



Medical University of Graz

WISSENSCHAFTLICHE UND MEDIZINISCHE RELEVANZ VON STANDARDS IN DER DIAGNOSTIK

Kurt Zatloukal

Diagnostic and Research Center for Molecular Biomedicine



Research Data Reproducibility

Reliability of 'new drug target' claims called into question

Bayer halts nearly two-thirds of its target-validation projects because in-house experimental findings fail to match up with published literature claims, finds a first-of-a-kind analysis on data irreproducibility.

Asher Mullard

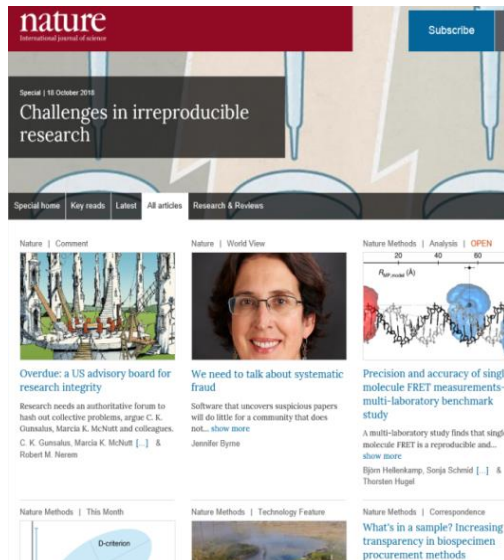
An unspoken industry rule alleges that at least 50% of published studies from academic laboratories cannot be repeated in an industrial setting, wrote venture capitalist Bruce Booth in a recent [blog post](#). A first-of-a-kind analysis of Bayer's internal efforts to validate 'new drug target' claims now not only supports this view but suggests that 50% may be an underestimate; the company's in-house experimental data do not match literature claims in 65% of

deep questions about whether we can really believe the literature, or whether we have to go back and do everything on our own."

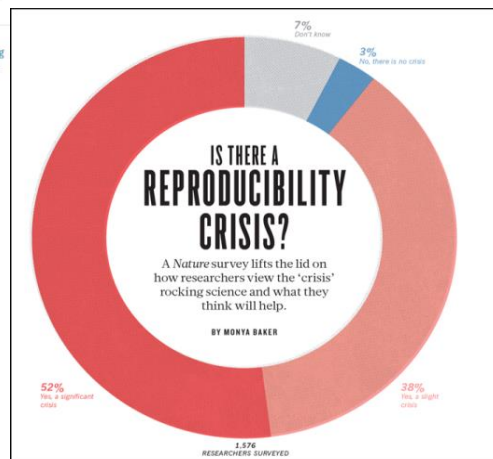
For the non-peer-reviewed analysis, Khursu Asadullah, Head of Target Discovery at Bayer, and his colleagues looked back at 67 target-validation projects, covering the majority of Bayer's work in oncology, women's health and cardiovascular medicine over the past 4 years. Of these, results from internal experiments matched up with the published findings in

and our own data," says Asadullah. These included inability to reproduce: over-expression of certain genes in specific tumour types; and decreased cell proliferation via functional inhibition of a target using RNA interference.

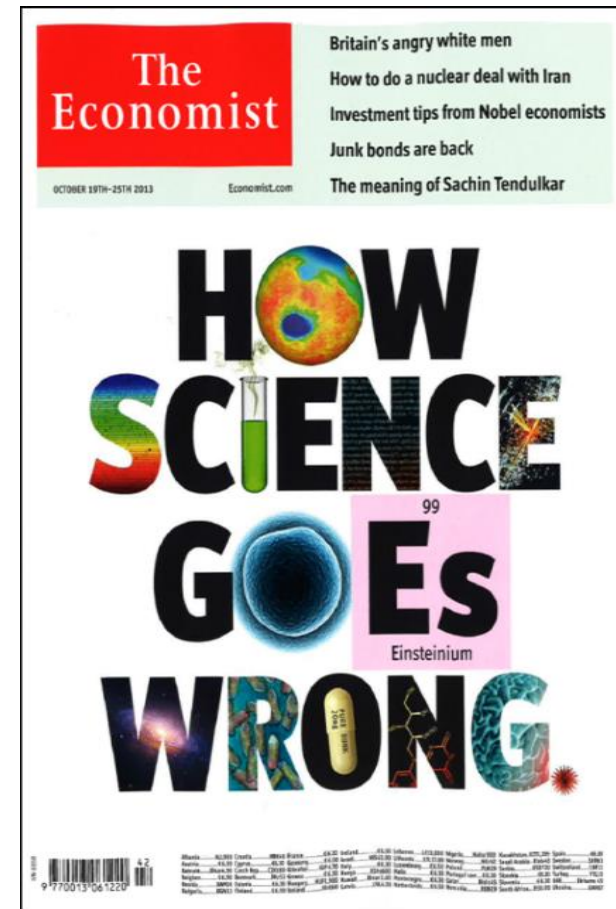
Irreproducibility was high both when Bayer scientists applied the same experimental procedures as the original researchers and when they adapted their approaches to internal needs (for example, by using different cell lines). High-impact journals did not seem



NATURE REVIEWS | DRUG DISCOVERY VOLUME 10 | SEPTEMBER 2011 | 643



M Baker & D Penny 454 | NATURE | VOL 533 | 26 MAY 2016

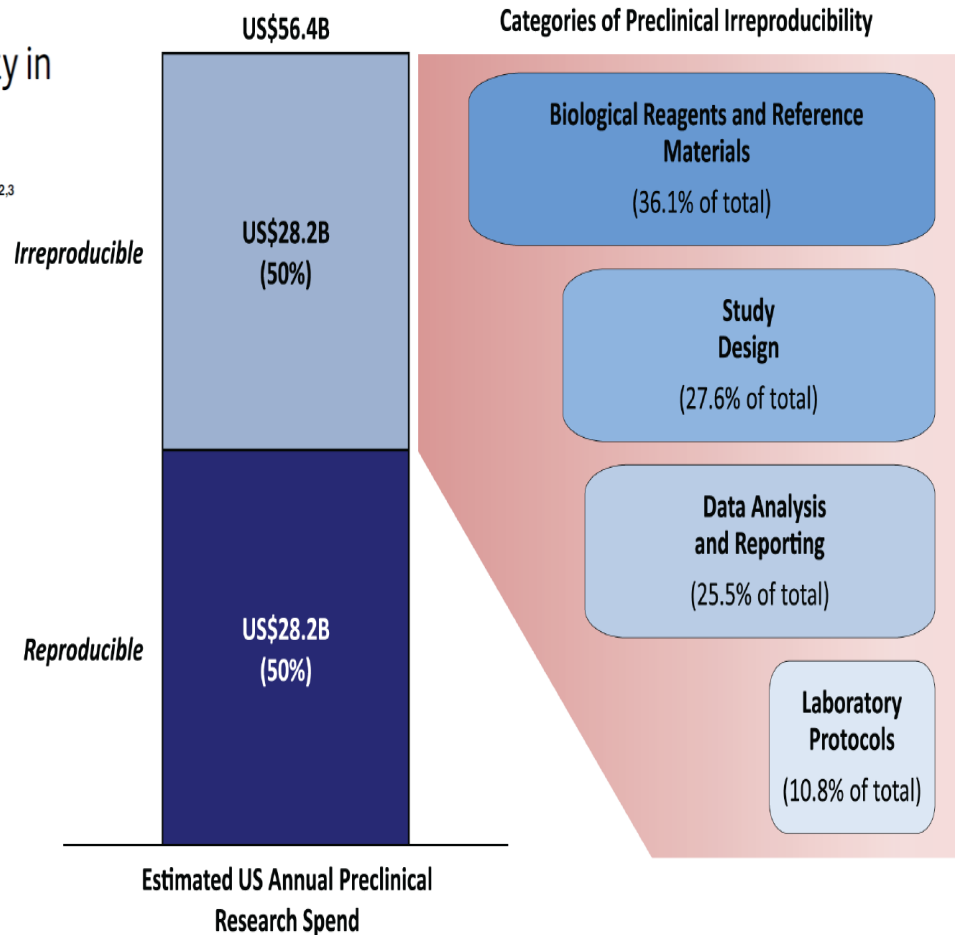


Data Reproducibility: Causes and Economic Impact

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

Leonard P. Freedman^{1*}, Iain M. Cockburn², Timothy S. Simcoe^{2,3}



Impact of Errors in Medical Diagnostics

- 46% - 68% of diagnostic testing process errors
- are in the pre-analytical phase

Plebani M, Clin Chem Lab Med. 2006

- 5 percent of U.S. adults experience a diagnostic error
- 10 percent of patient deaths can be attributed to diagnostic errors
- 6 to 17 percent of adverse events in hospitals are related to diagnostic errors

Institute of Medicine
SEPTEMBER 2015
Improving Diagnosis in Health Care
The National Academy of Sciences.



Companion Diagnostics:

A rapidly growing list (FDA)



DRUG	DISEASE	TARGET	BIOSAMPLE	ASSAY
ado-trastuzumab emtansine	Breast cancer	HER2	DNA/protein from FFPE tissue	IHC/FISH
ado-trastuzumab emtansine	Gastric cancer	HER2	DNA/protein from FFPE tissue	IHC/FISH
afatinib	NSCLC	EGFR	DNA from FFPE tissue	NGS/PCR
alectinib	NSCLC	ALK	DNA from FFPE tissue	NGS
ceritinib	NSCLC	ALK	DNA/Protein from FFPE tissue	NGS/IHC
cetuximab (1)	CRC	EGFR	Protein in FFPE tissue	IHC
cetuximab (2)	mCRC	KRAS	DNA from FFPE tissue	NGS/PCR
cobimetinib+ vemurafenib	Melanoma	BRAF	DNA from FFPE tissue	NGS
crizotinib	NSCLC	ALK	DNA from FFPE tissue	NGS/FISH
crizotinib	NSCLC	ROS1	RNA from FFPE tissue	NGS
crizotinib	NSCLC	ALK	Protein/DNA in FFPE tissue	IHC
dabrafenib	Melanoma	BRAF	DNA from FFPE tissue	NGS/PCR
dabrafenib+trametinib	NSCLC	BRAF	DNA/RNA from FFPE tissue	NGS
deferasirox	Thalassemia	Iron	Liver imaging	MRI
enasidenib	AML	IDH2	DNA from blood or bone marrow	PCR
Erlotinib	NSCLC	EGFR	DNA from FFPE tissue or cfDNA from blood	PCR/NGS
gefitinib	NSCLC	EGFR	DNA from FFPE tissue	PCR/NGS
imatinib mesylate	GIST	c-Kit	Protein in FFPE tissue	IHC
imatinib mesylate	MDS, MPD	PDGFRB	Fresh bone marrow	FISH
imatinib mesylate	ASM	c-Kit	Fresh bone marrow	PCR
midostaurin	AML	FLT3	DNA from blood or bone marrow	PCR
nilotinib	CML	BCR-ABL1	RNA from blood	RT-PCR
olaparib	Breast cancer	BRCA1/2	DNA from blood	PCR, Sanger seq.
osimertinib	NSCLC	EGFR	DNA from FFPE tissue or cfDNA from blood	PCR/NGS
panitumumab (1)	CRC	EGFR	Protein in FFPE tissue	IHC
panitumumab (2)	CRC	KRAS	DNA from FFPE tissue	PCR
panitumumab (3)	mCRC	KRAS/NRAS	DNA from FFPE tissue	NGS
pembrolizumab	NSCLC/gastric or GEJ Adenoca.	PD-L1	FFPE tissue	IHC
pertuzumab	Breast cancer	HER2/NEU	DNA/protein from FFPE tissue	NGS/IHC/FISH
rucaparib	Ovarian cancer	BRCA1/2	DNA from FFPE tissue	NGS
trametinib	Melanoma	BRAF	DNA from FFPE tissue	NGS/PCR
trastuzumab	Breast , Gastric Ca	HER2/NEU	DNA from FFPE tissue	NGS/FISH/IHC/CISH
vemurafenib	Melanoma	BRAF	DNA from FFPE tissue	NGS/PCR
venetoclax	CLL	LSI TP53	blood	FISH



