Medical University of Graz

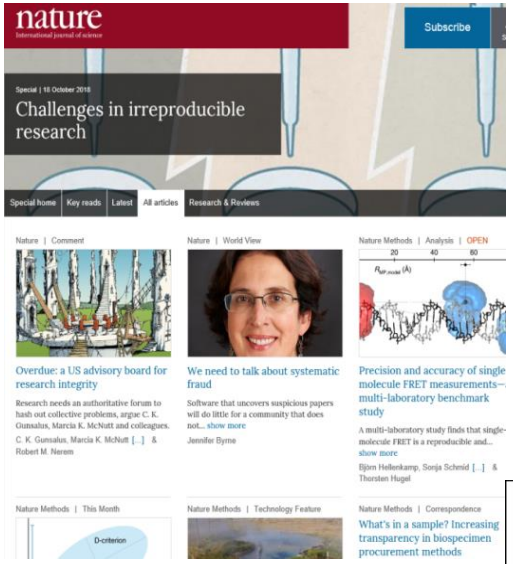
WISSENSCHAFTLICHE UND MEDIZINISCHE RELEVANZ VON STANDARDS IN DER DIAGNOSTIK

Kurt Zatloukal

Diagnostic and Research Center for Molecular Biomedicine

Research Data Reproducibility

Medical University of Graz



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.

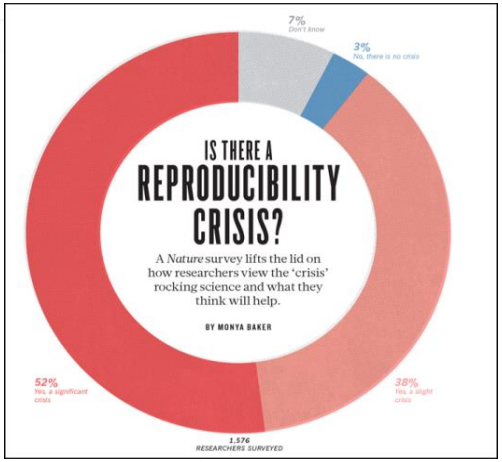
Asher Mullard

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."

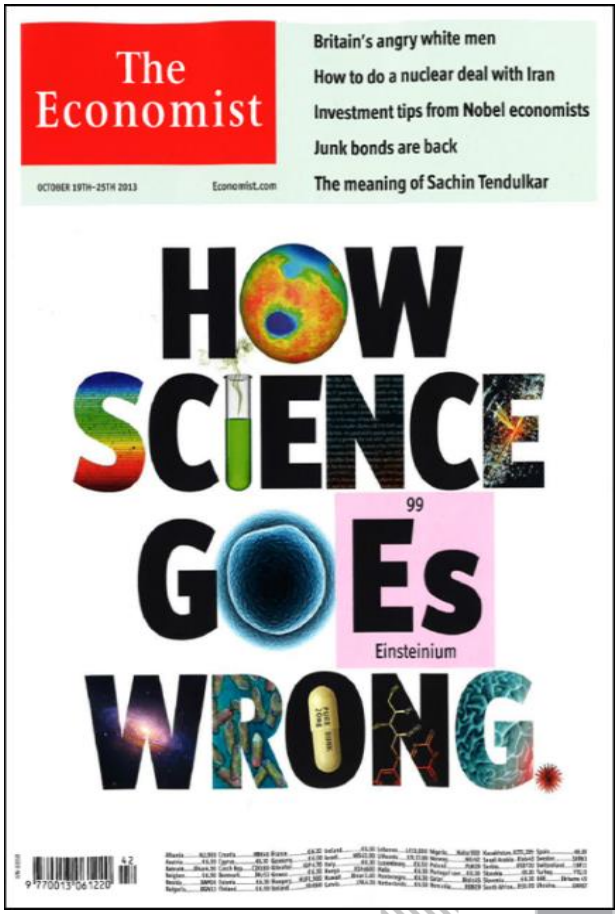
For the non-peer-reviewed analysis, Khusru Asadullah, Head of Target Discovery at Bayer, and his colleagues looked back at 67 target-validation projects, covering the majority of Bayer's work in oncology, women's health and cardiovascular medicine over the past 4 years. Of these, results from internal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

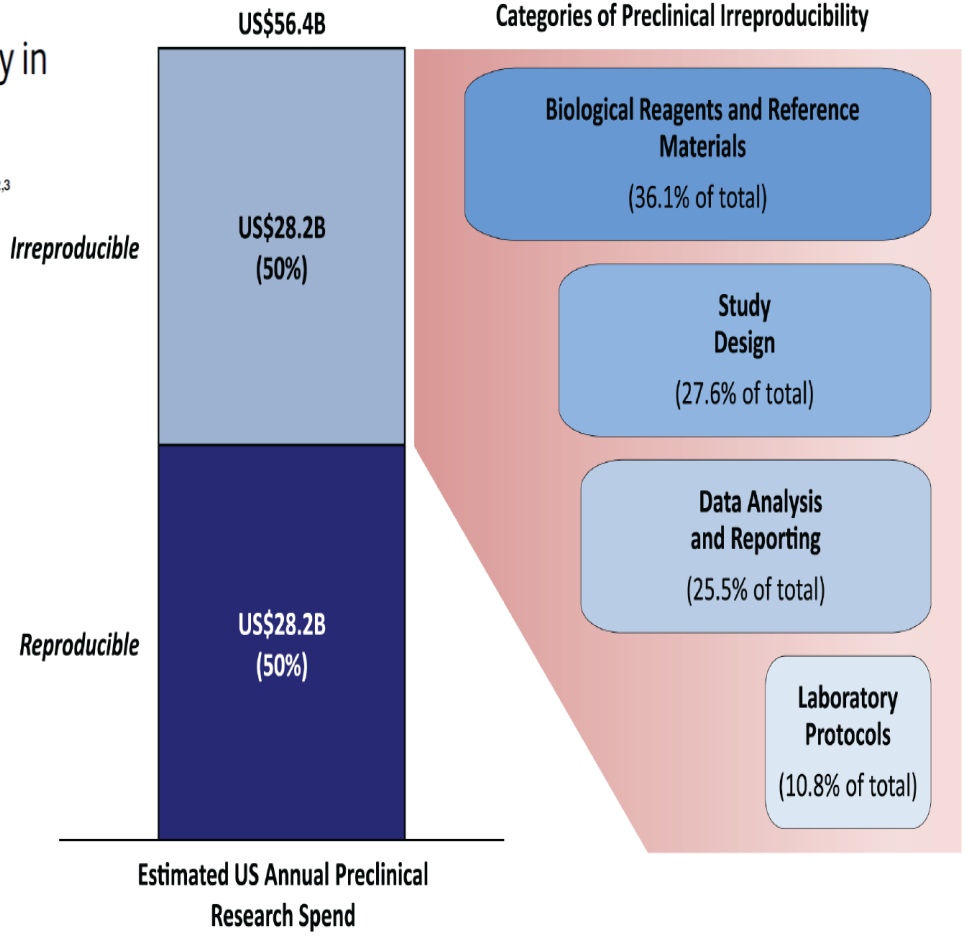
Medical University of Graz

PLOS BIOLOGY

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

Leonard P. Freedman[1]*, Iain M. Cockburn[2], Timothy S. Simcoe[2,3]



Impact of Errors in Medical Diagnostics

Medical University of Graz

- 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)

Medical

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

Medical University of Graz

L 117/176 EN Official Journal of the European Union 5.5.2017

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

Medical University of Graz

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 sion 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

Medical University of Graz

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;

