



CENTRAL LABORATORY SERVICES

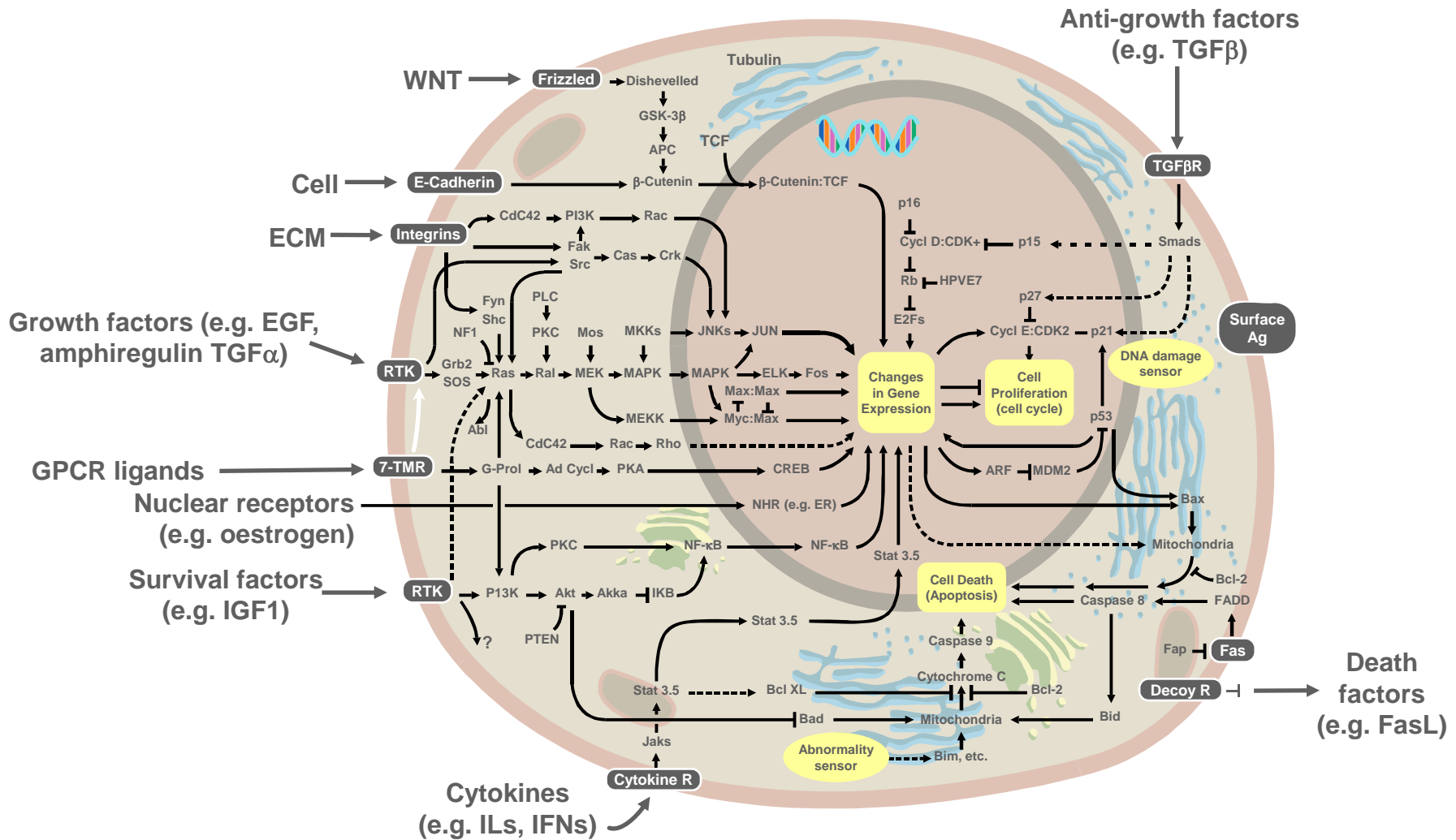
Bridging the Gaps in Biomarker Development and Testing for Global Clinical Trials
Biomarkers, Digital Pathology & the Central Lab

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TMD, A Quintiles Central Laboratory

It's all about results™

January 26, 2009

Complexity of Signaling Pathways in Cancer



Hanahan D. Weinberg RA. Cell (2000). Vol 100: 57 - 100

Challenge of Using Biomarkers in Drug Development

Validation

- > Is the biomarker specific?
- > What methods were used to establish/ confirm specificity?
- > Is it reproducible?
- > Were associated proteins activated or inhibited to confirm specificity?
- > How will regulatory bodies regard this data?