Regulatory Requirements for IVD in EU

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

In force since May 26th 2017

To be applied to all diagnostics on the market and put into service
(by manufacturer and lab-developed tests)
from May 26th 2022

80% of all diagnostics on market are expected to require additional data

- Scientific evidence
- Analytical performance (incl. pre-analytics)
- Clinical performance



Sample Quality Requirements for Performance Testing

EN

Official Journal of the European Union

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAM

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/2010/227/EU

**Needs
biosamples with
defined pre-
analytical quality**

6.1. Information on analytical performance of the device

6.1.1. Specimen type

This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage conditions such as duration, temperature limits and freeze/thaw cycles.

6.1.2. Analytical performance characteristics

Compliance with IVDR is Mandatory also for LDT for Pathology from 2022

Article 5.

With the exception of the relevant **general safety and performance requirements set out in Annex I**, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

- (a) the devices are **not transferred to another legal entity**;
- (b) manufacture and use of the devices occur under appropriate quality management systems;
- (c) the laboratory of the health institution is **Compliant with standard EN ISO 15189** or where applicable national provisions, including national provisions regarding accreditation;
- (d) the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an **equivalent device available on the market**;
- (e) the health institution **provides information upon request** on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;

ISO Standards and CEN/TS for Pre-examination Processes



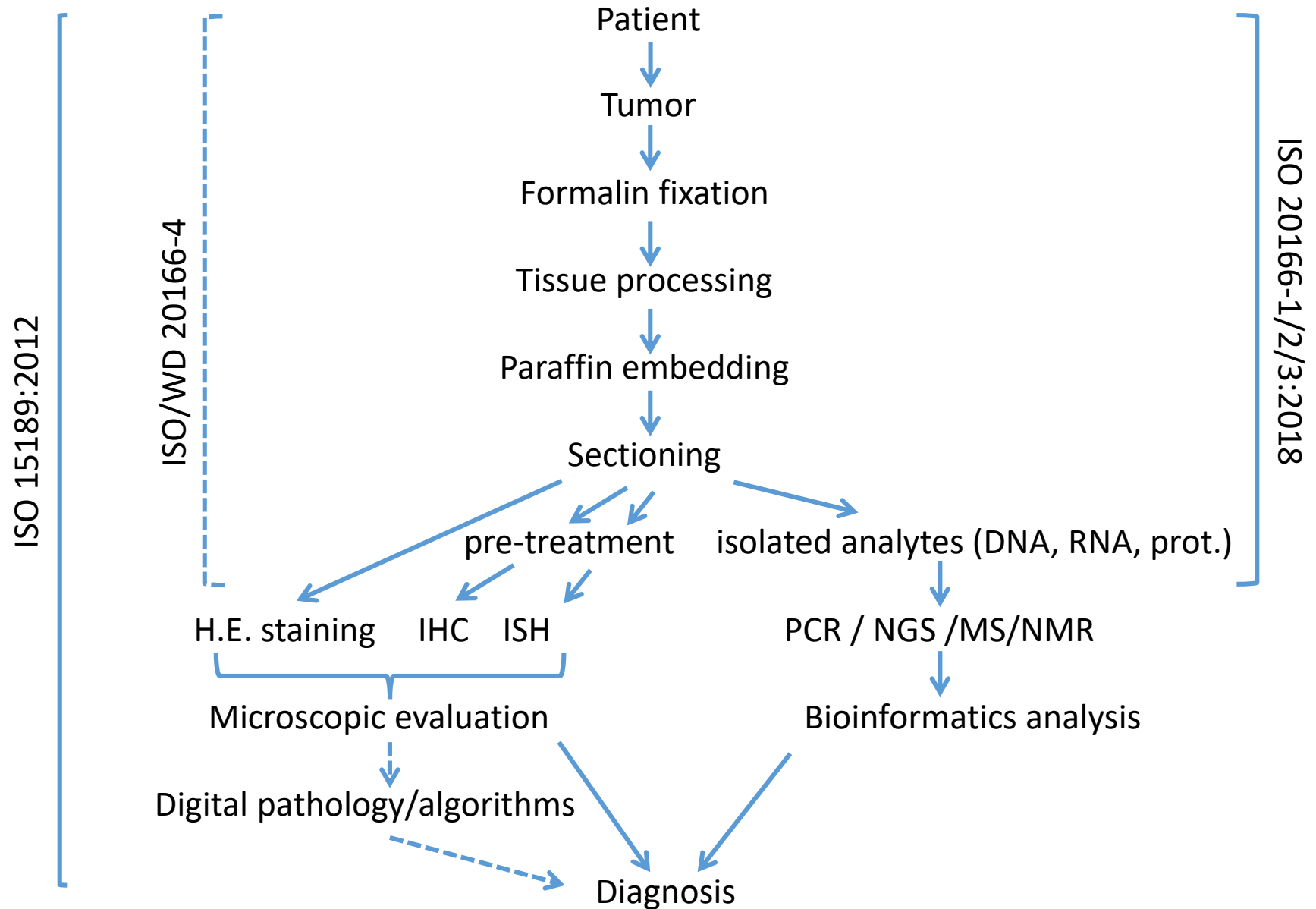
- Frozen tissue – Part 1: Isolated RNA; EN ISO 20184-1:2018
- Frozen tissue – Part 2: Isolated proteins; EN ISO 20184-2:2018
- Frozen tissue - Part 3: Isolated DNA; CEN/TS16826-3: 2018
- FFPE tissue – Part 1: Isolated DNA; EN ISO 20166-3:2018
- FFPE tissue – Part 2: Isolated RNA; EN ISO 20166-1:2018
- FFPE tissue – Part 3: Isolated proteins; EN ISO 20166-2:2018
- Venous whole blood – Part 1: Isolated cellular RNA; EN ISO 20186-1: 2019
- Venous whole blood – Part 2: Isolated genomic DNA; EN ISO 20186-2: 2019
- Venous whole blood – Part 3: Isolated circulating cell free DNA from plasma; EN ISO 20186-3: 2019
- Metabolomics in urine, venous blood serum and plasma; CEN/TS 16945:2016
- Saliva - Isolated human DNA; CEN/TS 17305:2019
- Circulating tumor cells (CTCS) - Part 1: Isolated RNA; CEN/TS 17390-1:2020
- Circulating tumor cells (CTCS) - Part 2: Isolated DNA; CEN/TS 17390-2:2020
- Circulating tumor cells (CTCS) - Part 3: Preparation for analytical CTC staining; CEN/TS 17390-3:2020

More To Come



- WI 00140126: Specifications for pre-examination processes for **Fine Needle Aspirates (FNA)** – Part 2: Isolated **proteins**
- WI 00140127: Specifications for pre-examination processes for human specimen - Isolated **microbiome DNA**
- WI 00140128: Specifications for pre-examination processes for **Fine Needle Aspirates (FNA)** – Part 1: Isolated **cellular RNA**
- WI 00140129: for pre-examination processes for **Fine Needle Aspirates (FNA)** – Part 3: Isolated **genomic DNA**
- WI 00140130: Specifications for pre-examination processes for **urine and other body fluids** – Isolated **cell free DNA**
- WI 00140133: Specifications for pre-examination processes for **exosomes** and other extracellular vesicles in venous whole blood – Isolated **RNA, DNA and proteins**
- prEN ISO 23118 (WI 00140132) : Specifications for pre-examination processes for **metabolomics in urine, venous blood serum and plasma**
- prEN ISO 20166-4 (WI 00140136): Specifications for pre-examination processes for **formalin-fixed and paraffin-embedded (FFPE) tissue** - Part 4: In situ detection techniques

Standards for Pre-examination and Medical Diagnostics



Topics Addressed by the ISO Standards

Example: FFPE tissue – Part 1:

Isolated DNA; EN ISO 20166-3:2018

Introduction

1 Scope

2 Normative reference

3 Terms and definitions

4 General considerations

5 Outside the laboratory

5.1 Specimen collection

5.1.1 General

5.1.2 Information about the specimen donor/patient

5.1.3 Information about the specimen

5.1.4. Specimen processing

5.2 Transport requirements

6 Inside the laboratory

6.1 Information about the reception of the specimen

6.2 Formalin fixation of the specimen or sample

6.3 Evaluation of the pathology of specimen and selection of sample(s)

6.4 Post-fixation of frozen samples

6.5 Decalcification

6.6 Processing and paraffin embedding

6.7 Storage requirements

6.8 Isolation of DNA

6.8.1 General

6.8.2 General information for DNA isolation procedures

6.8.3 Using commercial kits

6.8.4 Using laboratories' own protocols

6.9 Quality and quality assessment of isolated DNA

6.10 Storage of isolated DNA

Annex A: Impact of the storage temperature on DNA integrity in FFPE blocks of tissue

Bibliography

Need for Evidence-Based Standards

Reproducibility Depends on Quality

OBRR Office of Biorepositories
and Biospecimen Research

GARBAGE IN \Rightarrow GARBAGE OUT

Many SOPs Around the World: Which are the Best?

OBRR Office of Biorepositories
and Biospecimen Research

- Impossible to call any one "best" (even NCI's)
 - All have strengths and weaknesses
 - No single set of SOPs are applicable to all clinical and research analytical platforms
 - Very few SOPs are based on **scientific evidence**

Where we need to go

from C. Compton, NCI USA

USA



The screenshot shows the top section of the National Cancer Institute website. At the top is a red banner with the NCI logo on the left, the text "National Cancer Institute" in the center, and "U.S. National Institutes of Health | www.cancer.gov" on the right. Below the banner, the "OBBR" logo is prominently displayed next to the text "Office of Biorepositories and Biospecimen Research". To the right of the OBBR logo are two buttons: "Launch NCI Best Practices" and "Launch caHUB". Below these buttons is a search bar with a magnifying glass icon and a "Search" button. A navigation bar contains links: "About OBBR", "About NCI Best Practices", "Biospecimen Research Network", "caHUB", "News and Events", and "Public Resources". A large banner for the "Biospecimen Research Network" is at the bottom, featuring a microscopic image of cells.

