



the coalition for  
**21<sup>st</sup>**  
**centurymedicine**

[www.twentyfirstcenturymedicine.org](http://www.twentyfirstcenturymedicine.org)

# Agenda

- Introduction
  - Howard Birndorf
- ASR Issues and the Draft ASR FAQ Guidance
  - Patrick Balthrop
- IVDMIA Issues and the Draft IVDMIA Guidance
  - Randy Scott
- Q&A and Discussion
  - All

# Who Are We?

- Emerging and innovative diagnostic companies, stakeholders, and shareholders who wish to apply the fruits of 21<sup>st</sup> century medicine, including the Human Genome Project, to the creation of new molecular tests that greatly improve personal health while substantially reducing healthcare costs.
  - Diagnostic innovators
  - Emerging companies
  - Patient groups
  - Medical professionals
  - Venture capital firms



# Steering Committee



**Howard Birndorf**



**Brook Byers**



**Randy Scott**



**Patrick Balthrop**



**Vijay Aggarwal**



**Sharon Terry**

# Founding Members

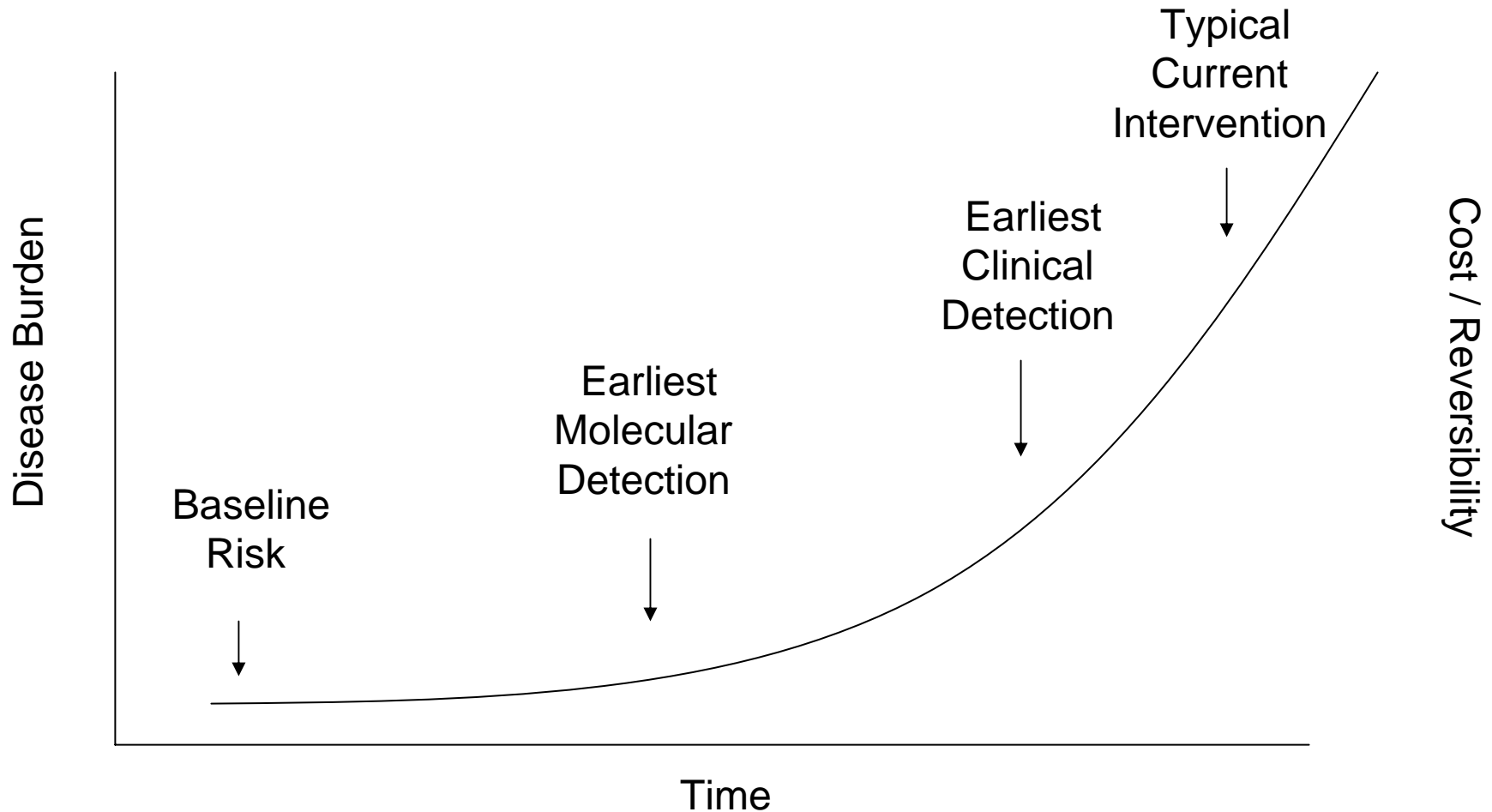


\* = steering committee

# Basic Principles

- The coalition believes:
  - That innovation and quality patient care are the keys to 21<sup>st</sup> century medicine
  - That timely access to new information by physicians and patients is critical to improving the quality of care and providing more personalized medicine
  - That we must balance regulation and innovation if we are to improve the quality and economics of our healthcare system

# Impact of Diagnostics



# Working with Congress and FDA

- **Support key elements of 21<sup>st</sup> century medicine**, including innovation and personalized medicine
- Engage in **positive and constructive** dialogue with **FDA and with Congress**
- Help determine the **most appropriate pathway for regulation** of IVDMIAs and ASRs
  - Provide FDA with feedback on the current draft guidances and to encourage formal notice and comment rulemaking
  - Encourage FDA to provide a smooth transition in the marketplace that facilitates patient access to clinical tests
  - Propose alternative regulatory pathways that reflect the nature and role of IVDMIAs and ASRs in laboratory medicine
- **Educate key stakeholders** about the importance of innovative new diagnostics to quality patient care and reducing healthcare costs

# ASRs

# ASR Guidance Issues and Alternatives

- 1) Definition
- 2) Concerns
- 3) Transition Period
- 4) Creation of a New Category
- 5) Clearance or Approval Based on Claims

# 1) ASR Definition

- Under 21 CFR 864.4020, ASRs are defined as
  - “antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens”
- The guidance introduces the terms “**moiety**” and “**endpoint**” and requires that an ASR consist of only a “single moiety” and detect a “single endpoint”

