Standards, Validation and Regulation

Relevance for Digital Pathology

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Advancing Diagnosis and Discovery

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

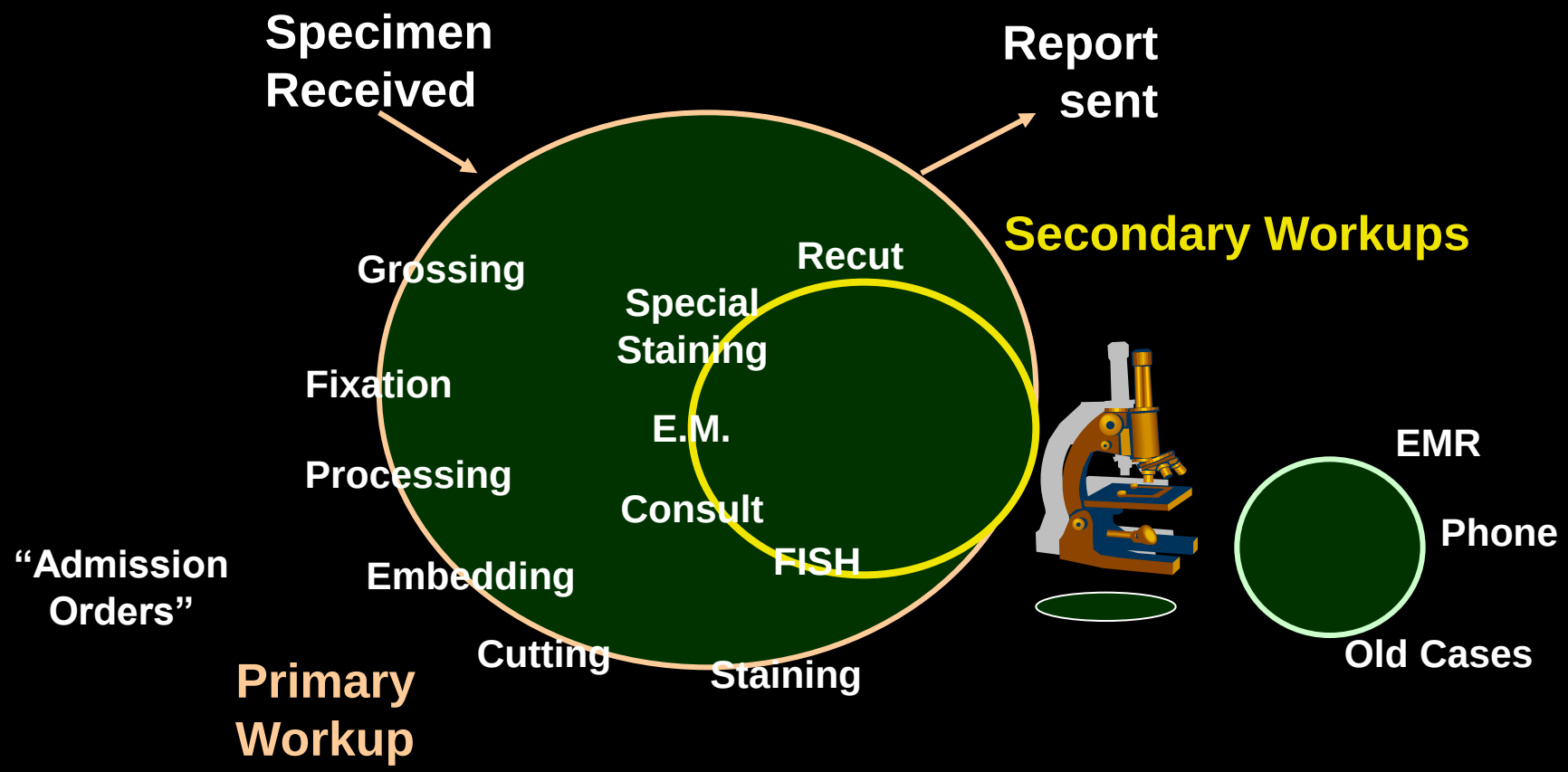
Q: Should there be minimal technical or clinical requirements for telepathology?

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

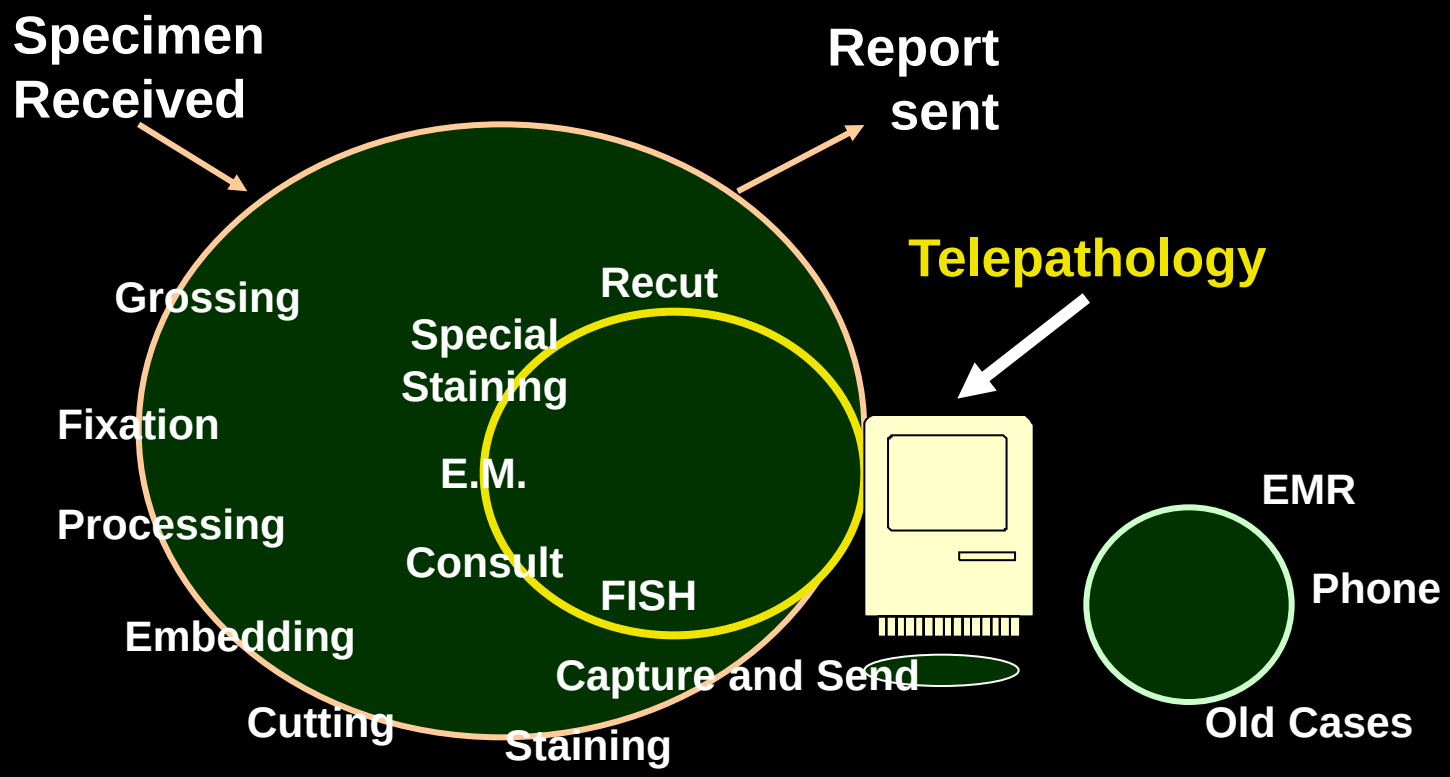
Image quality

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
"Would you be on a panel?"

