

Digital Pathology in Europe: Coordinating Patient Care and Research Efforts

Virtual microscopy scanning technology



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COST Action IC0604 WG 4

Technology and Automation in Pathology

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Factors that affect performance of the imaging system

- During image acquisition:
 - Camera
 - Illumination source
 - Optical performance of the stains
 - Presence and degree of multiplexing (multicolour IHC)
- After image acquisition:
 - Appropriate mathematical techniques to extract quantitative intensity and area measurements from the imaging data
- Validation of automated image analysis:
 Lejeune M, et al. Quantification of diverse subcellular immunohistochemical markers with clinicobiological relevancies: validation of a new computer-assisted image analysis procedure. J Anat. 2008 Jun;212(6):868-78.

Pre-Scanning phase

- Compatible slide glass
- Slide handling (trays)
- Slide loading
- Barcode Reader
- Focuses quickly and accurately on the specimen:
 - Whole region autofocus
 - Focusing some points of the whole region
- Automatically skips the area which has no tissue
- Slide Setup time

Sensor (Camera)

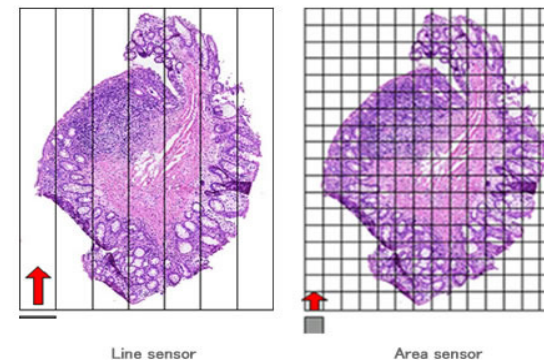
- Greyscale cameras and filter wheels
- Standard RGB colour cameras (usual in brightfield)
 - Single-chip, Bayerpattern red-green-blue (RGB) cameras generate imaging artefacts (edges)
 - 3-CCD: Better spatial fidelity. Sensor 1/2", 3 CCD, 1360 x 1024 pixels

Camera

- **Problems con RGB detectors (why multispectral imaging is necessary):**
- Colour values can vary significantly with the colour temperature of the illumination source
- Different camera chips have differing spectral responsiveness
- Limitations to its ability to distinguish between similar chromogens
- In theory, it is impossible to unmix more than three chromogens with an RGB sensor
- In practice, it has proven extremely difficult to unmix brown from red from blue

Scanning phase

- Objective lens (see details)
- Spatial resolution
- Scanning method
 - Area sensor (CCD)
 - Line sensor
 - Time Delay Integration (TDI)
- Automatic/manual Scanning
- Z-stack scanning
- Scanning time
- Focus Accuracy with high powered lens
- Lens aberration
- Anti vibration performance
- Fluorescence scanning



Line sensor

Area sensor

Objective lens and sensor

- Spatial Resolution (Pixel Size in Image Plane)
 - At 20x: 0.223 μ m/pixel
 - At 40x: 0.162 μ m/pixel
- Sampling Efficiency (Pixels per Optical Resolution)
 - At 20x: 1.92 pixels (96% of Nyquist)
 - At 40x: 2.3 pixels (115% of Nyquist)
- **Numerical Aperture (Objectives Optical Resolution)**
 - 1.25x PLAPO 0.04NA, 8.39 μ m
 - 10x UPLSAPO 0.40NA, 0.839 μ m
 - 20x UPLSAPO 0.75NA, 0.447 μ m
 - 40x UPLSAPO 0.95NA, 0.353 μ m
 - 60x UPLSAPO 1.35NA, 0.249 μ m

Post-Scanning phase

- Image processing algorithm, that makes a whole image with no dividing lines
- Image Compression
 - No compression (RAW, BMP)
 - JPEG with compression
- Slide format
 - JPEG
 - JPEG2000
 - TIFF
 - BMP

Digital microscopy (virtual slide) solutions

- ACIS (Dako)
- Applied Imaging Ariol (Genetix)
- Bliss HD (Bacus Labs/Olympus America)
- Dotslide 2.0 (Olympus)
- DX-40 (Dmetrix)
- iScan (BioImagene)
- MIRAX Scan (3DHistech / Zeiss)
- Nanozoomer (Hamamatsu)
- ScanScope (Aperio)
- SNC400 (Leica)
- Vassalo/Toco (Claro)
- Others: A. Menaniri Diagnostics

- Viewers and platforms:
- Digital SlideBox (SlidePath)
- mScope (Aurora MSC)
- Omnyx (GE)
- Philips (Integration)
- PathPACS® (Apollo)

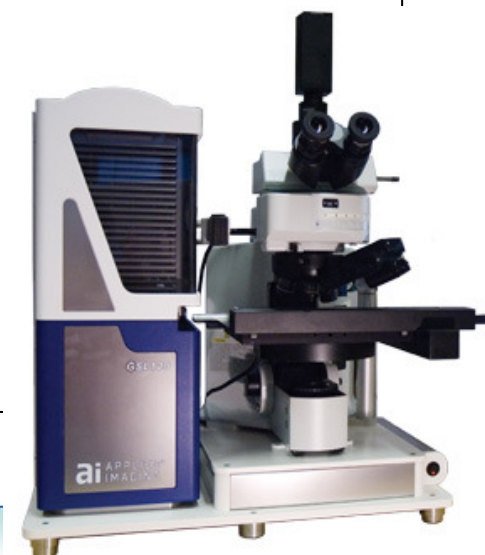
ACIS III (automated cellular imaging system)

