DEFINIENS®
Understanding Images

# Biomarker Analysis in Tissue-based Assays

**Image Analysis for Life Sciences and Medicine**

**Dr. Maria Athelogou**
**Senior Research Scientist**

# Company History

**1995:** **Delphi Systemsimulation GmbH**
founded by Physics Nobel Prize Laureate Prof. Dr. Gerd Binnig
funded by Deutsche Bundesstiftung Umwelt
focus on simulation of complex ecologies and economies

**1998:** **Cognition Network Technology (CNT)**
solves problem of knowledge extraction from unstructured data
20+ patents

**2000:** **Definiens AG, Commercialization**
funded by TVM (today also by CIPIO Partners)

**2003:** Focus on **Enterprise Image Intelligence**

**2008:** Staff 83, **1500+** licenses worldwide,
HQ Munich, US operations, Definiens Inc.




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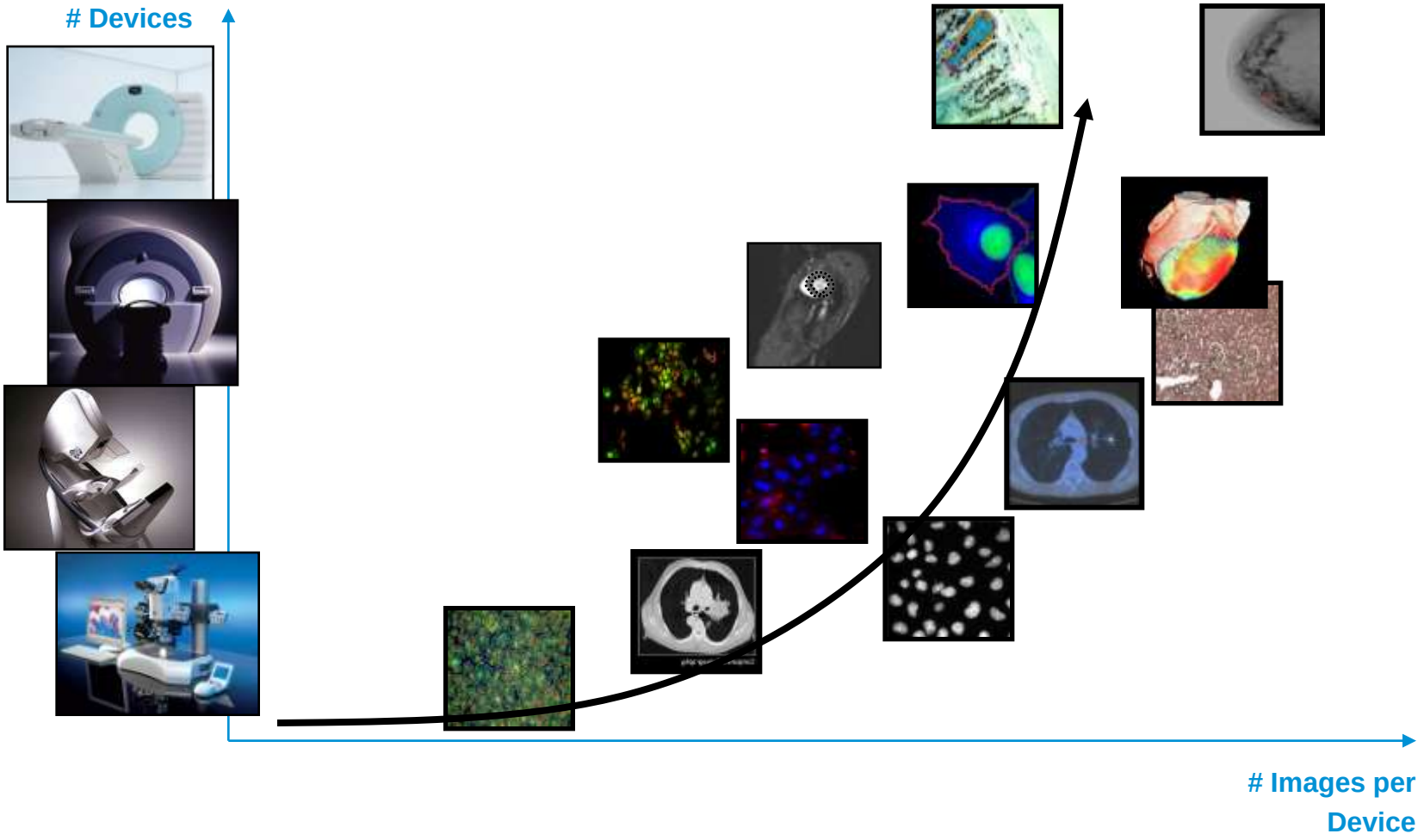
# Company Background

- Ground breaking Cognition Network Technology
- Focus on Digital Images
- Target Life Sciences and Earth Sciences markets
- Direct operations in Europe and North America
- Focus on Health Imaging as prime market

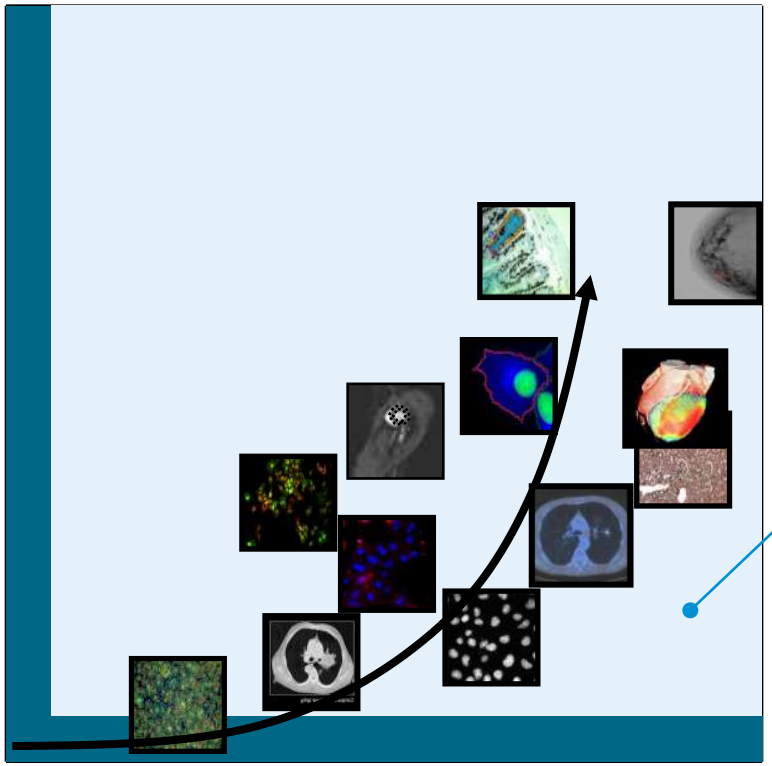
# The Explosion of Digital Image Content



# Image Analysis Represents a Major Bottleneck

Complexity

Human Mind



NOT SOLVED!

Productivity

Computer Based Methods

# Image Analysis Represents a Major Bottleneck

## Human Mind

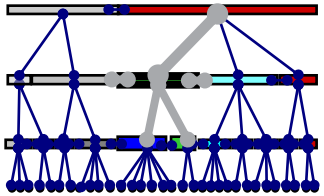
Intelligent handling of complex tasks, but the required manual quantification is

- expensive
- subjective
- very time consuming

## Conventional image analysis techniques

- Only very simple tasks can be addressed

## Definiens Technology



Complex tasks can be addressed automatically, quantification is

- inexpensive
- reproducible
- fast

# Cognition Network Technology, CNT

Human Min
Cognitive
Context

+

Computer
Based
Method

Definiens
Cognition Network
Technology

Deeper
insights

Faster
results

Better
decisions

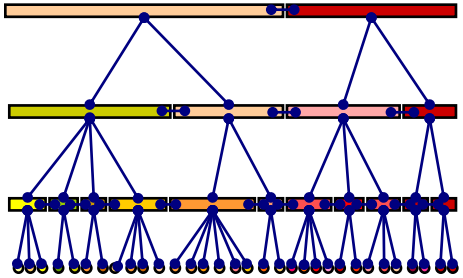
**The Definiens‘ Cognition Network Technology, CNT, enables automated context-driven analysis by emulating the human cognition process**

# Cognition Network Language is a meta language for Image Understanding

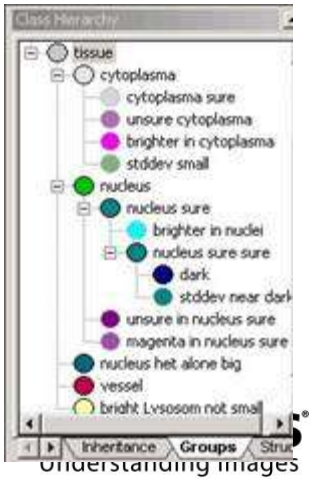
- Definiens image analysis software supports a GUI based meta language that allows for fast and efficient development of rule bases.
- A rule base addresses the solution of a specific image analysis task
- Basic components are processes and fuzzy classification that support knowledge based segmentation

Locally specific processes

**Result**



Classes with fuzzy class descriptions




Network of objects of interest with attributes and mutual relations

# Cognition Network Technology, CNT

## Three major markets are addressed by Definiens

- Life Sciences (Bio-Tech and pharmaceutical industries)
- Medical imaging (CT, MRI,..)
- Earth Sciences (satellite, air-born images)