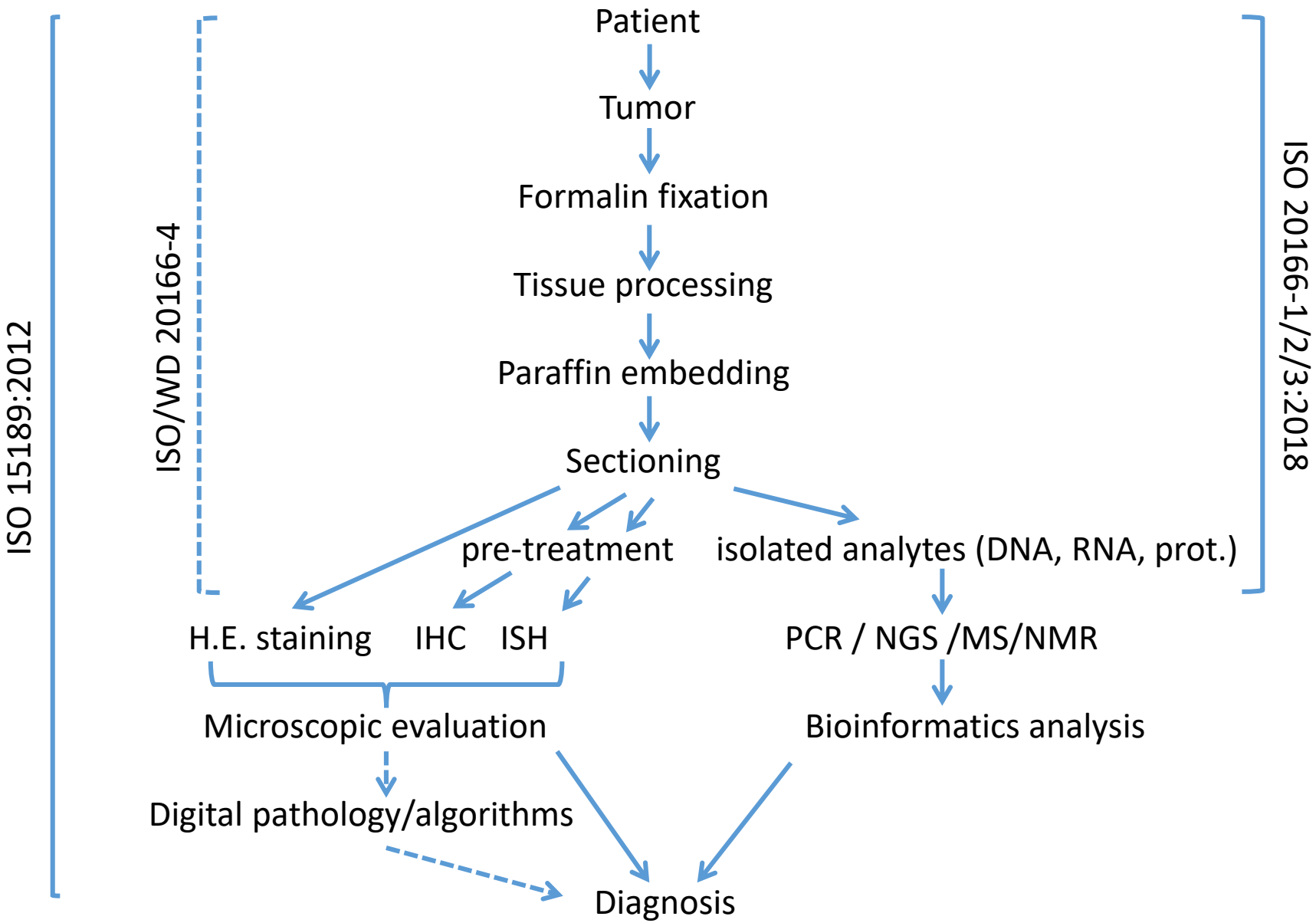
ISO Standards and CEN/TS for Pre-examination Processes

- 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

Medical University of Graz

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

Medical University of Graz

from C. Compton, NCI USA

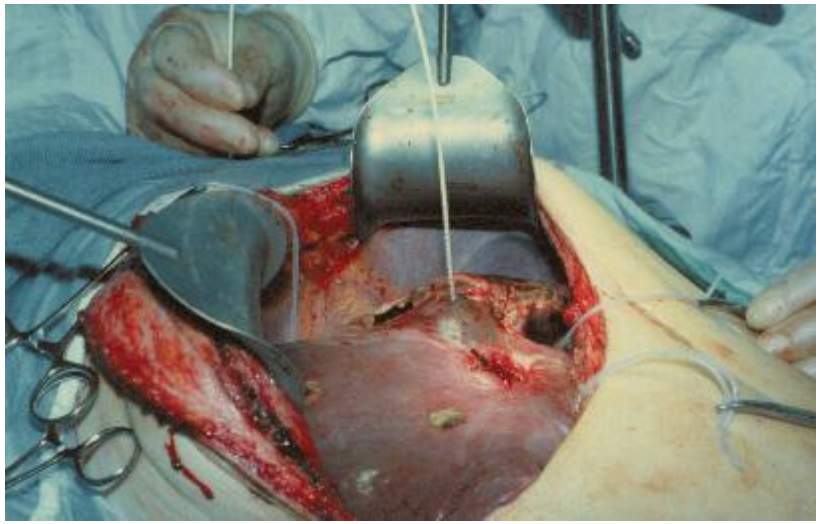
Medical University of Graz

USA

Europe

Warm and Cold Ischemia Effects

Medical University of Graz



Clinical study in Pringle manoeuvre liver surgery

Snap frozen liver samples collected at :

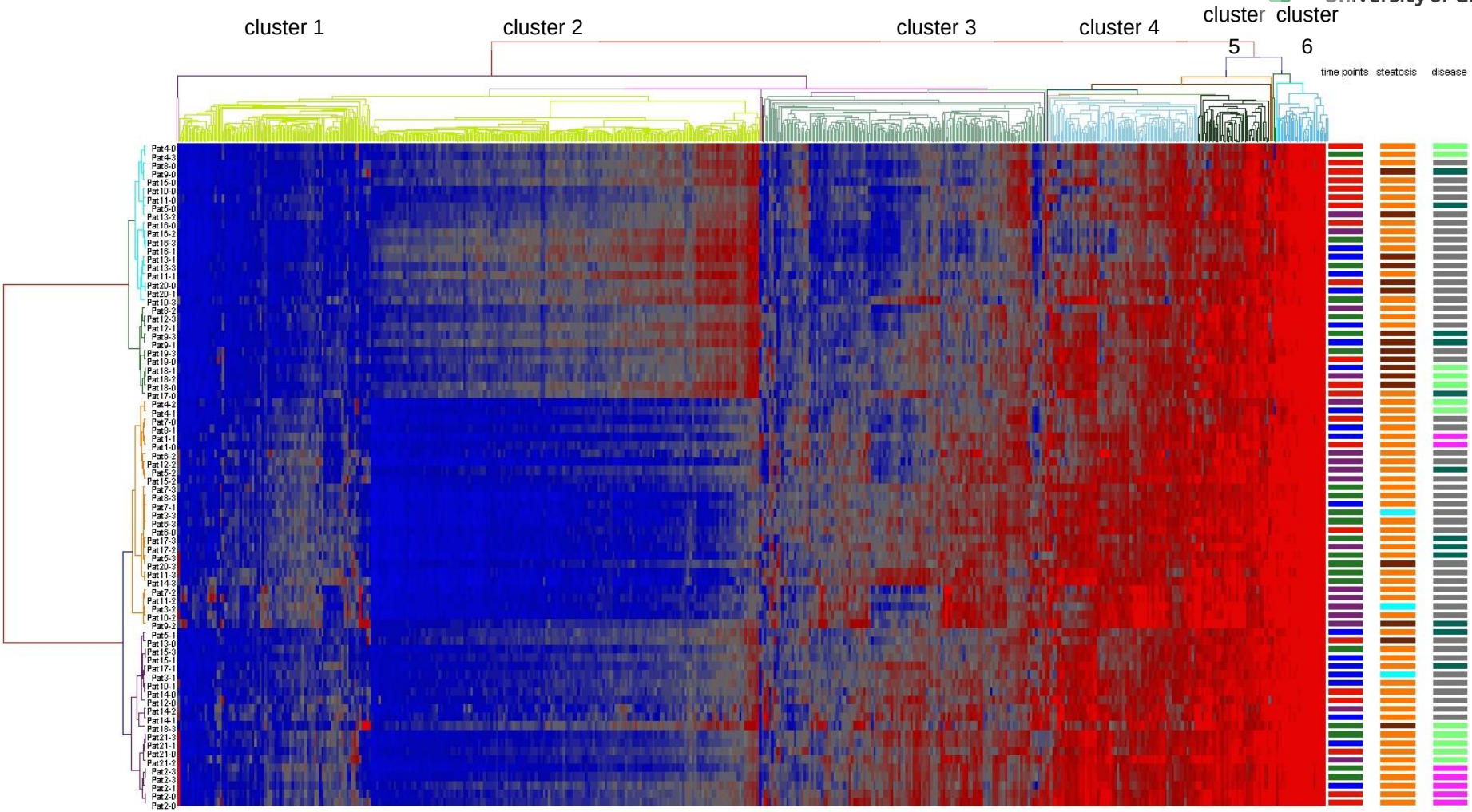
- **T0** sample before Pringle start: **medication**
- **T1** sample 30min after Pringle start: **warm ischemia**
- **T2** sample 30min after Pringle ending: **ischemia- reperfusion**
- **T3** sample after resection: **cold ischemia**

SPIDIA

GEN-AU
GENOMFORSCHUNG IN ÖSTERREICH

Ischemia and Gene Expression

Medical University of Graz



Affymerix HG-U219

RMAsignals Trasposed_UniqueList_no924

time points 0 1 3 2 steatosis <5% n/a >20% disease CCC CRC Met HCC other

2.2 5.8 9.4

FC1,5_p0,05 924 genes

Alteration in Gene Expression is an Active Respose

Medical University of Graz

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

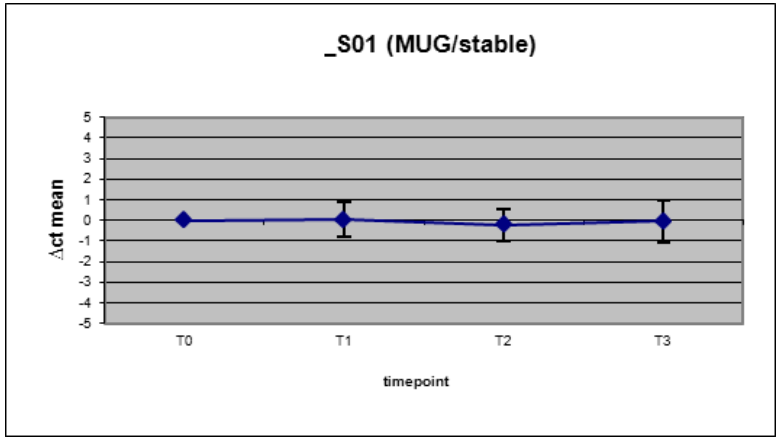
ABCC9	ATP-binding cassette transporter sub-family C member 9
ANGPTL4	Angiopoietin-related protein 4
CEBPB	CCAAT/enhancer-binding protein beta
CISH	Cytokine-inducible SH2-containing protein
CRP	Cysteine and glycine-rich protein 1
CXCL2	GRO-beta(5-73)
CXCR7	C-X-C chemokine receptor type 7
DNAJB1	DnaJ homolog 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