- Slide scanning speed: 15 x 15 mm, 10x, 9 minutes
- Objectives: 4x, 10x, 20x, 40x, 60x
- Automatic tissue finding
- Detects levels of hue, saturation, and luminosity
- Nuclear, Membrane, Cytoplasmic, rare event, TMA
 - FDA Clearance on HercepTest™, ER and PR Applications
- Network: Dako EyeShare software
- Daily calibration

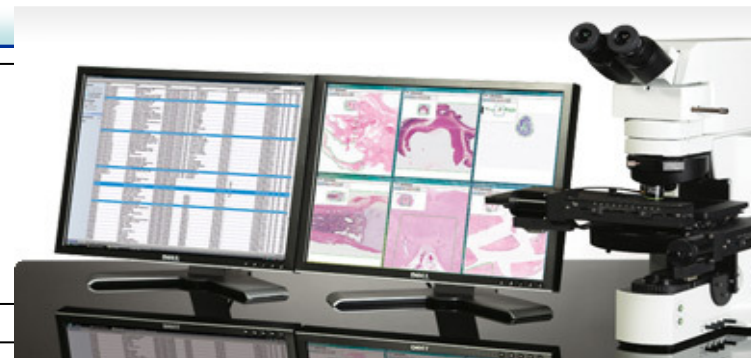


Genetix Applied Imaging Ariol

- Brightfield and fluorescent imaging,
- IHC, FISH, Immunofluorescence, Micrometastasis, Angiogenesis, DNA Ploidy, and Tissue Micro Array.
- Ariol Microsight (Cellular Rare Event)
- Hersight (for HER-2/neu)
- ER, PR, and PathVysion®
 - CytoVision (Cytogenetics)



Olympus BLISS HD (High definition)



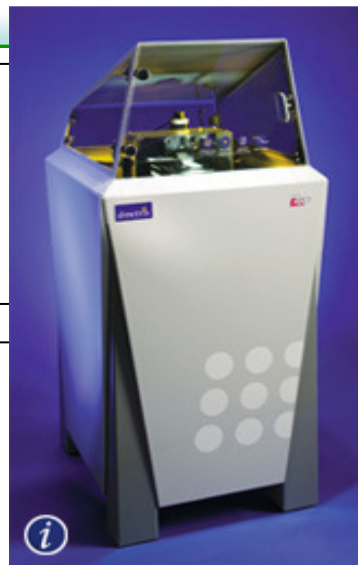
- Olympus America with Bacus Laboratories
- Single slide
- 20x and 40x, with an option for 60x oil (20x/0.75NA 0.223um/pixel; and 40x0.95NA → 0.162um/pixel)
- Color Digital Camera 1/2", 3 CCD. 1360 x 1024 pixels
- Automatic/manual scanning modes
- Virtual-Z, multiple z-plane scanning (9 Z-planes)
- WebSlide: Server, Viewer and Database software
- SlideTray software

Olympus Europe dotslide 2.0

- Models:
 - dotSlide MD, manual version;
 - dotSlide SL, fully automated version with slide loader;
 - dotSlide TMA, with tissue microarray module
- Olympus BX51 microscope
- Up to 15 Z-planes (Virtual Z)
- User can also set focus points manually
- Fluorescent-compatible
- New sharpness filter for the dotSlide camera
- Net Image Server (NIS) SQL database, JPEG2000,...



Dmetrix DX40



- Array-microscope technology
- Scans a slide in under one minute
- 40 slides/hour
- Fully automated operation
- On-board image server
- Slipstream® slide loader. Magazines, each 40 slides
- Viewer application digitalEyepiece

Bioimagene iScan



Input format	1in x 3in (25mm x 75 mm) Microscope Slides
Optional large slide	2in x 3in (50mm x 75mm) Microscope Slides
Slide Capacity	1 to 160 slides (1 to 80 large slide format) using 8 integrated standard Sakura™ racks
Microscope Objective	Olympus™ 20x/0.50 Plan Fluor (Nikon™ 20x/0.50 Plan Fluor)
Optional Objectives	Olympus™ 40x/0.75 Plan Fluor (Nikon™ 40x/0.75 Plan Fluor)
Scanning Resolution	0.46um/pixel @ 20x or 0.23um/pixel @ 40x
Barcode capability	1D and 2D option
Light Source	Integrated LED
Auto-Scan	Automated barcode reading, tissue identification, auto focus, scanning and JPEG 2000 compression for up to 160 slides
Manual Scan	User select scan area for single or batched slides with automated or manual naming
LCD	5.5" Diagonal Full Color Display (320 x 240 Resolution)
Slide Analysis	Fully integrated with all Biomagene image analysis/storage/collaboration software
Scan Viewing	24-bit true color
Slide Storage Format	JPEG 2000
Dimensions	18" W x 18" D x 17" H (45mm W x 45mm D x 41mm H)
Weight	~ 50 Lbs (23 Kg)
Power	110-220 VAC, 50/60 Hz, 150 Watts
Compliance	CE, CSA, UL