**Earth Sciences market is not addressed in this presentation**

# Life Sciences Customers *(samples)*



















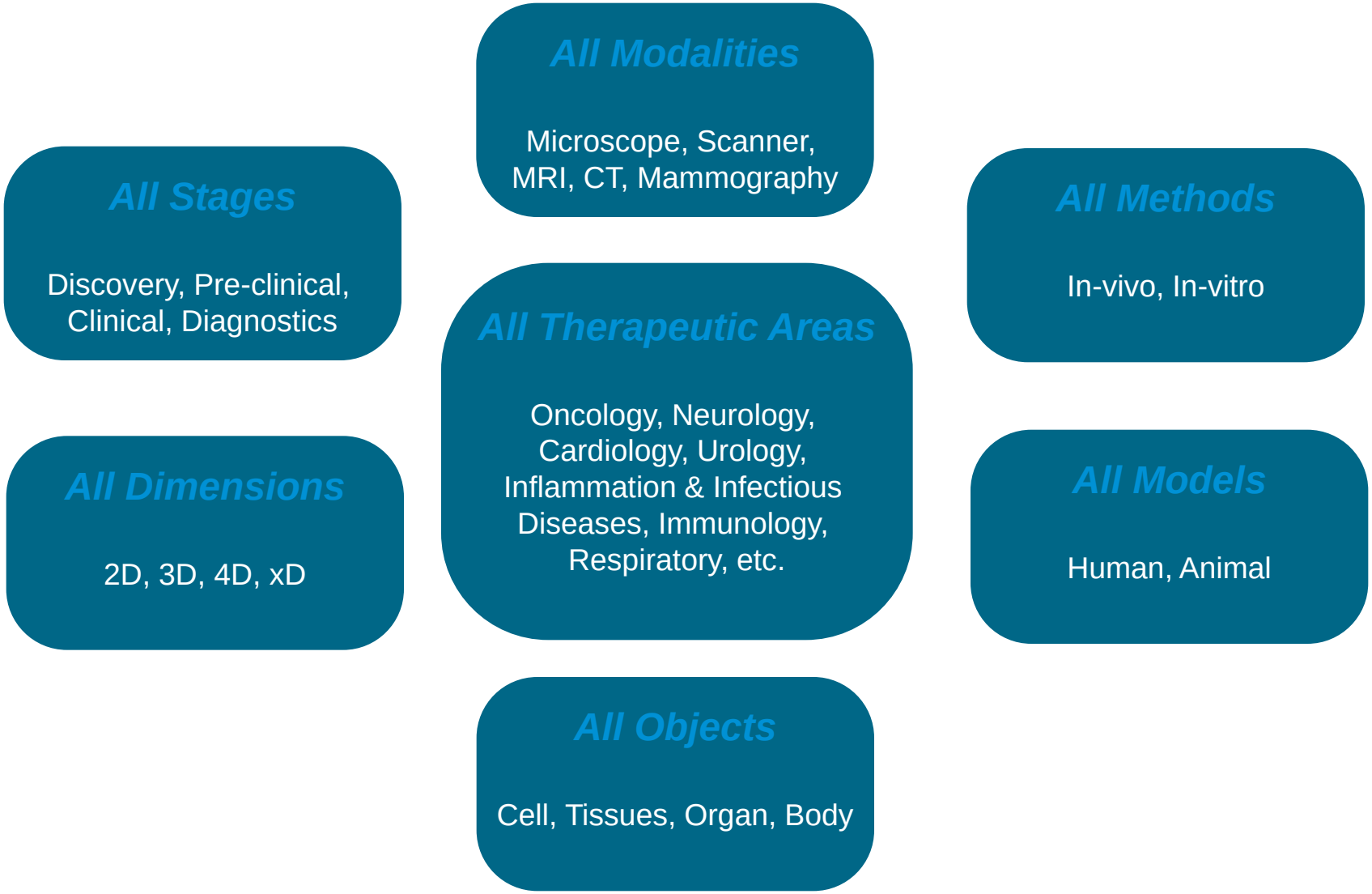








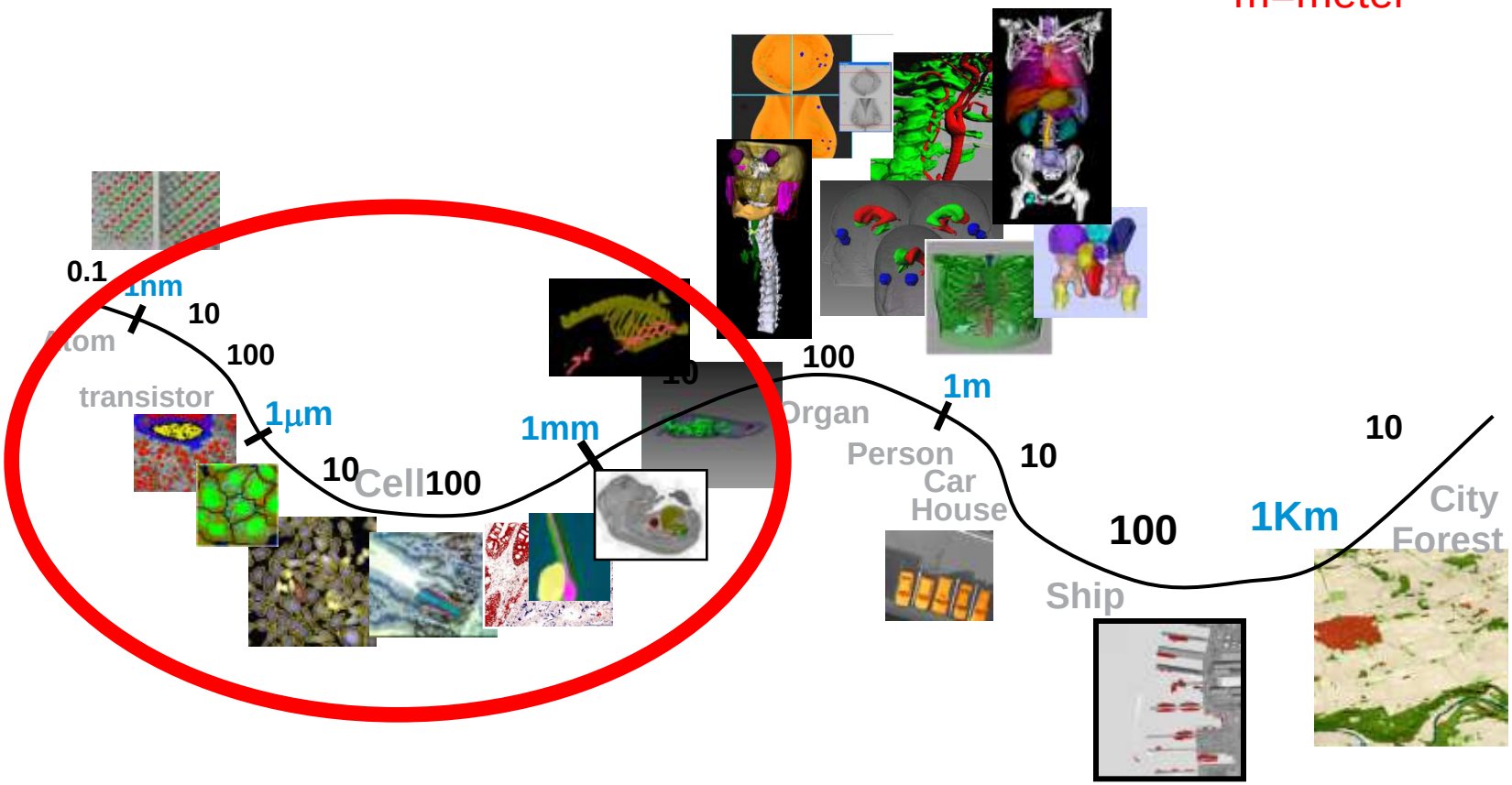

# Cross-Modality – Cross-Manufacturer – Cross-Domain



# Traveling through the Dimensions of Space

**Real Space / Size of Objects**

m=meter





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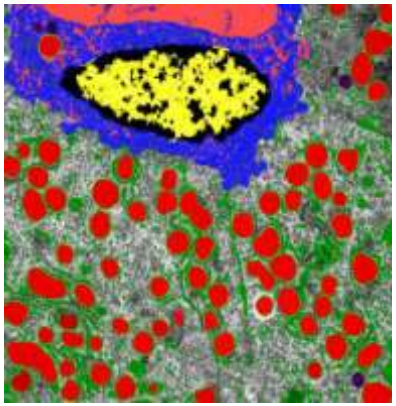
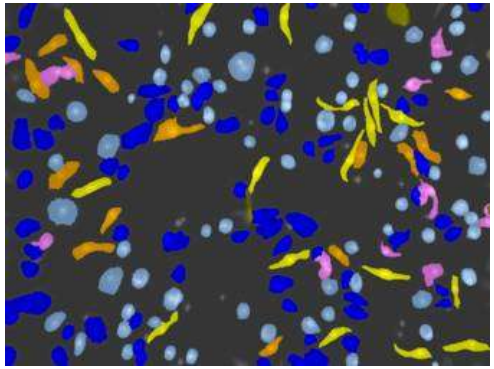
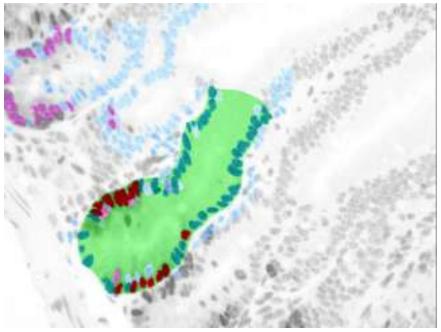
# One Technology – Many Applications
## Automatic Detection of Image Contents



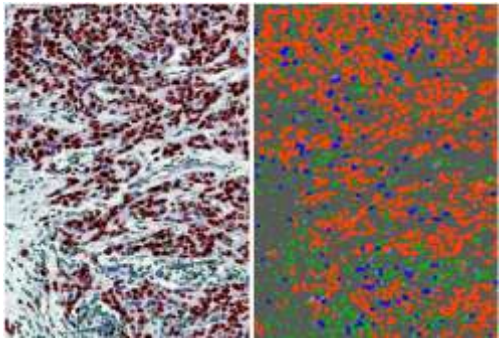
Electron Microscopy
**Tissue**



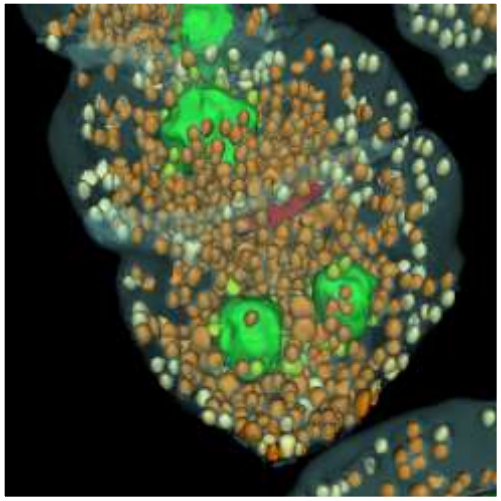
High Content Sreening
**Cells**



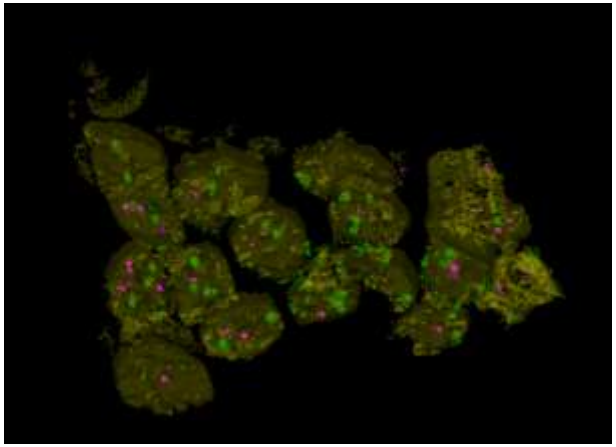
Proliferation index
**Tissue**



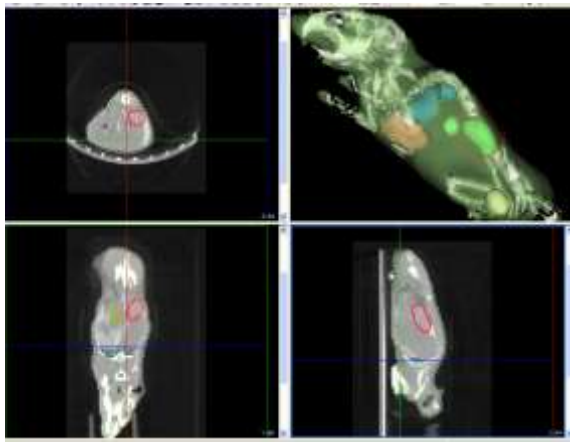
Cancer Biomarker
**Tissue**



3D-Confocal Microscopy
**Cell biology**



3D-Confocal Microscopy
**Tissue** Molecular Pathology



3D PET/CT
**Small animal**





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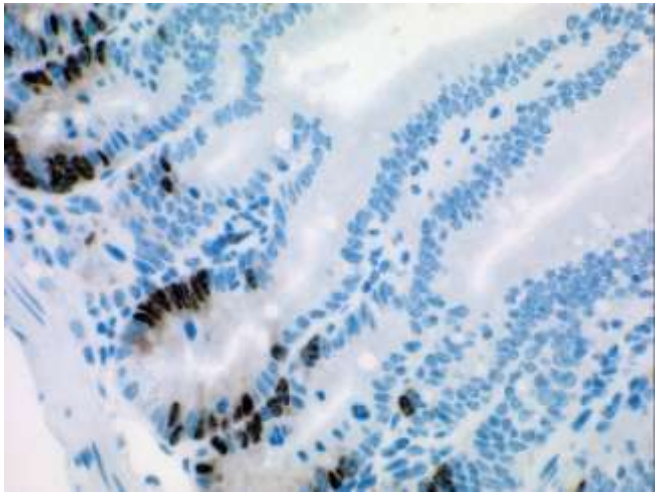
# Example: Preclinical Safety for Drug Development

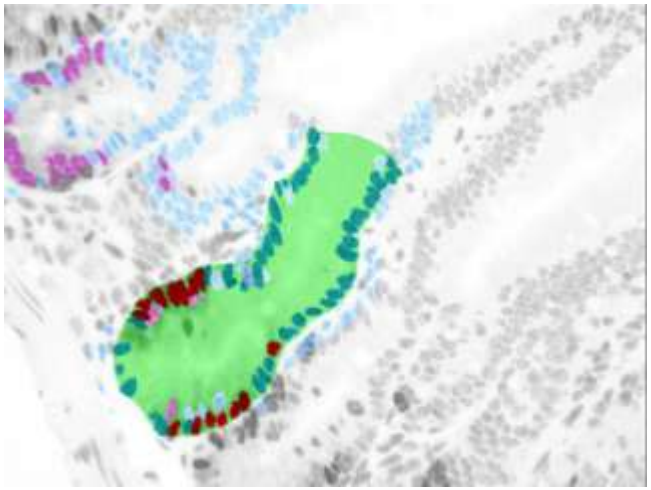
## Analysis of proliferation index in mouse jejunum