"OK"

Mail
(articles to read)
(forms to sign)

Airplane

Hotel
(meet Panel)
(forms to sign)

Scan" October 26 2009

Meeting begins
(multiple witnesses)
(you listen)

Car **Airplane** **Home**

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)

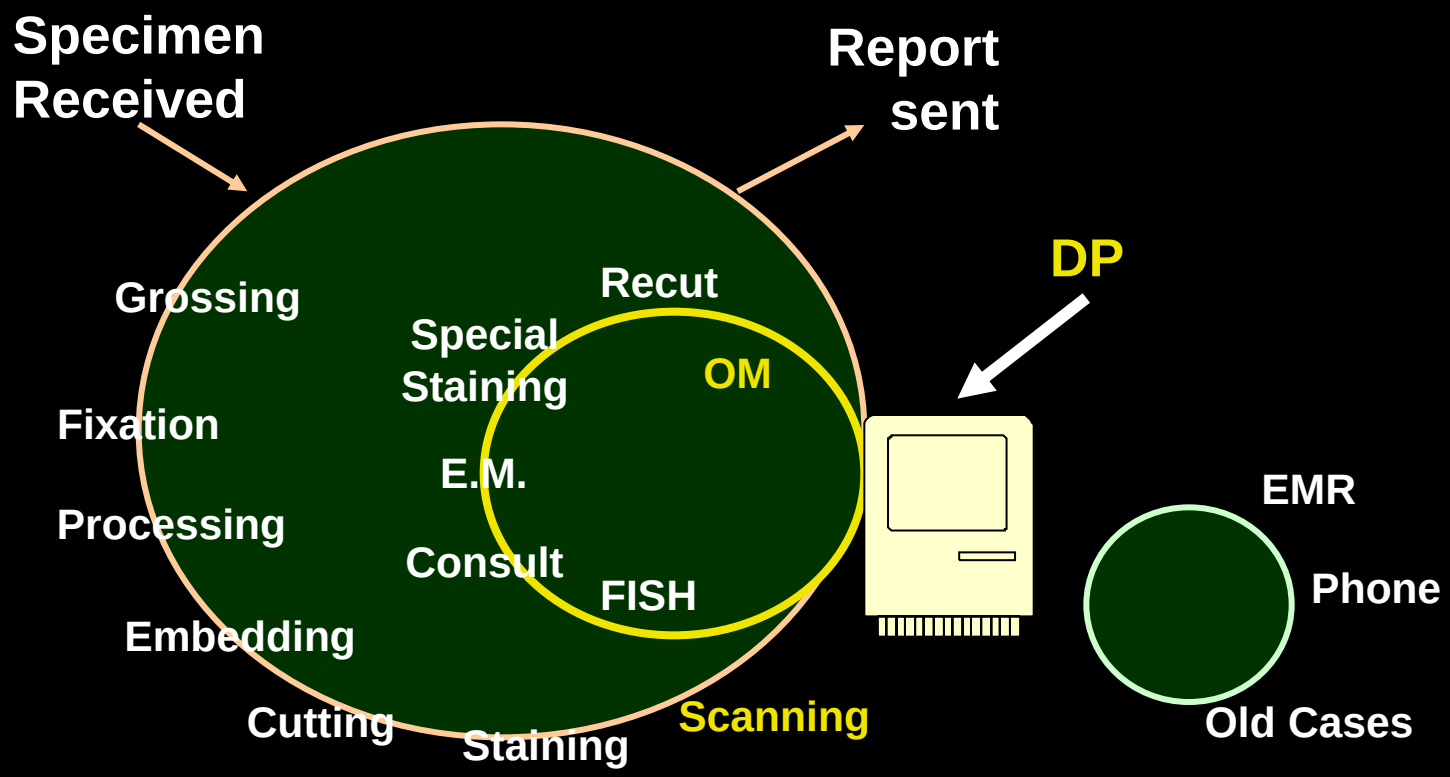
The FDA was interested in a specific use of DP

“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 option 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)