SPIDIA

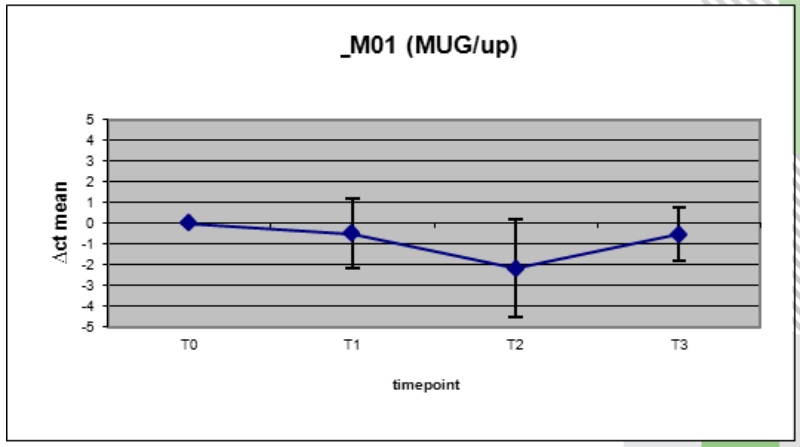
Individual Response to Ischemia (qRT-PCR Verification)

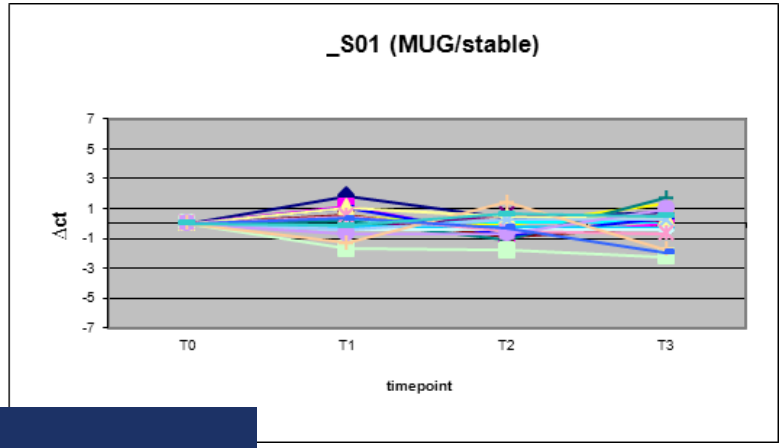
Medical University of Graz

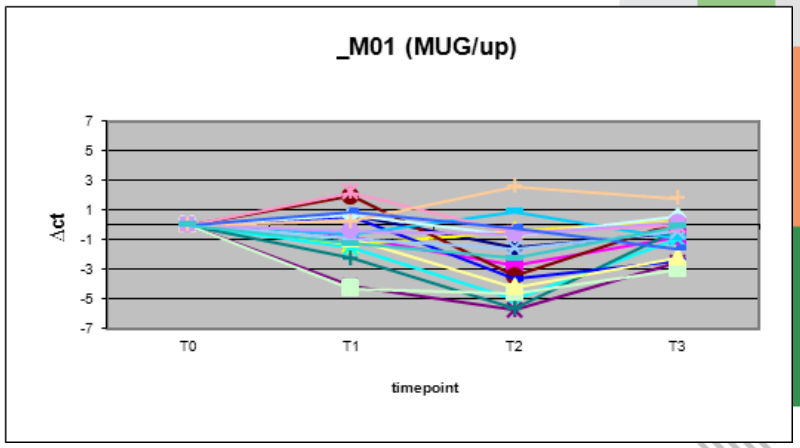
stable



unstable





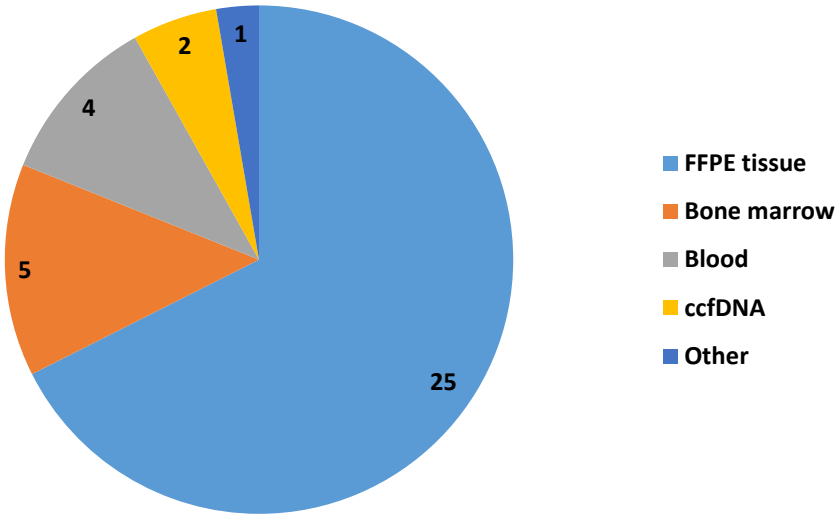


SPIDIA

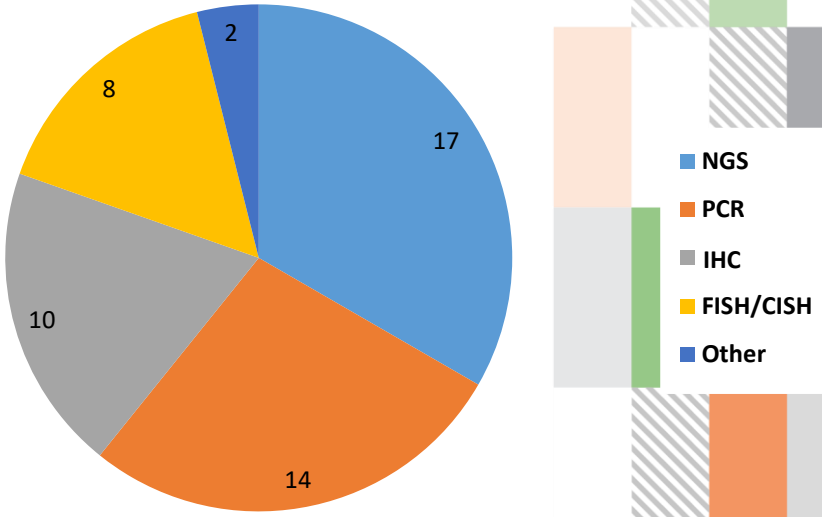
Companion Diagnostics (FDA-listed)