Input Data



BrDU stained mouse small intestine

Cellenger Result



Extracted krypt with
positive and negative nuclei

Image data courtesy Novartis Pharma AG; Pathology / Toxicology EU, E. Persohn

# Variability

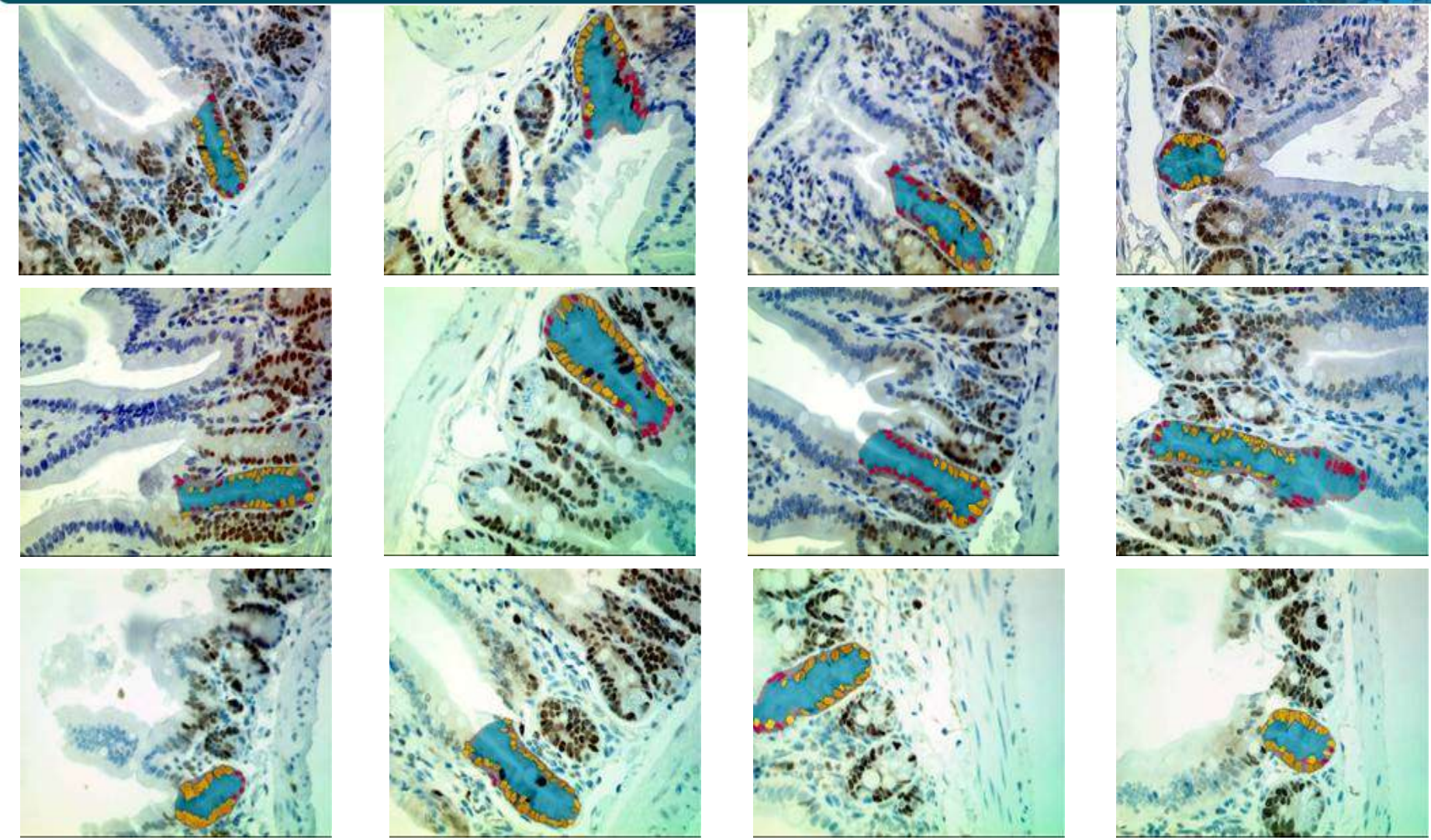
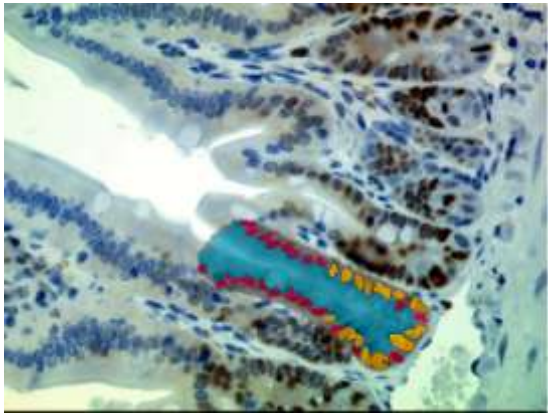


Image data courtesy Novartis Pharma AG; Pathology / Toxicology EU; E. Persohn

# Benefit of Definiens Technology

- Request from the FDA / EMEA) → additional Tox./ Histopath. – Data for the final submission
- Stack of approx. 15.000 images
- Based on state of the art technologies
- Expected 3 -4 Pathologists → 6 months



- Automated, quantitative Analysis of cell & tissues
- Benchmark (Pathologist / eCognition)
- Result within a few weeks
- Reduced the time from 6 to 1 months with 2 Pathologists
- Time to market benefit

