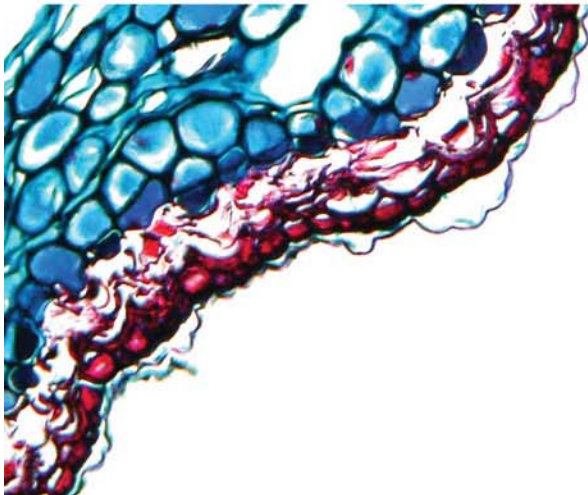


Tissue Biomarkers & Digital Pathology in Oncology Clinical Development



Christopher Ung
VP Strategic Business & Operations,
Oncology

clinical | commercial | consulting | capital

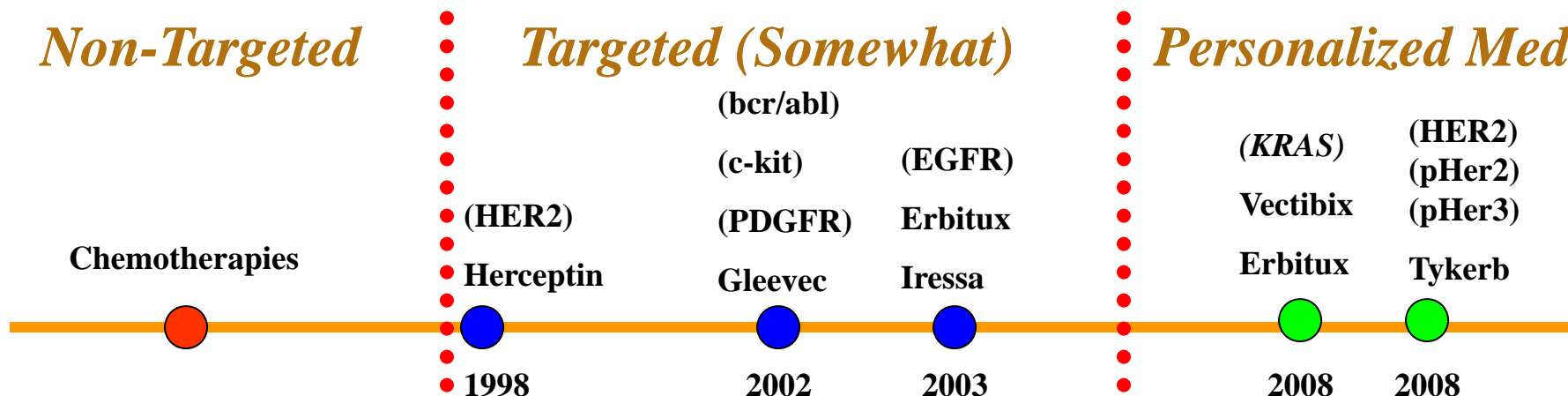
The Targeted Therapy Continuum



Non-Targeted

Targeted (Somewhat)

Personalized Med.



Time Consuming
Clinical Endpoints
(TTP, OS)

“More is better”
(MTD Approach)

No target
population

Earlier decisions based
on *Biological Endpoints*

Efficacy without
Toxicity (Biologically
Effective Dose)