Hamamatsu



- NanoZoomer
 - up to 210 slides
 - 4096 x 64 pixel CCD continuous scan technology
 - virtual slide in about 4 minutes at 20x
 - both brightfield and fluorescence (FITC, Texas Red, Triple with FITC, Texas Red and DAPI) imaging
 - Reduces bleaching problems with Fluorescence slides
- NanoZoomer RS
 - 6 standard slides. Approx. 3 min at the 20x mode
Approx. 12 min at the 40x mode
 - **Time Delay Integration (TDI) scanning: Two billion pixels are created in an area of 20mm x 20mm at 20x without the tiling of a regular CCD camera.**

Claro (Japan)



- Vassalo
 - up to 80 slides
 - 10mm square in 6min by 20x lens
 - Accuracies: XY axis $\pm 2\mu\text{m}$, Z axis for focusing $\pm 0.25\mu\text{m}$
 - Whole region autofocus (frozen section scanning)
 - Focusing technology “ZigZag scan” for thinner sections
 - Camera: Sony 1/2 inch IT CCD
 - Specimen management system (ACORDO)
- Toco
 - Single slide (loader optional)
 - Optional fluorescence scanning

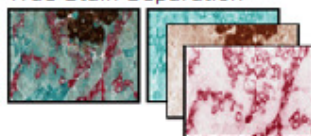


Aperio Scanscope

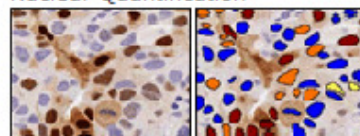


- Fast, reliable, flexible configurations: (1 slide to 120 slides).
- Linear scanning
- IA & TMA:

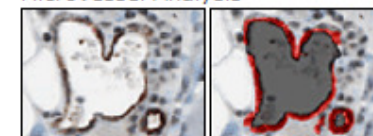
True Stain Separation



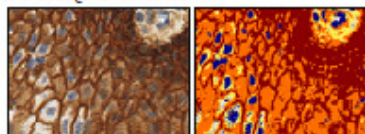
Nuclear Quantification



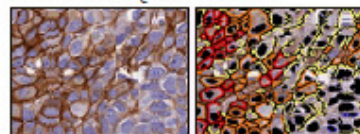
Microvessel Analysis



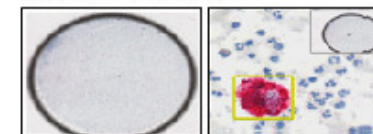
Area Quantification



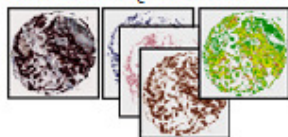
Membrane Quantification



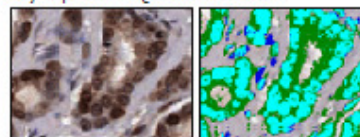
Rare Event Detection



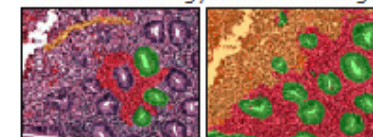
Multi-Stain Quantification



Cytoplasm Quantification



Genie™ Histology Pattern Recognition



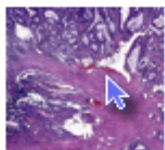
Leica SCN400

- “The fast, reliable, and flexible way to scan and digitize slides”
- Dynamic focusing
- Slide loader → continuous workload
- Multiple Z stacks scanning
- Multiple digital slide formats



Omnyx (General Electrics)

- A joint venture of GE Healthcare and University of Pittsburgh Medical Center



Overcoming challenges

Omnyx is dedicated to advancing the practice of pathology by overcoming the factors that have prevented digital pathology from being adopted on a widespread, standardized basis:

Magnification power

Images must be digitized at the same high power and quality as today's analog microscopes. This is often as high as 400x.

File size

At a minimum of 10 to 35 GB of uncompressed data for digitizing a typical case, it takes sophisticated image acquisition, compression algorithms to rapidly produce high-quality images for diagnosis.

High-volume workflow

Today's high-volume pathology practices place incredible demands on the time to acquire an image, view it over current networks, and store it. As pathologists are often mobile, the workflow should accommodate their tendency to work in a variety of locations.

Rapid slide navigation

Image compression, distribution and viewing technologies must keep pace with pathologists' workflow demands while they rapidly navigate the virtual slide.

FDA approval

Current digital pathology products are not cleared for equivalent diagnostic use by the FDA.

