

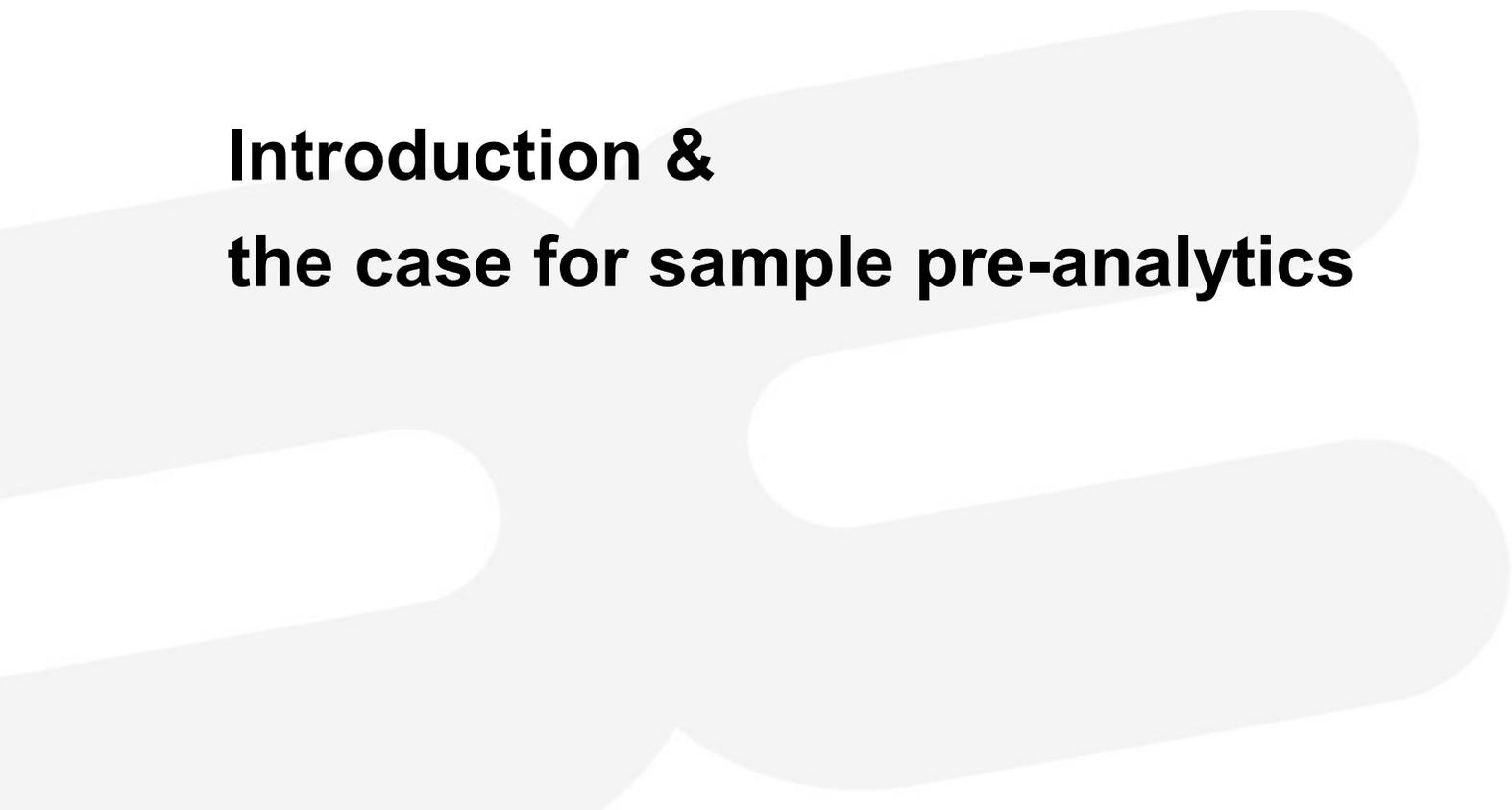
Pre-Analytical Sample Processing in Biobanking