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

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

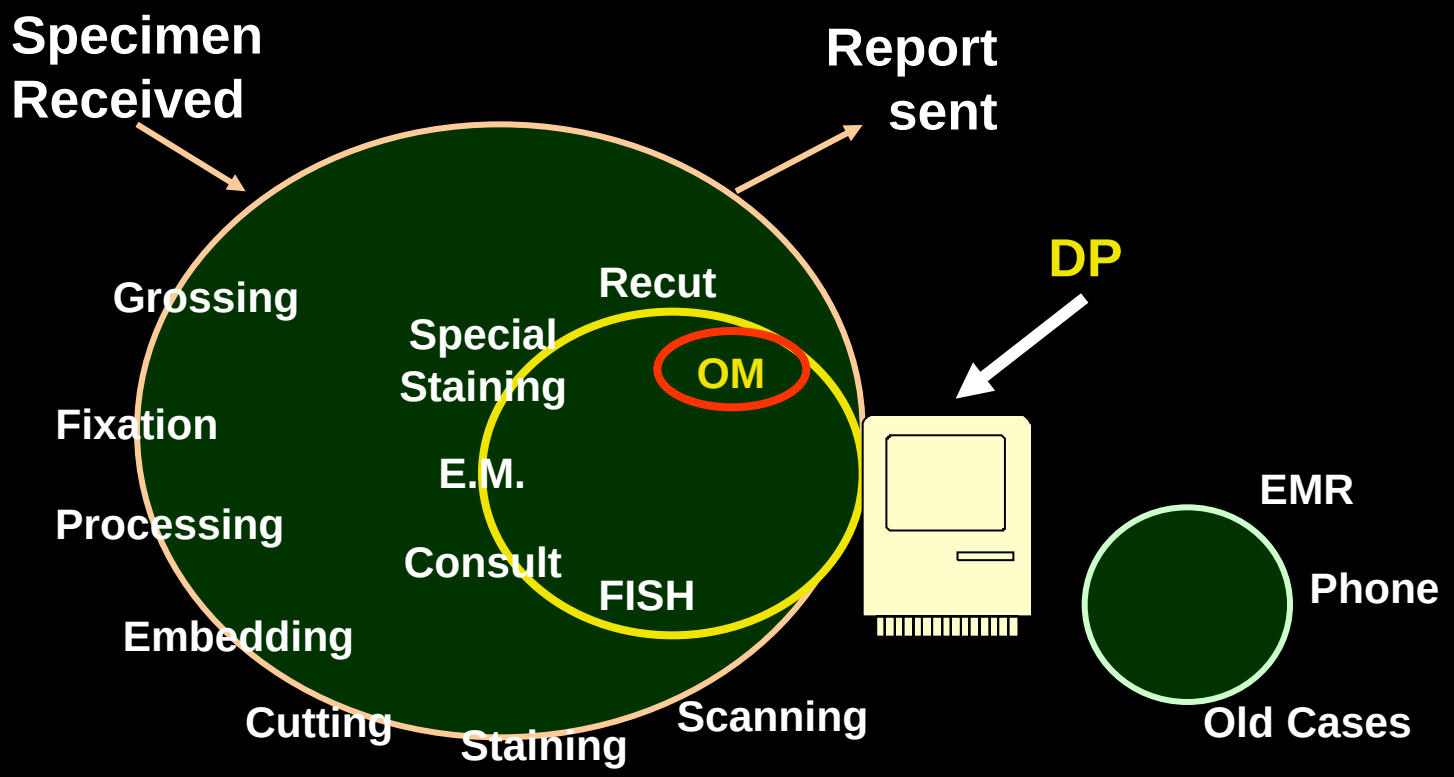
Note

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)

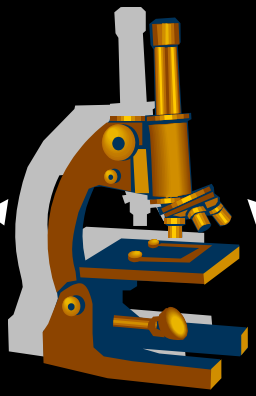
Digital Mammography as a model for Digital Pathology

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

Mammography	Pathology
Digitizing an existing process	Digitizing an existing process
Screening test	Diagnostic test
Grey on Grey	Staining
Responsibility of Radiology	Responsibility of Pathologist

Regulation of procedures

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



Truth Panel

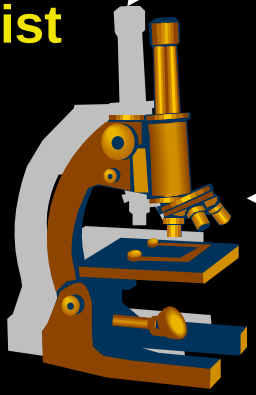
What is the truth?

Case mix?

Specimen Preparation

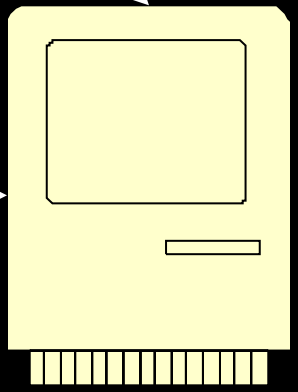
What Pathologists?

Pathologist



What is Measured

Diagnosis Features?



Pathologist

Wash out?

What is Measured

What is compared?

Top line? full field? confidence?

What is allowed?

Special stains? Recuts? Deferment?

What is allowed?

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

Features

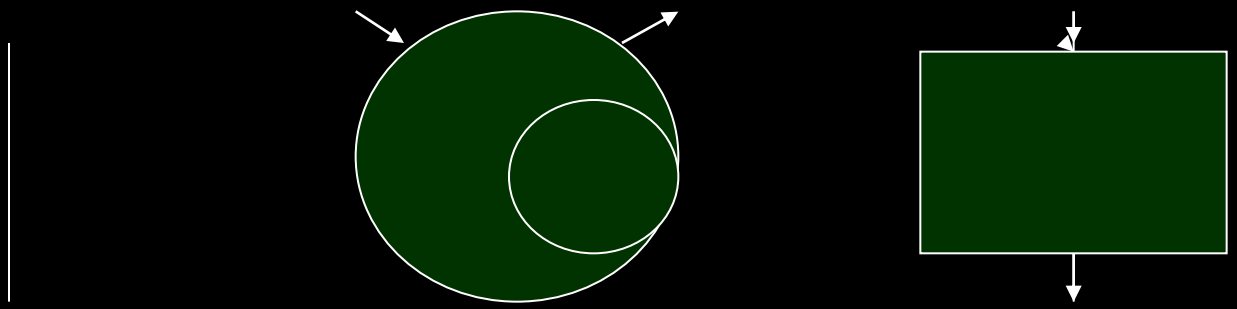
Diagnoses

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

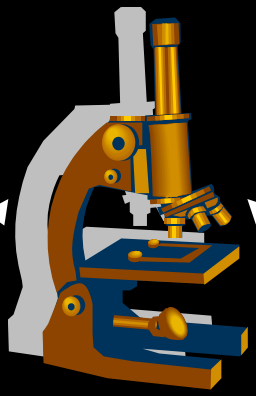
So what will happen?

(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



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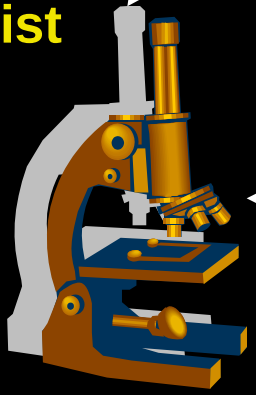

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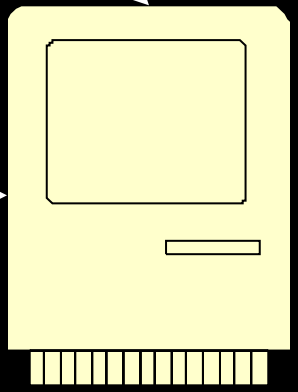

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What is allowed?