Targeted Population

Biomarker-Driven
Single or Combination
Therapy

Treat Based on
Histology

Treat Based on “some”
Biomarkers

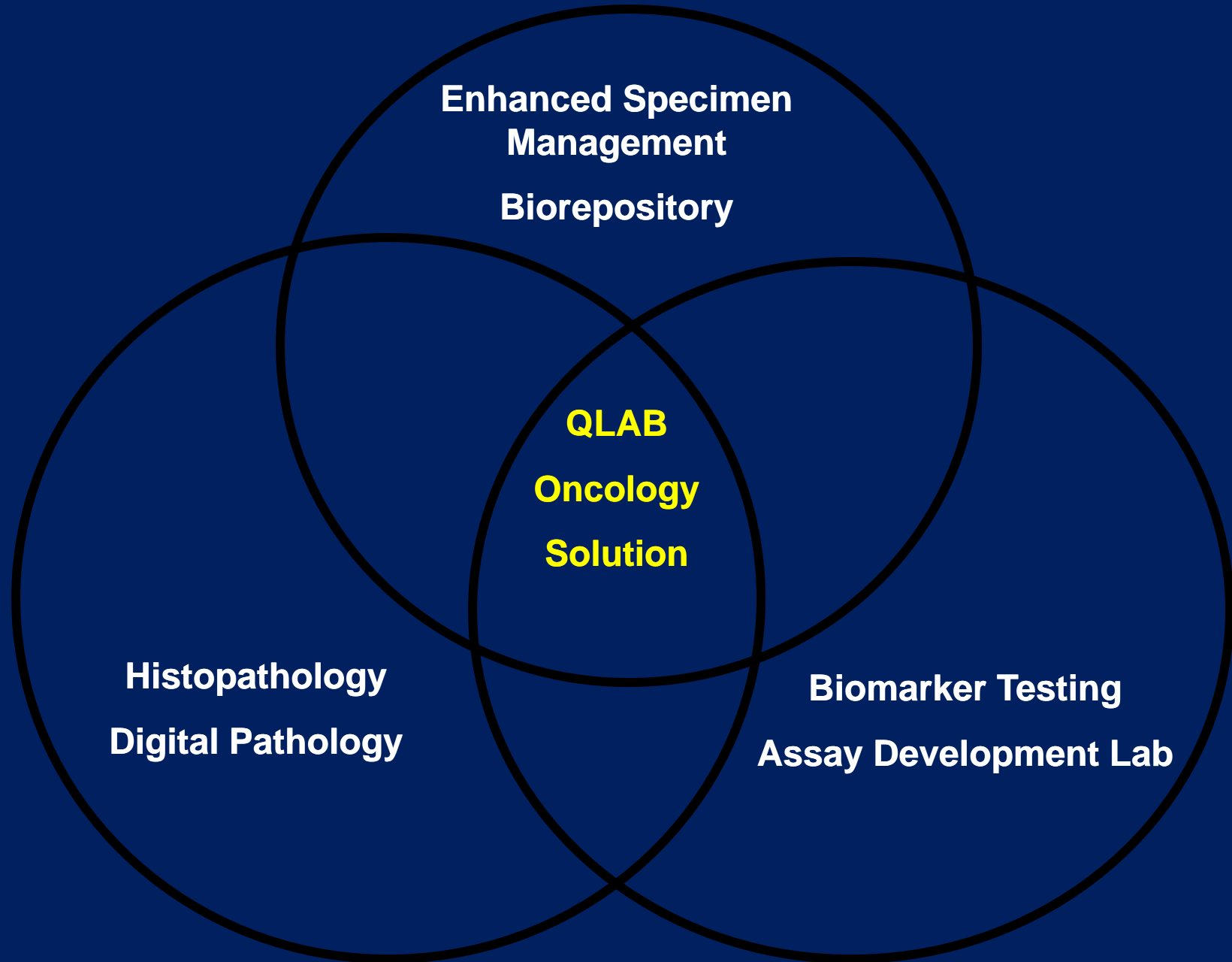
Treat Based on Molecular
Profile

Opportunity & Complexity of Oncology Biomarkers

Lung Cancer – just the NSCLC part....

