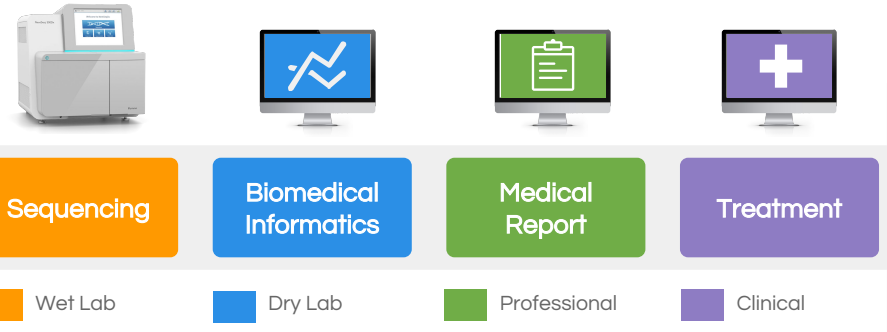
PierianDx

CAP Distributive Model of NGS Testing

A Rapid, Economical Approach to Building Your Clinical NGS Program

August 28, 2018



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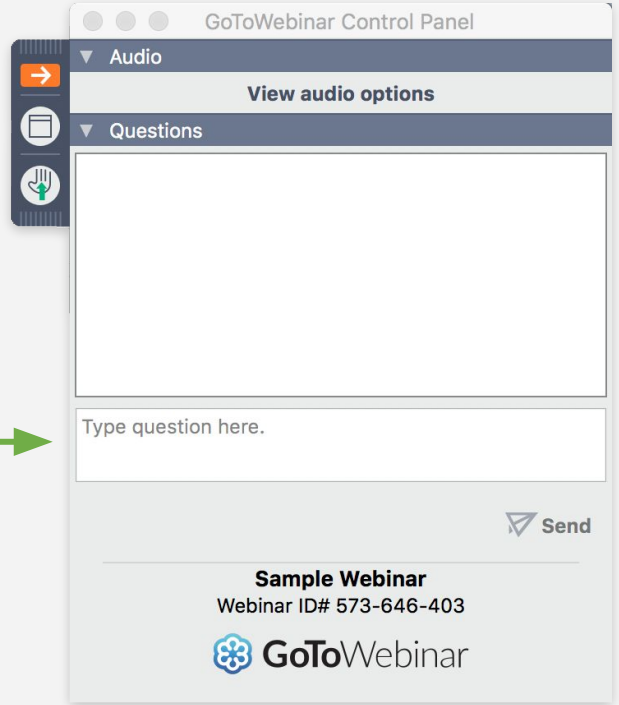
Shalini Verma, MD, FCAP
Medical Director, Laboratory Director
PierianDx

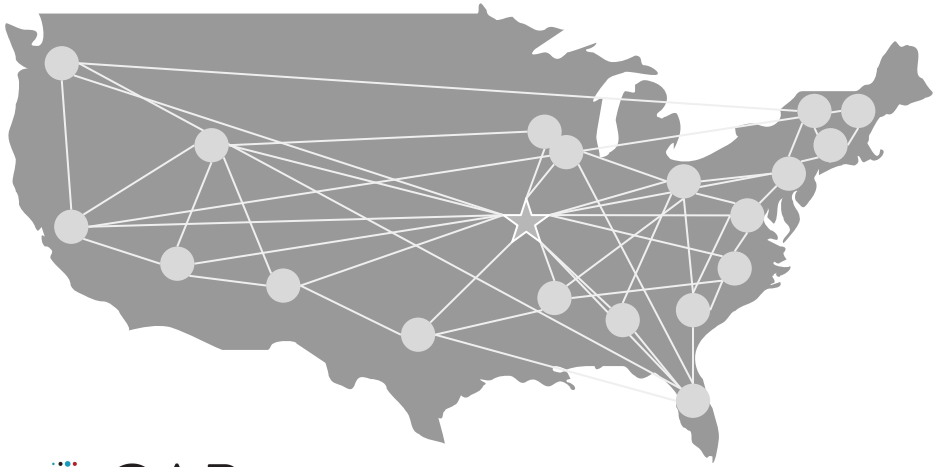
We Want to Hear from You

How to Submit Questions

Type questions here



Today's Topics



CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

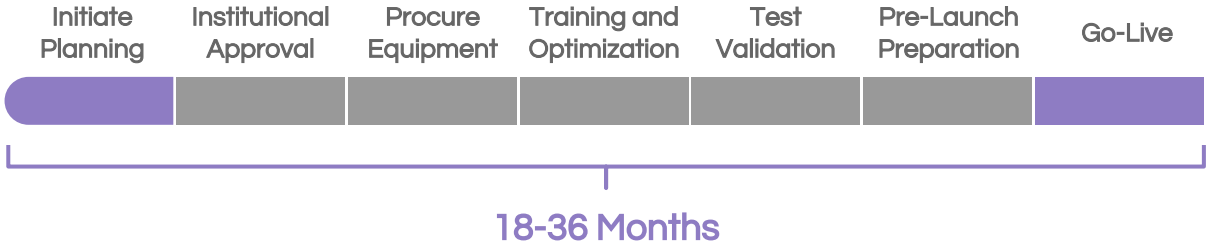
1. Why the Distributive Model?
2. Distributive Model Overview
3. CAP Requirements
4. PierianDx Clinical Lab
5. Quality Management Program
6. PierianDx Services

Why the Distributive Model?

Overcoming Barriers

Why a Distributive Model?

Challenges of Deploying NGS



Top Barriers

- Scarcity of informatics expertise
- Validation of clinical testing protocols
- Amount of data to curate
- Rapidly changing nature of technologies
- Expense of implementation
- Difficulty of getting first "application" deployed

Genetics in Medicine

"Common themes were that **implementation took or was taking longer**, ... than anticipated."

"The business of genomic testing: a survey of early adopters." *Genetics in Medicine.* December 2014

Why a Distributive Model?

A More Rapid, Economic Approach

~~18-36 Months~~
<6 Months

Top Barriers

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Pioneers in Precision Medicine

Leaders in Clinical Genomics

Today — **Software and services + CLIA/CAP "dry lab"**

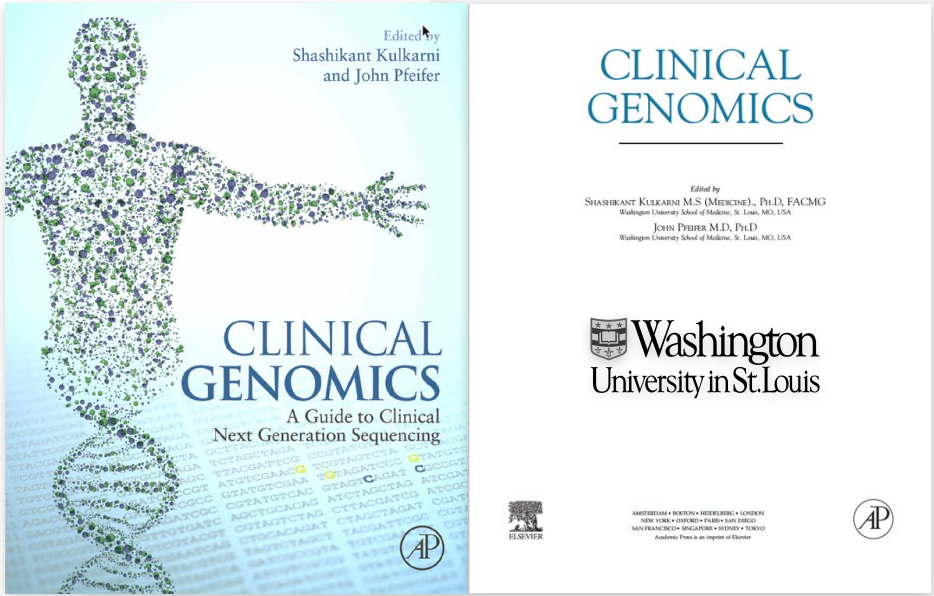
40+ leading medical center and hospital system clients

Staff of 60+ medical and scientific experts

2014 — PierianDx established after ~50 labs visit WashU to learn how clinical NGS is operationalized.

2011 — WashU builds CLIA lab; develops Clinical Genomics Workspace (CGW) for NGS testing.

2003 — WashU plays critical role in Human Genome Project.



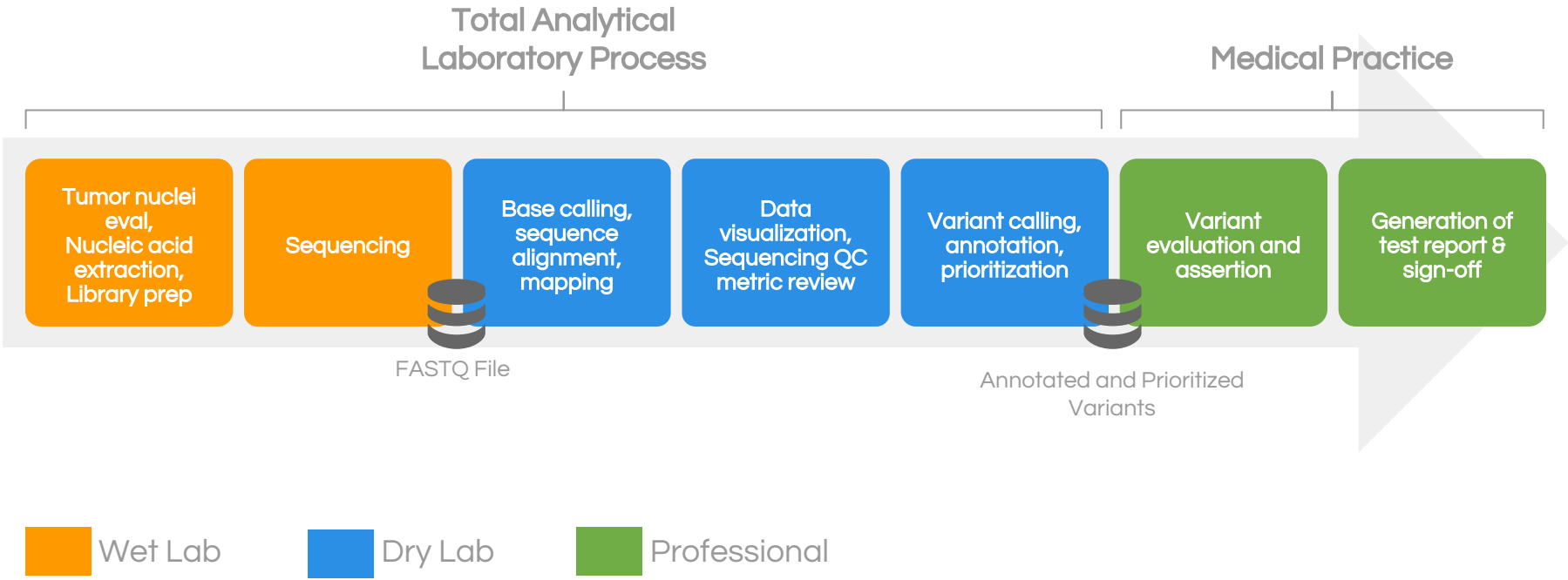
PierianDx founders among first to validate and clinically report on somatic cancer NGS panels.