Geography

- > Are the assays reproducible inter-laboratory?
- > Will the SOPs be the same in different countries?
- > Are the logistics capabilities standardized?
- > How will data from a multi-site trial be integrated?

Quintiles Oncology Service Offerings

Quintiles

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graph TD; Quintiles --> TRD[Translational Research & Development]; Quintiles --> CS[Consultation Services]; Quintiles --> CLS[Central Lab Services for Clinical Trials];
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Translational Research & Development

Early
Compound
Differentiation
Services

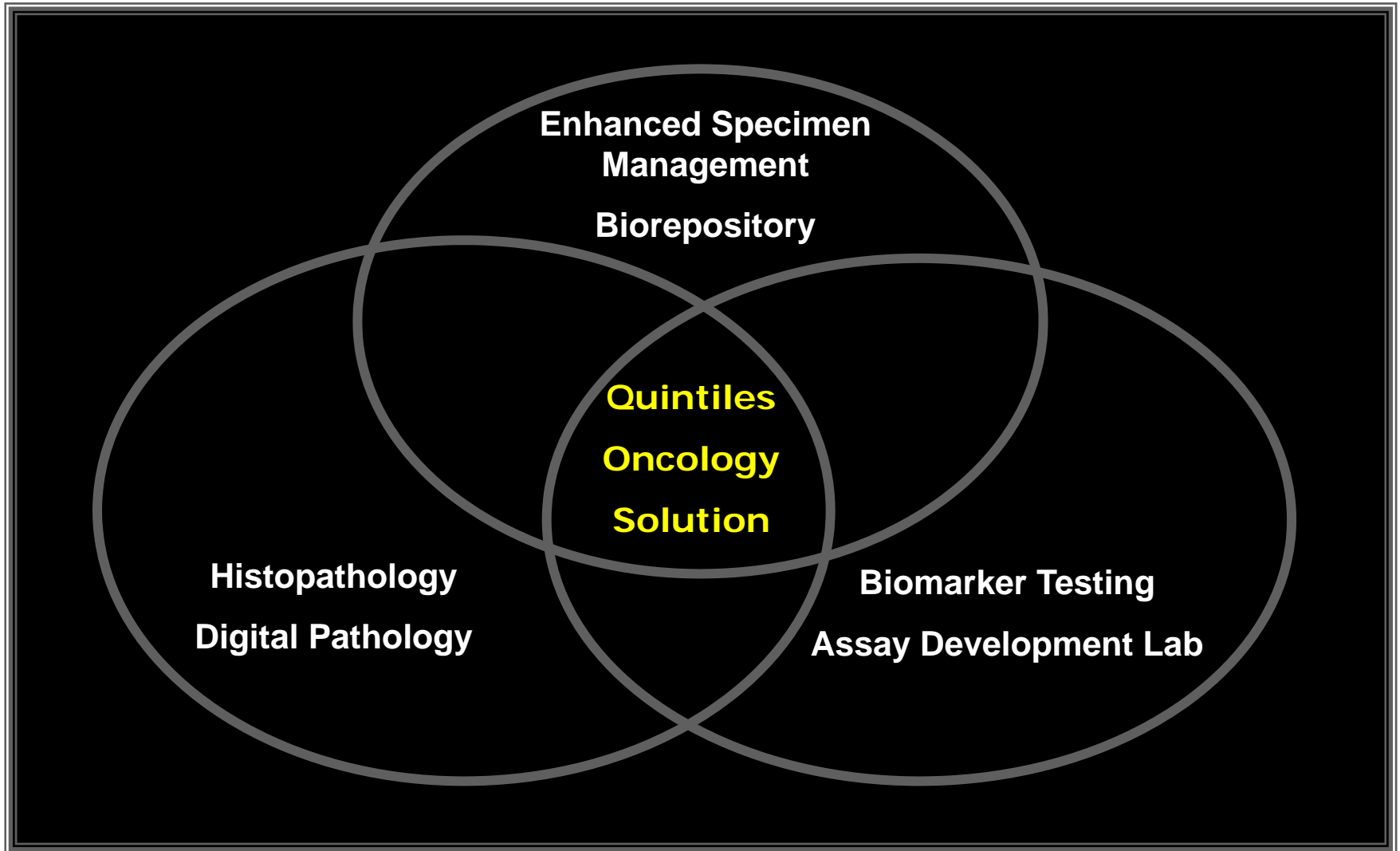
Consultation Services

Targeted
Therapy,
Biomarker,
Protocol
Design
Companion
Diagnostics

Central Lab Services for Clinical Trials

- Tissue Management
- Anatomic Pathology
 - Tissue-based Biomarkers
- Soluble Biomarkers
- Digital Pathology

