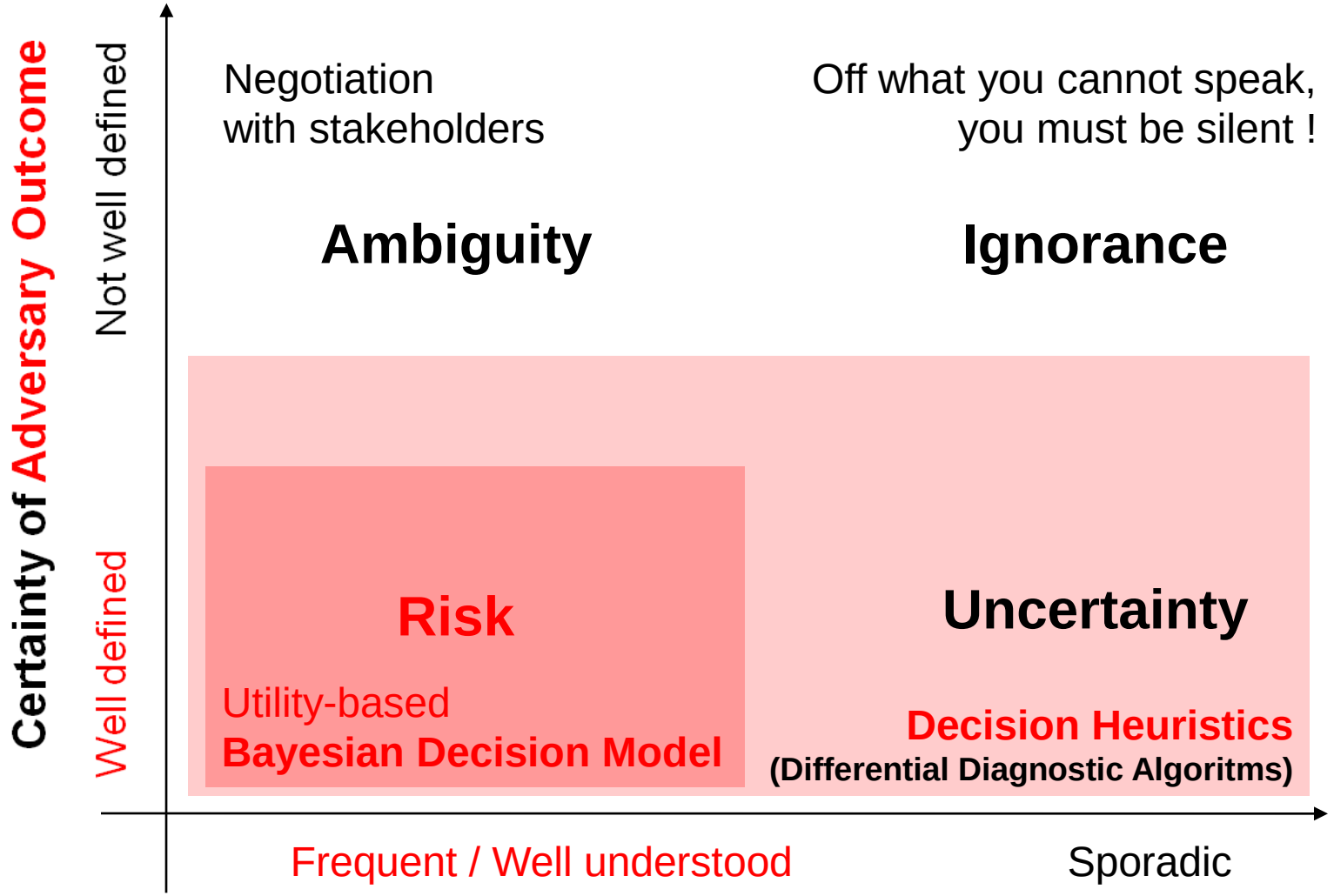


Dimension 3: Uncertainty



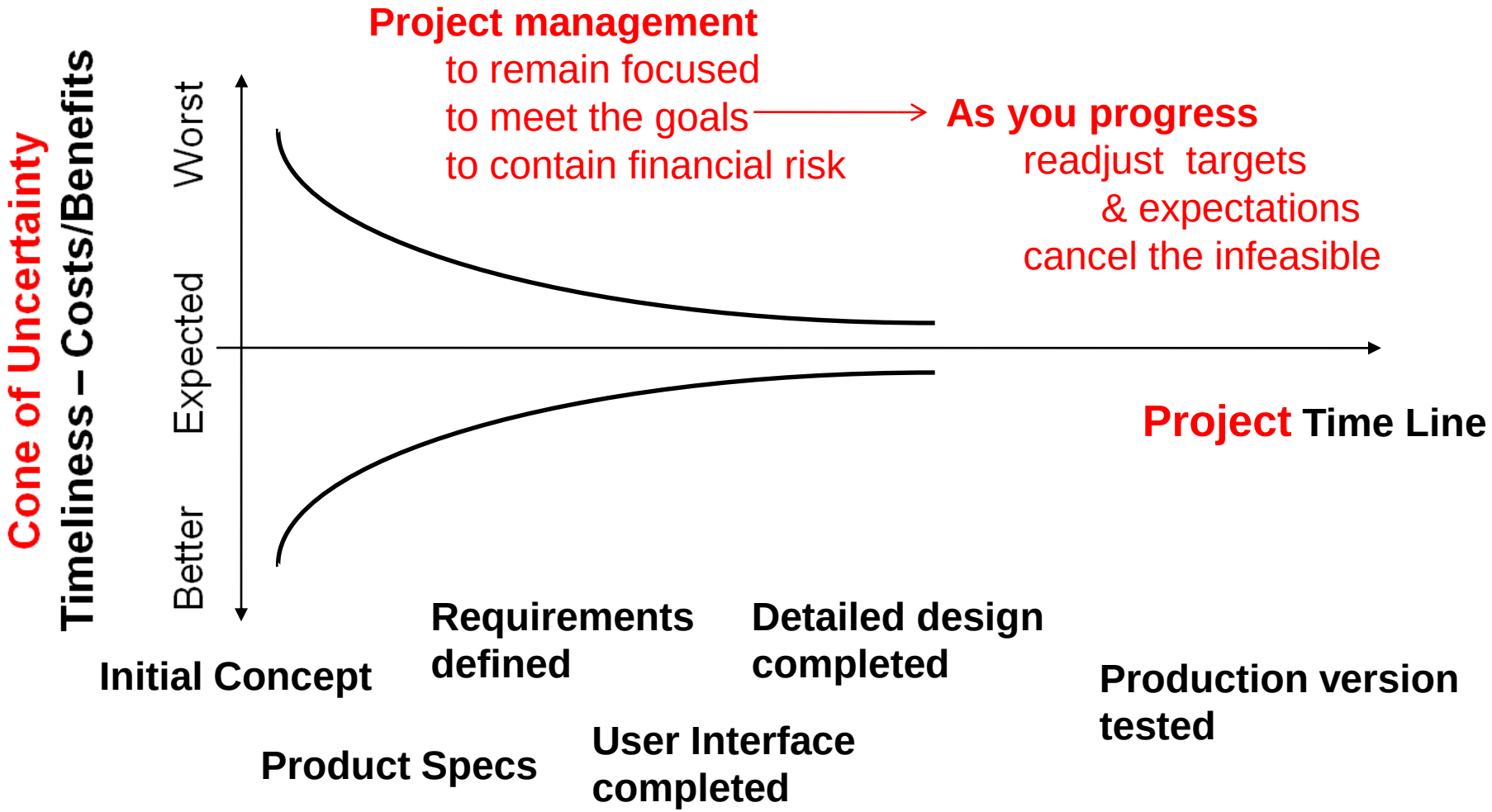
After Andy Stirling

Consequential Actions as function of Uncertainty

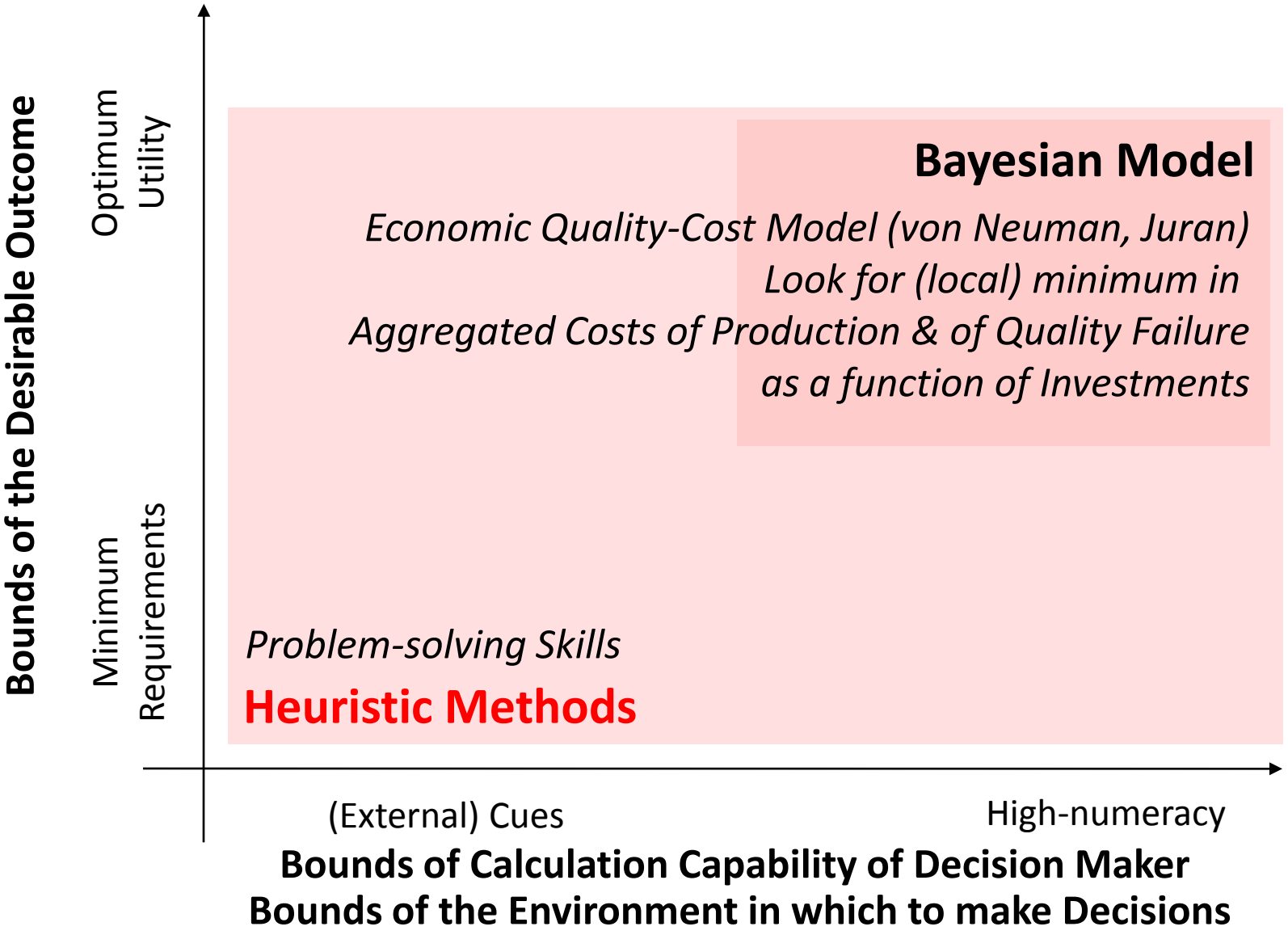


After Andy Stirling

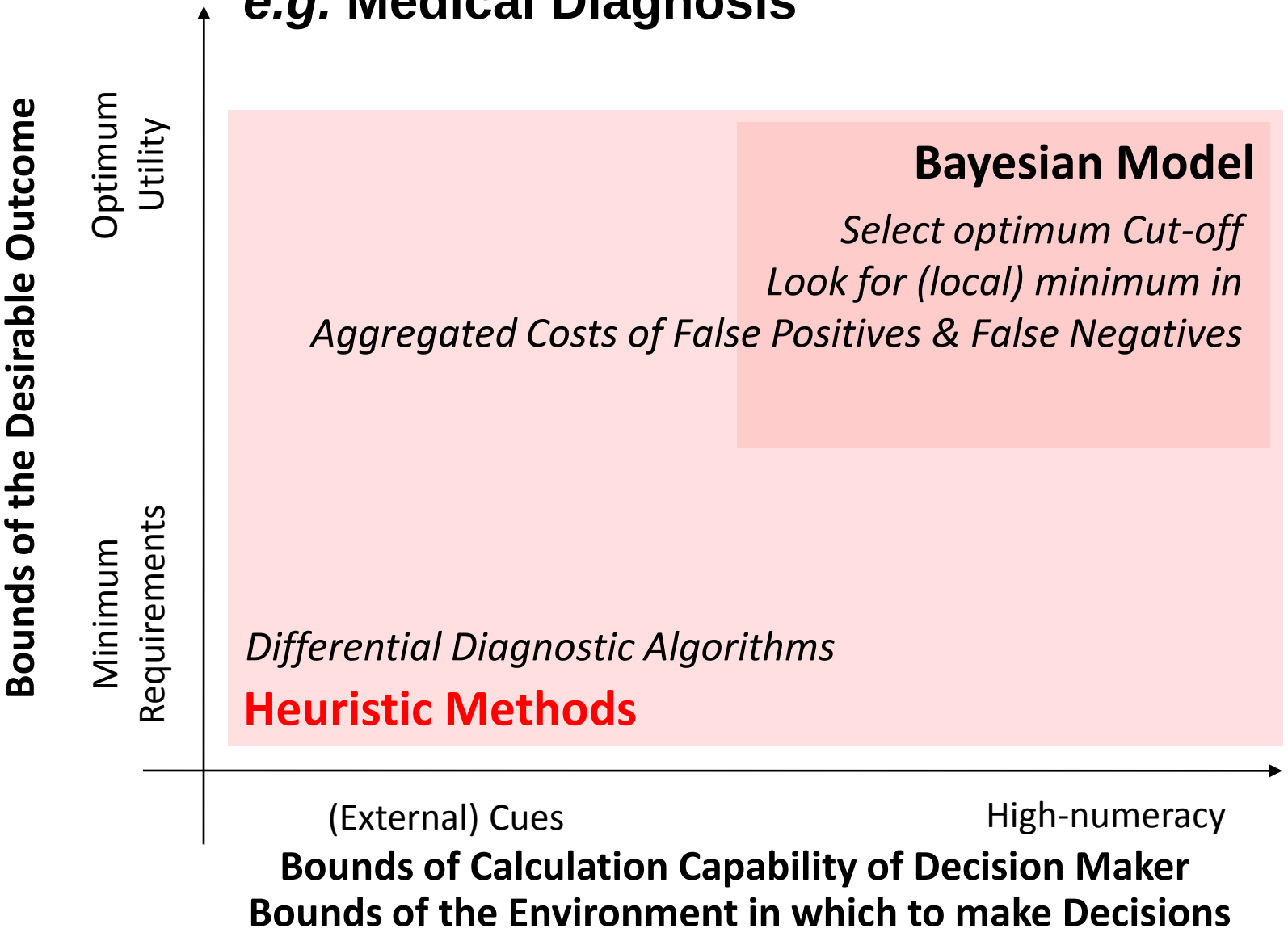
Dimension 4:
Uncertainty of (Preventive) Remedial Actions