# Inflammatory Areas in Liver Tissue

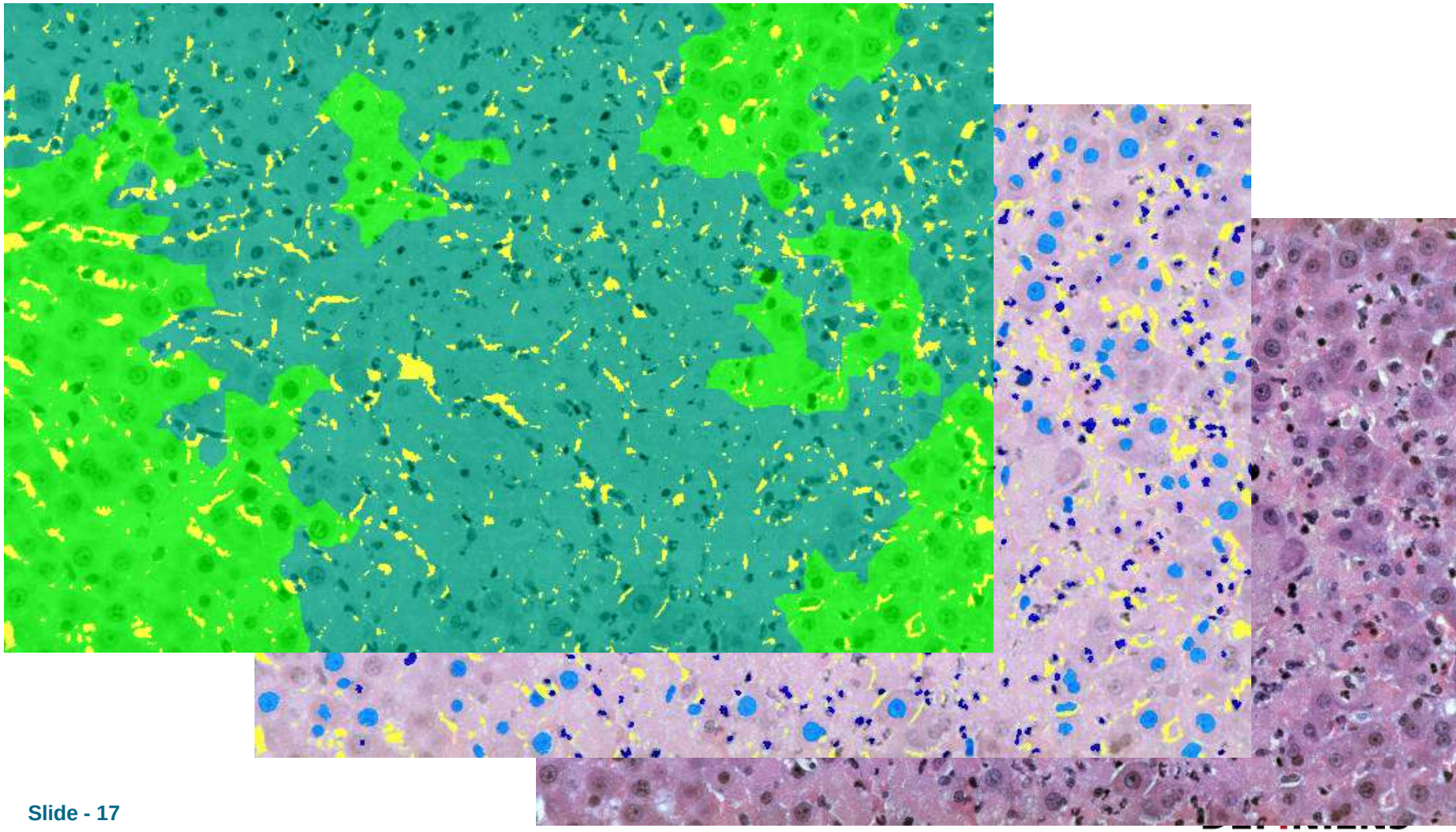


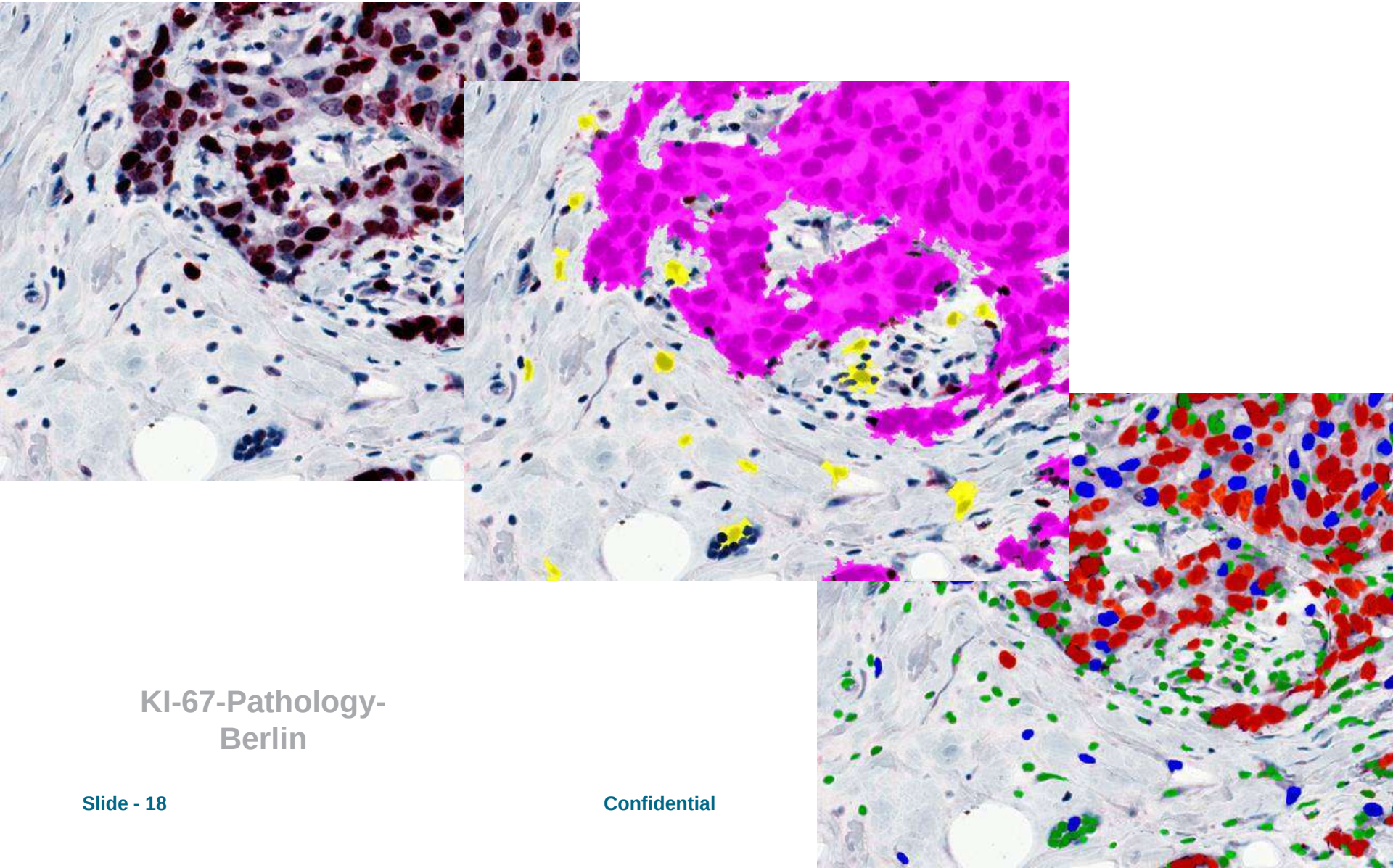




Image data courtesy Pathology LMU Munich

# Biopsy Breast Cancer, Biomarker Ki-67

## Single cell based solution

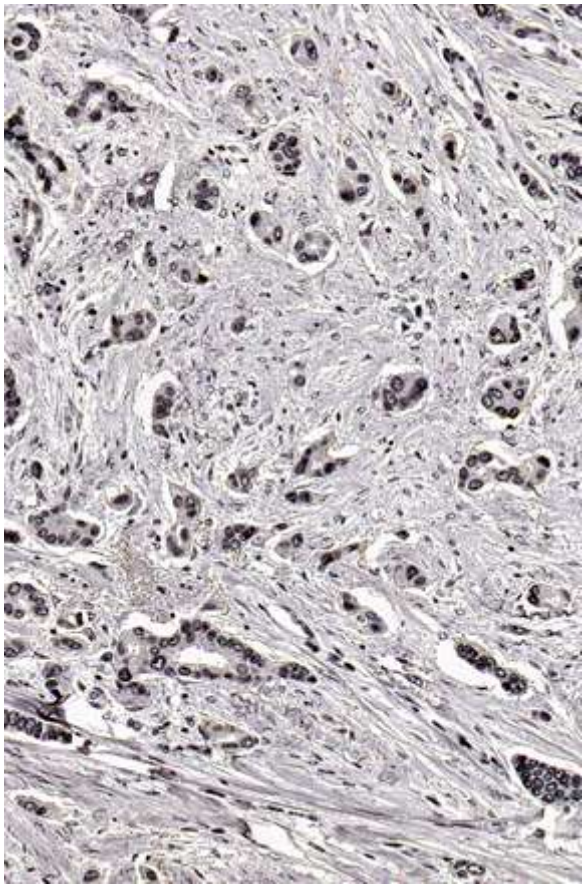


KI-67-Pathology-Berlin

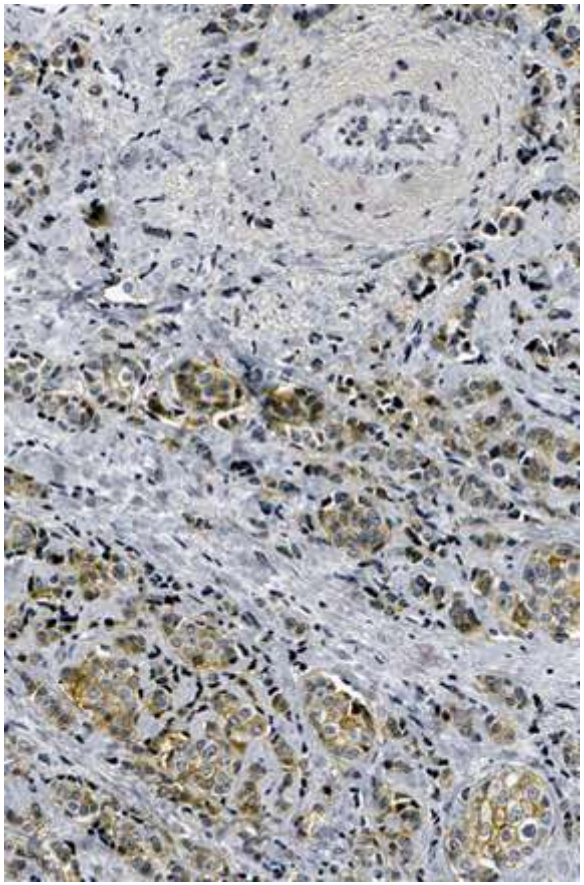
# Biopsy Breast Cancer, Biomarker Her2/neu