Quintiles Integrated Laboratory Solution for Oncology Clinical Trials



Validation – the Central Lab Approach

- > Assays will be developed in a single location
- > Technology transfer takes place in a standardized fashion following established SOPs
- > QC and QA metrics in place to ensure reproducibility
- > Standardized training for all activities
- > Use digital pathology for training, quality assurance *and* assessment of complex biomarkers (e.g. PTEN)

PTEN IHC Assay

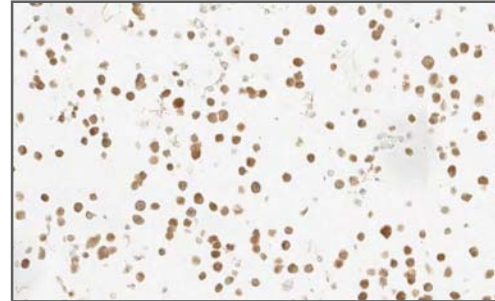
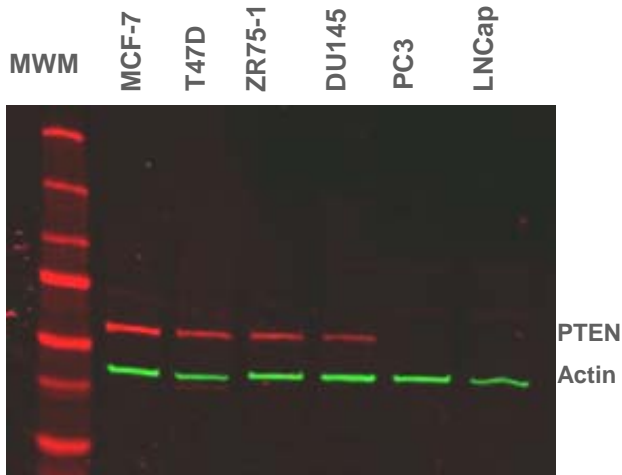
Background: PTEN is a tumor suppressor gene whose expression is frequently lost in human tumors (2nd only to loss of p53).

Objective: To develop a specific, sensitive and reproducible immunohistochemistry (IHC) assay for the detection of PTEN in human tissue specimens.

- > To develop an image analysis method to measure PTEN expression in both tumor and stromal cells in human specimens.

Importance: Comparison of tumor to stromal cell staining may indicate if a tumor has reduced PTEN expression relative to normal cells.

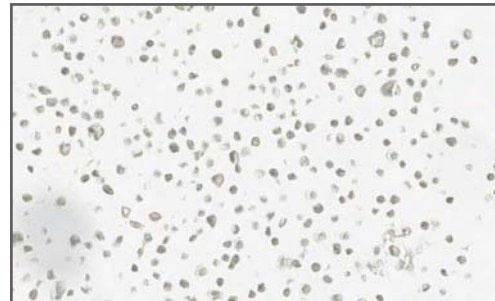
IHC Assay Validation



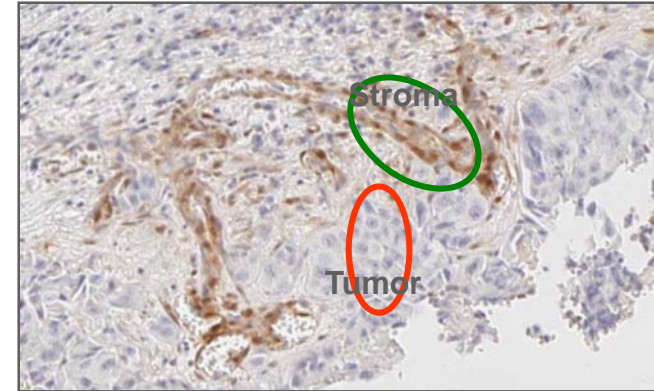
T47D (Wild-type PTEN)