## 2) Concerns

- GMP-compliant “**building blocks**” for tests may no longer be offered by manufacturers to laboratories
  - Many ASRs, especially molecular diagnostics, include “**multiple moieties**” (e.g., primers and probes in a single vial) that are used to develop and validate **hundreds of types of diagnostic tests**
  - Placing each primer and probe in a separate vial introduces **complexity and increased risk** of analytical error
- Laboratories may **revert to non-GMP** Research Use Only and Investigational Use Only **materials** to develop diagnostic tests
- **Negative impact on innovation**, especially for diseases with lower incidence, and on development of molecular diagnostics tests

## 3) Transition Period

### Current Status

- **No transition** for many ASR products that could no longer be offered

### Alternative

- Incorporate a **grace period** into any final guidance or regulation, to **minimize disruption** in the availability of tests
- Companies would be given **two years** to submit premarket notifications for ASRs deemed to require a **510(k)**
- Companies would be given **four years** to submit a **PMA** for ASRs deemed to require premarket approval

## 4) Creation of a New Category

### Current Status

- Requiring premarket clearance or approval may **impair laboratories' access** to high quality multiple moieties or building block products

### Alternative

- Promulgate a **new regulation** placing such products **in Class II**
  - **Exempt from 510(k)** premarket notification (unless they fall under 21 C.F.R. § 864.4020(b)(2), (3))
  - FDA could establish appropriate **special controls** and the building blocks could be subject to **design controls**
  - A **similar approach** could be used for ASRs which reference other laboratory equipment or require extensive processing
  - Building blocks would **remain available** during this new classification

## 5) Clearance or Approval Based on Claims

### Current Status

- FDA requires clinical data for clearance or approval of building blocks that **exceed their intended use**
  - As building blocks, ASRs are not intended to diagnose a disease or health condition and no diagnostic claims are made

### Alternative

- FDA should allow 510(k)s or PMAs for building blocks based on their **claims of analytical performance**, e.g., demonstrating that the mutation that is the subject of the claim is detected
  - QSRs, including design controls, would apply

# IVDMIA<sub>s</sub>

# IVDMIA Guidance Issues and Alternatives

- 1) Definition
- 2) Concerns
- 3) Transition Period
- 4) FDA Premarket Requirements
- 5) Clinical Laboratory Oversight
- 6) Test Improvements

