Pre-Analytical Sample Processing in Biobanking

Lecture Course

Diagnostic and Research Center for Molecular Biomedicine
Institute of Pathology, Medical University of Graz, Austria

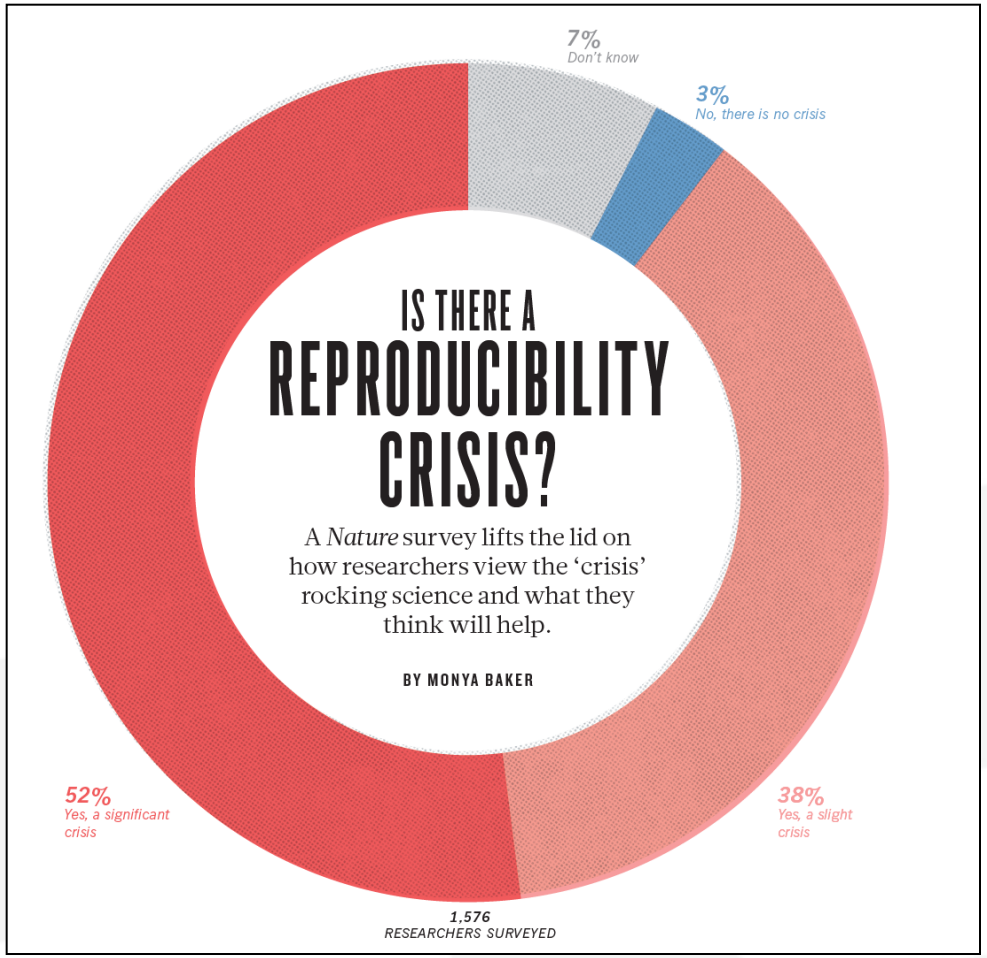
Organizers:

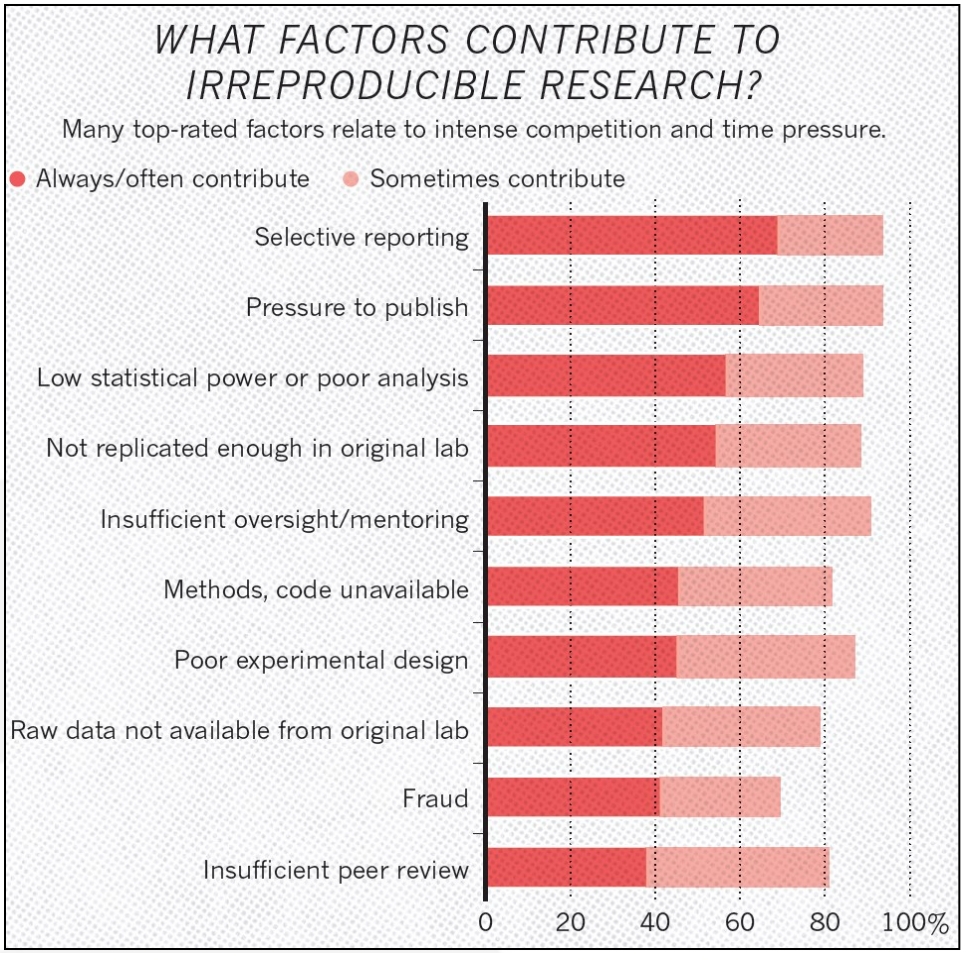
BBMRI.at
Biobanking and BioMolecular resources Research Infrastructure Austria

Medizinische Universität Graz

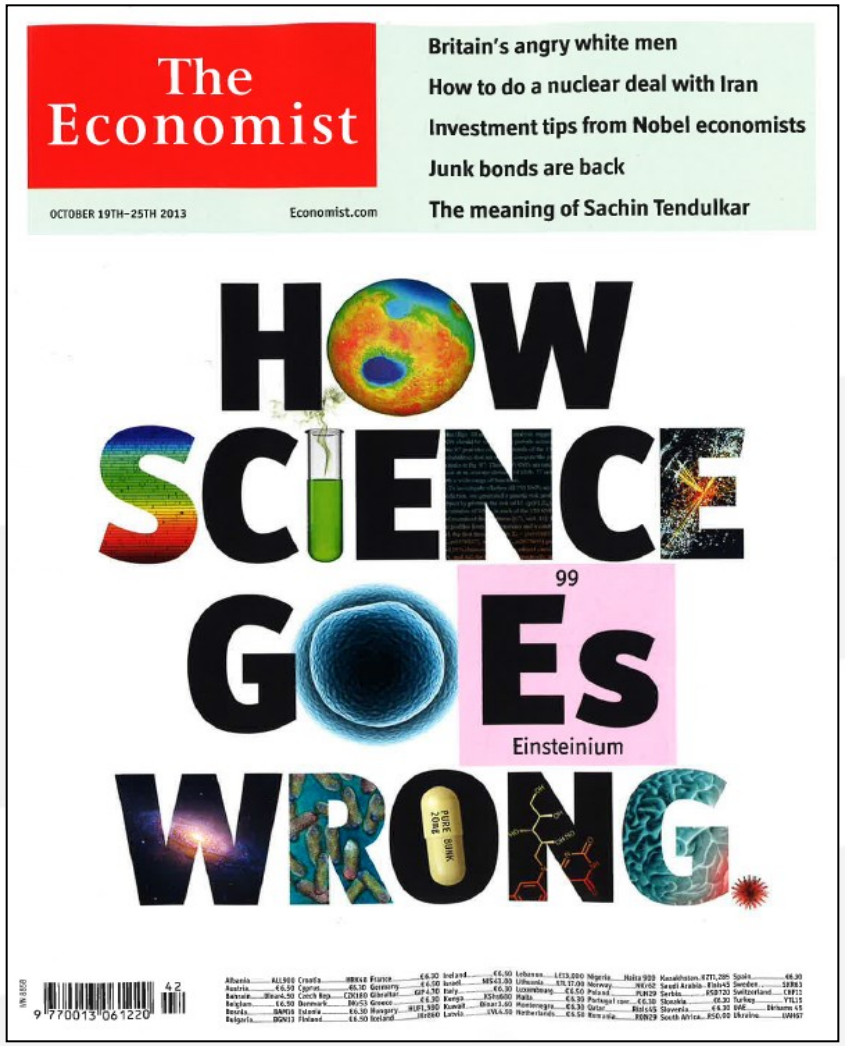
QIAGEN

Introduction &
the case for sample pre-analytics


7%
Don't know
3%
No, there is no crisis
IS THERE A
REPRODUCIBILITY
CRISIS?
A Nature survey lifts the lid on how researchers view the 'crisis' rocking science and what they think will help.
BY MONYA BAKER
52%
Yes, a significant crisis
38%
Yes, a slight crisis
1,576
RESEARCHERS SURVEYED


WHAT FACTORS CONTRIBUTE TO IRREPRODUCIBLE RESEARCH?
Many top-rated factors relate to intense competition and time pressure.
Always/often contribute
Sometimes contribute
Selective reporting
Pressure to publish
Low statistical power or poor analysis
Not replicated enough in original lab
Insufficient oversight/mentoring
Methods, code unavailable
Poor experimental design
Raw data not available from original lab
Fraud
Insufficient peer review
0
20
40
60
80
100%

The Problem of Not Reproducible Studies



Too many of the findings that fill the academic ether are the result of shoddy experiments or poor analysis (see pages 21-24). A rule of thumb among biotechnology venture-capitalists is that half of published research cannot be replicated. Even that may be optimistic. Last year researchers at one biotech firm, Amgen, found they could reproduce just six of 53 "landmark" studies in cancer research. Earlier, a group at Bayer, a drug company, managed to repeat just a quarter of 67 similarly important papers. A leading computer scientist frets that three-quarters of papers in his subfield are bunk. In 2000-10 roughly 80,000 patients took part in clinical trials based on research that was later retracted because of mistakes or improprieties.

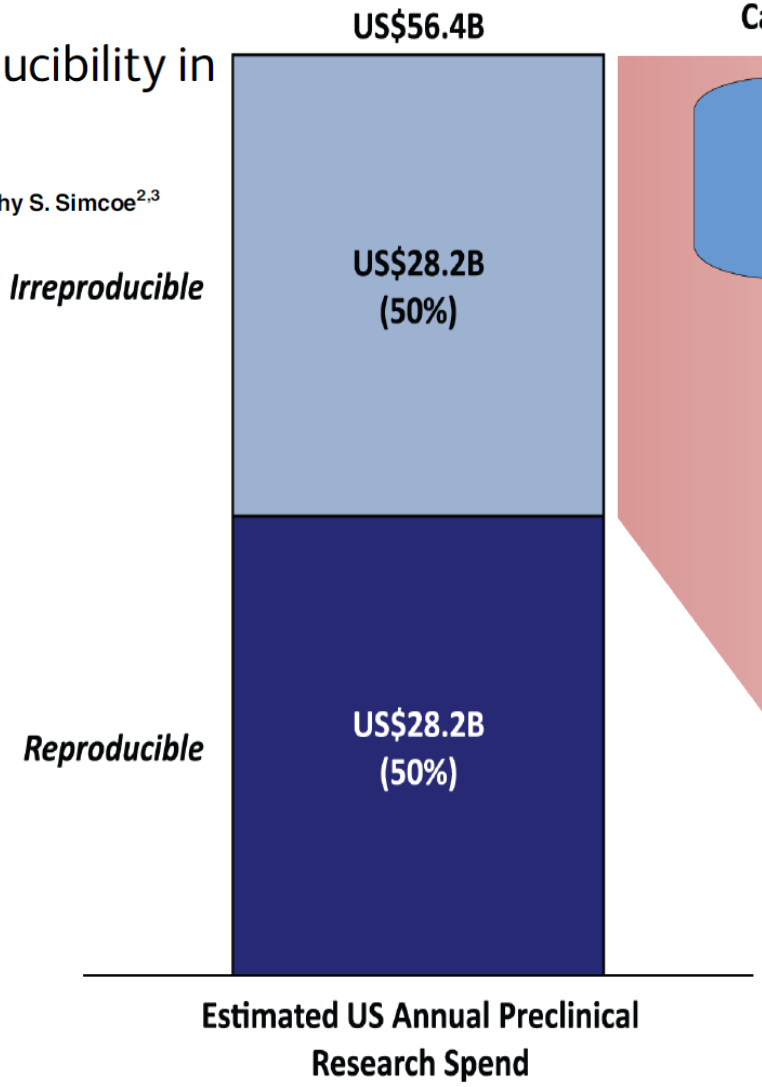
Economic Impact of Biosample Quality in R&D

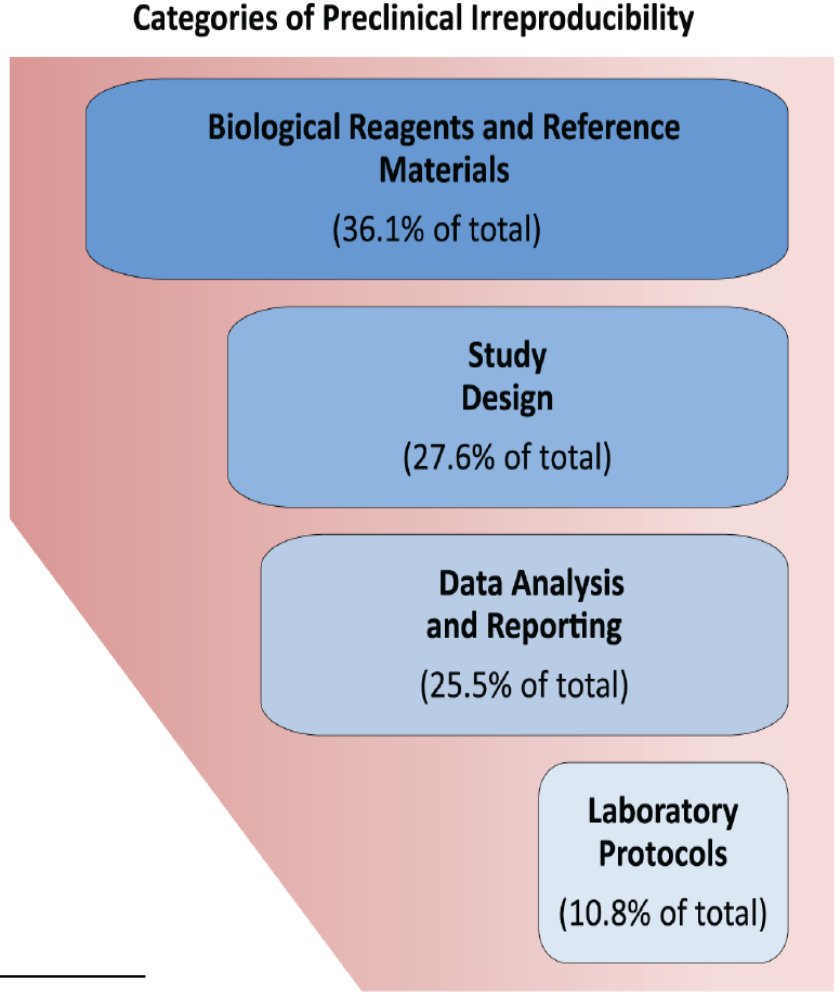
PLOS | BIOLOGY

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

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





Pre-analytical Errors in Medical Diagnostics

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

Plebani M, Clin Chem Lab Med. 2006

Impact of Errors in Medical Diagnostics

- 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 for Cancer Therapy (FDA)

