Be Specific:
Putting Biomarker Assay Validation in Context

EBF Biomarker Focus Workshop
15-17 September 2020

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Overview

- Setting the Foundation
  - What is Validation?
  - Context of Use – what it is and what it isn’t
  - First principles thinking
- COU specifics
  - Find it, Define it (specifically), Deploy it
- No COU, what do I do?
- Summary

What is Validation?

- A process to establish that the performance of a test, tool or instrument is acceptable for its intended purpose (BEST)
- Method/Assay Validation
  - Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use (Ludwig Huber, *Validation and Qualification in Analytical Laboratories)*
  - Assay validation provides an assurance of reliability during normal use and is sometimes referred to as "the process of providing documented evidence that the method does what it is intended to do" (www.fws.gov)
- **Validated = Fit for Purpose!**

What is Context of Use?

- BEST resource 2016:
  - The Context of Use (COU) is “A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development related purpose of the use”

- Or, more succinctly…
  - Context of Use = The ‘Purpose’ in Fit-For-Purpose

Validation Requires COU

- If Validated = Fit-for-Purpose, and
- COU = the Purpose in FFP
- Restated: Validation = Fit-for-COU

- No context, no validated assay

Context of Use – Confusion persists

- Q: What is the COU for the assay?
- Some common responses:
  - Exploratory
  - Internal decision-making
  - Primary endpoint
  - Secondary endpoint
  - Exploratory endpoint….

Exploratory

- Cambridge Dictionary
  - Done in order to discover more about something
- What's missing?
  - What exactly are you looking to discover more about?
  - What would a positive result look like? A negative one?
  - How will the data will be analyzed?
  - What conclusions do you hope to draw?
- 'Exploratory' is not specific enough
- Exploratory ≠ COU

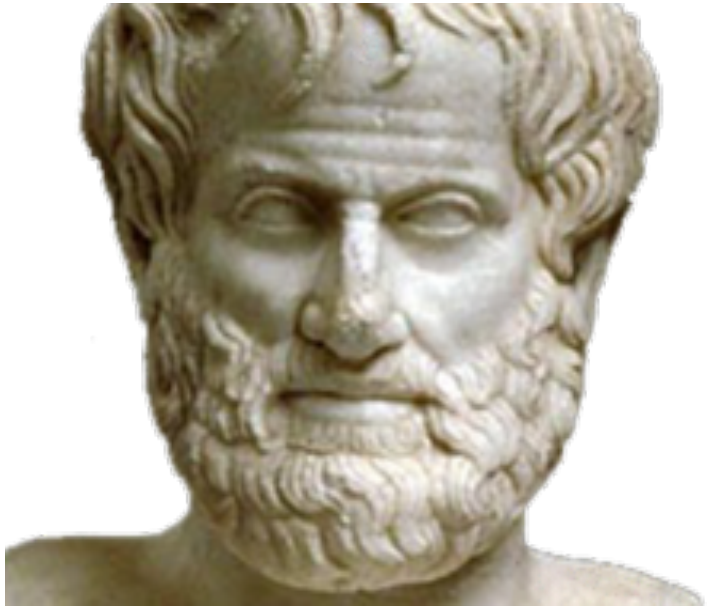
Endpoint

- BEST
  - An endpoint is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question
- What's missing?
  - What is the particular research question?
  - How will the data be analyzed?
  - What are the assumptions about the precision of the data?
  - What is (or even might be) considered clinically meaningful?
- 'Endpoint' is not specific enough
- Endpoints ≠ COUs

So, how do we ‘unstick’ our thinking and get to the specifics?

- Apply First Principles thinking
- Also known as “think like a scientist”

Over 2000 years ago… Aristotle



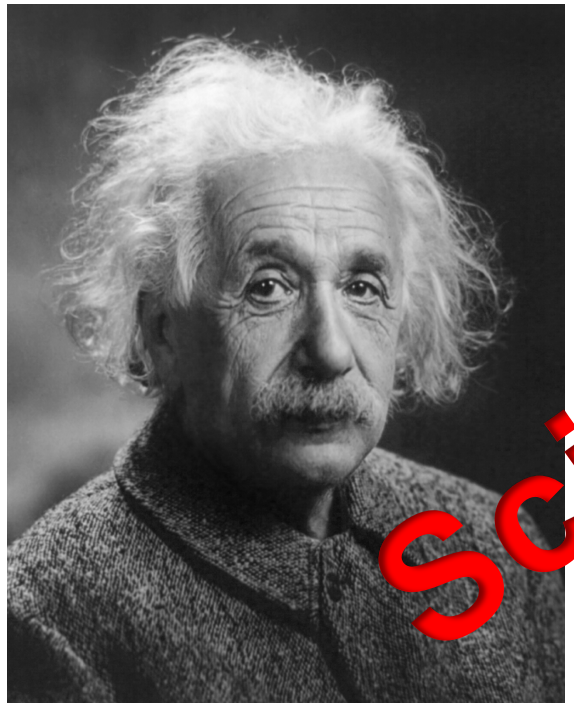
First Principles Thinking vs Reasoning by Analogy