National Cancer Institute

U.S. National Institutes of Health | www.cancer.gov

OBBR Office of Biorepositories and Biospecimen Research

Launch NCI Best Practices Launch caHUB

Sign Up For Updates Search

About OBBR About NCI Best Practices Biospecimen Research Network caHUB News and Events Public Resources

Biospecimen Research Network

Europe



The screenshot shows the top section of the SPIDIA website. The header is dark blue with the SPIDIA logo on the left and the text "Standardisation and improvement of generic pre-analytical tools and procedures for in-vitro diagnostics" on the right. Below the header is a navigation bar with links: "Home", "About Us", "About the Project", "News and Press", "Events and Trainings", "Publications", "Links", and a printer icon. The main content area is divided into two columns. The left column has a "NEWSLETTER" section with a link to "Subscribe to our newsletter to receive latest news about the project". The right column has an "ABOUT SPIDIA" section with a paragraph of text.

SPIDIA Standardisation and improvement of generic pre-analytical tools and procedures for in-vitro diagnostics

Home About Us About the Project News and Press Events and Trainings Publications Links

Home

NEWSLETTER

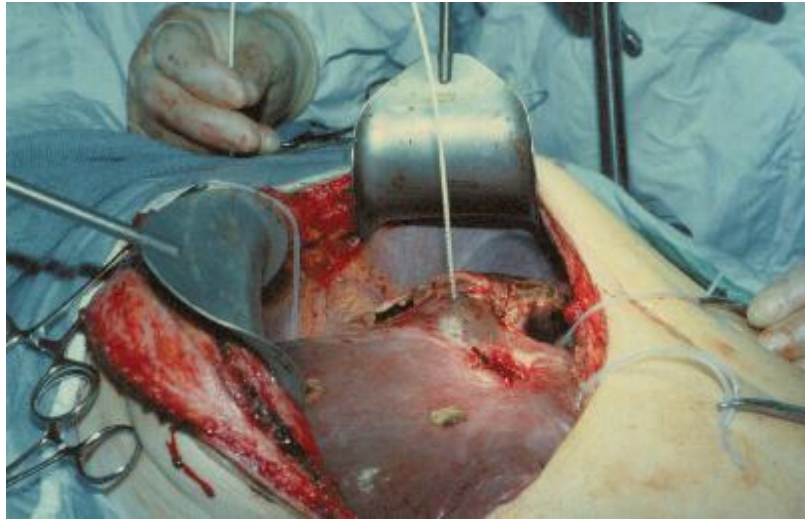
Subscribe to our newsletter to receive latest news about the project

ABOUT SPIDIA

SPIDIA is a 4.5-year project, funded by the European Union FP7 programme to the value of 9 million Euros, which brings together a consortium of 16 leading academic institutions, international organisations and life sciences companies.

Diagnostik- und Forschungszentrum für Molekulare BioMedizin

Warm and Cold Ischemia Effects



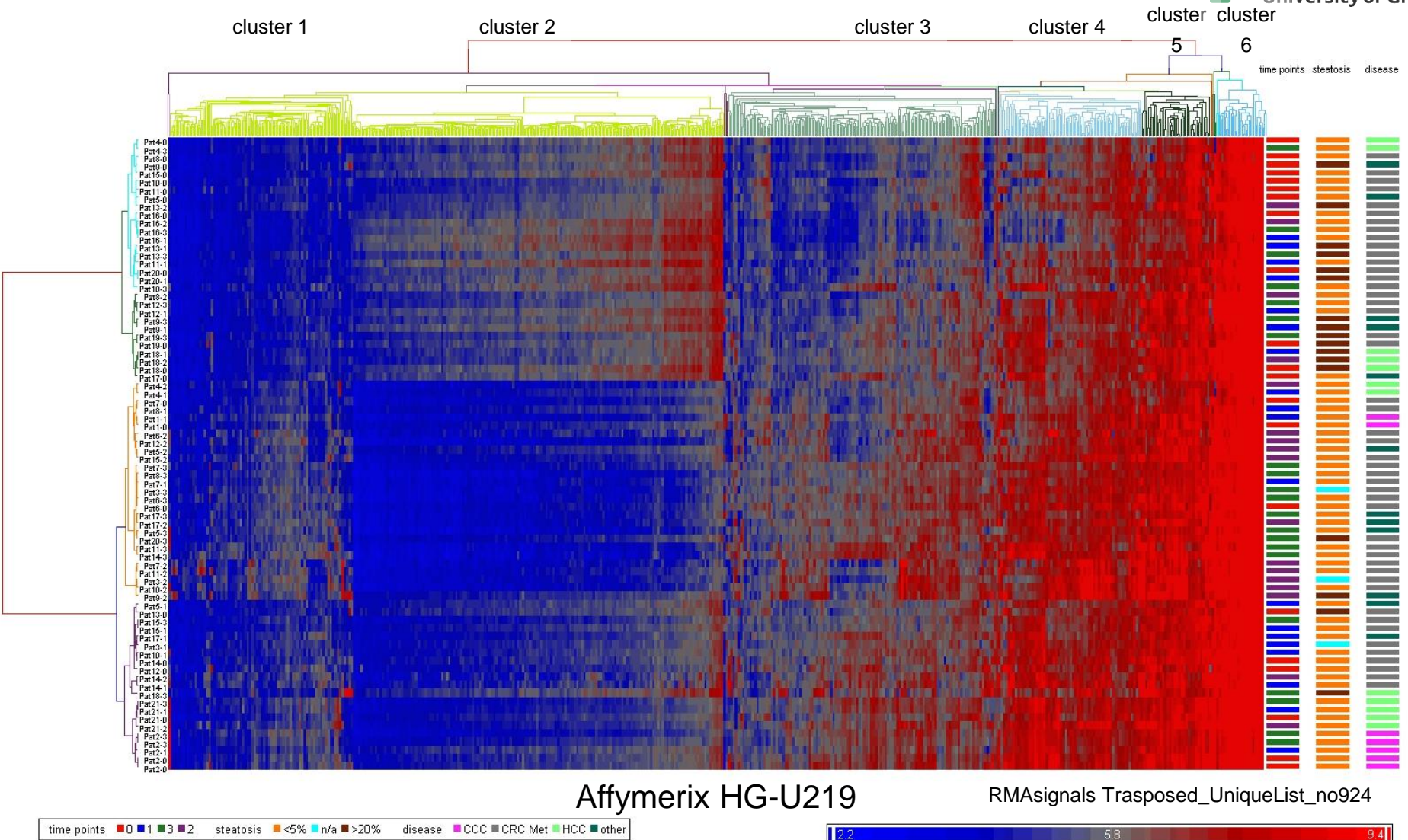
Clinical study in Pringle manoeuvre liver surgery

Snap frozen liver samples collected at :

- ▶ **T0** sample before Pringle start: **medication**
- ▶ **T1** sample 30min after Pringle start: **warm ischemia**
- ▶ **T2** sample 30min after Pringle ending: **ischemia- reperfusion**
- ▶ **T3** sample after resection: **cold ischemia**



Ischemia and Gene Expression



FC1,5_p0,05 924 genes

Alteration in Gene Expression is an Active Response

Response to stress

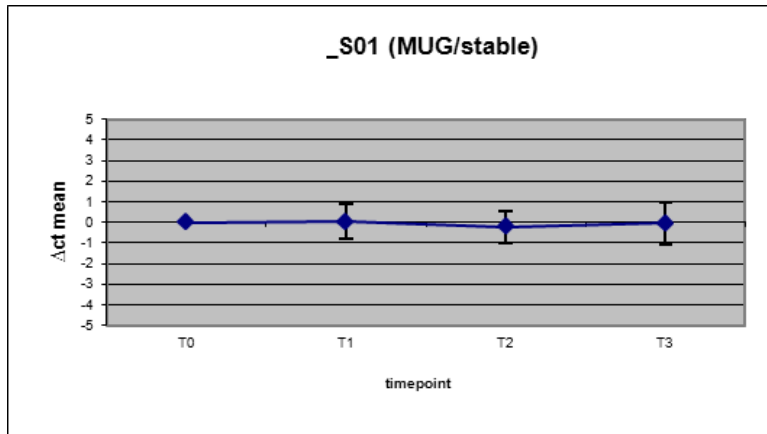
HSPA1B Heat shock 70 kDa protein 1
 HSPA6 Heat shock 70 kDa protein 6
 GADD45B Growth arrest and DNA-damage-inducible protein GADD45 beta
 CRP Cysteine and glycine-rich protein 1
 DNAJB4 DnaJ homolog subfamily B member 4
 DNAJB1 DnaJ homolog subfamily B member 1
 PLK2 Serine/threonine-protein kinase PLK2
 CRP C-reactive protein(1-205)
 DUSP1 Dual specificity protein phosphatase 1
 HSPA8 Heat shock cognate 71 kDa protein
 IER3 Radiation-inducible immediate-early gene IEX-1
 GADD45G Growth arrest and DNA-damage-inducible protein GADD45 gamma
 CEBPB CCAAT/enhancer-binding protein beta
 NFKBIA NF-kappa-B inhibitor alpha
 RNF152 RING finger protein 152
 FOSL2 Fos-related antigen 2
 HSPH1 Heat shock protein 105 kDa