Medical University of Graz

Biosamples



Assays



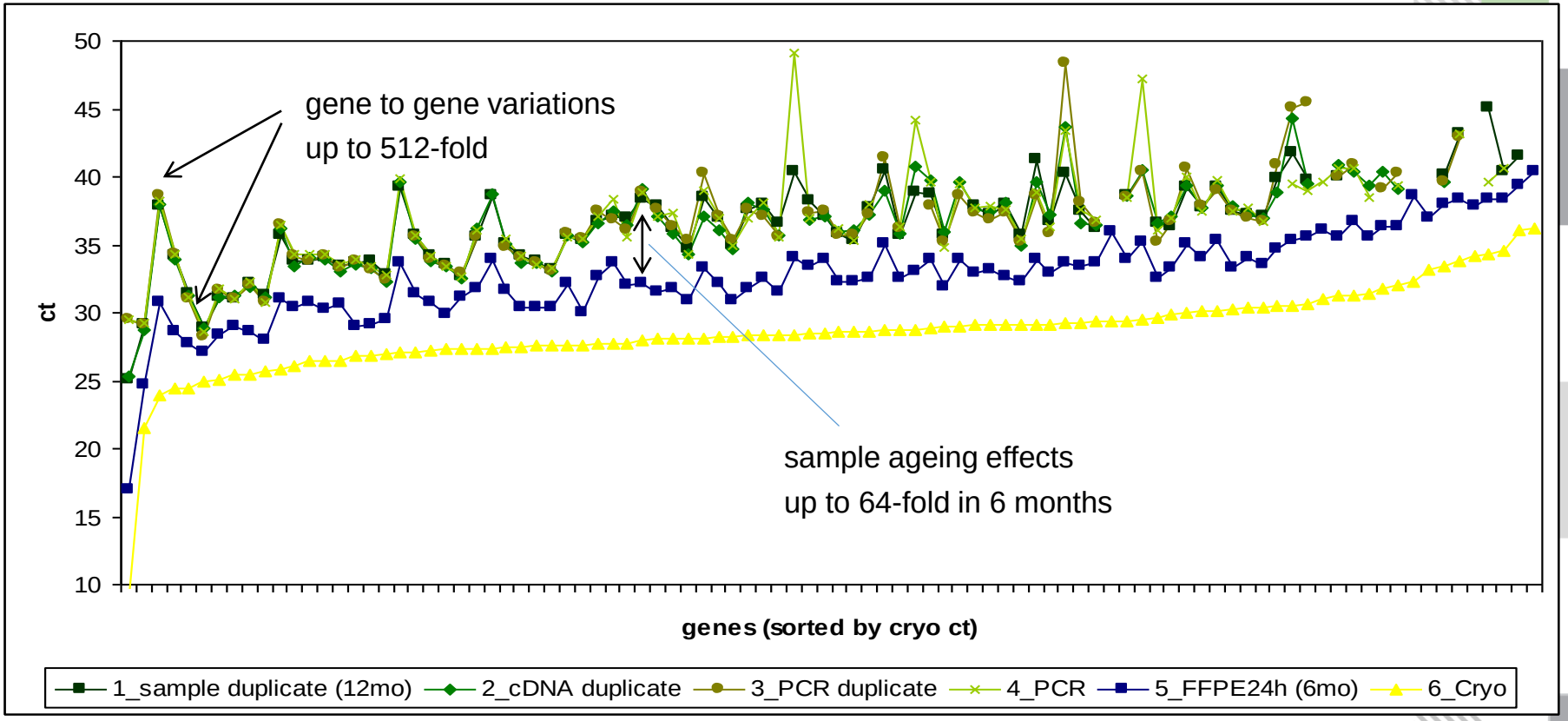
FFPE tissue is the most common biosample for companion diagnostics

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

Stumptner et al. in Handbook for Biomarkers in Precision Medicine, 2019

Formalin Fixation Interferes with qRT-PCR

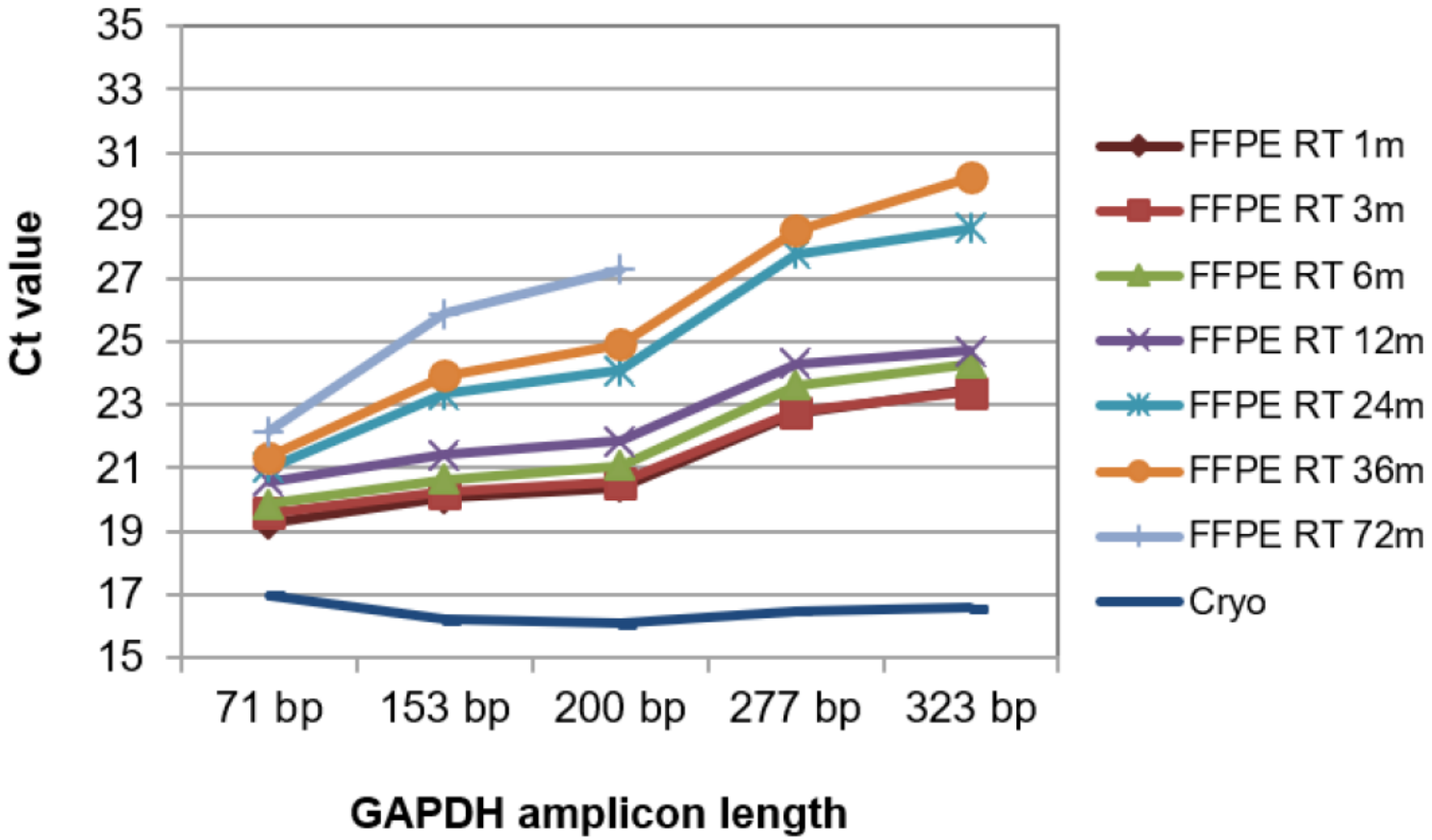
Medical University of Graz



Kashofer K, et al. PLoS ONE 8(7): e70714.

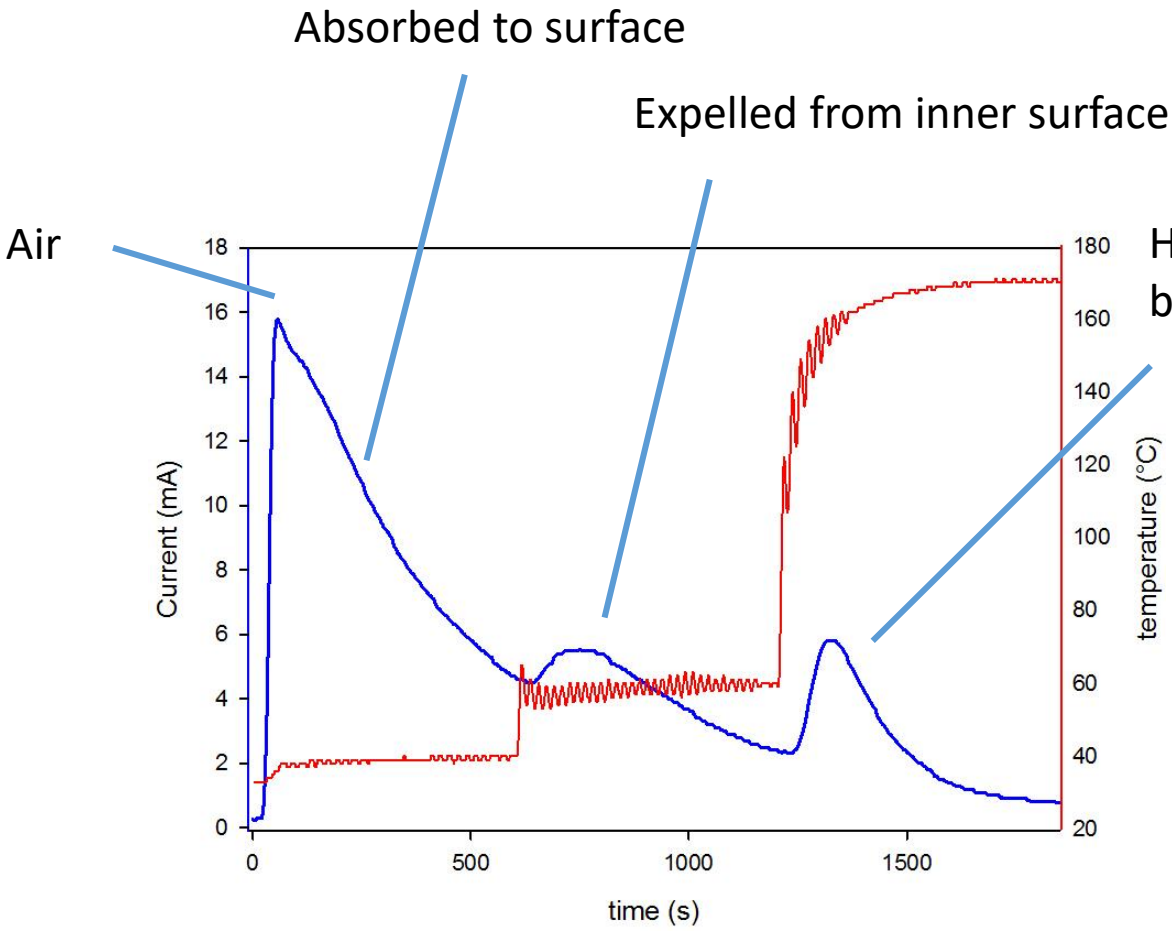
Ageing Effects on RNA Quality in FFPE Tissues