Overview

Distributive Model

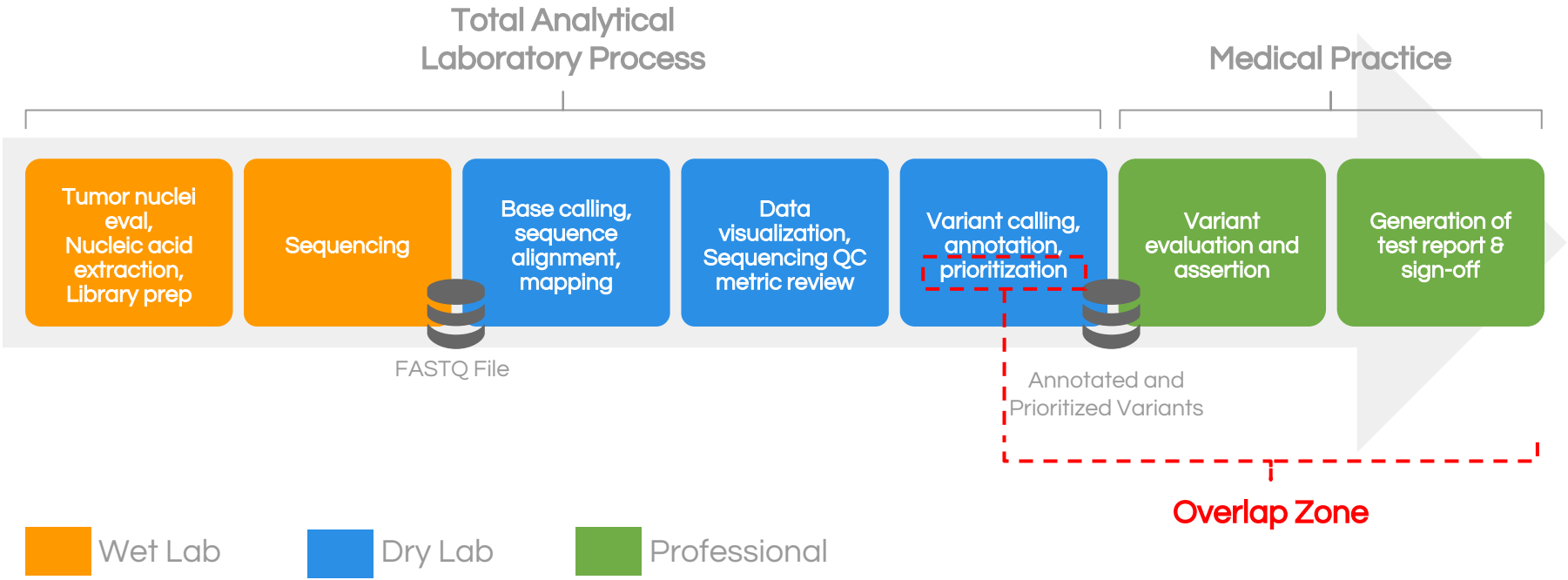
CAP Accreditation Requirements

Elements of an NGS Test



CAP Accreditation Requirements

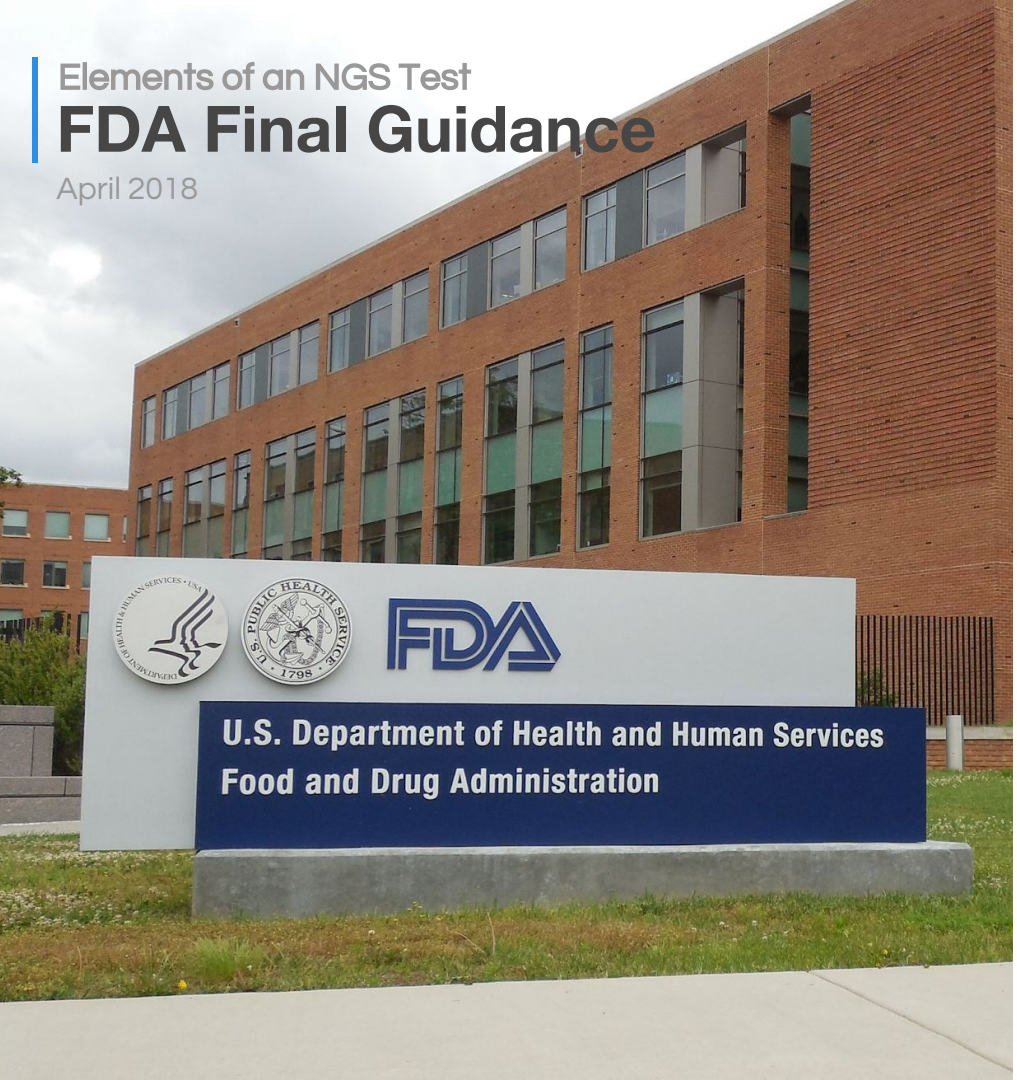
Elements of an NGS Test



Elements of an NGS Test

FDA Final Guidance

April 2018



"Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing-Based In Vitro Diagnostics"

NGS based tests may encompass the following steps:

a. Specimen collection, processing, and storage
b. DNA extraction
c. DNA processing and library preparation
d. Generation of sequence reads and base calling
e. Sequence alignment/mapping
f. Variant calling
g. Variant annotation and filtering
h. Variant evaluation and assertion
i. Generation of test report

Elements of a NGS Test

FDA Final Guidance

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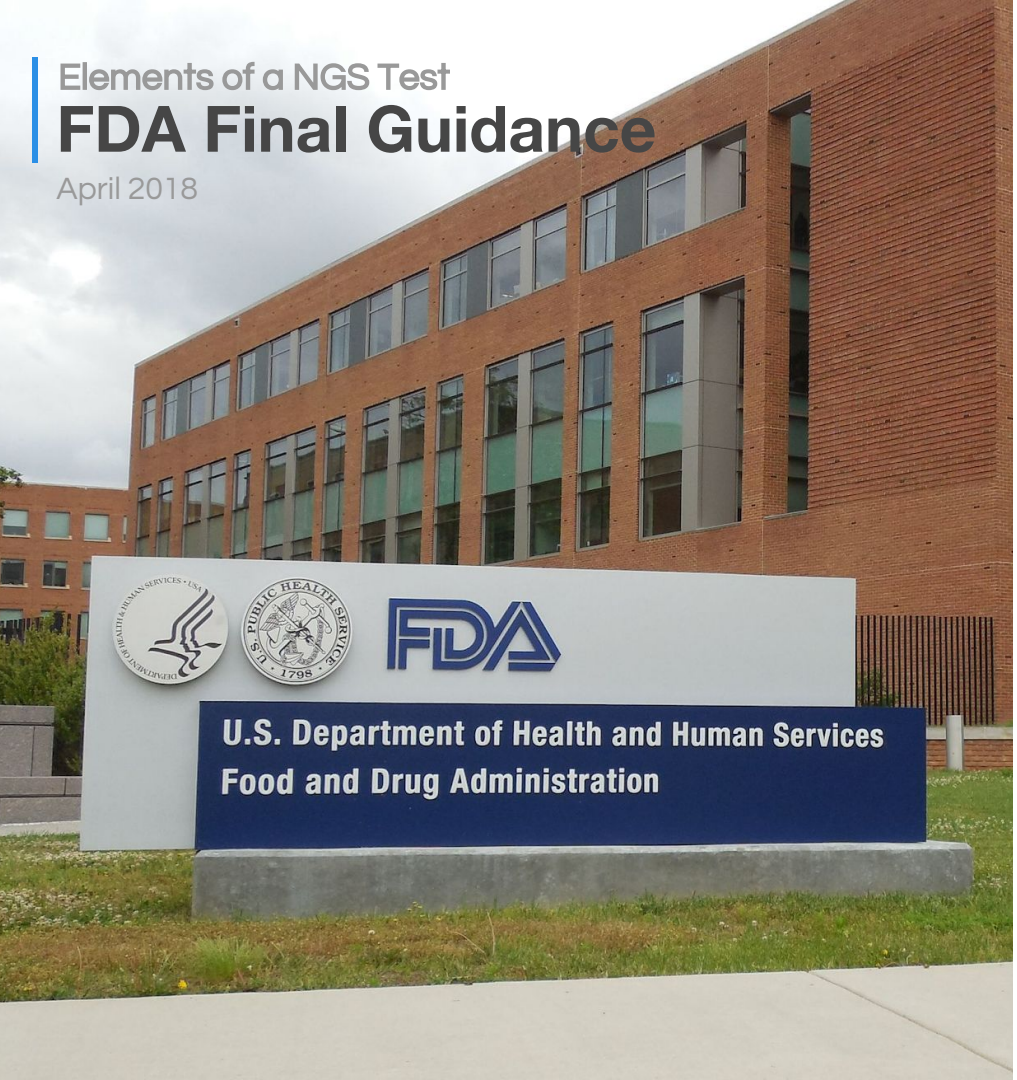