Response to stimulus

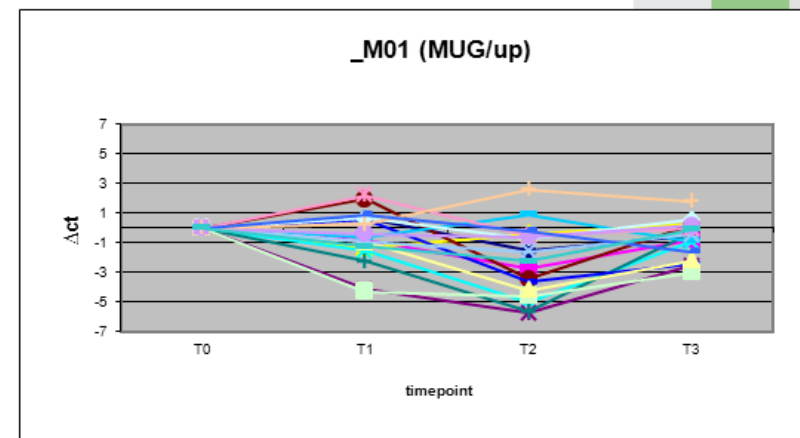
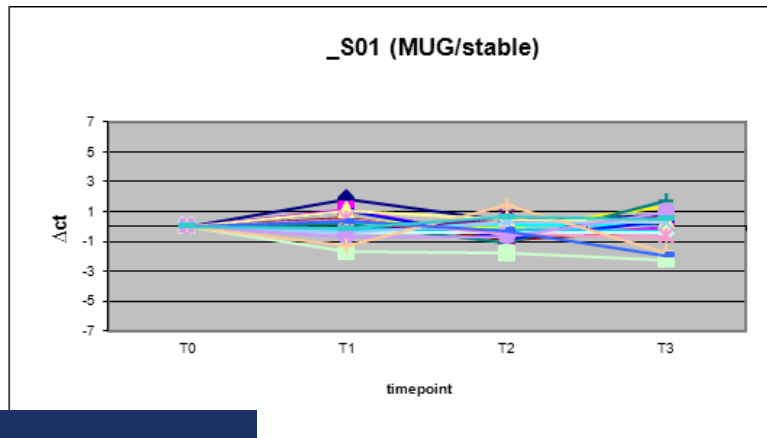
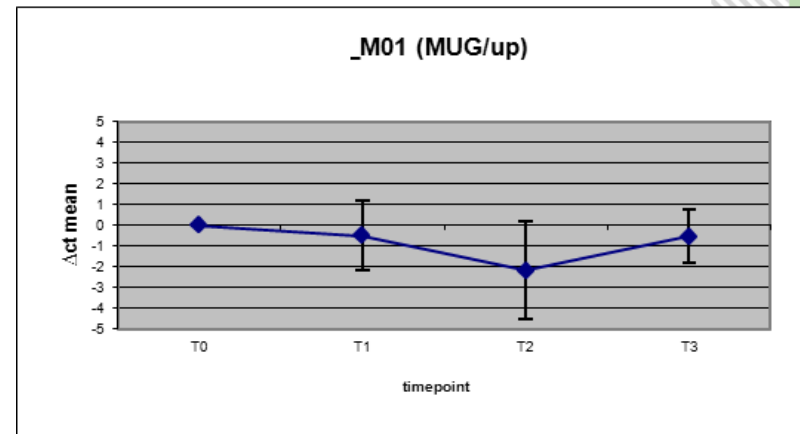
ABCC9 ATP-binding cassette transporter sub-family C member 9
 ANGPTL4 Angiopoietin-related protein 4
 CEBPB CCAAT/enhancer-binding protein beta
 CISH Cytokine-inducible SH2-containing protein
 CRP Cysteine and glycine-rich protein 1
 CXCL2 GRO-beta(5-73)
 CXCR7 C-X-C chemokine receptor type 7
 DNAJB1 DnaJ homolog subfamily B member 1
 DNAJB4 DnaJ homolog subfamily B member 4
 DUSP1 Dual specificity protein phosphatase 1
 ELF3 ETS-related transcription factor Elf-3
 ETS2 Protein C-ets-2
 FHL1 Four and a half LIM domains protein 1
 FOSL2 Fos-related antigen 2
 GADD45B Growth arrest and DNA-damage-inducible protein GADD45 beta
 GADD45G Growth arrest and DNA-damage-inducible protein GADD45 gamma
 HSPA1B Heat shock 70 kDa protein 1
 HSPA6 Heat shock 70 kDa protein 6
 HSPA8 Heat shock cognate 71 kDa protein
 HSPH1 Heat shock protein 105 kDa
 ICAM1 Intercellular adhesion molecule 1
 IER3 Radiation-inducible immediate-early gene IEX-1
 IL1RN Interleukin-1 receptor antagonist protein
 IRF1 Interferon regulatory factor 1
 IRF8 Interferon regulatory factor 8
 KLF6 Krueppel-like factor 6
 NFATC2 Nuclear factor of activated T-cells, cytoplasmic 2
 NFIL3 Nuclear factor interleukin-3-regulated protein
 NFKBIA NF-kappa-B inhibitor alpha
 NFKBIZ NF-kappa-B inhibitor zeta
 PLK2 Serine/threonine-protein kinase PLK2
 RNF152 RING finger protein 152
 TMPRSS2 Transmembrane protease, serine 2 catalytic chain

Individual Response to Ischemia (qRT-PCR Verification)

stable

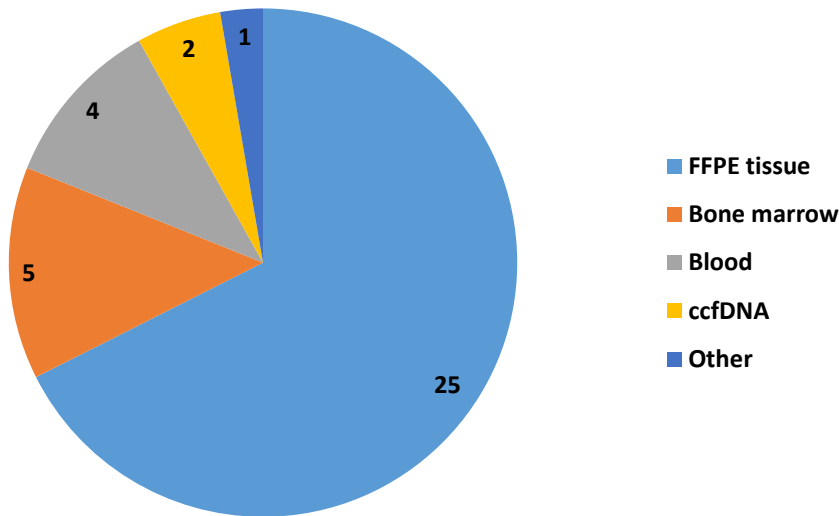


unstable



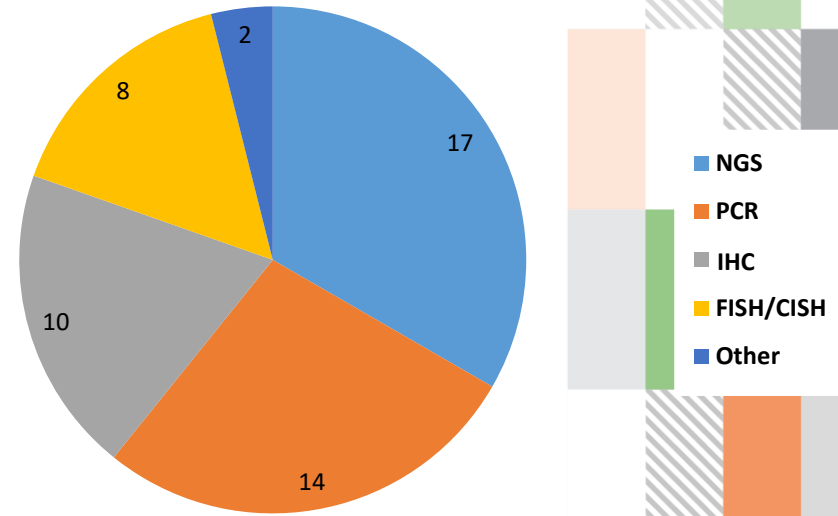
Companion Diagnostics (FDA-listed)

Biosamples



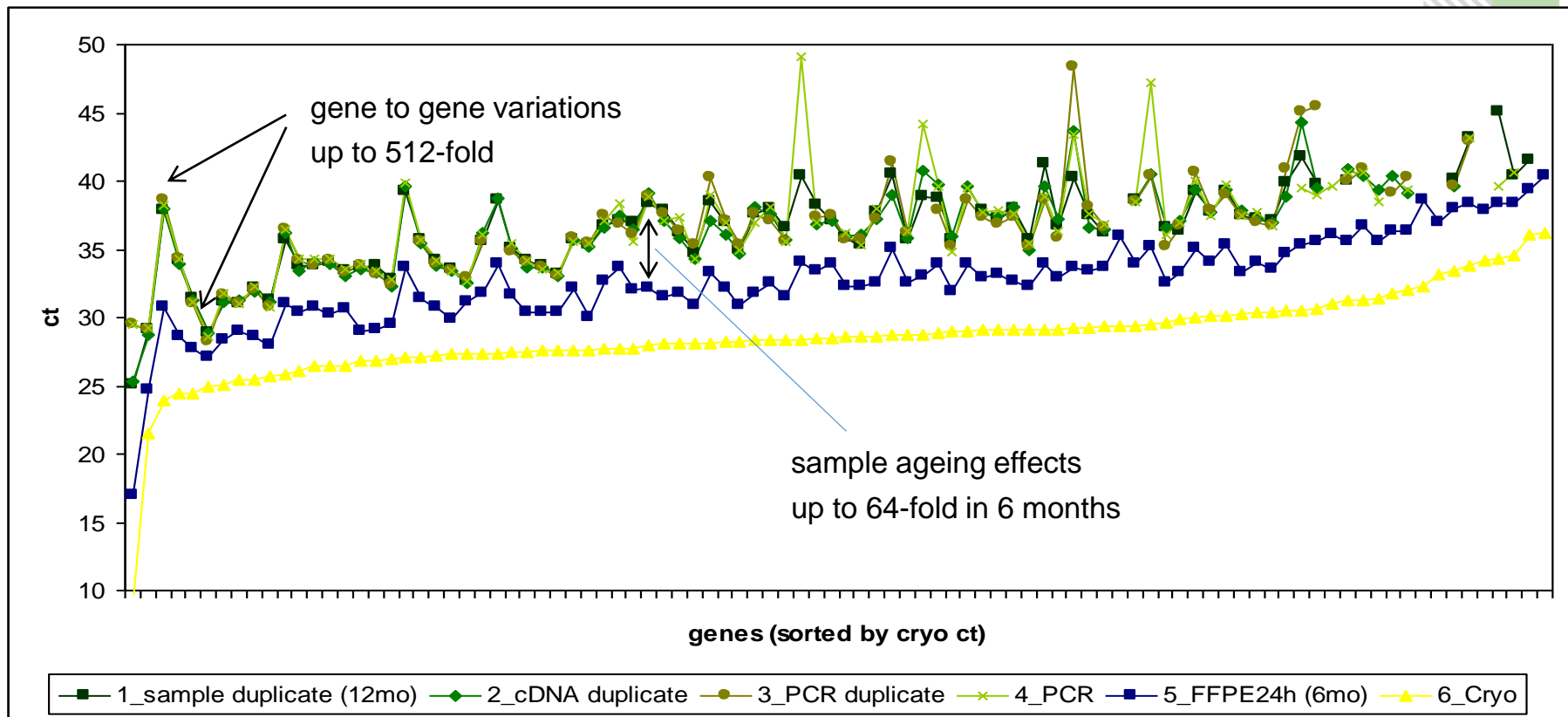
FFPE tissue is the most common biosample for companion diagnostics