## Single cell based solution

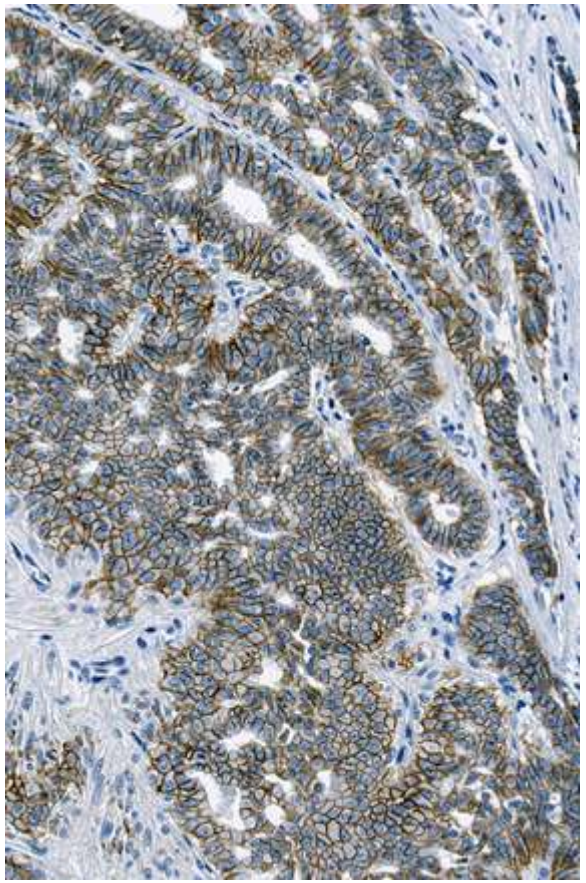
Original 0 : her2Neu_File174



Original 2 : her2Neu_File177

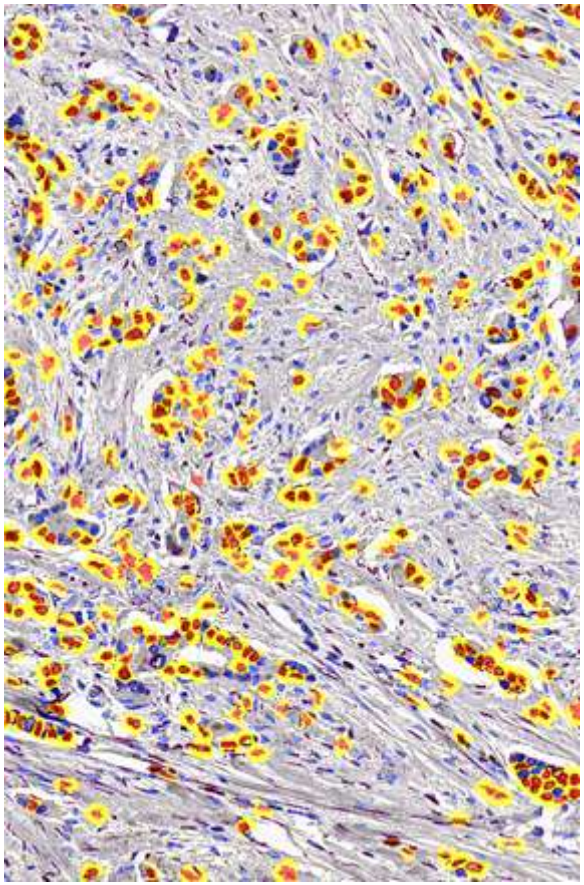


Original 3 : her2Neu_File179

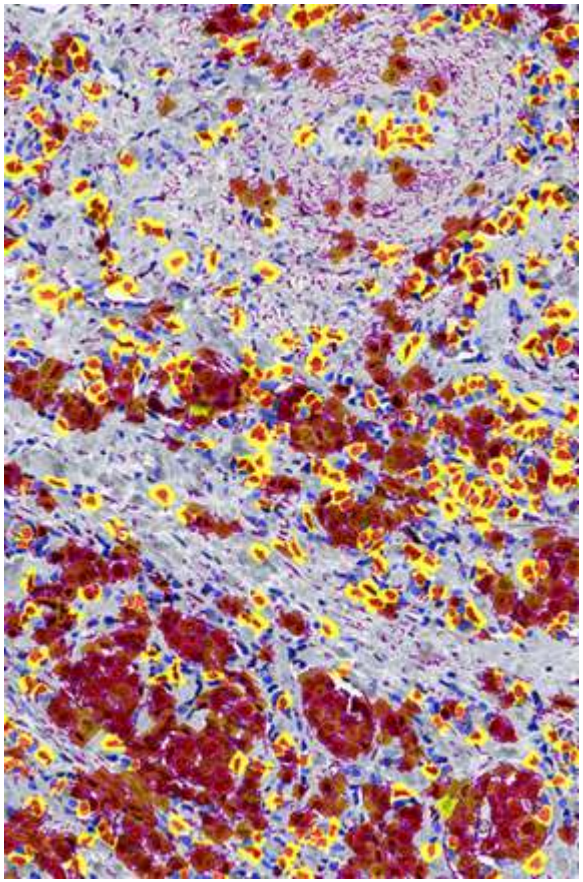


# Analysis Results

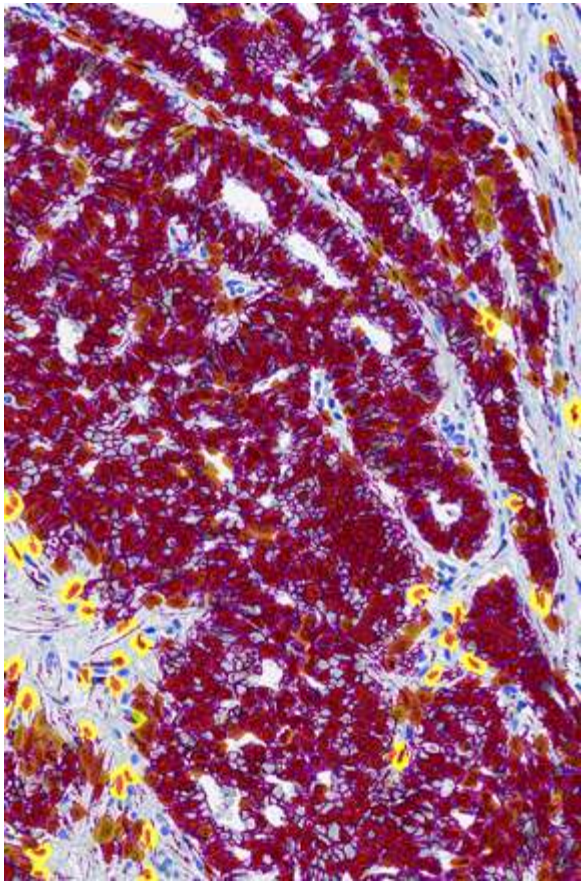
Original 0 : her2Neu_174



Original 2 : her2Neu_177



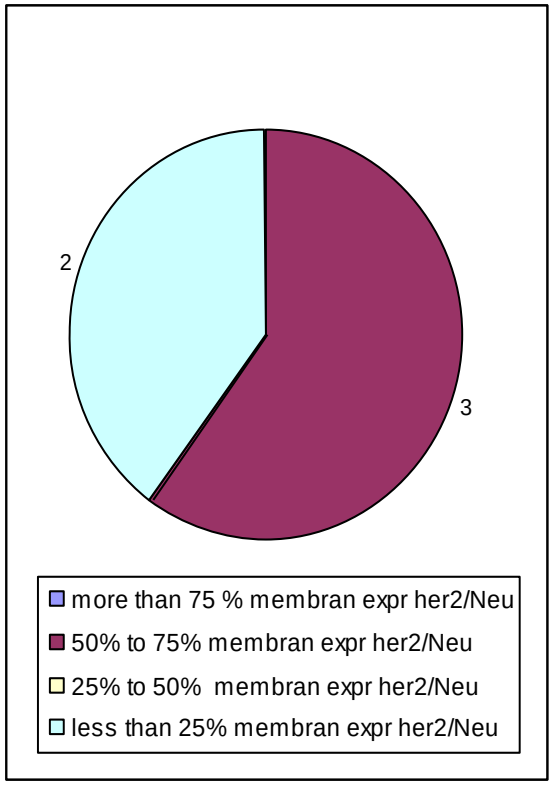
Original 3 : her2Neu_179



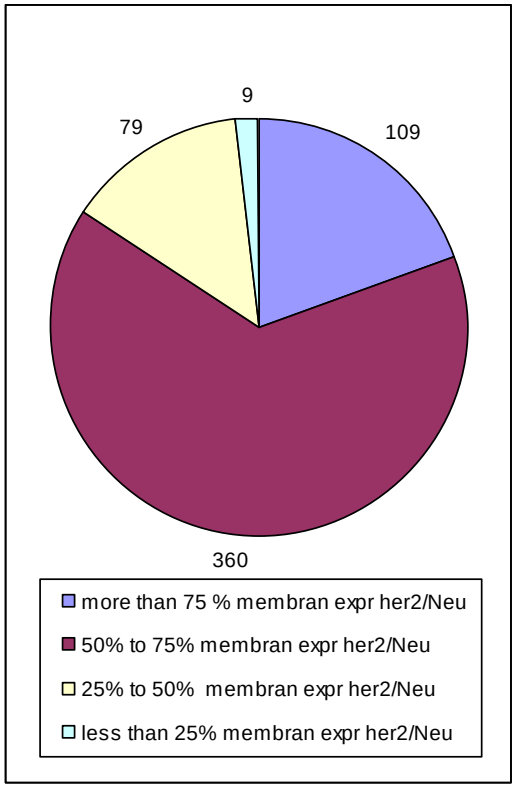
# Statistics

## Count of cells of different classes

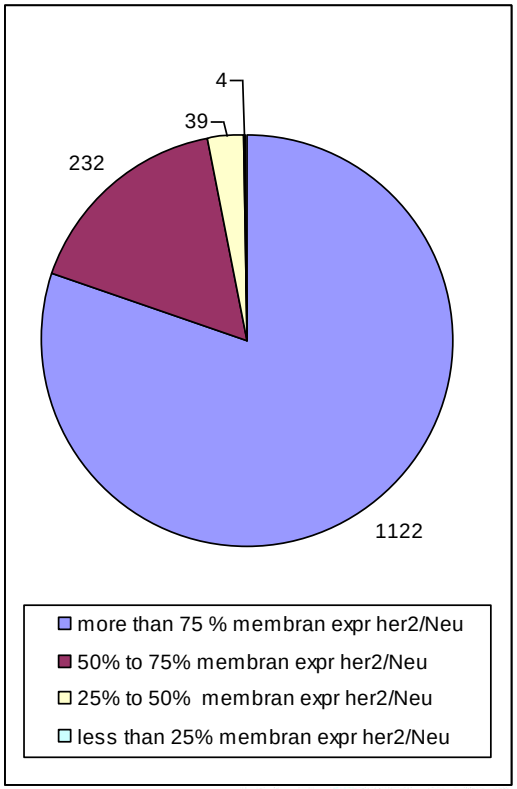
Original 0 : her2Neu_174



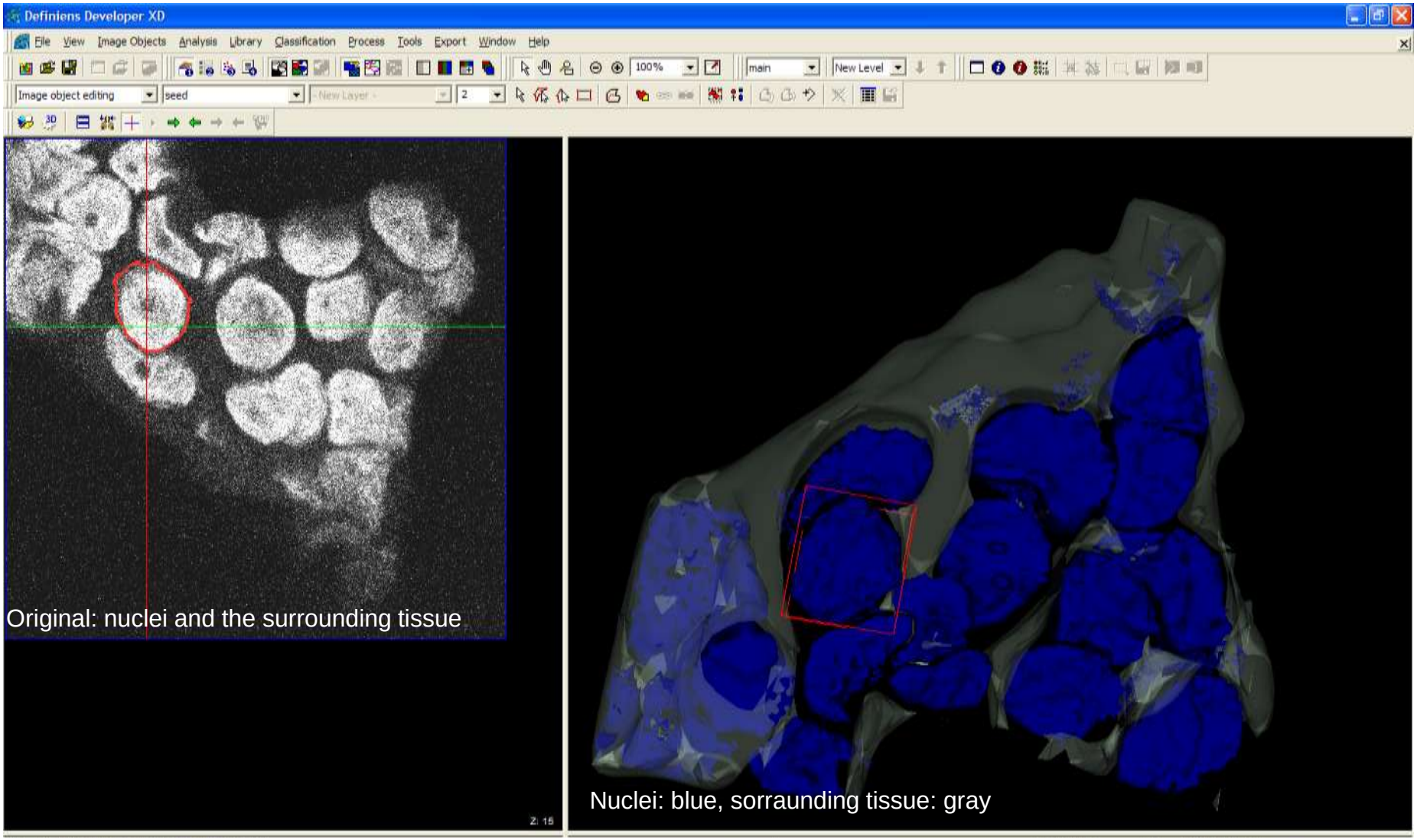

Original 2 : her2Neu_177

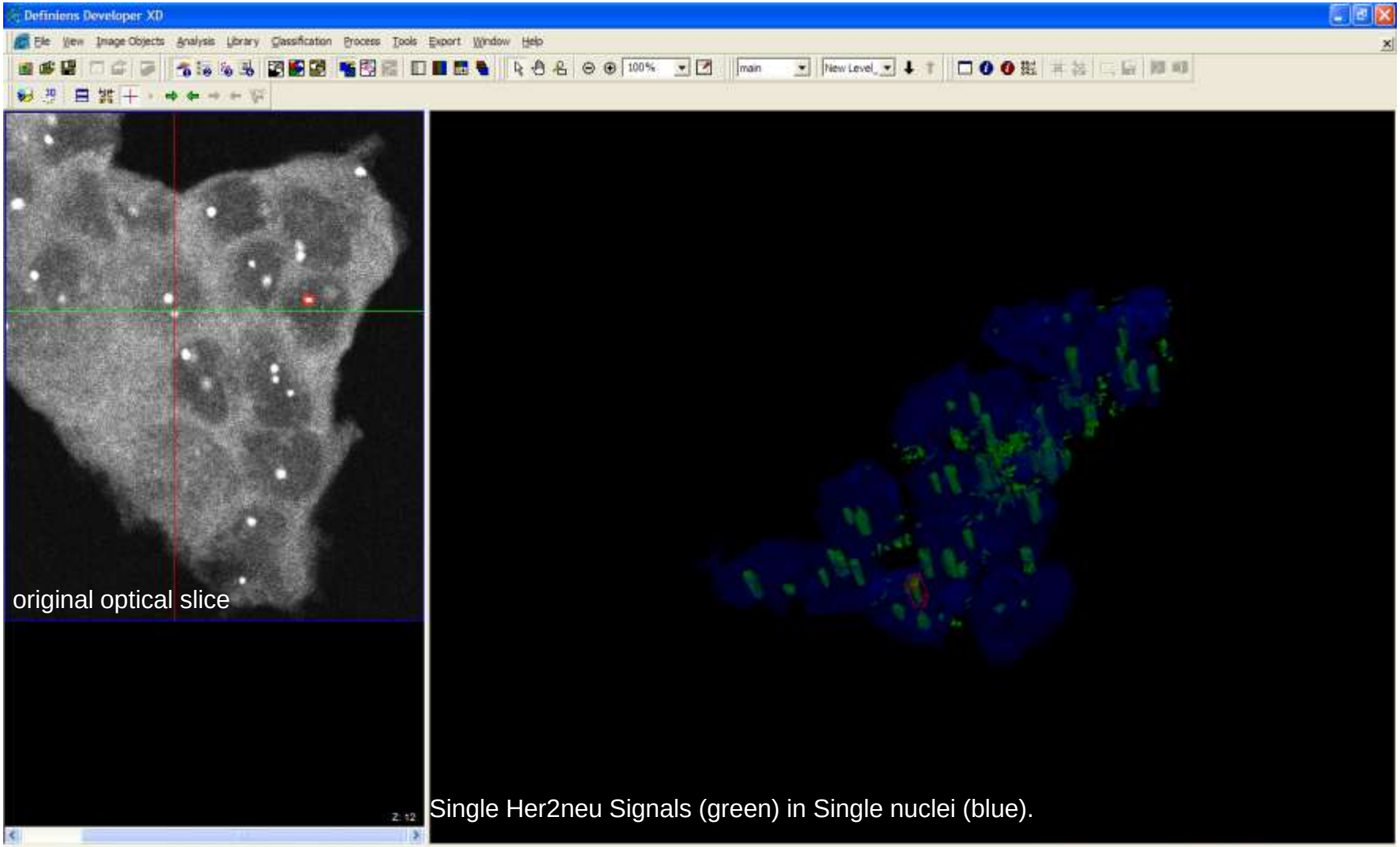


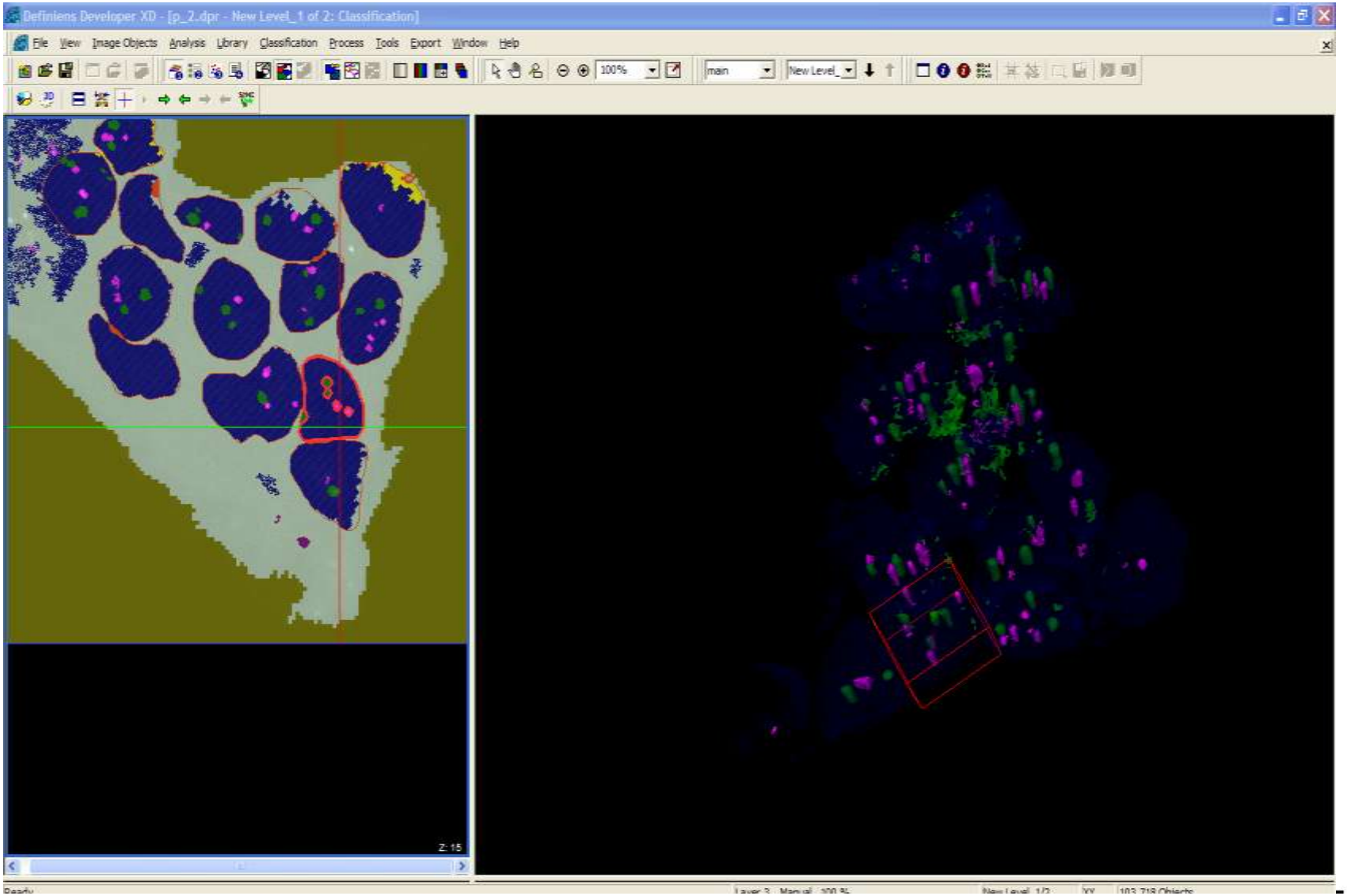

Original 3 : her2Neu_179



# 3D Tissue: optical slices
# Biopsy  Breast Cancer, Biomarker  FISH Her2/neu




Definiens Developer XD
File View Image Objects Analysis Library Classification Process Tools Export Window Help
original optical slice
Single Her2neu Signals (green) in Single nuclei (blue).


