

# Standards, Validation and Regulation

## Relevance for Digital Pathology

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Associate Professor of Pathology  
Harvard Medical School

## **Personal conflicts**

**I am PI on a validation study with Philips, though I am not funded**

**My department has R&D contracts with many whole  
slide imaging companies**

## **Credentials**

**I was a member of an American Telemedicine Association SIG that developed clinical guidelines for telepathology in the late 1990s**

**I am a member of an FDA advisory panel that “sought input” on digital pathology in October 2009**

## **The ATA Clinical Guidelines for Telepathology**

**ATA Telepathology SIG in ~ 1999**

**Scope: Telepathology: Technical and Clinical**

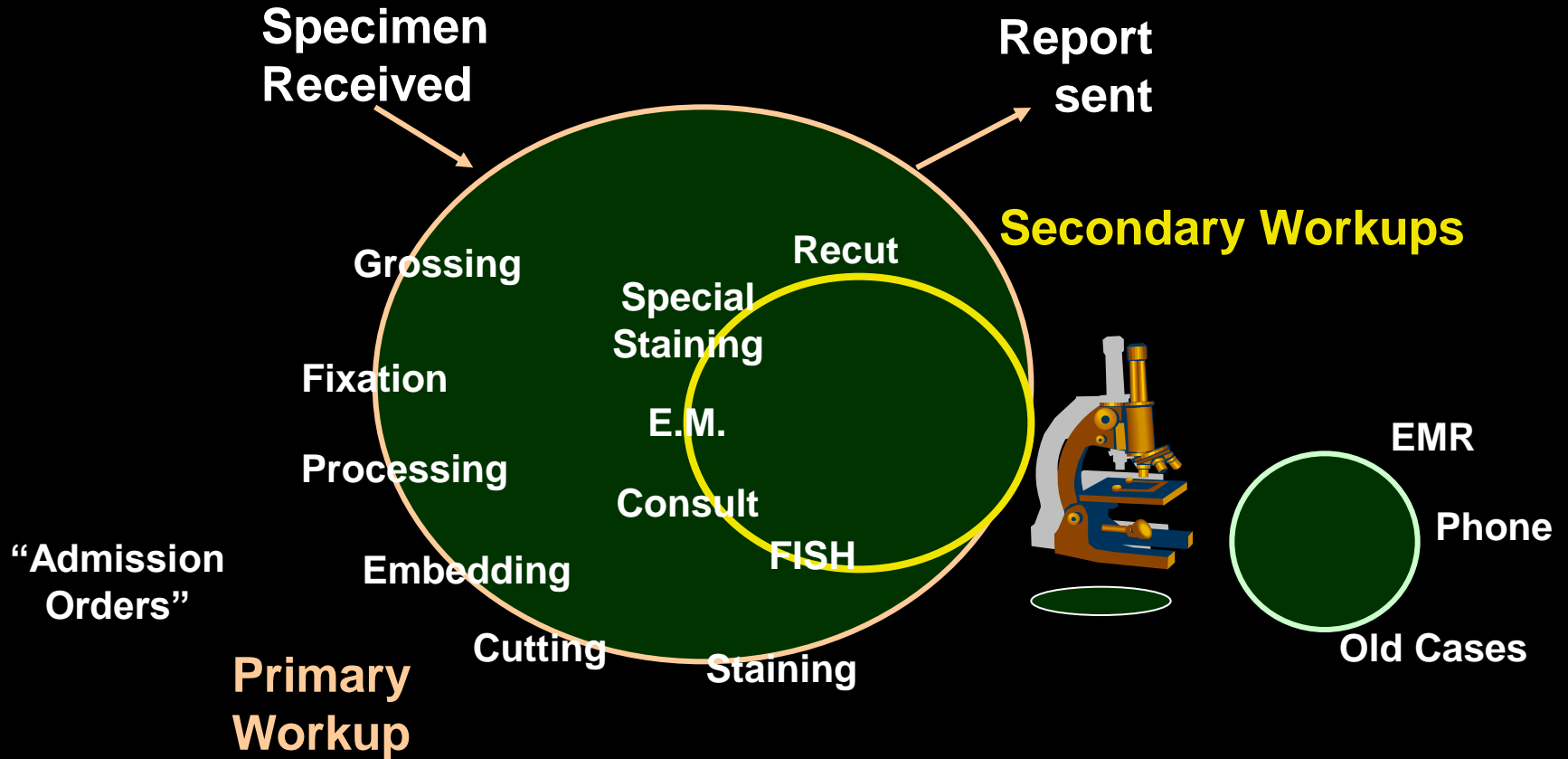
**Q: Should there be minimal technical or clinical requirements for telepathology?**

**A: The pathologist must assure that the information he has is adequate to make the diagnosis he is making**

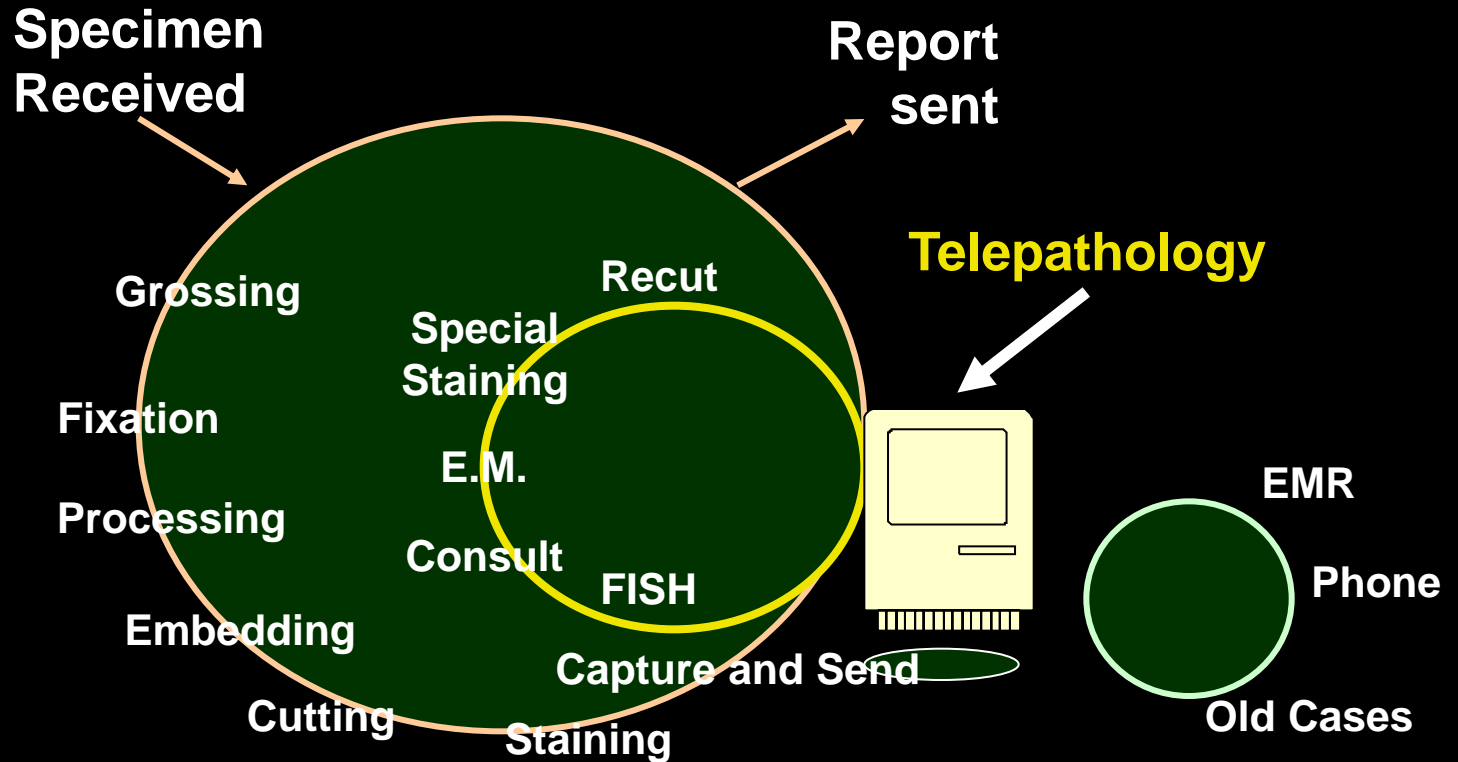
**Image quality**

**Static Image: Sub-sampling**

# Consistent with the way we traditionally practice pathology



# Consistent with the way we traditionally practice pathology



**Ten years later...**

## **The FDA Advisory Panel**

**October 2009**

**A two day special meeting\* to “seek input” on digital pathology**

**\*special meeting of the Hematology and Pathology Devices Panel**

## The FDA Advisory Panel

Just because I was on the panel does not mean I know anything

Phone call		Mail	Airplane	Hotel
“Would you be on a panel?”	“OK”	(articles to read) (forms to sign)		(meet Panel) (forms to sign)