Lecture Course

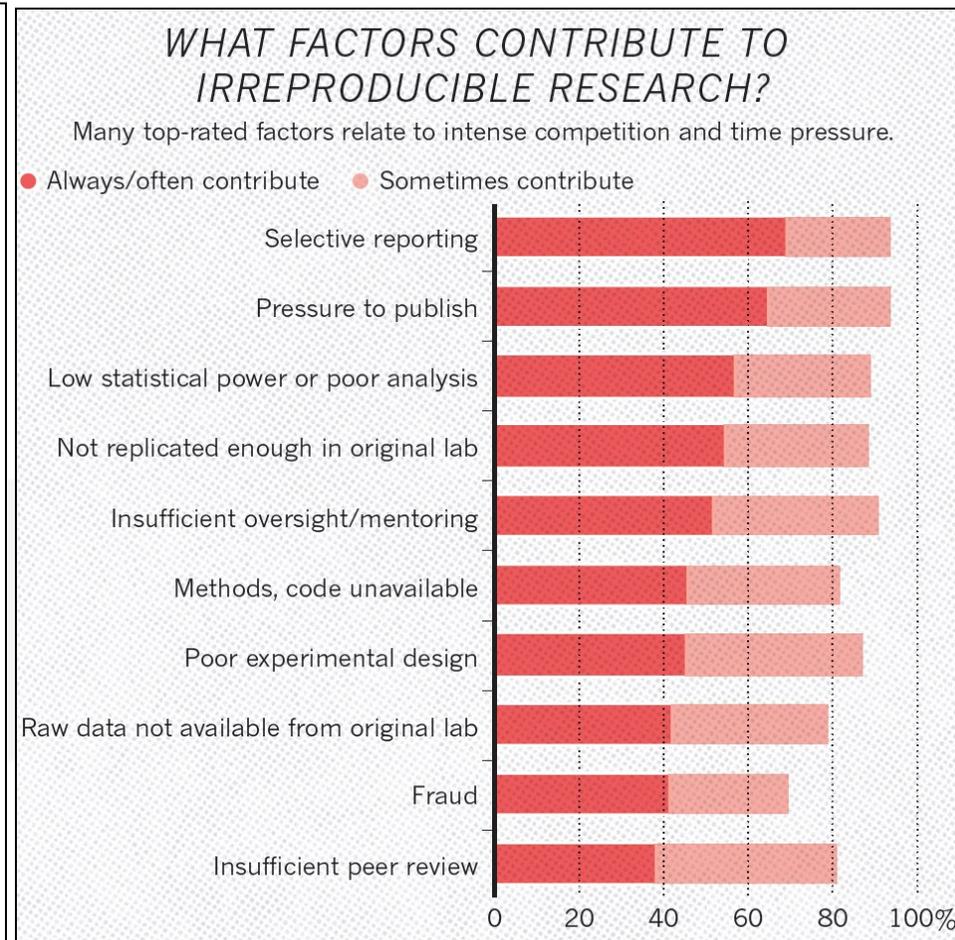
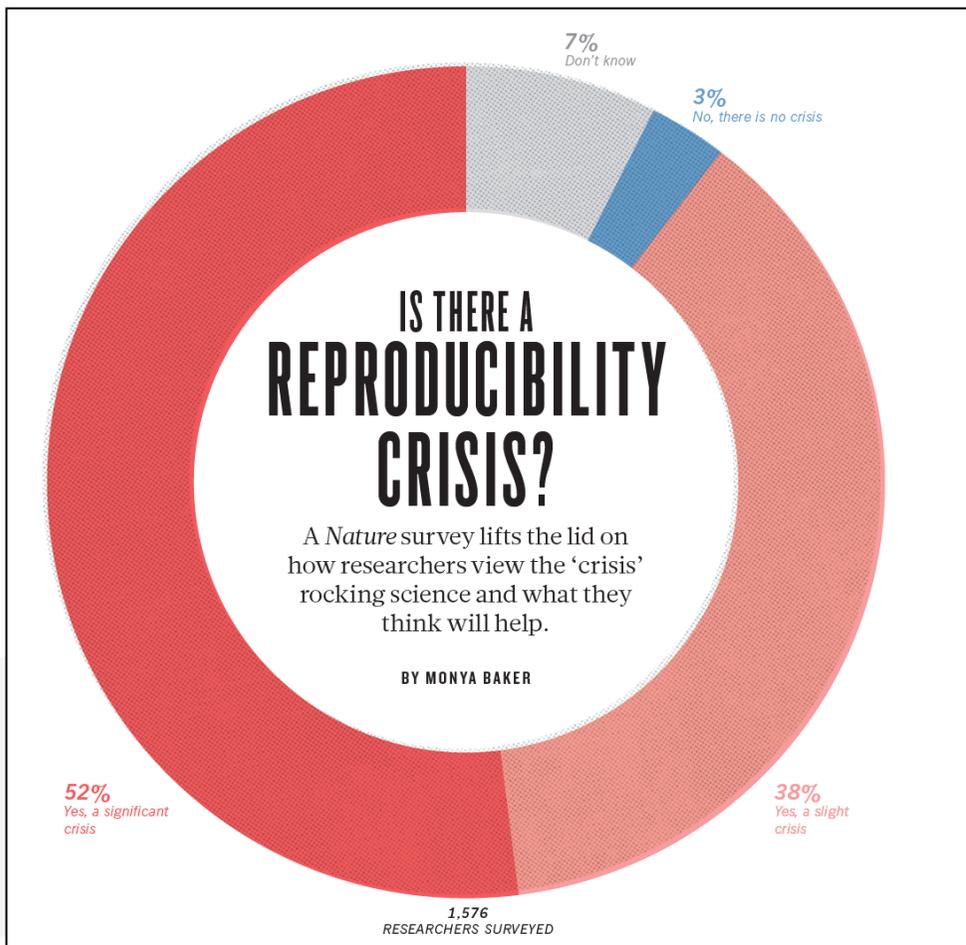
Diagnostic and Research Center for Molecular Biomedicine
Institute of Pathology, Medical University of Graz, Austria

Organizers:





**Introduction &
the case for sample pre-analytics**

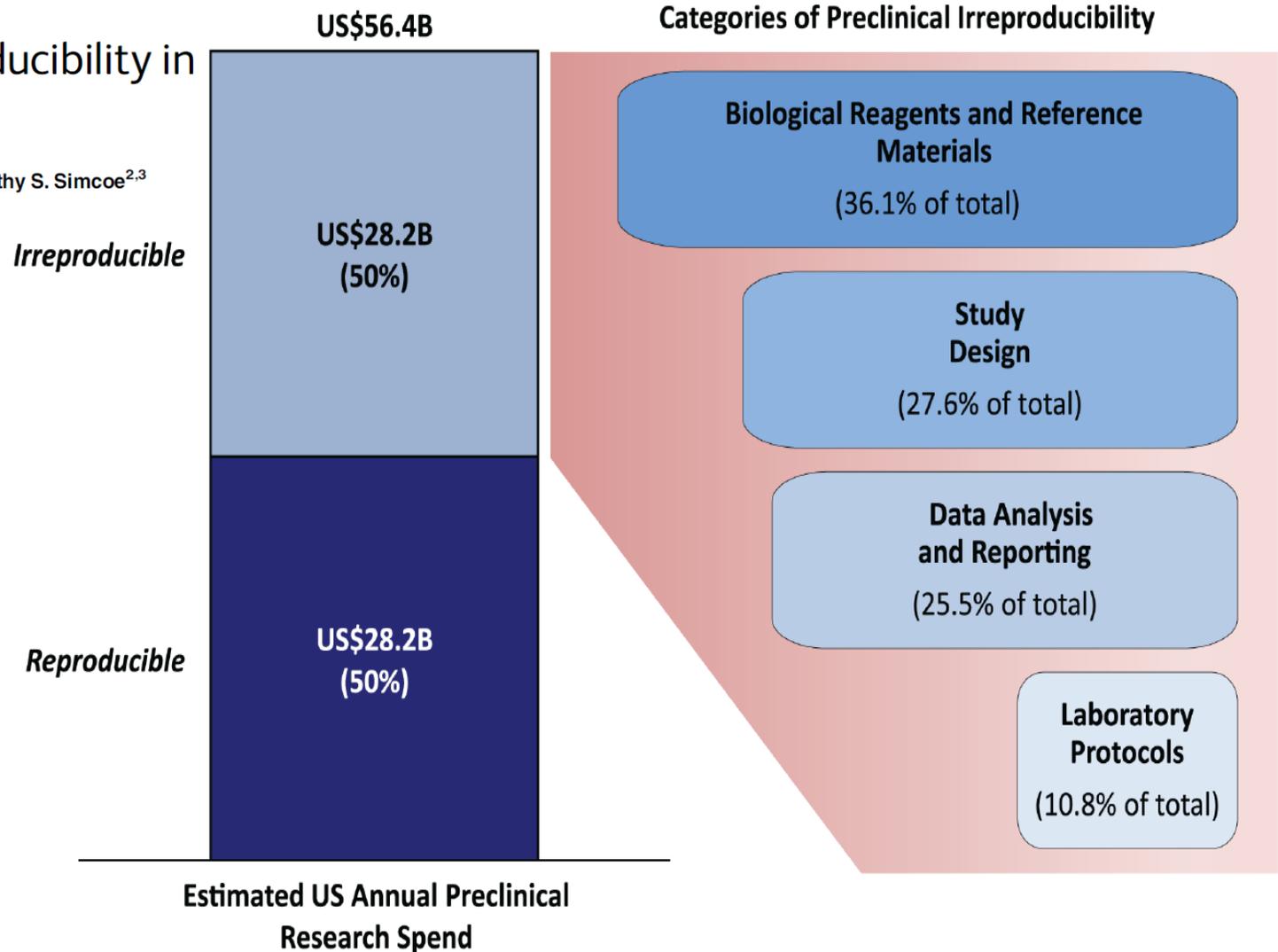


Economic Impact of Biosample Quality in R&D

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

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



Pre-analytical Errors in Medical Diagnostics

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

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

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-PDGFR α	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.-

USA

The screenshot shows the top section of the NCI website. At the top left is the NCI logo. To its right is the text "National Cancer Institute". Further right, it says "U.S. National Institutes of Health | www.cancer.gov". Below this are two buttons: "Launch NCI Best Practices" (blue) and "Launch caHUB" (green). The main heading "OBRR Office of Biorepositories and Biospecimen Research" is prominently displayed. Below the heading is a "Sign Up For Updates" link and a search bar with a "Search" button. A horizontal navigation menu contains links for "About OBRR", "About NCI Best Practices", "Biospecimen Research Network", "caHUB", "News and Events", and "Public Resources". A large banner for the "Biospecimen Research Network" features a microscopic image of cells.

NATIONAL CANCER INSTITUTE National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