Definiens Developer XD - [p_2.dpr - New Level_1 of 2: Classification]
File View Image Objects Analysis Library Classification Process Tools Export Window Help
100%
main
New Level_
Z: 15

# Definiens TissueMap*

## Automated Image Analysis for the Advanced Development of Predictive Biomarkers and Companion Diagnostics

**Is a powerful platform for developing multidimensional image analysis applications for cells, tissues and organs.**

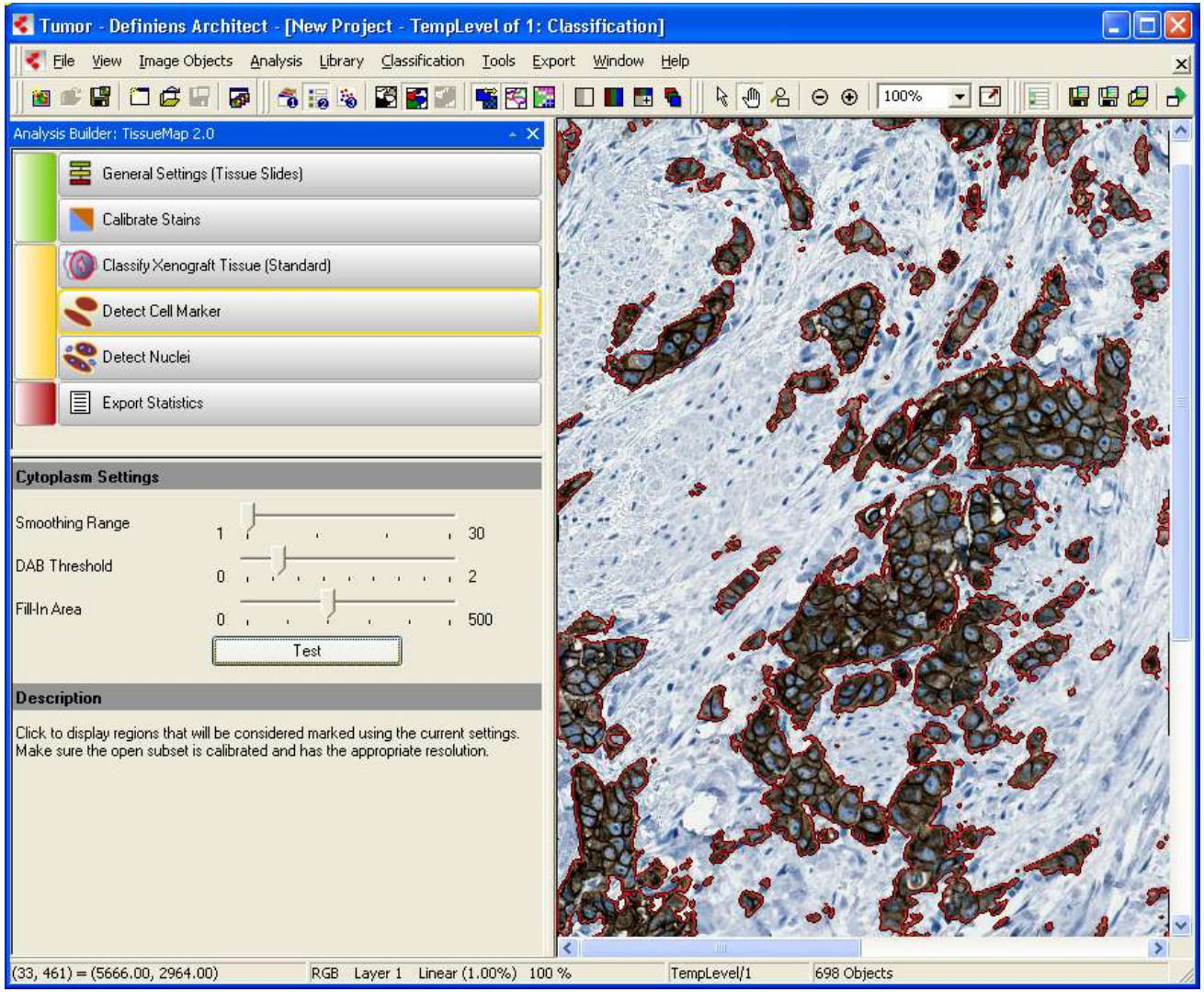
**Has been developed specifically for oncology research and comes with a dedicated suite of algorithms.**

automates the challenging task of image analysis,

supporting research scientists to discover, validate and measure new drug targets and disease-specific biomarkers.

It helps to monitor preclinical efficacy and safety, to stratify patients for clinical trials and supports personalized medicine.

# Tissue Slides




Analysis of antibodies and markers which co-stain the cell body, like cytokeratine markers (CD31, AE1/3, etc.) and other markers, such as CD45, CD23, etc.





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# TMAs

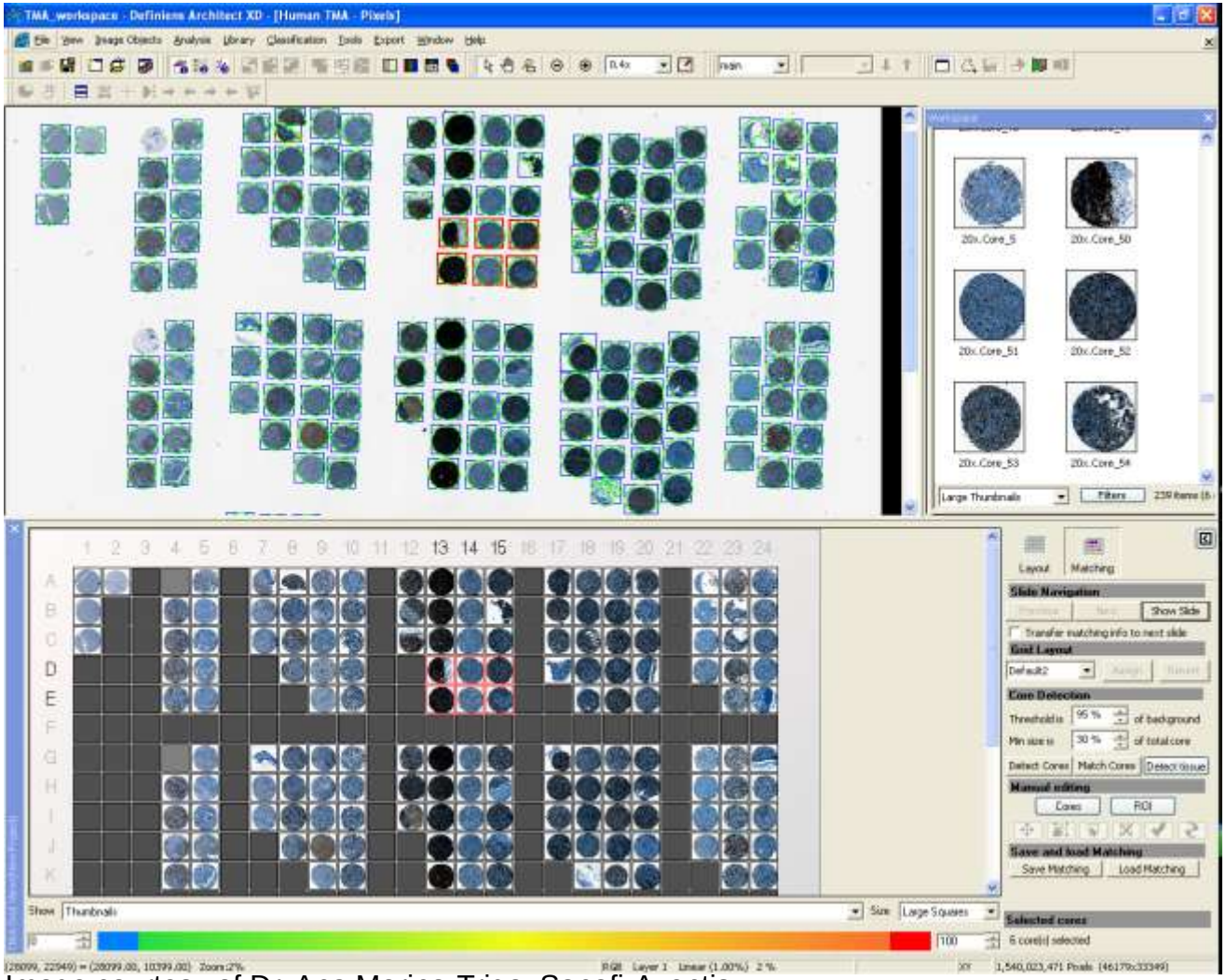
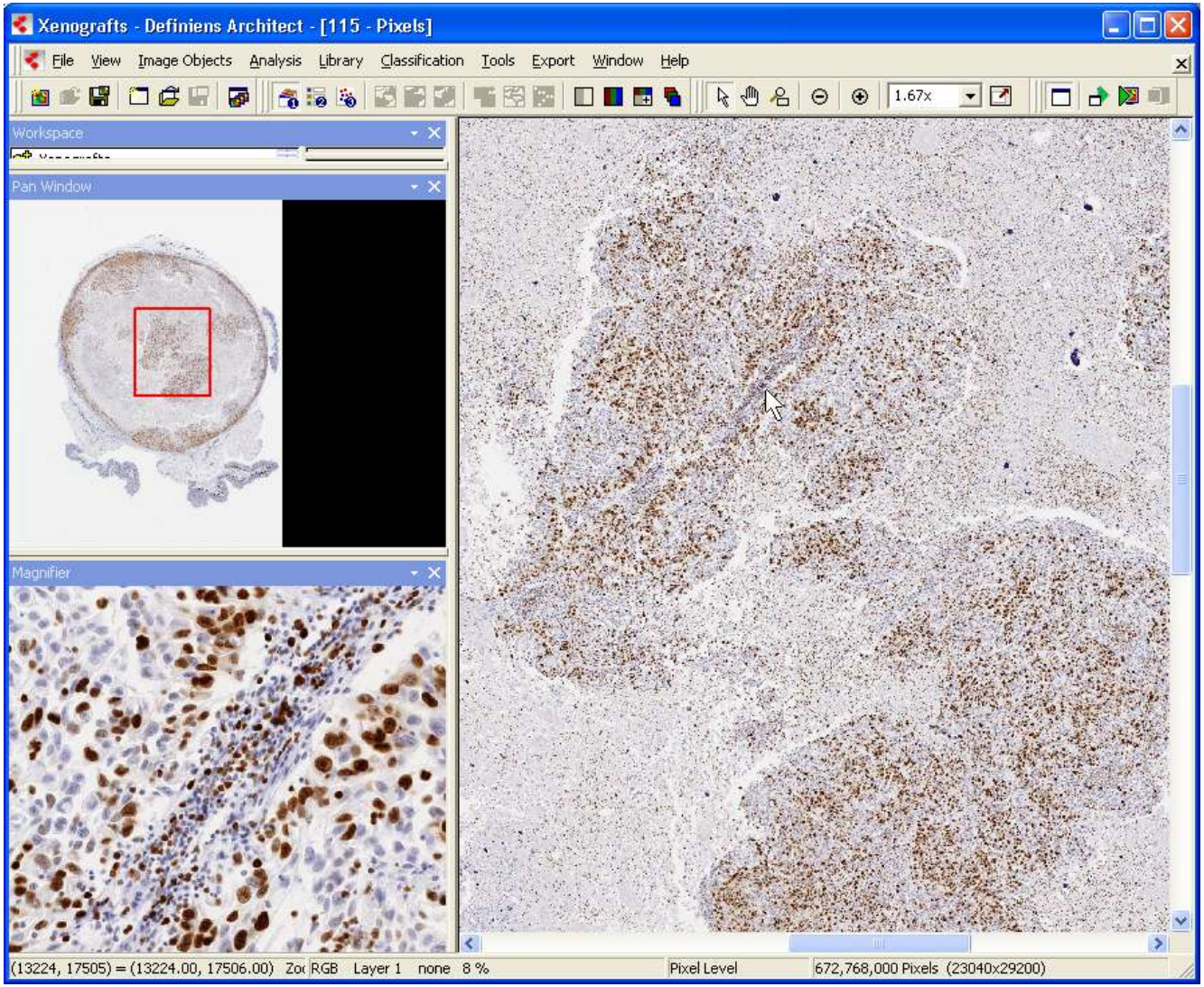