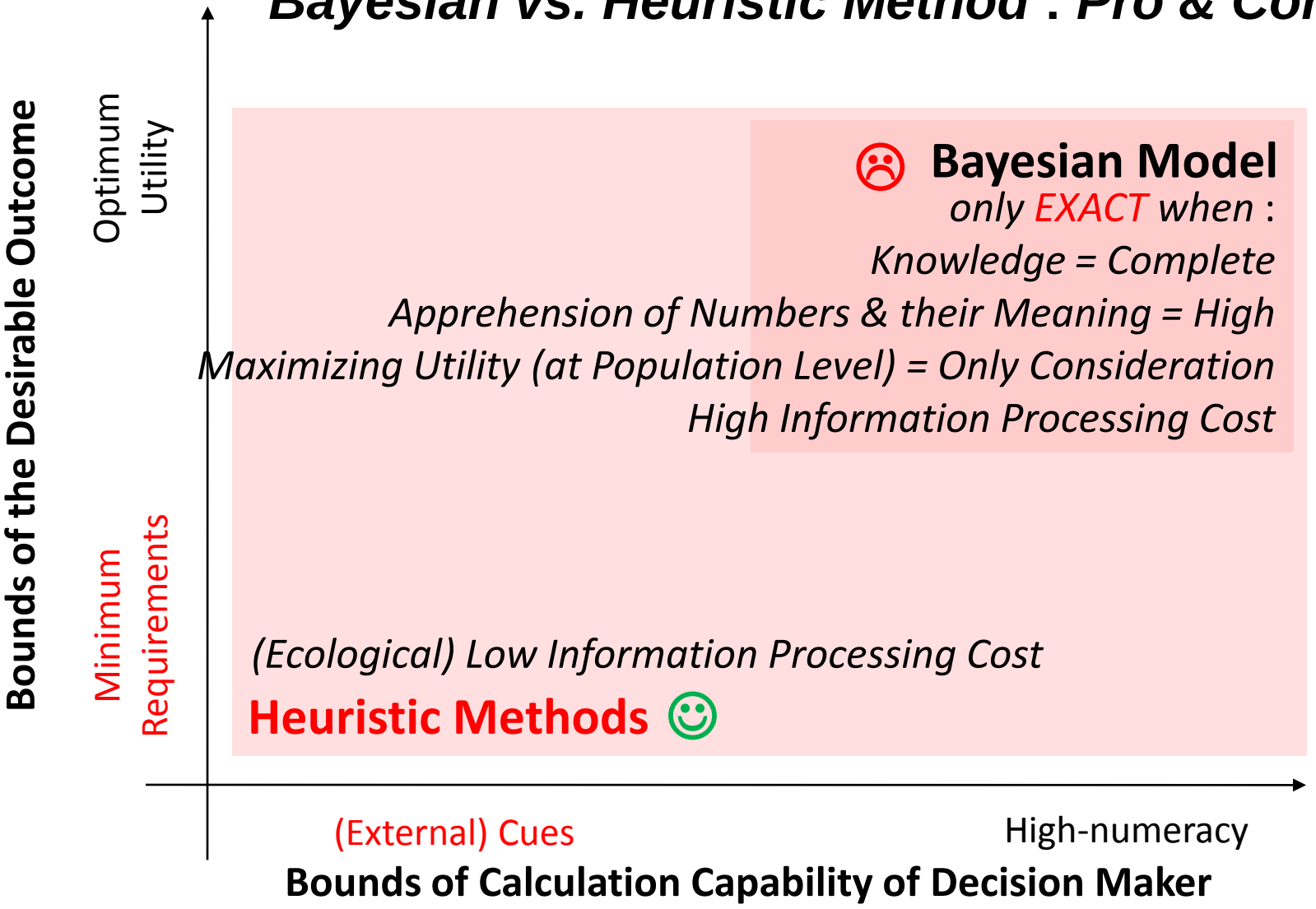
Dimension 5: Bounds on Decision Processes



Bounds on Decision Processes
e.g. Medical Diagnosis

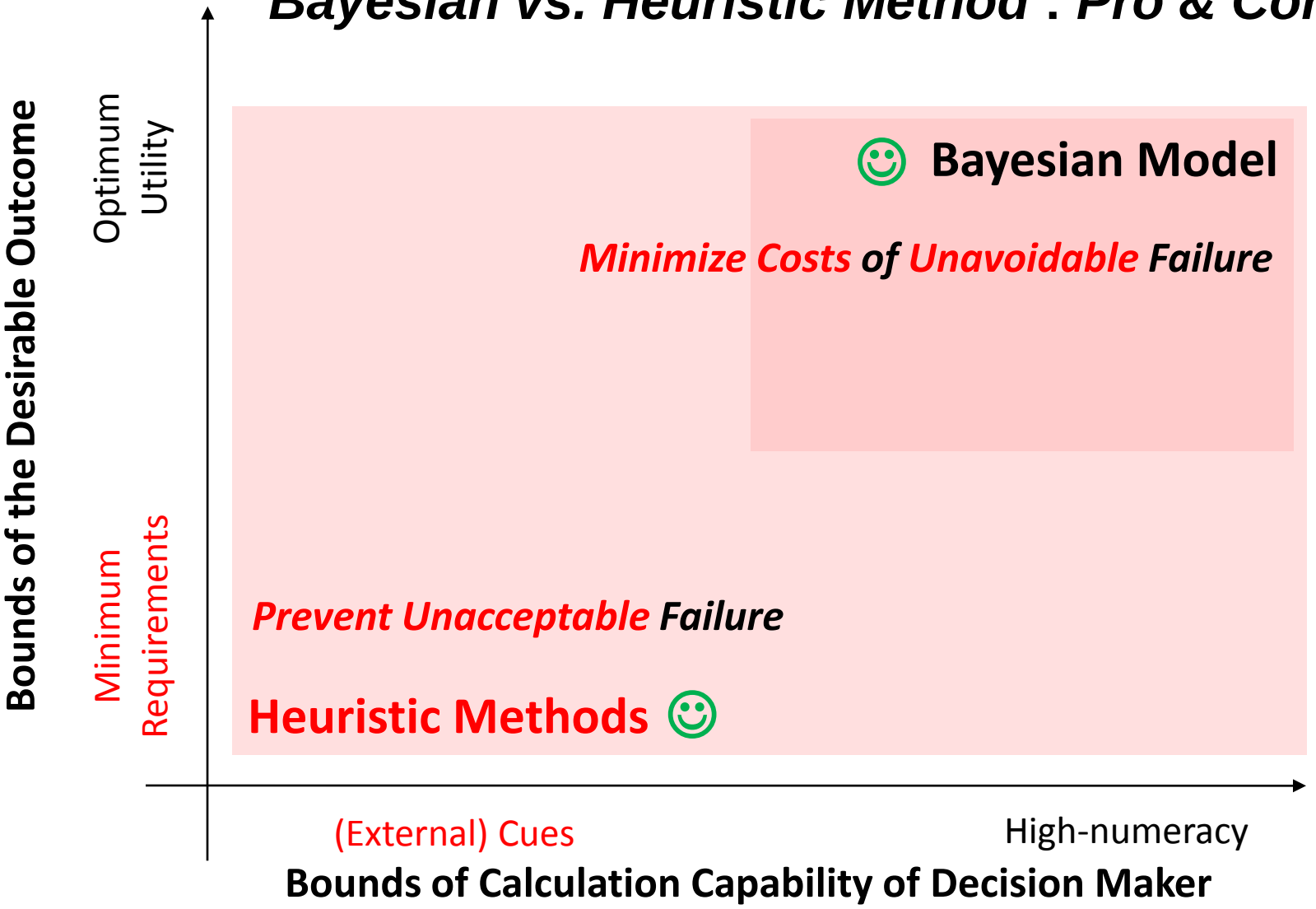


Bounds on Decision Processes
Bayesian vs. Heuristic Method : Pro & Contra (1/2)



Bounds on Decision Processes

Bayesian vs. Heuristic Method : Pro & Contra (2/2)



Understand Risk Analysis

Risk = Deciding in the face of Uncertainty

Fault Trees, Cause-Effect- & Root-Cause-Analysis
as a first step in Failure Control

Robust Designs
as a means of Failure Prevention

Fault trees

Non-conformities
Complaints
Failures

Dig for
the Source of all Evil
to come up with
a Fundamental
& Pro-active Solution

End Product

Root Cause Analysis
What can cause error ?

Top-Down

(Sub-)Assemblies

Failure Mode Effects Analysis
How can this component cause havoc ?

Bottom-Up

Components

Sensitivity Analysis =
δ (Outcome) / δ (Disturbance)

Method Validation
& Implementation
(measurement uncertainty)

Robust Design
to Prevent Failure

Fault trees

Components

↓

(Sub-)Assemblies

↓

End Product

PLAN
Method Validation
& Implementation

Failure Mode Effects Analysis

DO

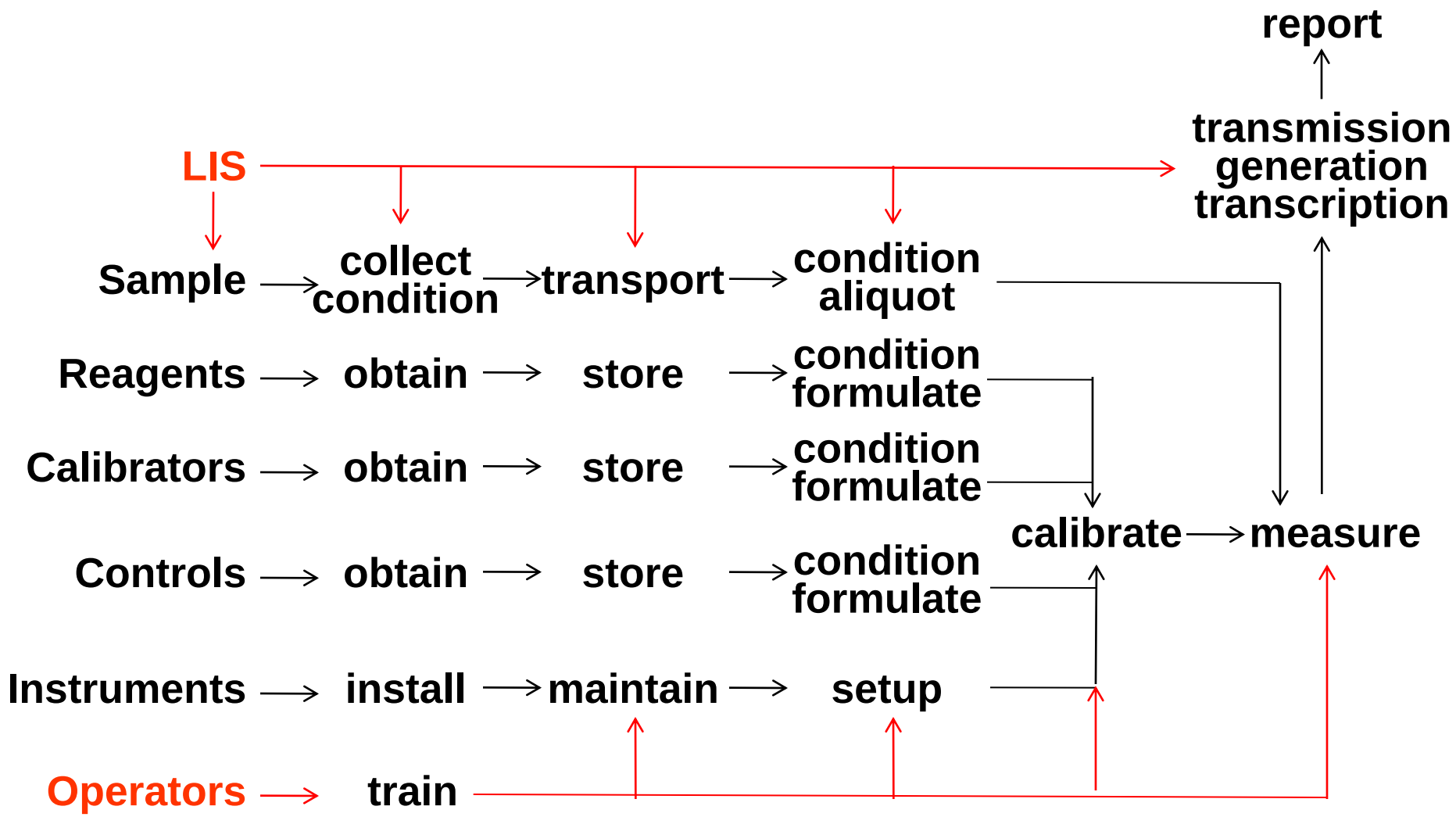
↓

Non-conformities
Complaints
Failures

CHECK

ACT
= System of Prevention
Root Cause Analysis

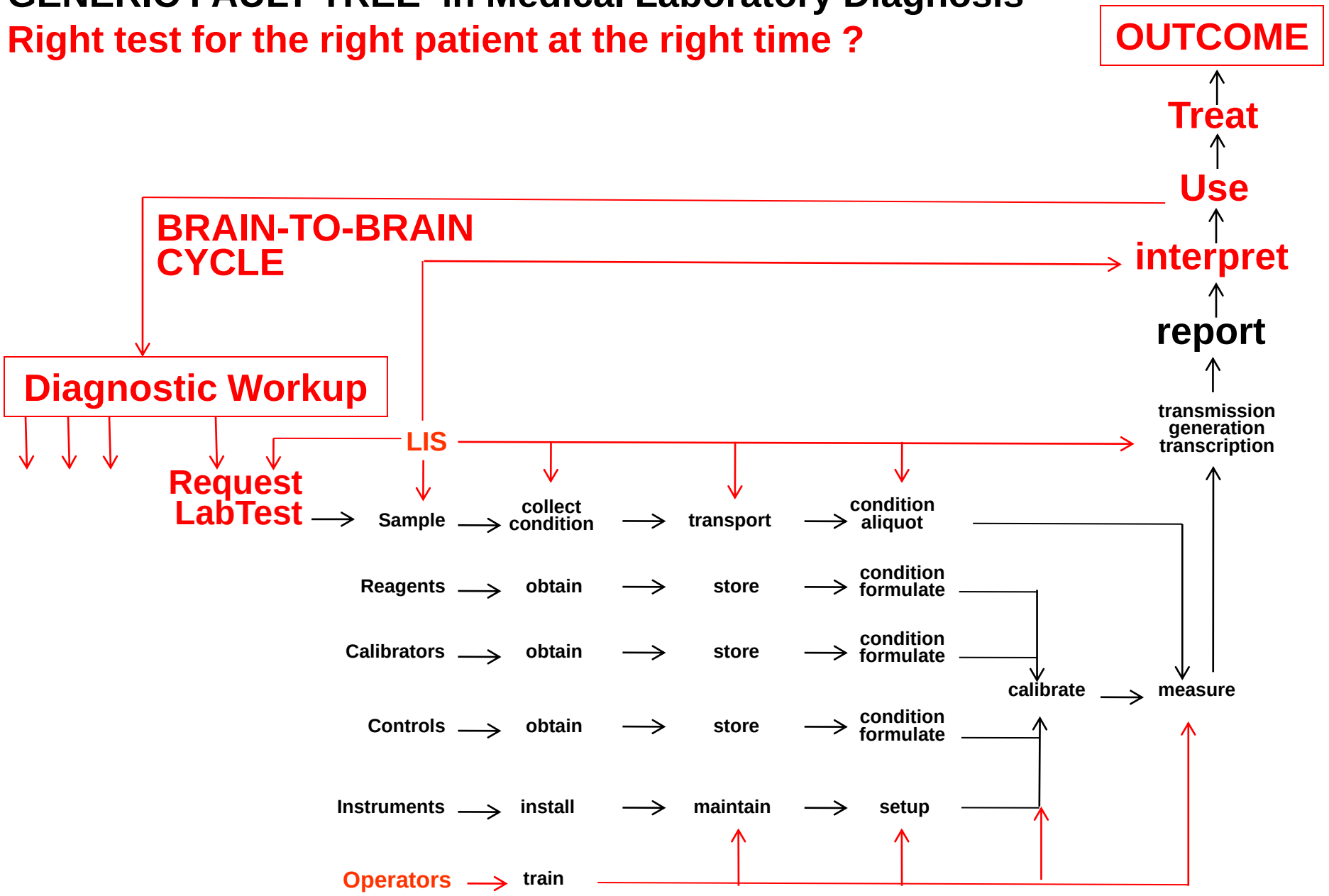
GENERIC FAULT TREE in the Medical Laboratory



After ISO/TS 22367:2008

GENERIC FAULT TREE in Medical Laboratory Diagnosis

Right test for the right patient at the right time ?



Heuristics = Problem Solving

Expertise = a loosely defined,
yet generally applicable approach

Intelligence

To put the right question, is to solve it.

Be specific about

1. your requirements
2. the problem to solve
3. all underlying assumptions

Be open-minded & remain critical

Understand Risk Analysis

Risk = Deciding in the face of Uncertainty

Fault Trees, Cause-Effect- & Root-Cause-Analysis
as a first step in Failure Control

Robust Designs
as a means of Failure Prevention

Robust Designs as a means of Failure Prevention

W R Ashby (cybernetics) cites C D Darlington (geneticist)

The foundation of all physiology must be the physiology of permanence

The PDCA-cycle = a case of negative feedback

How is robustness achieved in Biology ?

1. Feedback control

Negative feedback (autoregulation) :
to achieve a robust response to perturbations
(cfr. PDCA-cycle)

Positive feedback (autocatalysis) :
to amplify perturbations and increase sensitivity

How is robustness achieved in Biology ?

2. Redundancy:

To increase Contrast and to Cancel Noise

Homogeneous redundancy : parallel multiplication
Susceptible to common-mode failure

Heterogeneous redundancy : multiple variants
Allows escape from common-mode fragility

How is robustness achieved in Biology ?

3. Decoupling :
Isolate high level functionality
from low level disturbances
(cfr. POKA (fail-proof) Design)

4. Purging :
Shedding undesirable variants
(cfr. Lean Design / 5S)

How is fitness for survival achieved in Biology ?