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

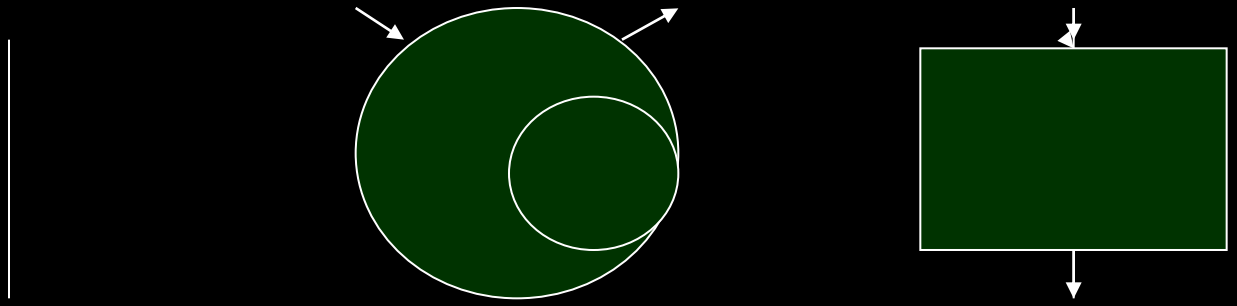
Limitations on integration

Rate of development

…

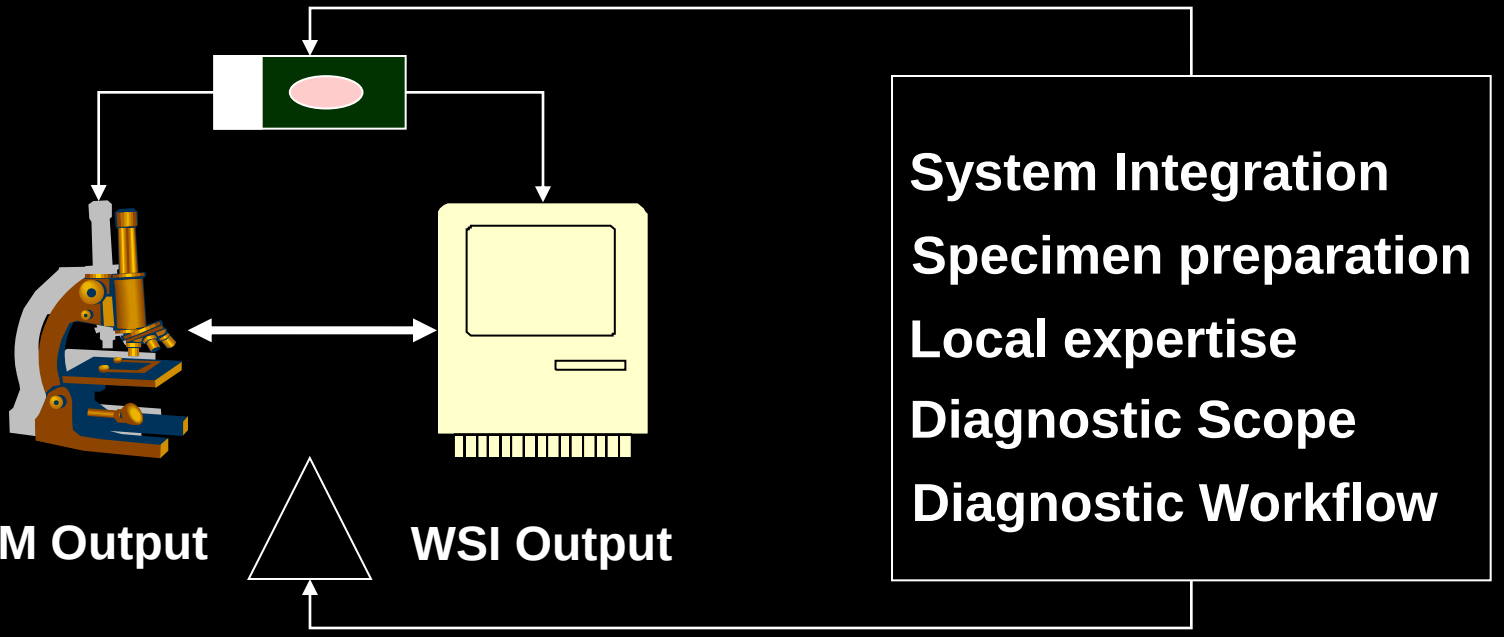
(Cytology Systems) **(Blood Bank Systems)**