DRUG	DISEASE	TARGET	ASSAY	TECHNOLOGY
Afatinib	NSCLC	EGFR	RT-PCR	Rotor-Gene
Brentuximab Vedotin	Hodgin Lymph., sALCL	CD30	IHC	
Cetuximab (1)	CRC	EGFR	IHC	
Cetuximab (2)	mCRC	KRAS	RT-PCR	Rotor-Gene
Crizotinib	NSCLC	ALK	FISH	
Dabrafenib	Melanoma	BRAF	PCR	ABI 7500
Denileukin Diftitox	cut TCL	CD25	IHC	
Erlotinib	NSCLC	EGFR	RT-PCR	Cobas
Everolimus	mRCC, NEC	mTOR	LC-MS/MS	
Exemestane	Breast Ca	Aromatase (ER/PR)	IHC	
Fulvestrant	Breast Ca	ER	IHC	
Gefitinib	NSCLC	EGFR	RT-PCR	Cobas
Imatinib (1)	CML	Ph+	RT-PCR, FISH	
Imatinib (2)	GIST	c-Kit	IHC	
Imatinib (3)	MDS	EGFR	FISH	
Imatinib (4)	HES	FIP1L1-PDGFRα	RT-PCR	
Lapatinib	Breast Ca	HER2/NEU	IHC, FISH	
Olaparib	Breast Ca	BRCA1/2	PCR,	Sanger seq.
Panitumumab (1)	CRC	EGFR	IHC	
Panitumumab (2)	mCRC	KRAS	RT-PCR	Rotor-Gene
Pertuzumab	Breast Ca	HER2/NEU	IHC FISH	
Tamoxifen	Breast Ca	ER	IHC	
Tositumomab	(f)NHL	CD20 antigen	IHC	
Trastuzumab	Breast , Gastric Ca	HER2/NEU	IHC, FISH, CISH	
Vemurafenib	Melanoma	BRAF	RT-PCR	Cobas

Examples of Drugs in Personalized Medicine

Drug	Action	Company	Cancer	Therapy costs US$
Bosutinib	Src Inh	Pfizer	CML	82000.-
Cetuximab	EGFR Inh.	ImClone BMS/Merck	Colon Ca	61000.-
Axitinib	Tyr K Inh.	Pfizer	Renal Ca	59000.-
Pomalidomid	Angiog Inh.	Celgene	Myeloma	52000.-
Lenalidomid	Angiog Inh.	Celgene	Myeloma	95000.-
Erlotinib	EGFR Inh.	Roche	Lung/Panc Ca	55000.-
Lapatinib	Her2 Inh.	GSK	Breast Ca	34000.-
Crizotinib	ALK Inh.	Pfizer	Lung Ca	67000.-
Vemurafenib	B-Raf Inh.	Roche/ Daiichi Sankyo	Melanoma	54000.-

Source: ISI Group, Economist

USA

National Cancer Institute

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

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Launch caHUB

OBBR Office of Biorepositories and Biospecimen Research

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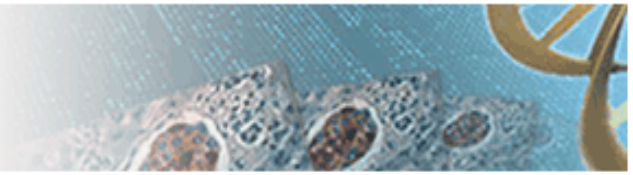
Biospecimen Research Network



Europe

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

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Subscribe to our newsletter to receive latest news about the project

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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.

Tissue Sample Quality: Critical Issues

Medication
Surgical procedure
Warm ischemia

Fixation
Fixative
Time

Transport
Temperature
Cold ischemia

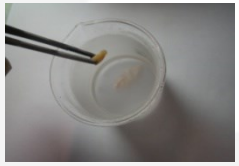
Embedding
Temperature

Sample processing
Mech. alteration
Selection+annotation

Diagnosis
Disease codes

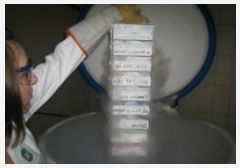
Aliquotting

Storage
Time
temperature



Freezing
Freezing rate
Temperature

Sample preparation



Cryostorage
Temperature
Temp. shifts

Analysis

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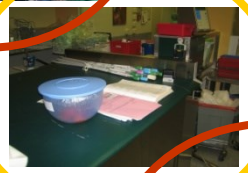
Sources of Diversity

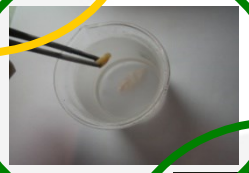
Medication
Surgical procedure
Warm ischemia



Transport
Temperature
Cold ischemia

Sample processing
Mech. alteration
Selection+annotation

Aliquotting



Freezing
Freezing rate
Temperature

Cryostorage
Temperature
Temp. shifts

Fixation
Fixative
Time

Embedding
Temperature

Diagnosis
Disease codes

Storage
Time
temperature

Sample preparation

Analysis

can be avoided

can be reduced

not avoidable

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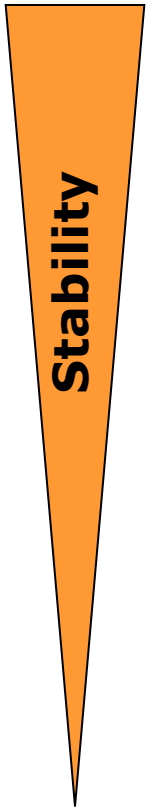
Parameters for Tissue-Based Analysis

Sample variables

- Tissue type (organ)
- Diseased/normal
- Sample type (biopsy/surgery)
- Peri-operative effects
- Ischemia
- Processing
- Fixation
- Storage
- Analysis

Readout

- Morphology
- Antigenicity
- Mol.structure
- Biomolecules
  - DNA
  - Protein
  - Protein mod.
  - RNA
  - Metabolites
- Interactomes



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Pre-analytical impact of ischemia and fixation

Definition: Warm and Cold Ischemia

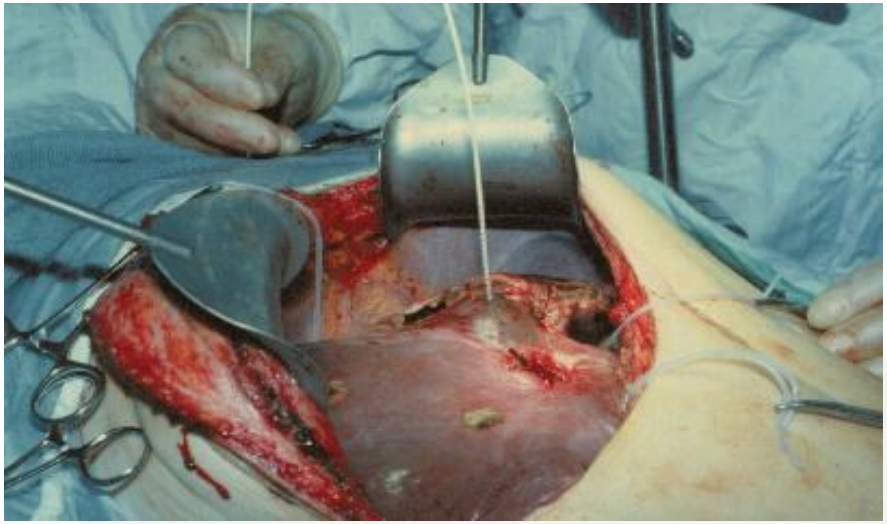
Warm ischemia:

Time interval of interruption of blood supply and removal of a tissue from the body

Cold ischemia:

Time interval between tissue removal from the body and stabilization or fixation

Warm and Cold Ischemia Effects



- The Pringle manoeuvre is applied to prevent blood loss during 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**

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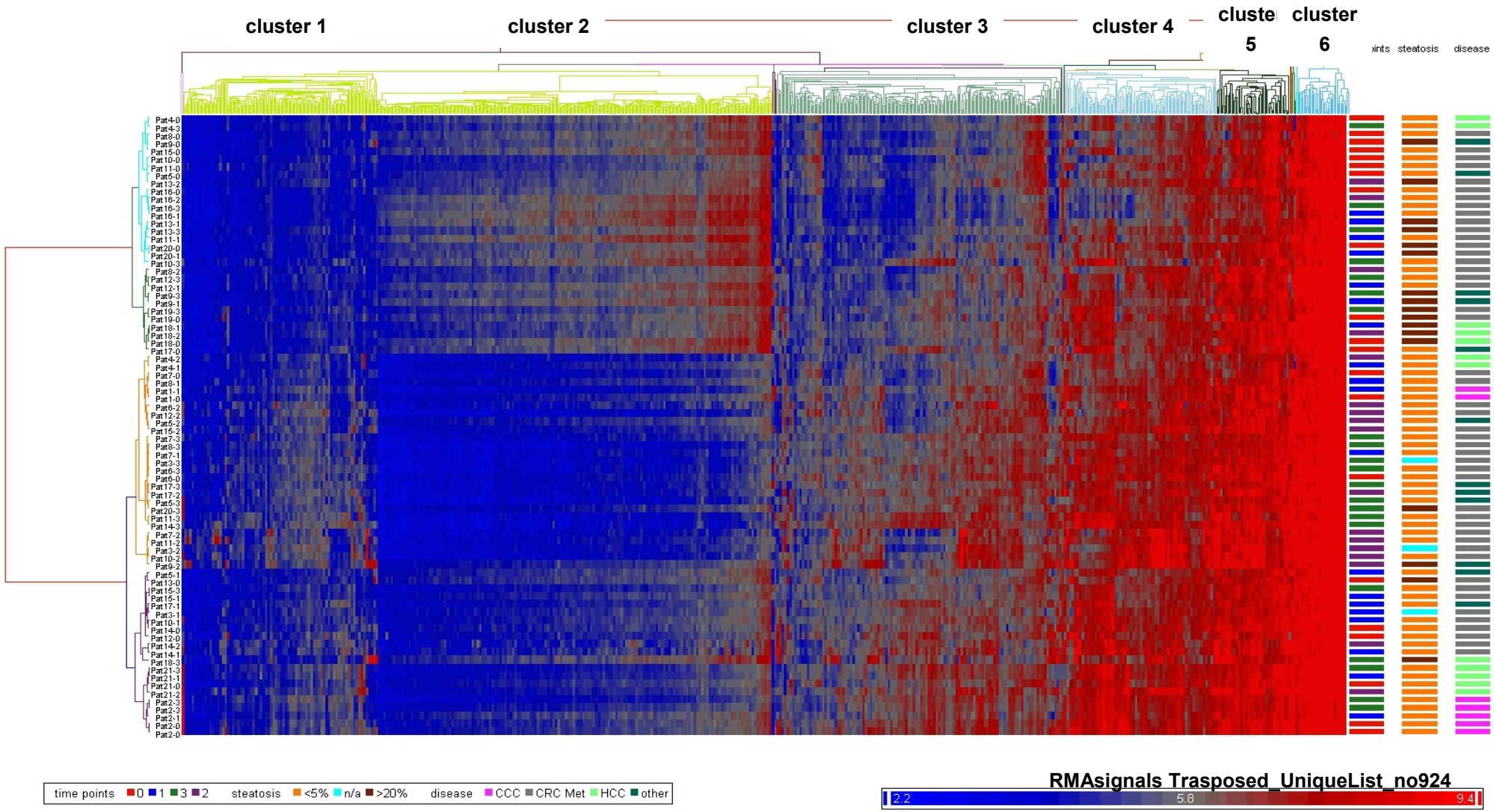
GEN-AU
GENOMFORSCHUNG IN ÖSTERREICH

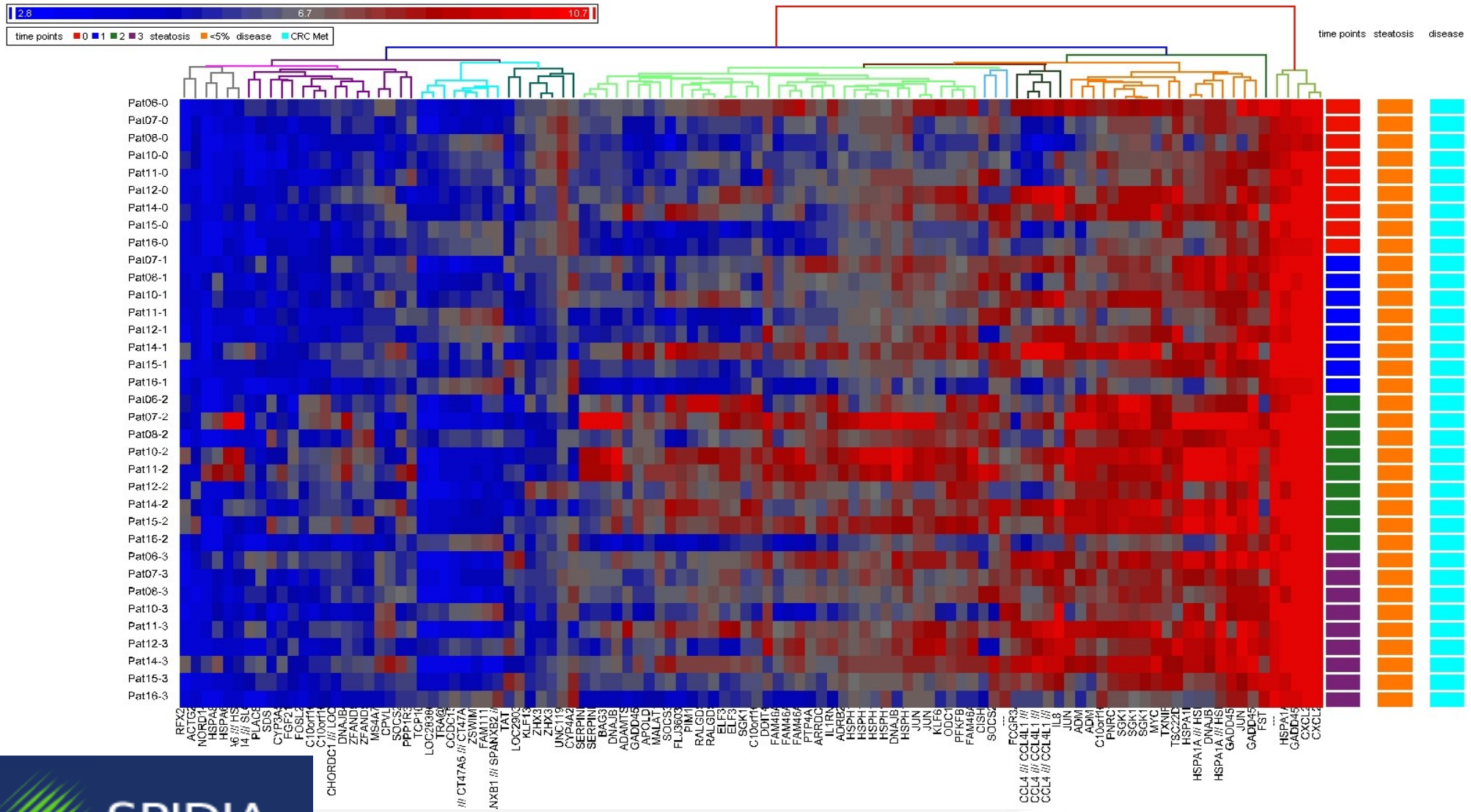
Ischemia and Gene Expression

Affymerix HG-U219



FC1,5_p0,05 924 genes

Ischemia and Gene Expression



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Alteration in Gene Expression is an Active Respose