Assays

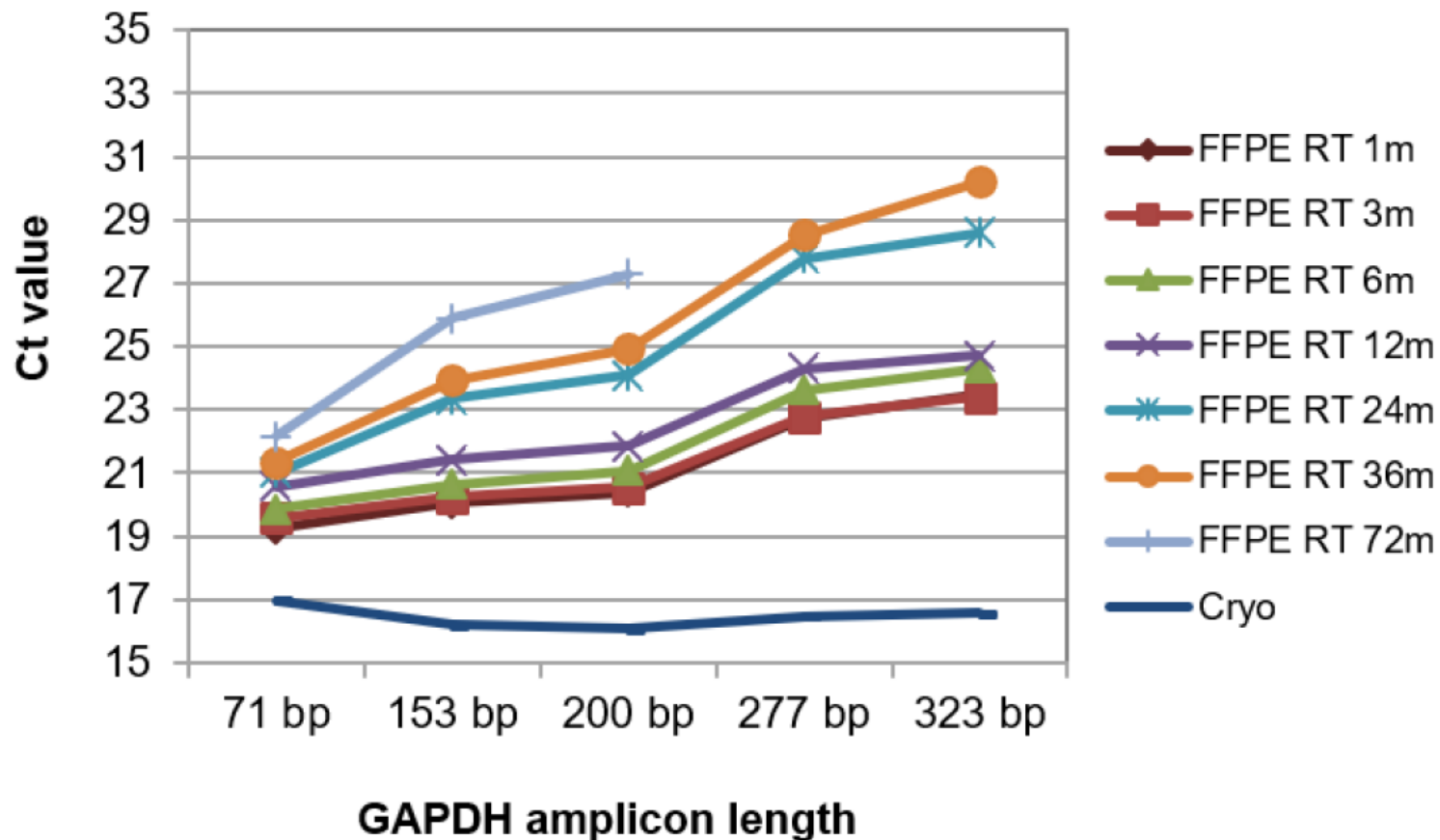


In-situ detection is the most common assay for companion diagnostics

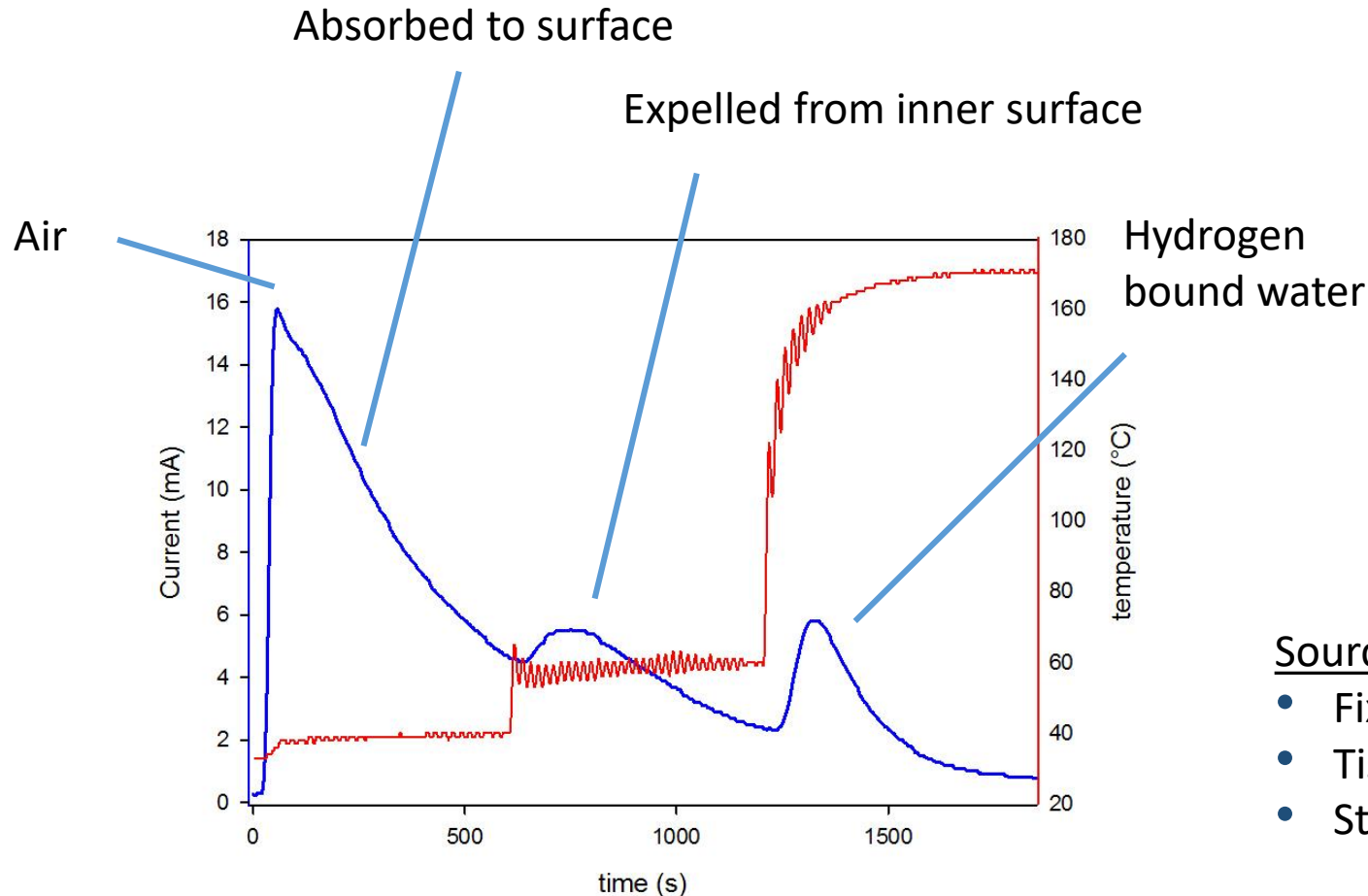
Formalin Fixation Interferes with qRT-PCR



Ageing Effects on RNA Quality in FFPE Tissues



Water Content of FFPE Tissue



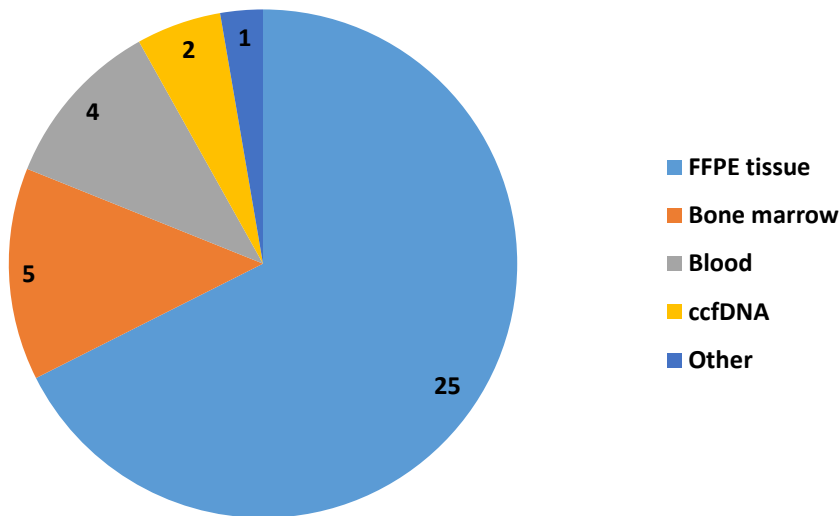
Phosphorous pentoxide – based water analysis

Sources of residual water:

- Fixation
- Tissue processing
- Storage

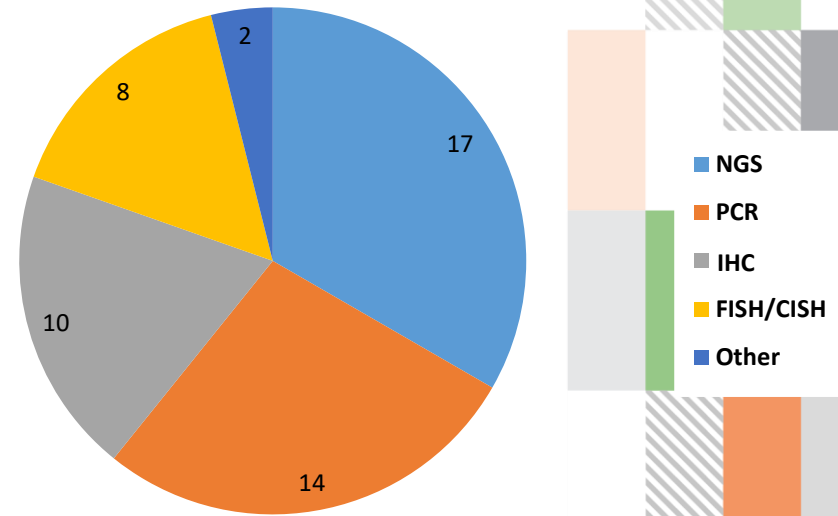
Companion Diagnostics (FDA-listed)