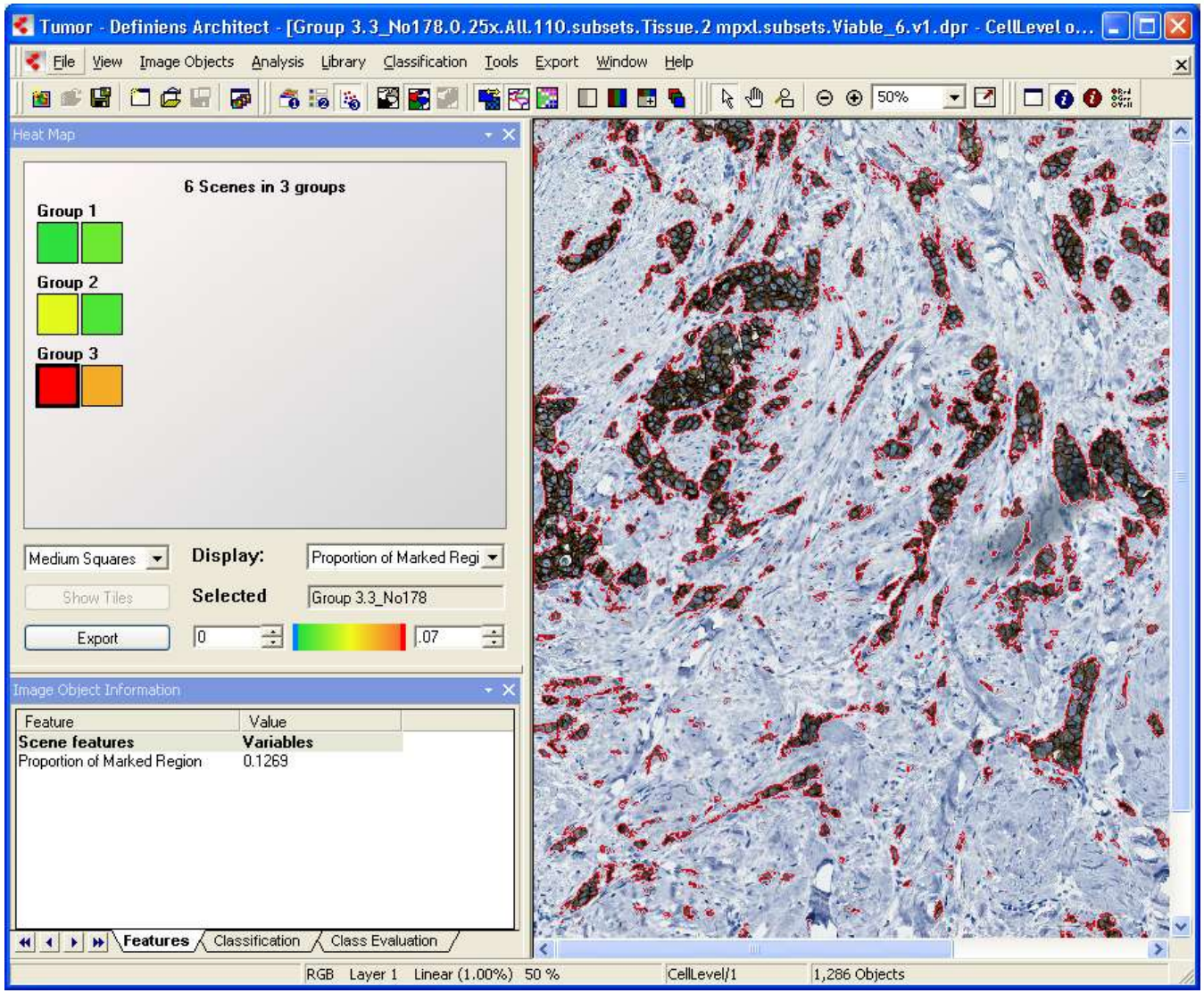

Image courtesy of Dr. Ana Merino-Trigo, Sanofi-Aventis

Assigned TMA-cores to layout. Upper left section: original TMA-slide with automatically detected cores (green circles) and selection (red rectangles). Lower section left: cores assigned to grid. Lower right section: core detection and matching control functions.

Magnifier and PanWindow for viewing images at multiple scales.



The HeatMap Visualization tool enables the comparison of statistical data in experimental samples.





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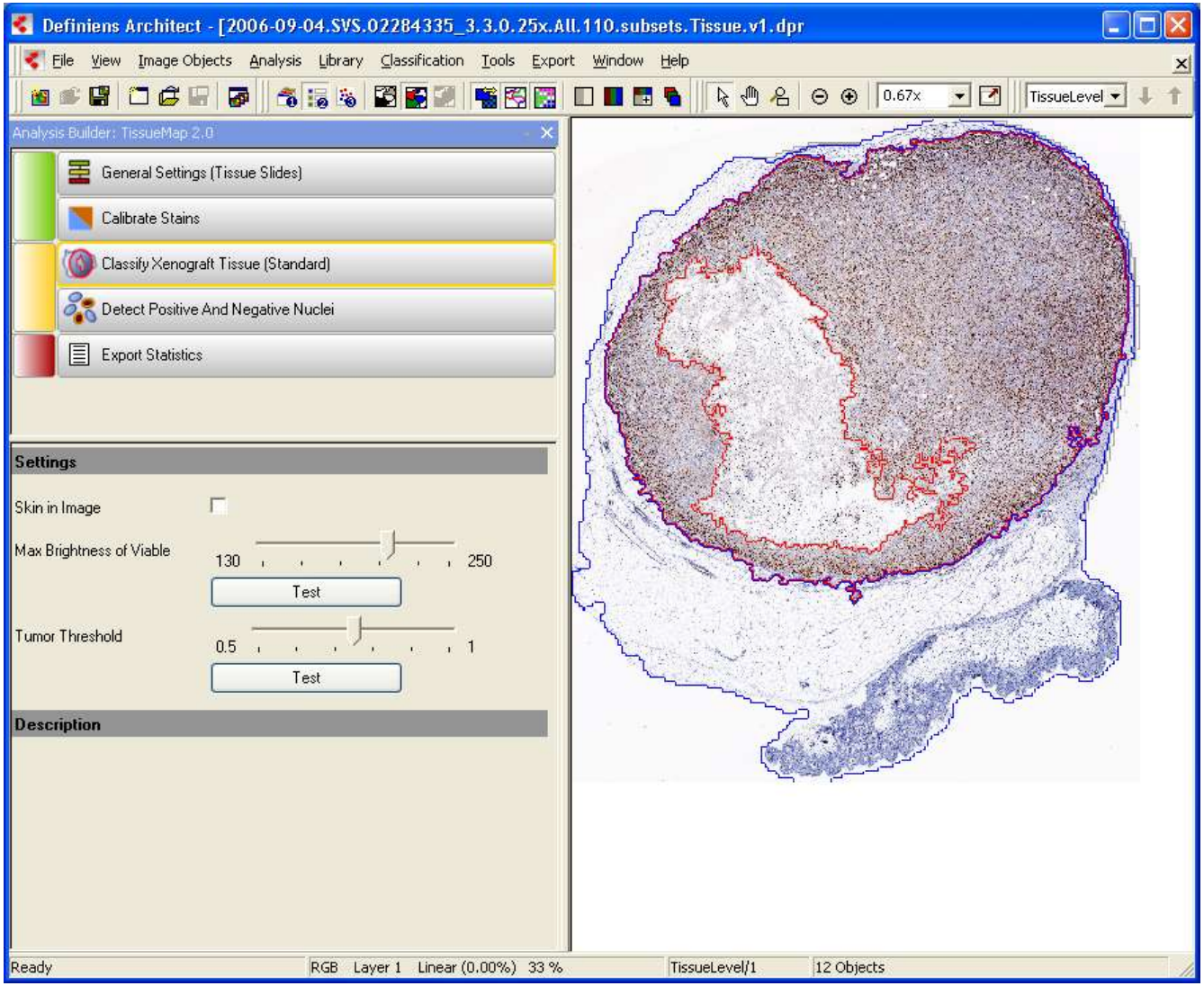
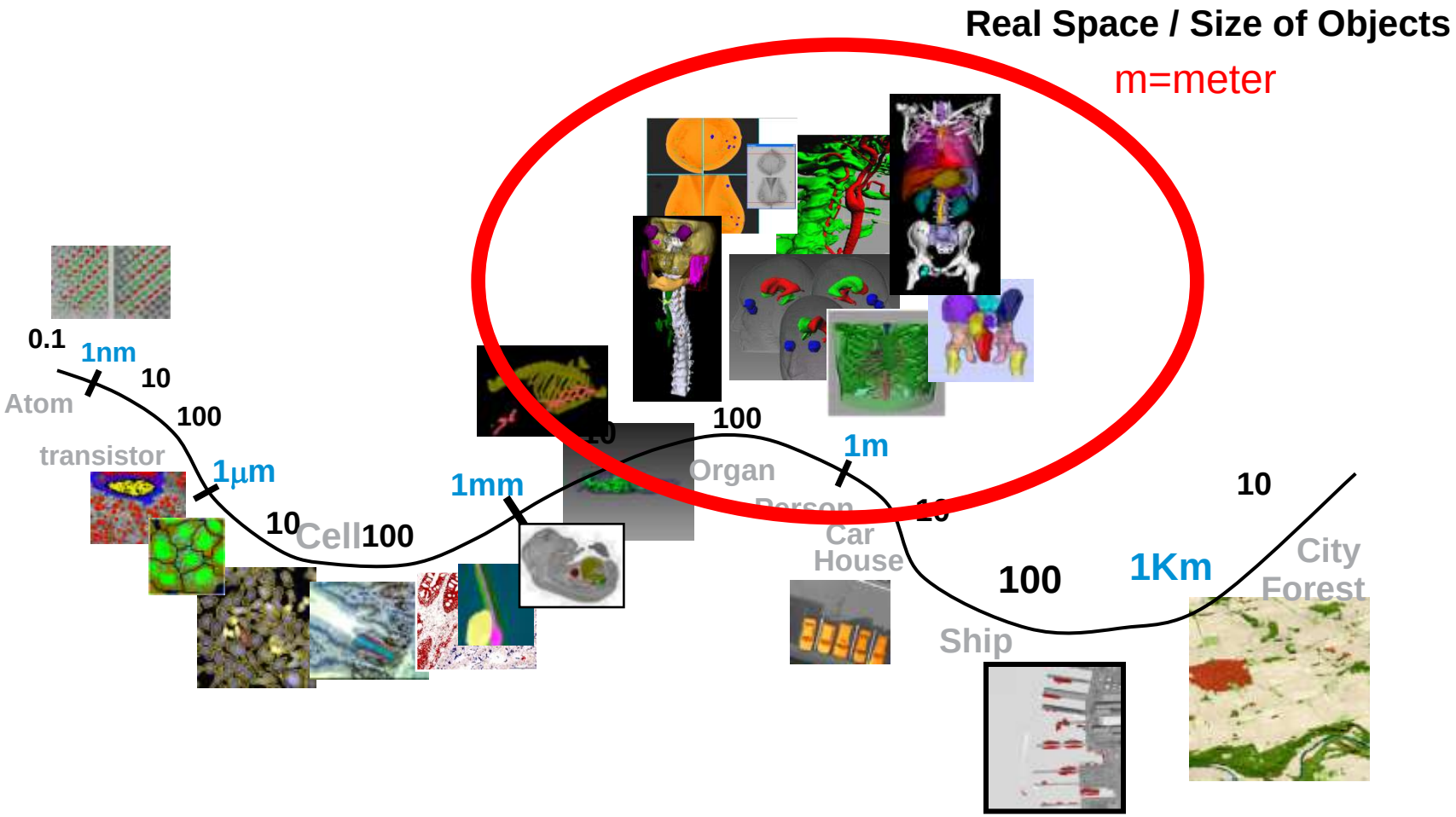
Fully automated detection of xenograft and separation of viable and necrotic regions of the tumor.