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

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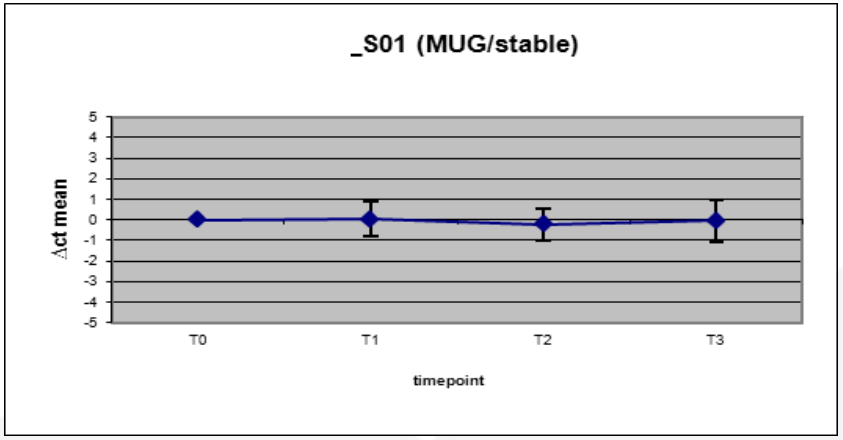
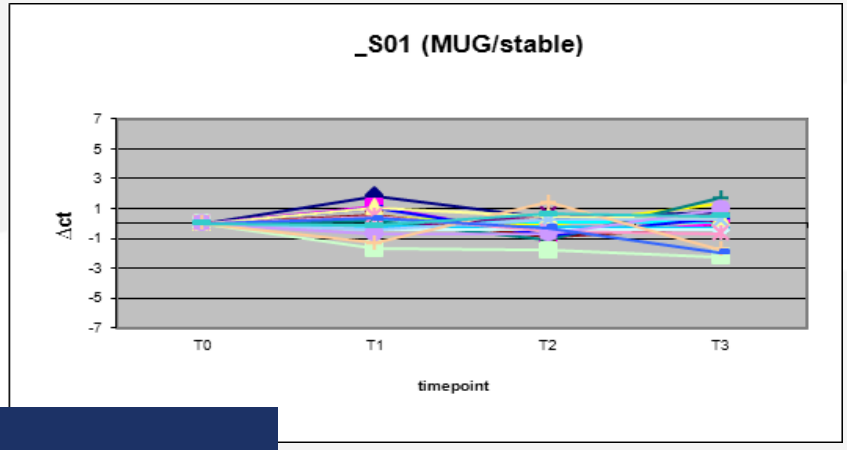
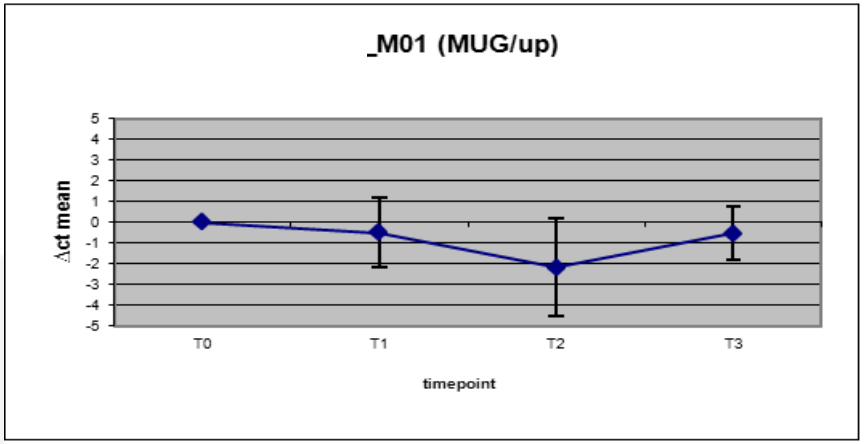
Tissue Quality Marker
(qRT-PCR Validation)

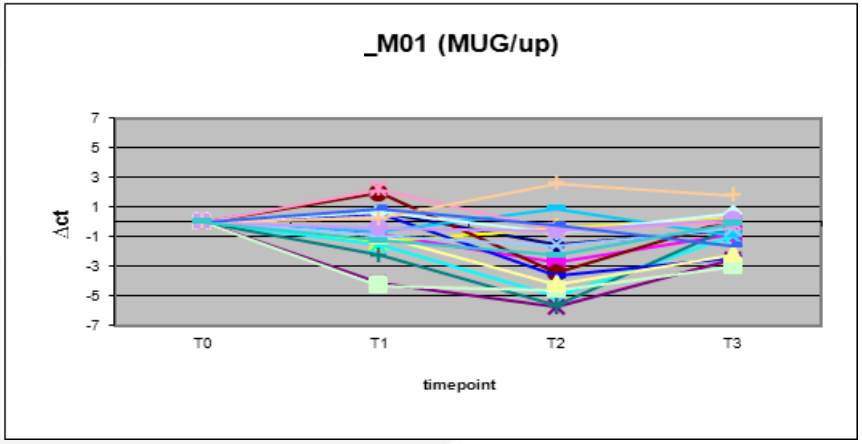
stable





unstable





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Conclusions and Recommendations

- Different RNA molecules show different susceptibility to ischemia effects
- There is an induvidual difference to ischemia effects (genetic diversity, co-morbidities)

Recommendations:

- Warm and cold ischemia times have to be documented
- Each biomarker needs to be validated for pre-analytical robustness

Companion Diagnostics for Cancer Therapy (FDA listed)

DRUG	DISEASE	TARGET	ASSAY	TECHNOLOGY
Afatinib	NSCLC	EGFR	RT-PCR	Rotor-Gene
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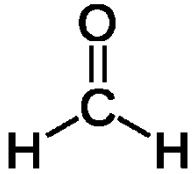
Trastuzumab	Breast , Gastric Ca	HER2/NEU	IHC, FISH, CISH	
Vemurafenib	Melanoma	BRAF	RT-PCR	Cobas

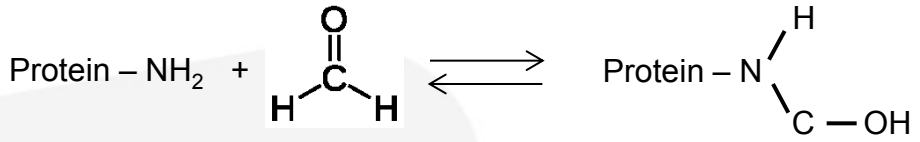
■ FFPE tissue based biomarkers

Interaction of Formaldehyde with Biomolecules

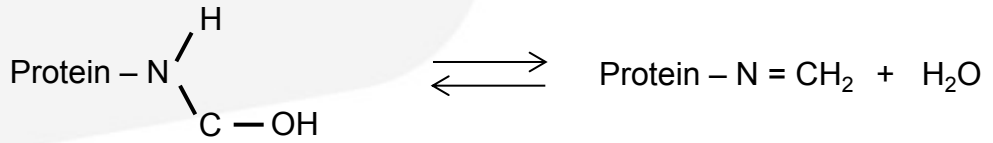
Formaldehyde: CH_2C 

MW: 30.03 g.mol^{-1} 10% formalin 1300 mO

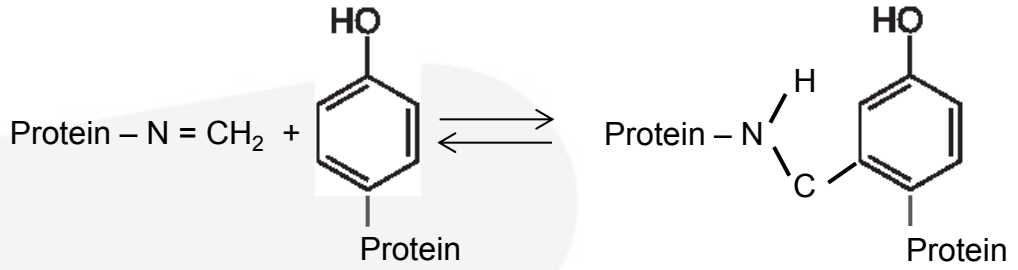
- Methylol adducts



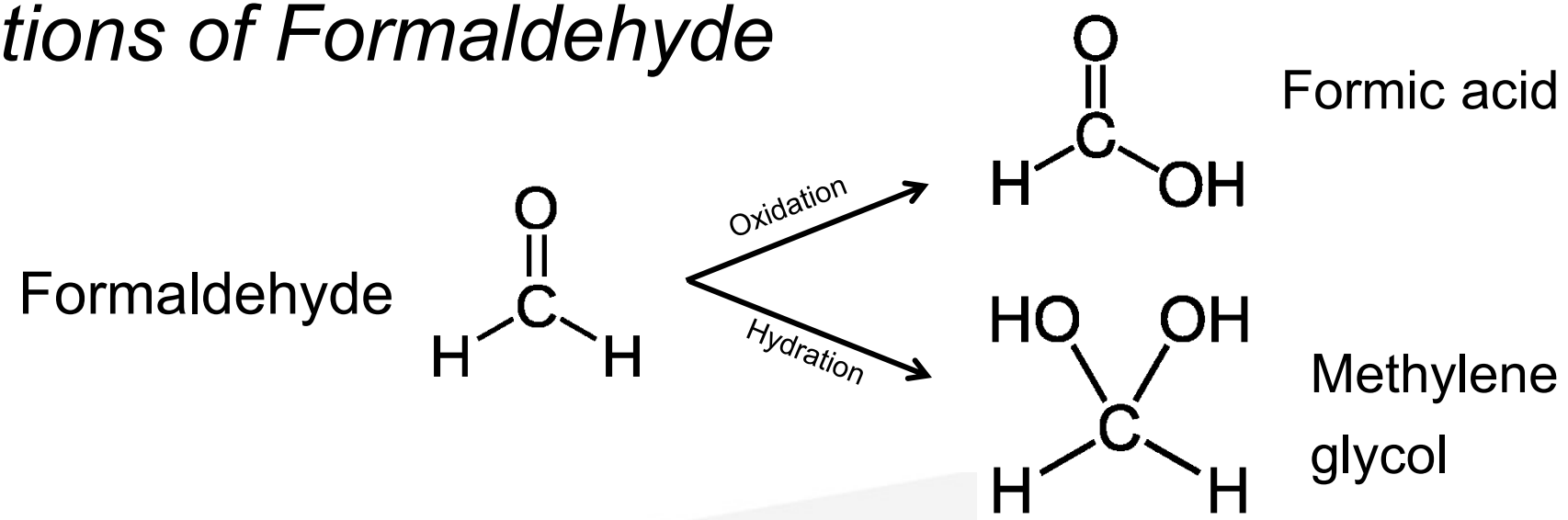
- Schiff base



- Cross-links
  - protein – protein
  - protein – DNA
  - DNA – DNA



Reactions of Formaldehyde

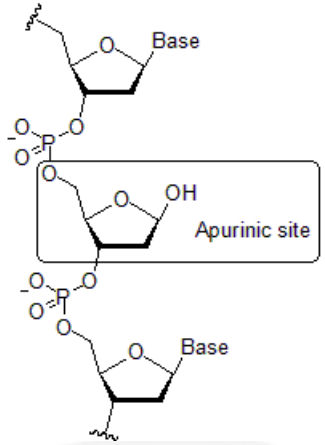


- Spontaneous oxidation to formic acid
  - Drop in pH of formalin
    - Depurination
    - Deamination 5-mC > T; C > U
    - Fragmentation

    } C:G > T:A
  - Formalin pigment

- Hydration to methylene glycol

Formalin-induced DNA Alterations



Cytosine **Uracil**

Molecular in-vitro diagnostic examinations — Specifications for pre-examination processes: Principles