Biosamples



FFPE tissue is the most common biosample for companion diagnostics

Assays



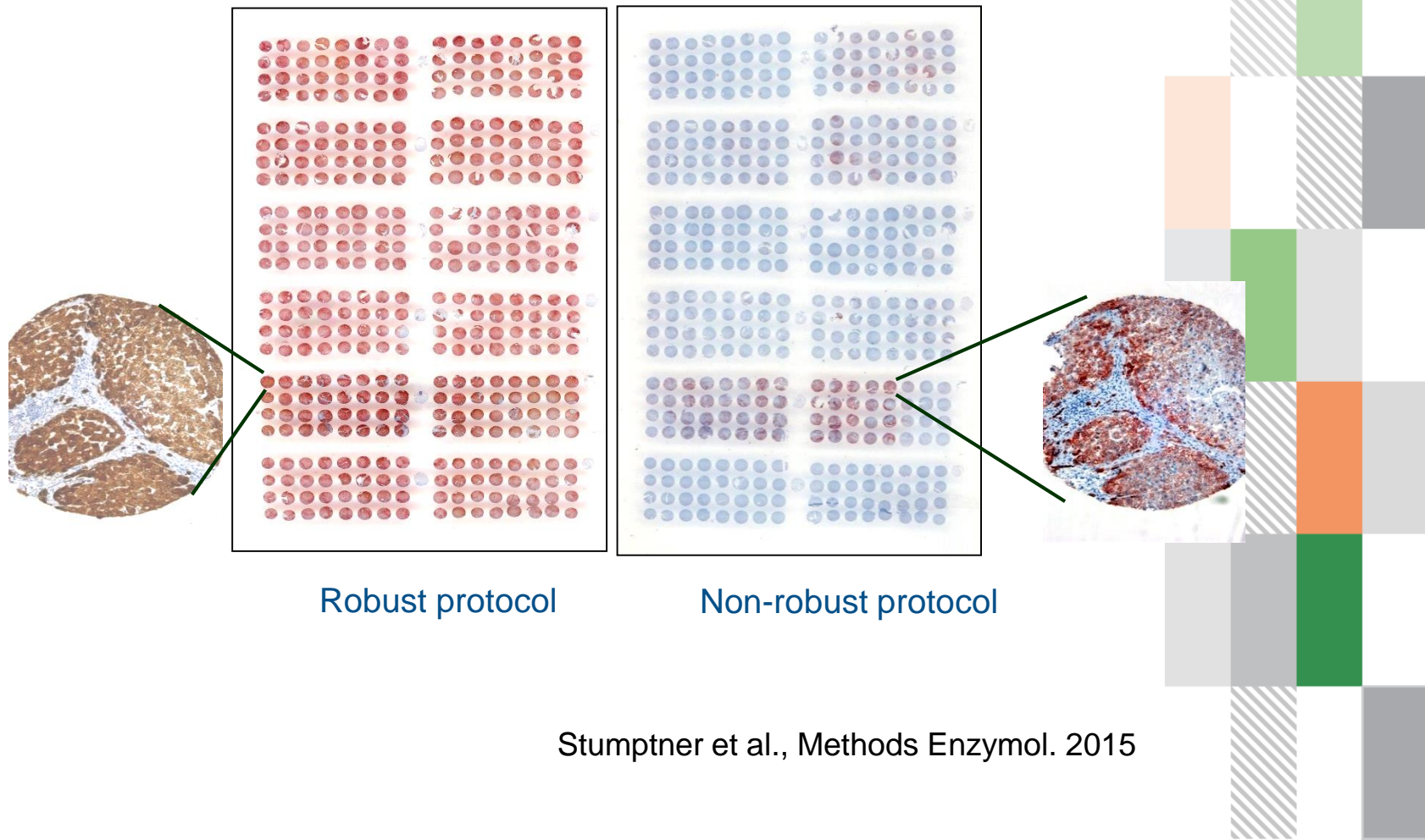
In-situ detection is the most common assay for companion diagnostics

IHC Protocol Verification

- ▶ 4x autolysis, 4x fixation, 6x cases, 4x replicas = 72 samples
- ▶ 5x antibodies, 3x concentrations, 4x retrieval, 2x detection systems =
120 IHC conditions
- ▶ **Total 8640 reactions for 1 antigen**

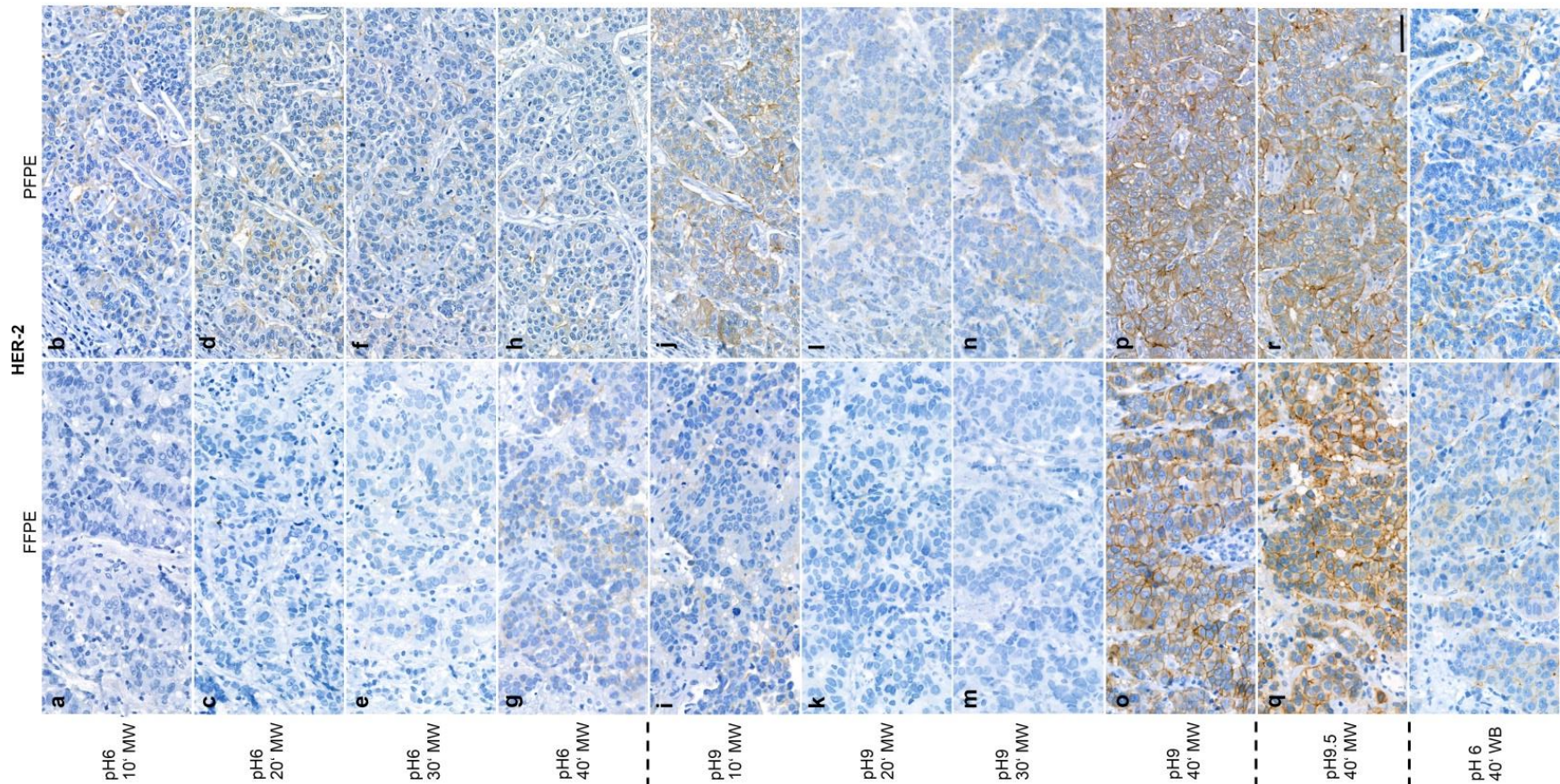


Differences in Protocol Robustness



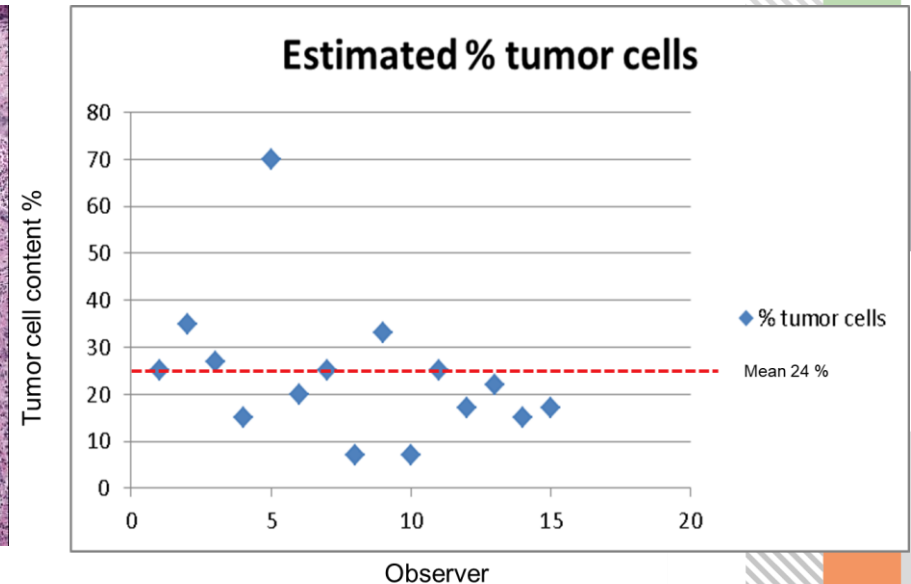
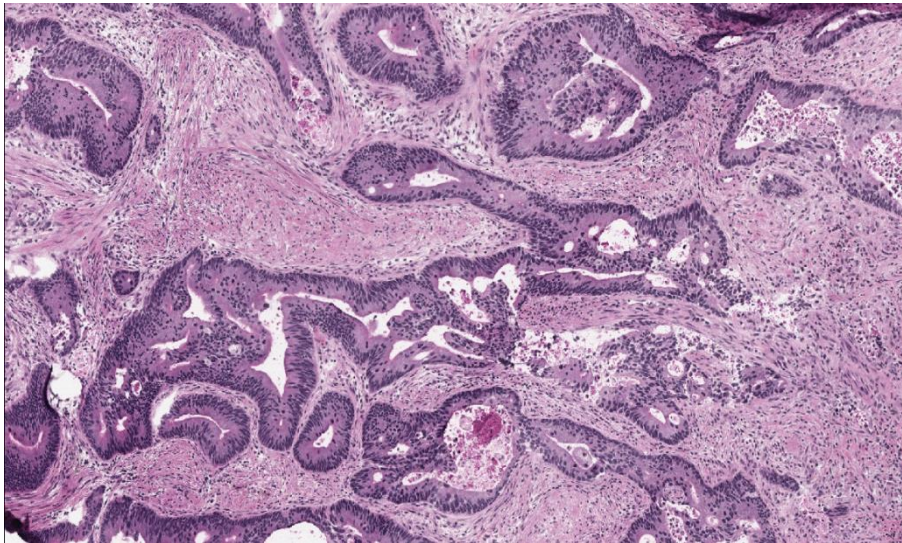
Differences: Analytical and Clinical Performance