Medical University of Graz



D. Groelz et al., PLOS one 2018

Water Content of FFPE Tissue



Phosphorous pentoxide – based water analysis

Sources of residual water:

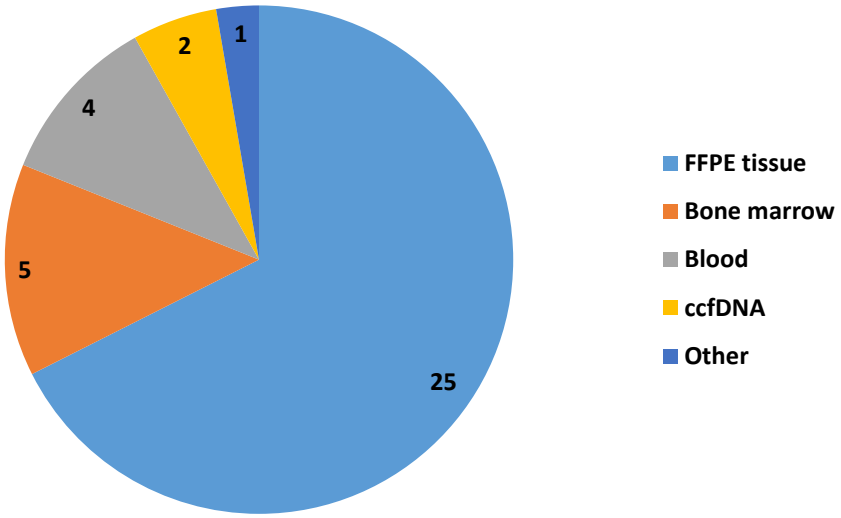
- Fixation
- Tissue processing
- Storage

P Abuja et al., unpublished

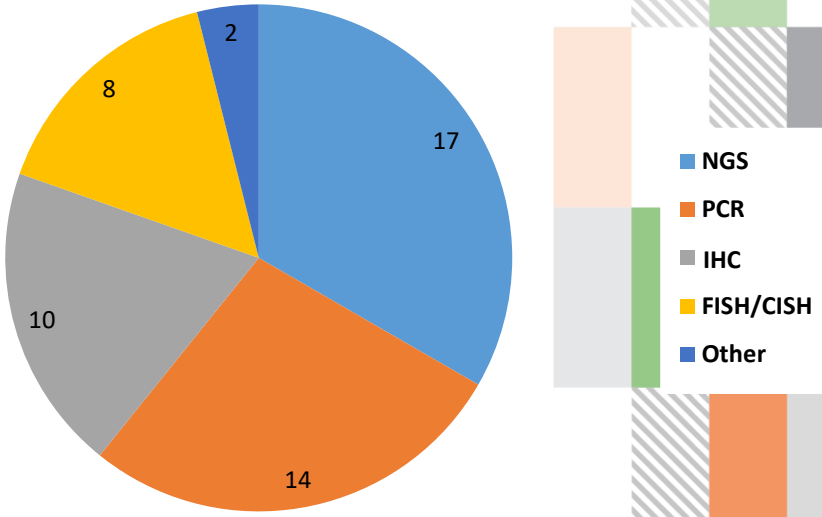
Companion Diagnostics (FDA-listed)

Medical University of Graz

Biosamples



Assays



FFPE tissue is the most common biosample for companion diagnostics

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

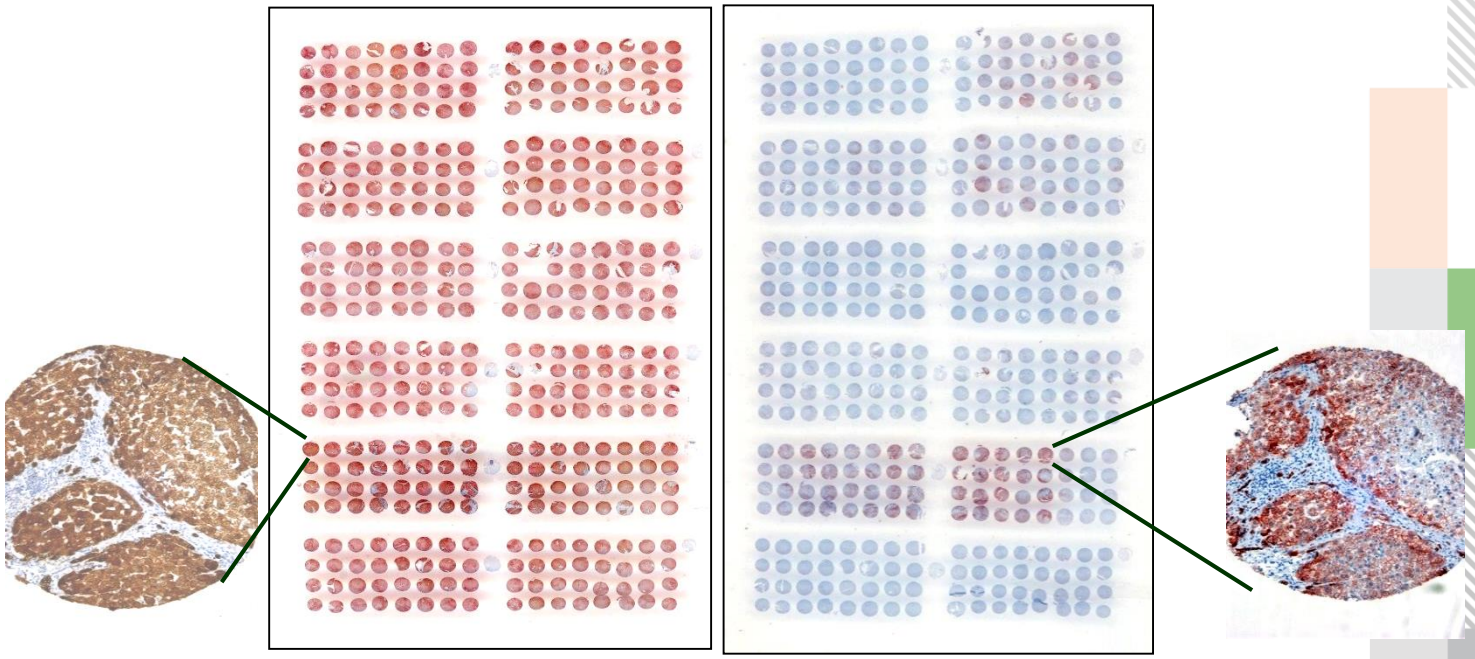
Stumptner et al. in Handbook for Biomarkers in Precision Medicine, 2019