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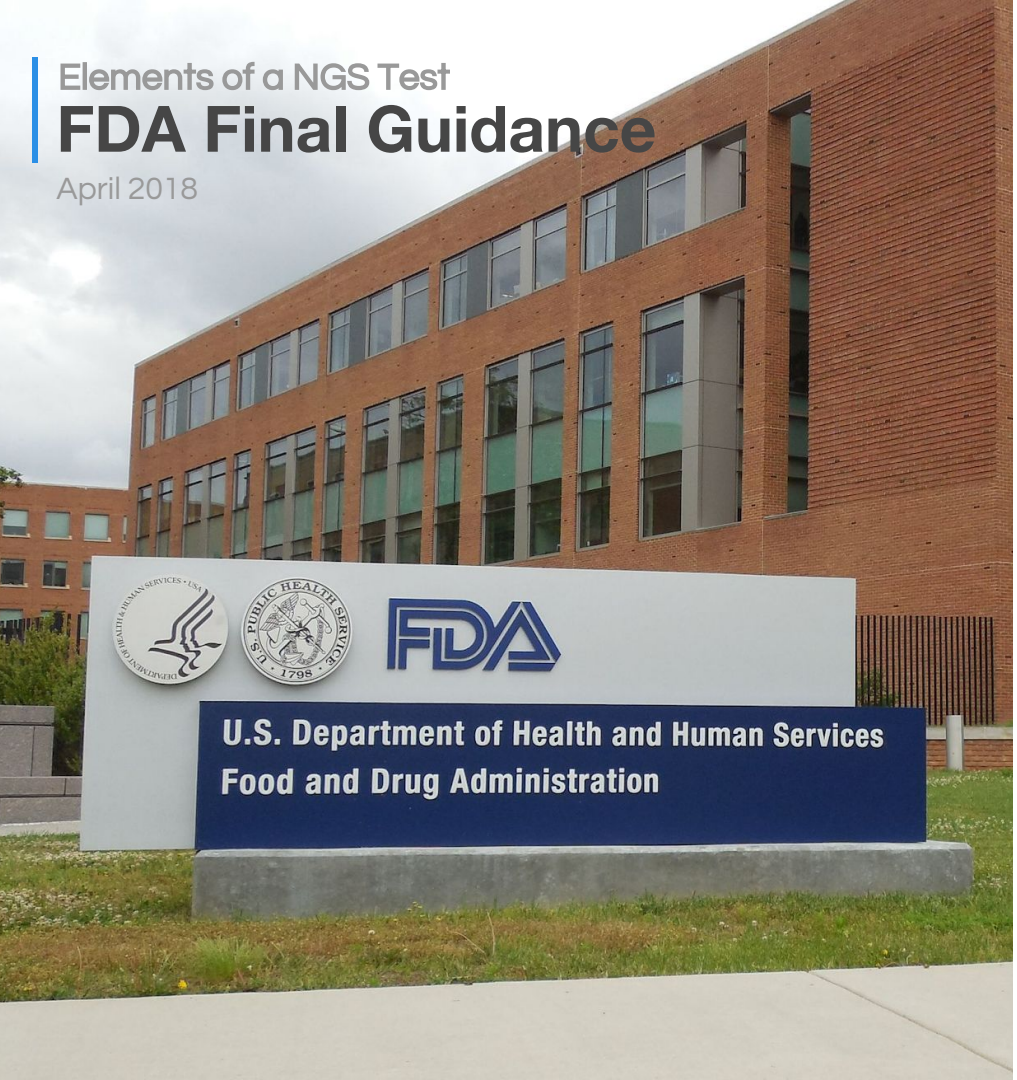
Overlap Zone

Elements of a NGS Test

FDA Final Guidance

April 2018



“Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing-Based In Vitro Diagnostics”

"Interpretation of the clinical significance of an identified variant, performed by healthcare providers and laboratory professionals for the sole purpose of diagnosing or treating a specific individual patient, is not considered part of the test, but certain standard operating procedures, including but not limited to **protocols for variant evaluation, and some software products may be considered test elements**.”

Laboratory Statistics

CAP Accreditation 2017

Overall Number of CAP Accredited Labs Performing Molecular Pathology Testing

821

Including 169 International labs

Number of CAP Accredited Labs Performing NGS-Based Molecular Pathology Testing

280

Including 51 International labs

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How Majority of Labs Perform NGS Testing

One Primary Physical Laboratory

Single CLIA License

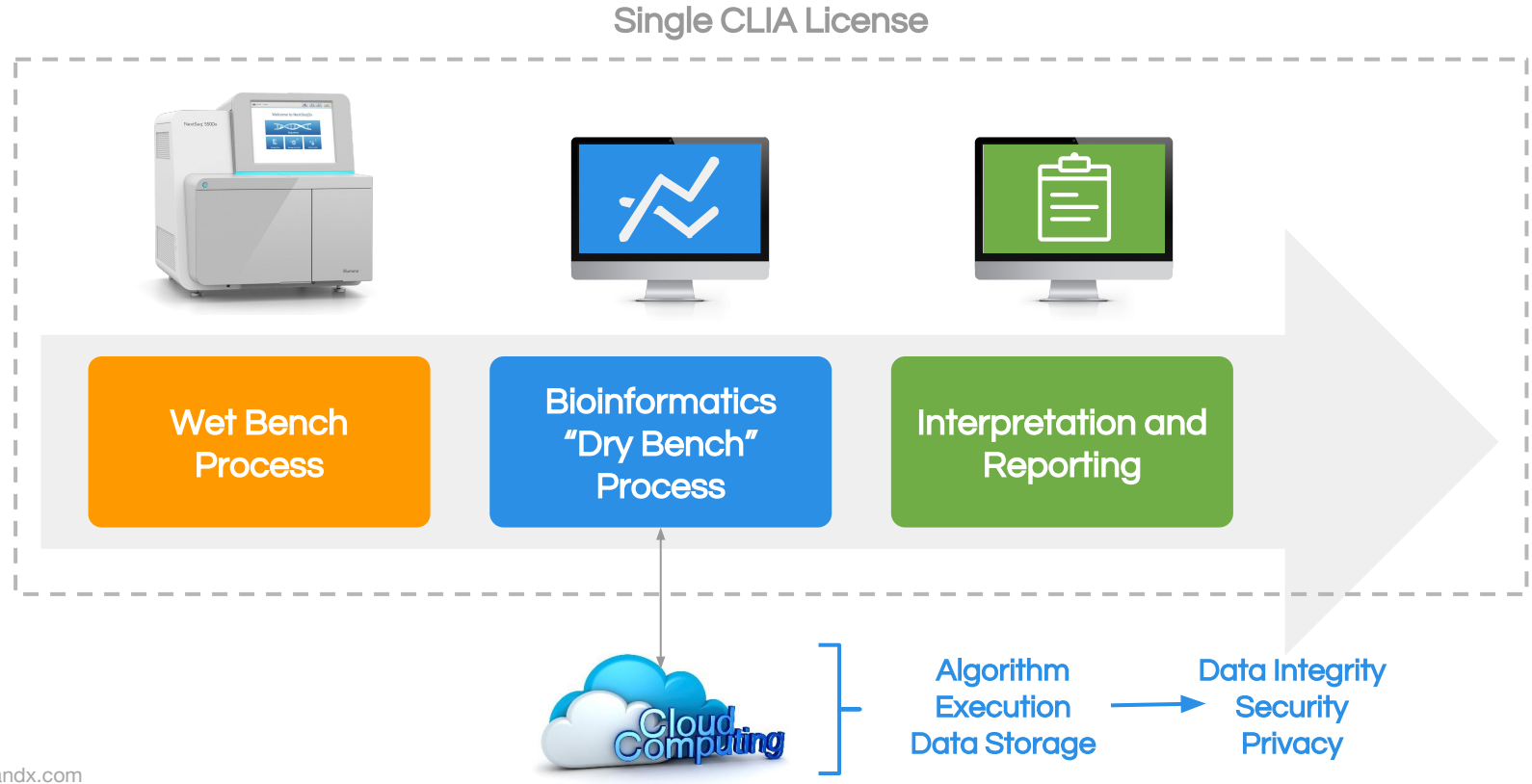
Wet Bench Process

Bioinformatics "Dry Bench" Process

Interpretation and Reporting

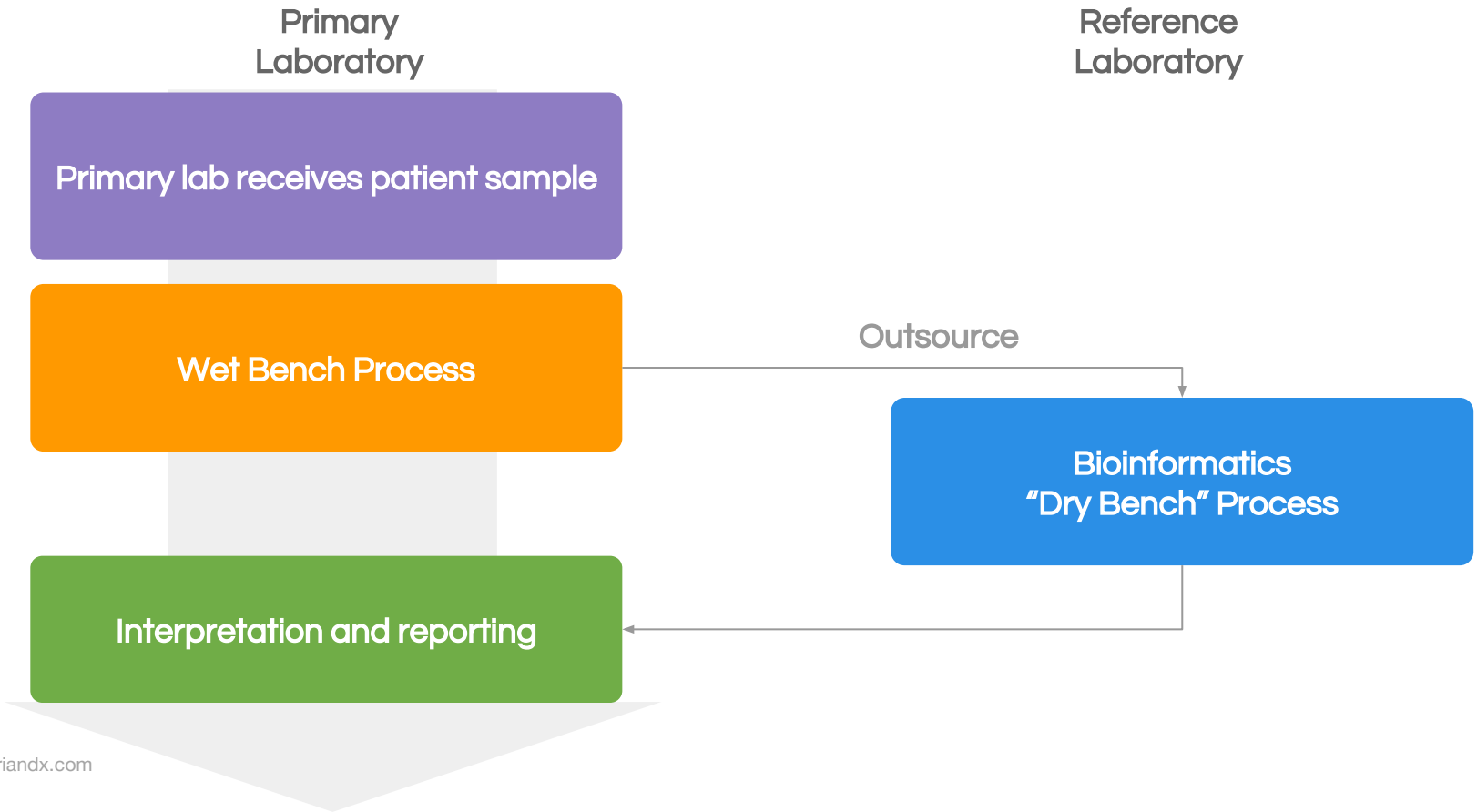
How Majority of Labs Perform NGS Testing

