Regulatory Considerations for Imaging Biomarkers in Clinical Trials

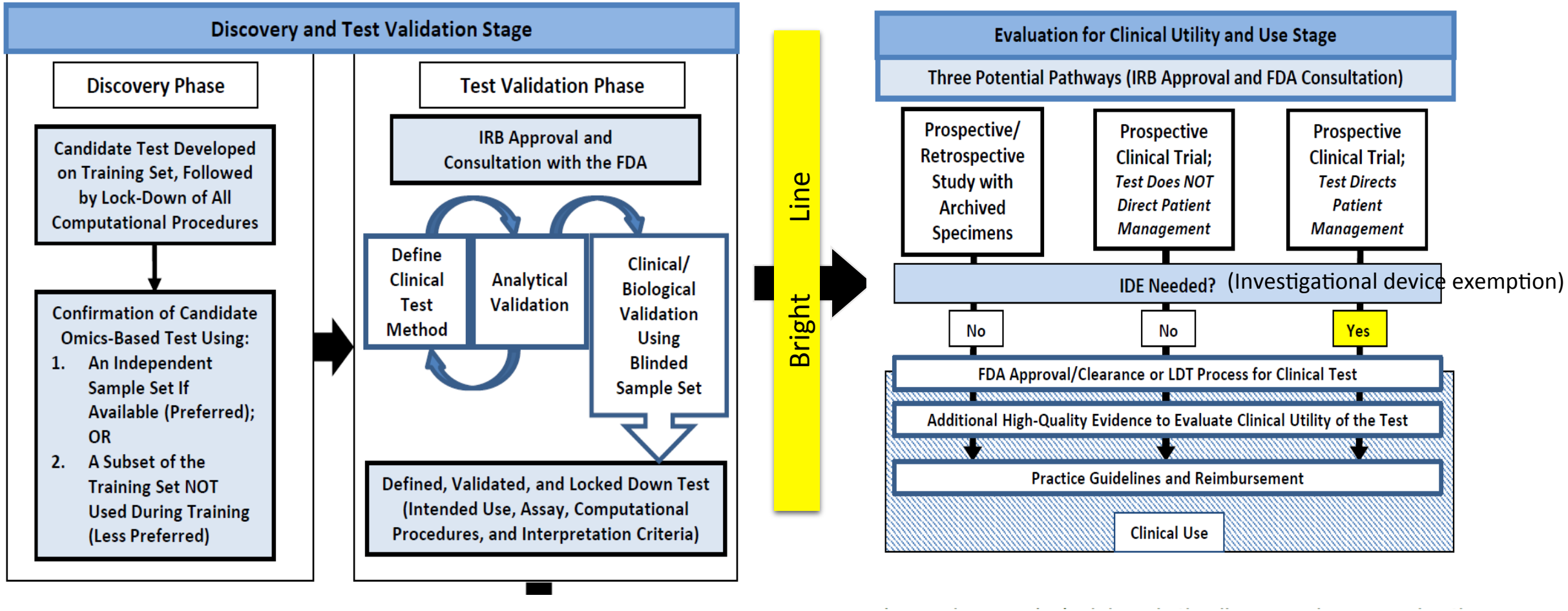
- Requirements for use in regulated trials:

1. Imaging biomarker validated
2. Software FDA 21 CFR Part 11 compliant (both in terms of development and usage in the trial)

1. Imaging Biomarker Validation

- Imaging Biomarker – quantitative measurement of biological property
- Two phases of validation: “Test / Analytic Validation” and “Clinical Validation”
  - First phase includes accuracy and reproducibility of the measure/classifier against a reference standard (as we typically do for journal publications)
  - Second phase is prospective use in clinical trials (this is much less commonly done)
- FDA Biomarker qualification is available
  - Currently only one imaging biomarker qualified (total kidney volume) - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm437988.htm
  - Not a requisite for use in clinical trials (commonly used techniques, e.g., RECIST, have not been qualified, but are validated as described above)

Omics-Based Test Development Process



Evolution of Translational OMICS lessons learned and the path forward (March 2012) by IOM (Institution of Medicine) report

2. FDA 21 CFR Part 11 compliant software

- Three major elements to achieve compliance:

1. Requirements on system/data controls
2. Software validation
3. Procedural controls on use of software

FDA 21 CFR Part 11 – system data controls

- System security with user authentication and authorization (for specific data access and functionality)
- Use of electronic signatures which lock data (regulations provide details on database fields required to record a valid electronic signature)
- Audit trail that records original measurements and reason for change if a measurement needs to be unlocked and updated (e.g., following a QC check)

FDA 21 CFR Part 11 – software validation

- Software validation must be performed and documented to demonstrate that the system fulfills its intended use
- Software development must be governed by Standard Operating Procedures (SOPs), e.g.,
  - System Development Life Cycle
  - Change Control
  - Test Execution/ Fault Investigation
  - Risk Management
- These procedures are similar to those required for development of 510(k) cleared products
  - 510(k) clearance is generally not required for use in a therapeutic clinical trial, but it can be made a requisite if the therapy relies on the software, e.g., for patient selection

FDA 21 CFR Part 11 – software validation

- The following documents are typically generating in the course of validating a computer system (which following the SOPs)
  - Requirements Specification
  - Design Specification
  - Validation Plan
  - Test installation Qualification
  - Operational Qualification (test results)
  - Traceability Matrix (confirming all requirements covered by tests)
  - Production Installation Qualification
  - Performance Qualification
  - Validation Summary

FDA 21 CFR Part 11 – procedural controls

- The following SOPs are also prepared
  - Administration SOP (for use by system administrators maintaining the system)
  - Operation SOP (for system users)
- Confirming of training and adherence to these procedures are required to ensure ongoing compliance
- If software is updated, re-validation is required according to a Change Control SOP

Summary

- Biomarker and software validation are important regulatory (FDA) requirements
- Engagement of appropriate support is necessary to support algorithm developers and software engineers
  - e.g., biostatisticians for biomarker validation
  - e.g., quality assurance specialists for software validation