5. Darwinian selection

Selection pressure with drift towards specialisation:
best balance between Maintenance, Repair, Remodelling
(cfr. Continuous Improvement, Lean Design)

versus

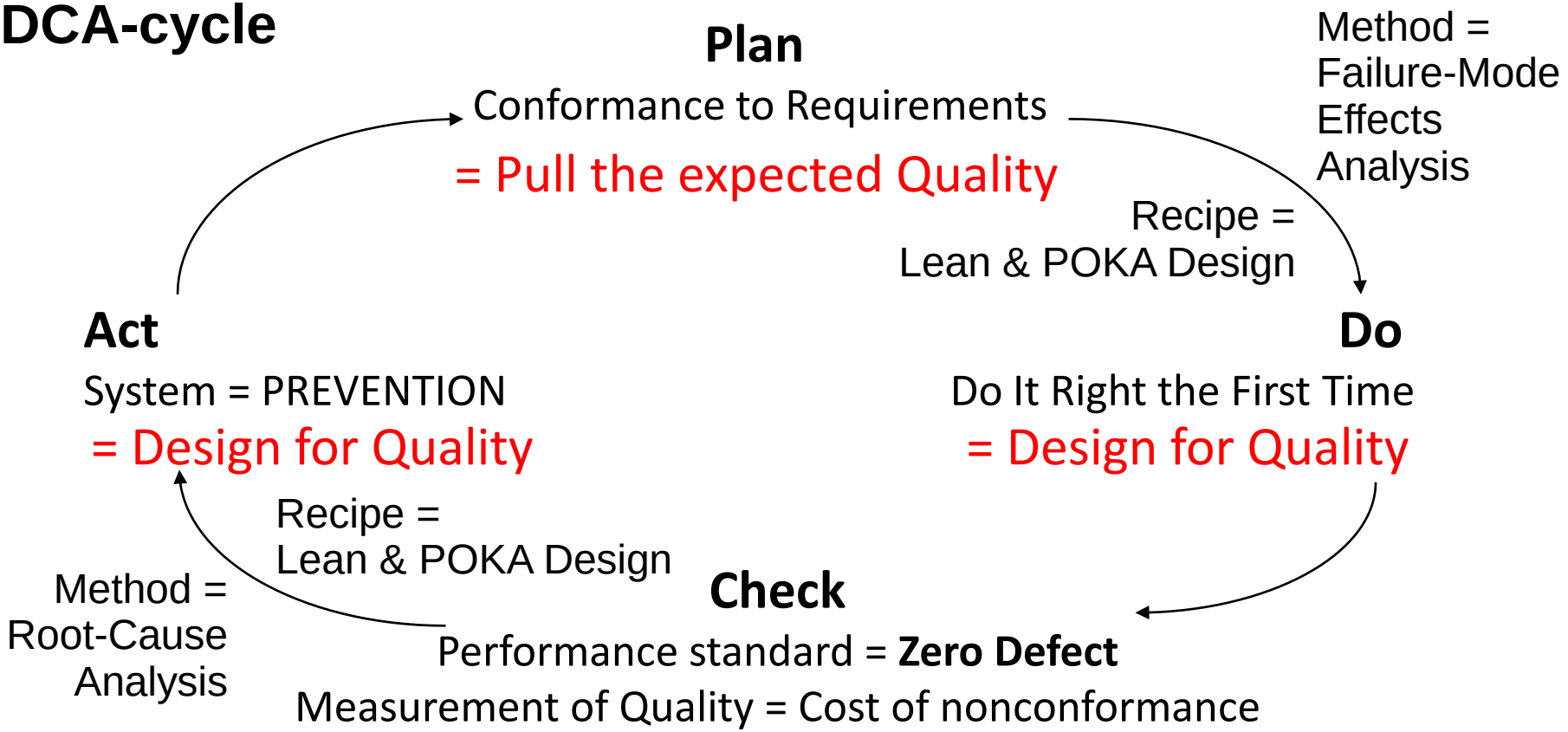
Survival of the fittest:
escape from / adaptability to changing conditions
(cfr. Versatility, Co-operativity)

How is fitness for purpose achieved in Clinical Practices ?

Stakeholders	Quality Paradigm	Evidence-based ?
Regulators Insurers	Audits Proficiency Testing	oratio pro domo ?
HMO Managers	PDCA	Success in the Market Place
Medical officers	Education Conferences Consensus-building	oratio pro domo ?

After R Grol

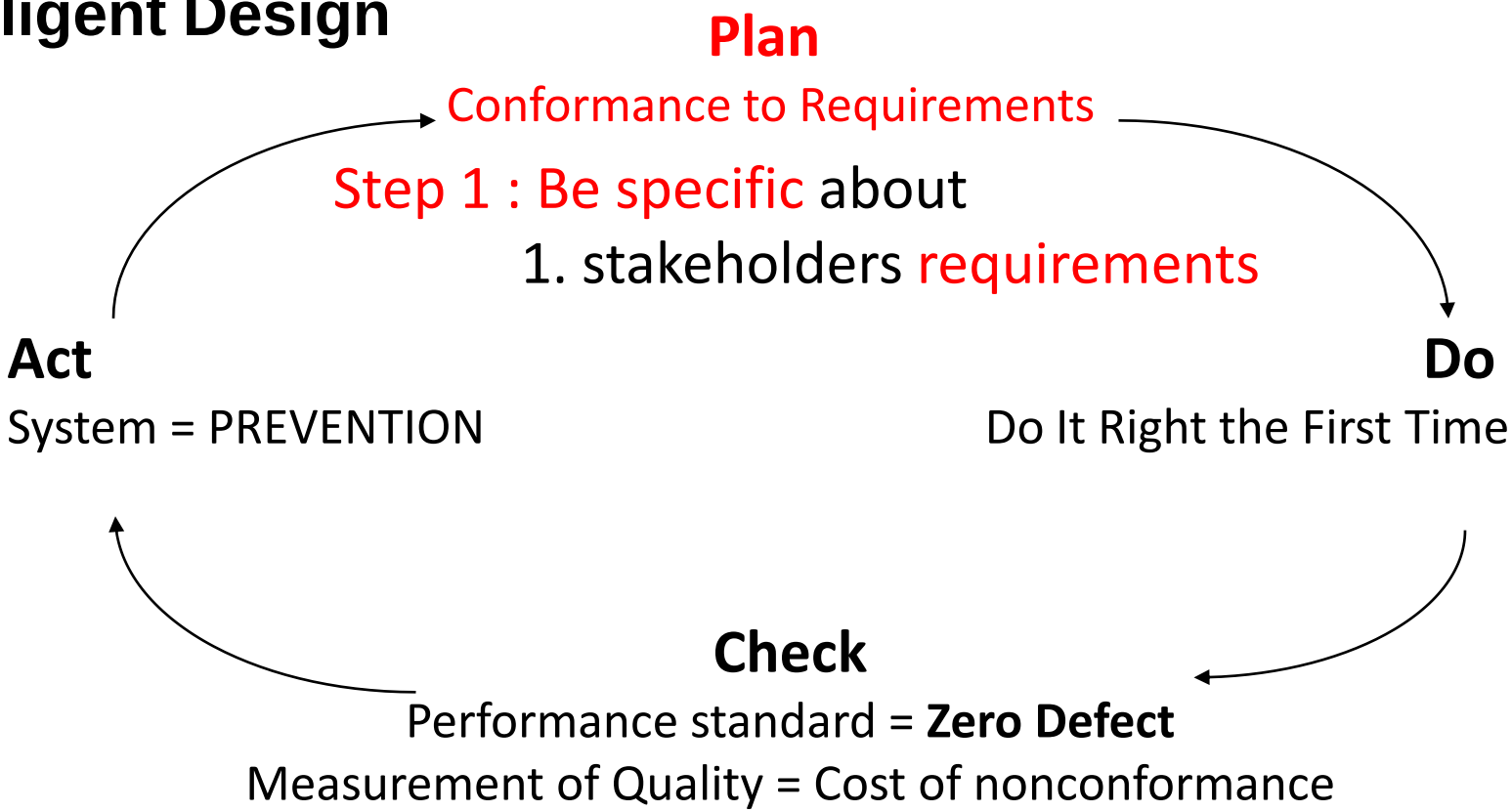
PDCA-cycle



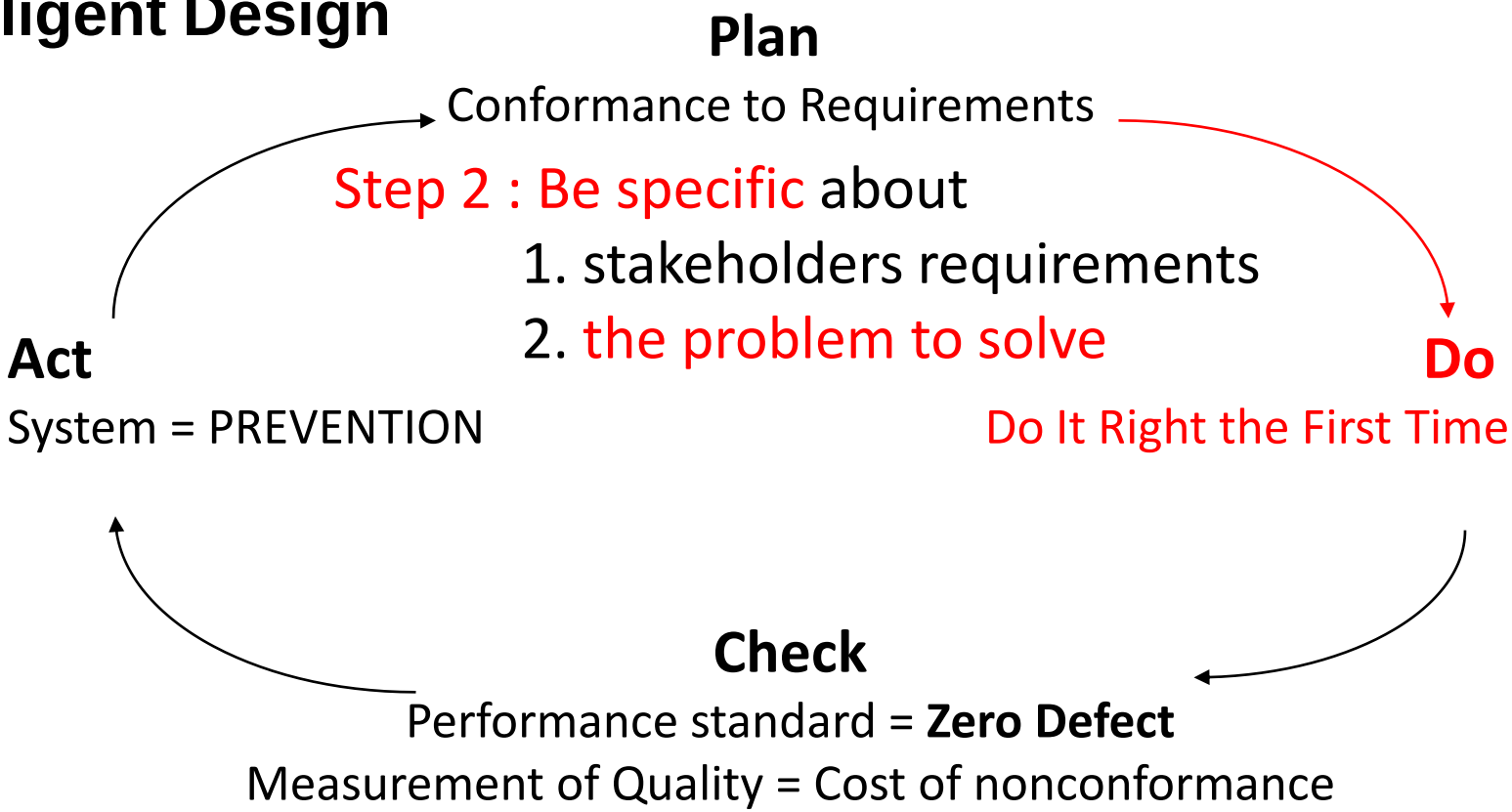
Reduced Costs of nonconformance pays for your quality = **Quality at No Costs**