scan" October 26 2009

**Meeting begins  
(multiple witnesses)  
(you listen)**

**Car**

**Airplane**

**Home**

Friday October 7

Pathology Informatics 2011

**I have no special insight any potential FDA decisions**

**The (2009) FDA Advisory Panel**  
(Initial State)

**Canada and Europe do not consider WSI as medical devices**

## **The FDA Advisory Panel**

**(Initial State)**

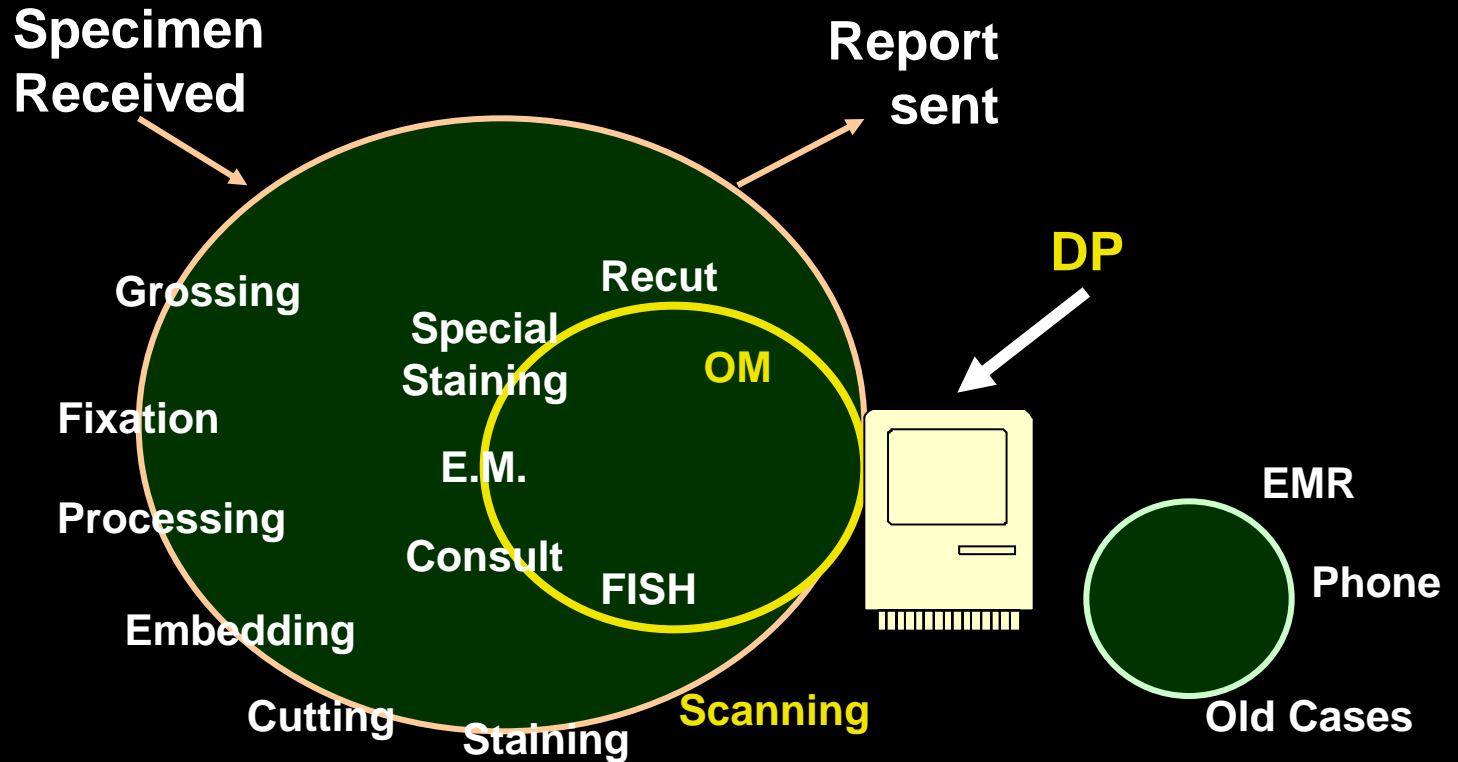
**The FDA was interested in a specific use of DP**

**“DP primary diagnosis of surgical  
pathology slides in lieu of a microscope”**

**The broad application of DP to surgical pathology  
primary diagnosis without OM confirmation**

**“with broad application”  
(not a specific test or procedure)**

# Replace the OM with a DP and change nothing



## **The FDA Advisory Panel**

(Initial State)

**Was there existing technology that is substantially similar to WSI for primary diagnosis in surgical pathology?**

## **The FDA Advisory Panel**

(Initial State)

**NO**

**Optical Microscopy (different technology)**

**WSI in frozen section and second opinion consultations (OM in Loop)**

**IVD devices that use digital images for very specific purposes  
(Automated cell counters, Urine sediment analyzers, IHC analyzers, ...)**

**Gyn (PAP) cytology analyzers (specific purpose)**

## **The FDA Advisory Panel**

**A new technology in a very broad and important application**

## **The FDA Advisory Panel**

**(Initial State)**

**Are there questions of safety and efficacy in the broad application of DP to primary diagnosis in surgical pathology?**


## Safety

**Reasonable assurance, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks**

**21 CFR 860.7(d)(1)**

**FDA Position Paper (July 2011)  
Tremel Faison MS, RAC, SCT(ASCP)**

**It is not just the device  
It is how it is used**



Note

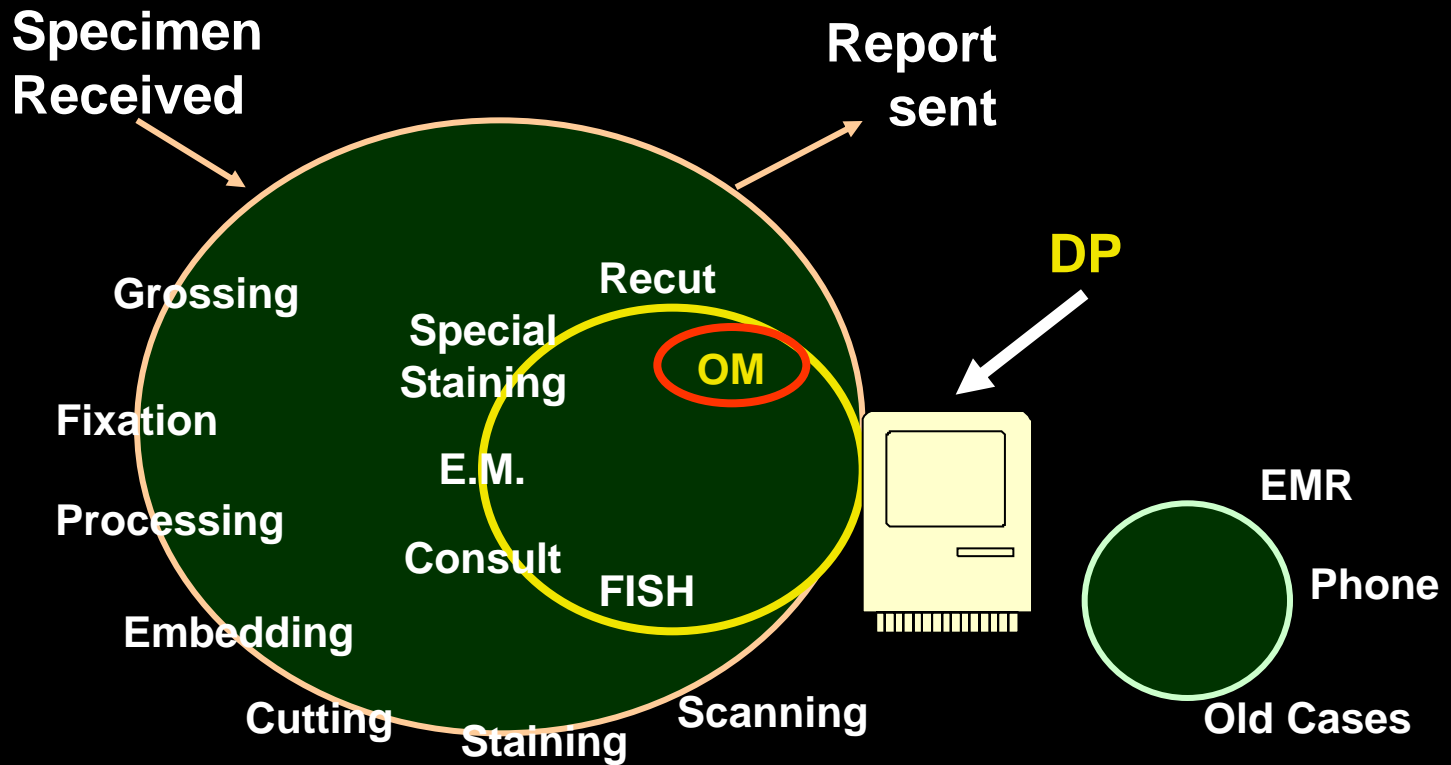


## **Effectiveness**

**Reasonable assurance, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended use and conditions of use, when accompanied by adequate directions for use and warning against unsafe use, will provide clinically significant results**