One Primary Physical Laboratory



A Modular Approach

Some Labs Outsource Process Steps



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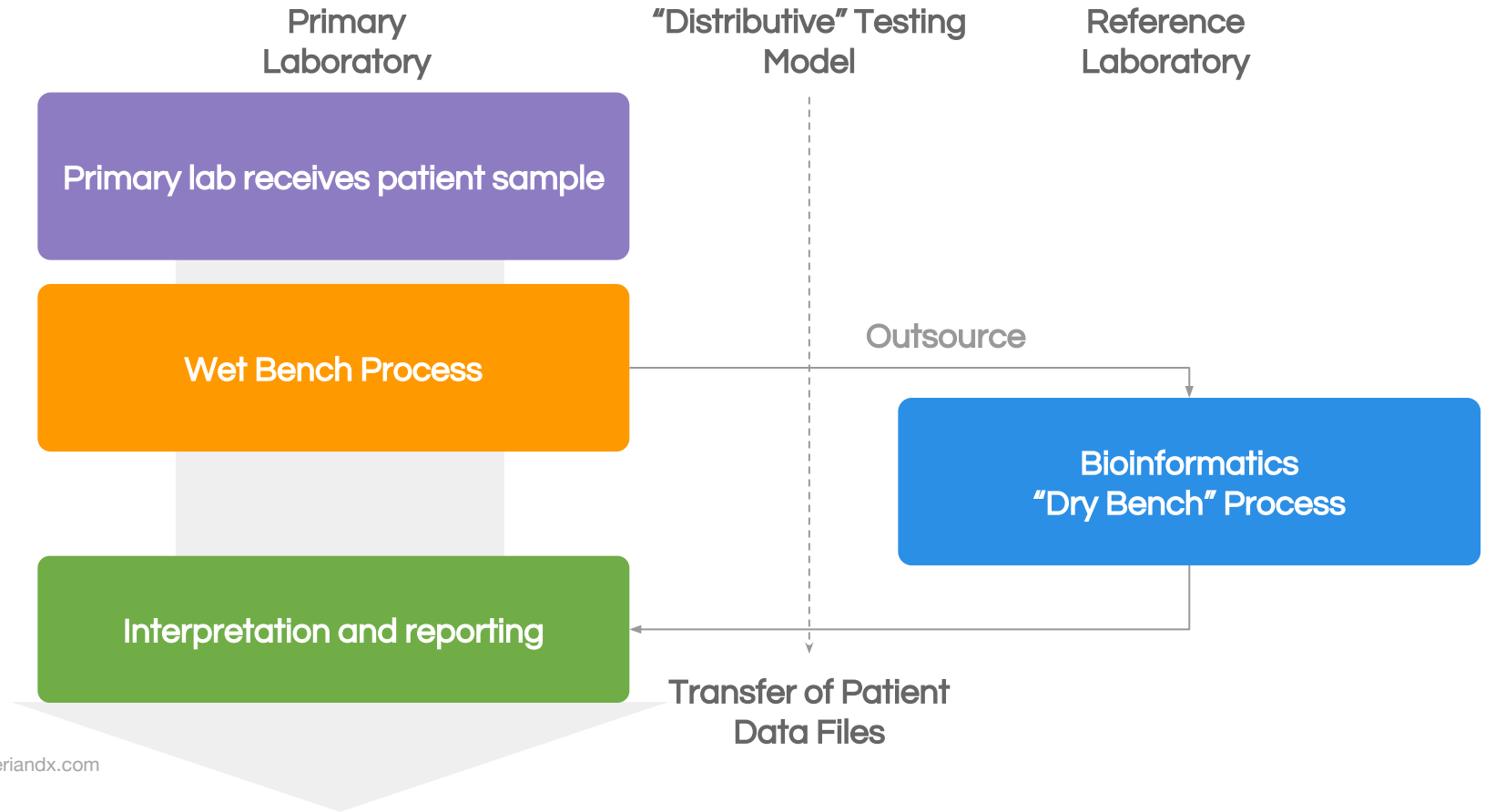

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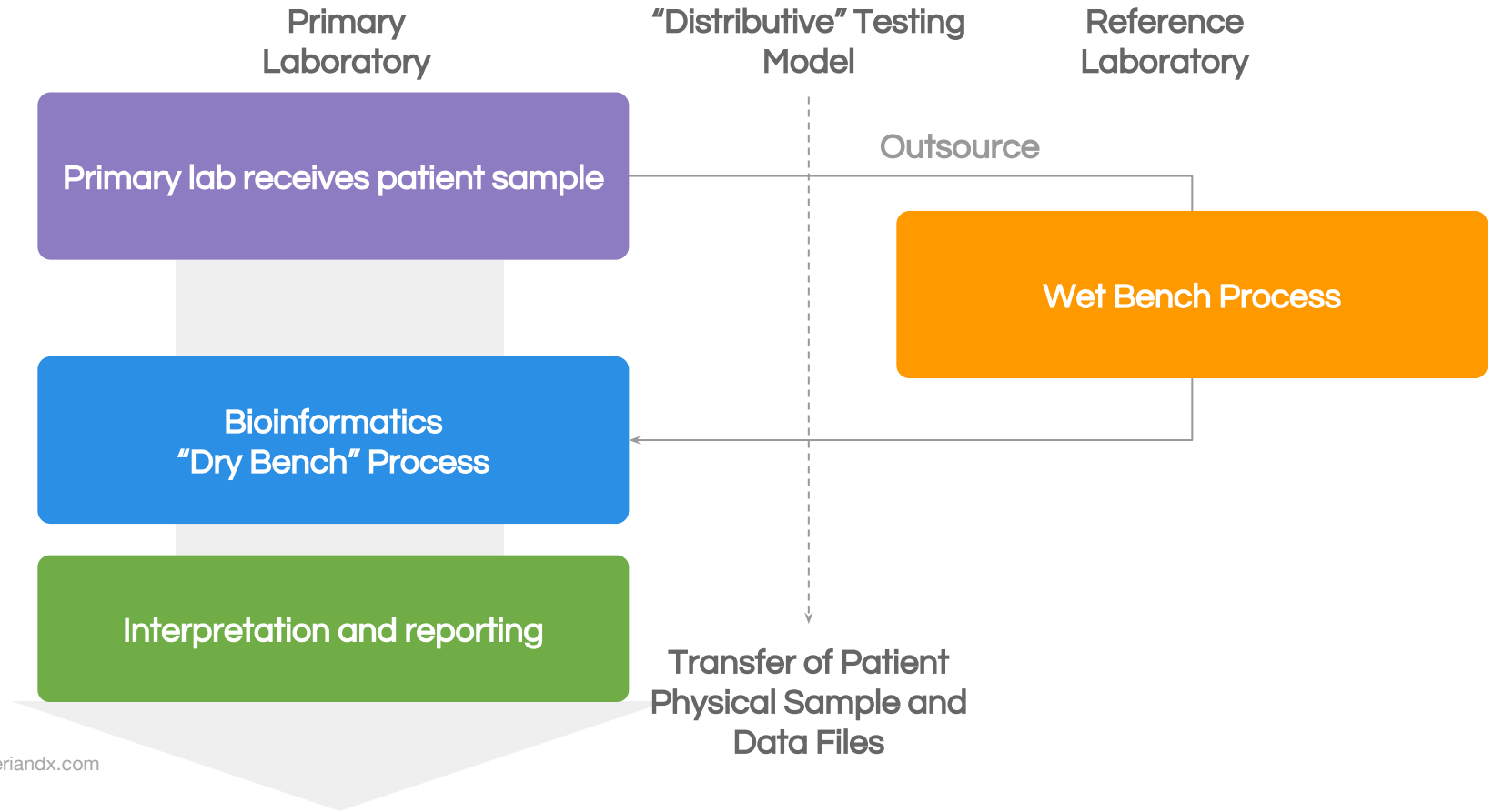
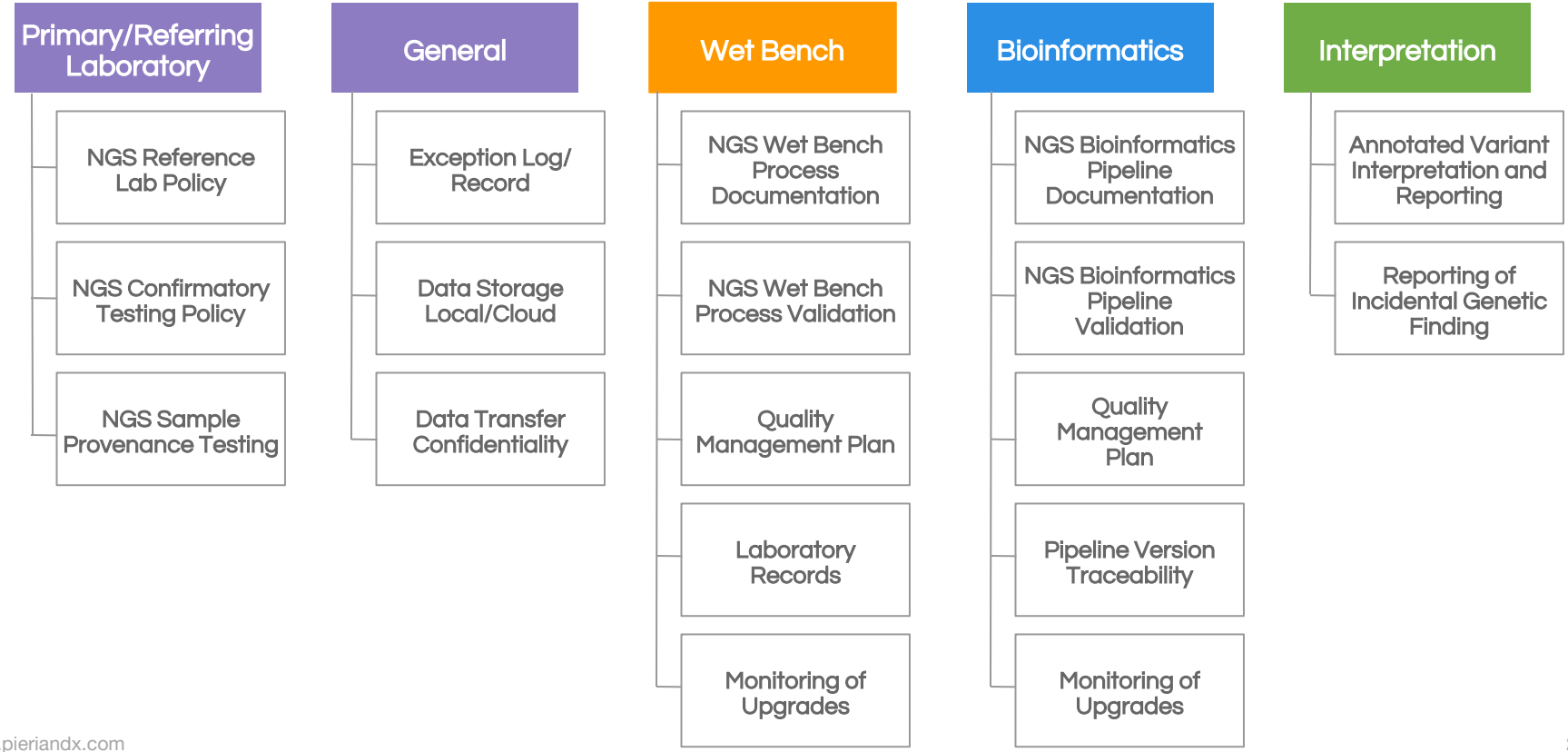