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



Robust protocol

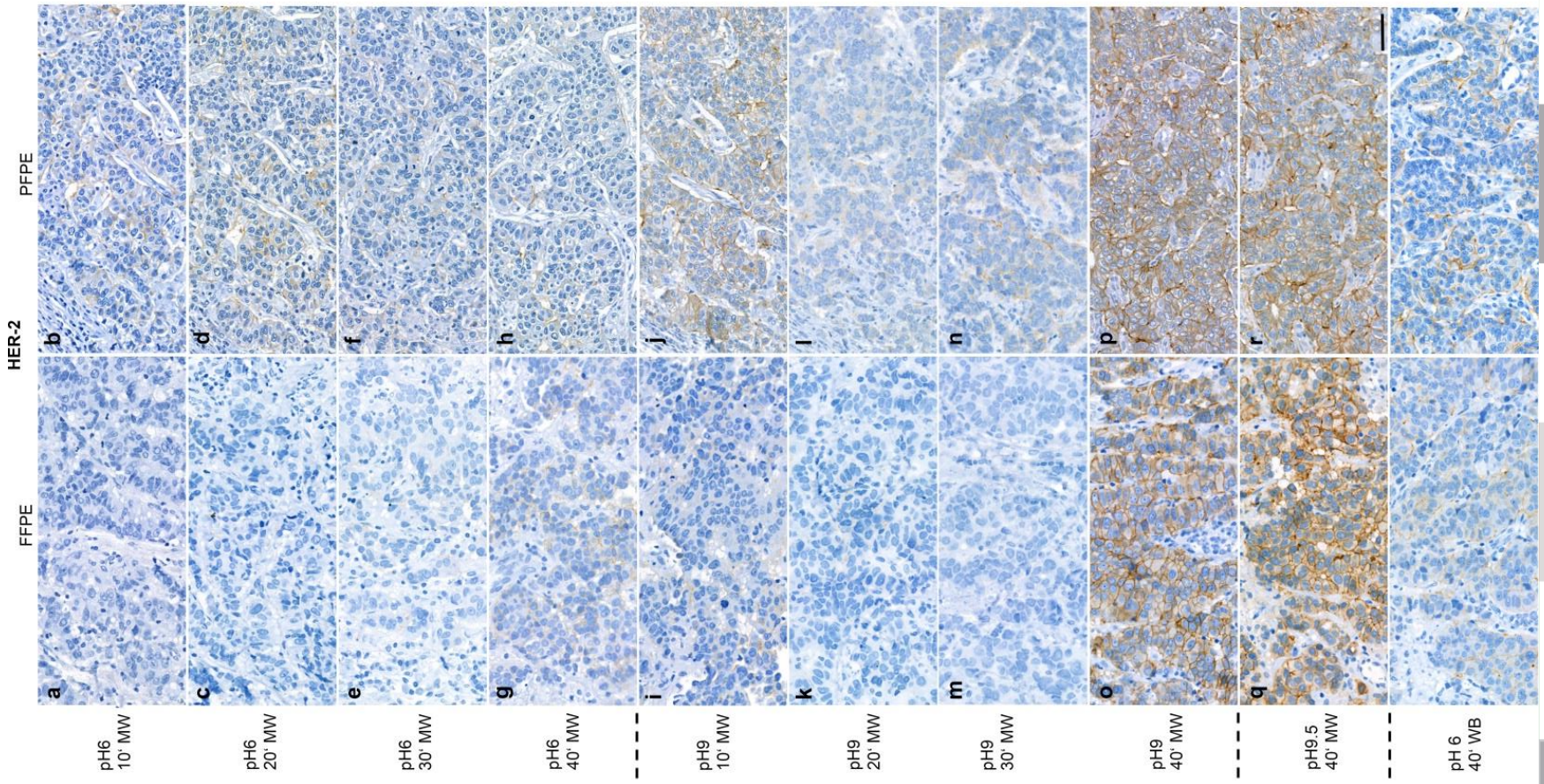
Non-robust protocol

Stumptner et al., Methods Enzymol. 2015

Differences:
Analytical and Clinical Performance

Medical University of Graz

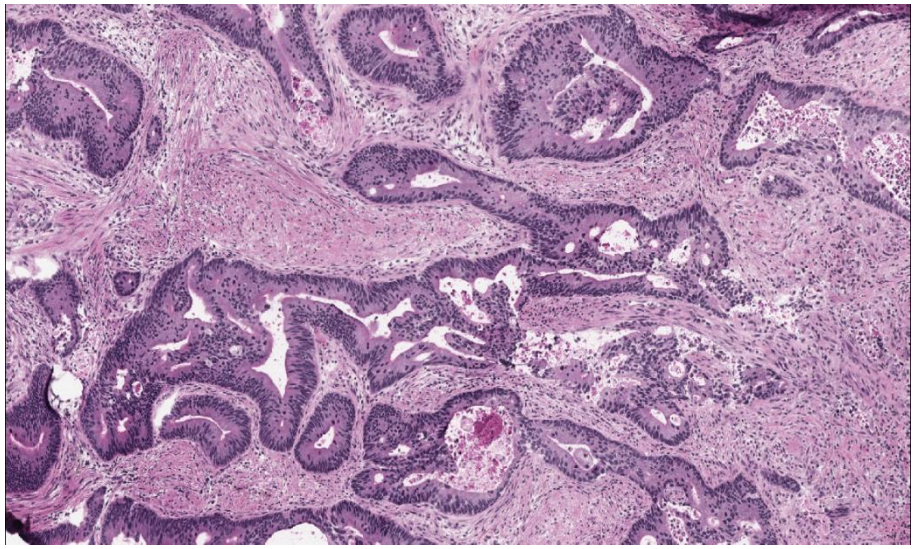
Breast cancer HER-2 IHC

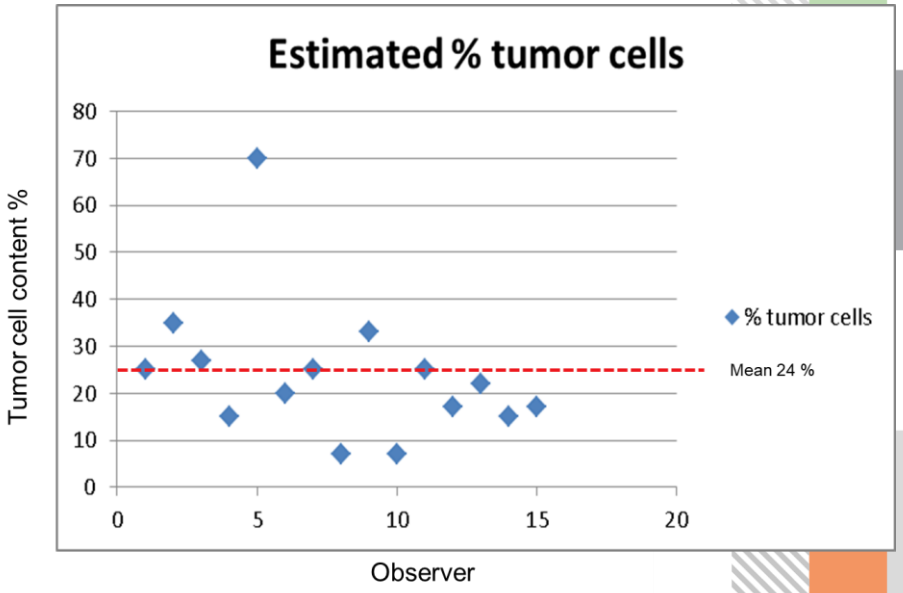


Stumptner at al., N Biotech 2019

Quantification of Complex Patterns

Example: Evaluation of Tumor Content



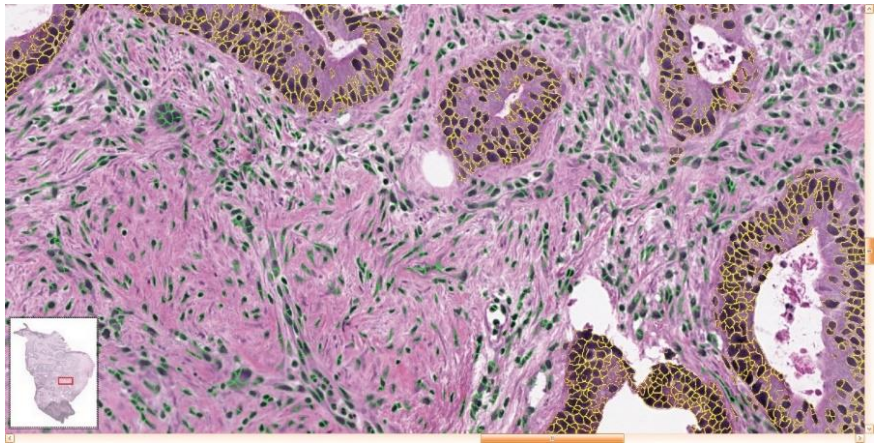


Bias by Visual Illusion

- 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

Medical University of Graz



TISSUE GNOSTICS
MEDICAL & BIOTECH SOLUTIONS

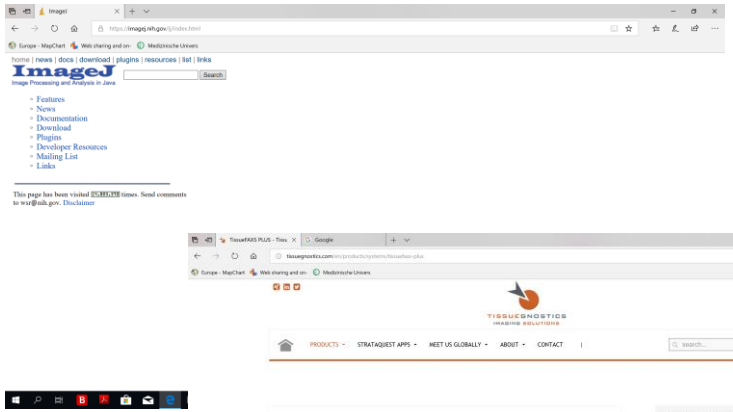
Sample ID	Stroma area in mm²	Stroma nuclei count	Stroma nuclei density /mm²	Epi-area	Epi-nuclei count	Epi-nuclei density /mm²	Total tissue area In mm²	Total lumen area In mm²
14706-08 colon tv cryo he tg1 24.4.12	4.66	31128	6680.02	4.42	90147	20393.47	11.38	2.13
14706-01 colon tv cryo he tg3	7.50	50078	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