**21 CFR 860.7(e)(1)**

**FDA Position Paper (July 2011)  
Tremel Faison MS, RAC, SCT(ASCP)**



**Tissue Finding**

**Reasonable assurance, based on valid scientific evidence...**

## **The FDA Advisory Panel**

(Initial State)

**Are there questions of safety and efficacy in the broad application of DP to primary diagnosis in surgical pathology?**

**YES**

## **The FDA Advisory Panel**

(Initial State)

**What studies should be done to understand those risks,  
and what regulation is needed to mitigate those risks?**

**??**

**Getting “reasonable assurance, based on valid scientific evidence” on the “safety and effectiveness” of a change in one step of a process as broad, complex and poorly understood as surgical pathology is not trivial**

## **The FDA Advisory Panel** (Initial State)

### **Digital Mammography as a model for Digital Pathology**

**(DM initially a Type III device, subsequently changed to Type II)**

#### **Mammography**

**Digitizing an  
existing process**

**Screening test  
Grey on Grey**

**Responsibility of Radiology**

**Regulation of procedures**

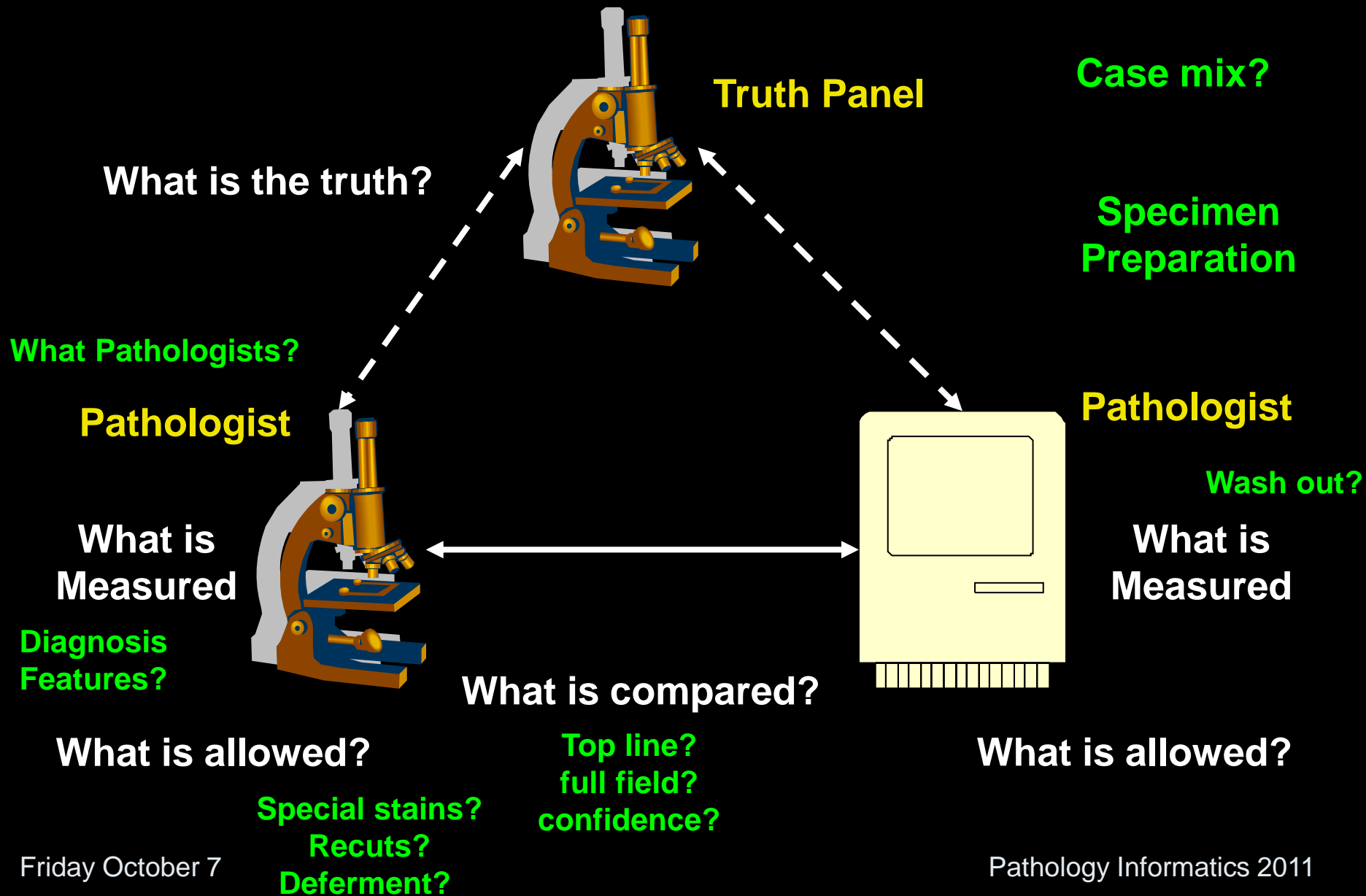
#### **Pathology**

**Digitizing an  
existing process**

**Diagnostic test  
Staining**

**Responsibility of Pathologist**

**A model of pathology** ----- A pathologist is a reader of slides



**What can the FDA do?**

## **What could/can the FDA do?**

**Require manufactures register, obtain approvals and follow current good manufacturing procedures (cGMP) and...**

**...define the target population and use, the procedures for using the device for its intended use and conditions of use, directions for use and warning against unsafe use**

**Require manufactures prove that the device is safe and effective**

## **FDA classifies medical devices as:**

**Class I: Devices that pose no potential unreasonable risk.  
Subject to “General Controls”**

**Class II: Devices that require additional mechanisms to assure safety and effectiveness, and methods exist to provide such assurances**

**Class III: Devices that pose potential unreasonable risk with insufficient information available to assure safety and effectiveness. Failure of a class III device could result in serious mortality and morbidity**

**It is the combination of the Device and the Intended Use that matters**

## How the FDA clears medical devices

**Class II** devices are often “cleared” (by the FDA) by showing “substantial equivalence” to another device already marketed – the **510K** process; or through PMA

Most **Class III** devices require specific pre-market approval from the FDA – the **PMA** process (more stringent process to prove safety and efficacy)

FDA can also mandate **post market surveillance** to validate or monitor safety or efficacy

The FDA suggests and approves the studies needed for 510K, PMA and post market surveillance, it is up to the manufacturer to design and implement those studies



## **Current FDA Thoughts**

**FDA Position Paper (July 2011)**

**“Current thoughts on FDA regulation of digital pathology imaging applications”**

**Tremel Faison MS, RAC, SCT(ASCP)**

## **FDA's Current Thoughts**

**There are questions of safety and efficacy in the use of  
WSI for Primary Diagnosis**

**“Is the WSI presented of such quality [or is the viewing  
environment of such a nature] that the same diagnosis  
could be made as when using the light microscope for  
all surgical pathology specimens?”**

**FDA Position Paper (July 2011)  
Tremel Faison MS, RAC, SCT(ASCP)  
(text in [ ] is mine)**

## **FDA's Current Thoughts**

**The potential of serious injury is high**

**“Serious consequences to public health if misdiagnosis is caused by poor quality image or improper use as surgical pathology diagnosis is the “final answer” for most conditions”**

**FDA Position Paper (July 2011)  
Tremel Faison MS, RAC, SCT(ASCP)  
(text in [ ] is mine)**

## **FDA's Current Thoughts**

**“[General use of WSI for Primary Diagnosis] raises new questions of safety and effectiveness that must answered through pre-market approval (PMA)”**

**“The risk is such that we believe they should be Class III and subject to pre-market approval”**

**FDA Position Paper (July 2011)  
Tremel Faison MS, RAC, SCT(ASCP)  
(text in yellow is mine)**

## **FDA's Current Position**

**How does FDA plan resolve these questions of safety and efficacy**

**Require analytical and clinical studies to objectively  
and precisely validate performance**

**Knowledge of the risks, benefits and limitations**

**Standardization**

**Post-market studies**

**FDA Position Paper (July 2011)  
Tremel Faison MS, RAC, SCT(ASCP)**

**The Industry's Current Position**  
(as I understand it)

**OK, tell us what studies you want done and let's get on with it**

**(not a direct quote)**

Diseases

Diagnoses

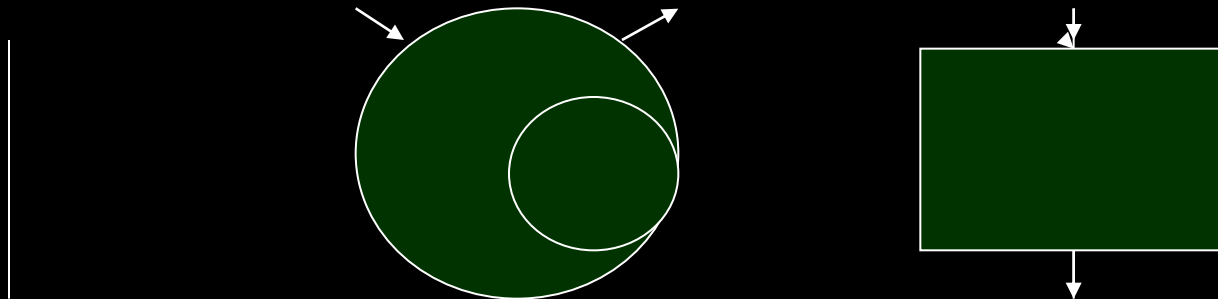
Features

Tissue Processing

In many combinations

Microscope

Getting “reasonable assurance, based on valid scientific evidence” on the “safety and effectiveness” of a change in one step of a process as **broad, complex and poorly understood** as surgical pathology is not trivial