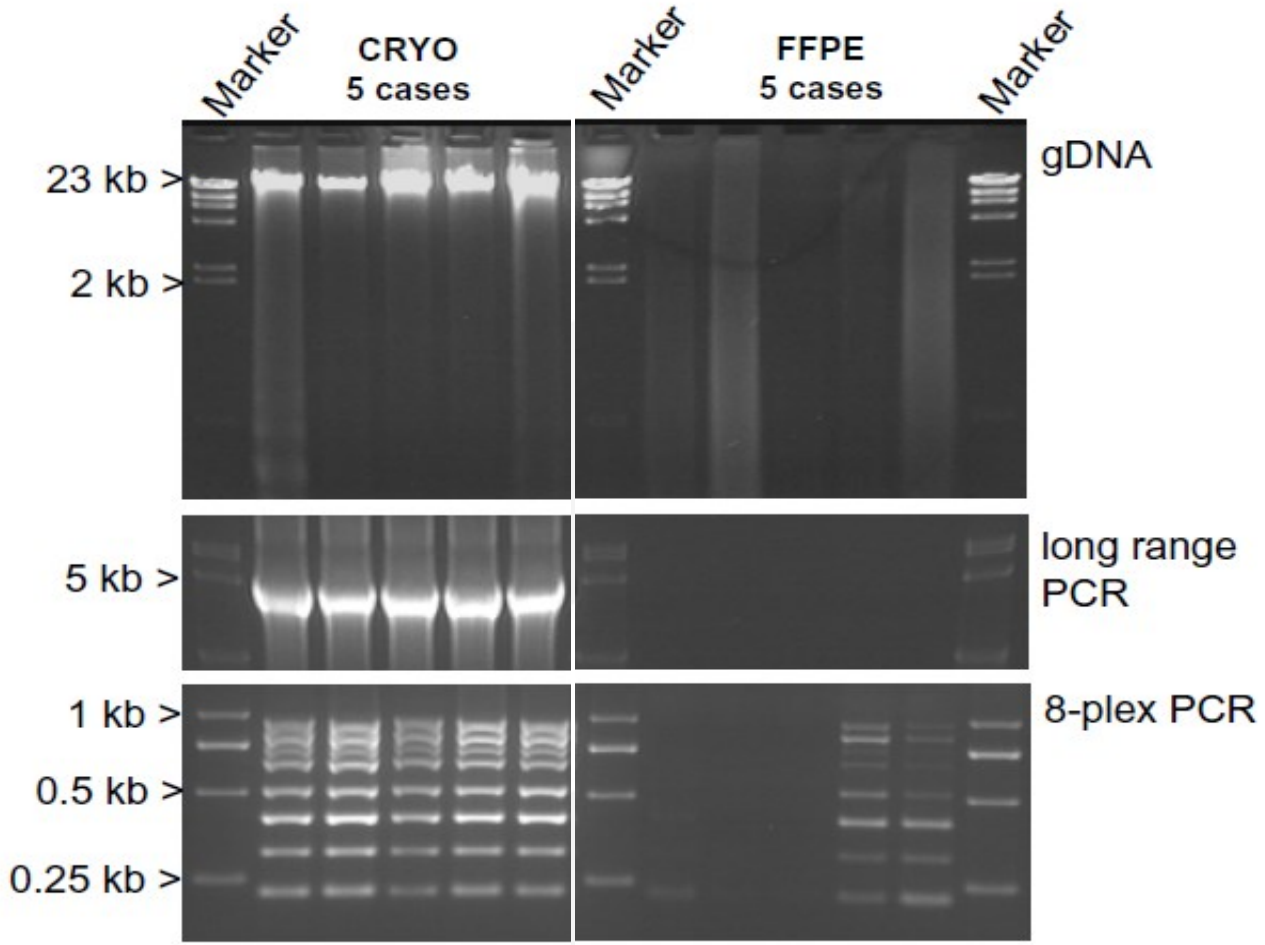
- Documentation, documentation, documentation …….
- Few concrete procedures

  Standard buffered formalin solution

  10 % formalin solution containing 3.7 % by mass (corresponding to 4% by volume) formaldehyde, buffered to pH 6.8 to pH 7.2

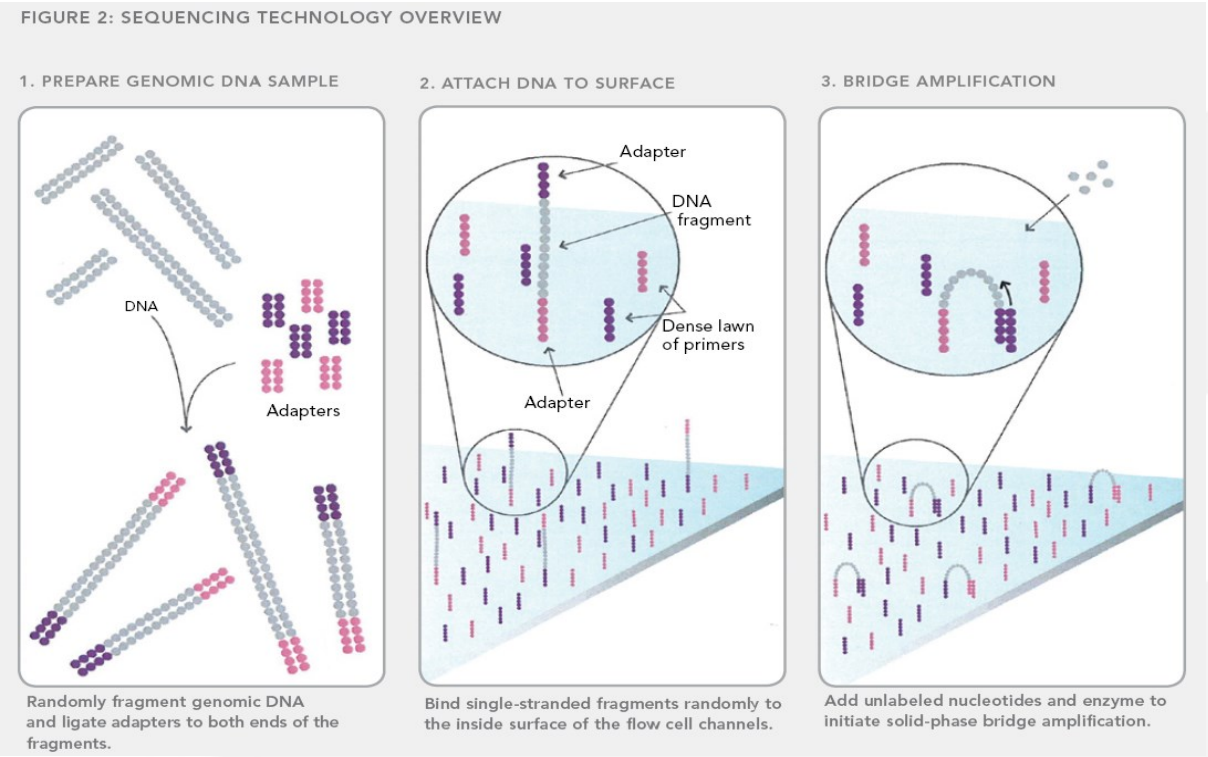
  no TE-buffer for RNA
- Definitions
- Not included:
  - Biosafety, biosecurity
  - Informed consent, counselling

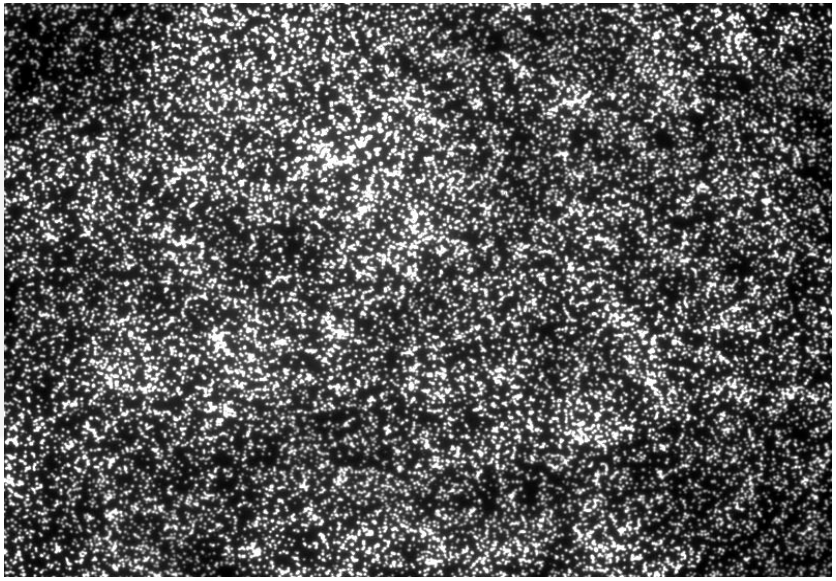
Fragmention of Genomic DNA in FFPE



C. Viertler et al., JMD 2012

Massive Parallel Sequencing (MPS)

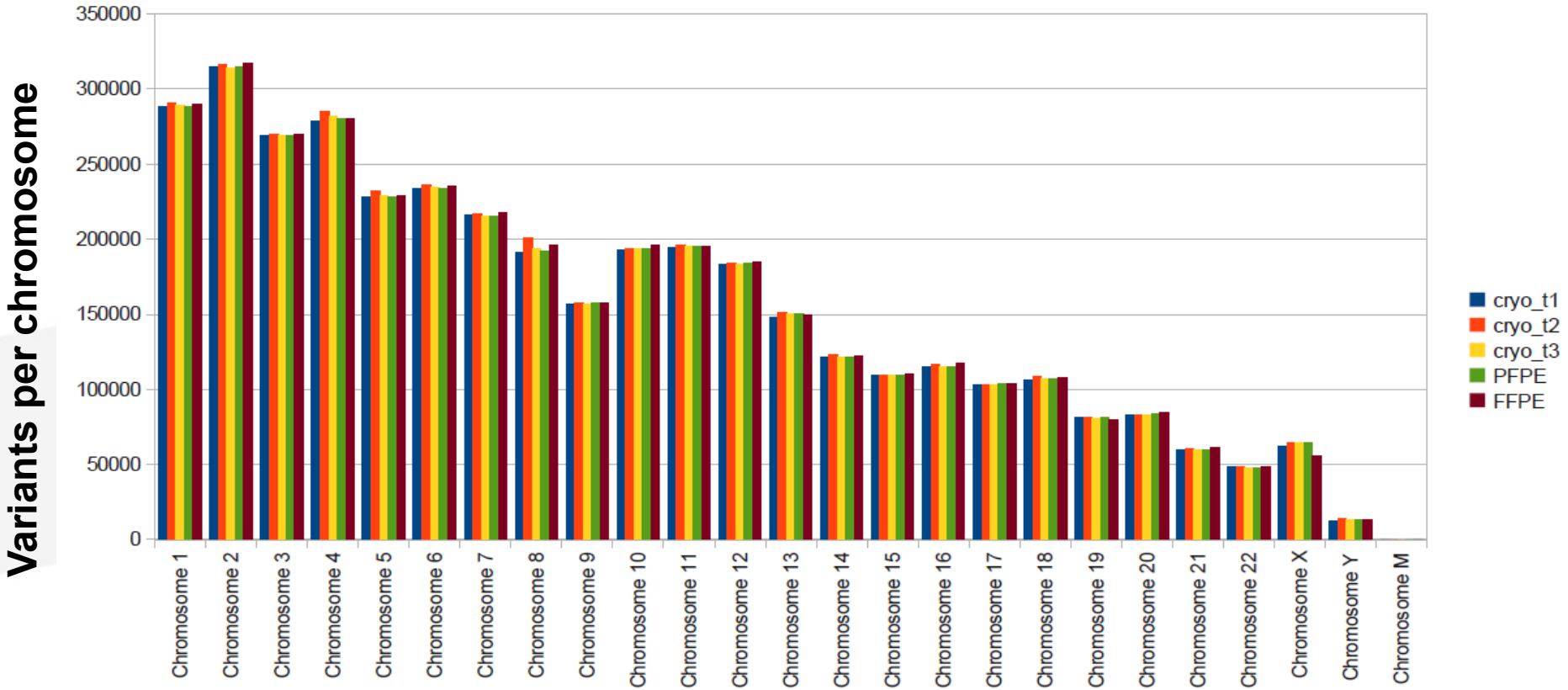




~ 40 mio clusters

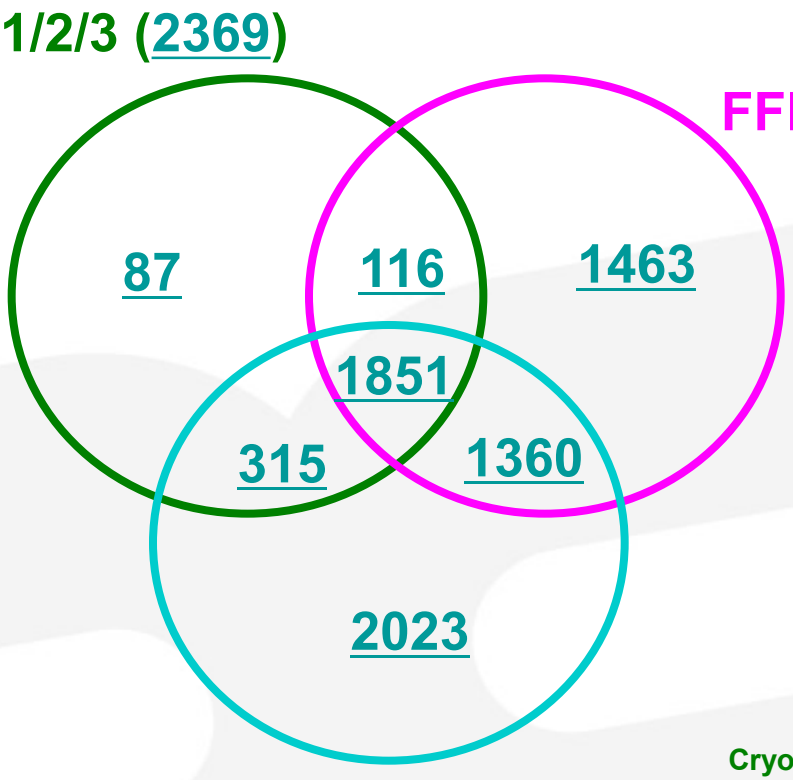
The Good News: FFPE samples are suitable for MPS

Illumina whole genome sequencing



cnag
Ivo Gut
Parc Científic de Barcelona

Whole Genome Sequencing: somatic variants in 3 related differently-preserved samples



Cryo1/2/3: Intersection of the 3 cryos: 2369 positions (see previous slide)
FFPE: 4790 positions passing som. filter
PFPE: 5549 positions passing som. filter

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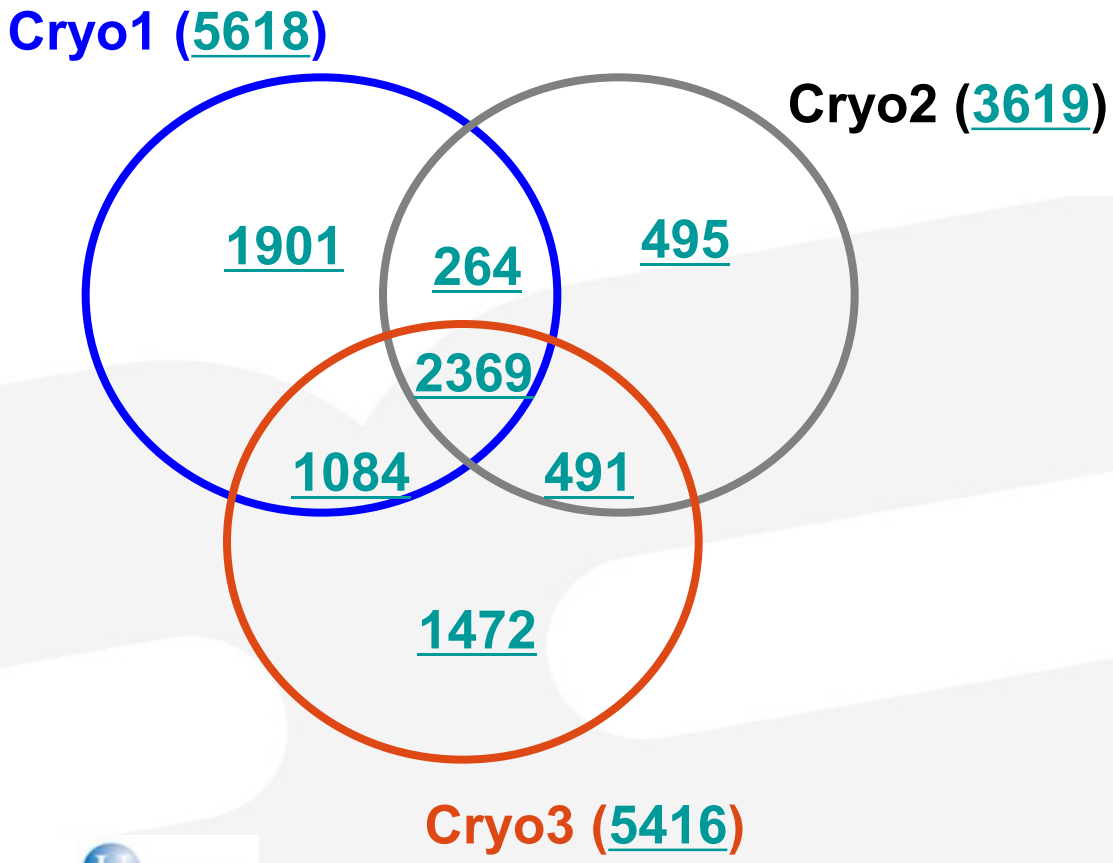
Whole Genome Sequencing: somatic variants in 3 related cryo-preserved samples