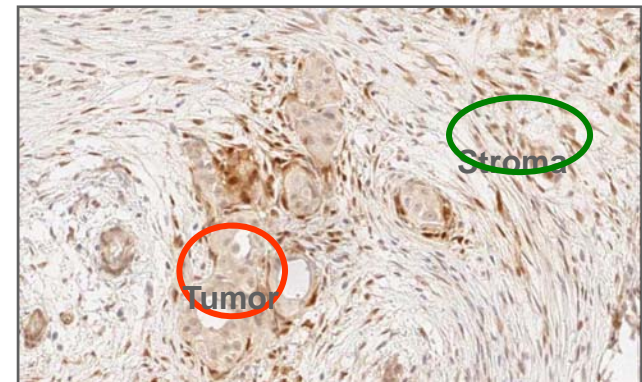
Du145 (1 Wild-type Allele, 1 Mutant Allele)



PC3 (PTEN homozygous deletion)



No tumor PTEN staining, high stromal cell staining



Moderate tumor PTEN staining, high stromal cell staining

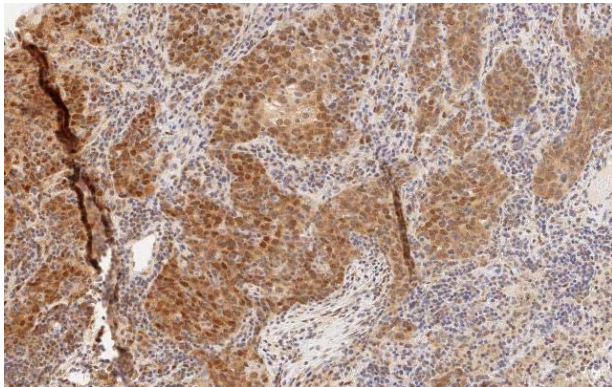
PTEN IHC Assay Reproducibility

	Optical Density (tumor)	Optical Density (stroma)
Day 1	24.73	6.49
Day 2	25.98	5.84
Day 3	25.12	6.30

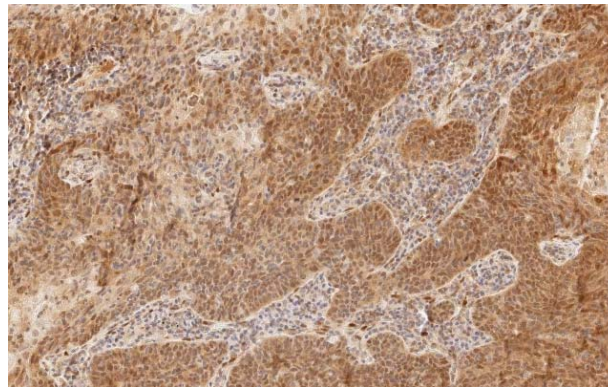
The PTEN IHC assay was run on an automated staining platform on 3 different days.

Tumor and stromal cells were measured by image analysis.

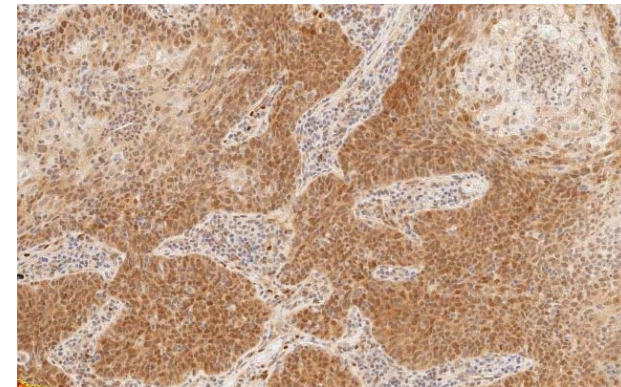
This particular tissue exhibits strong staining in the tumor and weaker staining in the stroma.