Models Matter

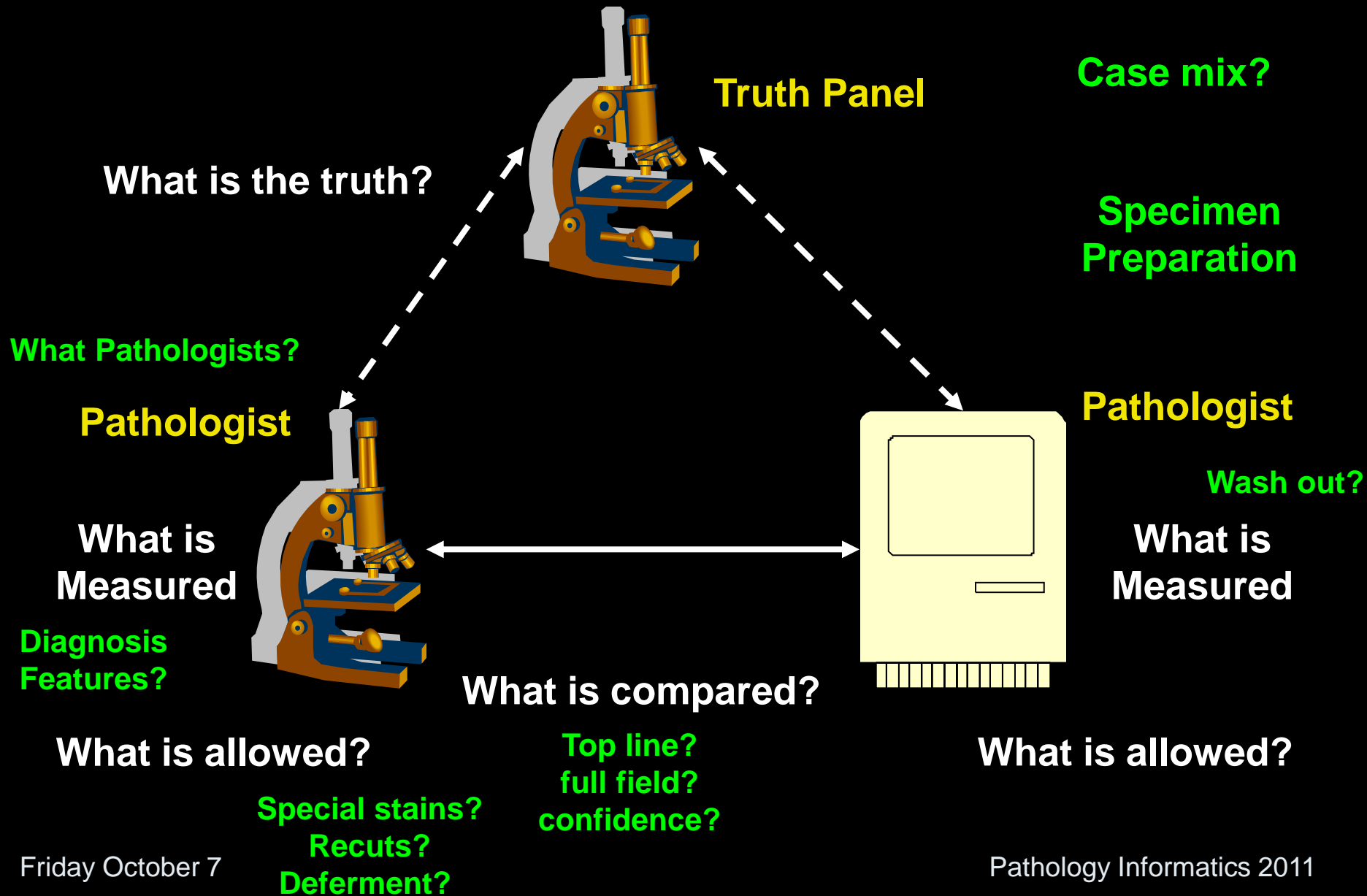
**So what will happen?**

**(I think)**

**At some point, the FDA will decide on one or more study protocols and rules of use that can be used to clear WSI systems for sale for primary diagnosis**

**The industry will design studies on the basis of these protocols**

**A model of pathology** ----- A pathologist is a reader of slides



## **So what will happen?**

**(I think)**

**At some point, the FDA will decide on one or more protocols that can be used clear WSI system for sale as primary diagnosis system**

**The industry will designed studies on the basis of these protocols**

**The studies will be done, the devices will clear**

**There will be a post market phase, and we will move on**

## **FDA regulation has potential implications**

**It is not whether DP will be approved  
For pathologists, it is what rules /  
limitations / caveats on use comes with  
that approval**