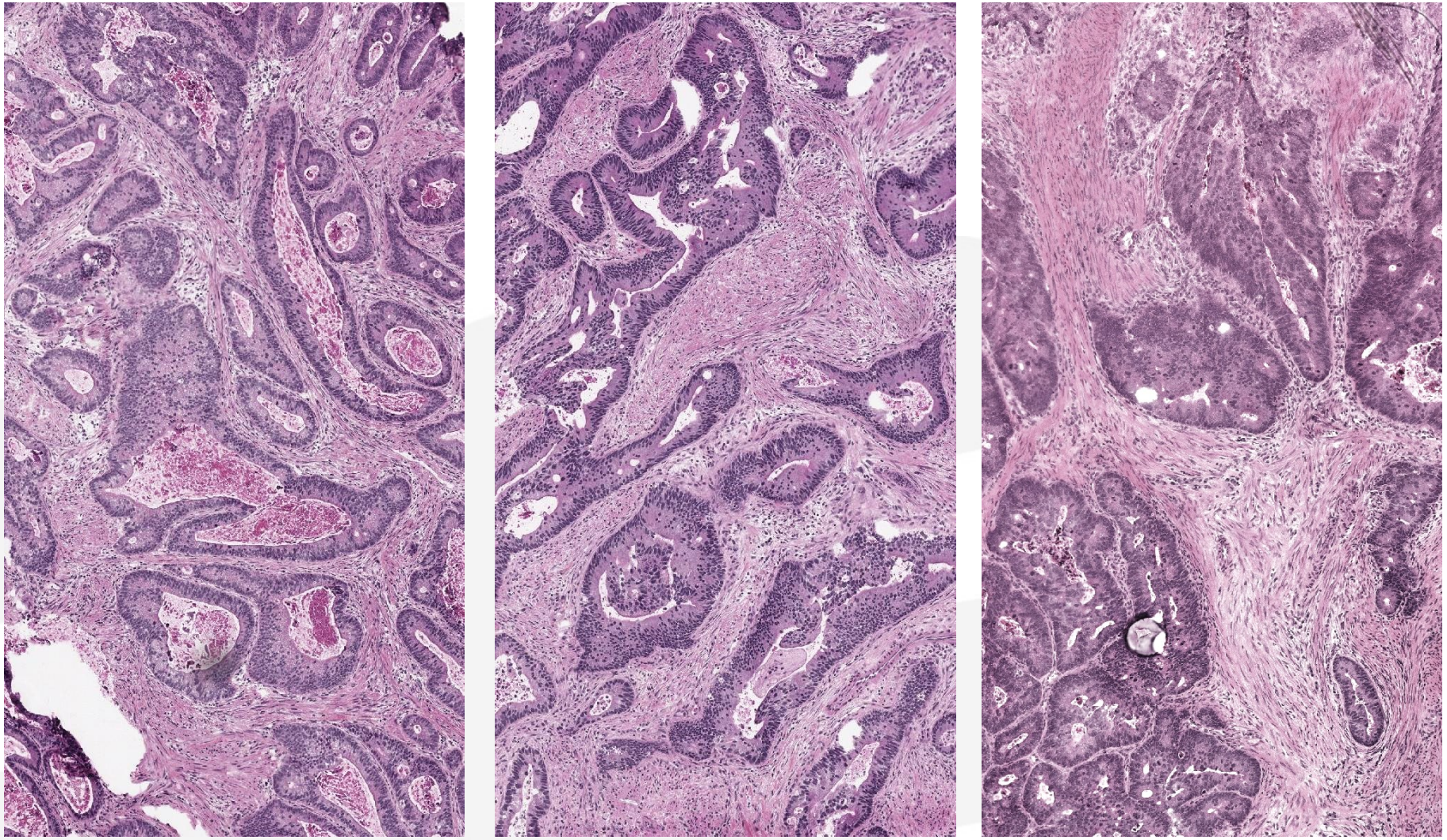


Cryo1: 5618 positions passing som. filter
Cryo2: 3619 positions passing som. filter
Cryo3: 5416 positions passing som. filter

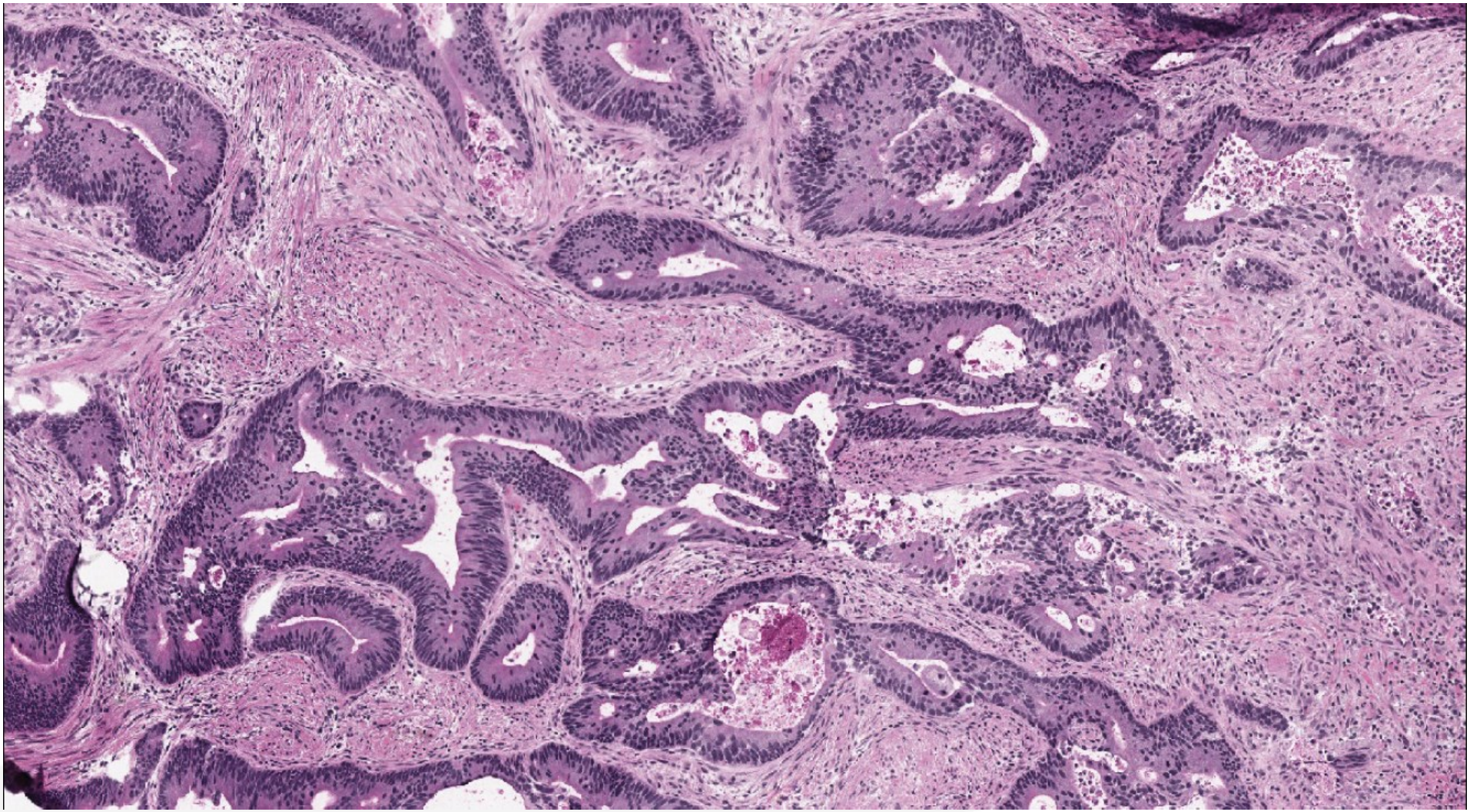
cnag
Ivo Gut
Parc Científic de Barcelona

Tumor Heterogeneity in the

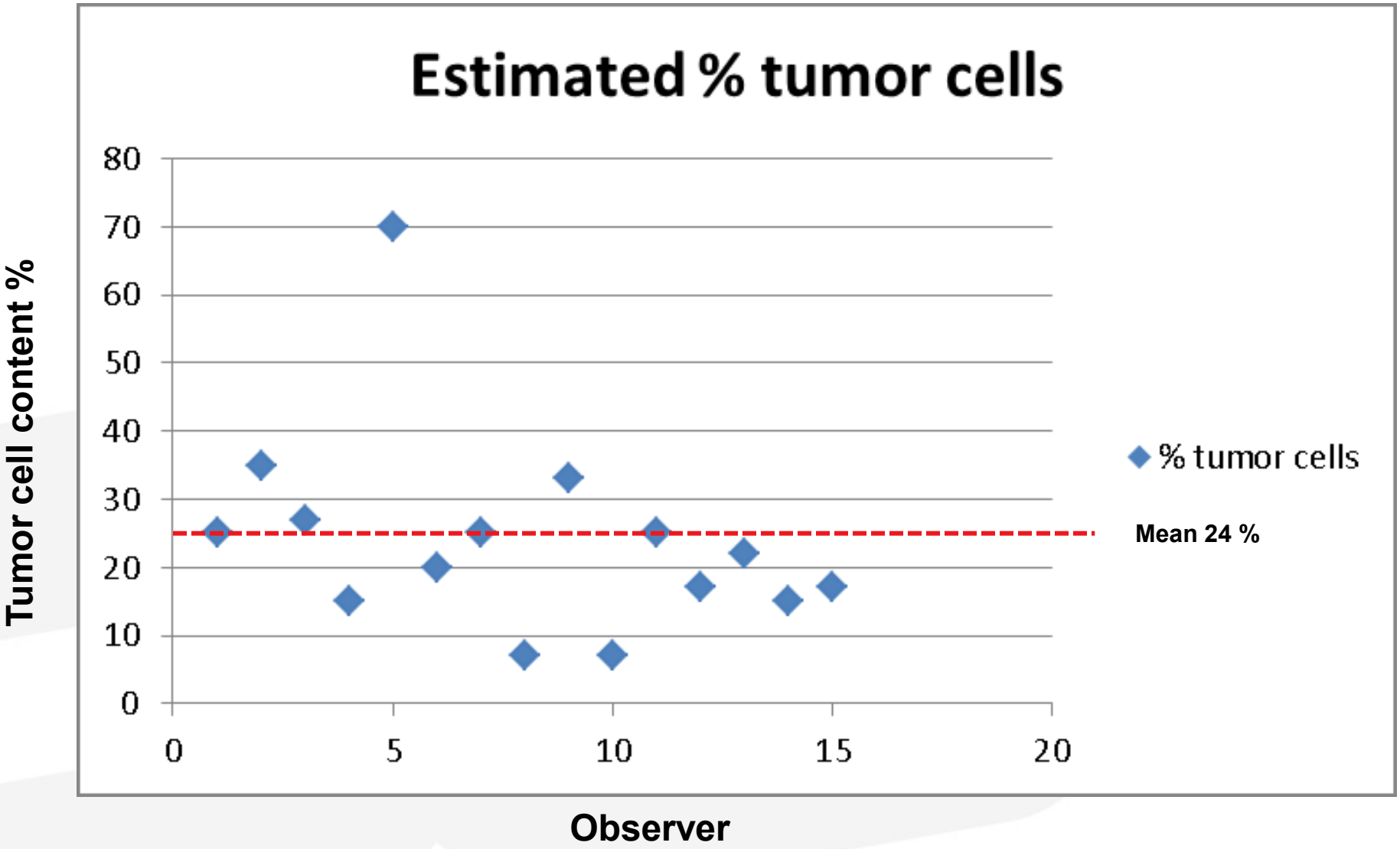
3 Related Cryo-preserved Samples



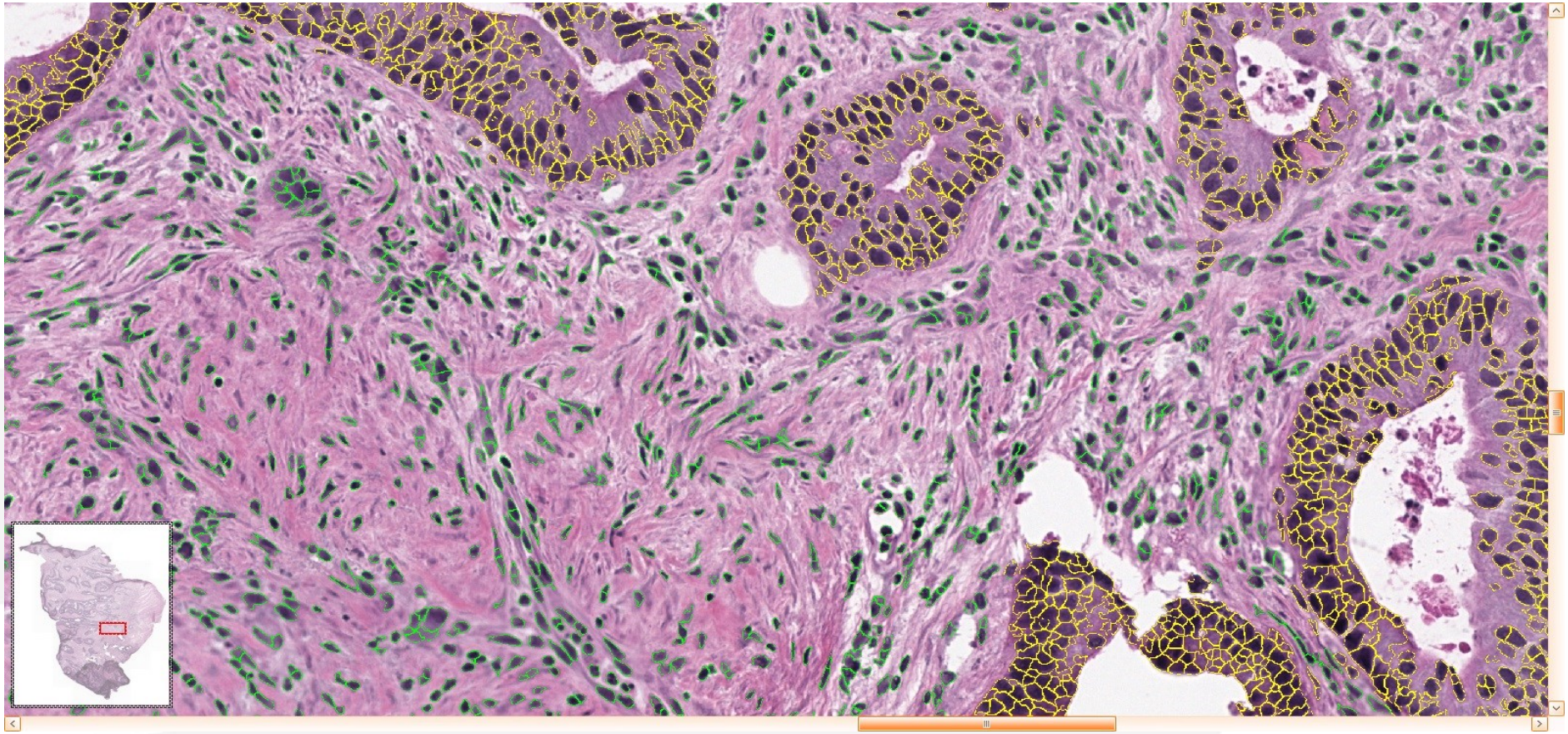
Evaluation of Tumor Content



Evaluation of Tumor Content



Morphometric Detection of Nuclei in Epithelial (yellow) and Stromal (green) Areas