Launch NCI Best Practices Launch caHUB

OBRR Office of Biorepositories and Biospecimen Research

Sign Up For Updates Search

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

Biospecimen Research Network

Europe

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

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

NEWSLETTER
Subscribe to our newsletter to receive latest news about the project

Home
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



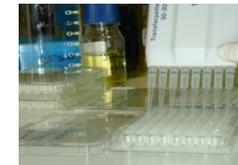
Aliquotting



Storage
Time
temperature



Freezing
Freezing rate
Temperature



Sample preparation

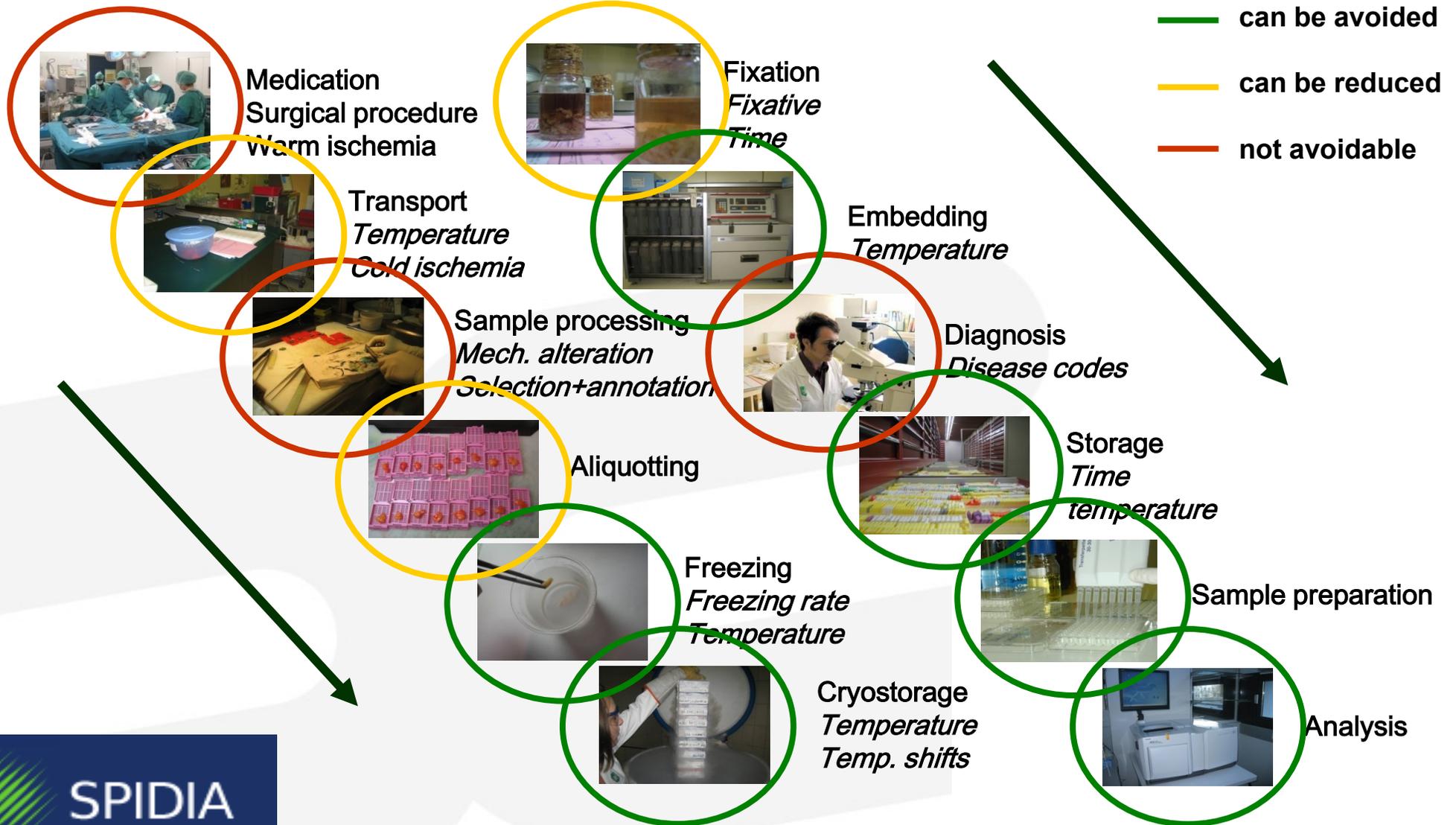


Cryostorage
Temperature
Temp. shifts



Analysis

Sources of Diversity



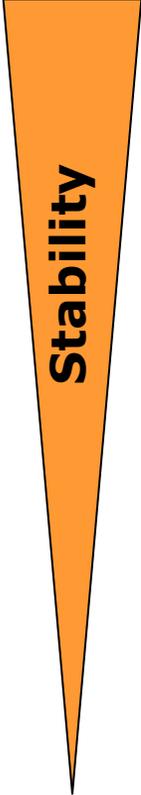
Parameters for Tissue-Based Analysis

Sample variables

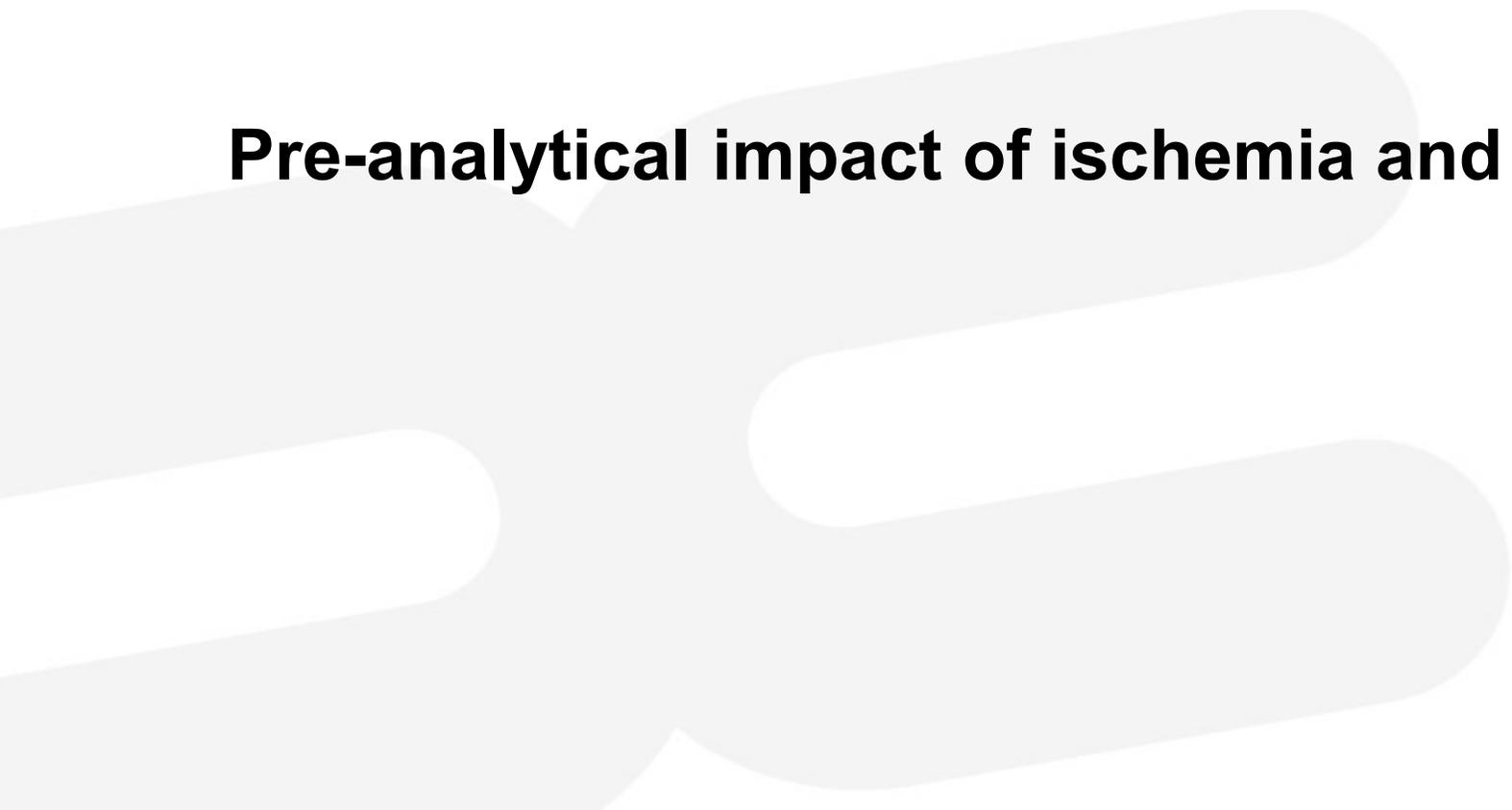
- Tissue type (organ)
- Diseased/normal
- Sample type (biopsy/surgery)
- Peri-operative effects
- Ischemia
- Processing
- Fixation
- Storage
- Analysis

Readout

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



Stability



Pre-analytical impact of ischemia and fixation

Definition: Warm and Cold Ischemia

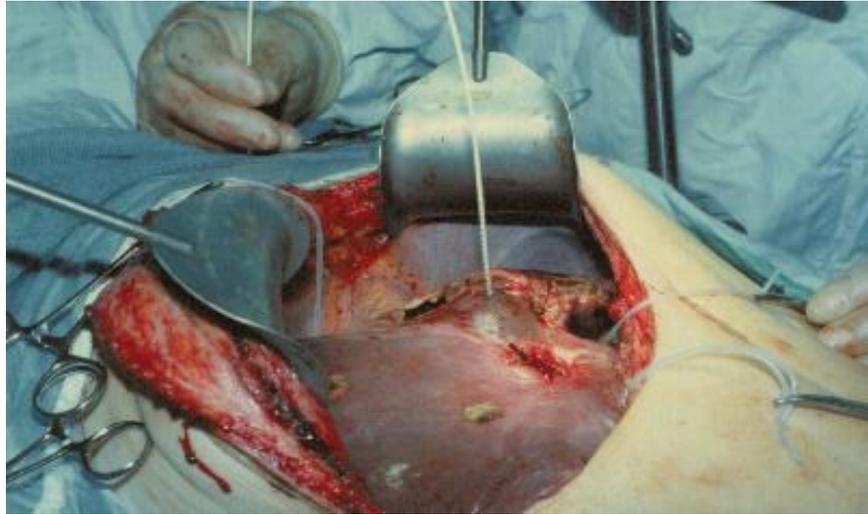
Warm ischemia:

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

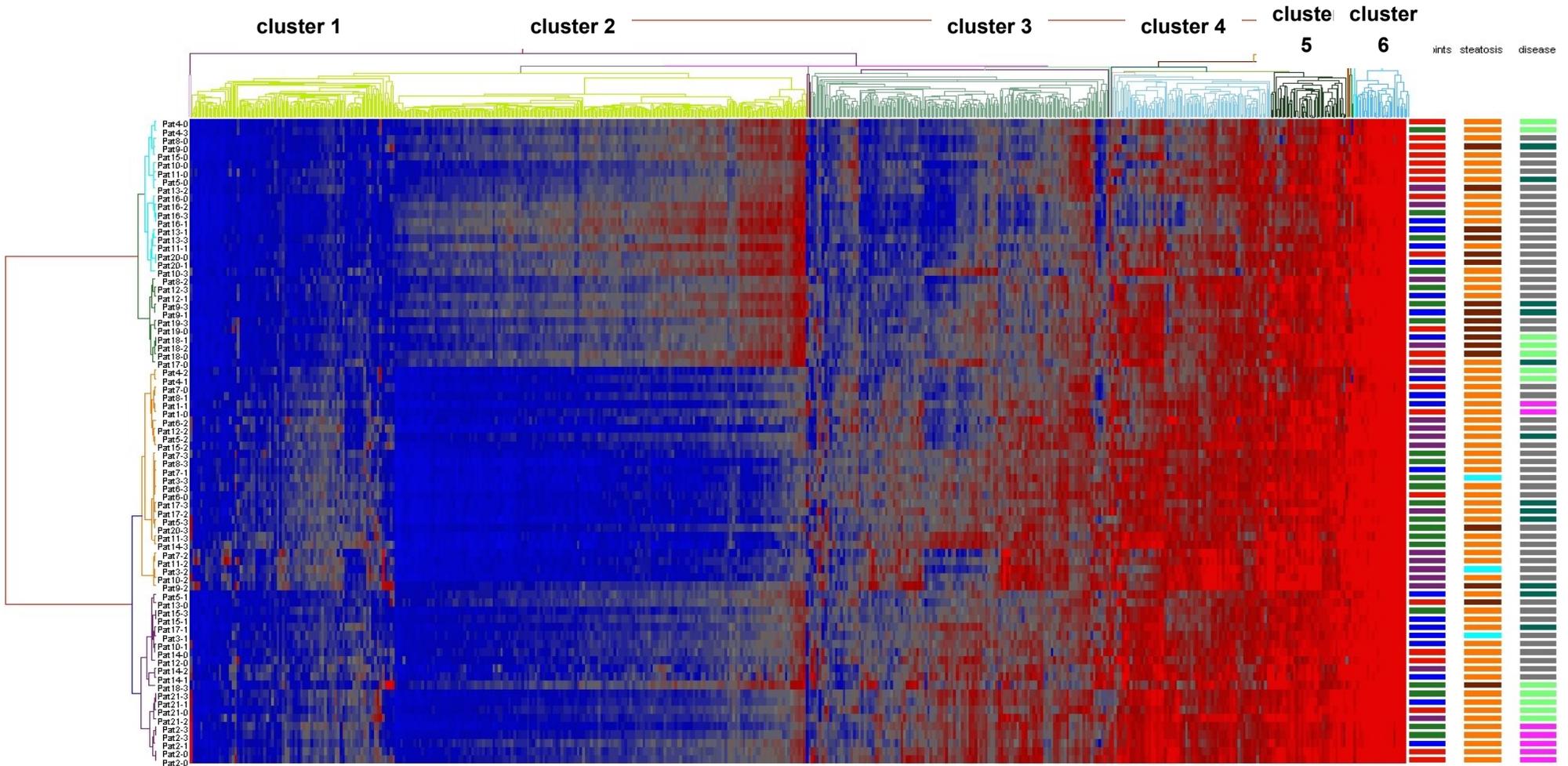
Warm and Cold Ischemia Effects



- 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**

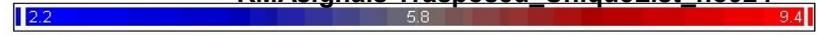
Ischemia and Gene Expression

Affymerix HG-U219



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

RMA signals Trasposed_UniqueList_no924



FC1,5_p0,05 924 genes

Alteration in Gene Expression is an Active Response

Response to stress

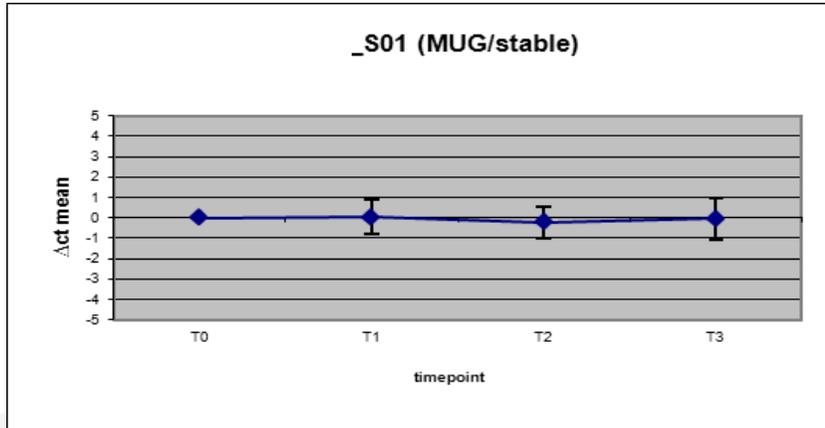
HSPA1B	Heat shock 70 kDa protein 1
HSPA6	Heat shock 70 kDa protein 6
GADD45B	Growth arrest and DNA-damage-inducible protein GADD45 beta
CRP	Cysteine and glycine-rich protein 1
DNAJB4	DnaJ homolog subfamily B member 4
DNAJB1	DnaJ homolog subfamily B member 1
PLK2	Serine/threonine-protein kinase PLK2
CRP	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