**Required training / certification**

**Standardization of protocols or devices**

**Limitations on integration**

**Rate of development**

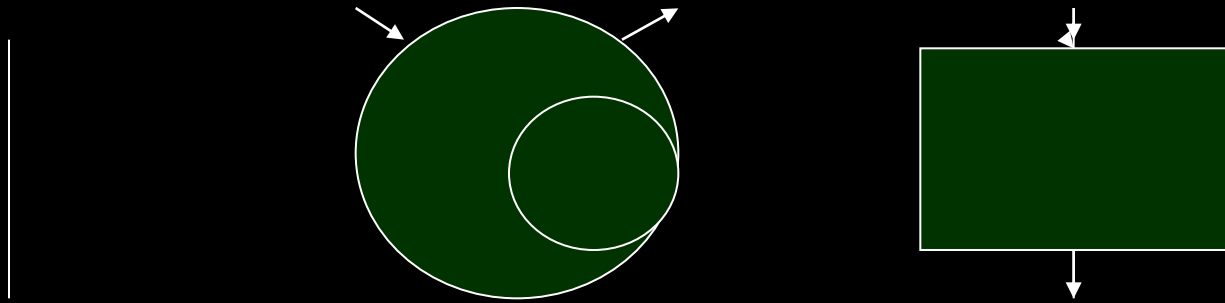
**...**

**(Cytology Systems)**

**(Blood Bank Systems)**

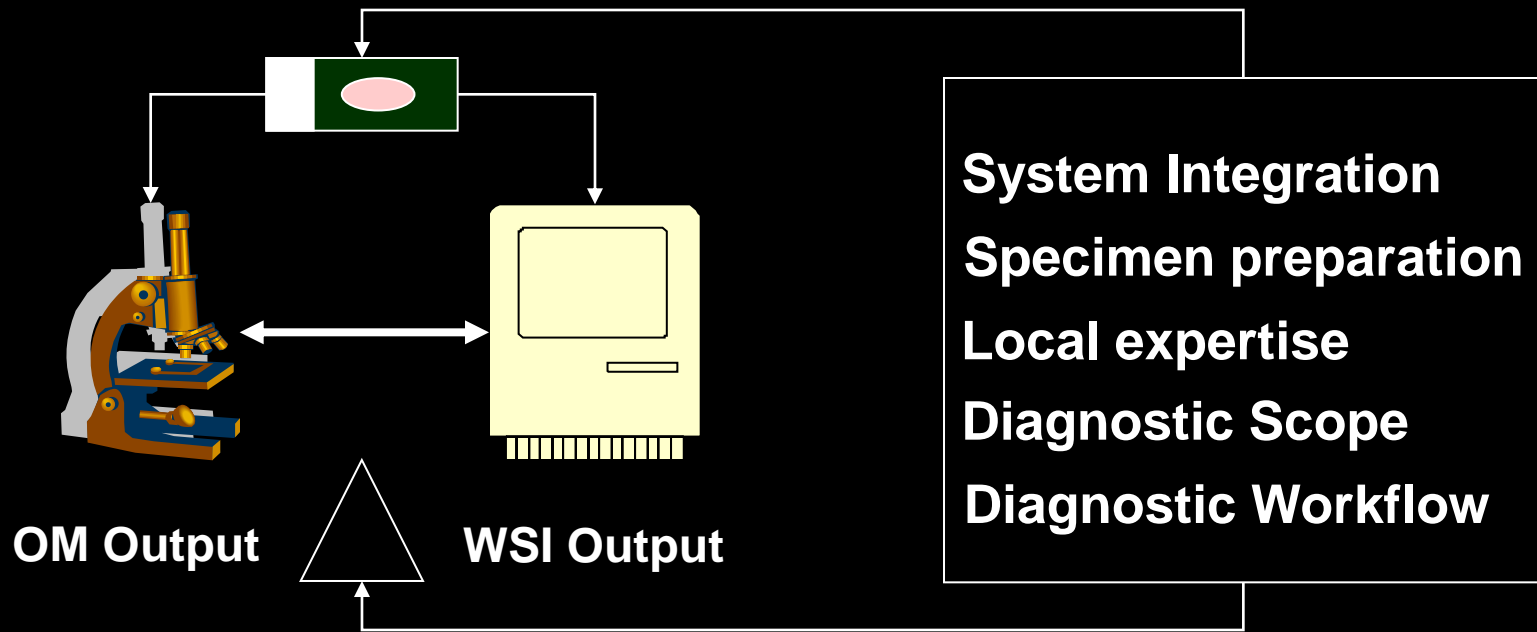


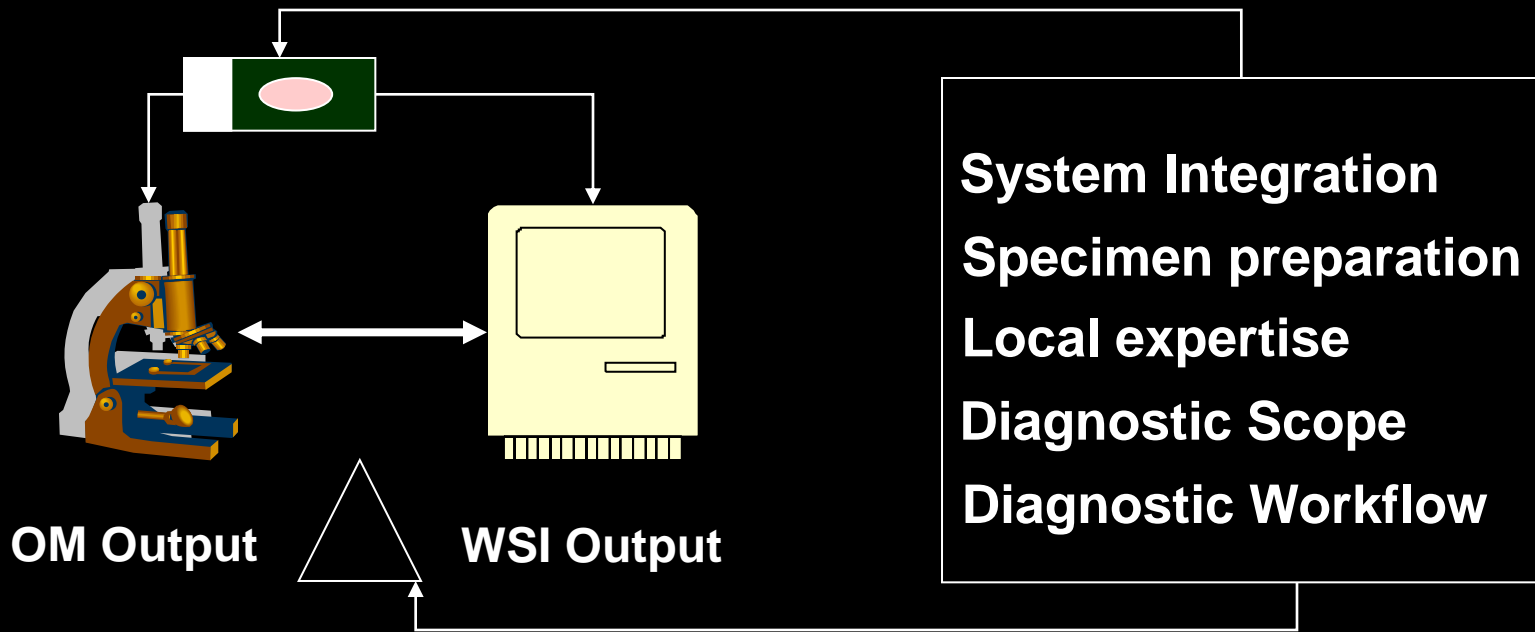
## Validation



**FDA approval will not negate the responsibility of the lab to validate  
WSI in its local environment**

## Local conditions are not the same as study conditions



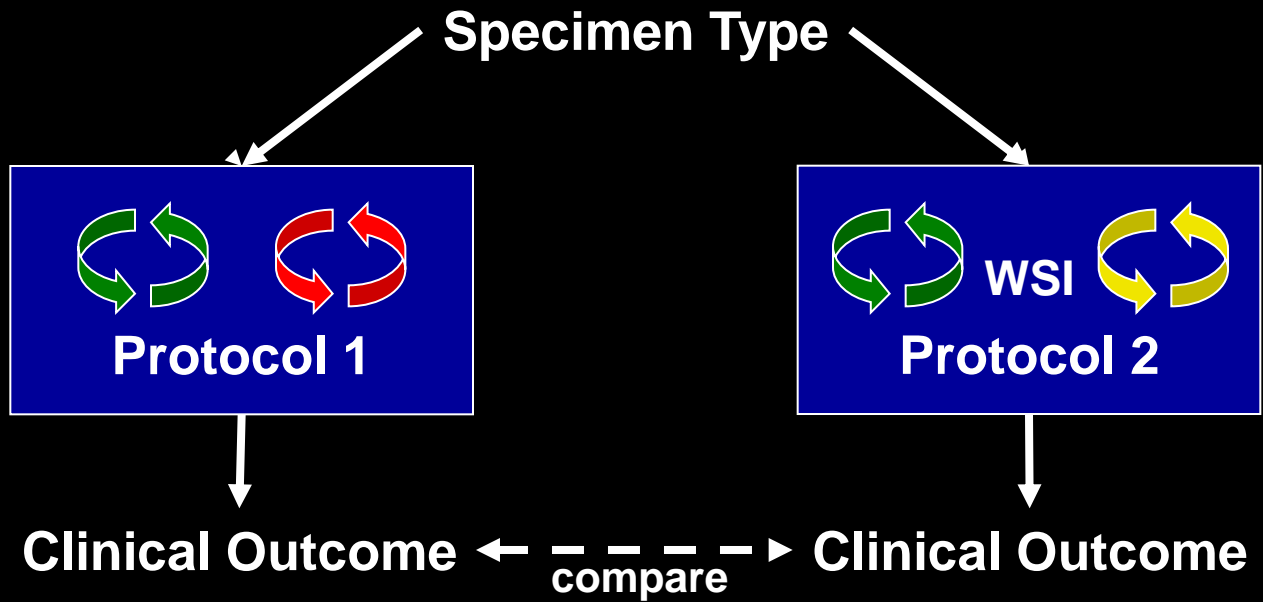


**Demonstrating that WSI can be diagnostic equivalent to “OM”  
Mano on mano is important...**

## **Validation is not the same as clearance**

**Once a WSI device is cleared, for “broad application”,  
one can use it anywhere within that broad application**

**What one will care about the development and validation  
of processes that improve the diagnostic quality of one’s lab**