- 30% have KRAS mutations – eliminate EGFR antibody Rx
- 10% have EGFR mutations – qualify for EGFR TKI Rx
- EML4-ALK fusion mutation – common in non-smokers, women and present in wildtype KRAS and EGFR – potential responders for
- Oncologists increasingly are looking for these mutations

Quintiles Integrated Oncology Development Model



Biomarkers and Collaborative Development



– Fluid- and Cell-based

- Dedicated Biomarker and Assay Development Laboratories within current central laboratory facilities
- Dedicated infrastructure
- Dedicated, experienced personnel (Research Scientists)
- New technology (e.g., MesoScale Discovery, BD FACSCanto)

– Tissue-based

- Tissue-based biomarker development lab
 - Dedicated infrastructure
 - Dedicated personnel experienced in tissue-based assay development
 - Internal tech transfer to histopathology labs within global central lab network
- Couple with image analysis

Biomarkers for Oncology Drug Development: An Example



Biomarkers to Analyze “Activation” Status of PI3K Pathway

- PI3KCA mutation, PI3KCA amplification
- PTEN expression by IHC (advantages over sequencing)

Other Biomarkers

- KRAS and/or BRAF mutation (depending on tumor type)
- EGFR, HER2, c-Met amplification (depending on tumor type)
- IGF-1R, p-EGFR, p-HER2, p-HER3

Biomarkers for PD/Target Modulation

- p-S6, p-4EBP1, p-mTOR, Cleaved Caspase 3, Ki67

Technologies & Equipment at Quintiles Global Labs



IHC



**Dako Autostainer
Primary Platform**



**Ventana Benchmark
Validate to Fit**

Fluorescent in situ hybridization (FISH)



**Zeiss AXIO FISH
System**

Digital Pathology & Image Analysis



**Aperio
ScanScope
XT**

Real-Time PCR



**QIAGEN Rotor
Gene Q**

***KRAS
BRAF
PI3KCA
EGFR***

- Standardized instrumentation at all labs
- Integrated databases driven by test codes
- General anatomic pathology services

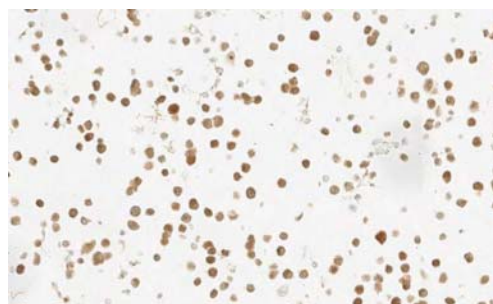
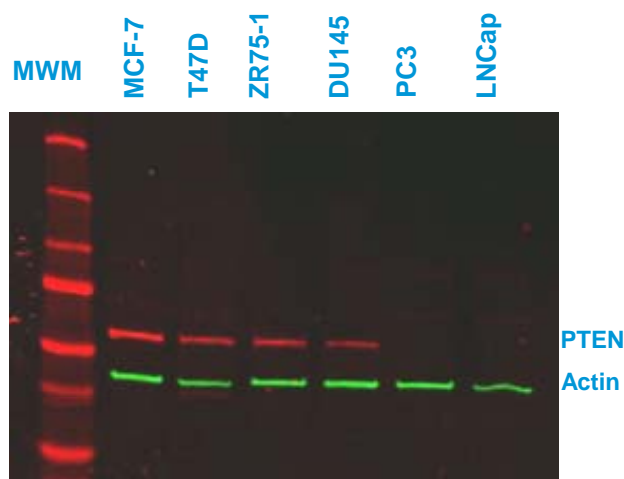
Tissue Biomarker Assay Development Model



- Proof of Robustness. Full development & validation in Chicago lab
- Lock in SOPs
- Teams trained at Chicago
- Performance qualification at global labs
- Extensive use of digital pathology platform to maintain quality and consistency

Develop Centrally, Perform Globally

IHC Assay Validation with Image Analysis



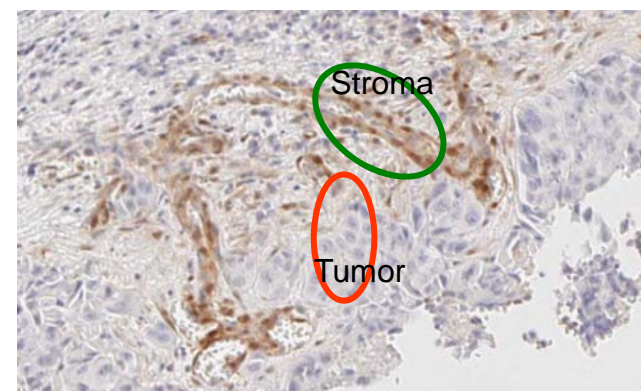
T47D (Wild-type PTEN)