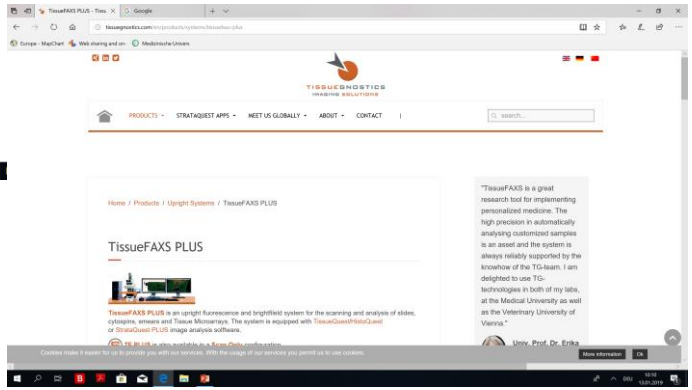
Tumor content: per area 30%

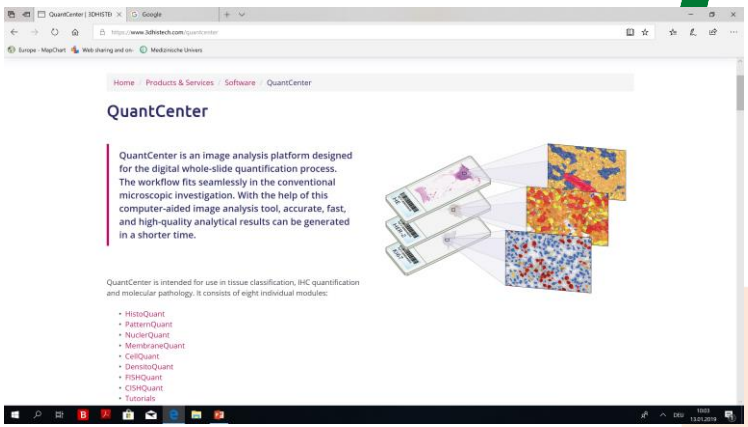
per nuclei 58%

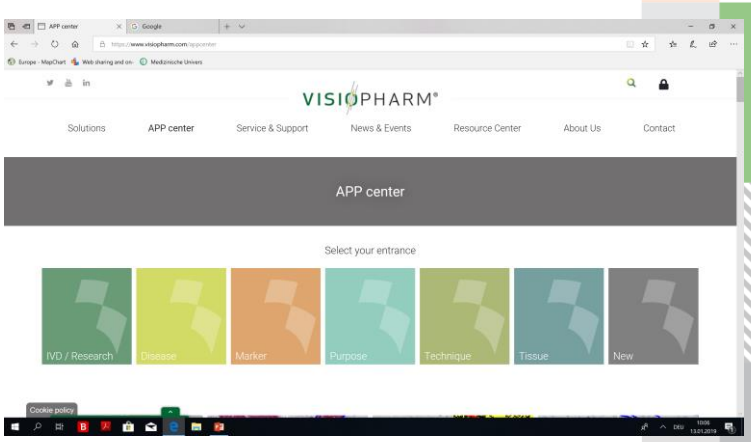
Software for Quantitative Analyses

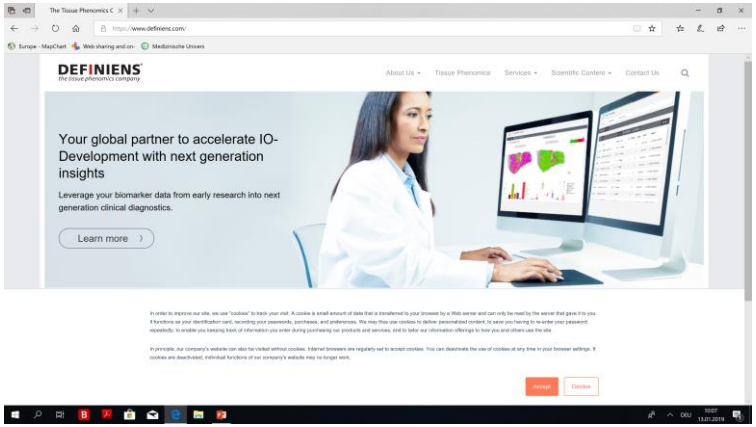
Medical University of Graz











Supervised Learning by Using Labeled Data

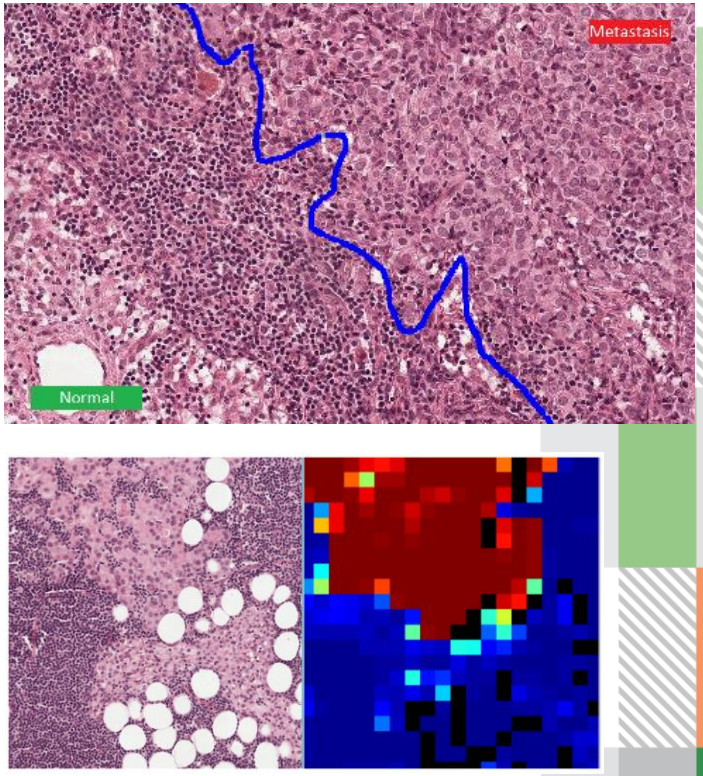
Medical University of Graz

Detecting Cancer Metastases on Gigapixel Pathology Images

Yun Liu[1*], Krishna Gadepalli[1], Mohammad Norouzi[1], George E. Dahl[1], Timo Kohlberger[1], Aleksey Boyko[1], Subhashini Venugopalan[2**], Aleksei Timofeev[2], Philip Q. Nelson[2], Greg S. Corrado[1], Jason D. Hipp[3], Lily Peng[1], and Martin C. Stumpe[1]

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

[1]Google Brain, [2]Google Inc, [3]Verily 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

Medical University of Graz
ARCHIVES of Pathology & Laboratory Medicine

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)

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; J
Arash Mohtashamian, MD; Niels Olson, MD; Lily H. Peng, MD, PhD; Jason D. Hipp, MD, PhD

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 Sirintrapun**[3], **Hikmat A. Al-Ahmadie**[3], **Peter J. Schüffler**[4], and **Thomas J. Fuchs**[2,3,4]

ARTICLE OPEN

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

Heather D. Couture[1], Lindsay A. Williams[2], Joseph Geradts[3], Sarah J. Nyante[4], Ebonee N. Butler[2], J. S. Marron[5,6], Charles M. Perou[5,7], Melissa A. Troester[2,5] and Marc Niethammer[1,8]

ORIGINAL ARTICLE

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

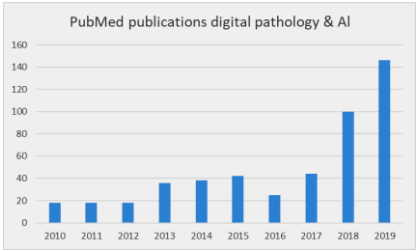
David F. Steiner, MD, PhD, Robert MacDonald, PhD,* Yun Liu, PhD,* Peter Truszkowski, MD,* Jason D. Hipp, MD, PhD, FCAP,* Christopher Gammage, MS,* Florence Thng, MS,† Lily Peng, MD, PhD,* and Martin C. Stumpe, PhD**

PLOS ONE

RESEARCH ARTICLE

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

Fei Dong[1,2☯], **Humayun Irshad**[3☯], **Eun-Yeong Oh**[3], **Melinda F. Lerwill**[1], **Elena Brachtel**[1], **Nicholas C. Jones**[1], **Nicholas W. Knoblauch**[3], **Laleh Montaser-Kouhsari**[3], **Nicole B. Johnson**[3], **Luigi K. F. Rao**[1], **Beverly Faulkner-Jones**[3], **D C. Wilbur**[1], **Stuart J. Schnitt**[3], **Andrew H. Beck**[3*]



nature medicine

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 Sakellaropoulos**[4], **Navneet Narula**[3], **Matija Snuderl**[3], **David Fenyö**[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

Yun Liu, PhD; Timo Kohlberger, PhD; Mohammad Norouzi, PhD; George E. Dahl, PhD; J
Arash Mohtashamian, MD; Niels Olson, MD; Lily H. Peng, MD, PhD; Jason D. Hipp, MD, PhD

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

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

Andrew J. Schaumberg[1,2], **S. Joseph Sirintrapun**[3], **Hikmat A. Al-A**
Schüffler[4], and **Thomas J. Fuchs**[2,3,4]

ARTICLE OPEN

Image analysis with d
grade, ER status,
cancer
sic subtype

Heather D. Couture[1], Lindsay A
Melissa A. Troester[2,5] and M
er[2], J. S. Marron[5,6], Charles M. Perou[5,7],

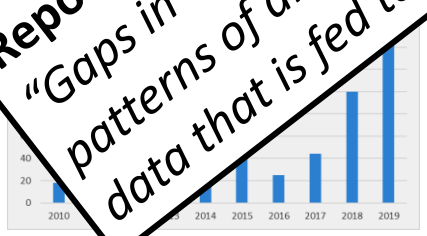
ORIGINAL ARTICLE

PLOS ONE

RESEARCH ARTICLE

Computati
Benign
Pro
te

nda F. Lerwill[1], Elena
uch[3], Laleh Montaser-
; Beverly Faulkner-Jones[3], D
k[3,*]



Impact of Deep Learning Assistance on the
topathologic 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**

nature medicine
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 Sakellaropoulos[4], Navneet Narula[3], Matija Snuderl[3], David Fenyö[5,6], Andre L. Moreira[3,7], Narges Razavian[8*] and Aristotelis Tsirigos[1,3*]

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."

