Pain Biomarker Development: Clinical Validation to Inform Decisions

Howard I. Scher, MD, FASCO

D. Wayne Calloway Chair in Urologic Oncology

Head, Biomarker Development Program

Member and Attending Physician,

Genitourinary Oncology Service

Department of Medicine

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Disclosures

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Advisory Board: WCG Oncology, Phosplatin (U)

I will discuss the investigational drug use in my presentation of:

None

Biomarker Development Program (BDP)

1. To establish an **organizational model to accelerate development, approval and coverage** of simple, accurate, and reliable symptom, blood and imaging based tests for cancer diagnosis and precision treatment.

2. To utilize the **BDP-specific infrastructure** to **validate the performance** of new assays and devices – **a courtship / marriage – once you start you can't turn back.**

3. To ensure that the **devices** and **assays** needed are **"fit for purpose"** of **specific contexts of use** so that clinical validation can begin.

4. To **focus** the effort of laboratory and clinician scientists, drug and assay developers, computational biologists, statisticians and regulators **on enhancing medical decision making** to **improve patient outcomes.**

Translational Science: The Clinic is the Laboratory Where Unmet Diagnostic and Therapeutic Needs Are Identified and Studies Are Designed to Address Them

We are Physician's first, applying a patient centric approach in all that we do, be it in a routine clinical practice or research setting.

Diagnostic: Understanding an individual's disease and it's symptoms.

Therapeutic: Selecting and/or developing treatments from which a patient or patients are likely to benefit.

Objectivs

1. To understand the focus of biomarker development on decision making.

2. To understand the parallels between the development of a PAIN biomarker for a context of use to those used for drugs.

3. To create a clinical validation effort to generate the evidence to support use of PAIN related biomarkers as contexts (decisions) defined in the FDA Biomarkers, EndpointS and Other Tools (BEST) Resource.

Central to the Mission is to Approach Biomarker Development Analogous to the Development of a Drug

	Drug	Biomarker
Unmet Need	Indication Patient population	Context of use Patient population
Trial Design and Conduct	Formulation: Dose and Schedule	Validated device, assay, **Symptom measurement:** Assessment schedule
Evidence Generation	Outcome measures ***Clinical benefit**	Outcome associations ****Clinical utility**

***Improving how a patient feels, functions or how long he/she survives.**

****Showing that use of the biomarker result to inform a decision improves patient outcomes relative to non-use of the test result.**

Evidence Generation for Unmet Needs in Therapy (Drugs for an Indication) Parallels that for More Informed Diagnostic/Therapeutic Decisions (Biomarkers for Contexts of Use)

Biomarker Development Parallels Drug Development

Most Critical, is Can You Trust the Biomarker?

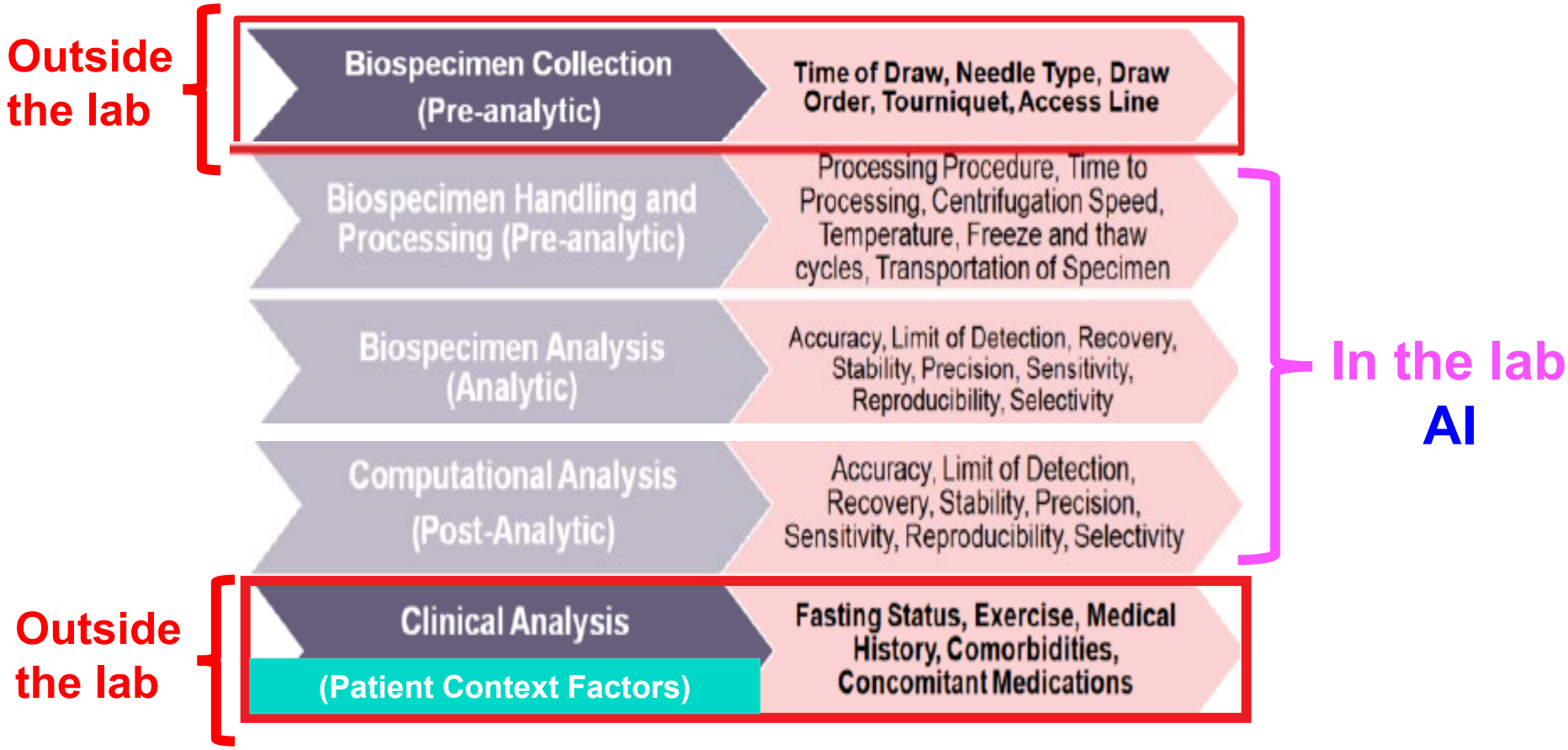
In our opinion the **most critical step** before implementing **novel biomarkers** in routine patient care **is the validation of the reported data being used**.