- First Principles Thinking
  - Actively questioning everything you think you know (or assumptions you have) about a given problem and then creating new knowledge and solutions from the ground up
  - #BeAScientist
- Reasoning by Analogy
  - Building knowledge and solving problems based on prior assumptions and beliefs, and perceived ‘best practices’
- Reasoning by Analogy tends to lead to bad decisions
  - Misapplication/overapplication
  - Hasn’t been fully thought through
  - Example: Applying PK Assay BMV Guidance for biomarker assays

Ref: https://medium.com/the-mission/elon-musks-3-step-first-principles-thinking-how-to-think-and-solve-difficult-problems-like-a-ba1e73a9f6c0

First Principles

"If I had an hour to solve a problem, I'd spend 55 minutes thinking about the problem and 5 minutes thinking about solutions" – Albert Einstein



Science

Reasoning by Analogy

"The person who says he knows what he thinks but cannot express it usually does not know what he thinks" – Mortimer Adler

- That's how we've always done it
- It's in the (BMV) guidance
- Because regulators might ask about it

Not Science

Context of Use Specifics

COU – Find it, Define it, Deploy it

- Start with questions
- Demand and define COU (Be specific!)
- Build and properly characterize the assay
- Justify its suitability

Find and define

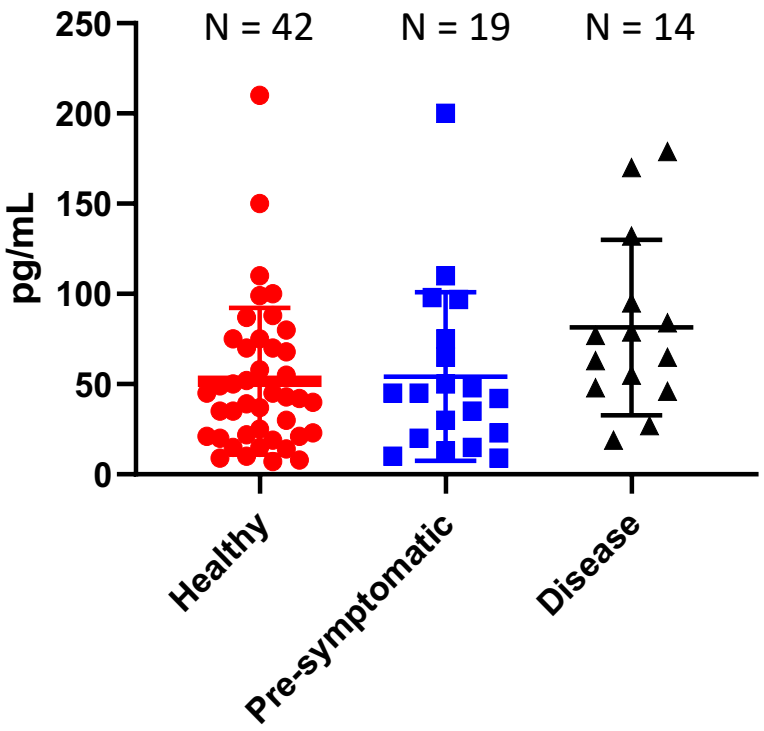
Deploy

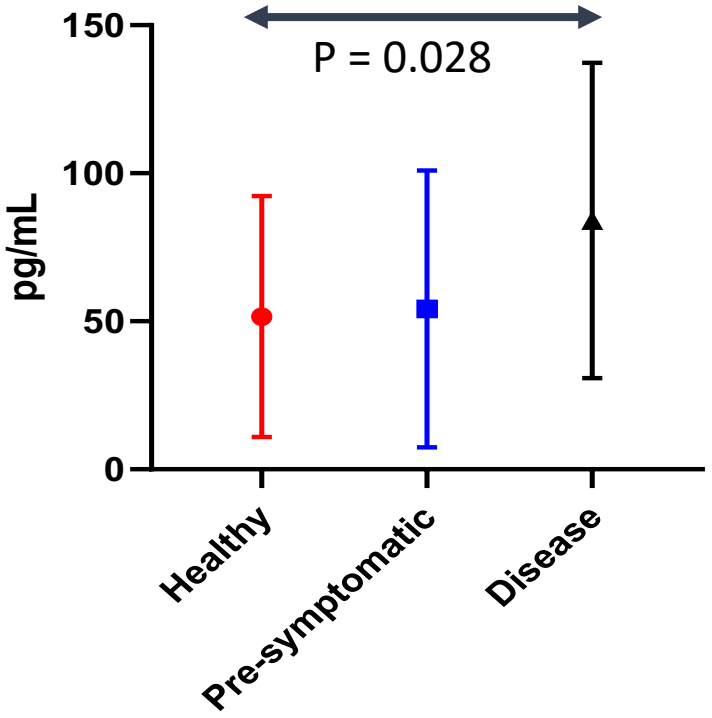
How specific is specific enough?

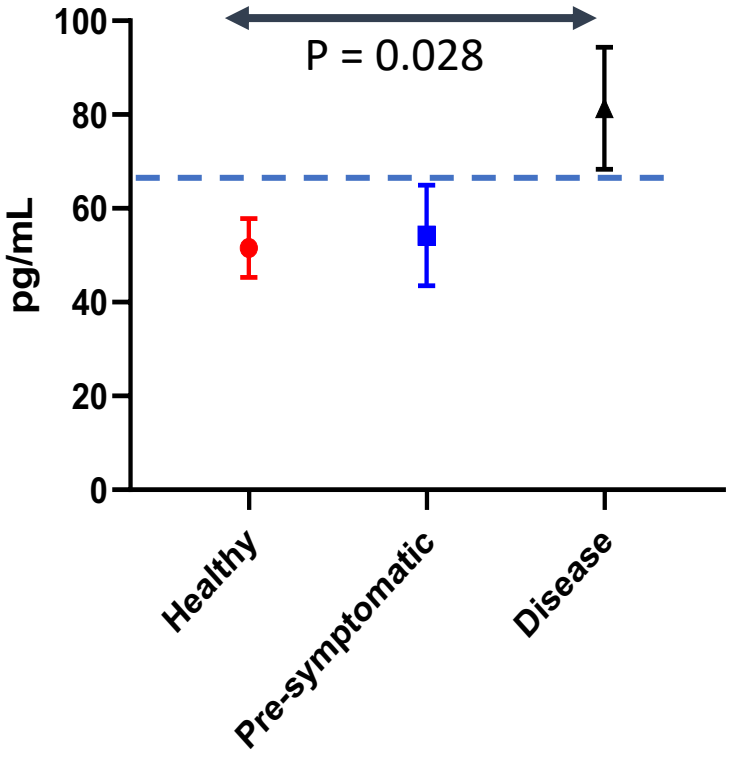
Exploratory Biomarker

- **Question:** Are levels of targeted biomarker different in healthy vs pre-disease and disease state?
- **COU:** Explore levels in cross sectional set of samples and determine if biomarker warrants further exploration
- **Assay:** LBA with EQC inter-assay precision ≤ 25%
- **Samples:** Procured samples from multiple vendors/sites

Rapid mutation of a data set…







Biomarker Scientist conclusion:
"Potentially interesting"

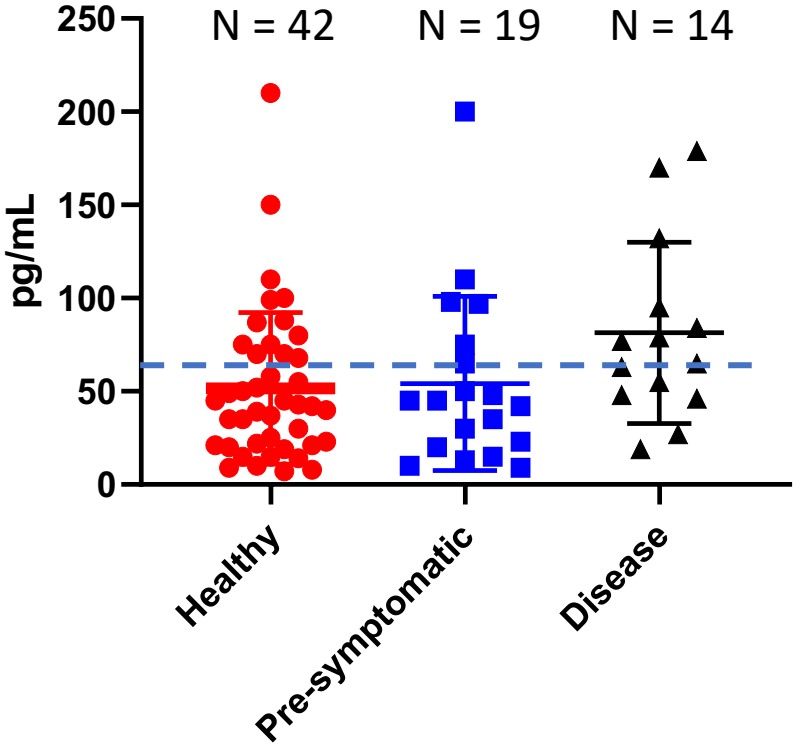
Research colleague conclusion:
"Potential disease biomarker!"