Pre-analytical and Scanning Quality Requirements

Medical University of Graz

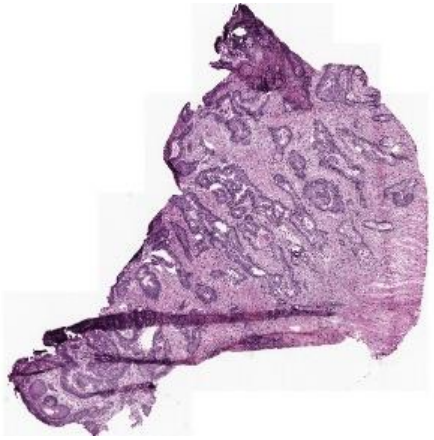
- Algorithms are sensitive to artefacts
- Pre-analytical artefacts
- Scanning artefacts

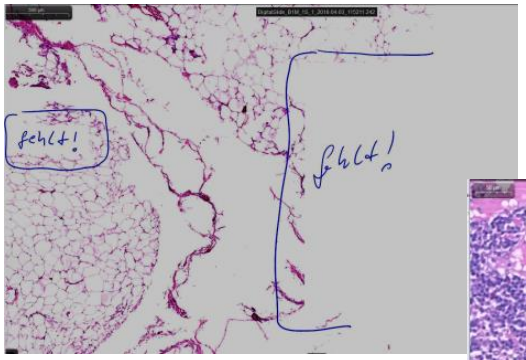
  missed region

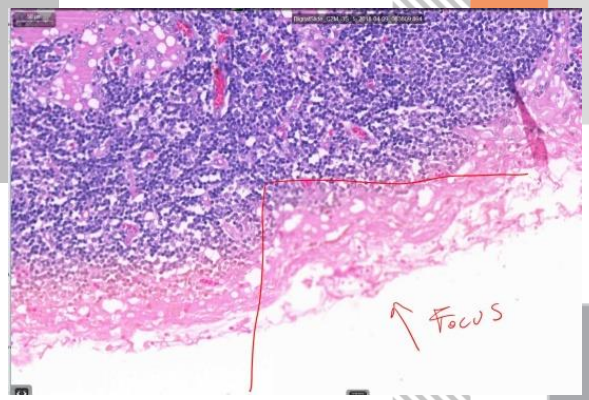
  out of focus

  Stiching

  background adjustment







ISO: New Draft ISO Standard

Medical University of Graz

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

BBMRI.at
Biobanking and BioMolecular resources Research Infrastructure Austria

Medical University of Graz

How BBMRI.at can help

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

Search : www.bbmri.at/catalog
Contact: contact@bbmri.at, cornelia.stumptner@medunigraz.at

Discount details:
www.bbmri.at/news

Funded by:
BMBWF-10.470/0010-V/3c/2018
(2018-2023)

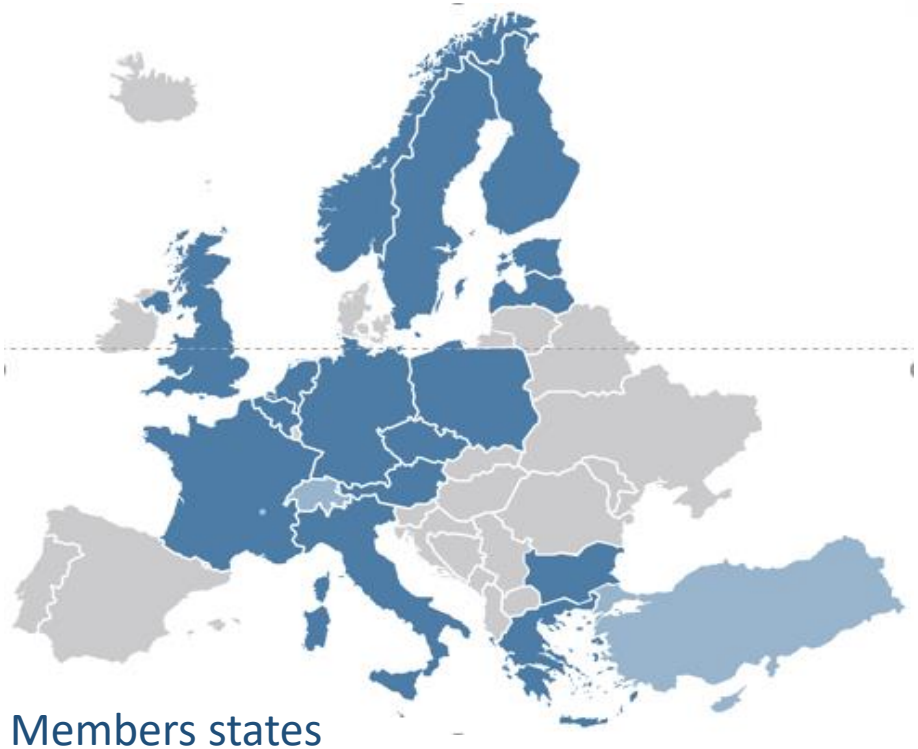
Bundesministerium
Bildung, Wissenschaft und Forschung

BBMRI.at - Who we are

BBMRI.at
Biobanking and
BioMolecular resources
Research Infrastructure
Austria

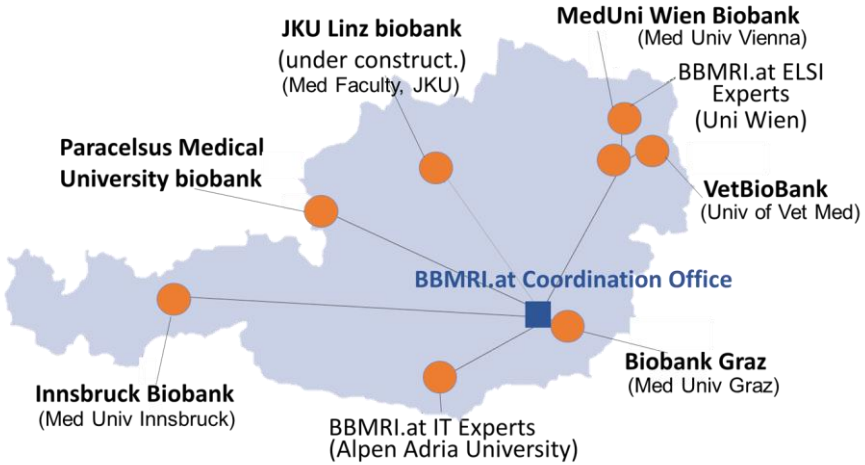
THE AUSTRIAN NODE OF THE EUROPEAN BIOBANKING RESEARCH INFRASTRUCTURE

BBMRI-ERIC
Biobanking and
BioMolecular resources
Research Infrastructure



17 Members states
4 Associated members

BBMRI.at
Biobanking and
BioMolecular resources
Research Infrastructure
Austria



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

SPIDIA

SPIDIA4P

NGS for Personalized Therapy

ESGI

Medical University of Graz

EASI Genomics

BBMRI.AT
Biobanking and BioMolecular Resources Research Infrastructure Austria

Funded by:
BMBWF-10.470/0010-V/3c/2018
(2018-2023)

QIAGEN

Bridging the gap ... CORBEL

JPI a healthy diet for a healthy life

Christian Doppler Forschungsgesellschaft

ID Information und Dokumentation im Gesundheitswesen

Google

BBMRI-ERIC
Biobanking and BioMolecular Resources Research Infrastructure

100 YEAR STARSHIP™ canopus 310 LY

kapsch

BBMRI.AT
Biobanking and BioMolecular Resources Research Infrastructure Austria

erinha
European Research Infrastructure on Highly Pathogenic Agents

BioBank GRAZ

ADOPT BBMRI-ERIC
gateway for health

Project number: 676550

acib

BioMedBridges

Innophore
enzyme discovery

B3 Africa
BRIDGING BIOBANKING AND BIOMEDICAL RESEARCH ACROSS EUROPE AND AFRICA

CBmed
BIOMARKER RESEARCH

bbmri-lpc
BBMRI – Large Prospective Cohorts

Cell-based regenerative medicine : new challenges for EU legislation and governance

CY-Biobank

MEFO graz

CAPACITIES

BBMRI GA Nr. 212111
1.2.2008-30.04.2010

European Commission

EUCelLEX

Fraunhofer

bmwfw
Bundesministerium für Wissenschaft, Forschung und Wirtschaft