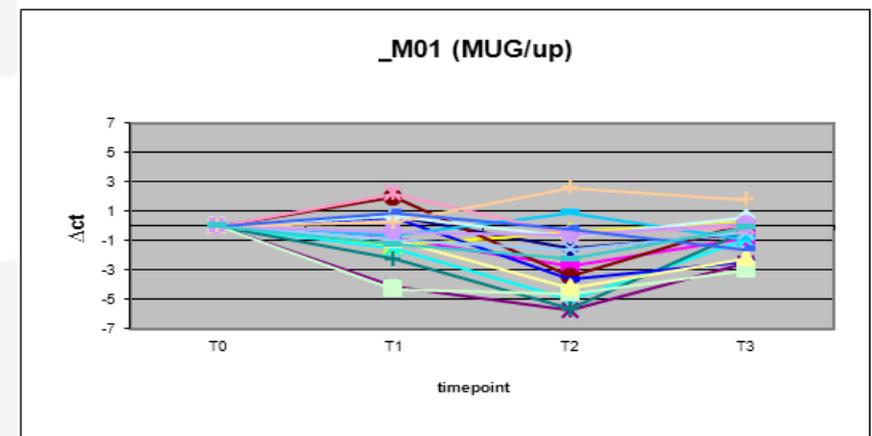
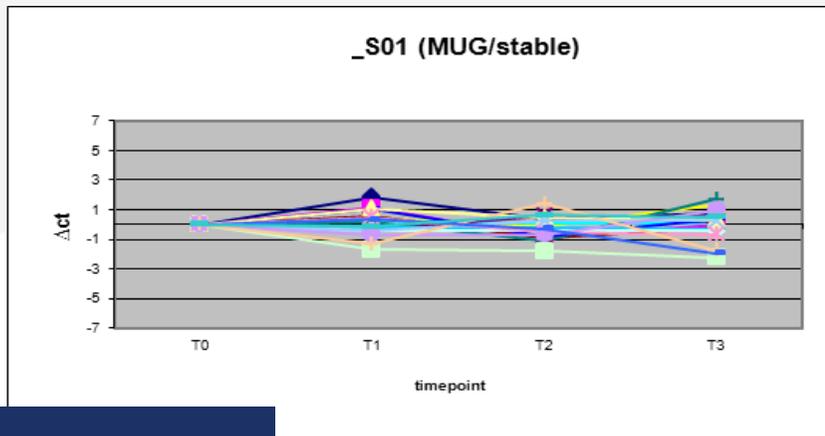
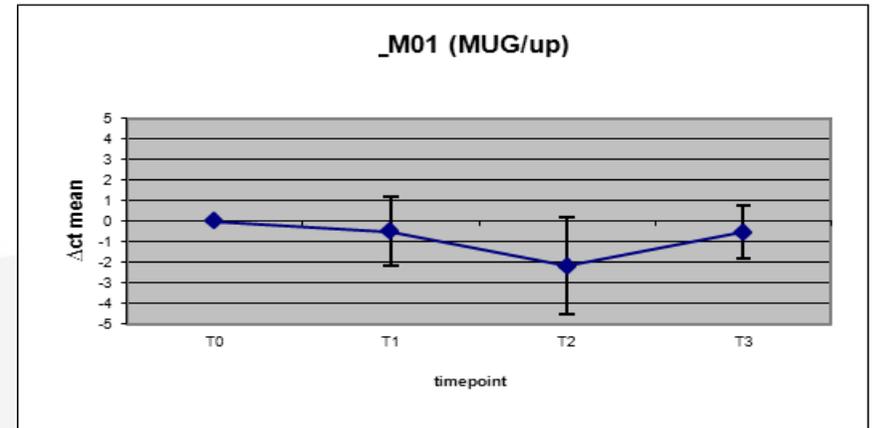
ABCC9	ATP-binding cassette transporter sub-family C member 9
ANGPTL4	Angiotensin-related protein 4
CEBPB	CCAAT/enhancer-binding protein beta
CISH	Cytokine-inducible SH2-containing protein
CRP	Cysteine and glycine-rich protein 1
CXCL2	GRO-beta(5-73)
CXCR7	C-X-C chemokine receptor type 7
DNAJB1	DnaJ homolog 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 beta	Growth arrest and DNA-damage-inducible protein GADD45
GADD45G gamma	Growth arrest and DNA-damage-inducible protein GADD45
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	Kruppel-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

Tissue Quality Marker (qRT-PCR Validation)

stable



unstable



Conclusions and Recommendations

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

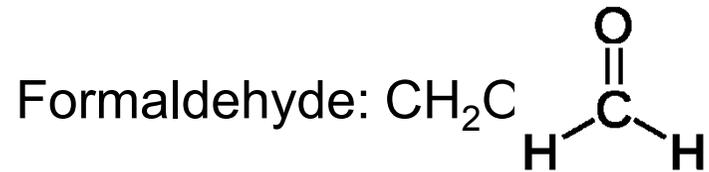
Recommendations:

- 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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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-PDGFR α	RT-PCR	
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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