Breast cancer HER-2 IHC

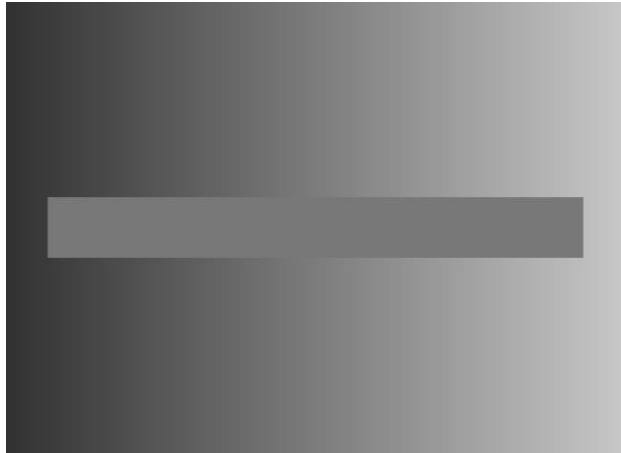


Quantification of Complex Patterns

Example: Evaluation of Tumor Content



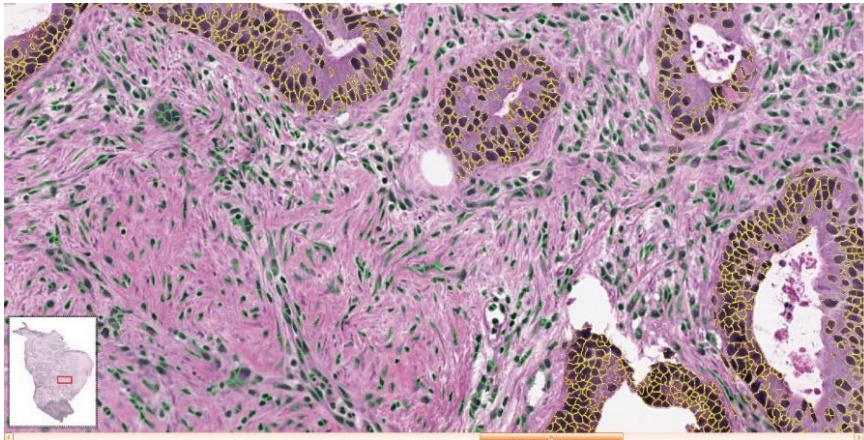
Bias by Visual Illusion



- ▶ Source: Wikipedia Creative Commons Licence
- ▶ Von Dodek - Eigenes Werk, CC BY-SA 3.0,
- ▶ <https://commons.wikimedia.org/w/index.php?curid=1529278>



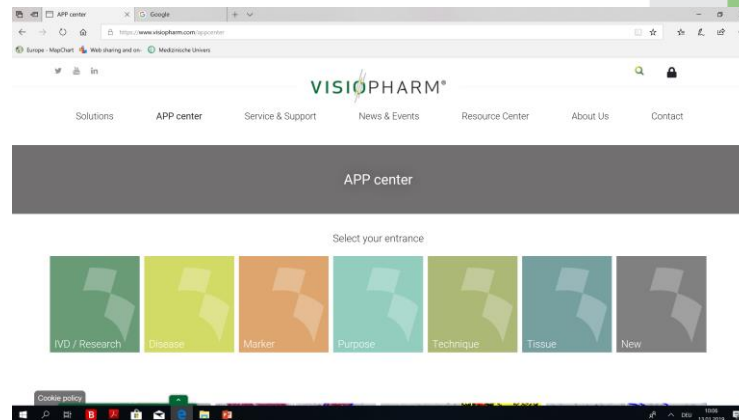
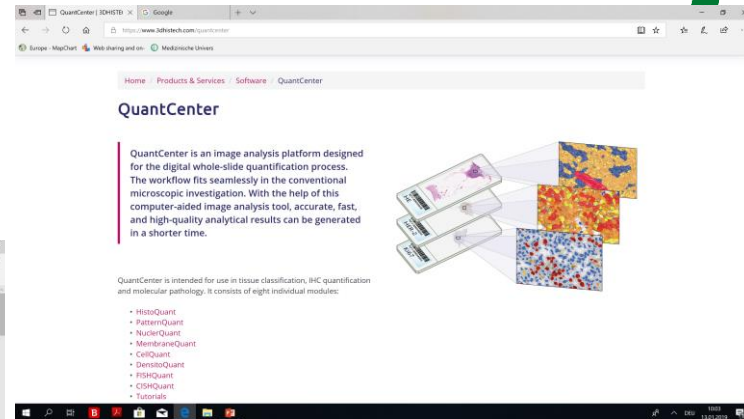
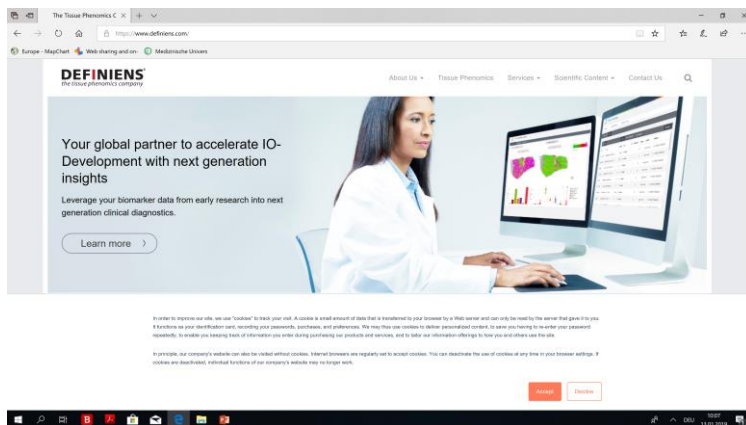
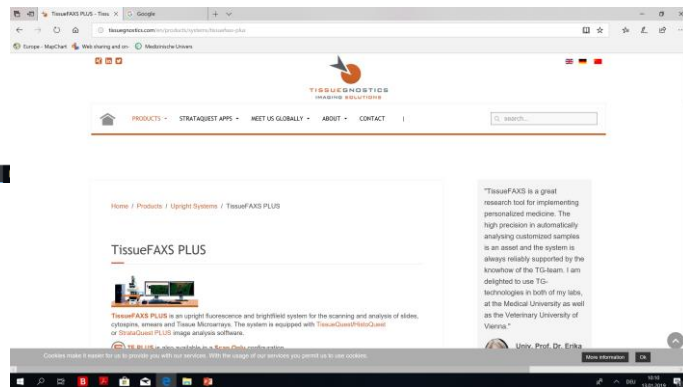
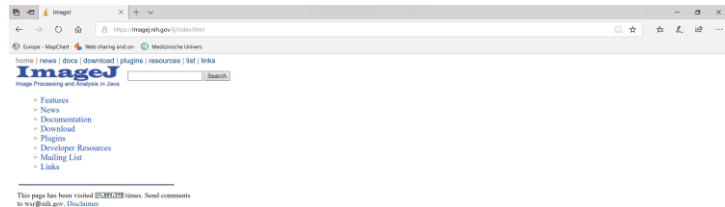
Digital Evaluation of Tumor Content



Sample ID	Stroma area in mm ²	Stroma nuclei count	Stroma nuclei density /mm ²	Epi-area	Epi-nuclei count	Epi-nuclei density /mm ²	Total tissue area In mm ²	Total lumen area In mm ²
14706-08 colon tv cryo he tg1 24.4.12	4.66	31128	6680.02	4.42	90147	20393.47	11.38	2.13
14706-01 colon tv cryo he tg3	7.50	50078	6680.27	4.74	72054	15214.1	14.24	1.17
14706-01 colon tv cryo he tg2 24.4.12 towards label	4.28	27664	6460.33	2.76	48233.00	17485.71	8.20	0.88
14706-01 colon tv cryo he tg2 24.4.12 away from label	4.58	27878	6083.65	2.28	38412.00	16815.37	7.54	0.55
14706-04 colon tv cryo he tg4 away from label	4.11	55037	13400.10	2.52	36168	14347.15	7.22	0.58
14706-04 colon tv cryo he tg4 towards label	3.20	26422	8269.42	2.44	57719.00	23654.49	6.19	0.47
Median	4.43	29503.00	6680.15	2.64	52976.00	17150.54	7.87	0.73
SD	1.46	12733.55	2783.18	1.09	20890.76	3477.73	3.06	0.63

Tumor content: per area 30%
per nuclei 58%

Software for Quantitative Analyses



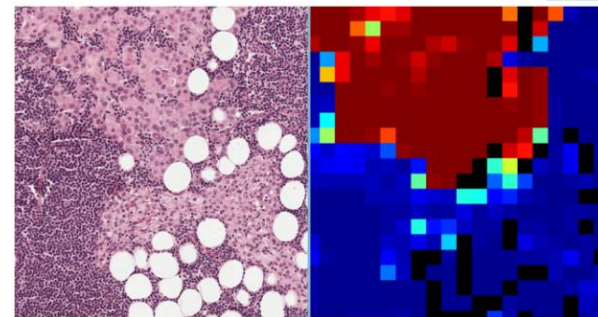
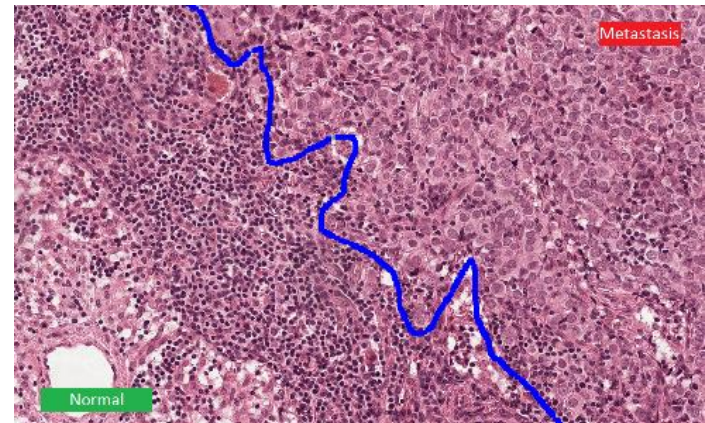
Supervised Learning by Using Labeled Data