After P B Crosby

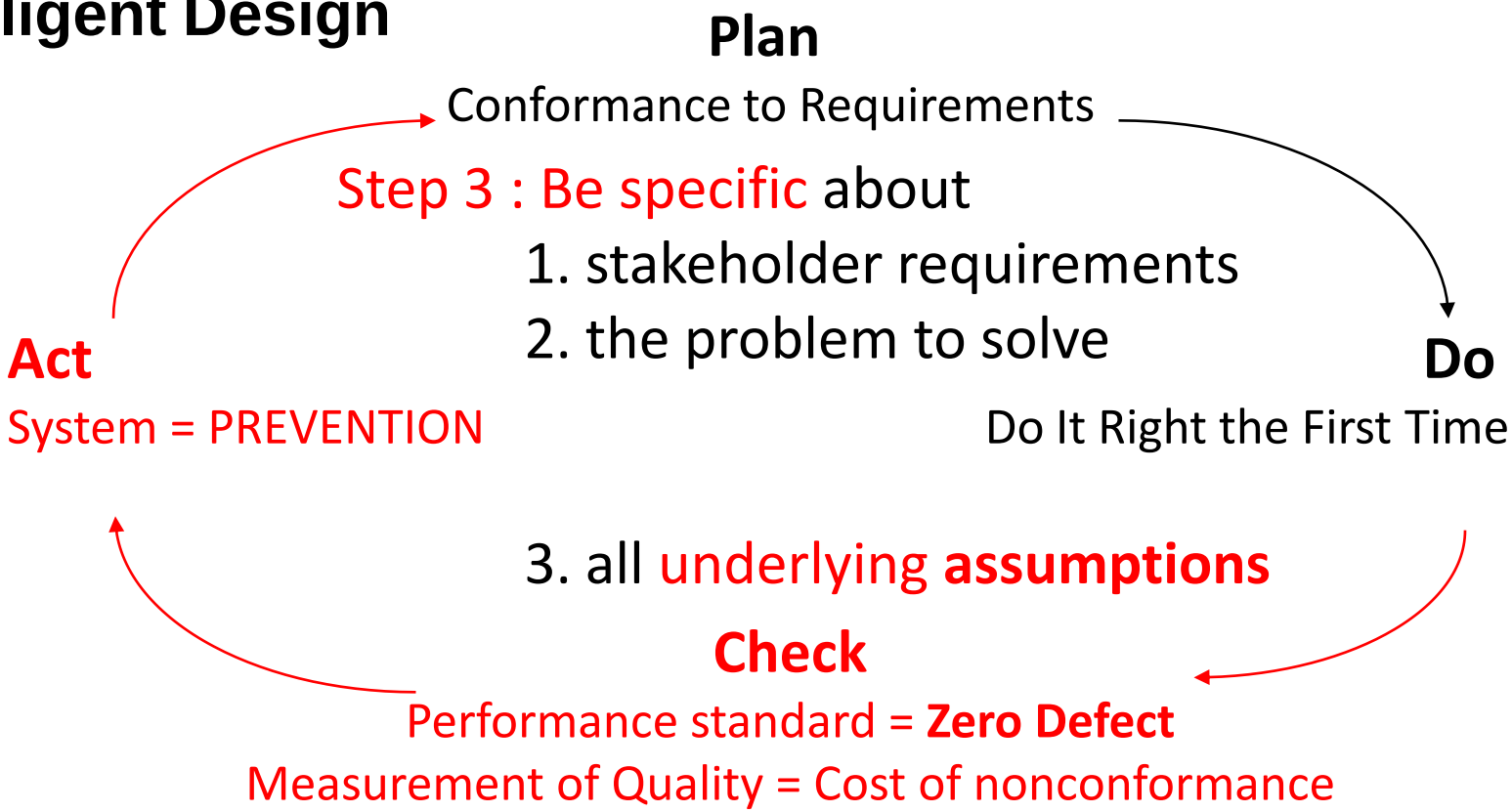
Intelligent Design



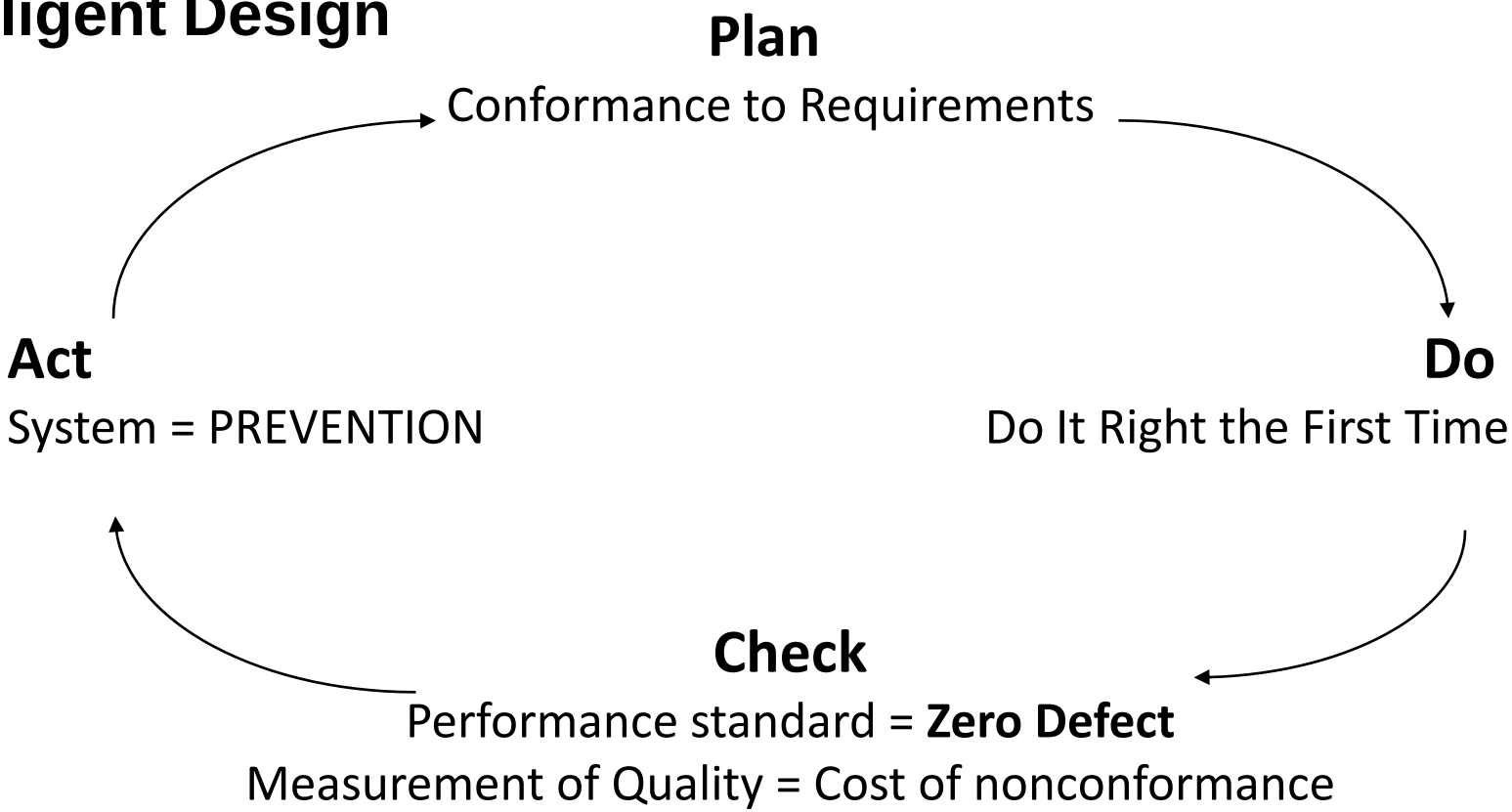
Intelligent Design



Intelligent Design



Intelligent Design

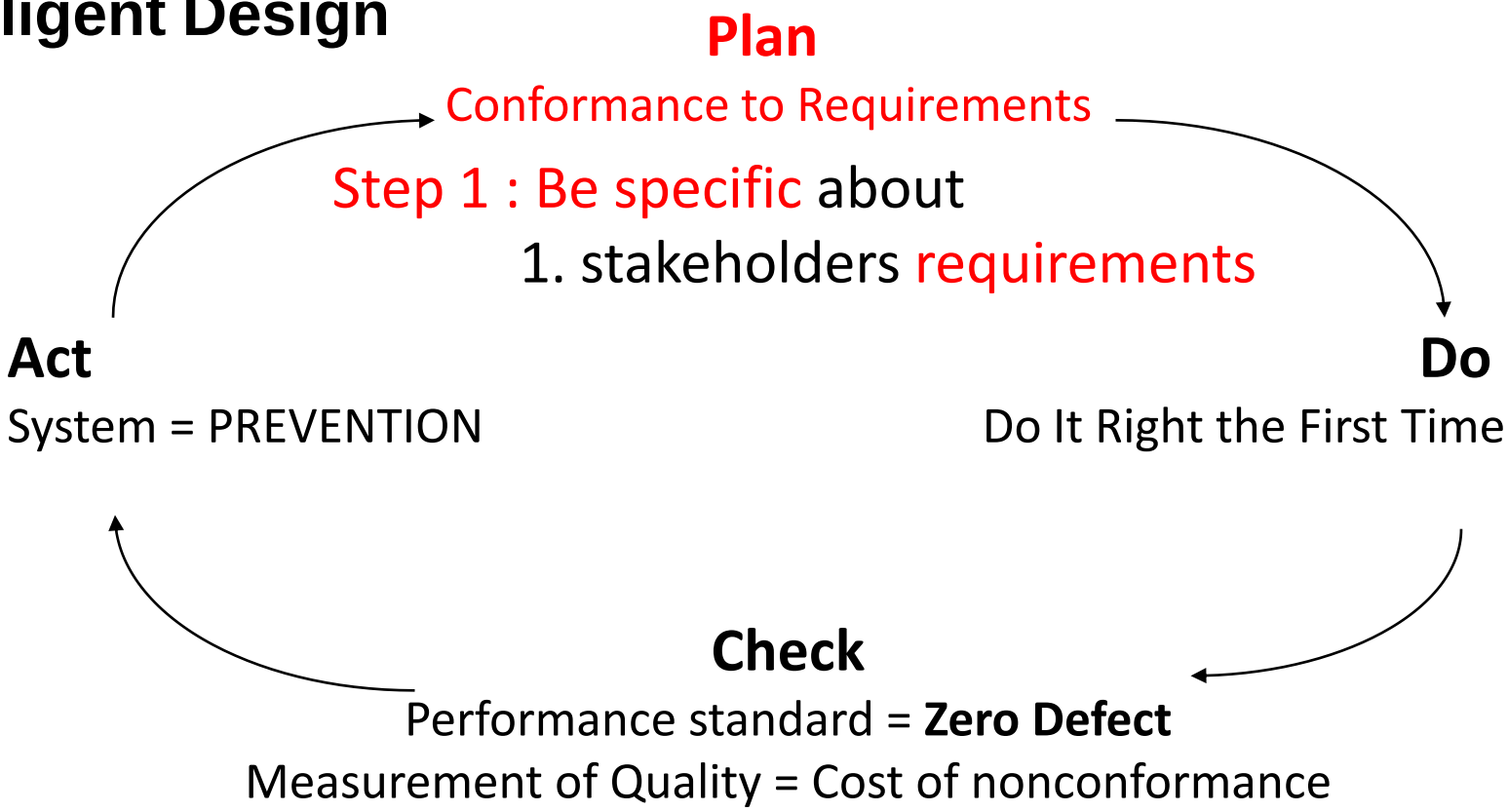


PDCA corresponds also to a PROJECT Cycle

There is a RISK that your project will not materialize the deliverables

If your PDCA didn't work, you must have been wrong somewhere ?

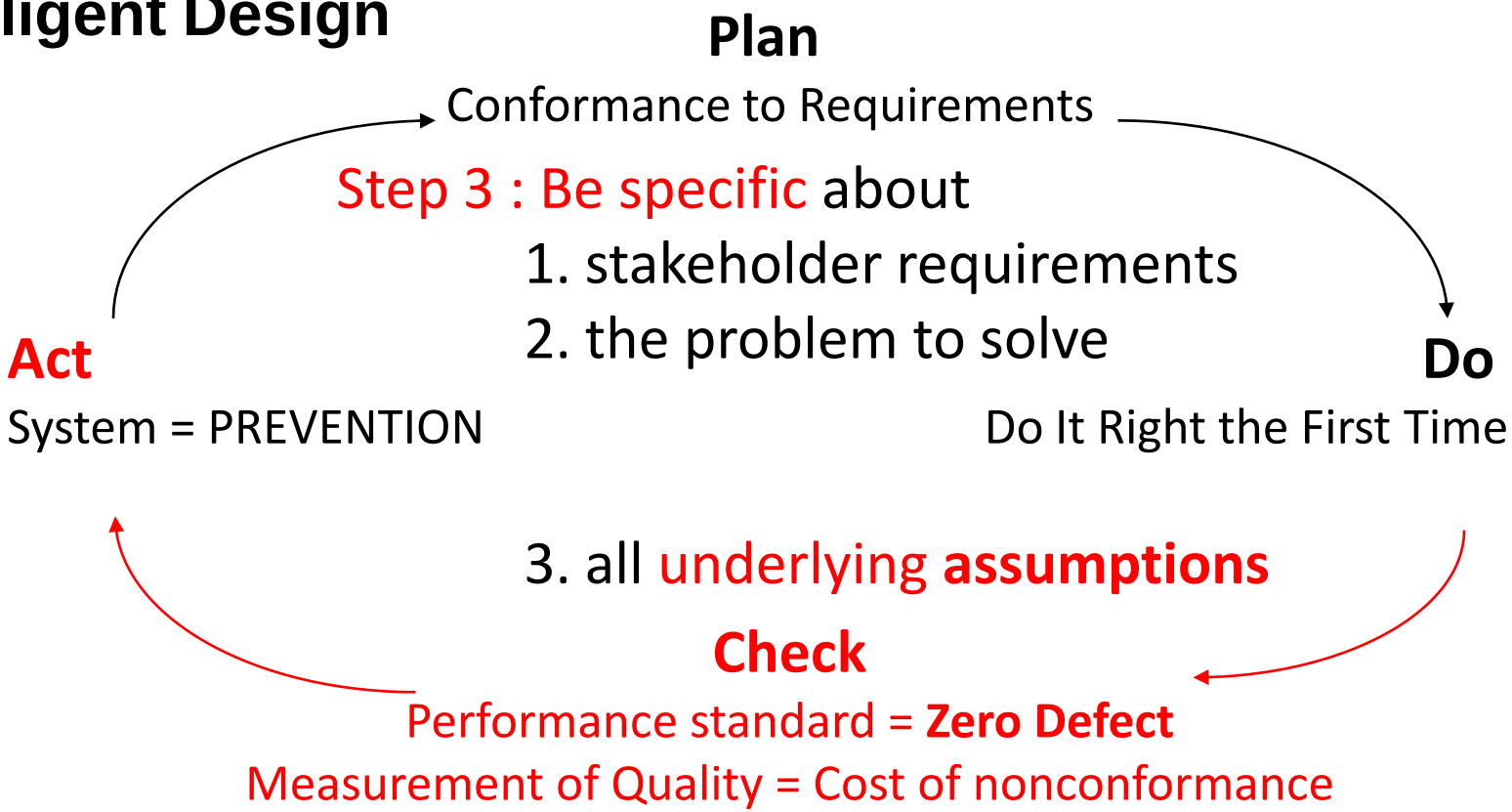
Intelligent Design



If your PDCA didn't work, you must have been wrong somewhere ?

1. Are you **pulling desired quality : Buy-in from stakeholders ?**

Intelligent Design



If your PDCA didn't work, you must have been wrong somewhere ?

2. Are your checks valid ? (SMART)

Is what you measure **related to value for relevant stakeholder** ?

Is your measurement timely, … ?

Incentive
= tension between what you get and what you think you are entitled to

Ownership

If you really are concerned about patient safety, get the ultimate stakeholder involved !

How to select a health care provider ? (after a webpage of The Joint Commission, 2008)

= What are you, as a patient, entitled to expect ?

General

- Does your doctor discuss the selection of the lab with you ?
- Can you identify the lab on the report ?

Quality Oversight

- Is there a number that you can contact for complaints ?
  And what happens afterwards ?
- Is the lab accredited ?

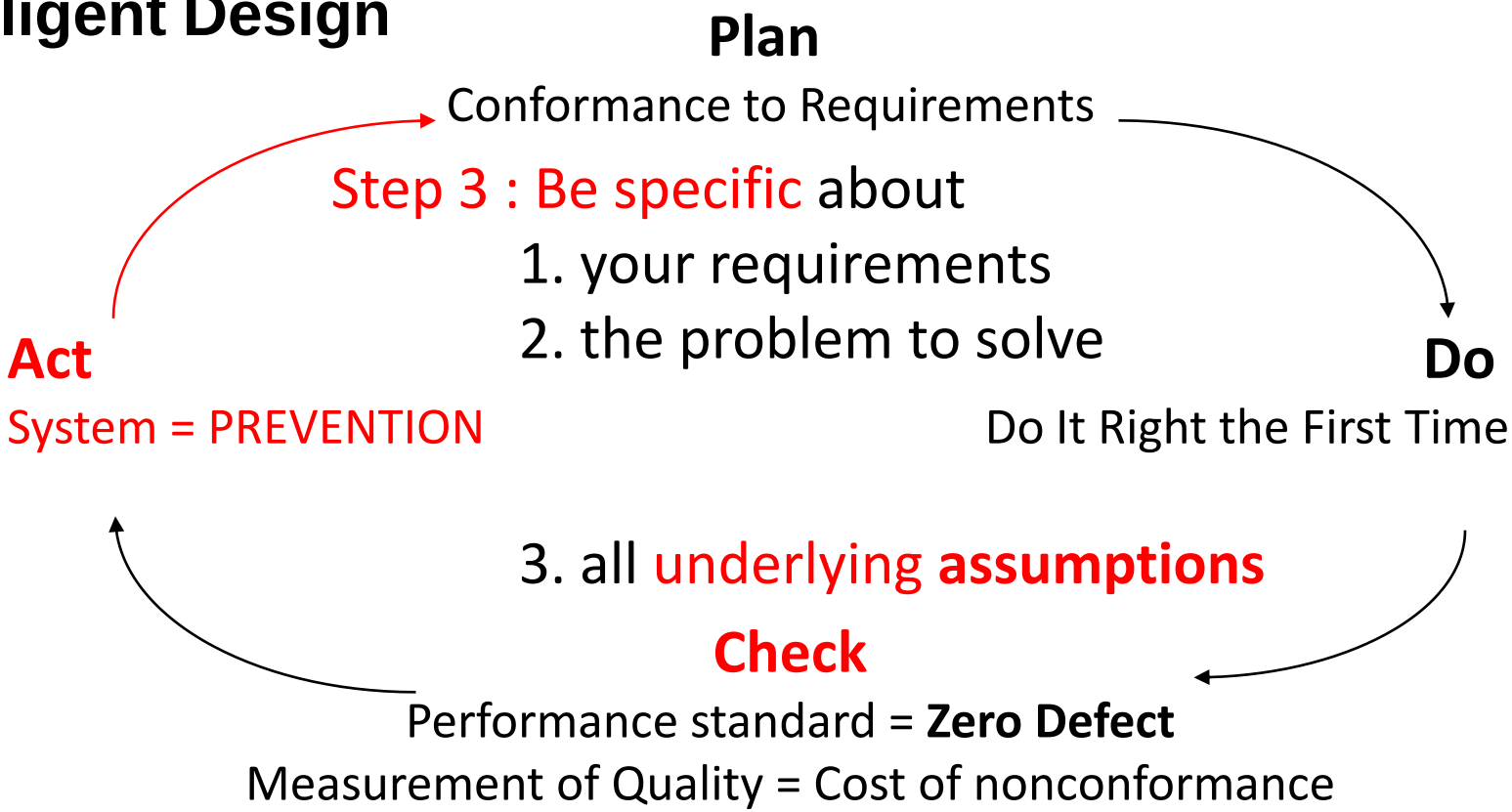
Sample Collection

- Do you get instructions from your doctor about how to prepare for a sample collection ?
- When you have to collect the sample yourself, do you get clear instructions ?
- Does your doctor follow instructions about how to collect samples ?
- **Was the sample properly labeled in front of you ?**
- Does the lab notify your doctor when the specimen was incorrectly collected ?
  And what happened afterwards ?

Reporting

- How soon can you expect results ?
- Are you informed timely ? and conveniently ?
- Is there a number that you can call when you have problems ?
- Did your doctor ever discuss unlikely results with you ?
  And what happened afterwards ?

Intelligent Design



If your PDCA didn't work, you must have been wrong somewhere ?

3. Is your **system of prevention** valid ?

Economy of the Quality System = System of Prevention

POKA

Root Cause Approach

If it ~~can~~ *break*,

Risk

Primary Prevention

Universal Protocols
Maintenance Schemes
Start-up Inspections
Bayesian & Heuristic
Decision Models

it will *break* one day.

Failures

Secundary Prevention

In-line Inspections
Intervention Cascades

Better be prepared !