# Definiens TissueMap: enables research scientists to examine whole tissue section slides and tissue micro arrays in many different ways.
# It can:

- Manually select and quantify complex regions of interest in whole section slides
- Analyze xenografts including the detection of viable and necrotic regions
- Automatically detect and match cores in TMAs
- Analyze nuclear markers: detection of proliferation marker, e.g. Ki67/MIB1, PCNA, BrdU, steroid, hormone receptor marker like estrogen (ER), progesterone (PR) and apoptosis marker
- Analyze cytoplasmic markers: detection of regions of IHC stained cells using cytoceratin stains like AE1/3, CK5, CK15, CK8, CK14.
- Analyze membrane markers: detection and quantification of amount and intensity of stains in membranes, e.g. detection of membrane resident hormone-receptors like Her2neu or EFGR
- Classify positive nuclei based on intensity of IHC stain
- Customize and extend the Action Library with new image analysis routines
- Use clearly defined and documented interfaces between analysis steps
- Calculate fractions/ratios, areas, number and relationships
- Export statistics per slide or per TMA core respectively

# Traveling through the Dimensions of Space





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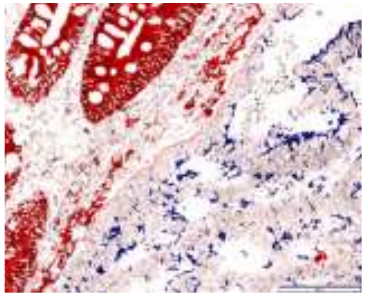
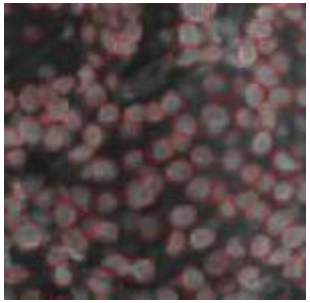
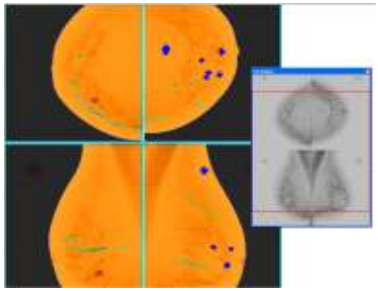
# One Technology – Many Applications
## Automatic Detection of Image Contents



**Biopsy**
Tissue

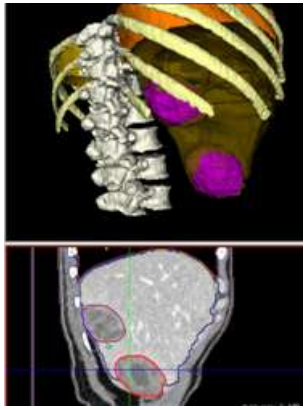


**Serum**
Cells

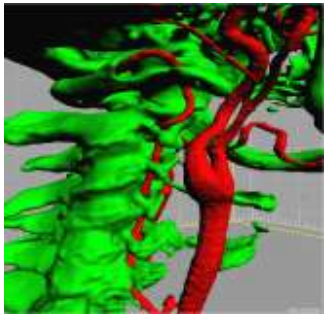


**X-Ray**
Mammography

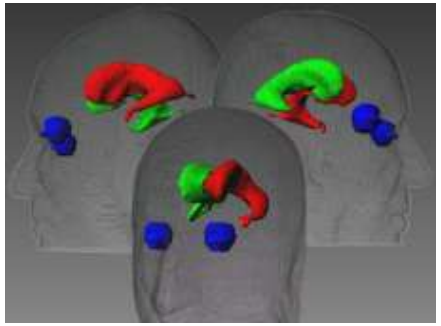
**CT**
Head/Neck



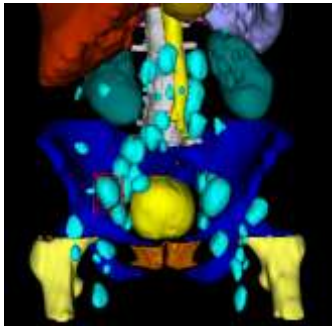
**CT**
Liver tumor



**CT**
Blood vessels



**MRI**
Ventricles



**CT**
Lymph Nodes

# Lymph Node Evaluation across the diagnostic and therapeutic chain

Comprehensive Diagnosis including lymph nodes

Assessment of metastasis by evaluation of lymphatic system

Assessment of therapy response by measuring lymph nodes

**Breast Cancer**

**Prostate Cancer**

**Colon Cancer**

**Lung Cancer**

## Screening

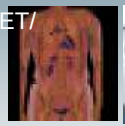
eg. Mammogr.

## Diagnostic

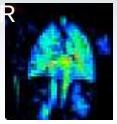
eg. CT Colonscopy

## Staging

eg. PET/ CT



eg. MR

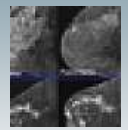


## Therapy

eg. Radio Therapy

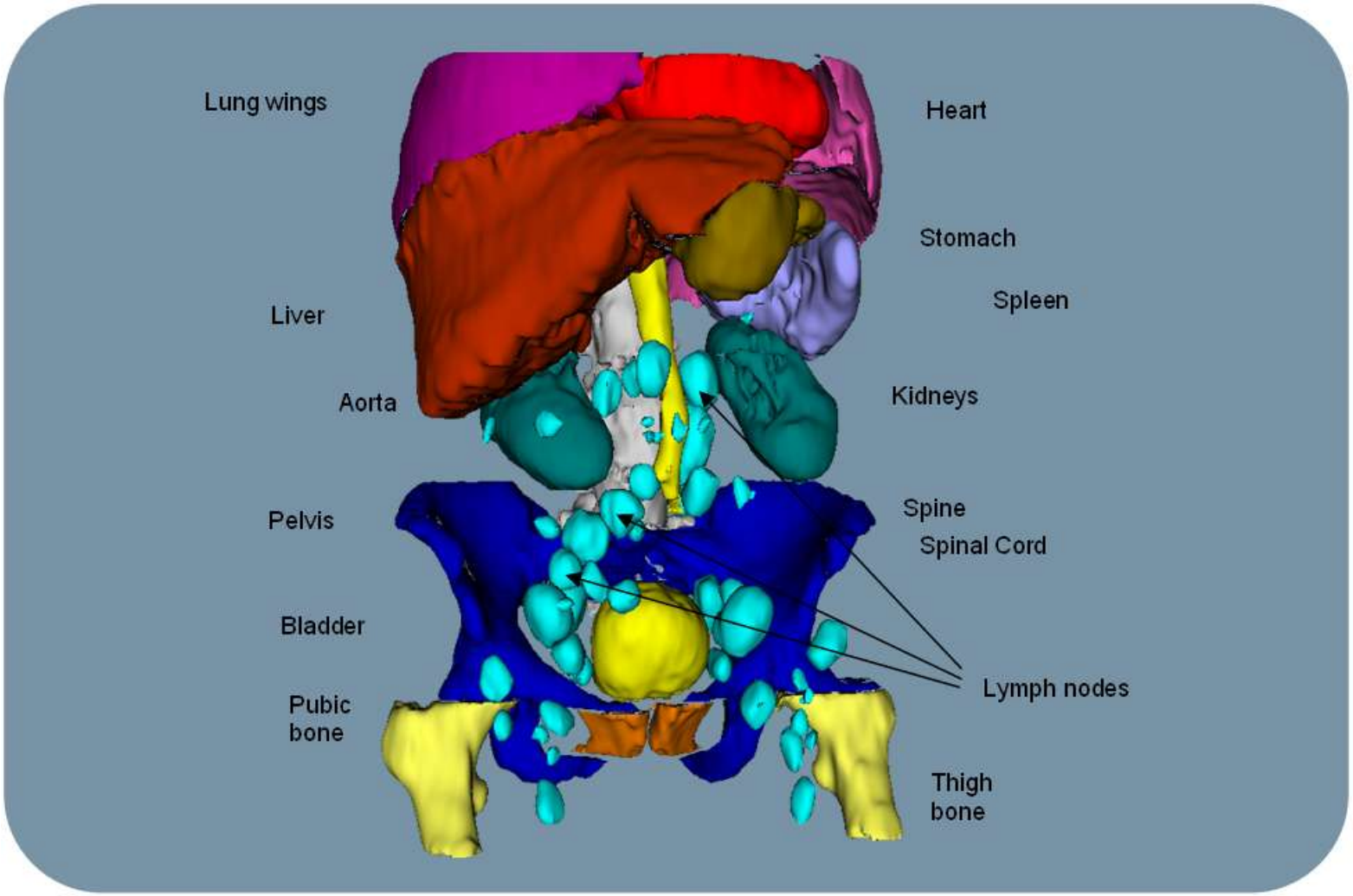
## Follow-up

eg. MR



eg. PET/ CT

# Tomorrow: 3D-View and 3D-Quantification






Lymph Nodes in the Context of Anatomical Objects

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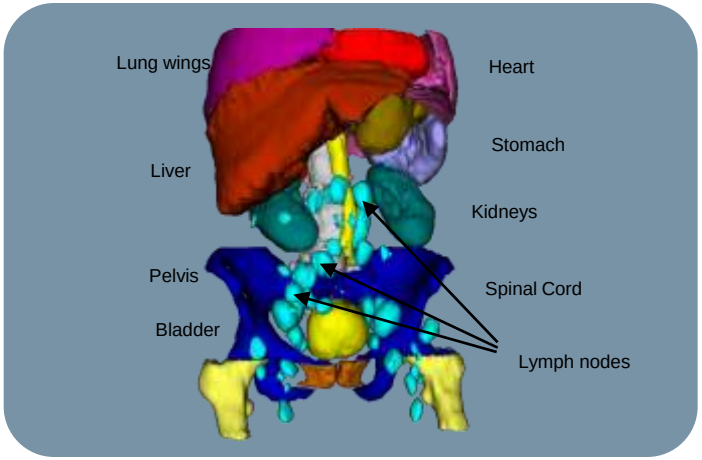
# Definiens Lymph Node Applications

## Semi-Automatic


## Fully Automatic

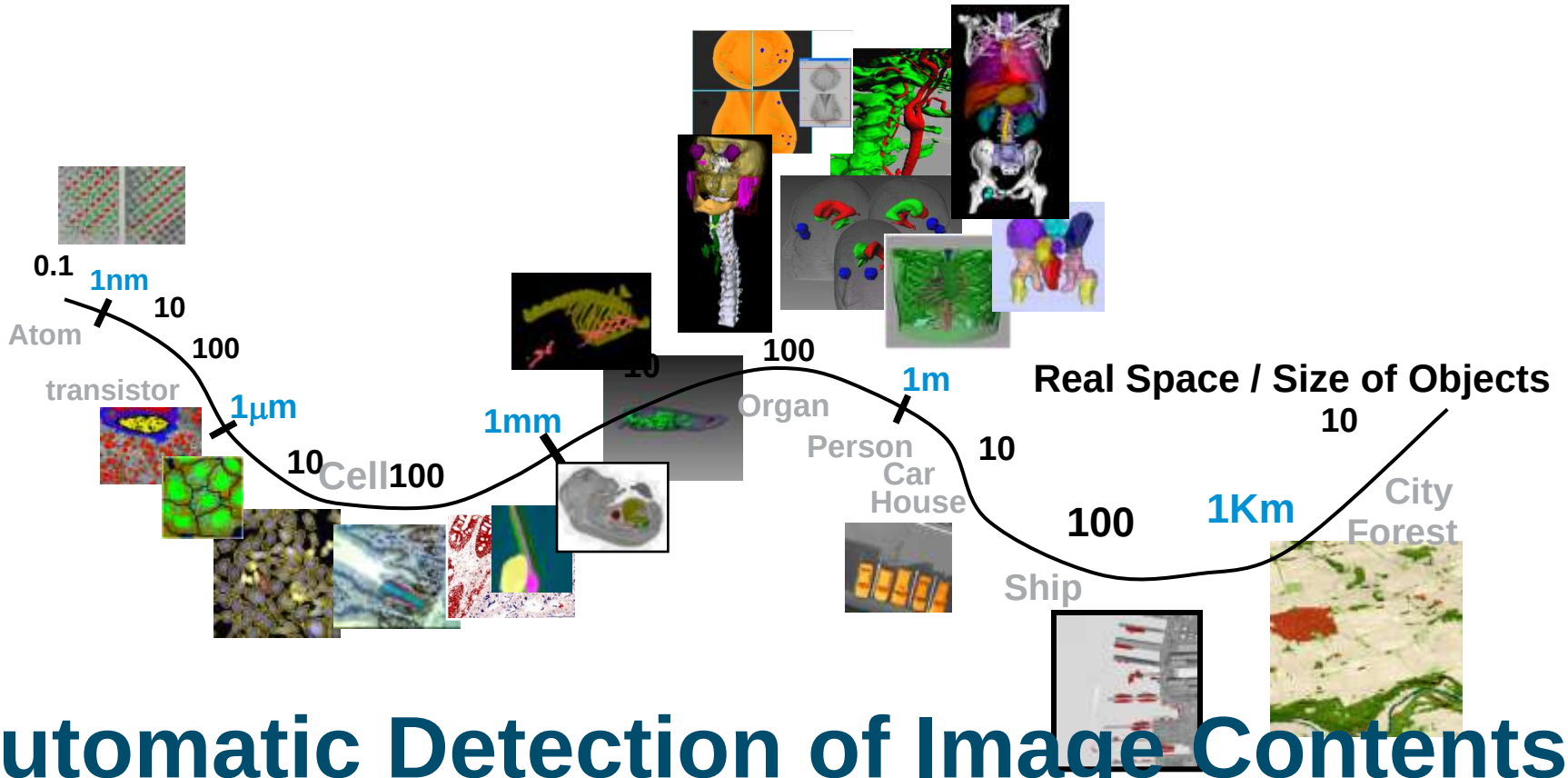



## Target Markets

- Semi-Automatic: Pharma and CRO companies to support clinical phase trials
- Fully-Automatic: Radiological institutes of all sizes; equipment manufacturers and SW companies as OEM partners

# One Technology – Many Applications

## Traveling through the Dimensions of Space




## Automatic Detection of Image Contents







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# Thank You for Your Attention

Further information is available on

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