TISSUE GNOSTICS
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Morphometric Analysis of Epithelial and Stromal Tumor Components

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%

TISSUE GNOSTICS
MEDICAL & BIOTECH SOLUTIONS

Conclusions and Recommendations

- Interpretation of NGS data require exact quantification of tumor cell content

Recommendations:

- Morphometric analysis of digital slides

Example from CEN/TS 16827-3:2015 (E)

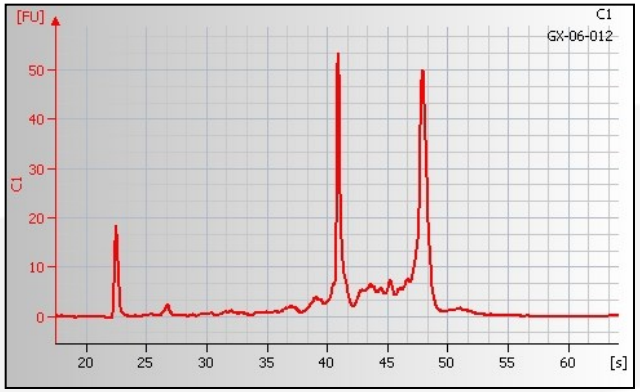
6.3 Evaluation of the pathology of the specimen and selection of the sample
The evaluation and documentation of the pathology of the specimen and the selection of the sample from the specimen for further processing shall be done by or under supervision or responsibility of a medically qualified (e.g., board certified) pathologist.

6.7 Isolation of DNA
6.7.1 General
Where a histopathological characterization of the cellular composition and disease condition of the sample was not performed under 6.3, and is needed, it shall be performed at this stage to quantitatively assess the cellular composition and disease condition.

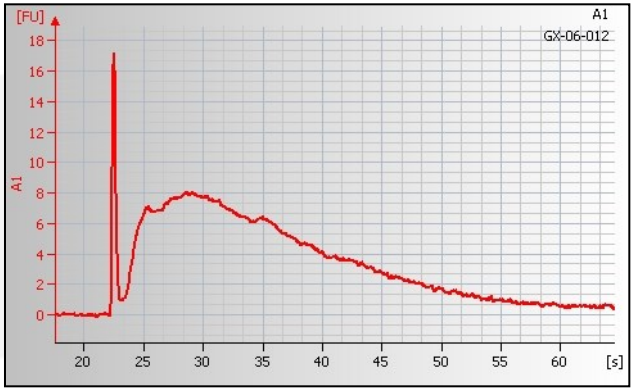
Quality Control for Pre-analytical Procedures