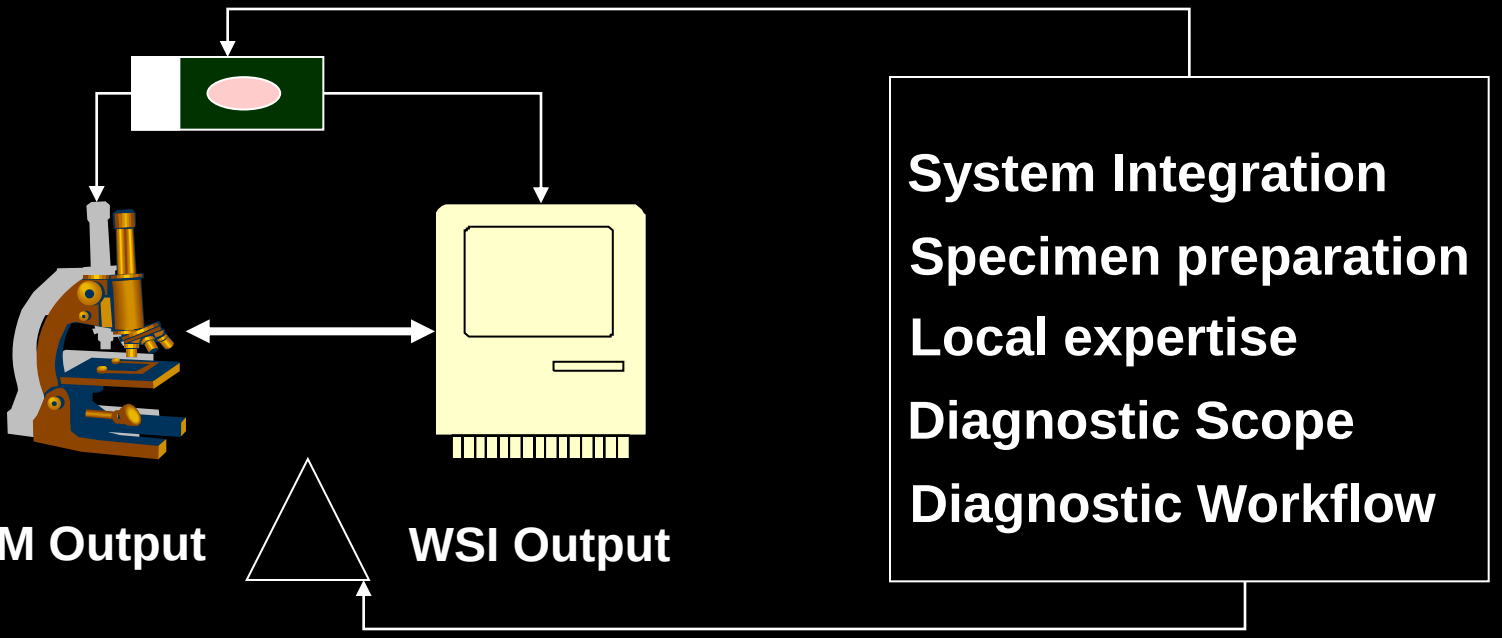
Validation



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



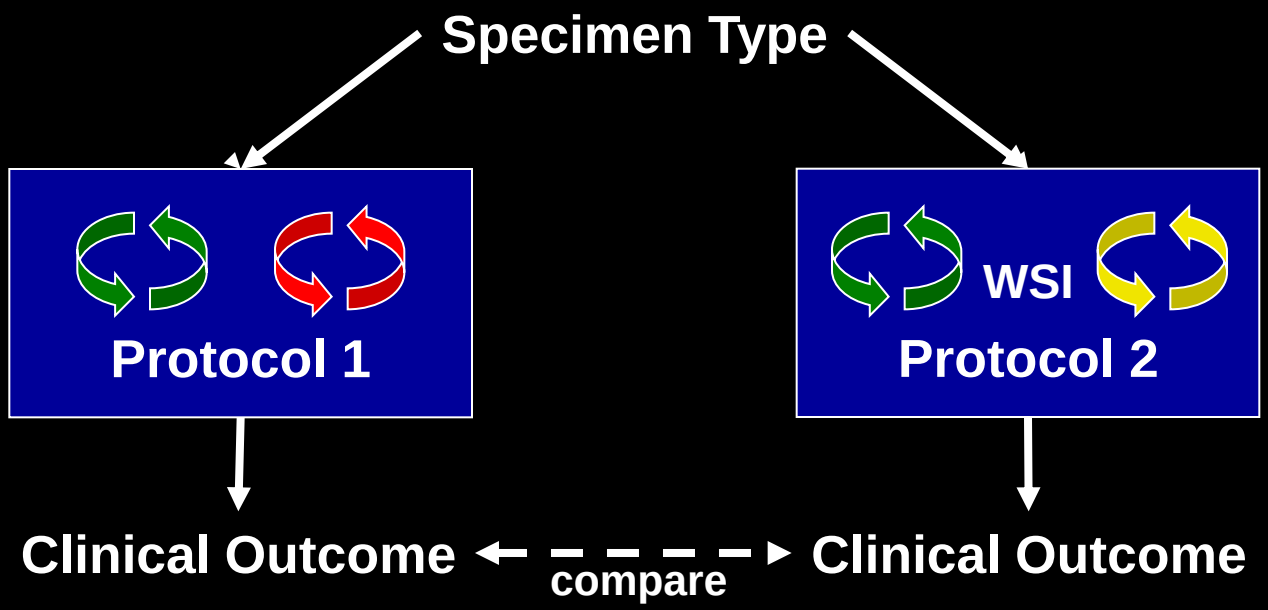


Demonstrating that WSI can be diagnostic equivalent to "OM"
Mano on mano is important…

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

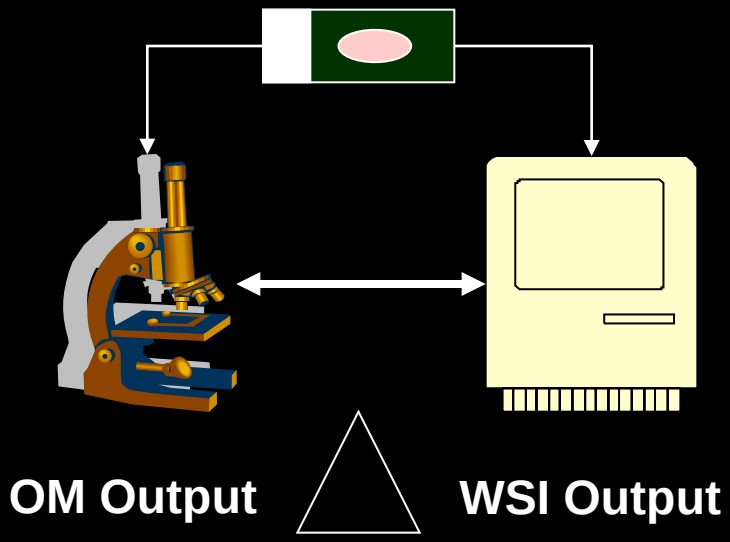


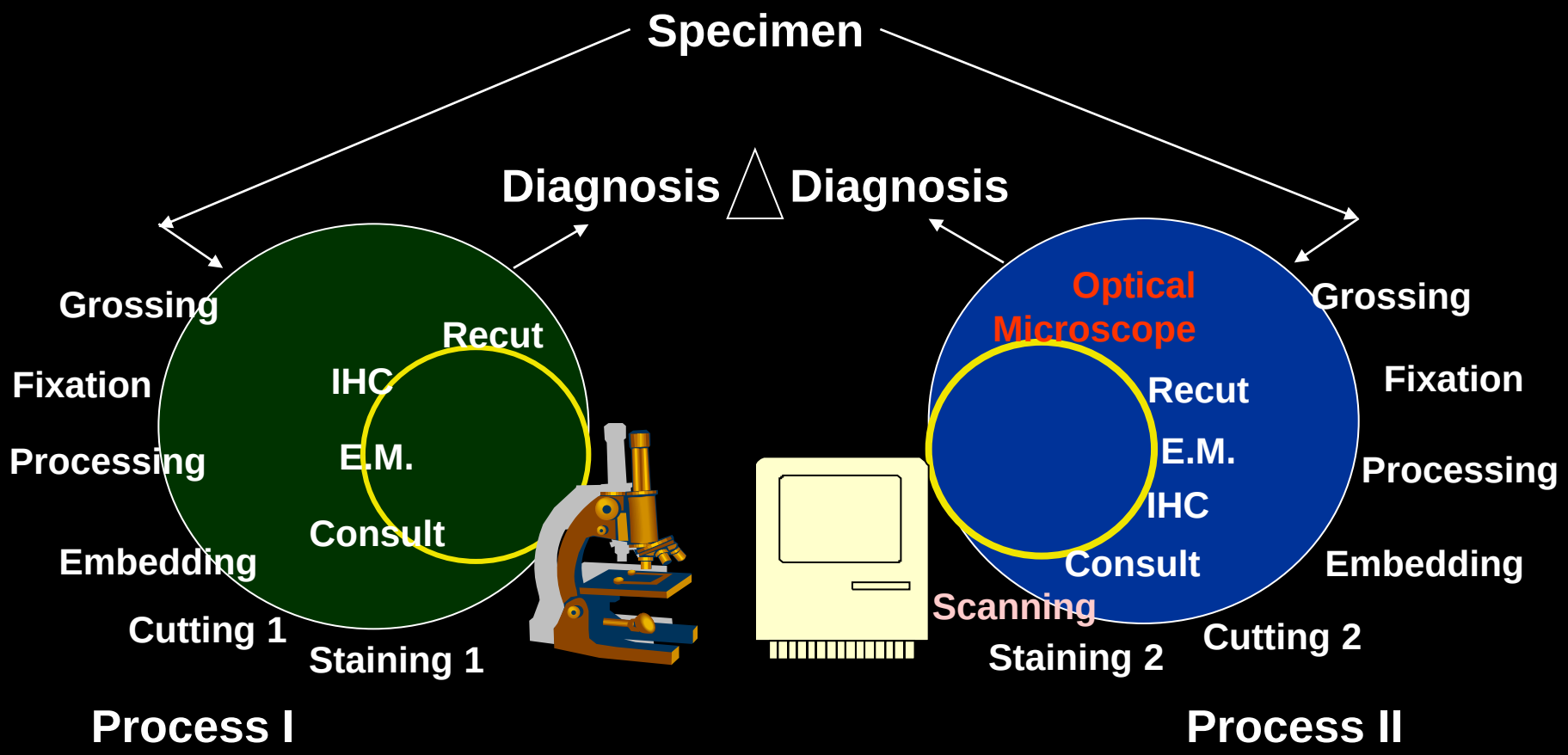
Does this work? **Is it better?**

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

ossing | Processing & Embedding | Cutting & Adhesion | Staining | Optics & Digitization | Image Analysis | Interpreta