**Does this work?**

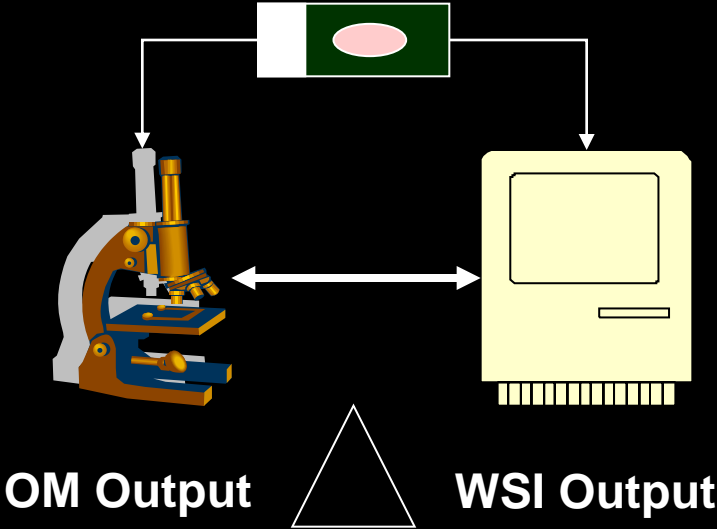
**Is it better?**

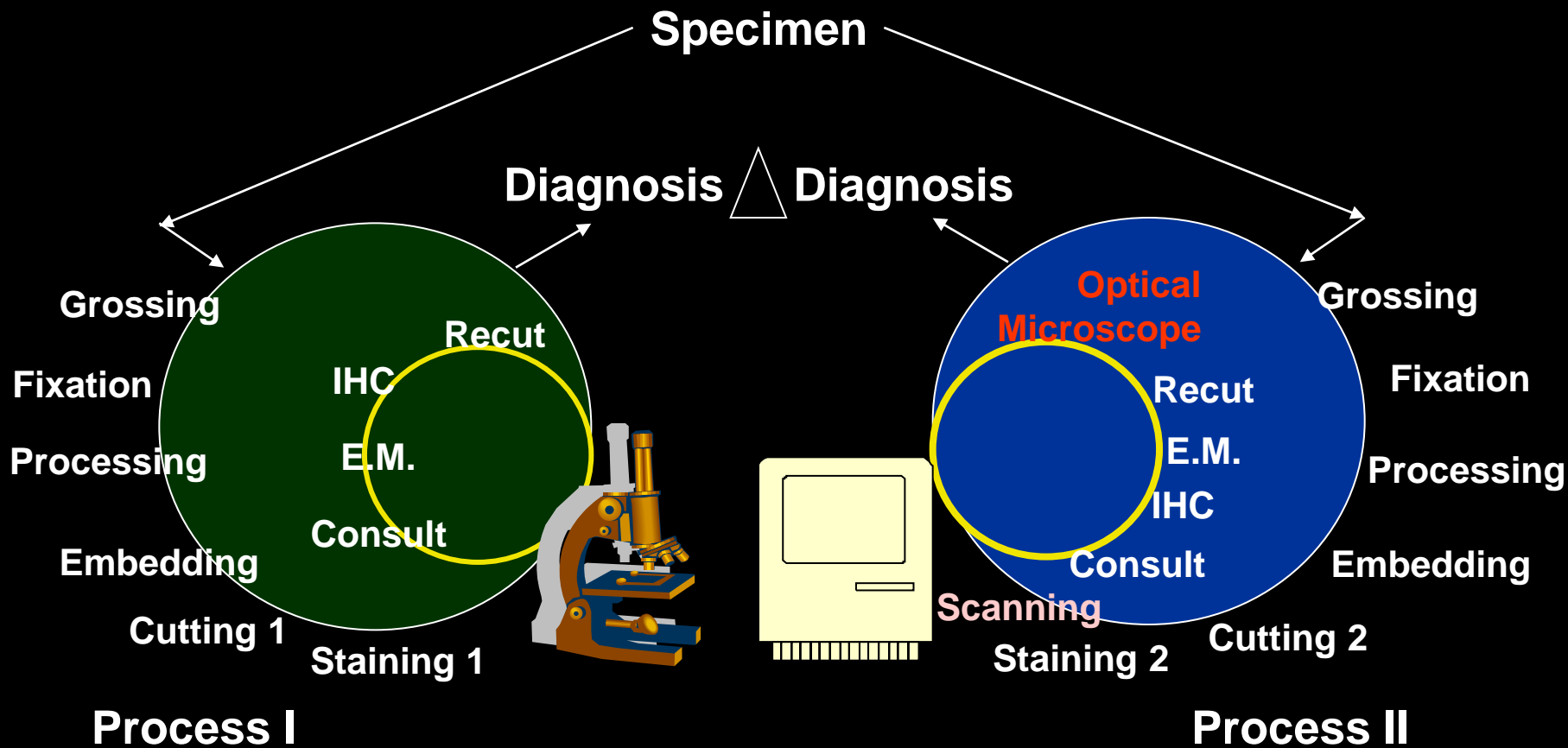
**Validation**

**Key**

**The experimental model will be different**

**From**





**Process I and Process II can be different**

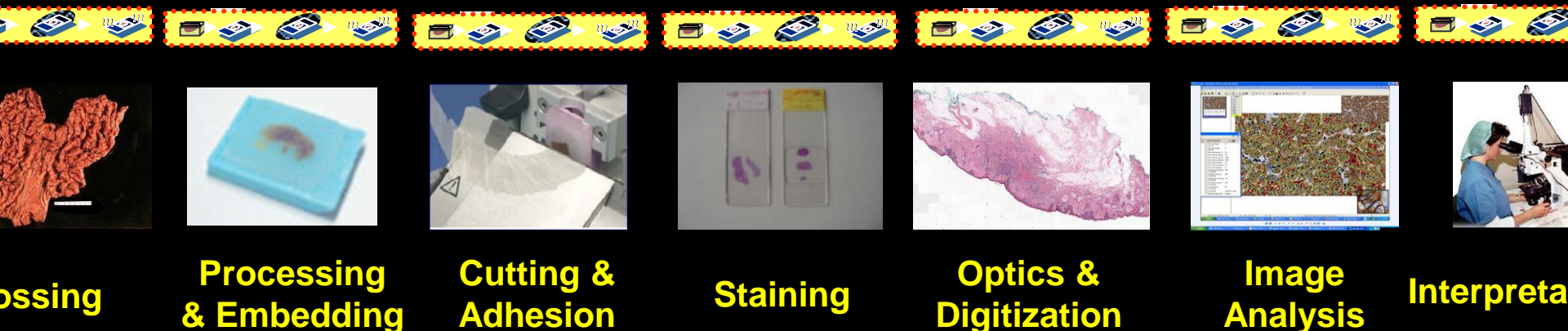
## **AP is changing in other ways**

**Automation**

**LIS Workflow**

**Digitization**

# Pathology Imaging Engine



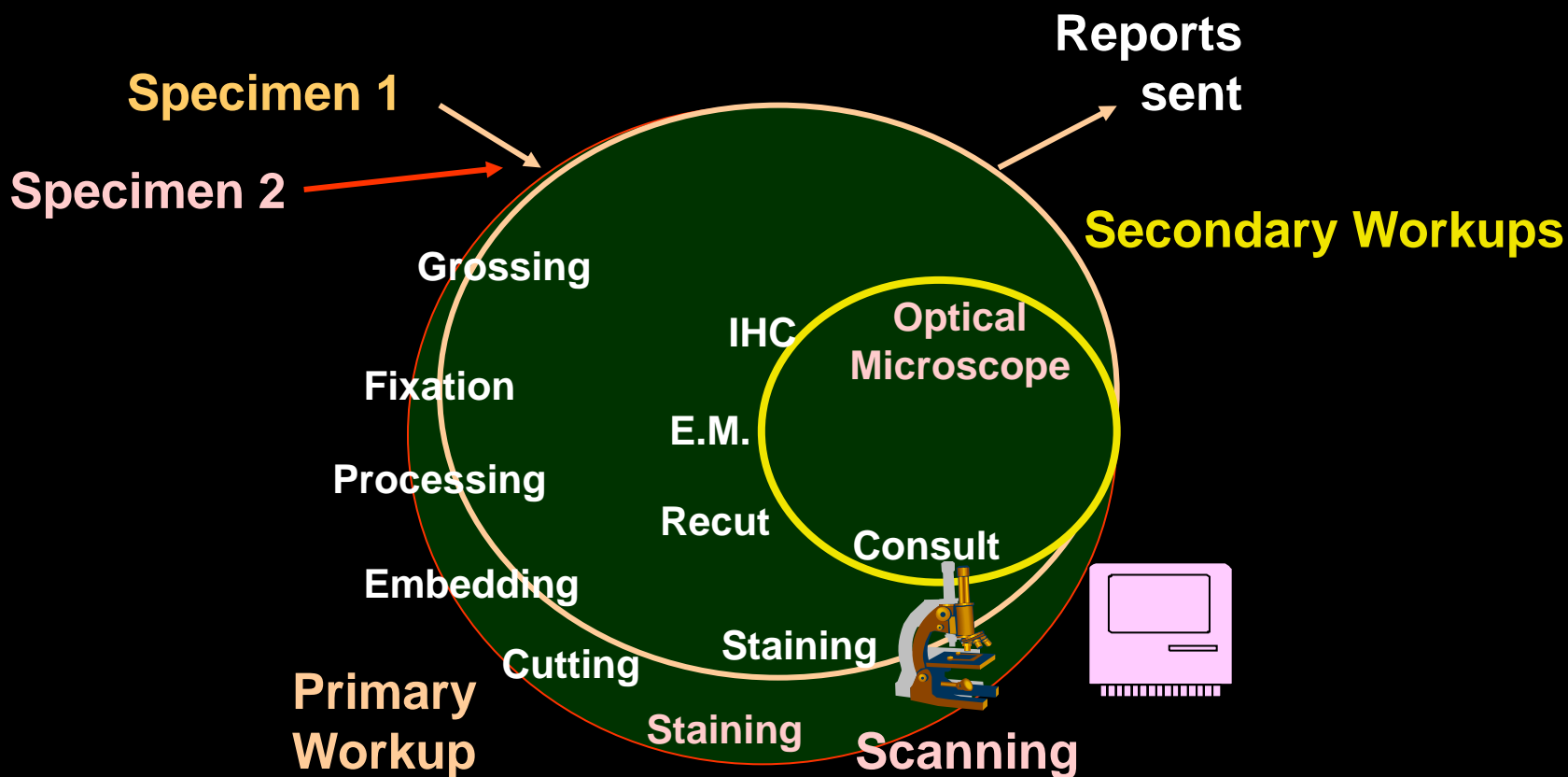
## Workflow and Dataflow Infrastructure (LIS)