RNA Quality in Cryo-preserved and FFPE Tissues

Cryo-conservation

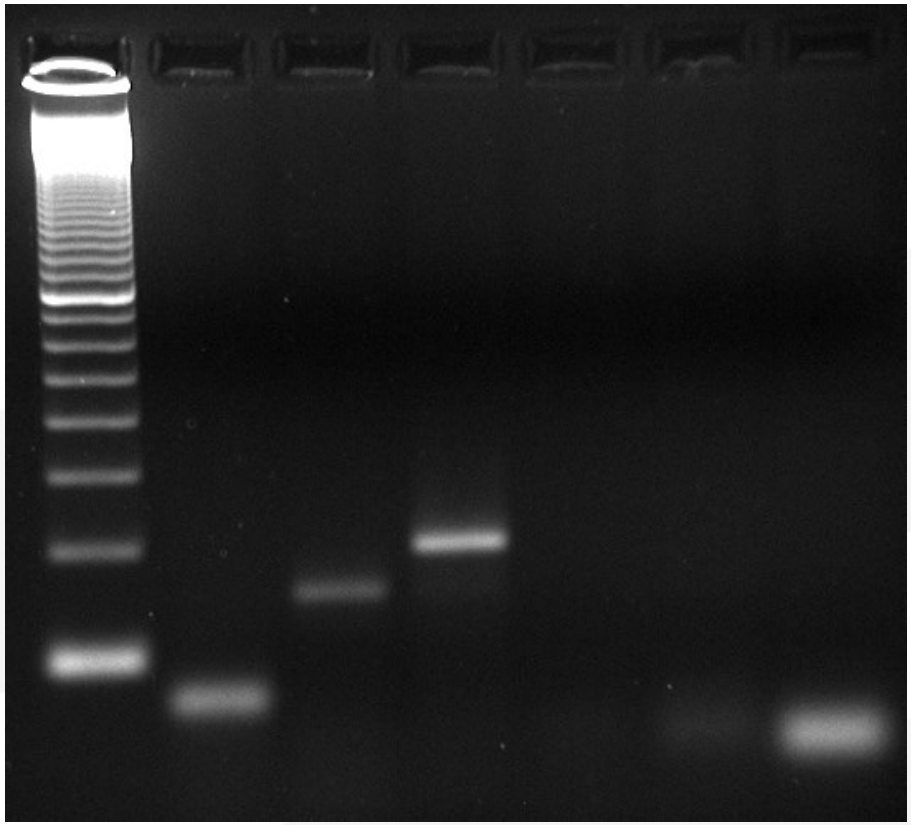


4% buffered formaldehyde



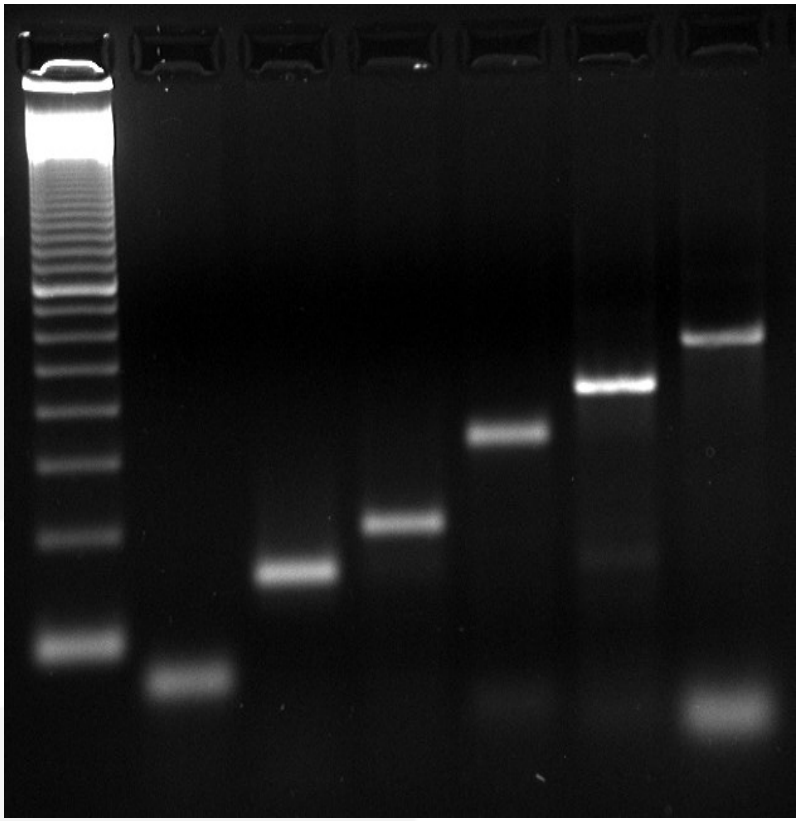
RT-PCR of RNA from FFPE Tissues

4% buffered formaldehyde



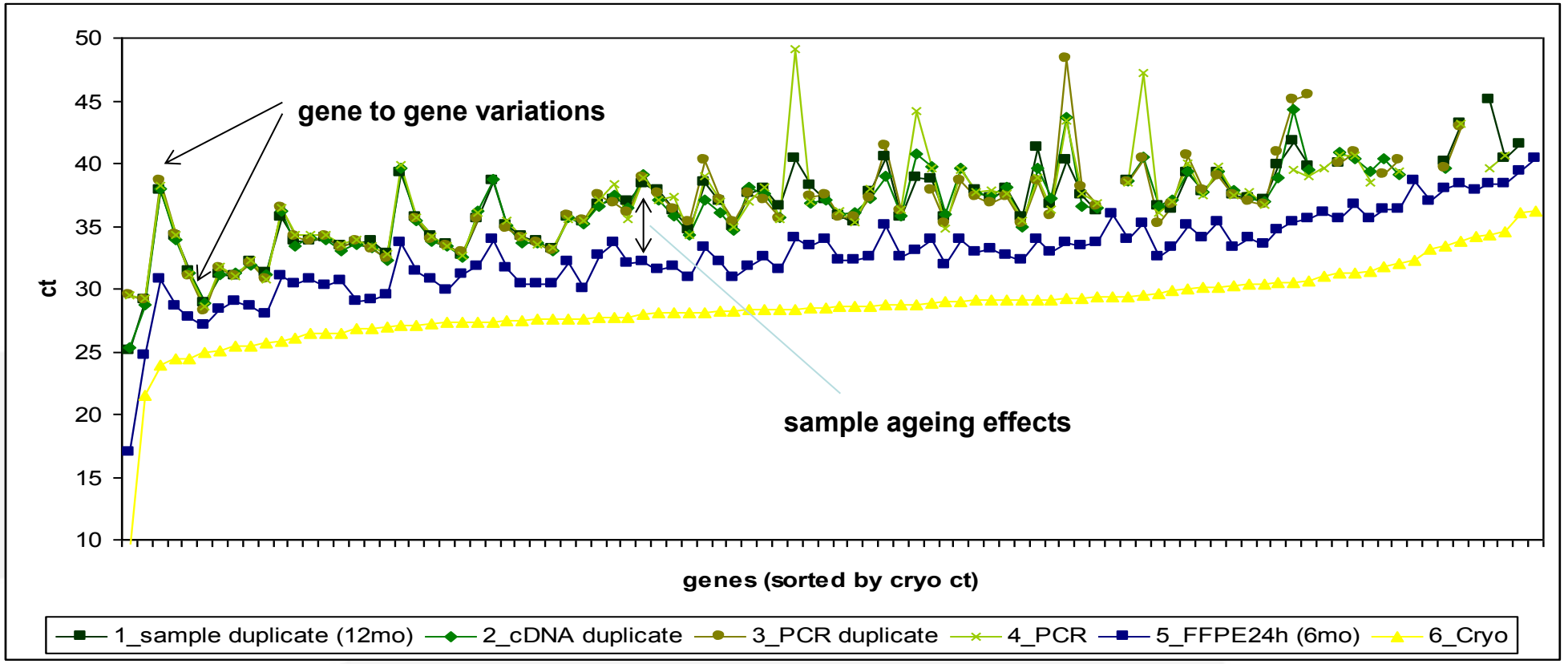
71 153 200 323 413 530 nts

methyl-alcohol/polyethyleneglycol



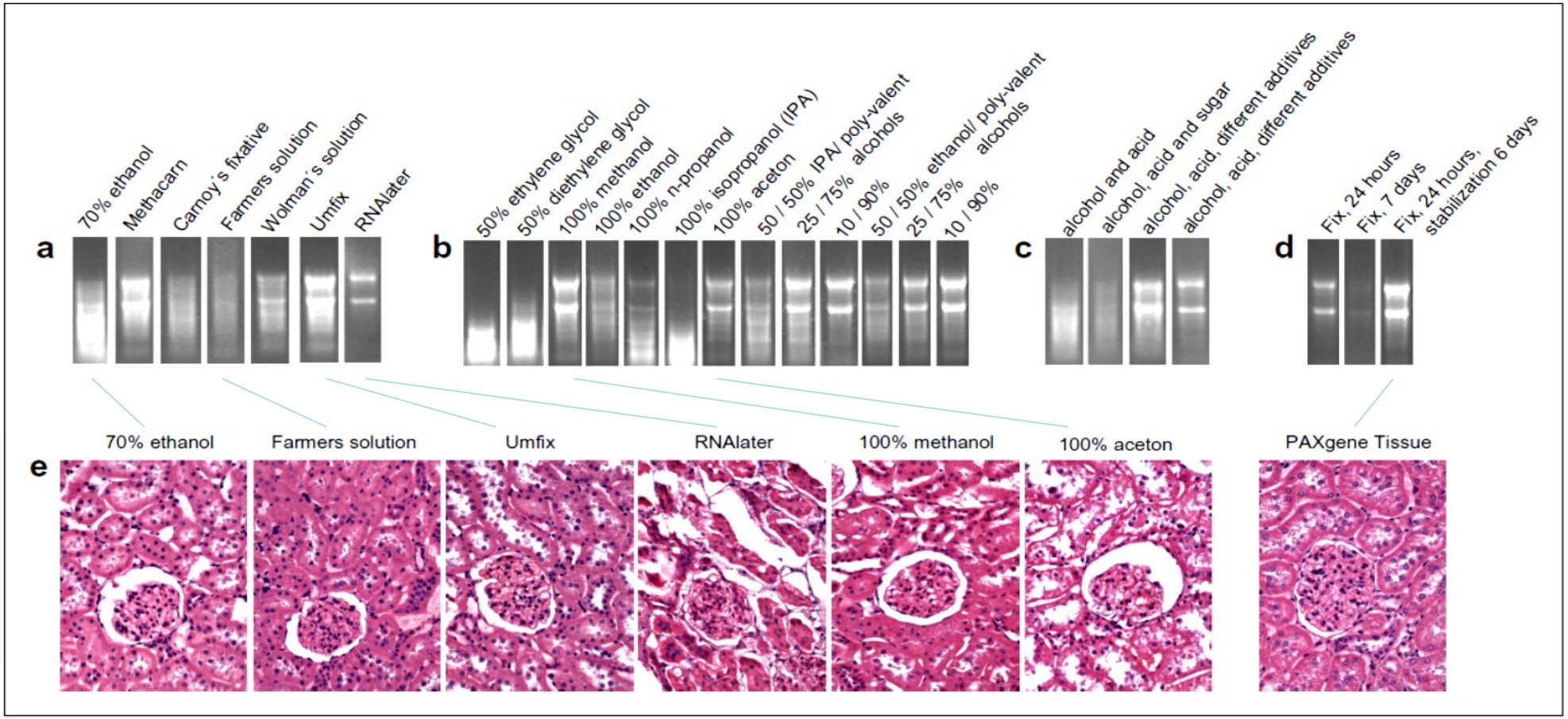
71 153 200 323 413 530 nts

Formalin Fixation Interferes with qRT-PCR



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

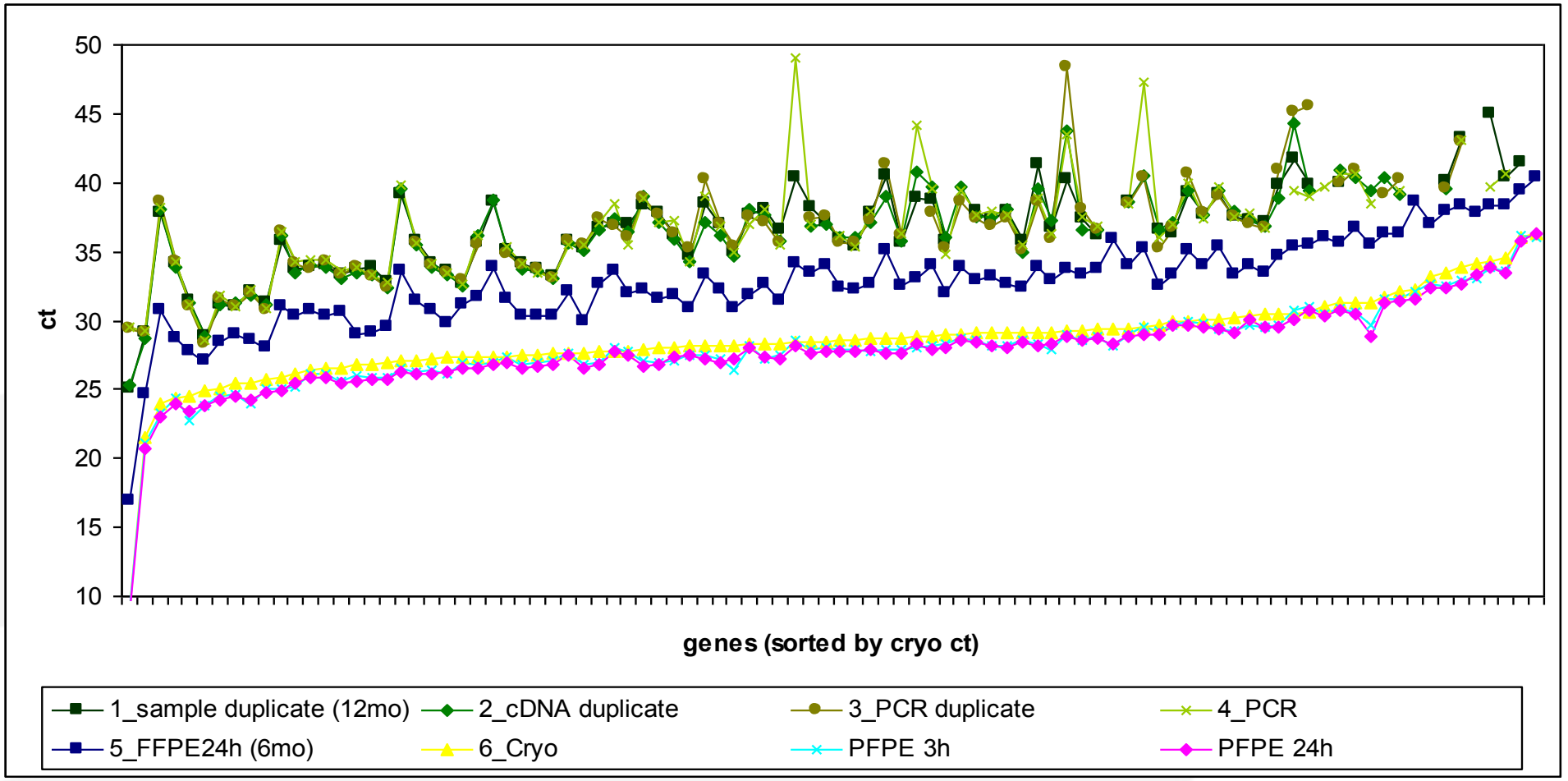
Impact of Fixation on Tissue Morpholgy and RNA Integrity



SPIDIA

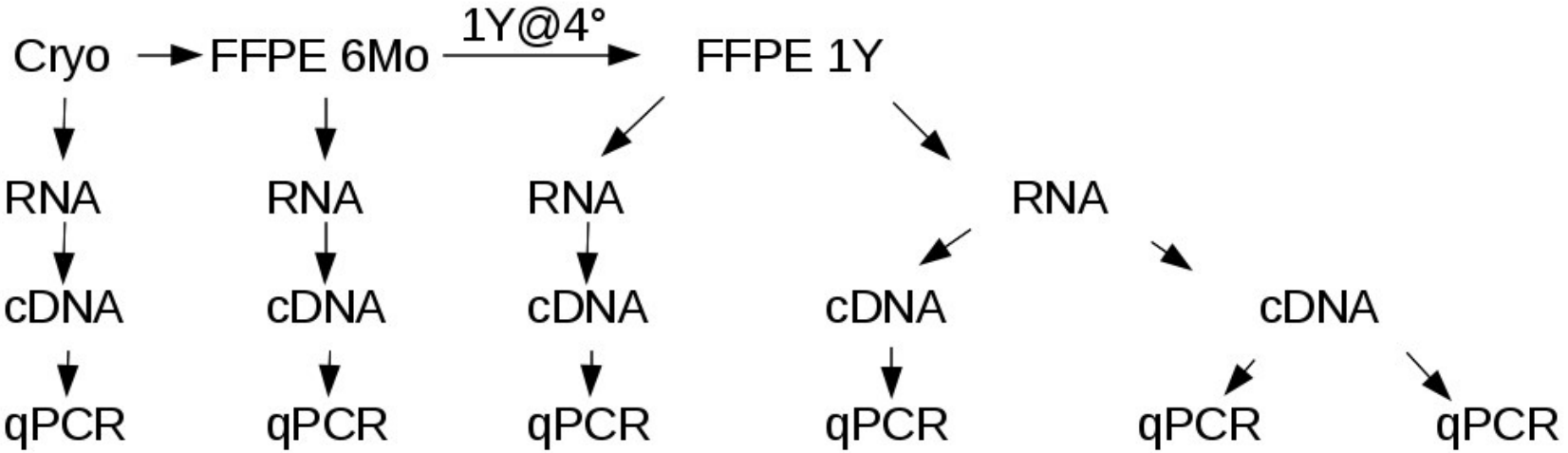
C. Viertler et al., JMD 2012

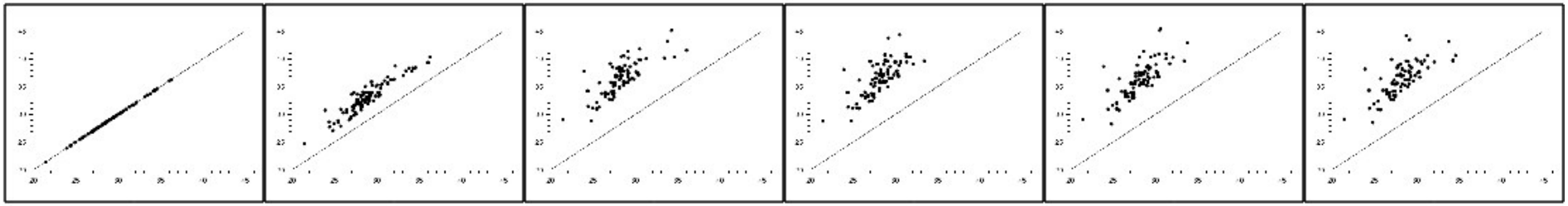
Comparison of qRT-PCR from Cryo-perserved, FFPE, PFPE Tissues



C. Viertler et al., JMD 2012

Sources of Variations in FFPE Tissue



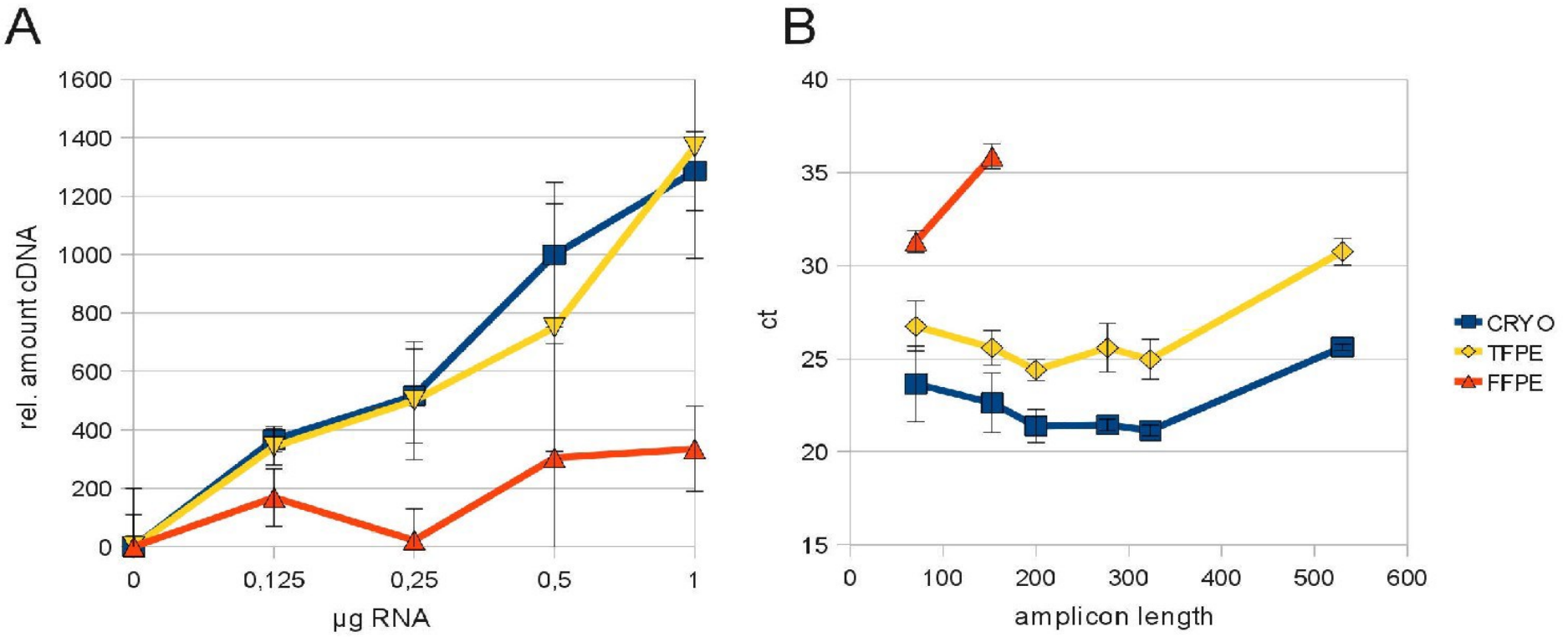


Pearson	1,0000	0,9411	0,7944	0,7462	0,6454	0,6040
Avg. dCt	0,0000	3,9952	8,0566	8,0446	8,0676	8,1876

TaqMan Array Gene Signature Plate

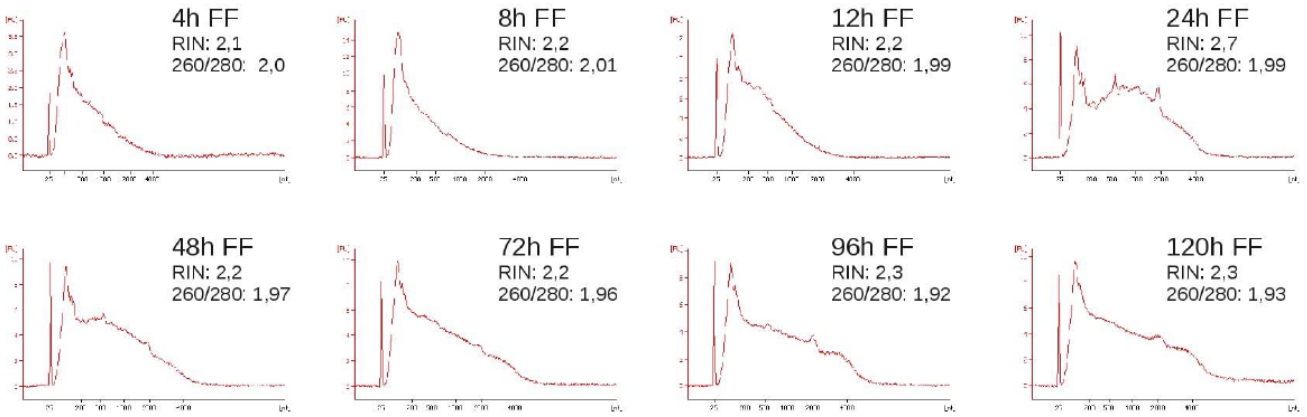
C. Viertler et al., JMD 2012

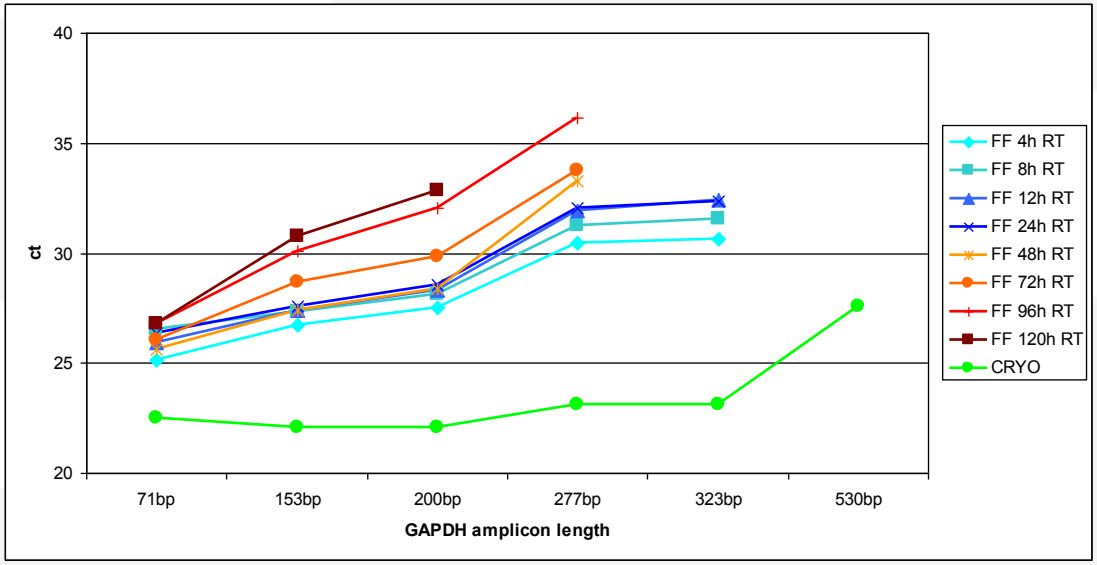
Formalin Fixation Reduces cDNA Synthesis and Amplification Efficiency