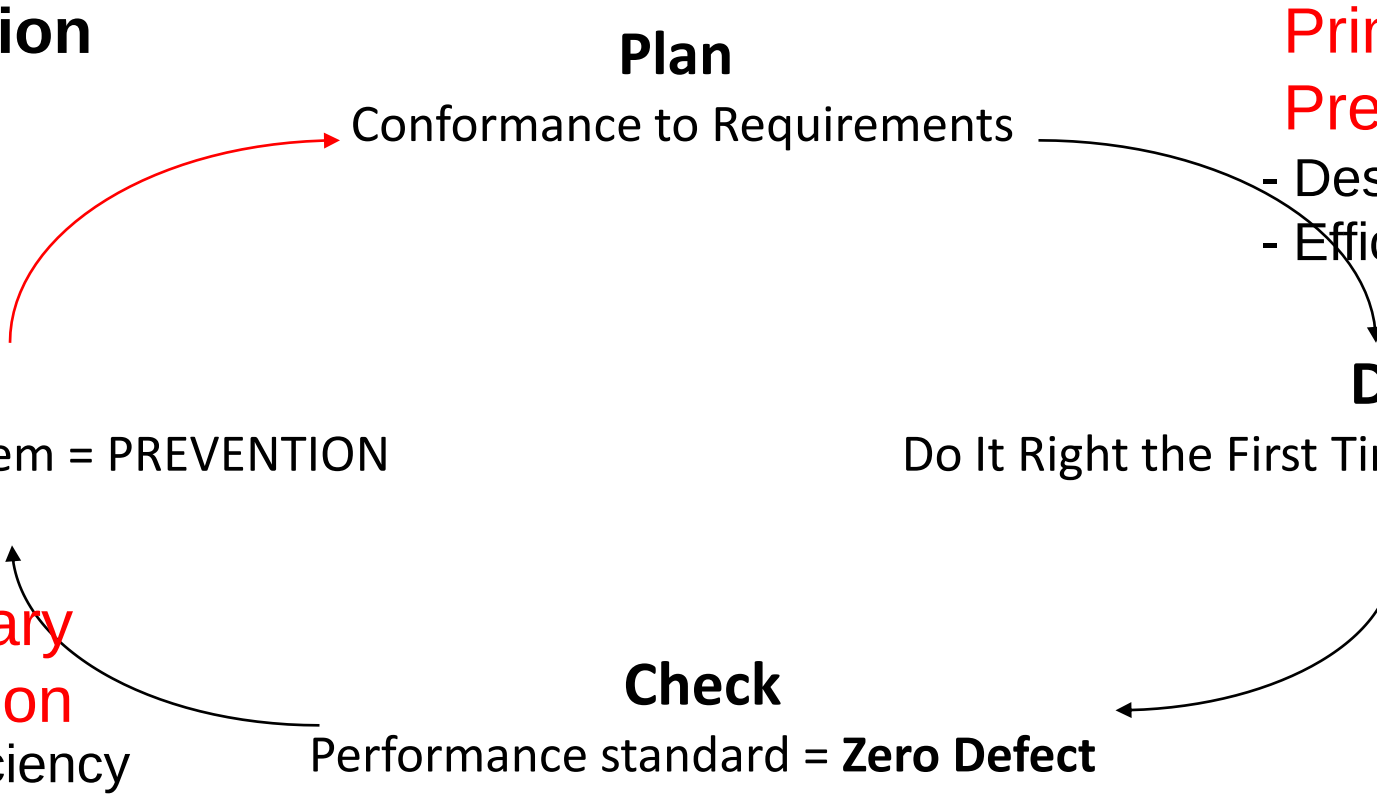
~~**Adversity**~~

Damage Mitigation

Mopping
with the faucet open

Murphy's Law

Prevention



Primary Prevention
- Design driven
- Efficient

Secondary Prevention
- Low efficiency
- Driven by incidents
- Prioritization:
  - business goals
  - acceptable / unacceptable failure
  (Bayes / Heuristics)

ADD VALUE

CUT LOSSES

COMPONENTS OF QUALITY INVESTMENT

After A V Feigenbaum

Investment in CONFORMANCE

PREVENTION

Training
Calibration
Maintenance
Lean
DESIGN
for QUALITY

ROOT-CAUSE APPROACH

APPRAISAL

In-Line Inspection

Costs of QUALITY FAILURE

INTERNAL

Scrap
Rework

EXTERNAL

Adverse Effects in Patients
Complaints
Customer support

secondary prevention →

damage mitigation →

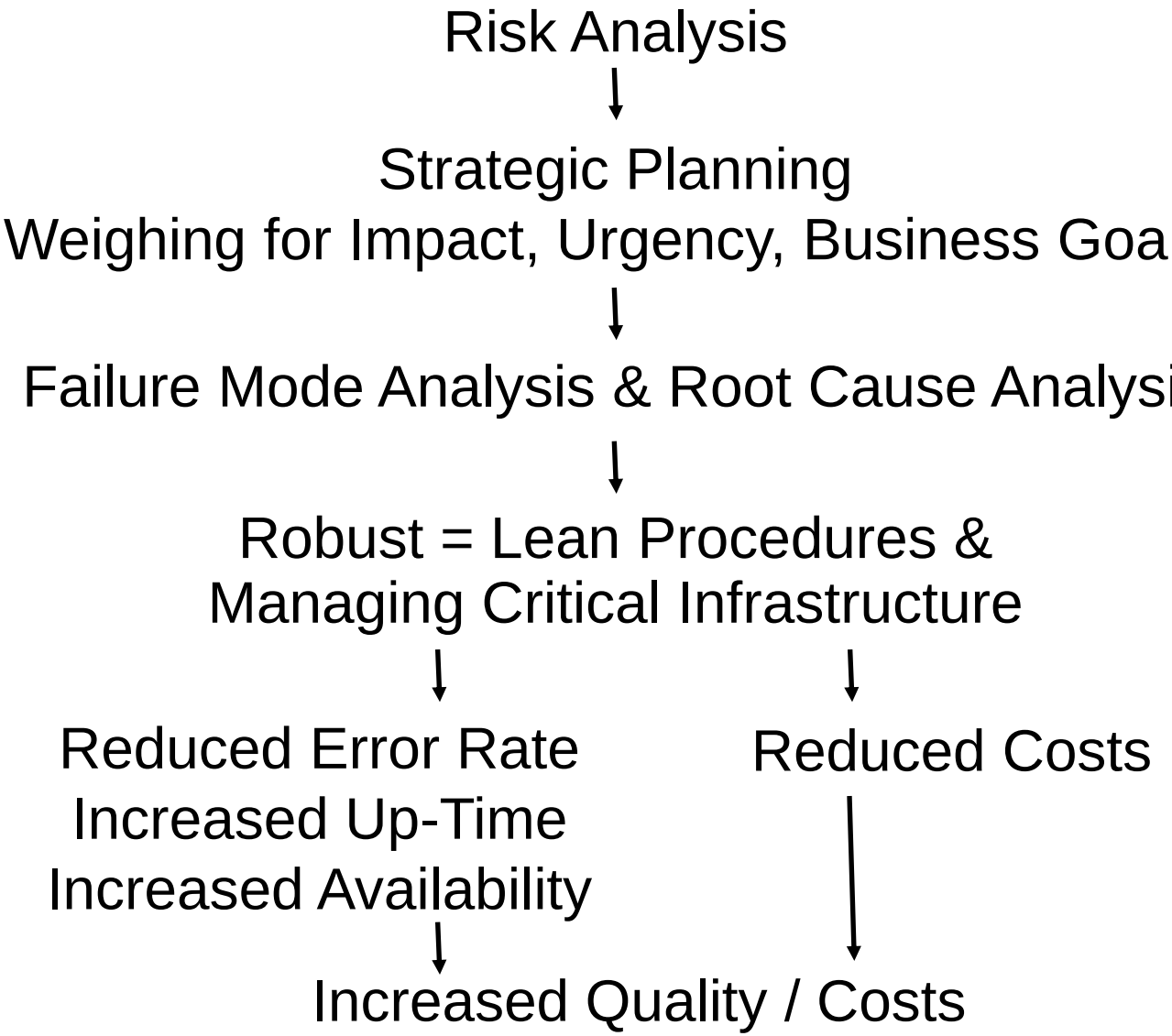
NOT-VALUE-ADDING, VALUE-RECUPERATING COSTS

The less, the better
The more, the more opportunity costs

Summary (1/2) : When the Decision Process is Risky !

- **Risk = uncertain consequences of uncertain decisions**
  - The Risk Matrix is multidimensional
    - Uncertainty, Impact, Urgency, …
  - The decision process remains bounded
    - incompleteness of our knowledge
    - limited numeracy of decision maker
    - goals other than plain utility
    - external cues & emotional aspects, …
- **Bayesian Model**
  - maximizes utility by minimizing adversity
  - requires **expectations about value & prevalence**
- **Heuristic Methods**
  - reduce (unacceptable) risk
  - **problem solving** requires to **be explicit about the goals, the problem & underlying assumptions**

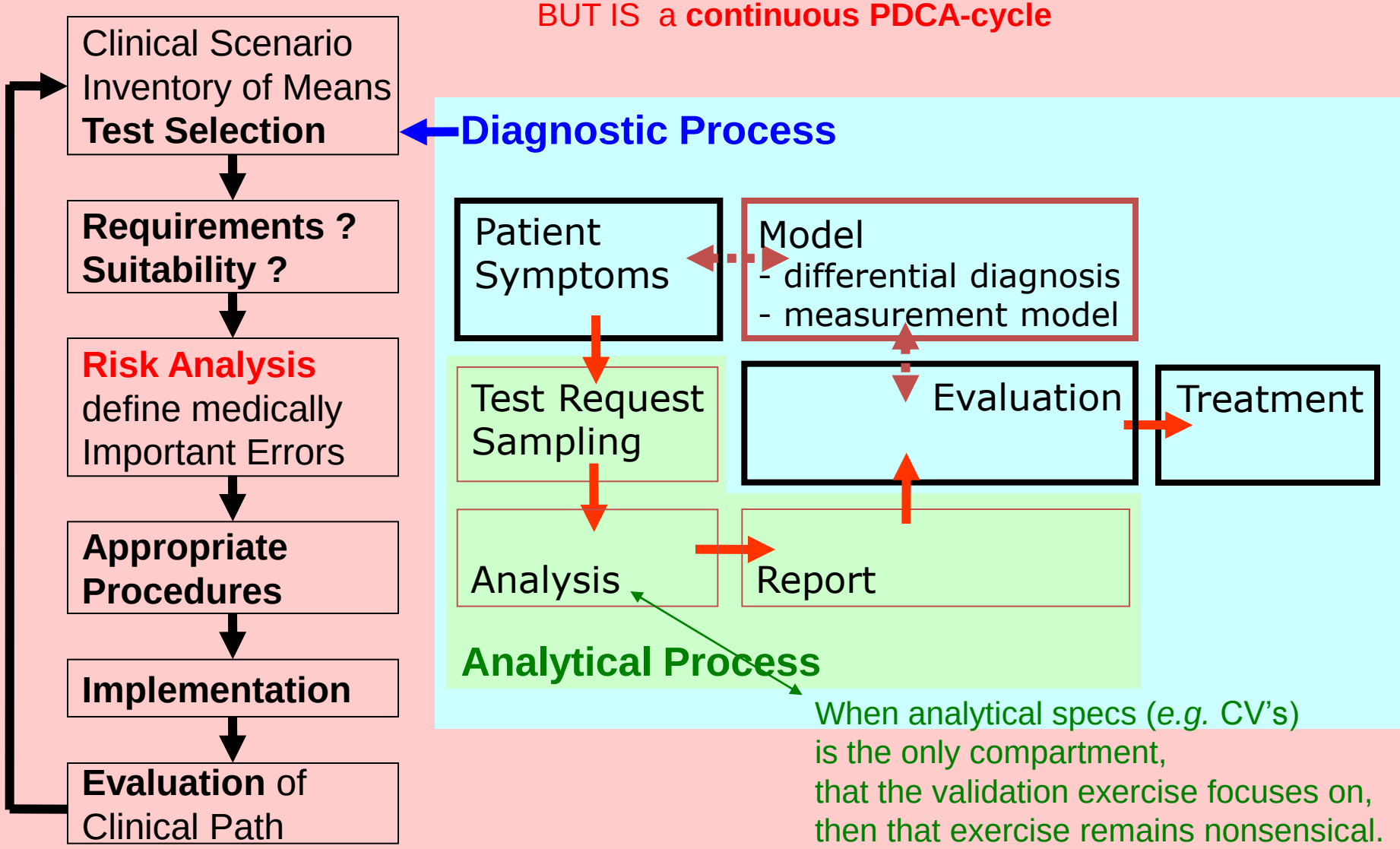
Summary (2/2) : The Economy of the Quality System



1. Understanding Risk = Uncertain Decisions
2. **Method Validation = Risk Management**
3. Laboratory Diagnosis = Risk Communication

METHOD VALIDATION: PROCESS FLOW CHART

Method Validation Process IS NOT the one-time inauguration of a new method
BUT IS a **continuous PDCA-cycle**



Method Validation - Step 0 :
Be specific about the Use Case = clinical scenario

Diagnostic Scenario's	Diagnostic Intent
Screening Case Finding	Low-cost detection of treatable conditions with low-prevalence
Differential Diagnosis	Confirm / Disprove
Staging	Classify in a continuum
Follow-up	Evaluate expected changes

Method Validation - Step 0 : Be specific about the clinical scenario

Diagnostic Scenario's	Diagnostic Prior Knowledge
Screening Case Finding	Prevalence Knowledge of separating power
Differential Diagnosis	Professional Judgement
Staging	Knowledge of continuum
Follow-up	Knowledge of expected changes Sensitivity = f (RCV)

Method Validation - Step 1 : Be specific about your requirements

Diagnostic Scenario's	Needed Characteristcs of Diagnostic Test
Screening Case Finding	Good diagnostic ability = separating power
Differential Diagnosis	
Staging	Low S_{RCF} & Low bias
Follow-up	High Effect / S_{RCF} Good analytical reproducibility

These are the clinical scenario's where **Control** of the **Analytical Process** is most relevant|

Main Issue = Commutability in time & across walls of the lab and of institutions

Method Validation - Step 1 : Be specific about your requirements

Logistic requirements of laboratory test

- Relevant : position / function in care algorithm(s) ?
- Accurate : sampling design / patient & sample identification
- Timely : timing / TAT with respect to care program(s)
- Accessible : test request / reporting of results & conclusions
- Understandable : cumulative reports / reference & decision limits
- Comparable : over methods / time frames
- Coherent : with other tests & procedures
- Complete : identification of lacking / censored data
- Right price/costs : low financial & user burden to patients & staff

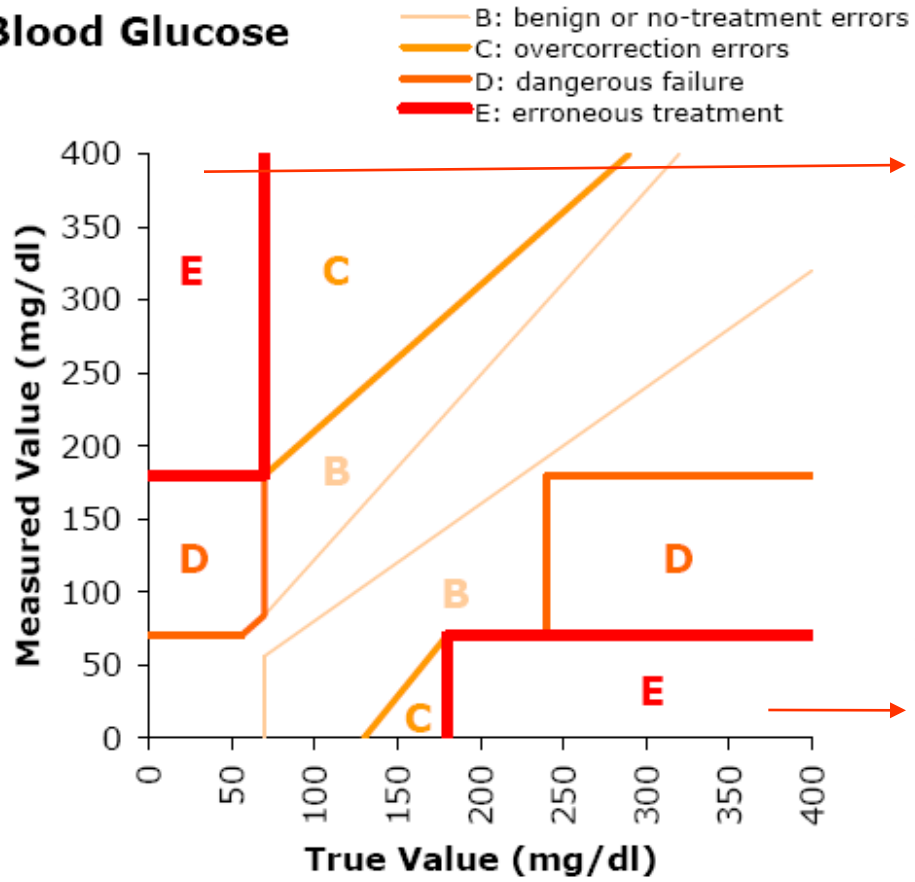
Method Validation - Step 1 : Be specific about your requirements

Analytical requirements of laboratory test

- Relevant :
- Accurate : data processing / analytical traceability
- Timely :
- Accessible :
- Understandable : traceability to the applicable clinical studies
- Comparable : commutability over methods / time frames
- Coherent : diagnostic specificity of measurement
- Complete :
- Right price/costs :

This list is far shorter than the former &
many analytical requirements can only be specified
when knowing the circumstances (= logistics) of the diagnostic scenario

Method Validation - Step 2:
Be specific about which problem is relevant



Hypoglycaemia treated with insulin i.s.o. glucose

Hyperglycaemia treated with glucose i.s.o. insulin

W.L. Clarke, D. Cox, L.A. Gonder-Frederick, W. Carter, S.L. Pohl
Evaluating clinical accuracy of systems for self-monitoring of blood glucose
Diabetes care 10:622-28 (1987)

Method Validation – Step 2 – BOTTOM-UP ANALYSIS

Robustness of the Diagnostic Process ? What can cause significant failures ?