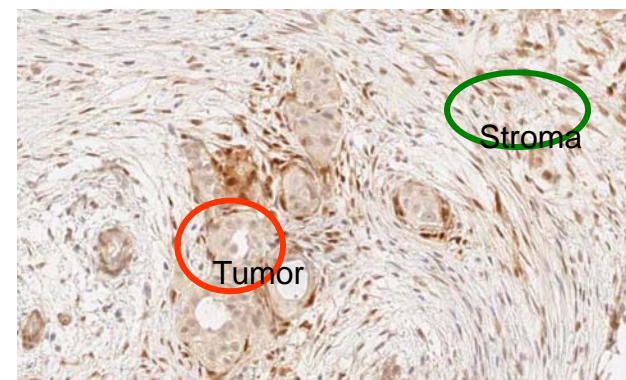
Du145 (1 Wild-type Allele, 1 Mutant Allele)



PC3 (PTEN Homozygous Deletion)



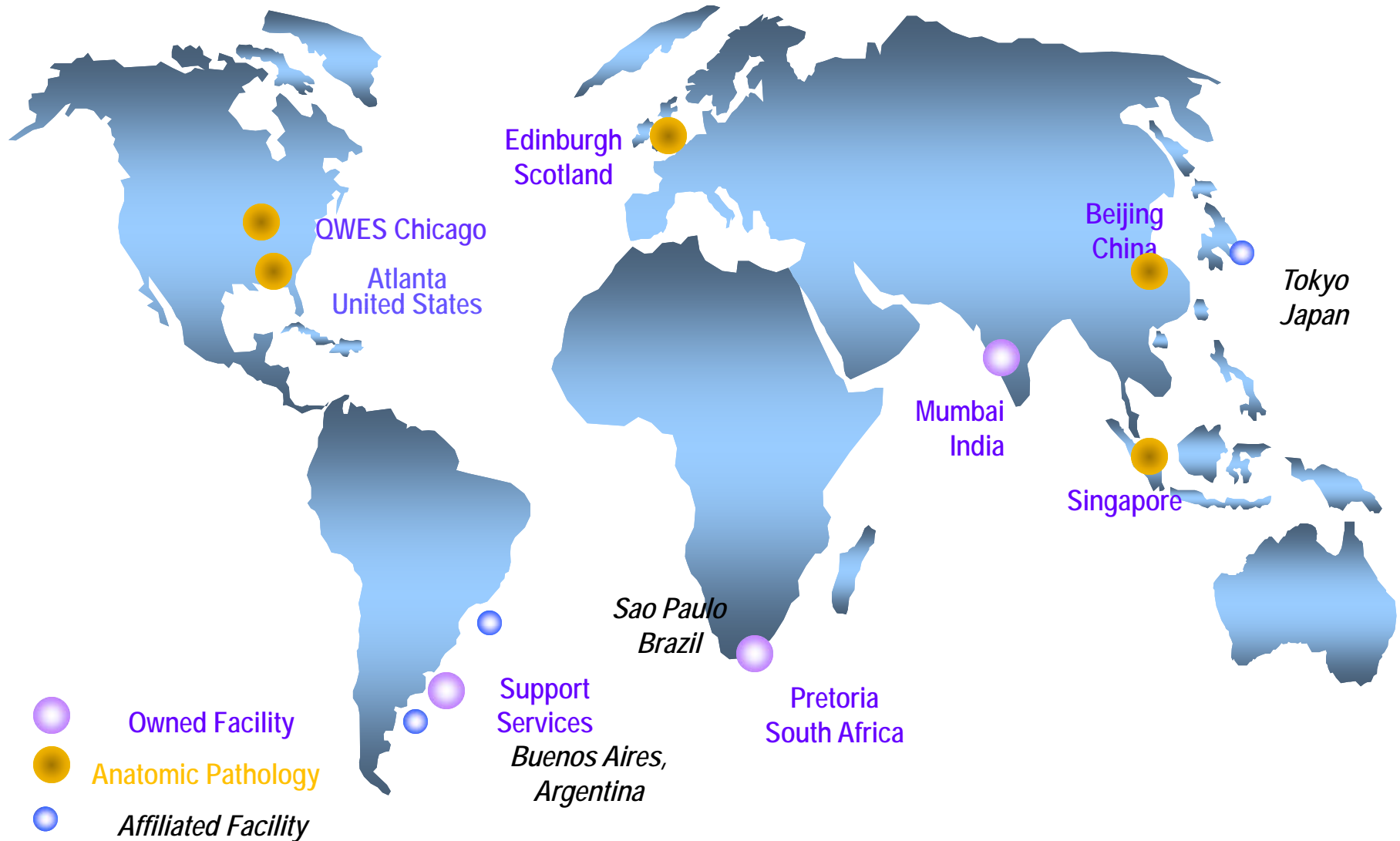
No tumor PTEN staining, high stromal cell staining