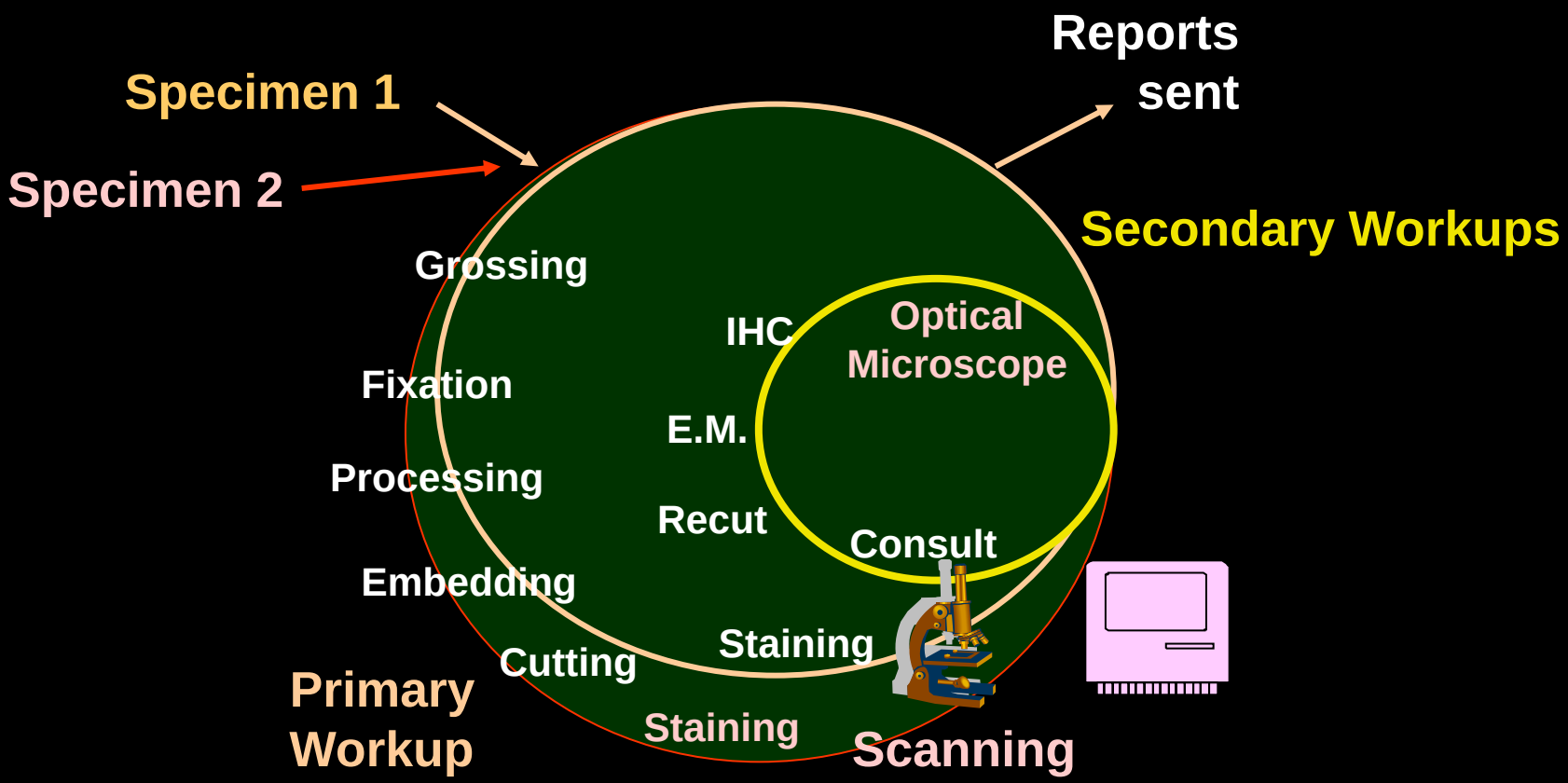
Workflow and Dataflow Infrastructure (LIS)

Pathology imaging is both a physio-chemical and digital process

Each step affects image quality Each can be modified for WSI

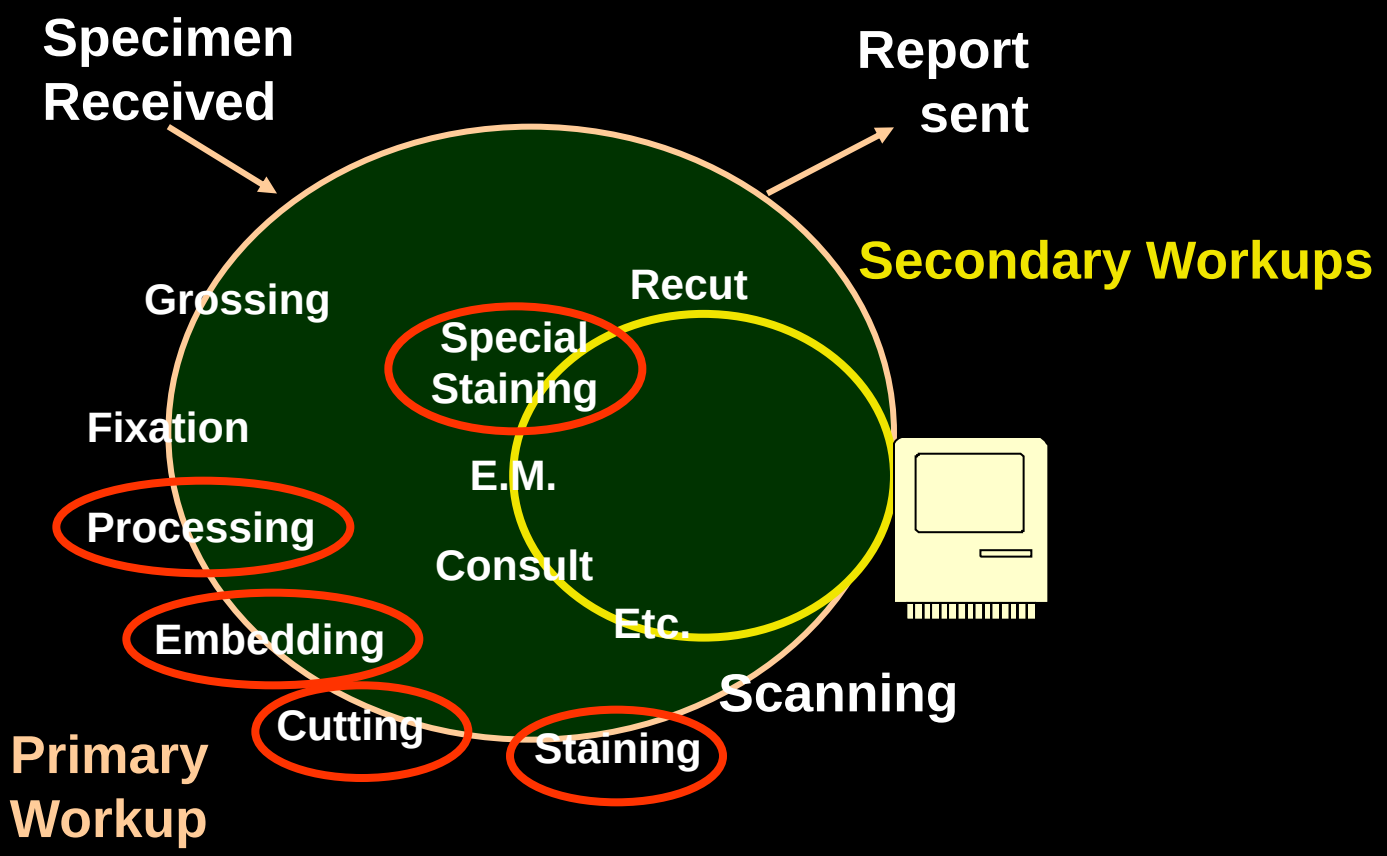
Automation should decrease variance

Workflow and Dataflow Infrastructure (LIS)