Pathology PACS screen shot:

The screenshot displays the Philips Medical Workspot interface for a Pathology PACS. The main window shows a histology slide titled "1: Breast HE/HerR2" for patient Mary Davis (ID: 3948329573, Birth Date: 15-03-1967, Sex: Female). The slide shows brown-stained cells on a blue background. The interface includes a menu bar (File, Edit, View, Navigation, Image, Help), a toolbar with icons for navigation and analysis, and a sidebar with patient information and image thumbnails. The thumbnails are organized into a grid:

- Top row: 3: 2 images (OT Breast HE/H...), 5: 1 image (OT Breast HE/H...)
- Middle row: 1: 1 image (CR Breast), 1: 1 image (CR Breast)

At the bottom right, there is a label for the slide with the following text:

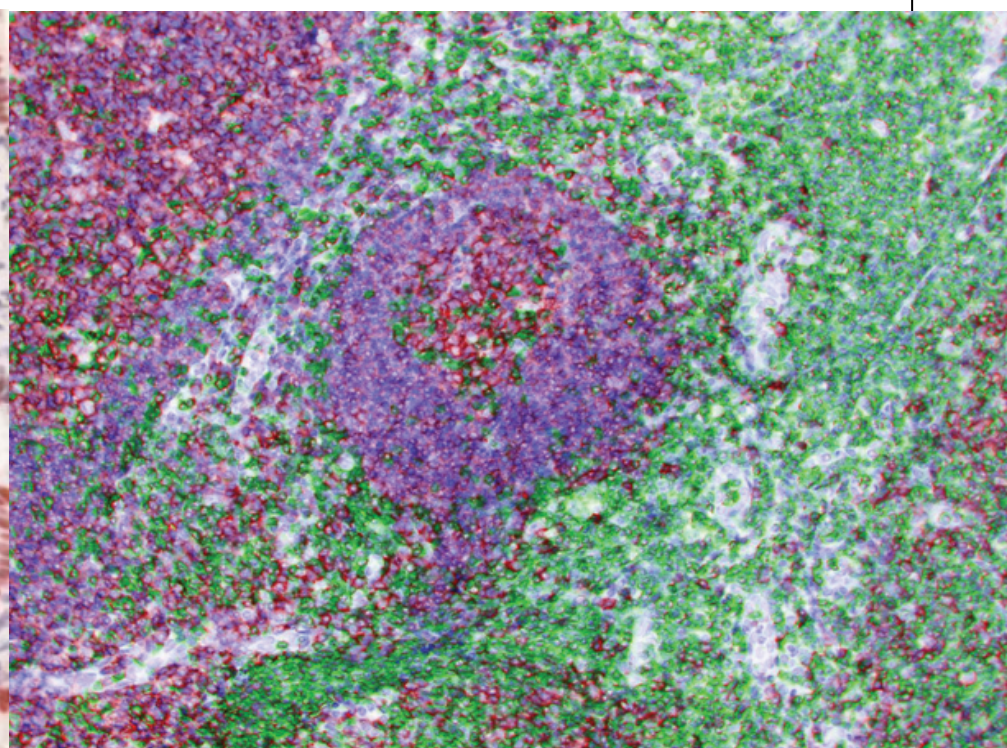
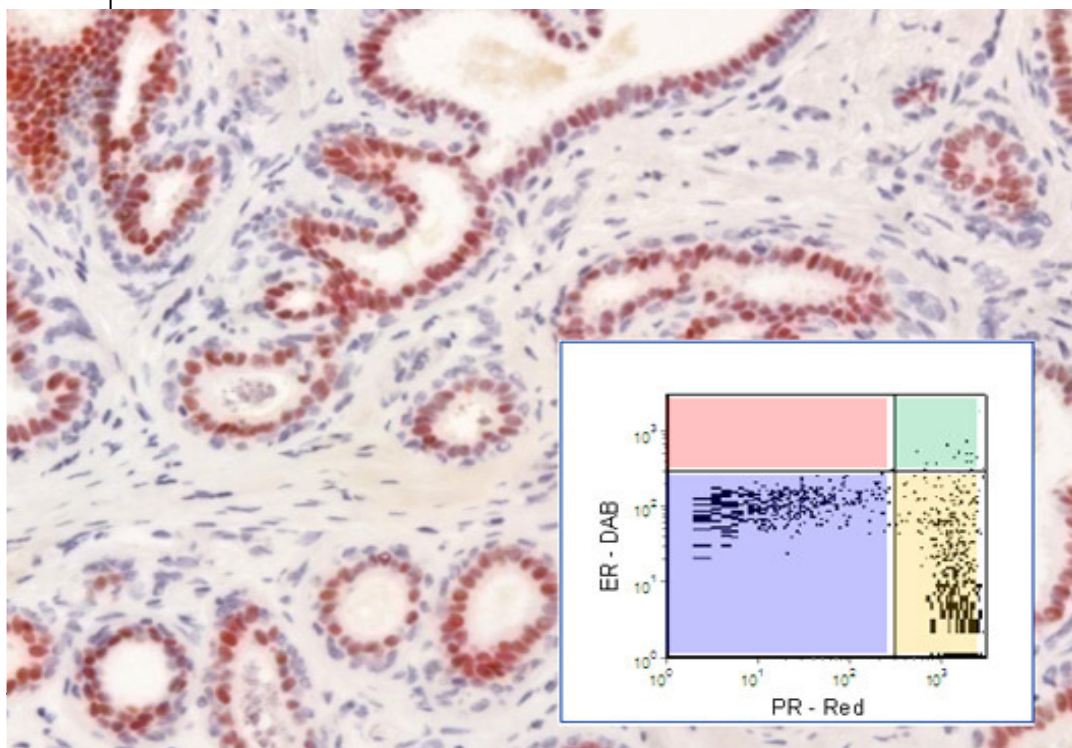
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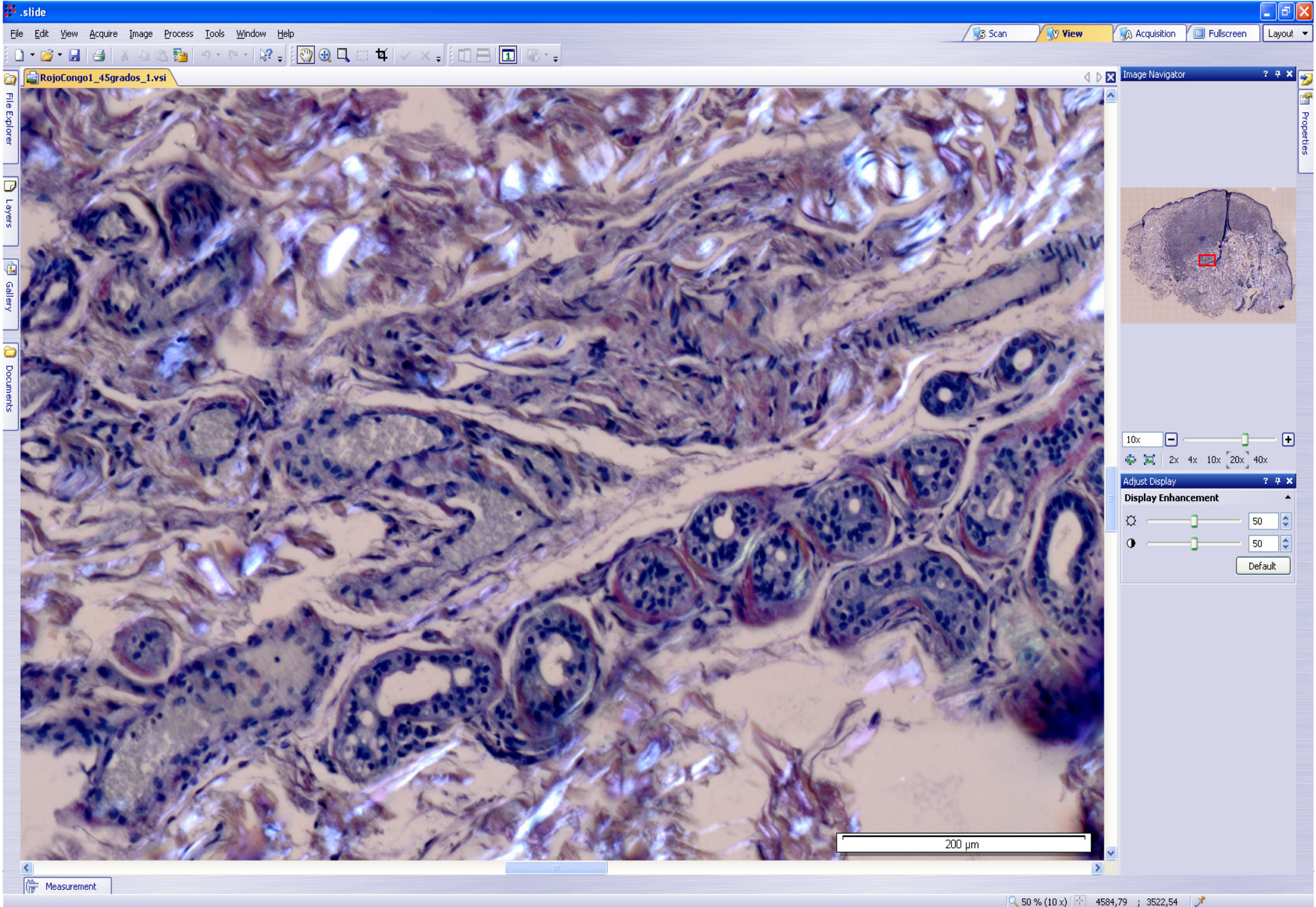
The Windows taskbar at the bottom shows the system tray with the date 17:48 and the Philips Medical Workspot application running.