PTEN Day 1

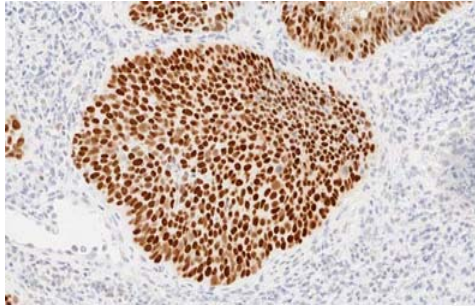


PTEN Day 2

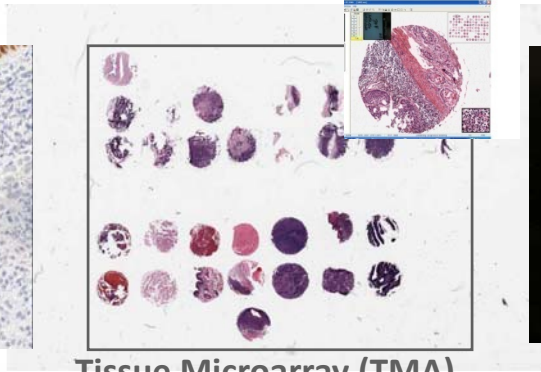


PTEN Day 3

(Analyzing) Tissue is the Issue



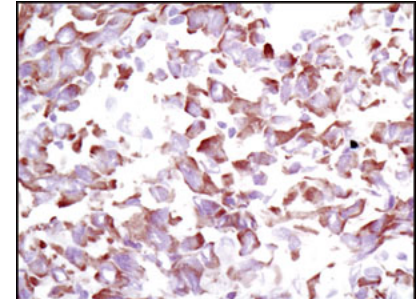
FFPE Tissue



Tissue Microarray (TMA)



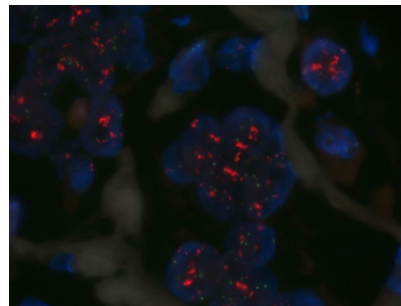
Xenografts



Frozen Tissue



Immunohistochemistry (IHC)
Immunofluorescence (IF)



Fluorescent in situ hybridization
(FISH)
Chromogenic in situ hybridization
(CISH)



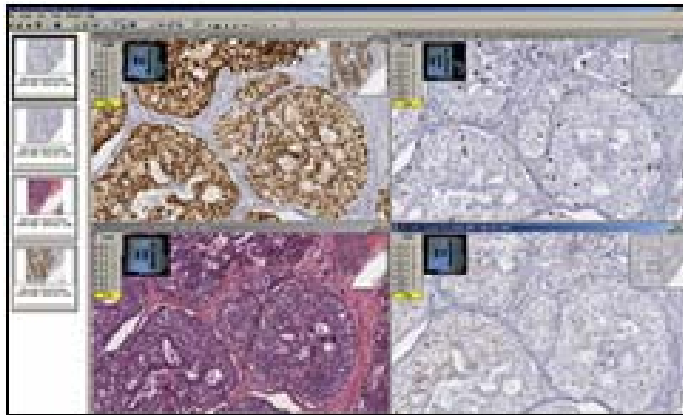
Digital Pathology & Image
Analysis



Real-Time PCR

Image Analysis in the Era of Digital Pathology

- > Optical density measurement of biomarker stains to convert subjective IHC assessment into semi-quantitative data
- > Whole slide captured as digital image – anyone, anywhere can review specimens together via internet
- > Multiple biomarker stains including H&E can be reviewed on the same screen (useful for pre- and post-treatment paired specimens)



Geography – the Central Lab Approach

- > Reduces logistics, cost and risks (loss of specimens, slide breakage, etc.)
- > Greater flexibility (ie. faster TAT) globally with high quality consistent validations transferred from a central assay development laboratory
- > Regional shipping/processing of specimens increases stability and quality (ie. less transit time)
- > Eliminate challenges associated with import/export restrictions

Quintiles Laboratories Global Coverage

Today, Quintiles has the greatest global reach of wholly owned, entirely CAP-accredited central laboratories in the industry.

Quintiles Laboratories

- US
- Europe
- South Africa
- India
- China
- Singapore
- Japan



Oncology Laboratory Support in China



- > CAP, CLIA, GLP, GCP Laboratory
- > Stage 1 Offerings
 - > Basic anatomic pathology (accessioning, microtomy, processing, H&E)
 - > Immunohistochemistry (common signaling pathways)
 - > FISH HER2, EGFR
 - > High resolution scanning of images (Aperio ScanScope)
 - > Tissue MicroArray prep, staining and reporting
 - > Biorepository
- > Supported by experienced histotechnologists
- > Dual platform – DAKO + Ventana

Conclusions

- > With the expanding use of morphological biomarkers in drug development, standardized biomarker validation is critical
- > Quintiles harnesses digital pathology to quantitatively assess consistency and reproducibility of IHC assay development and check lot to lot variation
- > By centrally developing these assays and then deploying these methodologies globally via digital pathology, QLAB leverages the experience and consistency of its experts
- > This enables analysis of routine and complex biological markers (eg. PTEN) for our clients globally



Thank You

For more information, please leave a business card or contact us at clinical.info@quintiles.com.