Project Team conclusion:
"DISEASE BIOMARKER!"

Biomarker Scientist Message Control

- Wait! Additional exploration of biomarker is warranted…
- Need more samples and to collect information on biological variability and to understand potential impact from sample collection and handling

- Using the proposed “cut off”…
  - 31% of healthy samples would be incorrectly identified as disease
  - 50% of disease samples would be incorrectly identified as healthy
- **This is outside the context of use!**



Message Control…a little too late

Biomarker Enabler vs Biomarker Slayer

- Biomarker enabler
  - Progression mindset: “I’ll know it when I see it”
  - Predisposes perception towards positive outcomes
  - The Accidental Biomarker Enabler
    - Leaves COU open to interpretation = COU not specific enough
- Biomarker slayer
  - Mantra: Always try to kill the biomarker
  - If it survives, try to kill it again…
  - Focus on designing the killer experiment - what would kill any future investment?
- The Biomarker Slayer is better at crafting specific COUs and proactively controlling messaging

Becoming a Biomarker Slayer

COU: Explore levels in cross sectional set of samples and determine if biomarker warrants further exploration

Biomarker Slayer

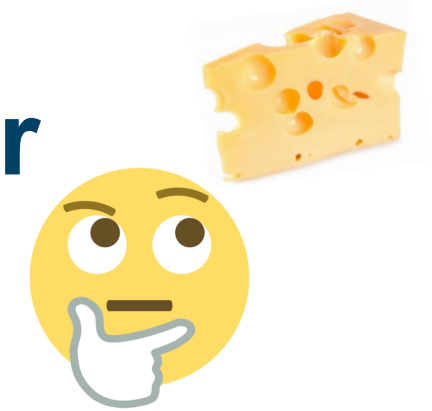
- Define ‘determine’
  - Difference in the mean values? Median values?
  - What magnitude of difference?
- Define what constitutes ‘further exploration’
  - More cross-sectional samples?
  - Longitudinal samples to interrogate biological variability?
  - Preanalytical considerations and sample provenance?
- Define feasibility, time and cost for further exploration
  - Is further exploration even going to be worth it?

Biomarker Slayer COU

- Explore levels in cross-sectional set of (N) samples to determine whether the median concentration in the disease samples is ≥x% different from the healthy samples to gate decision to collect/purchase at least y number of cross-sectional and/or longitudinal samples for analysis

How to solve for x?

Solving for x: Be a Biomarker Slayer



Question Everything

- What is the minimum value of x to make a Go decision?
- Or, restated: What result would make you kill the biomarker?
- If the answer is ‘nothing’, then why do the experiment now?

Demand Clarity

By forcing an articulation of go/no-go criteria, a better experiment can be designed, and messaging can be managed **before** the experiment is even run

No COU…what do I do?

Biomarker Slayer approach still applies…

- First Principles Thinking - Think it through!
  - Help your stakeholder think it through and articulate it
  - What are likely COUs? Potential aspirational COUs?
- Analytically characterize the assay
  - Determine relevant parameters
  - Considerations, not criteria
- Communicate clearly and proactively (documented in the report)
  - Describe assay performance and limitations
  - Highlight caveats beyond the analytical - e.g. no knowledge of biological variability

When COU becomes available: Evaluate performance against COU to claim validation

Summary

- COU is specific (regardless of development phase)

  - Start with First Principles thinking
    - Biomarker assays are not PK assays
    - No context, no validated assay

  - Become a biomarker slayer
    - To craft specific COUs
    - Design killer experiments
    - Control the messaging even before generating the data

- Effective, often relentless, communication is requisite

Critical thought partners: John Allinson (ILX) Devangi Mehta (ILX) Linda Terry (GSK)

If there's no scientific rationale, it's not science

No Context, No Validated Assay