Spectral imaging. CRi Nuance™



- 450 to 950 nm (most chromogens/ fluorophores)
- Chromogenic and fluorescence microscopy
- 2+ Antibody co-localization





Physical characteristics

- Dimensions (including its base)
- Weight
- Power Consumption
- Compliance (eg: CE, CSA, UL, 21 CFR Part 11)

Control Computer (Workstation)

- 3.0 GHz Quad Core Xeon Processor
- 8 MB L2 Cache Memory
- 4 GB Ram Memory
- Operating System (Microsoft Windows Vista)
- Hard Drive Storage (0.5 Tb)
- Monitor
 - Dual 20" Flat Panel Monitors, each
 - 1600 x 1200 @ 32-bit color

Software included

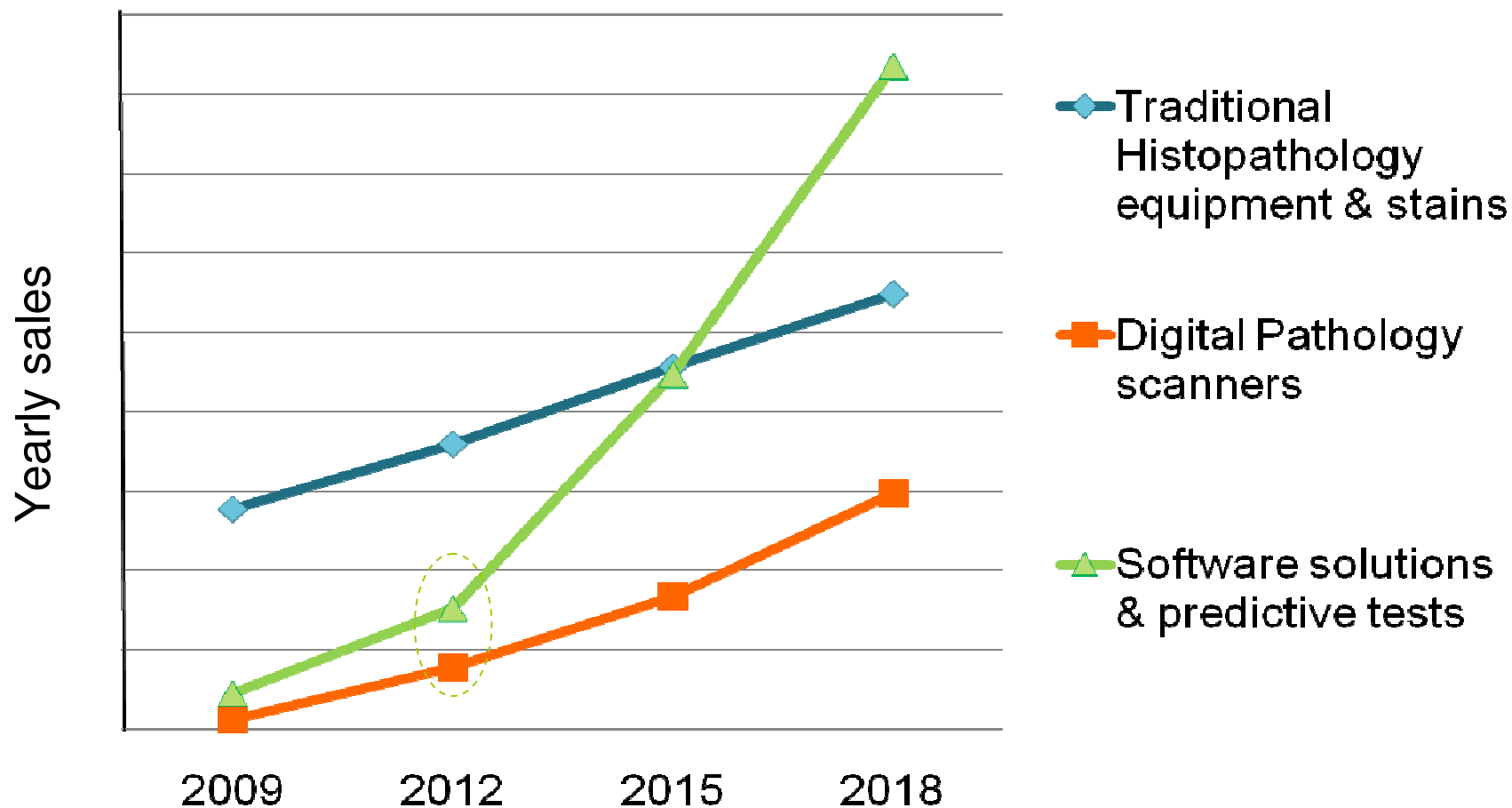
- Scanning Software (scanner control)
- Slide Viewer
- Web viewer
- Slide Database
- Workflow management (SlideTray)
- Are they integrated with LIS / HIS / PACS...?

Maintenance

- Non stop service
- Updates (software /hardware)

Installed base and growing no. of cad/cds solutions causes inflection of pathology software sales