Test Ordering

Right Test at the Right Time … for the Right Patient …

Pre-analytical

Biological Variation
Pulsitility, Diurnal & Seasonal Variation
Physiological (Starvation, Exercise, …) Variation, …

Specimen Collection
Posture
Stasis, Hemolysis, Filling of the tube
Right patient, Correct labelling, sample, recipient, …

Interpretation

Adequacy, sampling details , specimen quality, …, …
Adequacy cut-offs, reference ranges, …
Adequacy interpretation support

Post-analytical

Reporting for the right patient
Transcription errors , …, …
Data transfer errors, ….

Analytical = Measurement Process

Sample reception & processing
Right identification of primary and secondary sample
Completeness of coagulation, …
Micro cloths: obstruction needle, light scattering, …
Membrane ghosts and fragments, …

Uncertainty of Measurement
Bias, Specificity, …
Calibration, Linearity, …
Inter-batch random error, …
Other sources of (random) imprecision
Equipment faults (aspiration, carry-over, sporadic faults, ..)

Method Validation - Step 2:
Be specific about what can cause relevant problems

Logistic problems causing treatment failures
- faulty test requests
- faulty patient identification & sample labelling
- faulty sampling procedures and sample recipients
- untimely sampling & reporting

Analysis of uncertainty of measurement
- list sources of unavoidable & of avoidable error
- sensitivity analysis = analyze potential magnitude of error
- analyze weak spots = potential occurrence

Analysis of nature of risk
- intermittent or persistent / catastrophal
- random or bias

Valid Logistic Implementation

What are critical area's amenable to improvement ?

Joint Commission of Accreditation of Healthcare Organizations (JCAHO)

National Patient Safety Goals (NPSG) 2006

Laboratory-related goals

NPSG #1: **Accuracy of Patient & Sample Identification**
NPSG #2: **Effectiveness of Communication among Caregivers**
- 2.a. read-back verification
- 2.b. unambiguous acronyms
- 2.c. timeliness of critical results

NPSG #4: **Universal Protocols**

Method Validation - Step 2:
Be specific about what can cause relevant problems

Logistic problems causing treatment failures
- faulty test requests
- faulty patient identification & sample labelling
- faulty sampling procedures and sample recipients
- untimely sampling & reporting

Analysis of uncertainty of measurement
- list sources of unavoidable & of avoidable error
- sensitivity analysis = analyze potential magnitude of error
- analyze weak spots = potential occurrence

Analysis of nature of risk
- intermittent or persistent / catastrophal
- random or bias

Method Validation - Step 3:
Be specific about your System of Prevention

POKA-design & Primary Prevention

Define and implement the best conditions for operation

Choose for robustness, not for fragility

- Universal Protocols
- Maintenance

…

Secundary Prevention : Know that it went wrong

If it can go wrong, it will break one day

- iQC

…

Action Cascades & Damage Mitigation

When it went wrong, know what to do

(Murphy's law: be prepared)

- …

Step 3 – ANALYSIS OPERATIONS on the WORK-FLOOR

System of Prevention: in function of source of error

Setup-dominant	Machine-dominant	Operator-dominant	Component-dominant
Items			
Labeling Worklists Dispension …	Pipetting Analysis …	Adjusting Expert judgements …	Formulation Consumables …
Typical Control Procedures			
Precontrol First-piece inspection Attribute inspection …	Maintenance In-line periodic inspection iQC …	Acceptance inspection iQC Operator scoring …	Vendor Rating Incoming inspection Prior-operation control Acceptance inspection iQC …

After LA Seder

Proactive = Good Manufacturing Practice

Step 3 – ANALYSIS OPERATIONS on the WORK-FLOOR
System of Prevention: in function of Process Approach

Lab = Work-shop with Repeat Jobs
From analysis of historic data much can be learned to affect the future

Approaches	Basic Control Technique
Current-job	In-line control with immediate feedback
Repeat-job	Corrective pro-active actions with respect to next job
Chronic-offenders	Root-cause analysis of high-impact problems
Product-families	Concentrate efforts on common-mode failure
Systems-centered	Improve PDCA-cycles
Basic-premises	Revise managements presumptions = **clean-up obsolete items** of the quality system

= Good Manufacturing Practice

After LA Seder

To negotiate Risk =
to allow some level of Risk
while economizing on efforts

Balancing
Opportunity Costs
Ecologic paradigm (# 26)
Darwinian paradigm (# 39)
Economic paradigm (# 52, 53)

You accept Risk while you minimize Low Gain Activities
by a more or less Educated Gamble.

Bayesian Model

You don't accept Low Gain Activities & you economize
by a more or less successful Work-around.

Heuristics

We are hard-wired "pour se débrouiller"
Procedures are not fail-safe = RISK

Acceptance & adherence depends on
- perceived utility & efficiency
- perceived fairness & predictable outcome, …

Prim Prevention
Robust =
Universal & Lean
Scnd Prevention
Internal Audits

Method Validation - Step 3: Principles of design for quality

Choose for robustness, not for fragility

- Inventory of Process Steps
- Retain what is necessary
- Inventory of remaining Critical Steps
- POKA where possible
- (? Redundancies ?)
- Plan Maintenance
- Plan management critical resources
- (? Proactive Checks ?)

CAVE
don't create waste !

Method Validation
a typical Recipe

1. Method Validation :
   evaluate CV's = Uncertainty of Measurement (UM)

2. Limit Risk :
   set a limit to acceptable error = bias ± k * CV

3. Statistical Process Control (iQC)
   define the rules to detect unacceptable UM

Method Validation

a Valid Recipe ?

1. Method Validation :
   evaluate CV's = Uncertainty of Measurement (UM)

2. Limit Risk :
   set a limit to acceptable error = bias ± k * CV

3. Statistical Process Control (iQC)
   define the rules to detect unacceptable UM

What is your system of prevention ?
Your ONLY FOCUS = SECONDARY PREVENTION ?

Method Validation

a Valid Recipe ?

1. Method Validation :
   evaluate CV's = Uncertainty of Measurement (UM)

2. Limit Risk :
   set a limit to acceptable error = bias ± k * CV

3. Statistical Process Control (iQC)
   define the rules to detect unacceptable UM

Is this a VALID SYSTEM of Secondary Prevention ?
Step 3 : Be specific about your ASSUMPTIONS !

Method Validation : Rectification of a few Misconceptions

1. Method Validation
≠ an evaluation of the Uncertainty of Measurement (UM)

2. Uncertainty of Measurement (UM)
CV ≠ a factor of Risk

3. Statistical Process Control (iQC)
statistically significant aberration
≠ absolutely certain
≠ relevant failure

(Statistical) **Process Control** is about **Process Care**

(Statistical) **Process Care** is 

1. evaluation of past & current behaviour of the system

2. appraisal of appropriate statistics
to diagnose current or pending relevant failure

3. actions to influence future behaviour of the system

(Statistical) Process Control is about Process Care

The strategy is only cost-effective if you are specific about

1. the risk to be detected

A statistically significant aberration ≠ a relevant failure
Do not fall for false error detection
& quality failure due to down-time and long TAT's

Appropriateness of your statistic diagnostic tool
depends on an H_1-hypothesis :
- what is the undesirable behaviour to be detected ?
- what is the unacceptable behaviour to be detected ?

2. corresponding trouble-shooting actions

(Statistical) Process Control is about
Maintenance to influence the Future

The futility of (statistics)

significant ≠ absolutely certain

significant ≠ relevant

Statistical Process Control

≠ a fail-proof tool of secondary prevention

= a secondary tool of primary prevention

its proper frame is **maintenance**

Test-drive
our Simulator

Make the operator owner of the tool

What are cost-effective tools of primary prevention ? see # 68 & 69

Method Validation : Rectification of a few Misconceptions

1. Method Validation
≠ an evaluation of the Uncertainty of Measurement (UM)

2. Uncertainty of Measurement (UM)
CV ≠ a factor of Risk

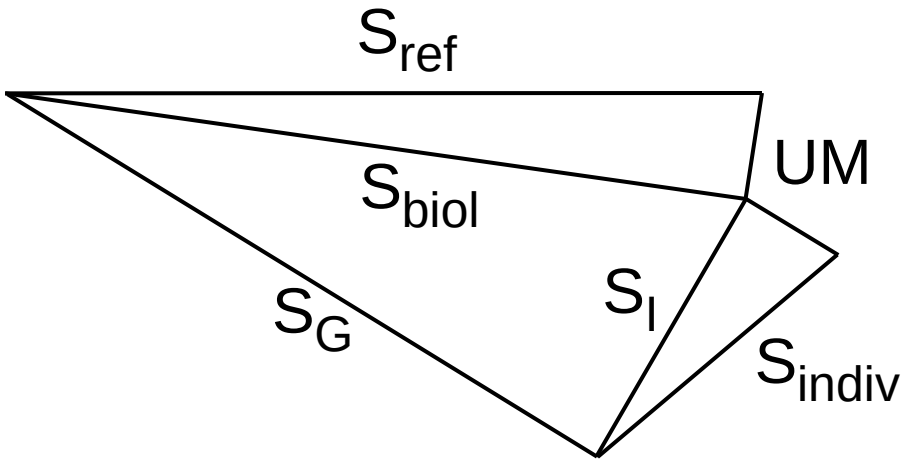
3. Statistical Process Control (iQC)
statistically significant aberration
≠ absolutely certain
≠ relevant failure

Risk is about Interpretation not about Measurement

iQC delivers you an estimate of Uncertainty of Measurement However !

Uncertainty of Measurement (UM) ≠ Risk

1. The Uncertainty of Interpretation is determined by the Reference Change Value (RCV = $2^{0.5}$ k S_{indiv}). The contribution of UM to RCV normally is small.



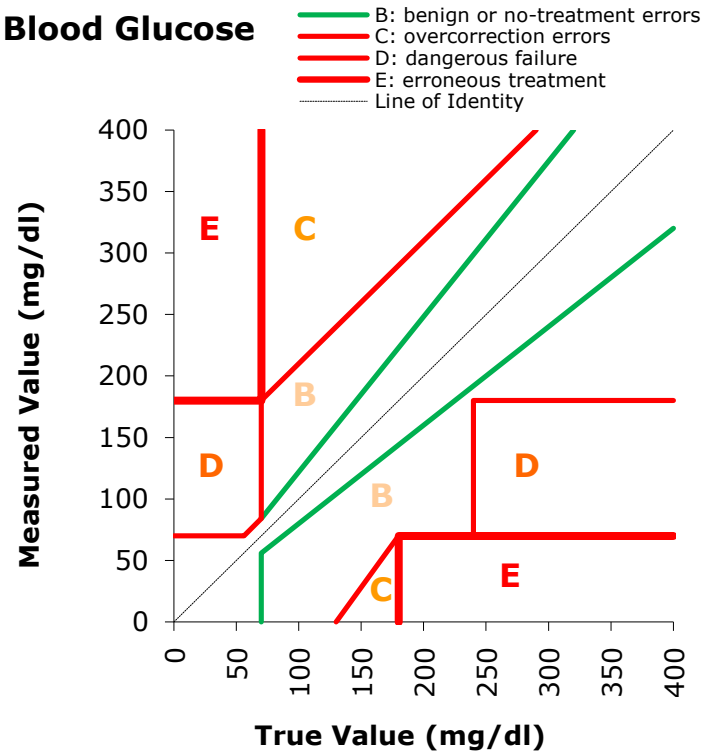
Pythagorean rule :

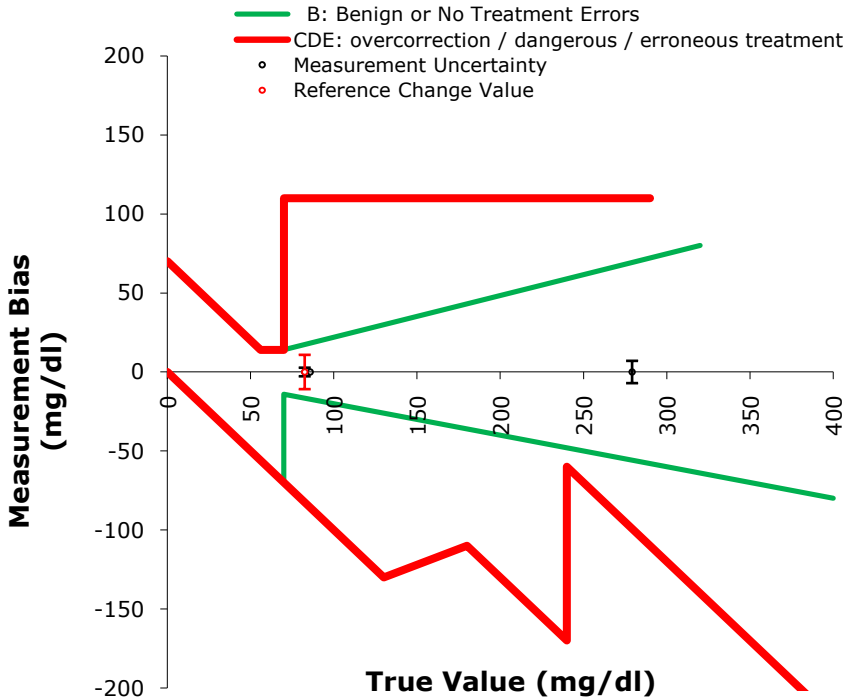
- random error adds destructively

- effect of UM is typically small to the extent that it may be irrelevant

Test-drive our simulator

Put things in the right perspective, if you want to be taken seriously.



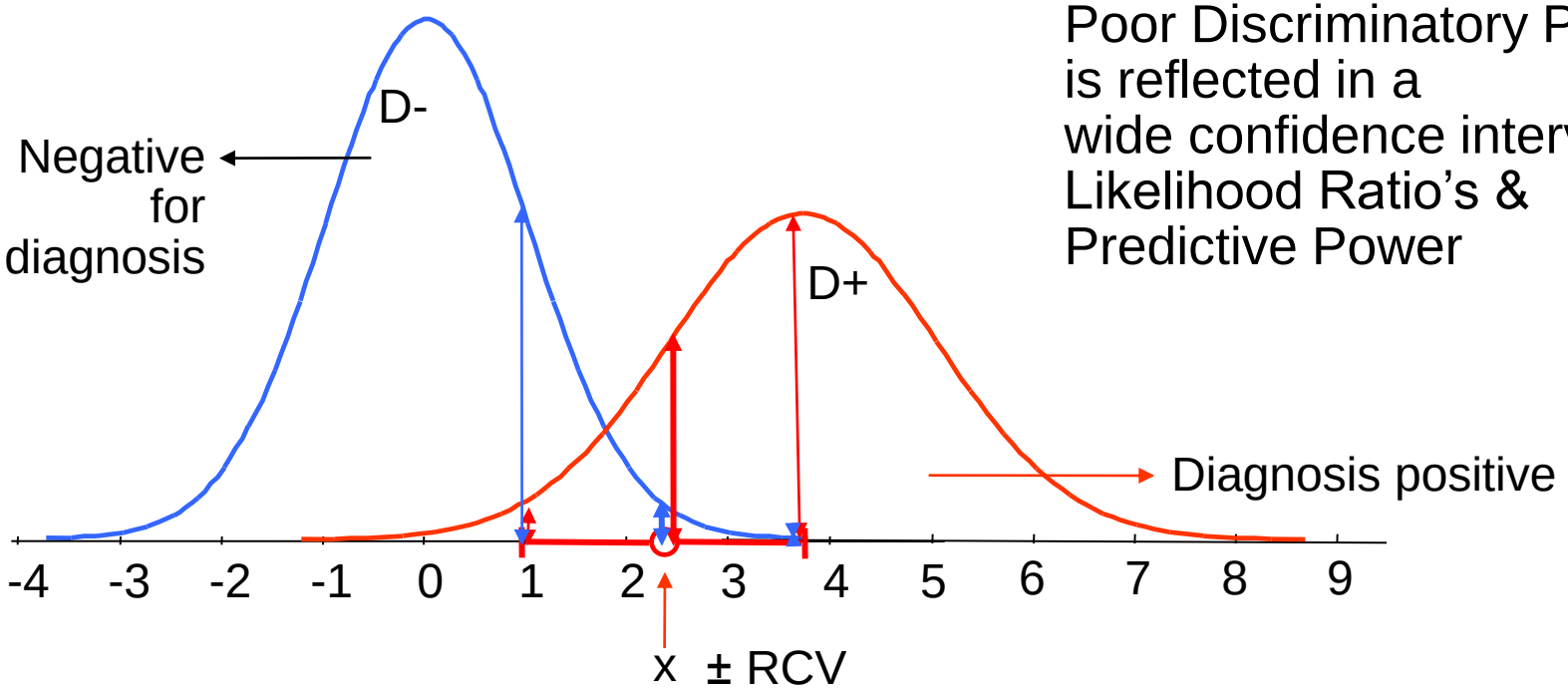


Clarke → Bland & Altman equivalent

Evaluate Analytical performance

Uncertainty of Measurement (UM) ≠ Risk

2. The Uncertainty of Interpretation is determined by Biological Overlap & RCV.
The problem cannot be remedied by analytical means.