Moderate tumor PTEN staining, high stromal cell staining






Numerical Data May Enable Further Resolution in Analyses





Quintiles Labs Global Coverage

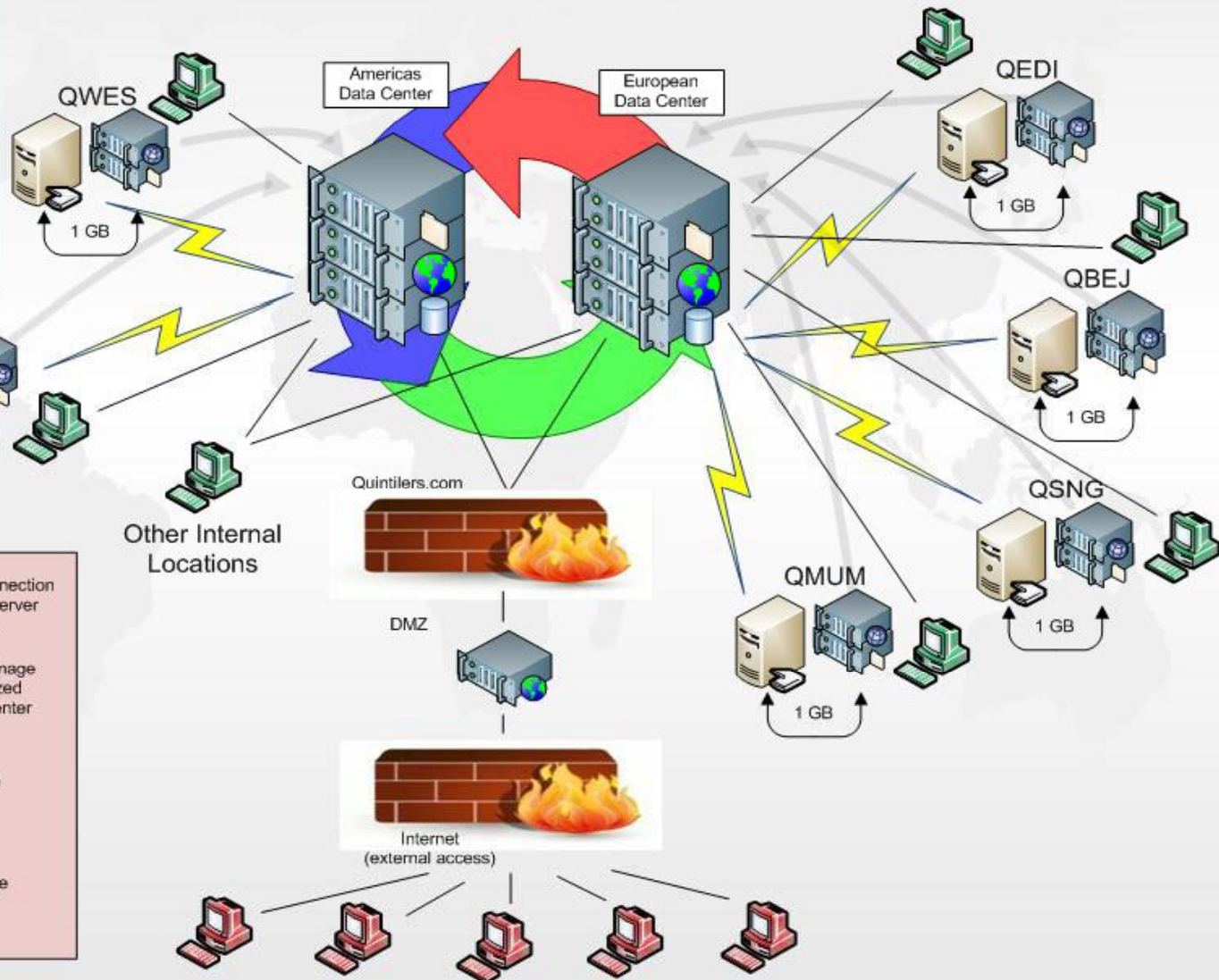


Regional Labs Allow for Rapid TAT and Lower Shipping Costs

Quintiles Central Laboratory Digital Pathology

-  Multisite Server
-  Image File Server (NAS)
-  Digital Conferencing Server
-  Digital Slide Repository
-  Slide Scanning Station

-  WS SOAP connection to DSR Data Server in data center.
-  Movement of image files to centralized store in data center
-  Internal Image Viewer
-  External Image Viewer



Quintiles Digital Pathology Applications for Drug Development



- Image Analysis & Technology Transfer for Image Analysis Algorithms
- Collaboration & education – Digital Pathology conferencing
- Global review of tumor presence prior to genotyping of solid tumors
- Simultaneous biomarker review of patient data
- Tissue Micro Array and Cell Micro Array analysis
- Digital Slide Scanning

The interface displays four main image windows, each showing a histology slide with a text overlay. The text overlay in all windows reads: "Subject ABC", "8/11/08", "Study QWES", and "Pre PharmaX". The specific treatments for each window are: "Her4" (top-left), "Her3" (top-right), "H&E" (bottom-left), and "Her2" (bottom-right). Each window includes a zoom control panel with buttons for "Fit", "1X", "2X", "4X", "5X", "10X", and "20X", and a zoom level indicator set to "0.2X".

Quintiles Global Oncology Laboratories



- CAP, CLIA, GLP, GCP Laboratories