PHILIPS



Open tech questions

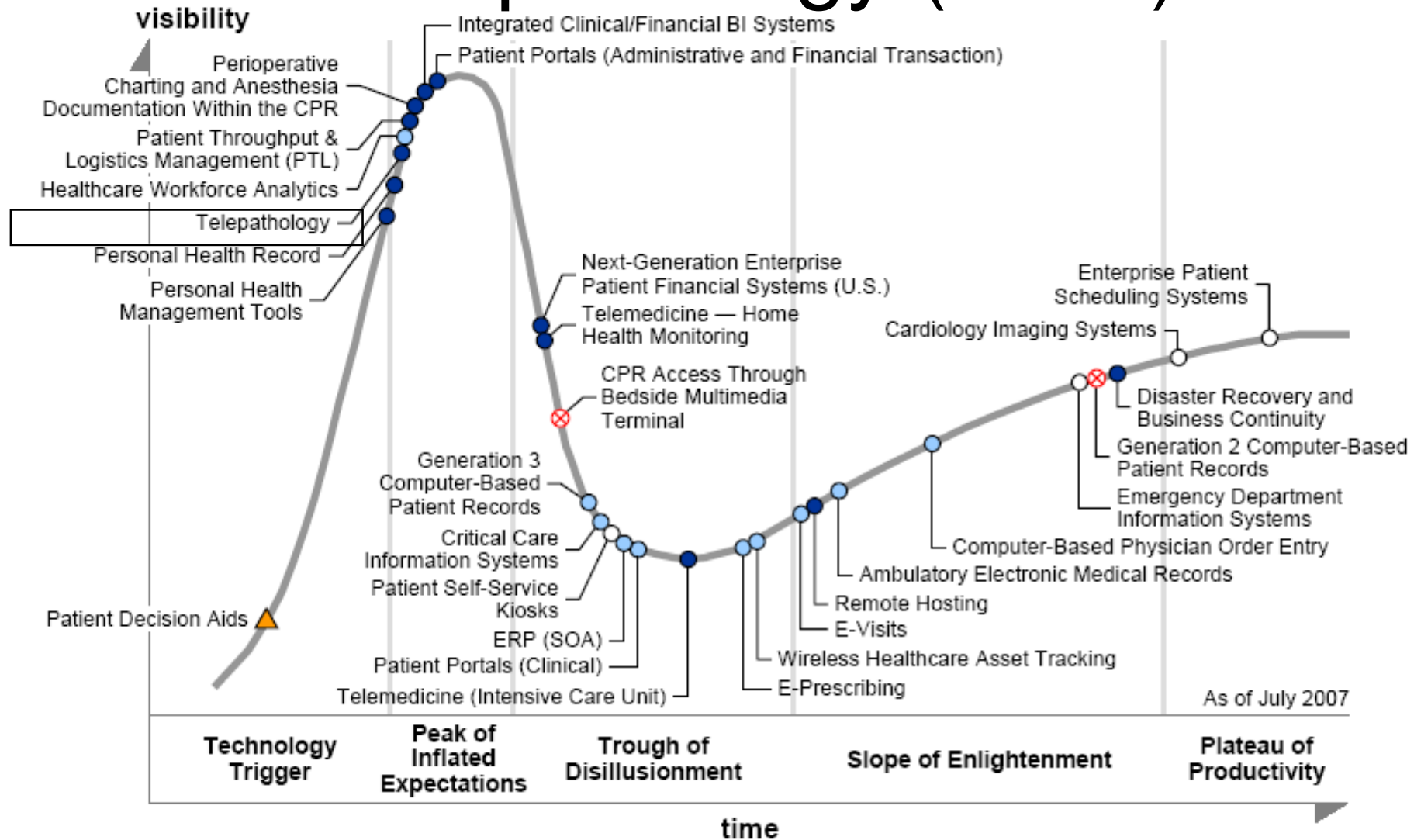
- A standard format is necessary: single file (JPEG2000), DICOM (tiling)
- Software integration: LIS vendors must be aware of VM solutions
- Image analysis independent of scanning phase
- A stable market

Open user questions

- Main limitations: scanning speed, unfocused areas
- Price too high for a Pathology department budget
- Some of them are too large devices

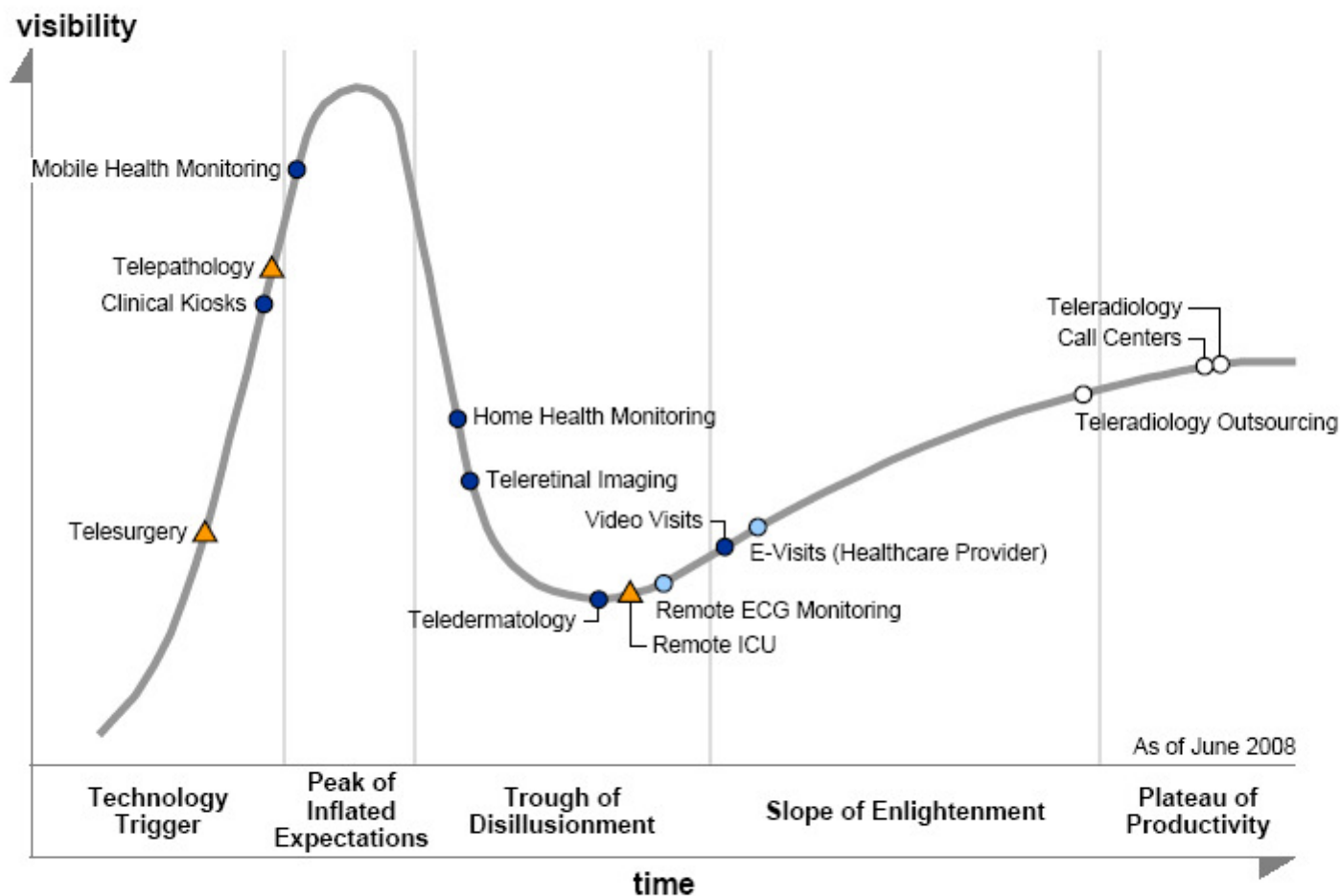
- Gartner forecast: >10 years until telepathology is widely accepted by users
(2006: Real-time and virtual telepathology will provide greater clinical benefit, but these technologies remain immature and expensive.)