Poor Discriminatory Power is reflected in a wide confidence interval for Likelihood Ratio's & Predictive Power

Uncertainty of Measurement (UM) ≠ Risk

3. The so-called European Guideline on "desired Quality" expresses allowed UM and bias as a fraction of components of biological variability.

It addresses the question how good the measurement tool has to be to determine the central tendency and dispersion of
- the "reference" population
- the position of an individual within that population

The answers have some bearing on the staging and follow-up clinical-scenario.

See slide #59

Method Validation : Rectification of a few Misconceptions

1. Method Validation
≠ an evaluation of the Uncertainty of Measurement (UM)

2. Uncertainty of Measurement (UM)
CV ≠ a factor of Risk

3. Statistical Process Control (iQC)
statistically significant aberration
≠ absolutely certain
≠ relevant failure

UM focuses on Robustness of the Measurement Compartment

≠ Robustness of the Diagnostic Process : " Where occur significant failures ? "

Test Ordering

Right Test at the Right Time … for the Right Patient …

Pre-analytical

Biological Variation
Pulsitility, Diurnal & Seasonal Variation
Physiological (Starvation, Exercise, …) Variation, …

Specimen Collection
Posture
Stasis, Hemolysis, Filling of the tube
Right patient, Correct labelling, sample, recipient, …

Interpretation

Adequacy, sampling details , specimen quality, …, …
Adequacy cut-offs, reference ranges, …
Adequacy interpretation support

Post-analytical

Reporting for the right patient
Transcription errors , …, …
Data transfer errors, ….

Analytical = Measurement Process

Sample reception & processing
Right identification of primary and secondary sample
Completeness of coagulation, …
Micro cloths: obstruction needle, light scattering, …
Membrane ghosts and fragments, …

Uncertainty of Measurement
Bias, Specificity, …
Calibration, Linearity, …
Inter-batch random error, …
Other sources of (random) imprecision
Equipment faults (aspiration, carry-over, sporadic faults, ..)

Is this where most significant failures originate ?

METHOD VALIDATION: PROCESS FLOW CHART

Method Validation Process

Clinical Scenario
Inventory of Means
Test Selection

Requirements ?
Suitability ?

Risk Analysis
define medically
Important Errors

Appropriate Procedures

Implementation

Evaluation of
Clinical Path

Steering the Diagnostic Process = a continuous PDCA-cycle !!!

Diagnostic Process

Patient Symptoms

Model
- differential diagnosis
- measurement model

Test Request
Sampling

Evaluation

Treatment

Analysis

Report

Analytical Process

When analytical specs (*e.g.* CV's)
is the only compartment,
that the validation exercise focuses on,
then that exercise remains nonsensical.

Summary (1/3)

The validation plan shall identify valuable targets

Who's PURPOSE does it serve ?

Is it fit for PURPOSE ?

Is it optimized for PURPOSE ?

Summary (2/3)

The validation plan shall identify relevant issues

The poorer the diagnostic ability of a test,
the less you have to bother about analytical performance.
Or, a poor diagnostic test cannot be improved
by being particular about analytical performance. ☺

The better the diagnostic ability of test,
the less analytical performance matters.
Or, a good diagnostic test,
is insensitive to analytical performance. ☺

Not to understand " relevance "
= to incur the costs of missed opportunities

Summary (3/3)

The validation plan shall realize valuable targets

Focus on where the greatest gains can be realized :

pre-analytical : good sampling plans & robust procedures

post-analytical : adequate interpretation support (next section)

Go for Universal Protocols :

applicable to many tests and circumstances. ☺

Method Validation  = Continuous Risk Management

- **know what is at stake**
- **identify weak spots (validation & non-conformity registration)**
- **implement robust procedures to remedy weaknesses**
- **organize proactive prevention (manage critical resources / acceptance-testing , maintenance , calibration / operator scoring)** #68
- **organize follow-up of relevant benchmarks (TAT, corrections)**
- **be prepared for failures (intervention cascades)**

1. Understanding Risk = Uncertain Decisions
2. Method Validation = Risk Management
3. **Laboratory Diagnosis = Risk Communication**

Laboratory Diagnosis = Risk Communication

Patient (
- recognize problem
- select physician
- present symptoms
- **Physician** (
  - recognize relevant symptoms
  - request the proper test
  - **Laboratory** (
    - perform test
    - report result)
  - interpret result
  - propose treatment to patient)
- **comply**)

Lab has to facilitate the best decision

Brain 2 to Brain 2

Brain 1 to Brain 1

1. Be specific about your requirements
- **who has to be informed ?**
- **end of the ride is compliance of patient with the best decision**

Laboratory Diagnosis = Risk Communication

How the Doctor Thinks

RISK TAKING versus RISK ADVERSION

CONFIDENCE versus AMBIGUITY

GESTALT versus DECONSTRUCTION

After J Groopman

R) Heuristic Approach
gain in error variability
reduction in uncertainty
broadened sensitivity
find unexpected but relevant features

2. Be specific about the problem to solve
- How does the party concerned come to a decision ?

Laboratory Diagnosis = Risk Communication

How the Patient Thinks

RISK TAKING versus RISK ADVERSION

(LIMITED) NUMERACY versus CERTAINTY

ALTRUISM versus SELFISHNESS

R) emotional involvement
follows external cues

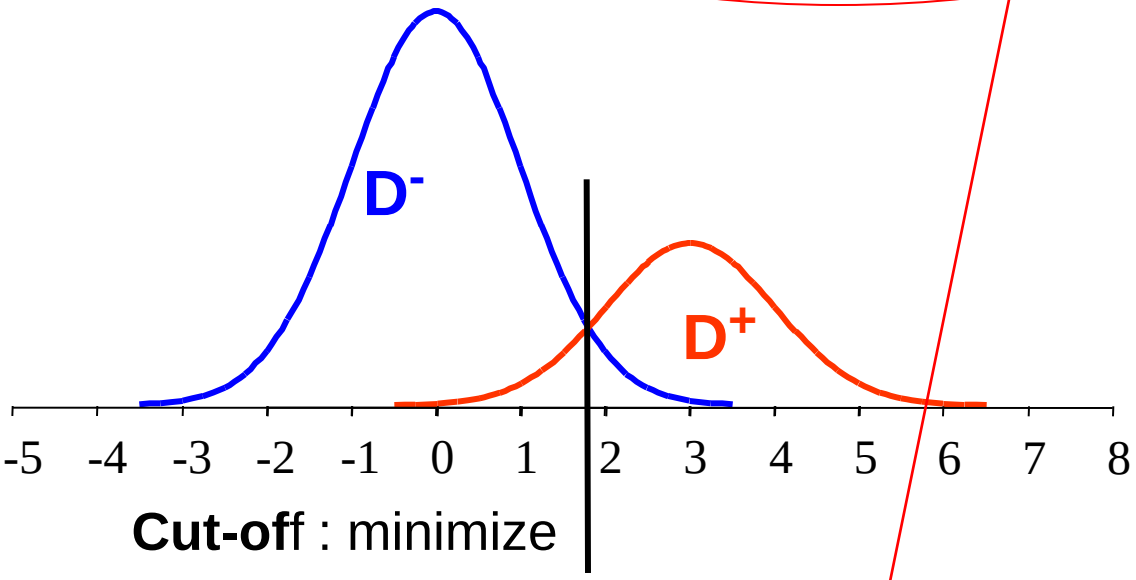
2. Be specific about the problem to solve
- How does the party concerned come to a decision ?

Laboratory Diagnosis = Risk Communication

The Bayesian Model of Risk Communication

Differential Diagnostic Question = known
Corresponding Spectrum = known

Frequency Distribution
*** Prevalence = Number Distribution**
*** relative value = Value Distribution**

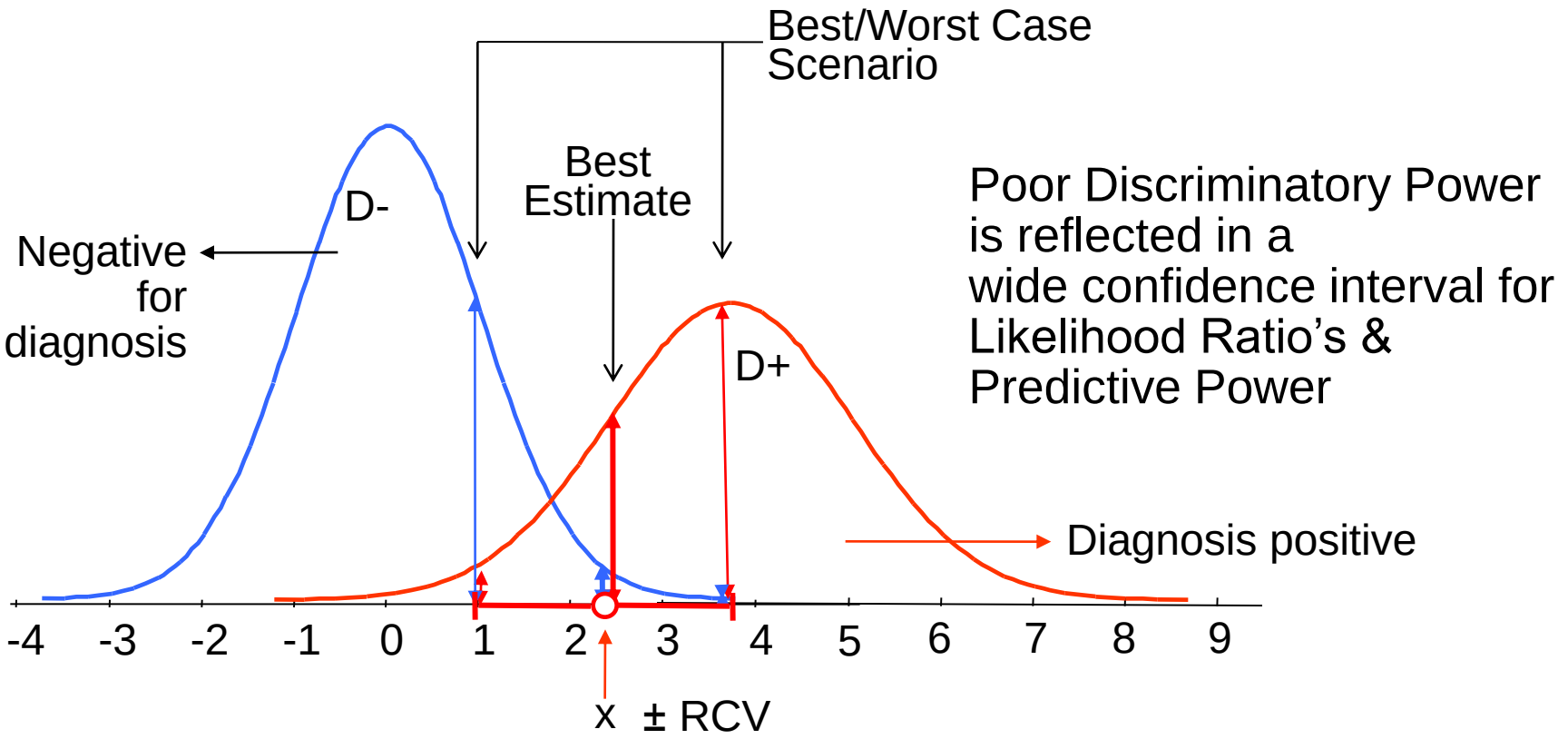


3. Be specific about the underlying assumptions
- Use Case is known
- Complete knowledge of (pre-test) Prevalence & Costs / Benefits
- Net Utility is the only consideration Clinical Decisions

Knowledge is almost invariably fragmentary

Laboratory Diagnosis = Risk Communication

The Bayesian Model of Risk Communication



3. Be specific about the underlying assumptions

- While following the cue defines the best gamble, that gamble is perceived as extremely uncertain, read " risky "

Laboratory Diagnosis = Risk Communication

The Bayesian Model of Risk Communication

Given:

$P(D+)$ = **Prevalence**

$P(T+|D+)$ = **Sensitivity**

$P(T+|D-)$ = **1- Specificity**

Bayes theorema:

solves $P(D+|T+)$ from $P(T+|D+)$ & $P(T+|D-)$ & $P(D+)$

$$\frac{P(D+|T+)}{1 - P(D+|T+)} = \frac{P(D+)\ P(T+|D+)}{P(D-)\ P(T+|D-)} = \text{OddsRatio}$$

$$P(D+|T+) = \frac{\text{OddsRatio}}{1 + \text{OddsRatio}} = \text{Probability}$$

3. Be specific about the underlying assumptions

- Decision-Maker is Numerate and Stress-resistant ?

Risk Communication : Likelihoods & Probabilities

Pre-test Odds ↓ | Likelihood Ratio's ↓ | Post-test Odds ↑

$$\frac{P(D+)}{P(D-)} \quad \frac{P(T+|D+)}{P(T+|D-)} = \frac{P(D+|T+)}{1 - \mathbf{P(D+|T+)}}$$

↑ What the requesting physician is supposed to know

↑ What the lab may have on offer

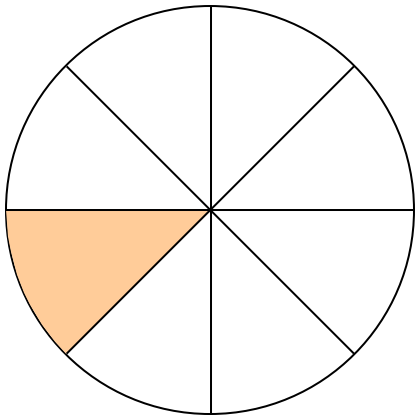
↓ ± Confidence Interval ?
Do you want the patient to follow your cue ? (see #89)

What the Patient is after
(informed consent)

(provided the differential diagnostic question and the corresponding patient spectrum are known)

Risk Communication : Formats

I got 1/8
of the cake

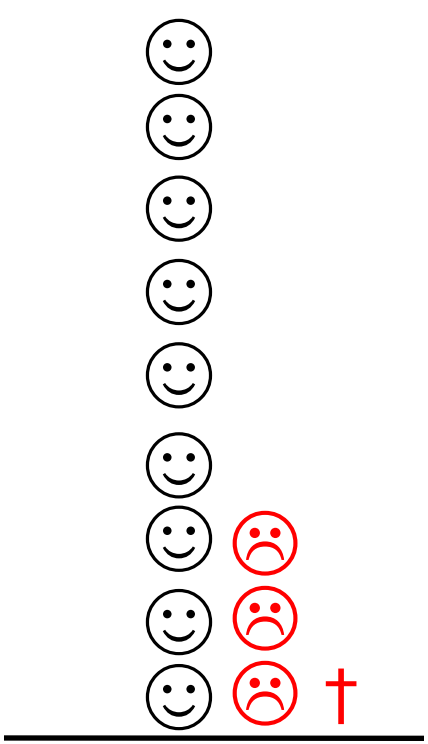


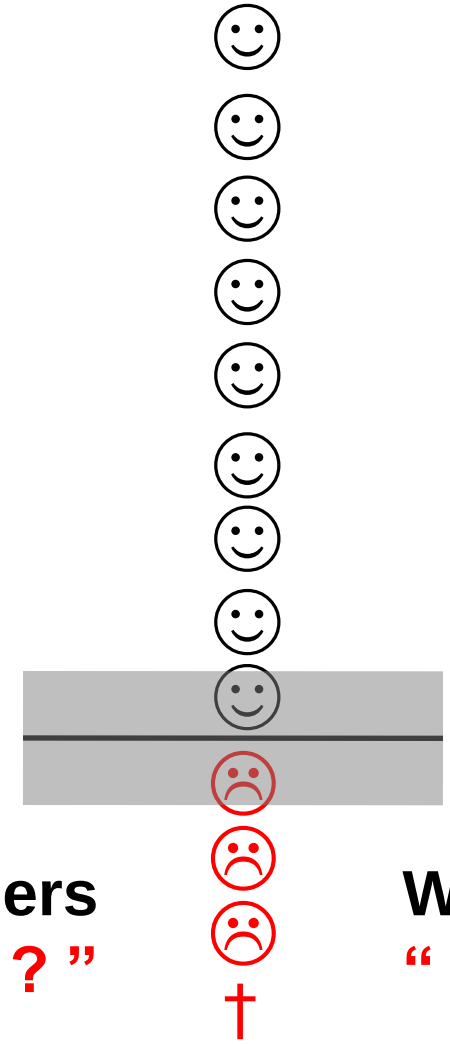
Proportions		Odds ratio's
$p = O / (1 + O)$ (all possibilities)	**Formula's**	$O = p / (1 - p)$ (all alternative possibilities)
1/2	**Break-Even-Point**	1/1
0 ≤ 1/8 ≤ 1	**Range**	0 ≤ 1/7 ≤ ∞
%-transformed 0% ≤ 12.5% ≤ 100%		log-transformed - ∞ ≤ -0.903 ≤ ∞