2018

CAP Requirements

Designed to Accommodate Distributive Test Models

CAP Accreditation Requirements 2018



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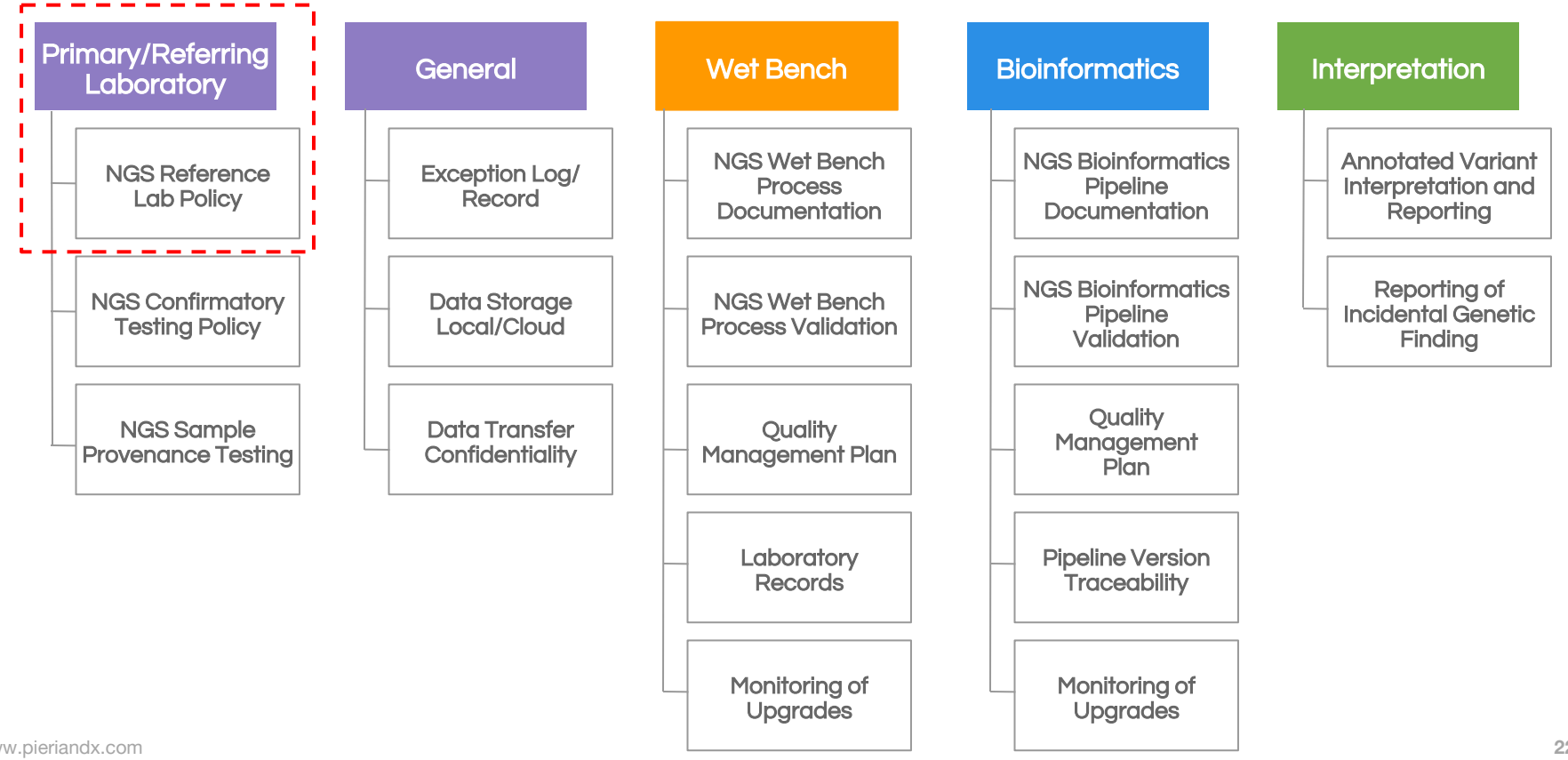
CAP Accreditation Requirements 2018



Designed to Accommodate Distributive Test Models

Overarching CAP Requirement

****REVISED**** ***08/17/2016***

MOL.35840 **Next Generation Sequencing (NGS) Referral Laboratory Selection** **Phase II**

The laboratory has a written policy for selection and evaluation of referral laboratories for NGS testing.

NOTE: The laboratory director, in consultation with the institutional medical staff or physician clients (where appropriate), is responsible for the selection and evaluation of referral laboratories.

Referral may include the total NGS analytical testing process or portions of the process (e.g. only the wet bench or bioinformatics portions).

For laboratories subject to US regulations referring the total NGS analytical testing process, or portions of the process (e.g. only the wet bench or bioinformatics portions), referrals must be made to a CLIA-certified laboratory or a laboratory meeting equivalent (or more stringent) requirements as determined by the CAP and/or the Centers for Medicare and Medicaid Services (CMS).

For non-US CAP accredited laboratories, referral of the total NGS analytical testing process, or portions of the process (e.g. only the wet bench or bioinformatics portions) must be sent to a laboratory accredited by the CAP, or a laboratory meeting equivalent requirements as determined by the CMS, or accredited by an established international standard from a recognized organization, or certified by an appropriate government agency. The inspector may need to exercise judgment in determining the acceptability of referral laboratory accreditation.

NGS Reference Lab Policy: MOL.35840

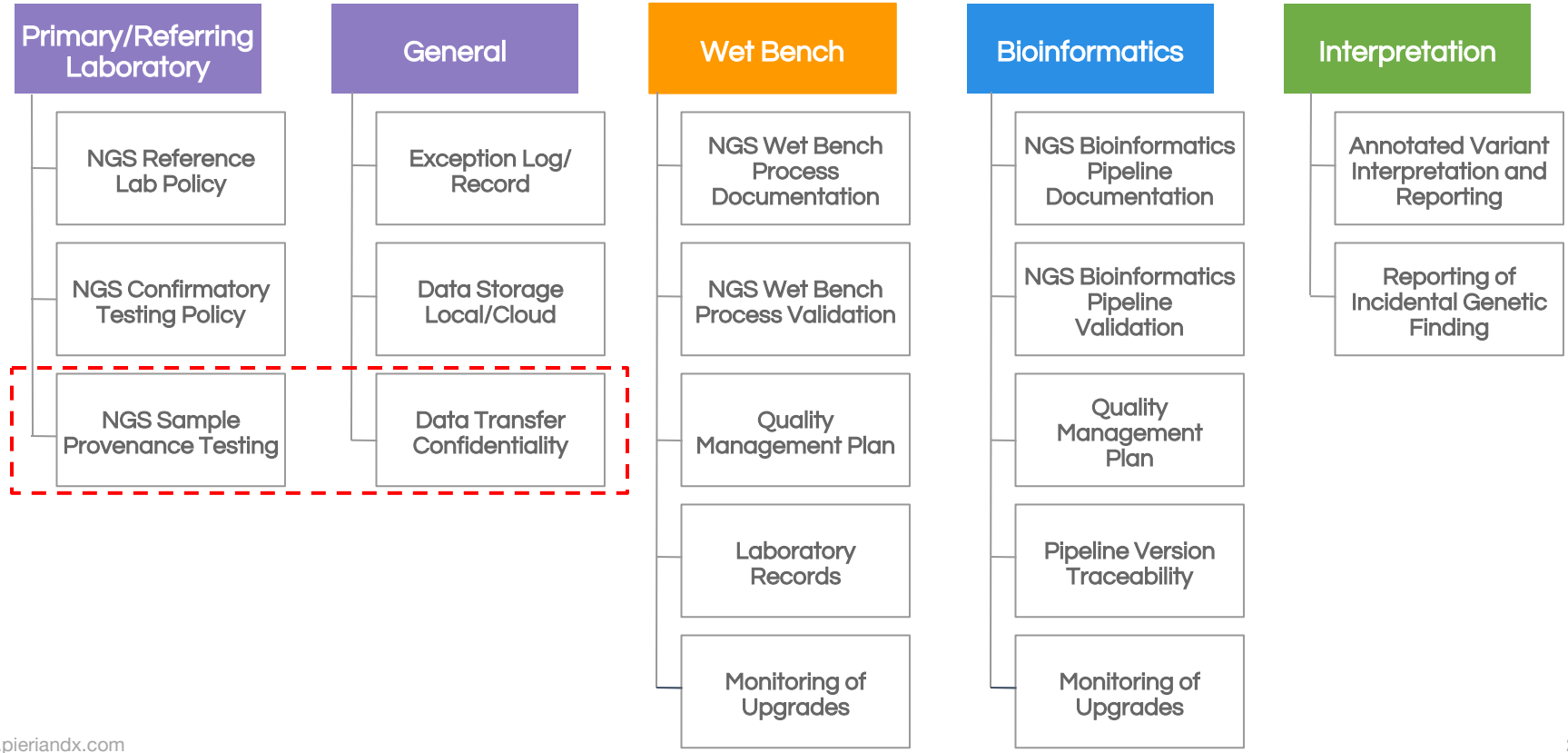
Accommodates distributive models

Assigns responsibility to Lab Director for selection and evaluation of referral laboratories

Referrals may include total NGS testing process or portions only

Designed to Accommodate Distributive Test Models

CAP Accreditation Requirements 2018



Designed to Accommodate Distributive Test Models

Overarching CAP Requirement

REVISED *08/17/2016*

MOL.35845 **Tracking of Specimens Referred for NGS Testing** **Phase I**

The laboratory has records for the tracking of each specimen referred to other laboratories as part of NGS testing.

REVISED *08/17/2016*

MOL.35865 **NGS Data Transfer Confidentiality** **Phase I**

The laboratory ensures that internal and external storage and transfer of NGS data maintains patient confidentiality, security, and data integrity.

NOTE: It is recognized that laboratories may transfer NGS sequencing data, by physical shipment or electronic means, to referral laboratories for analysis or to external companies for storage, including through cloud-based computing.

Procedures must be in place to ensure confidentiality of patient data including data encryption, use of secure and encrypted protocols for electronic data transfer (e.g. SFTP, HTTPS, FTPS), system and user authentication, activity logs, access restrictions, and appropriate data backups. These procedures must ensure that patient confidentiality is maintained and meets local, state, and/or federal requirements, as applicable (e.g. HIPAA).