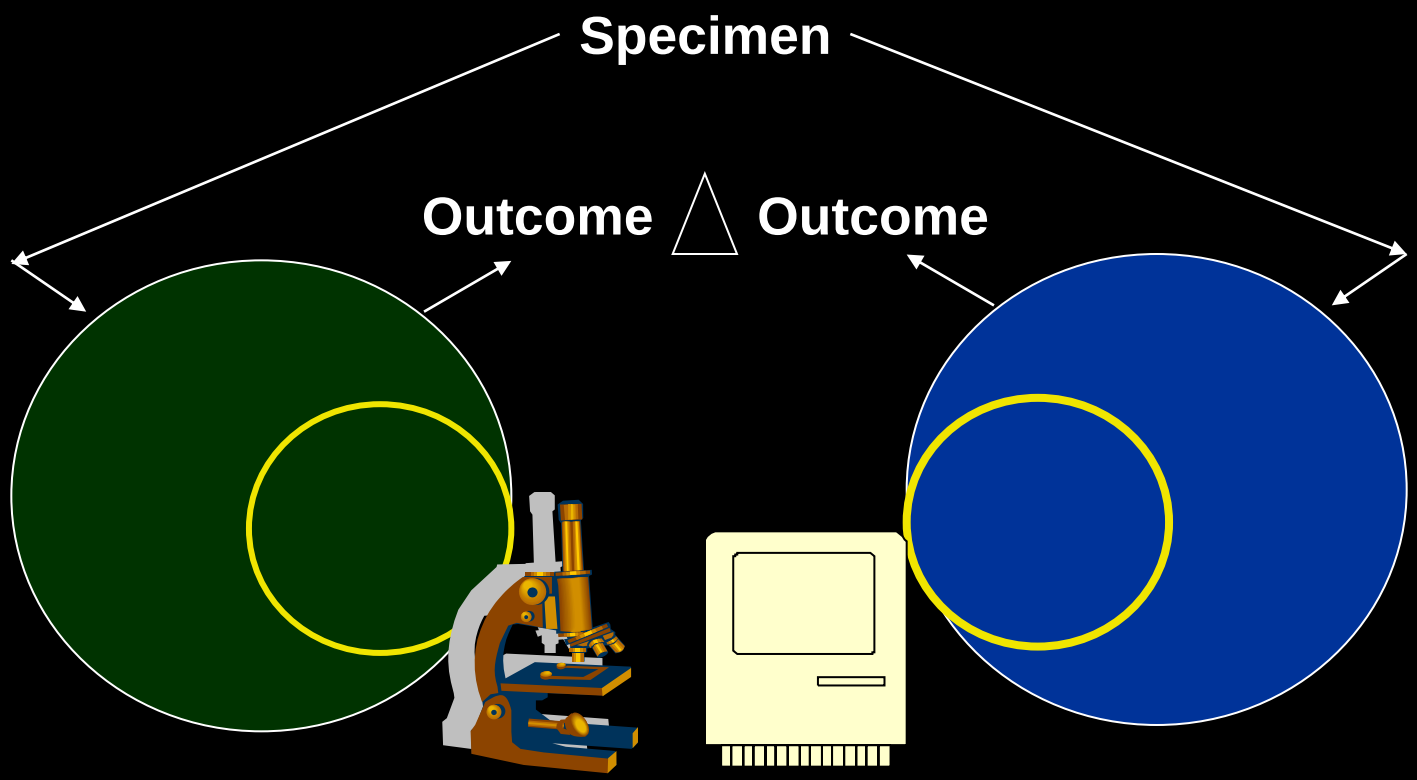
Modern LIS can impose different diagnostic workflows for different specimen types (or pathologists…)

DP enables quantitative QA in Histology



LIS can collect much more process and quality data

LEAN **Six Sigma** **cGMP**



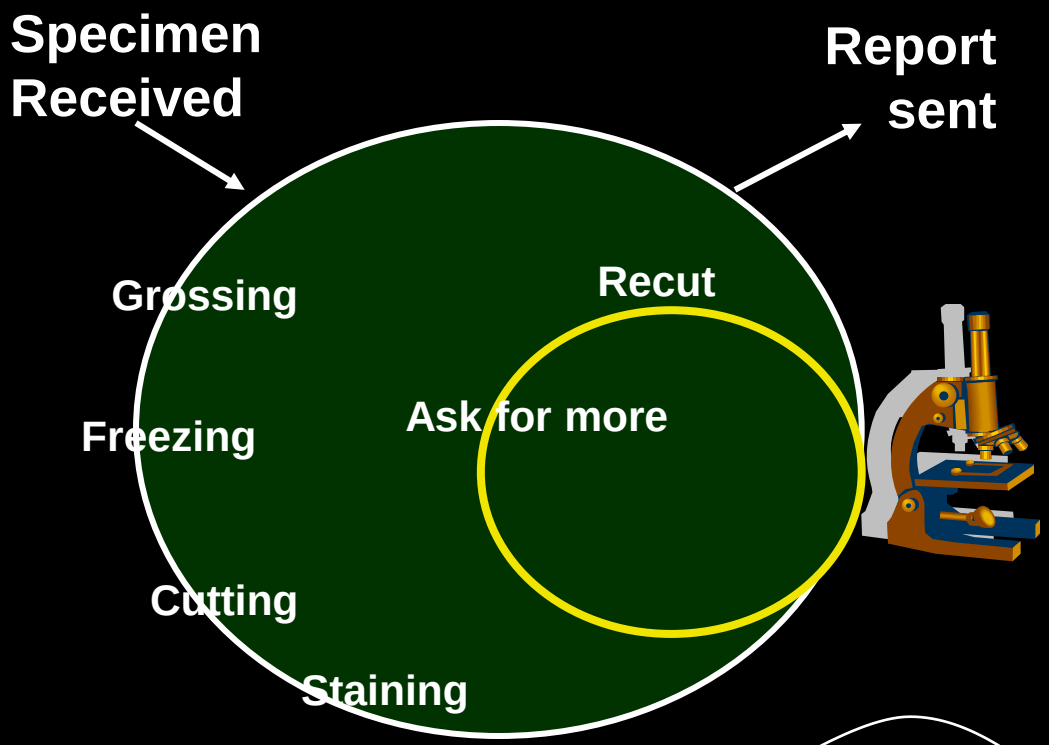
One may find that microscope is "better" than WSI
But Process II has better outcomes