Pathology imaging is both a physio-chemical and digital process

Each step affects image quality      Each can be modified for WSI

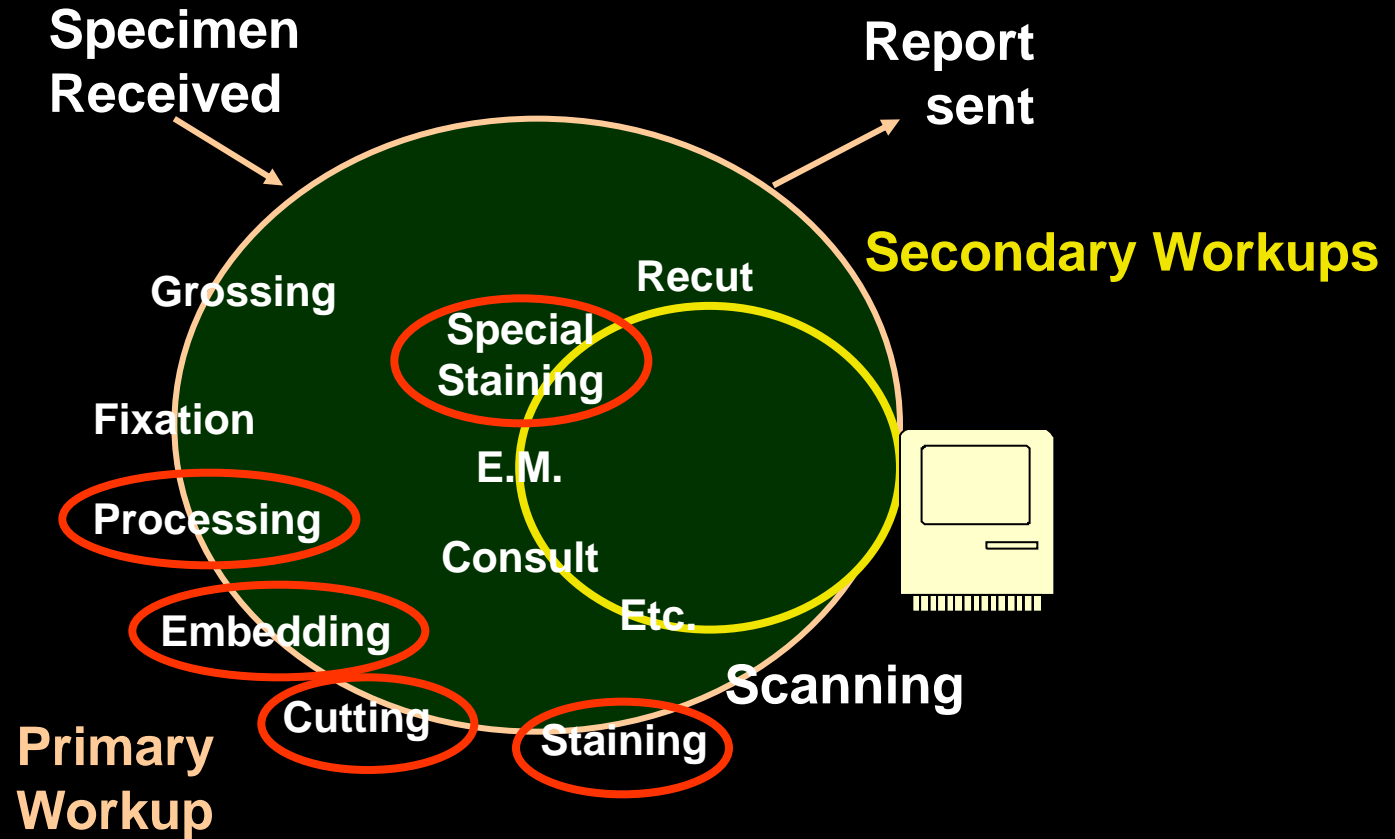
Automation should decrease variance

## Workflow and Dataflow Infrastructure (LIS)



**Modern LIS can impose different diagnostic workflows for different specimen types (or pathologists...)**

# DP enables quantitative QA in Histology

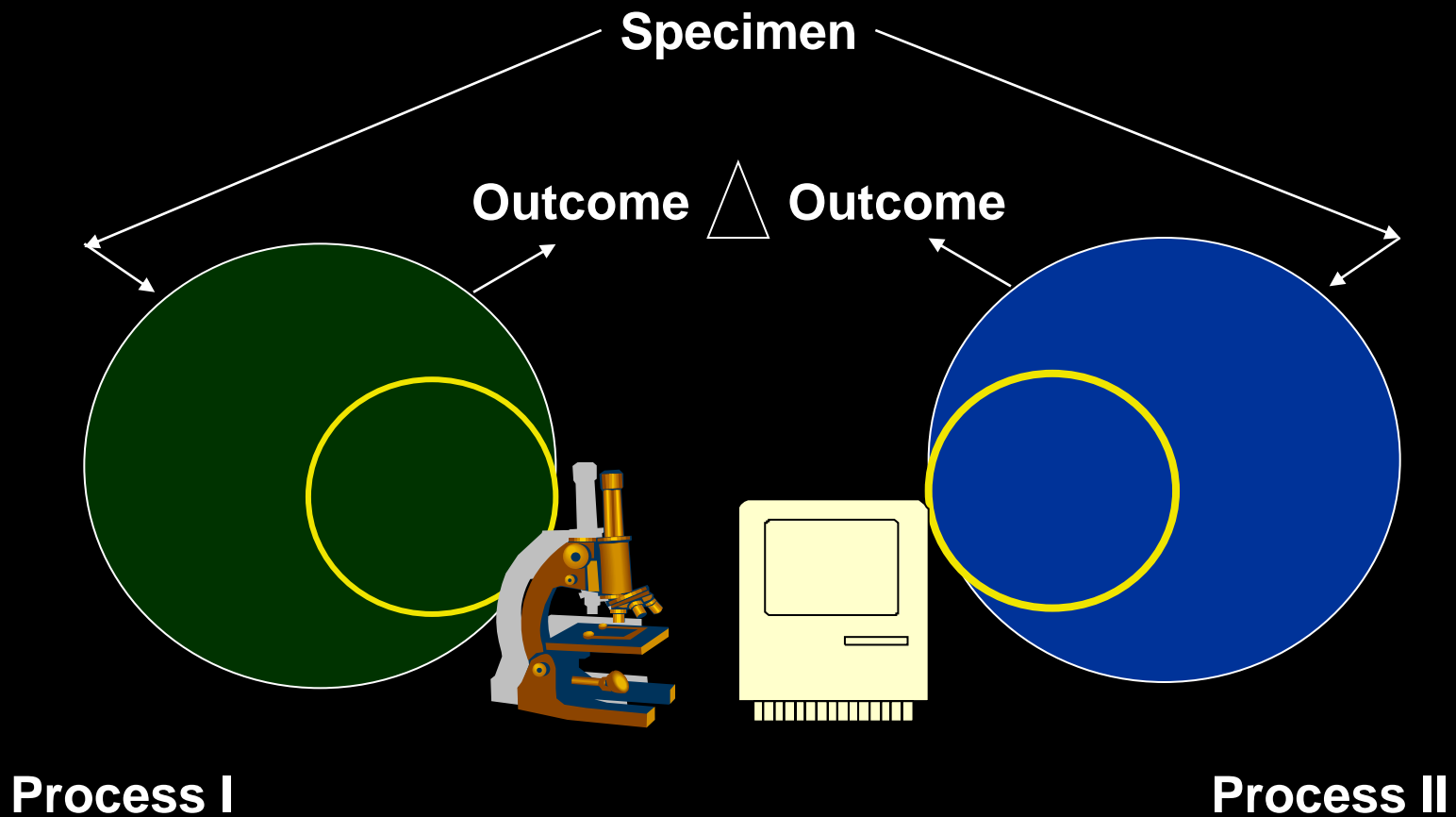


**LIS can collect much more process and quality data**

**LEAN**

**Six Sigma**

**cGMP**



**One may find that microscope is “better” than WSI  
But Process II has better outcomes**

**This should not surprise anyone**

**That is what WSI was designed to do**

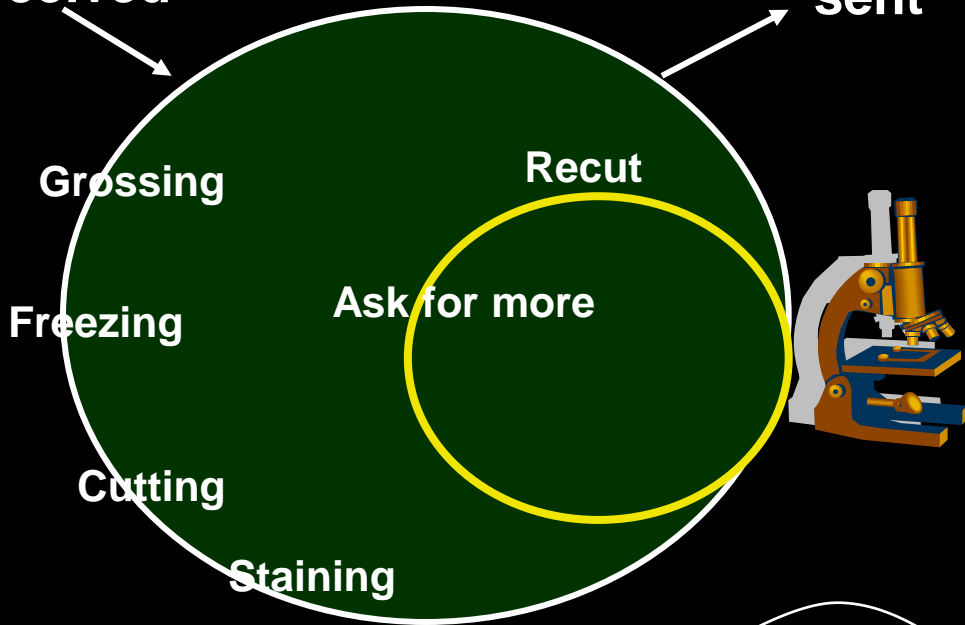
**That is what digitization always does**

**It even happened at the FDA advisory panel**

Specimen Received

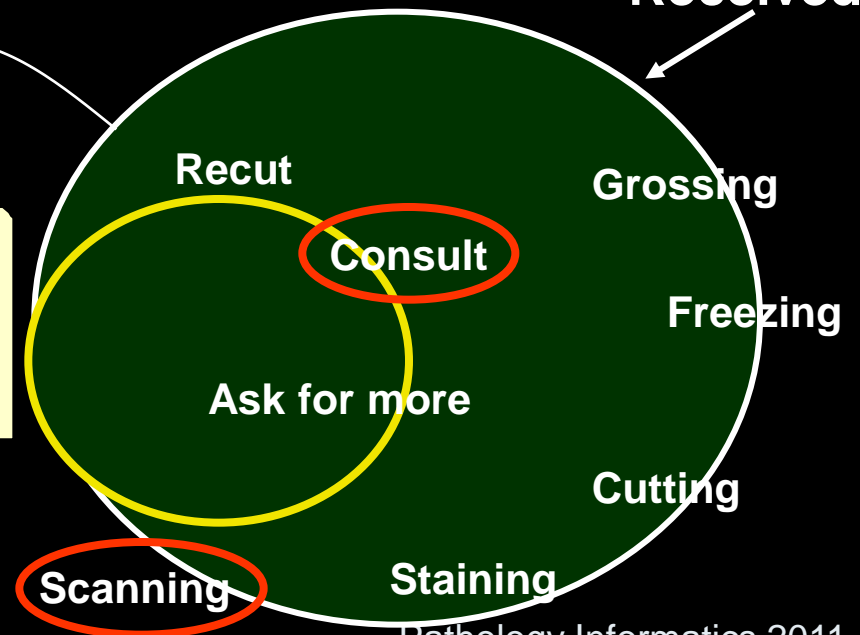
Report sent

WSI gave the pathologist more options



Specimen Received

Report sent



**What have we awoken**

**If Surgical Pathology is so important that WSI needs to be regulated as a type III device, why not the entire lab?**

# Pathology Imaging Engine



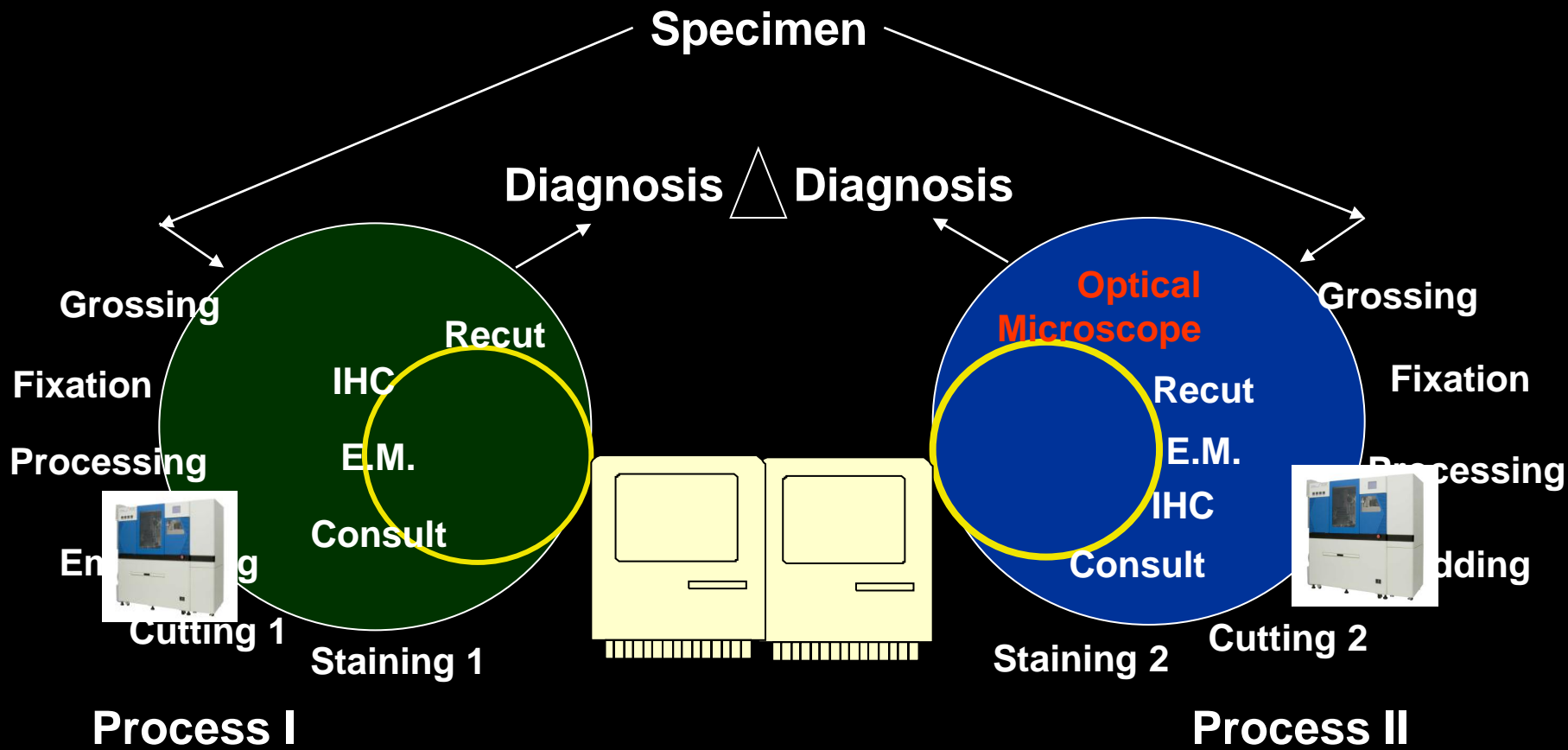
<b>Grossing</b>	<b>Processing &amp; Embedding</b>	<b>Cutting &amp; Adhesion</b>	<b>Staining</b>	<b>Optics &amp; Digitization</b>	<b>Image Analysis</b>	<b>Interpretation</b>

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## Workflow and Dataflow Infrastructure (LIS)

**Process**                      **Devices**                      **cGMP**

**LIS**



**There is precedent**

**Blood Bank as a biologic factory  
Blood Bank Equipment  
Processes (cGMP)  
Information Systems Class II**

**“Histopathology labs are like production lines”**

**“Surgical Pathology report as prescription”**

**“HIT software [systems] are medical devices”**

## **Sunquest and “LEAN QSR”**

**Initiative to incorporate FDA’s Quality System Regulation (QSR)  
(21 CFR Part 820) in Class I systems**

**“using FDA quality requirements so that their Class 1  
solutions will meet the quality requirements of their  
Class 2 systems”**

## Summary

I hope it wasn't to dry

**FDA is considering a Type III (PMA) status for WSI primary dx**

**Developing studies to prove safety and efficacy  
across such wide field as surgical pathology is challenging**

**No matter what is decided, will be need for  
serious validation in by the individual labs**

## **Summary**

**WSI is not simply a fancy microscope, it is one of a number of agents that have the potential to change diagnostic workflow in very positive ways**

**These potential workflows will also require validation**

**If WSI needs to be regulated, then one can argue that the laboratory itself is potential target of regulation**

**There is precedent**

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