Sample Provenance MOL.35847

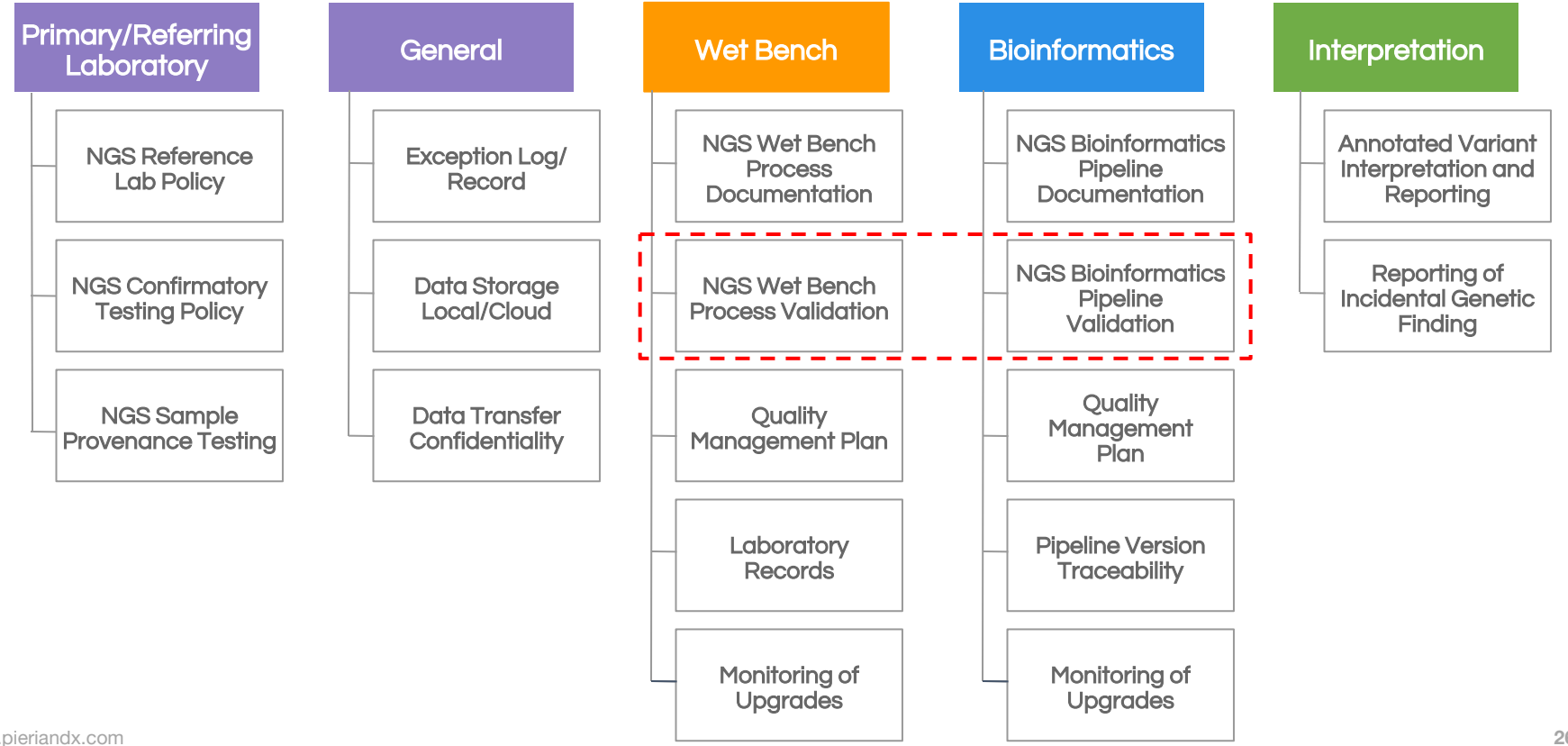
Laboratories must track each specimen referred to other laboratories

Data Security MOL.35865

Laboratories must ensure that storage and transfer or NGS data maintain patient confidentiality, security, and data integrity.

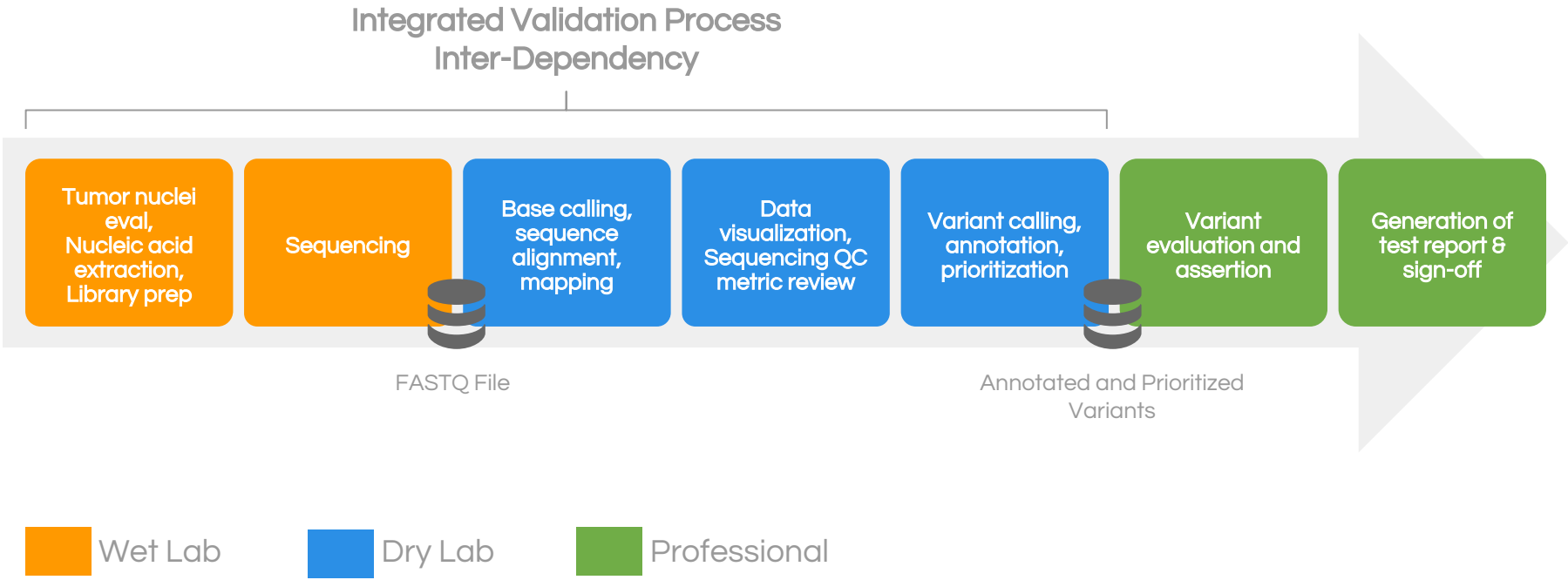
Designed to Accommodate Distributive Test Models

CAP Accreditation Requirements 2018



Designed to Accommodate Distributive Test Models

Integrated Validation



Designed to Accommodate Distributive Test Models

Integrated Validation

REVISED *08/21/2017*

MOL.36015 NGS Analytical Wet Bench Process Validation Phase II

The laboratory validates the analytical wet bench process and revalidates the entire process and/or confirms that the performance of the components of the process is acceptable when modifications are made.

NOTE: The output of the NGS analytical wet bench process is a collection of sequence data that requires additional bioinformatics processing and analysis to determine whether the sequence is of sufficient quality and quantity for the intended test. To determine this, and to ensure acceptable beginning-to-end test performance, validation of the NGS analytical wet bench process must be integrated with the bioinformatics process validation for the intended test (see MOL.36115).

NGS Analytical Wet Bench Process Validation MOL.36015

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Designed to Accommodate Distributive Test Models

Integrated Validation

REVISED *08/21/2017*

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REVISED *08/21/2017*

MOL.36115 **NGS Analytical Bioinformatics Process Validation** **Phase II**

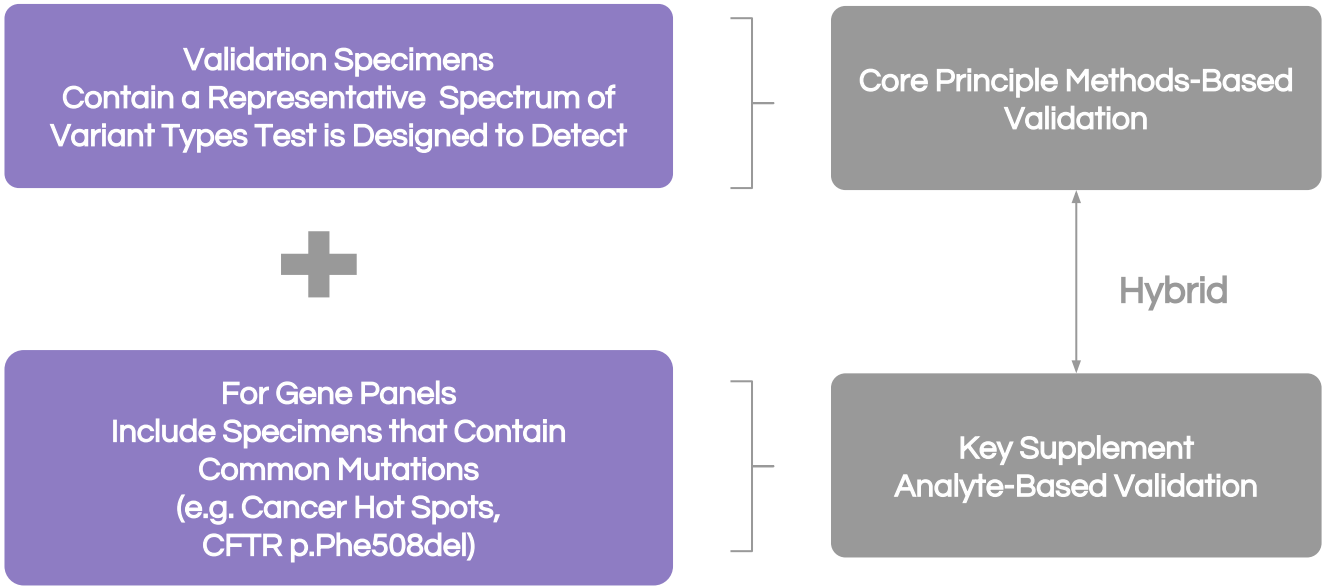
The laboratory validates the analytical bioinformatics process (also termed pipeline) and revalidates the entire process and/or confirms the performance of the components of the process as acceptable when modifications are made.

NOTE: The outputs of the NGS analytical bioinformatics process are data files containing information such as target read coverage, and numbers and types of variants. This information is used to determine if the sequence generated by the wet bench process is of sufficient quality and quantity for the intended test. To ensure acceptable beginning-to-end test performance, validation of the bioinformatics process must be integrated with the wet bench process validation for the intended test (see MOL.36015).

NGS Analytical Bioinformatics Process Validation MOL. 36115

To ensure acceptable beginning-to-end test performance, validation of the NGS bioinformatics process must be integrated with the wet bench process validation for the intended test (see MOL. 36015).

Choice of Specimens



Distributive Test Model

Role of Primary Lab Director

Selection of Referral Laboratory

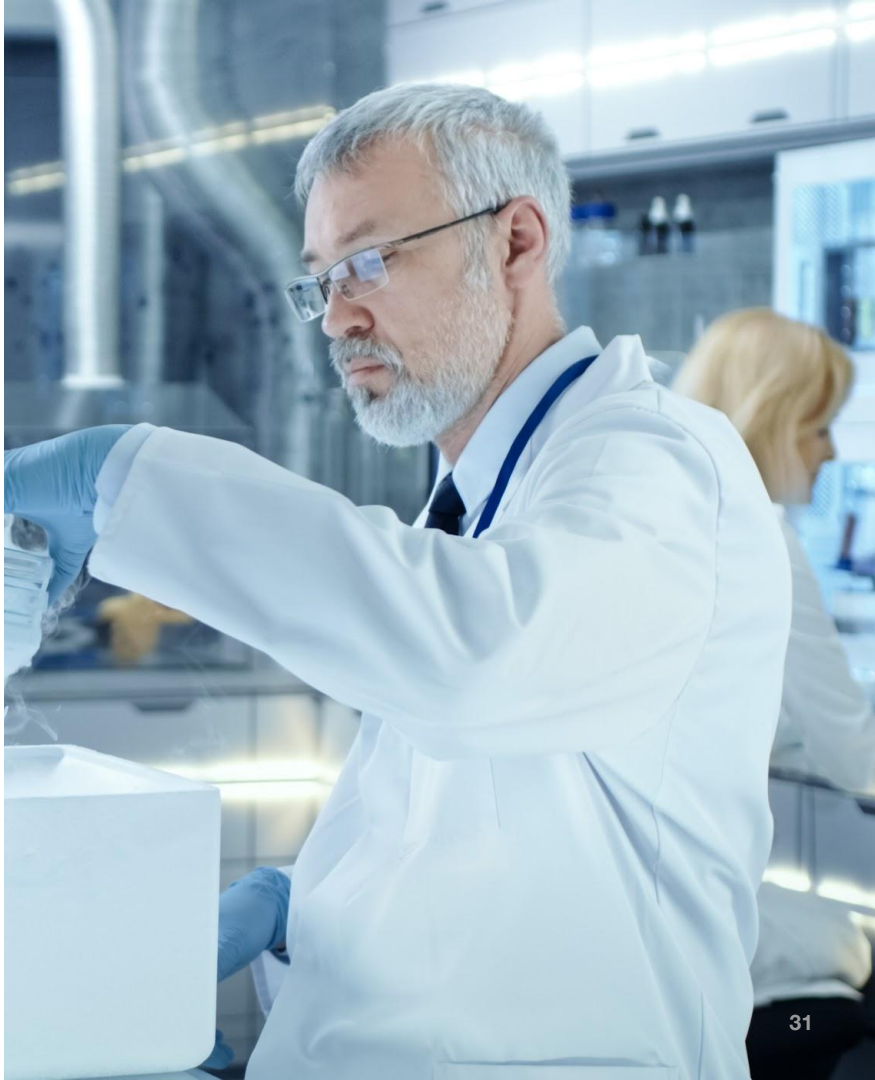
Certification Status-CLIA/CAP
Ability to Perform Required Testing Elements
Ability to Meet Turnaround Times