Detecting Cancer Metastases on Gigapixel Pathology Images

Yun Liu^{1*}, Krishna Gadepalli¹, Mohammad Norouzi¹, George E. Dahl¹,
Timo Kohlberger¹, Aleksey Boyko¹, Subhashini Venugopalan^{2**},
Aleksei Timofeev², Philip Q. Nelson², Greg S. Corrado¹, Jason D. Hipp³,
Lily Peng¹, and Martin C. Stumpe¹

{liuyun,mnorouzi,gdahl,lhpeng,mstumpe}@google.com

¹Google Brain, ²Google Inc, ³Verily Life Sciences,
Mountain View, CA, USA



270 slides pixel-level annotation (Camelyon16 data set)

- Few data sets required
- Annotation process very laborious, expensive, error prone

Artificial Intelligence–Based Breast Cancer Nodal Metastasis Detection

Insights Into the Black Box for Pathologists

Yun Liu, PhD; Timo Kohlberger, PhD; Mohammad Norouzi, PhD; George E. Dahl, PhD; Jenny L. Smith, MD; Arash Mohtashamian, MD; Niels Olson, MD; Lily H. Peng, MD, PhD; Jason D. Hipp, MD, PhD; Martin C. Stumpe, PhD

Method	Slide-Level Area Under Receiver Operating Characteristic Curve (AUC)
LYNA (our algorithm)	99.3 (98.1, 100)
Camelyon16 winning algorithm	99.4 (98.3, 99.9)
Camelyon16 runner-up algorithm	97.6 (94.1, 99.9)
Single pathologist (without time constraint)	96.6 (92.7, 99.8)
Average of 11 pathologists (simulated clinical time constraint)	81.0 (73.8, 88.4)

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ARTICLE OPEN

Image analysis with deep learning to predict breast cancer grade, ER status, histologic subtype, and intrinsic subtype

Heather D. Couture¹, Lindsay A. Williams², Joseph Geradts³, Sarah J. Nyante⁴, Ebonee N. Butler², J. S. Marron^{5,6}, Charles M. Perou^{5,7}, Melissa A. Troester^{2,5} and Marc Niethammer^{1,8}

Comput Intell Methods Bioinform Biostat (2016). 2017 ; 10477: 42–58. doi: 10.1007/978-3-319-67834-4_4.

DeepScope: Nonintrusive Whole Slide Saliency Annotation and Prediction from Pathologists at the Microscope

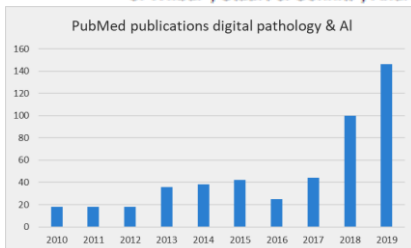
Andrew J. Schaumberg^{1,2}, S. Joseph Sirintrapun³, Hikmat A. Al-Ahmadie³, Peter J. Schöffler⁴, and Thomas J. Fuchs^{2,3,4}



RESEARCH ARTICLE

Computational Pathology to Discriminate Benign from Malignant Intraductal Proliferations of the Breast

Fei Dong^{1,2*}, Humayun Irshad^{3*}, Eun-Yeong Oh³, Melinda F. Lerwill¹, Elena Brachtel¹, Nicholas C. Jones¹, Nicholas W. Knoblauch³, Laleh Montaser-Kouhsari³, Nicole B. Johnson³, Luigi K. F. Rao¹, Beverly Faulkner-Jones³, D. C. Wilbur¹, Stuart J. Schnitt³, Andrew H. Beck^{3*}



Impact of Deep Learning Assistance on the Histopathologic Review of Lymph Nodes for Metastatic Breast Cancer

David F. Steiner, MD, PhD,* Robert MacDonald, PhD,* Yun Liu, PhD,* Peter Truszkowski, MD,* Jason D. Hipp, MD, PhD, FCAP,* Christopher Gammage, MS,* Florence Thng, MS,† Lily Peng, MD, PhD,* and Martin C. Stumpe, PhD*

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ARTICLES

<https://doi.org/10.1038/s41591-018-0177-5>

Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning

Nicolas Coudray^{1,2,9}, Paolo Santiago Ocampo^{3,9}, Theodore Sakellaropoulos⁴, Navneet Narula³, Matija Snuderl³, David Fenyo^{5,6}, Andre L. Moreira^{3,7}, Narges Razavian^{8*} and Aristotelis Tsirigos^{1,3*}

Artificial Intelligence–Based Breast Cancer Nodal Metastasis Detection

Insights Into the Black Box for Pathologists

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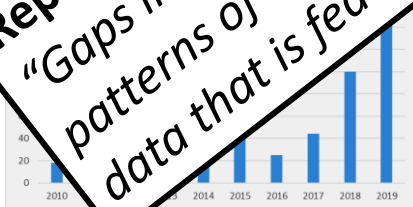
Andrew J. Schaumberg^{1,2}, S. Joseph Sirintrapun³, Hikmat A. Al-Ahmad⁴, Schöffler⁴, and Thomas J. Fuchs^{2,3,4}



RESEARCH ARTICLE

Computational
Benign
Prostate

David F. Lerwill¹, Elena
Fuchs², Laleh Montaser-
Beverly Faulkner-Jones³, D



Report of UN Secretary-general's high-level Panel on Digital Cooperation:
"Gaps in the data on which algorithms are trained can likewise automate existing patterns of discrimination, as machine learning systems are only as good as the data that is fed to them."

ARTICLE OPEN

Image analysis with deep learning for breast cancer grade, ER status, and HER2 status

Heather D. Couture¹, Lindsay A. Melisa A. Troester^{2,3} and M



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University of California
cancer
subtypes



ORIGINAL ARTICLE

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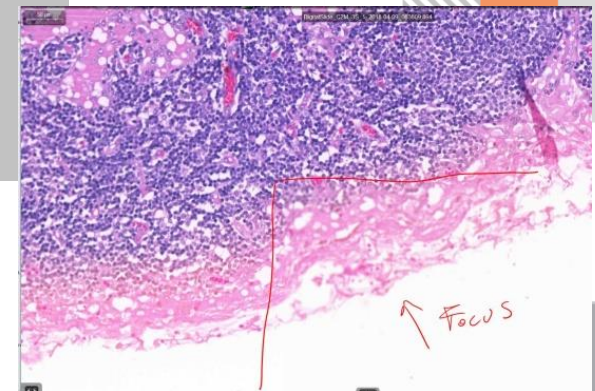
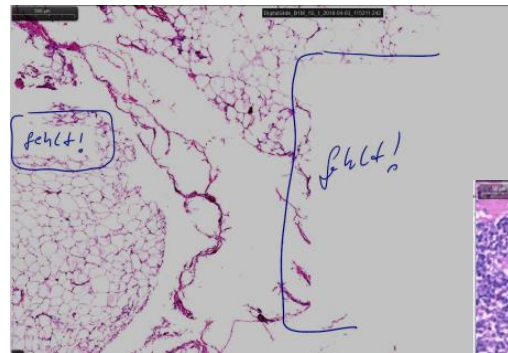
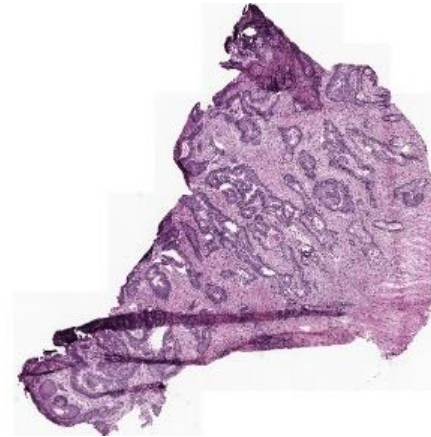
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Pre-analytical and Scanning Quality Requirements

- ▶ Algorithms are sensitive to artefacts
- ▶ Pre-analytical artefacts
- ▶ Scanning artefacts
 - missed region
 - out of focus
 - Stiching
 - background adjustment



ISO: New Draft ISO Standard

ISTO TC 212 N0578 N577 Draft for ISO Standard

“Molecular *in vitro* diagnostic examinations – Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue for *in situ* detection techniques

Introduction

“Developments in personalized medicine and new technologies, such as multi-label immunostaining and **computer-based analysis of digital images pose new requirements on standardization of pre-analytical procedures to obtain reproducible qualitative and quantitative results.**”

This standard includes but is not limited to:


- classical histological staining, *e.g.* Hematoxylin & Eosin staining (H&E)
- histochemistry
- immunohistochemical staining (IHC) or immunofluorescence staining
- *in situ* hybridization (ISH) techniques
- *in situ* sequencing, imaging mass spectrometry

How BBMRI.at can help

- Support with **access** to biobank samples, data, services, expertise and network to clinical partners
- **Education & training** on pre-analytical sample processing according to pre-analytics standards for performance testing
- Initiation of **discount by Austrian Standards** on pre-analytical ISO standard, ISO 15198, ISO 20387



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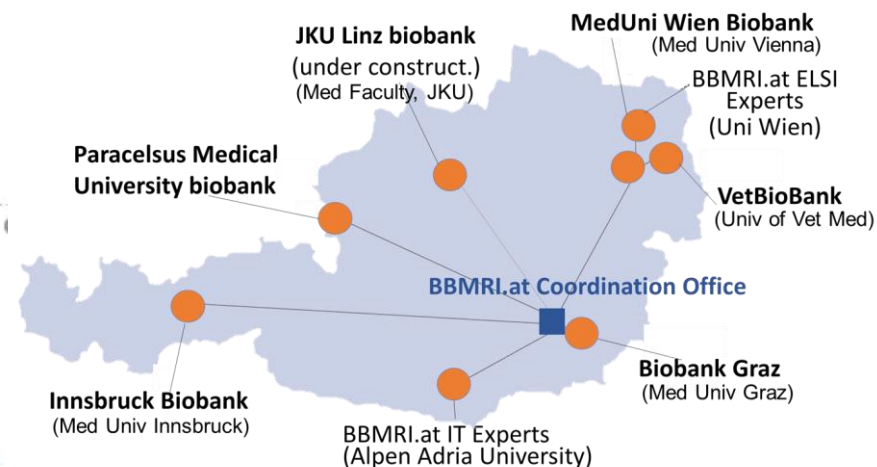
BBMRI.at - Who we are



THE AUSTRIAN NODE OF THE EUROPEAN BIOBANKING RESEARCH INFRASTRUCTURE



17 Members states
4 Associated members



Funded by BMBWF:
1.12.2013 -30.11.2018 3.50 m€ 5 yrs
1.12.2018 -30.11.2023 3.65 m€ 5 yrs

Acknowledgement

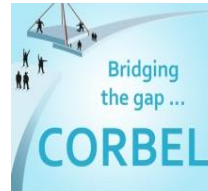


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*a healthy diet
for a healthy life*



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gateway for health

Project number: 676550



European Research Infrastructure
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