This should not surprise anyone

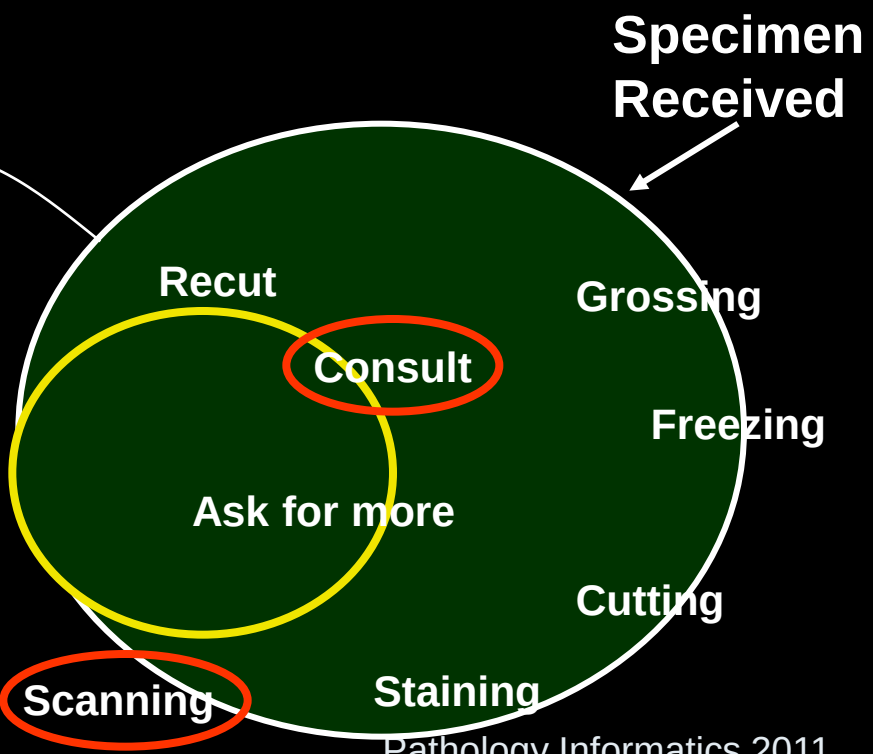
That is what WSI was designed to do

That is what digitization always does

It even happened at the FDA advisory panel



WSI gave the pathologist more options



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

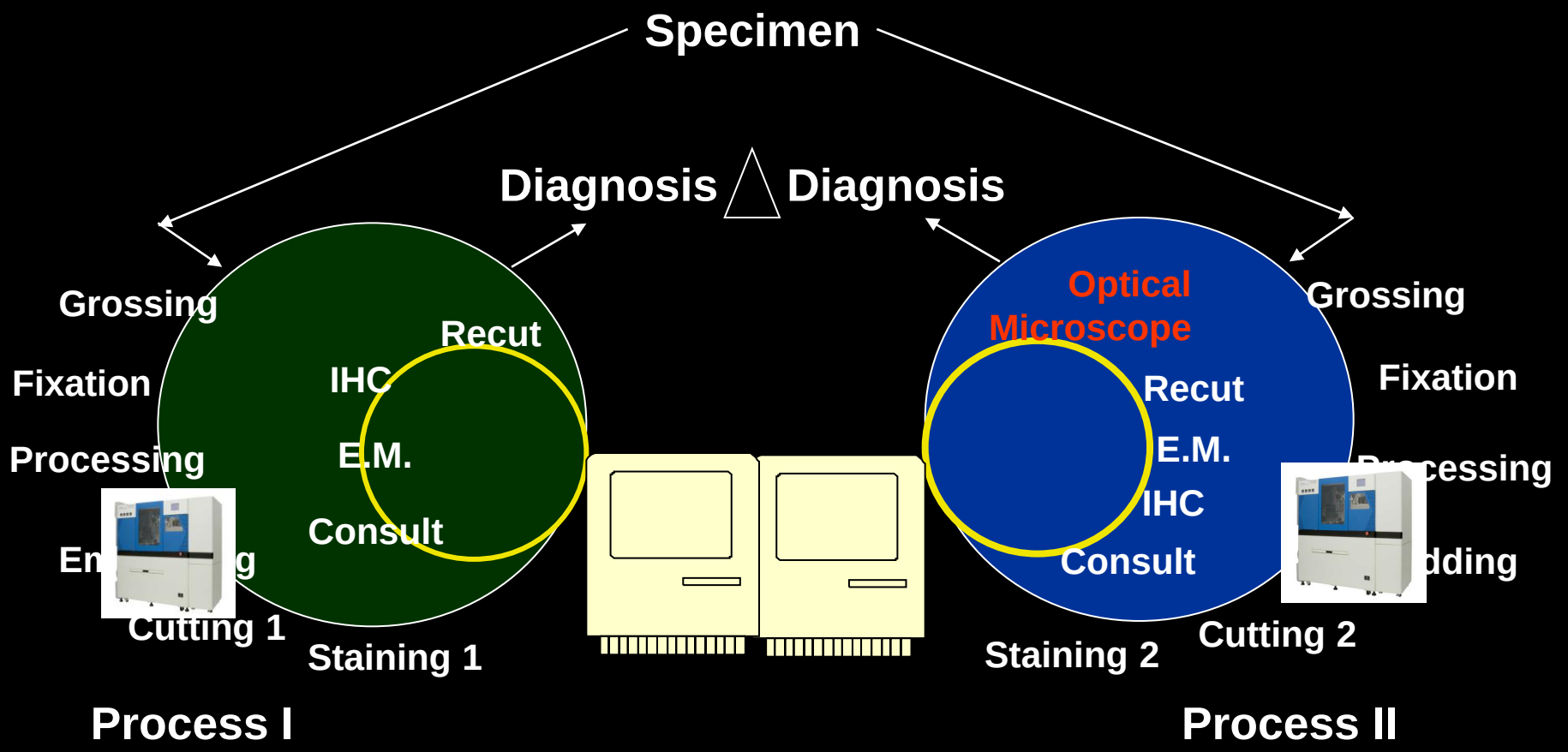
ossing | Processing & Embedding | Cutting & Adhesion | Staining | Optics & Digitization | Image Analysis | Interpreta

Workflow and Dataflow Infrastructure (LIS)

Devices

Process **cGMP**

LIS


Specimen
Diagnosis
Diagnosis
Grossing
Fixation
Processing
Recut
IHC
E.M.
Consult
Cutting 1
Staining 1
Process I
Optical Microscope
Recut
E.M.
IHC
Consult
Grossing
Fixation
Cutting 2
Staining 2
Process II

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 CRF 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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