Assuring an Integrated Validation

Close Working Relationship with Referral Lab
Review of Total Process Validation Documents
Expected Performance Metrics Achieved

Oversight of Test Results Quality

Continuous Quality Monitoring
Addressing Upgrades to Wet and Dry Bench Processes
Iterative Process When Re-Validation Required



Operational Examples

PierianDx Clinical Lab

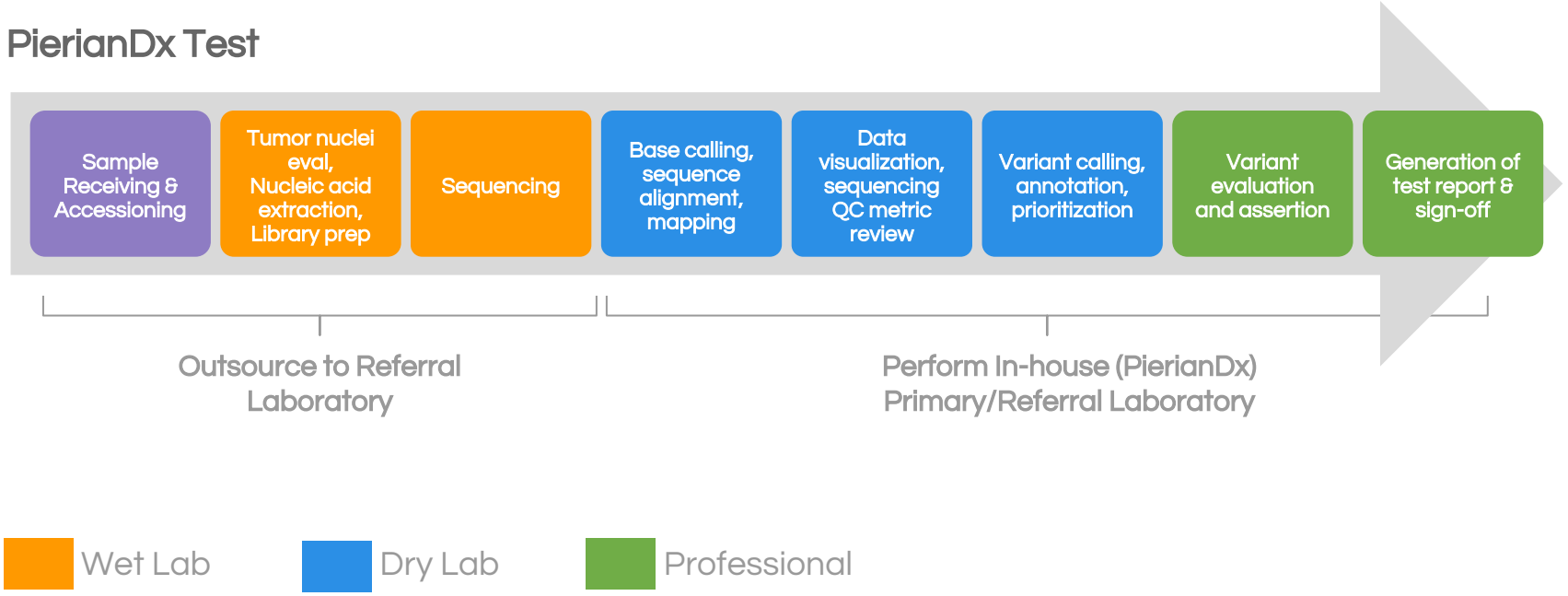
Setting Up NGS Testing Under Distributive Model

Step 1: Define the test features and intended use

PierianDx Test	Specs	Details
Genes	Total: 179	**Subpanels:** Solid Tumors (122); Hematopoietic Disorders (54); Breast Tumors (42); CNS Tumors (48); Genitourinary Tumors (44); Gynecologic Tumors (50); Head and Neck Tumors (41); Melanoma (38); Thoracic Tumors (36).
Chemistry	Hybridization Capture	Targeted
Variant Types	SNVs, Indels (1-21bp) and FLT3 ITD, SVs	Fusions: ALK; KMT2A (MLL); ROS1; RET; NTRK1; FGFR2; FGFR3
Sample Type	Hematologic cancer specimens, tumor tissue	Liquid: peripheral whole blood or bone marrow aspirate Tumor tissue: formalin fixed paraffin embedded (FFPE)
Intended Use	Molecular pathology results	Aid in diagnosis, prognosis and therapy of hematological and solid tumors
Turnaround Time	Target: 21 days	

Setting Up Distributive NGS

Step 2: Identify the beginning to end components of NGS test and define the sites for execution (Primary/Referring vs Referral laboratory)



Setting Up Distributive NGS

Step 3A: Define the CAP checklist items that are applicable to ensure beginning-to-end test performance

PierianDx Test

Reviewed CAP Checklists (ALL COM., GEN., Molecular, Team Leader) and consolidated checklist items applicable to PierianDx.

Approximately 250 checklist items were found and broadly fell under the following categories:

a. Assay validation
b. Procedure manuals for various components of test (wet bench , dry bench, reporting) including requisitions and results reporting
c. Specimen – collection, requisition, handling, tracking etc.
d. Proficiency testing / Alternate Assessment
e. Personnel
f. Laboratory computer services
g. Physical Facilities and Safety
h. Quality management program

Setting Up Distributive NGS

Step 3B: Evaluate the referral laboratory for NGS referral testing

PierianDx Test

Interacted with the Referral Laboratory Director.

Reviewed:

- CLIA and CAP certificates
- Past CAP inspection results
- Assay validation
- Laboratory policies and procedures

Assessed the overall quality of performance of the Referral Laboratory

Agreed upon the assay, validation, and procedures.*

**The assay that PierianDx wanted to bring up was already validated and operational in the referral laboratory.*

GEN.41350 Referral Laboratory Selection **Phase II**

The laboratory has a written procedure for the selection and evaluation of laboratories to which it refers specimens or materials for testing.

2. *Selection of referral laboratories must be based primarily upon the quality of performance of such laboratories*

4. *For laboratories subject to US regulations: for tests in disciplines covered by CLIA, specimens and materials for testing must be referred only to a CLIA-certified laboratory or a laboratory meeting equivalent (or more stringent) requirements as determined by the CAP and/or the CMS; this includes off-site*

5. *For disciplines not covered by CLIA (e.g. histology), laboratories subject to US regulations must refer specimens to a laboratory accredited by CAP or a CAP-accepted organization.**

7. *It is the responsibility of the laboratory director or designee to monitor the turnaround time and quality of test results received from referral laboratories.*

Setting Up Distributive NGS

Step 4 A & B: Identify the personnel in the Primary (Referring) Laboratory, including roles and how they will contribute to procedures and policies

PierianDx Test

#	Role	Document Development Assignments
	Laboratory Director	Provided complete oversight and reviewed all the documents prior to finalization
	Laboratory Supervisor	Physical facilities and Safety, Personnel, PT/ Alternate assessment, QM Program
	Sample Tracking, Accessioning, Requisition, Report Delivery, Help Desk	Specimen – collection, requisition, handling, tracking etc., assay procedure manual
	Bioinformaticians	a. Assay validation, b. procedure manuals for various components of test (wet bench , dry bench, reporting) including requisitions and results reporting, and c. laboratory computer services

Setting Up Distributive NGS

Step 5: (A) Validate the test, (B) simultaneously apply for CLIA certification and CAP accreditation.

PierianDx Test

Completed validation integrating both the wet bench and dry bench portions

Satisfied all of the CAP/CLIA requirements for Laboratory Developed Test validation

Note *CAP accreditation has to be completed within 11 months from the date of issuance of Certificate of Registration. Successful CAP inspection leads to CAP accreditation and receipt of full laboratory license (i.e. CLIA certificate of Accreditation) for 2 years (renewed with successful CAP inspections every 2 years).*

***REVISED** 08/21/2017

MOL.36015 NGS Analytical Wet Bench Process Validation **Phase II**

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The analytical wet bench process and the bioinformatics process for a test may occur within a single laboratory, or in a combination of primary and referral laboratories (see MOL.35840). ***Whether performed in a single laboratory, or in a distributive model*** *involving primary and referral laboratories, the validations of the wet bench and bioinformatics processes for an intended test must be* ***integrated to ensure acceptable beginning-to-end test performance.*** *It is the responsibility of the laboratory director or designee meeting CAP director qualifications to review and approve all validations relevant to the intended test for processes performed within their laboratory, and to review all validations relevant to the intended test for processes performed in referral laboratories, if applicable.*

MOL.36115 NGS Analytical Bioinformatics Process Validation **Phase II**

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Setting Up Distributive NGS

Step 6 Finalize by (A) developing procedures, (B) establishing a quality management program, (C) launching the test, (D) performing a mock inspection, and (E) going through full CAP inspection.

PierianDx Test

- Developed procedures.
- Established a quality management program.
- Launched the test.
- Performed a mock inspection.
- Went through full CAP inspection.

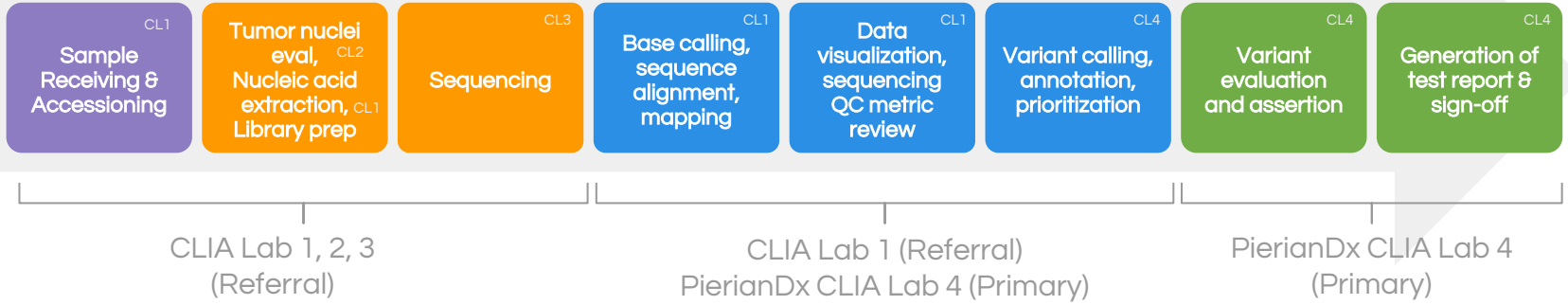
Recommendation

If there is any doubt about CAP checklist requirements or associated evidence of compliance, **reach out to CAP for guidance**. We immensely benefited from this approach during the setting up of our laboratory and NGS program.