# 1) IVDMA Definition

## Current Status

The draft guidance states:

- “Use **clinical data** ... to empirically identify variables and to derive weights or coefficients employed in an algorithm”
- **Employ the algorithm** to integrate these variables in order to calculate a patient-specific result ... [that] **cannot be independently derived and confirmed by another laboratory**
- Report this **result, which cannot be interpreted by the well-trained health care practitioner** ... without information from the test developer regarding its clinical performance and effectiveness”
- The current definition creates **uncertainty** as to which tests are subject to regulation due to **ambiguity** around key terms

# 1) IVDMIA Definition

## Alternative

- The final definition should:
  - Clearly discriminate between an IVDMIA subject to FDA regulation and all other LDTs not subject to FDA regulation
  - Clarify what components constitute the medical device and what elements are the clinical laboratory service that uses the device

## 2) Concerns

- Basing regulation on the technology approach **rather than on health risks** creates a disincentive against developing **innovative new** technology
- Older “**low**” **technology** tests become advantaged in the marketplace
- Tests for **rare or underserved** patient populations may not be developed
- Patients and physicians may experience a **delay in access to state of the art tests** in rapidly advancing fields, such as genetics, oncology, and infectious disease
- State of the art **improvements** in tests may also be delayed or halted

## 3) Transition Period

### Current Draft

- **No transition** to bring IVDMIAs from the current CLIA regulatory path to a new CLIA+FDA regulatory path

### Alternative

- Incorporate a transition period of two to four years into any final guidance or regulation, to **minimize disruption** in the availability of tests
- **Timeframe** and **510(k)/PMA** would be dependent upon product risk (see 4)
- Transition period for **GMP compliance**

## 4) FDA Premarket Requirements

### **Current Draft**

- 510(k) for prognosis claims and PMA for predictive claims

### **Alternative**

- **FDA registration and low volume exemption**
  - FDA registration and listing of all IVDMIAs validated by CLIA–certified labs until a testing volume threshold based on tests performed is met. Tests must be labeled to reflect absence of FDA clearance/approval
  - If a test with only analytical performance claims is an IVDMIA, it should be Class I, 510(k)-exempt.

## 4) FDA Premarket Requirements

### Alternative

- **510(k) transition period** of two years for submission from date when an IVDMA exceeds a volume threshold
  - For prognostic tests
  - For decision aids (neither fully prognostic or predictive) that are advisory and/or do not give a binary therapy recommendation
  - For predictive tests that have multiple peer-reviewed publications
  - For other tests to be determined
- **PMA transition period** of four years for submission from date when exceed a volume threshold for high risk products where the predictive claim directly recommends use or not of a particular therapy
- Establish a **mechanism to obtain FDA determination** at early stage as to applicable regulatory pathway, and guidelines on premarketing requirements

## 5) Clinical Laboratory Oversight

### Current Draft

- FDA regulates the **entire “test system”** including test development, labeling, manufacture and clinical laboratory performance

### Alternative

- Establish clear delineation of responsibility and authority to avoid overlapping regulations and inspections and facilitate compliance
- FDA regulates **assay design and “manufacturing” steps**
  - Lab test **development and validation of claims** consistent with laboratory’s intended use
  - **Modified QSR** requirements reflecting internal use by single lab only
  - **Complaint handling/investigation** and manufacturer **MDR** regulations
  - Clarification of **labeling and promotion limitations**
- CLIA regulates **laboratory service components**
  - Lab inspections, performance and proficiency testing
  - Test requisition and reporting
  - Specimen handling

## 6) Test Improvements

### Current Draft

- How would process or product improvements be dealt with?

### Alternative

- FDA regulates laboratory manufacturing changes or new intended uses
  - **Well-established changes** made based on internal testing and MTF
  - Incorporate into 510(k)/PMA **process criteria** to enable changes without new marketing applications, e.g., pre-defined protocols
  - Mechanisms for **abbreviated clearance** when submissions are needed for changes
  - **Fast track approval** process
- CLIA regulates process improvements under current regulations
  - **Process automation** changes
  - **QA/QC** process changes
  - **Updates** to test requisition forms and test reports as required by CLIA based upon new information needed to interpret test results

# Next Steps

- 1. Continue working cooperatively and productively with FDA**
- 2. Propose next meeting**
- 3. Members of the Coalition will be filing comments with FDA**

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