Quality management and reproducibility must be determined prior to clinical use.

Method (Analytical) validation: The process of ***assessing the parameters and their measurement performance characteristics***, and determining the range of conditions under which they will reproducible and accurate data.

Emmy Boerrigter, Exp Rev of Molecular Diagnostics 11:1, 2019.

Analytical Validation Also Includes Specimen Acquisition and Patient Factors That Can Influence the Reported Result Independent of the Laboratory Where it is Measured



The Conclusion of a Recent Review of Clinical Applications of Liquid Biopsies Noted ….

In our opinion the **most critical step** before implementing novel liquid biomarkers in routine patient care **is the validation of the assay**.

Quality **management and reproducibility** must be determined prior to clinical use – particularly as the technology and technological capabilities are rapidly increasing..

Information everybody wants but nobody wants to pay for.

Emmy Boerrigter, Exp Rev of Molecular Diagnostics 11:1, 2019.

Pain is a Challenging Multifacted Symptom Reported By Most Cancer Patients – Examples – There Are Many

1. Pain intensity – Pain
2. Analegic drug use.
3. Pain management index – (WHO analgesic ladder) – a combined pain and analgesic score.
4. The inflammatory component.

Salama et a. Journal of Pain and Symptom Management. 68:E462, 2024.

Vyong et al: Support Care Cancer 24:887-892.

Post: FDA BEST Modified to PAIN Requires the Ability to Serially Profile An Individual Patient's Disease To Determine When an Intervention is Needed and if so, What

BEST (**B**iomarkers, **E**ndpoint**S**, and other **T**ools) Resource

Pre-intervention:

Susceptibility	**Risk biomarkers (Includes Germ line) - falls, functional deterioration**
Diagnosis:	Early detection, etiology (what's the cause)
Prognosis:	Probability of events – recurrence, progression, survival.
Prediction:	Sensitivity – what given intervention will work.
	Resistance – **de novo** - what not to give that won't,

INTERVENTION + STATISTICAL DESIGN

Post intervention:

Safety:	Adverse events
Pharmacodynamic	Proof of mechanism – anti-inflammatory.
Response	Treatment efficacy
Monitoring:	**Intervals and measurements.**
Progression	**Worsening symptoms, functionality, depression**

Reasonably likely surrogate endpoint :
– an indication of clinical benefit with regulatory implications

https://www.ncbi.nlm.nih.gov/books/NBK326791/pdf/Bookshelf_NBK326791.pdf
Last updated: November 29, 2021

Artificial Intelligence and Machine Learning in Cancer Pain and Pain Management: A Systematic Review

1. Search of Ovid MEDLINE, EMBASE and Web of Science databases using terms:

   Cancer, Pain, Pain Management, Analgesics, Artificial Intelligence, Machine Learning and Neural Networks published up toe September 2024.

2. 44 studies were included.

3. Advances the development of tools for:

   Classification
   Risk stratification
   Management decisions.

Salama et a. Journal of Pain and Symptom Management. 68:E462, 2024