- Anatomic Pathology Services
 - Basic anatomic pathology (accessioning, microtomy, processing, H&E)
 - Immunohistochemistry (common signaling pathways),
 - FISH: HER2, EGFR, PI3KCA , CMYC
 - Mutation analysis (Real-Time PCR)
 - High resolution scanning of images (Aperio ScanScope)
 - Tissue MicroArray prep, staining and reporting
 - Biorepository
- Experienced Quintiles histotechnologists



Leveraging Digital Pathology for the Development of Targeted Therapies



- Invest in a standardized system for global deployment
- Use the platform to increase collaboration and learning, internally and with key constituents
- Engage the benefits of archiving, secure back up, image management and image retrieval
- Use tools such as TMA Lab and image analysis algorithms to create assay development value
- Obtain input for additional creativity and solutions
- Stay strong in the vision

New Technologies Under Consideration

- CTC Analyses (counting, CTC-FISH, biomarker profiling)
- Messenger RNA in situ hybridization
- Pyrosequencing

Conclusion

- Quintiles' has built the necessary services and capabilities to develop and robustly validate tissue-based assays that can be used to support clinical development on a global basis.
- The Quintiles global anatomic and digital pathology laboratory infrastructure has been built. We will continue to evolve and expand with our clients' input.
- Quintiles is committed to evaluating, investing in and implementing novel methodologies to improve and properly support the clinical development of oncology therapeutics.