Telepathology (2007)



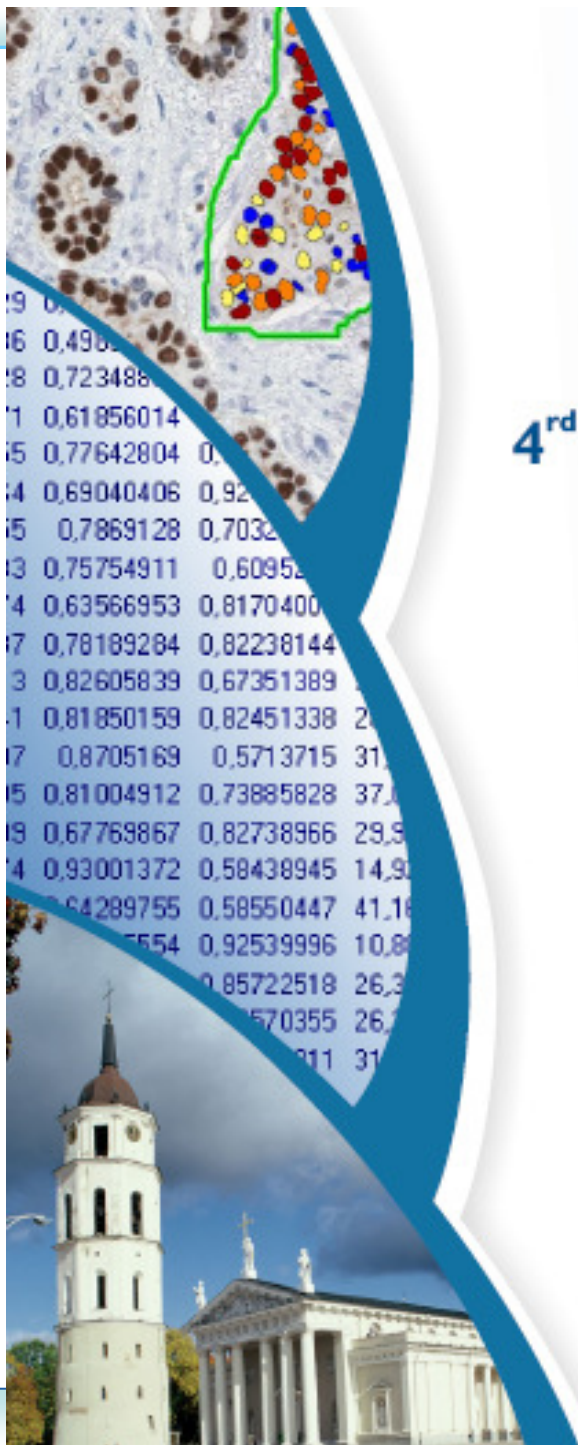
from "Hype Cycle for Healthcare Provider Applications and Systems, 2007," 11 July 2007)

Gartner Hype Cycle for Telemedicine, 2008



Years to mainstream adoption:

- less than 2 years
- 2 to 5 years
- 5 to 10 years
- ▲ more than 10 years
- ⊗ obsolete before plateau



10th European Congress on Telepathology and 4rd International Congress on Virtual Microscopy

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From Analogue to Digital -
Enabling Precision in Pathology

ANNOUNCEMENT
www.telepathology2010.com