Kashofer K, et al. PLoS ONE 8(7): e70714. doi:10.1371/journal.pone.0070714

RIN does not Correlate with Amplification Efficacy of RNA from FFPE Tissue





Kashofer K, et al. PLoS ONE 8(7): e70714. doi:10.1371/journal.pone.0070714

Conclusions and Recommendations

- Different pre-analytival requirements depend on the concrete protocol and method (e.g., RNA isolation, cDNA synthesis etc.)
- RIN is no appropriate quality control for RNA from FFPE

Recommendations:

➢ Each assay component of a workflow needs to be validated

ISO
New Work Item Proposal

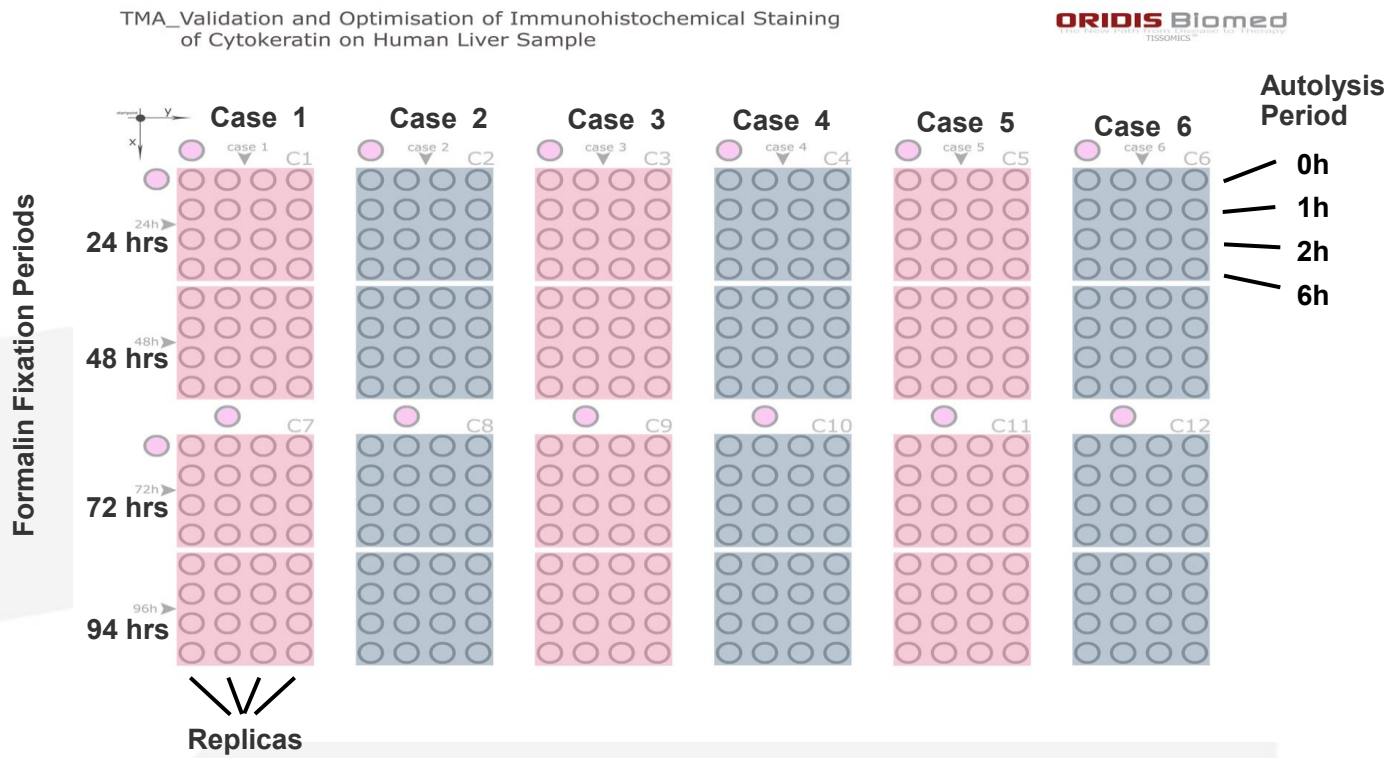
Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for formalin-fixed and paraffin-embedded (FFPE) tissue for *in situ* detection techniques”

Companion Diagnostics for Cancer Therapy (Examples FDA listed)

DRUG	DISEASE	TARGET	ASSAY	TECHNOLOGY
Afatinib	NSCLC	EGFR	RT-PCR	Rotor-Gene
Brentuximab Vedotin	Hodgin Lymph., sALCL	CD30	IHC	
Cetuximab (1)	CRC	EGFR	IHC	
Cetuximab (2)	mCRC	KRAS	RT-PCR	Rotor-Gene
Crizotinib	NSCLC	ALK	FISH	
Dabrafenib	Melanoma	BRAF	PCR	ABI 7500
Denileukin Diftitox	cut TCL	CD25	IHC	
Erlotinib	NSCLC	EGFR	RT-PCR	Cobas
Everolimus	mRCC, NEC	mTOR	LC-MS/MS	
Exemestane	Breast Ca	Aromatase (ER/PR)	IHC	
Fulvestrant	Breast Ca	ER	IHC	
Gefitinib	NSCLC	EGFR	RT-PCR	Cobas
Imatinib (1)	CML	Ph+	RT-PCR, FISH	
Imatinib (2)	GIST	c-Kit	IHC	
Imatinib (3)	MDS	EGFR	FISH	
Imatinib (4)	HES	FIP1L1-PDGFRα	RT-PCR	
Lapatinib	Breast Ca	HER2/NEU	IHC, FISH	
Olaparib	Breast Ca	BRCA1/2	PCR,	Sanger seq.
Panitumumab (1)	CRC	EGFR	IHC	
Panitumumab (2)	mCRC	KRAS	RT-PCR	Rotor-Gene
Pertuzumab	Breast Ca	HER2/NEU	IHC, FISH	
Tamoxifen	Breast Ca	ER	IHC	
Tositumomab	(f)NHL	CD20 antigen	IHC	
Trastuzumab	Breast , Gastric Ca	HER2/NEU	IHC, FISH, CISH	
Vemurafenib	Melanoma	BRAF	RT-PCR	Cobas

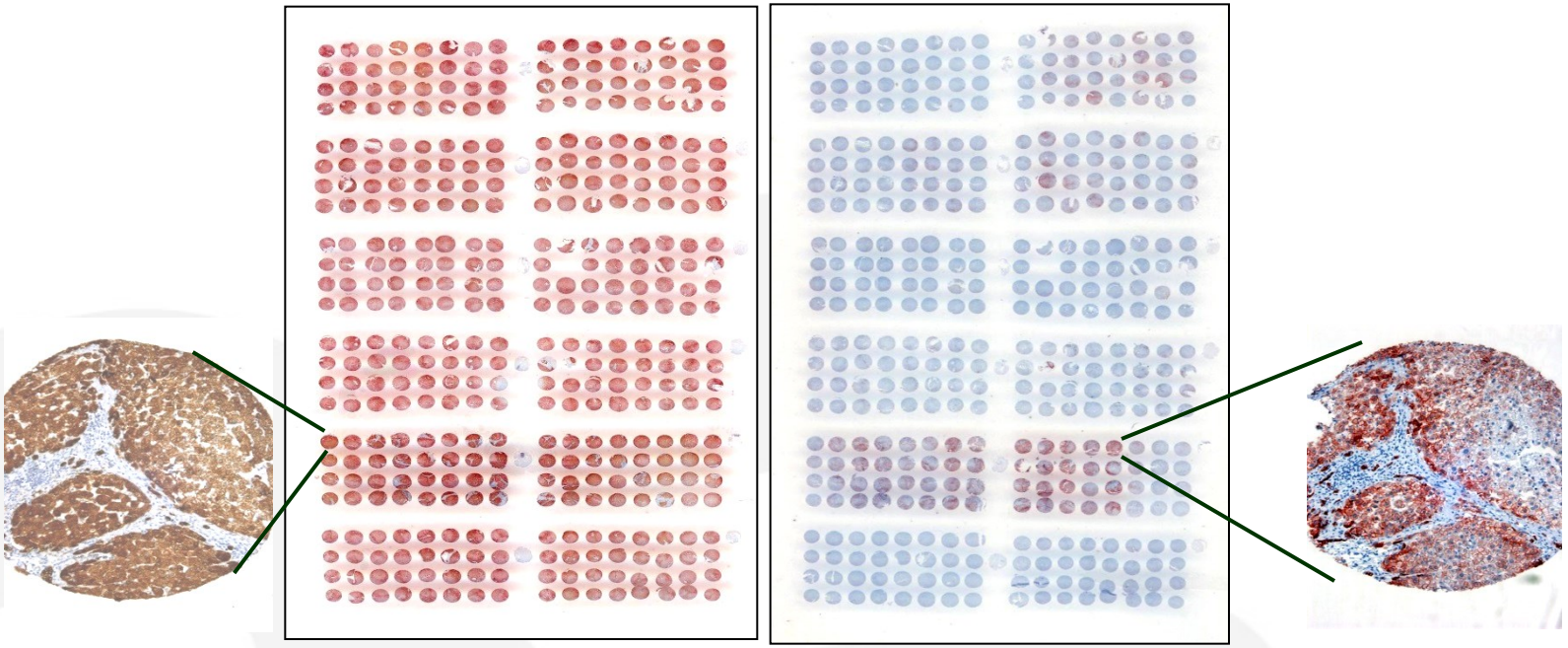
ICH Verification Platform

Example: Immunohistochemistry Protocols



Stumptner et al., Methods Enzymol. 2015

Differences in Protocol Robustness



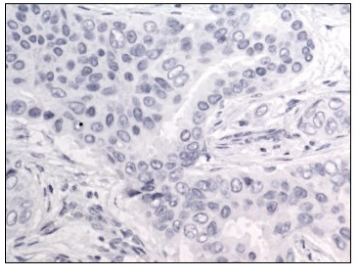
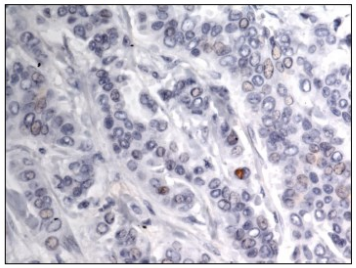
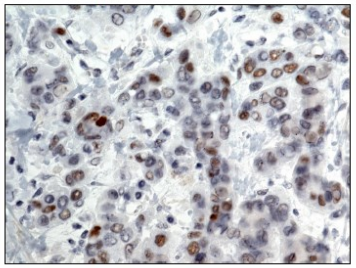
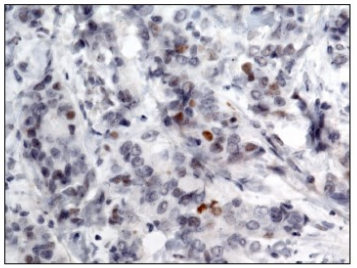
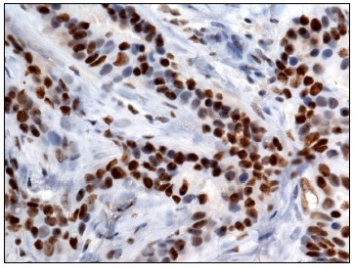
Robust protocol **Non-robust protocol**

Stumptner et al., Methods Enzymol. 2015

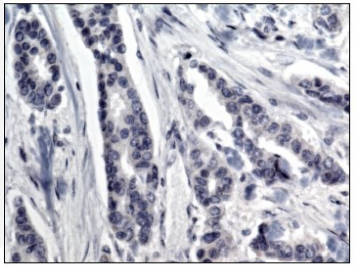
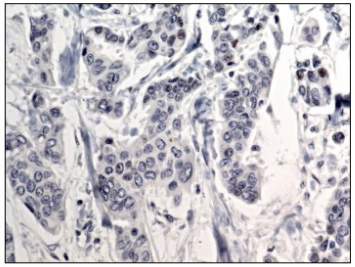
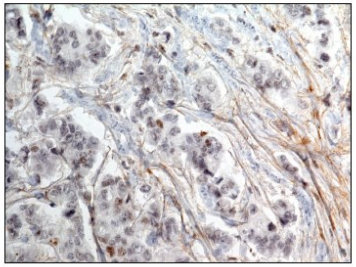
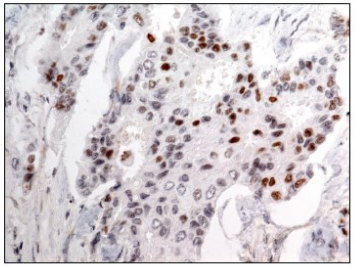
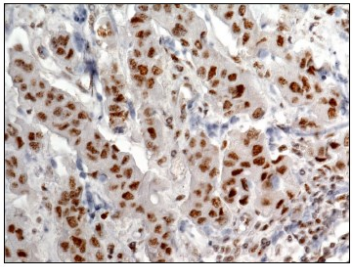
Sample pre-analytics and Antigen Retrieval

P53_H853_Mamma TU_72h_40x

Formalin

pH 6 MW 30	pH 6 MW 40	pH 9 MW 30	pH 9 MW 40	pH 9,5 MW 40
				

PAXgene

The Team

Project Management
Daniela Schaar
Penelope Kungl
Simone Findling
Cornelia Stumptner

Scientists
Peter M. Abuja
Martina Dieber
Karl Kashofer
Martina Loibner
Heimo Müller
Lisa Oberauner-Wappis
Christian Viertler
Stella Wolfgruber

PhD Students
Zahara Safari
Andrija Matak
Meghana Somlapura
Michael Haider

Medical Bioanalytics
Iris Kufferath
Daniela Pabst
Christine Ulz
Ulrike Fackelmann

IT-Assistants
Robert Reihs
Markus Plass

Collaborations
A. Holzinger, IMI, MUG
C. Luchinat, P. Turano, L. Tenori, Univ. Florence
H. Lehrach MPIMG Berlin, Alacris
BBMRI-ERIC consortium
BBMRI.at consortium
HRSM Digital Pathology Consortium
SPIDIA consortium
Biobank Graz

Thank You for Your Attention

Medizinische Universität Graz

SPIDIA4P

BioBank GRAZ

QIAGEN

Christian Doppler Forschungsgesellschaft

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Biobanking and BioMolecular Resources Research Infrastructure

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Project number: 676550

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GEN-AU
GENOMFORSCHUNG IN ÖSTERREICH

kapsch

CAPACITIES

BBMRI GA Nr. 212111
1.2.2008-30.04.2010

European Commission

Fraunhofer

bmwfw
Bundesministerium für Wissenschaft, Forschung und Wirtschaft