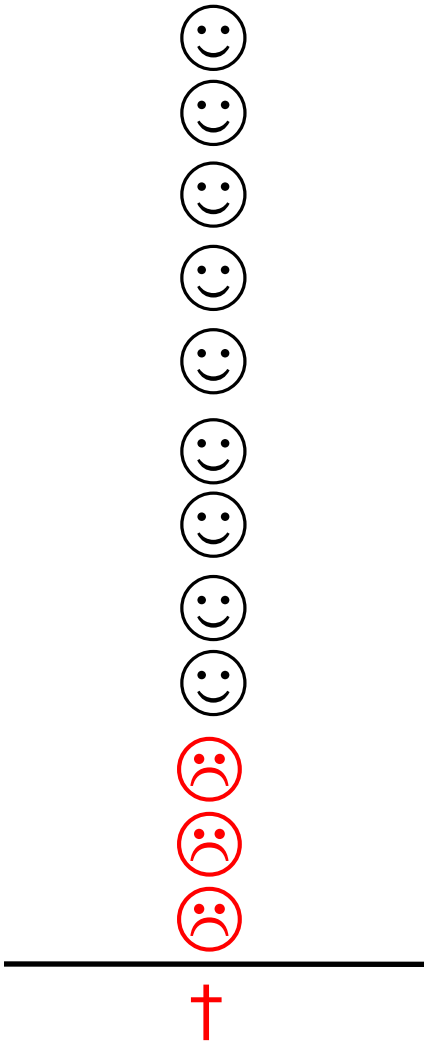
We call this 50/50 because most people come only to grasp with proportions

We transform this in % because most people can only grasp whole numbers

Risk Communication : Odds ratio's Graphical Formats







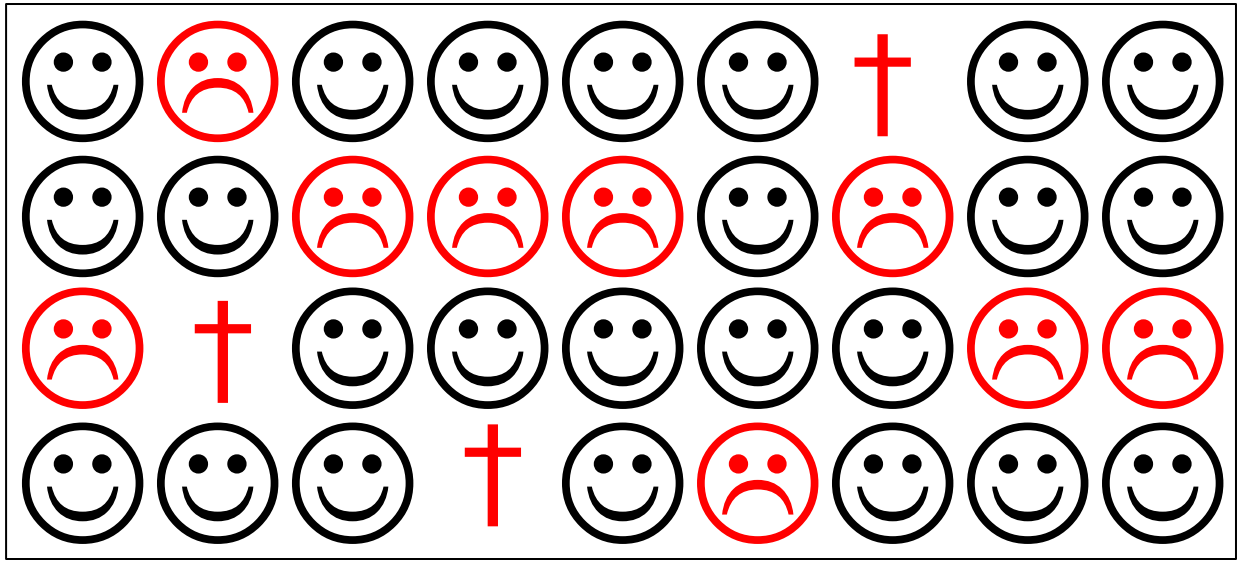
What the Doctor bothers

" How certain ? "

What the Patient bothers

" How unjust ! "

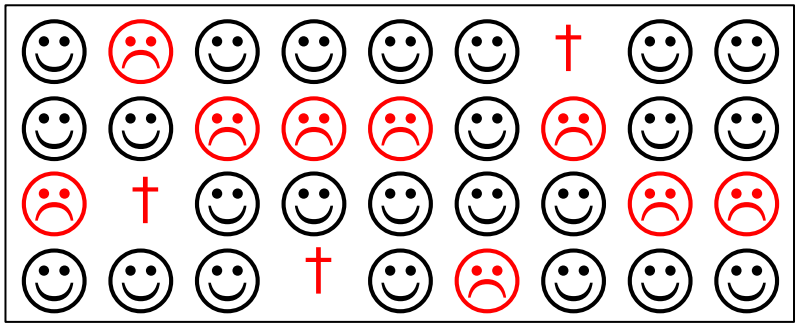
Risk Communication : Proportions
Graphical Formats



The doctor can make a bed,
but the patient wants to know “ Which one am I ? ”

How good is your test at Predicting Risk ?

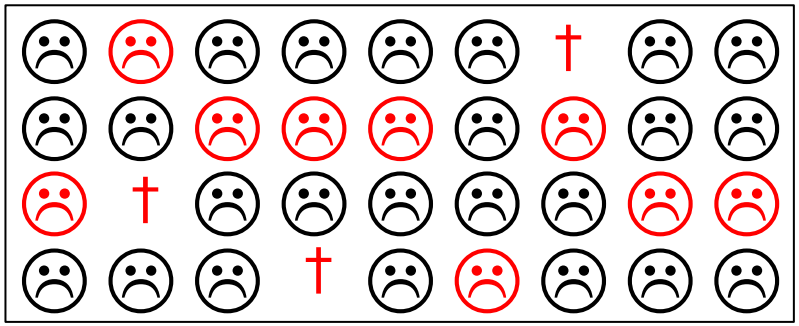
In the Literature



☺

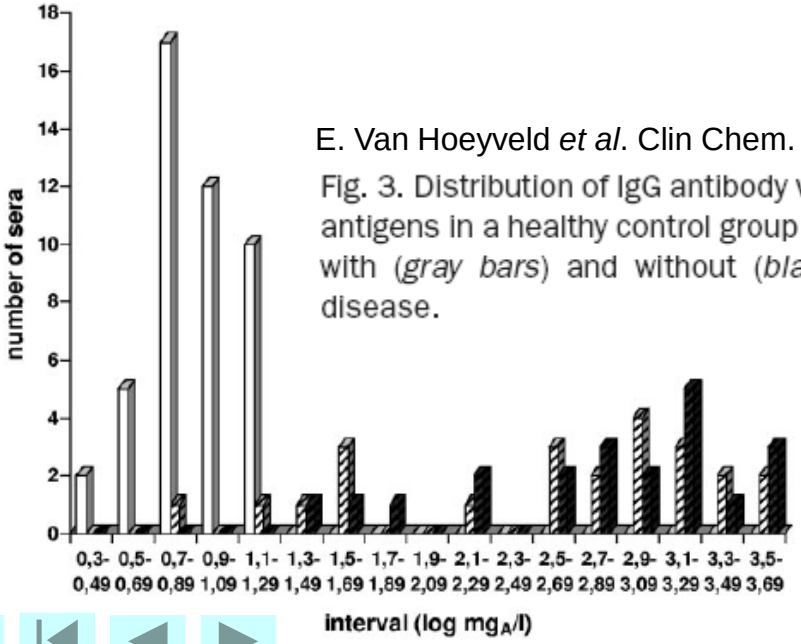
"Hi, I'm a healthy volunteer"

In the Doctor's Office



☹

"Hi, I got a bill for my test.
I may or may not have PBD"



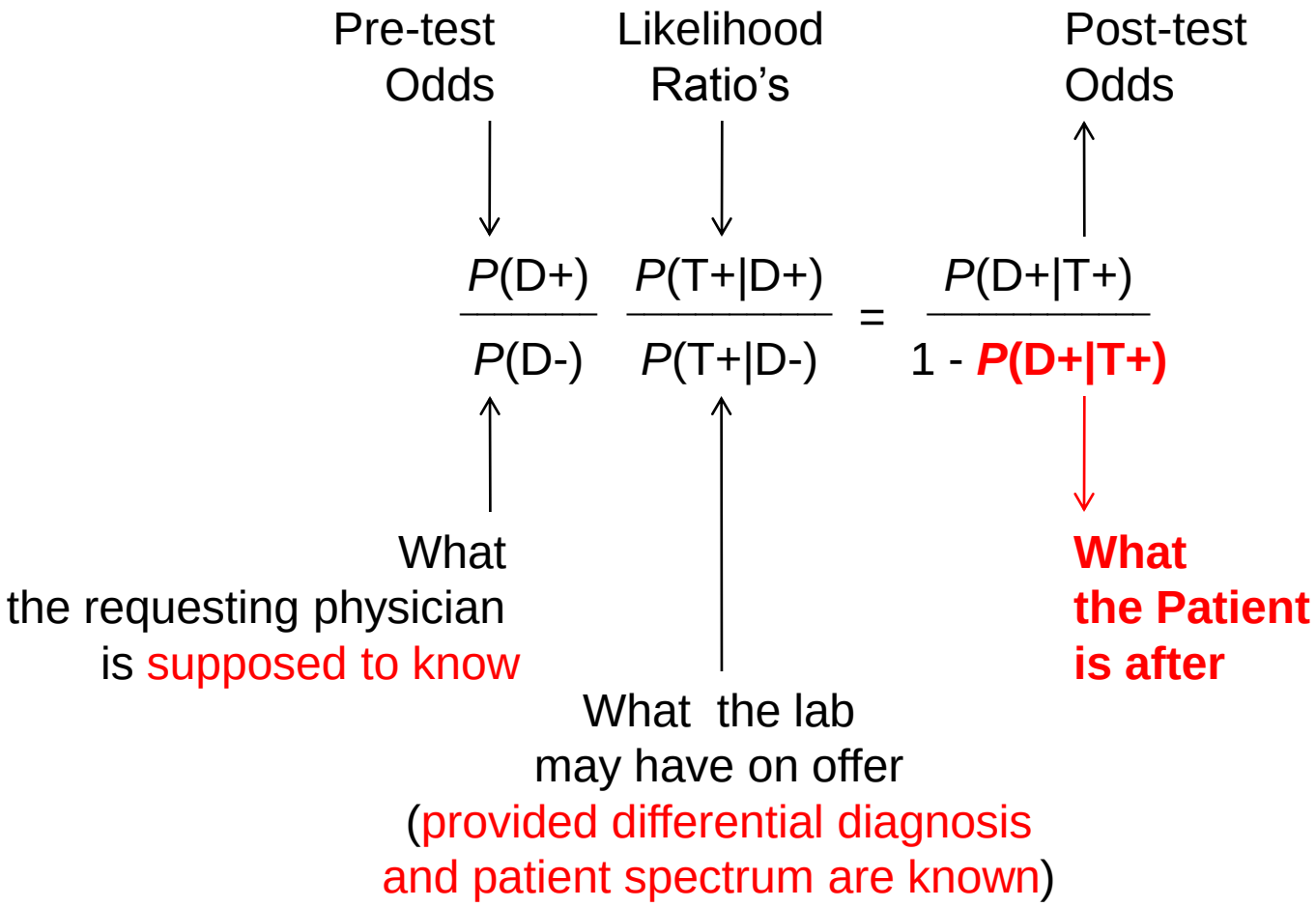
E. Van Hoeyveld *et al*. Clin Chem. **52**:1785-93 (2006)

Fig. 3. Distribution of IgG antibody values (log mg$_A$/L) to pigeon antigens in a healthy control group (*white bars*) and in patients with (*gray bars*) and without (*black bars*) pigeon breeder's disease.

☹

"And the test didn't tell me either"

Bayesian Decision Model



- **Even when knowledge is uncertain, we have to and we do make decisions ☺**
- **Even when knowledge is certain, our decisions are biased by …**
- **Emotions are part and parcel of making decisions …**

Bayesian Decision Model

may not exactly be able to realize a dream of
rational and utilitarian decision-making (Descartes, Bayes, Laplace)

but remains valuable as an Experimental Tool

Choose a problem for which prior-knowledge is nearly complete or
Simulate a problem

Weigh experimental (real-life) decisions, against
the optimum decision predicted by the Bayesian model

- Compare relative bias of physician and patients

- Use relative bias to measure " intangible components of value "

- Investigate effect of data-formats on decision outcome

A glance in the future ?

- An evolution to
  central internet depositories of patient data, owned by the patient ?
  Advantages:
  - patient-driven: involvement of patient in own care
  - general-physician-driven: low-cost integration of
    data from patient-contacts with multiple health-care providers
  - market-driven: opens a competitive market for outsourcing of lab-tests

  Challenges:
  - commutability of results
  - patient's understanding of the data / (lab-)physician as a counselor
  - equitable health-care / cost-containment
  - *privacy issues*
- True automated expert systems
  NOT automated algorithms, BUT automated information-generating systems
  - results analyzed by physician and by patient characteristics, …
    helps to fill the gaps in knowledge of prevalence and spectrum
  - graphical representations of patient results
    - with respect to other similar diagnostic problems
    - with respect to follow-up
      helps to communicate the meaning of these results
      helps to understand aleatory (chance) & relevant variance

Summary (1/3)

The Bayesian Model

The Bayesian Model provides us with
- a useful conceptual framework ☺
- on how to live with " fate forcing our hand " ☹

In the mind of the clinician
- incomplete knowledge is ☹
- substituted for by elicitation ☺

Work / Research in Progress ☺
- completeness of knowledge
- numeracy of parties involved
- risk perception & effective communication

Summary (2/3)

The Bayesian Decision Model is supplemented by a Differential Diagnostic Model (Heuristics)

The Clinician Decides on the basis of anamneses, clinical presentation, and multiple (technical) exams.
The value of a laboratory test is determined by its position in this differential diagnostic framework.
This heuristic framework allows to alleviate uncertainties & to detect errors ! ☺

Summary (3/3)

Detection of medically-significant errors

To negotiate the uncertainty of interpretation
the **clinician** will request additional or follow-up tests to **evaluate**
- the **internal consistency** with previous results
- the **external consistency** with the body of knowledge

In order to come to a decision
the corresponding mental process is geared at
- neglecting inconsistent results
- overvaluing confirmatory evidence
- resort to additional testing

The clinician may have
a blind eye for lab errors
NO CONTROL PROCEDURE HAS
ABSOLUTE SENSITIVITY & SPECIFICITY

The **clinician** is best positioned for
detection of medically important errors
PROVIDE A DIRECT CHANNEL
FOR IMMEDIATE FEEDBACK

Current-job approach :
quality and **immediacy** of reaction
from the lab determines whether
physician will ever bother to inform the lab

Living with Risk =
a Culture of Communication & Understanding

Understanding = Empathic Thinking

- take the viewpoint of the ultimate stakeholder
- identify with the "system" and think from within

Understanding = Innovative Thinking

- rethink the use of resources for optimal result
- out of the box thinking

Empathic & Innovative = Creative Thinking

Risk brings zest to our profession

Literature – Internet Resources

Medical laboratories – Reduction of error through risk management and continual improvement ISO/TS 22367:2008

The 8 principles of Quality Mangement

http://www.iso.org/iso/en/iso9000-14000/understand/qmp.html