NGS Test Distributive Models

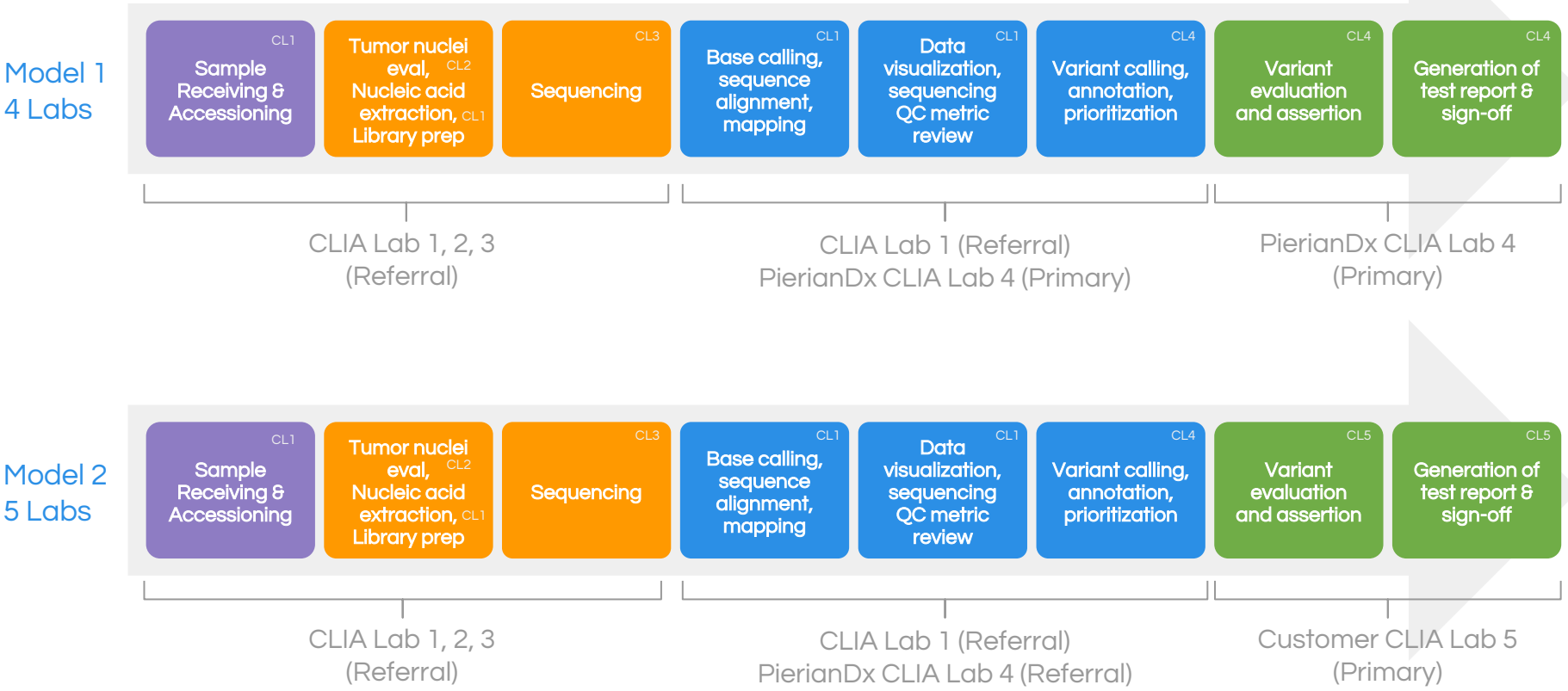
In Use at PierianDx Clinical Laboratory

Model 1
4 Labs



NGS Test Distributive Models

In Use at PierianDx Clinical Laboratory



Quality Management Program

Key Points

- Cover all sections of the laboratory
- Utilize CAP and CLSI guidelines to develop the program – QM Manual and QM report template
- Ensure that all applicable CAP checklist items for QM program are covered
- Document all the evidence of compliance in quality control report during monthly quality meetings.

QM MANUAL INDEX	APPLICABLE CAP CHECKLIST ITEMS COVERED
Overview **Section 1**: Organization **Section 2**: Customer Focus **Section 3**: Facilities and Safety **Section 4**: Personnel **Section 5**: Purchasing and Inventory **Section 6**: Equipment **Section 7**: Process Management **Section 8**: Documents and Records **Section 9**: Information Management **Section 10**: Non-Conforming Event Management **Section 11**: Assessments **Section 12**: Continual Improvement **Section 13:** CAP Checklist items Not Applicable to PierianDx Clinical Laboratory	■ Written QM Program [COM.04000] ■ QM Program [GEN.13806] ■ QM Implementation [GEN.16902] ■ QM Extent of Coverage [GEN.20100] ■ Effective QM [TLC.10440] ■ CLIA Certificate Type [GEN.20361] ■ Federal/State/Local Regulations [GEN.20374] ■ Organizational Chart [GEN.54000] ■ Employee and Patient Quality Communication [GEN.20325] ■ Terms of Accreditation [GEN.26791] ■ Customer Satisfaction [GEN.20335] ■ CAP Sign [GEN.20330] ■ Notifications From Vendors [GEN.20340] ■ QM Indicators of Quality [GEN.20316] ■ Monitoring Analytic Performance [GEN.30000] ■ Monthly QC Review [MOL.34495] ■ Test Result Statistics [MOL.20550] ■ Correction of Laboratory Records [GEN.20450] ■ Error Detection and Correction [COM.04050] ■ QM Patient Care Services [GEN.20208] ■ Turnaround Time [MOL.20300] ■ Document Control [GEN.20375] ■ Record/ Specimen Retention [GEN.20377] ■ Record Retention [GEN.20425] ■ Interim Self Inspection [GEN.23584] ■ Director Responsibility - Interim Self-inspection [TLC.10445]

PierianDx Clinical Laboratory Experience

Quality Control Report

Designed to cover:

- All sections of the laboratory
- All the checklist items that the laboratory needs to track and maintain evidence of compliance.

Monthly Updates

1. Pre-analytic section of laboratory
2. Analytic section of laboratory
3. Post- analytic section of laboratory
4. Physical facilities and safety
5. Personnel – training , competency, continuing education
6. R&D Updates
7. Employee and Patient quality communication
8. Key quality indicators
9. Policy procedures – changes, updates
10. CAP notification (CAP terms of accreditation)
11. Referral laboratory meeting minutes and updates

Quarterly Updates

1. Vendor policy and procedure updates, changes
2. Key quality indicators tracking

Semi-Annual Updates

1. Personnel - training , competency, continuing education

Annual Updates

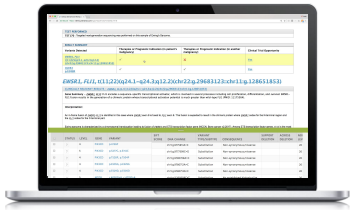
1. Personnel - training , competency, continuing education
2. Technical incident and corrective action annual review
3. Physical facilities and safety
4. Laboratory policy and procedure review
5. HIPAA Audit
6. customer Satisfaction survey
7. Annual review of key quality indicators
8. Annual review of test result statistics
9. Referral laboratory policy and procedure review
10. Self inspection

How can we help build your NGS program?

PierianDx Services

Technology Enabled Solutions

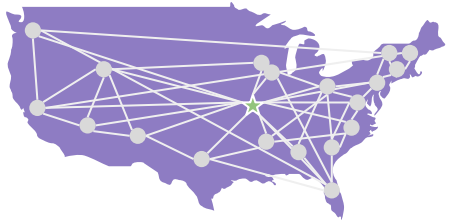
Complete NGS Testing Support



Clinical Genomics Workspace (CGW)

Medical and Scientific Services

Largest Peer Sharing Network



Gateway Lab Services

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

Clinical Laboratory Improvement Amendments

Washington University in St. Louis

"**Only unified solutions** that address the entire spectrum of the clinical workflow, from sequencing to final report, **will pave the way for realizing the promise of precision medicine**."

John Pfeifer
Vice Chair for Clinical Affairs

PierianDx Gateway Lab Services

Rapid, Economical Insourcing

Insource only the components that make sense for each test.

Leverage the CAP Distributive Model

Low Risk

- Your test, under your brand
- Zero validation or capital costs

Invaluable Learning

- Access all discrete data
- Build diagnostic sample repository
- Learn ordering patterns
- Establish billing and reimbursement best practices
- Develop core competencies

PierianDx Gateway Lab Services

Validated, Turnkey Assays

PierianDx Test

Somatic: Hybrid Capture	# of Genes*
Solid Tumors	122
Heme Disorders	54
Breast Tumors	42
CNS Tumors	48
Genitourinary Tumors	50
Head and Neck Tumors	41
Melanoma	38
Thoracic Tumors	36

*Gene sets are customizable

3rd Party Bill Available

Somatic: Amplicon-Based	# of Genes
Myeloid	65
Lymphoid	61

Germline	# of Genes
Hereditary Cancer	94
Cardiomyopathy	91
Exome Sequence	All

We Learn from the Best

Select Customers and Partners

We leverage the expertise of the most advanced labs and **productize for every hospital.**

Top 50 Cancer Hospitals

Washington University in St. Louis

Cleveland Clinic

Moffitt Cancer Center

University of Maryland Medical Center

University of Virginia Health System

Northwestern Medicine

Cedars-Sinai

UAB The University of Alabama at Birmingham

The University of Vermont Medical Center

TriCore Reference Laboratories

NorthShore University HealthSystem

Adventist Health System

Dartmouth-Hitchcock

The George Washington University Washington, DC

Seattle Children's

Augusta University Medical College of Georgia

Wake Forest Baptist Medical Center

Human Longevity, Inc.

Alpha Genomix Laboratories

Nicklaus Children's Hospital

HackensackUMC

Atrium Health

PathGroup Physician Centered. Patient Focused.

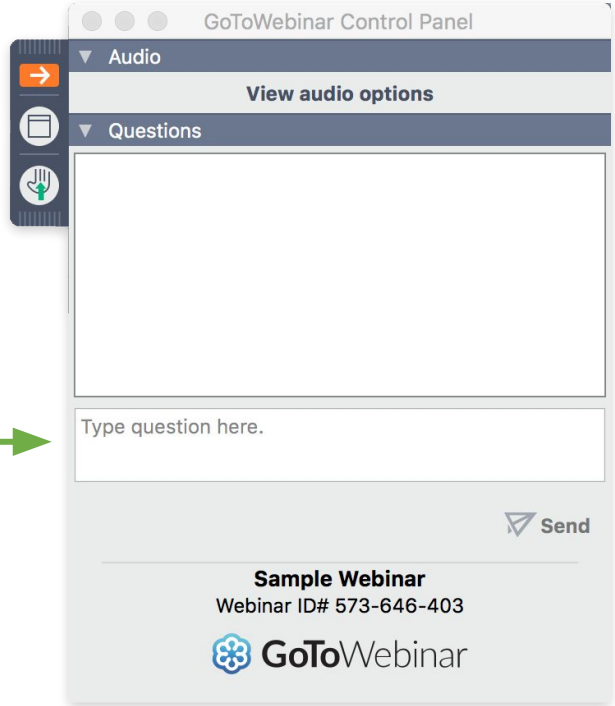
ARUP Laboratories

Cancer Genetics Incorporated Empowering Personalized Cancer Treatment

PerkinElmer

Thank You

Q&A



Type questions here

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