Interaction of Formaldehyde with Biomolecules



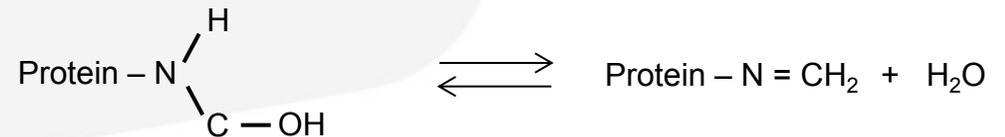
MW: 30.03 g.mol⁻¹

10% formalin 1300 mO

- Methylol adducts

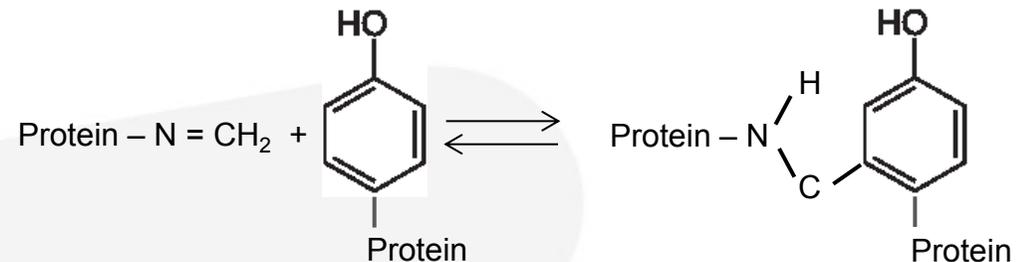


- Schiff base

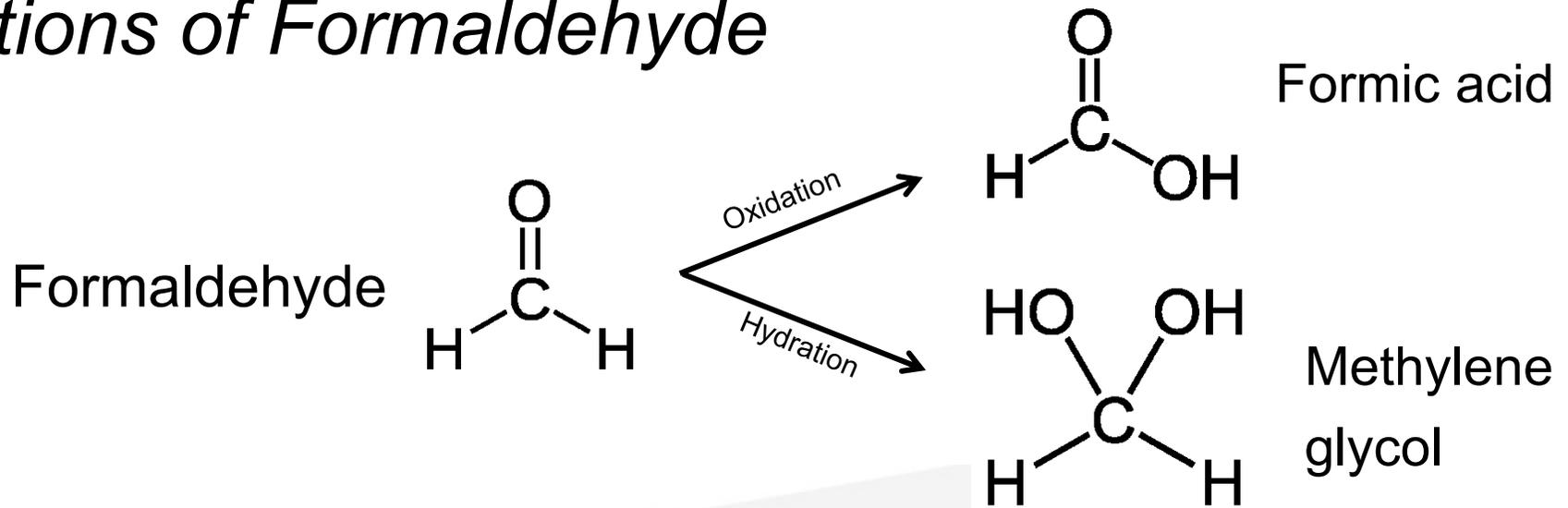


- Cross-links

- protein – protein
- protein – DNA
- DNA – DNA



Reactions of Formaldehyde



- Spontaneous oxidation to formic acid

- Drop in pH of formalin

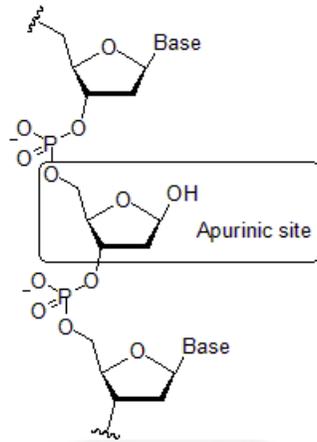
- Depurination
- Deamination 5-mC > T; C > U
- Fragmentation

} C:G > T:A

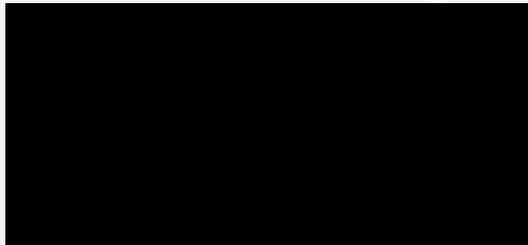
- Formalin pigment

- Hydration to methylene glycol

Formalin-induced DNA Alterations



"Apurinic Site" by Chemist234 - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Apurinic_Site.png#mediaviewer/File:Apurinic_Site.png



<http://commons.wikimedia.org/wiki/File:DesaminierungCtoU.png#mediaviewer/File:DesaminierungCtoU.png>">DesaminierungCtoU" by Yikrazuul - Own work. Licensed under Public Domain via Wikimedia Commons.

Cytosine

Uracil

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

- Documentation, documentation, documentation
- Few concrete procedures

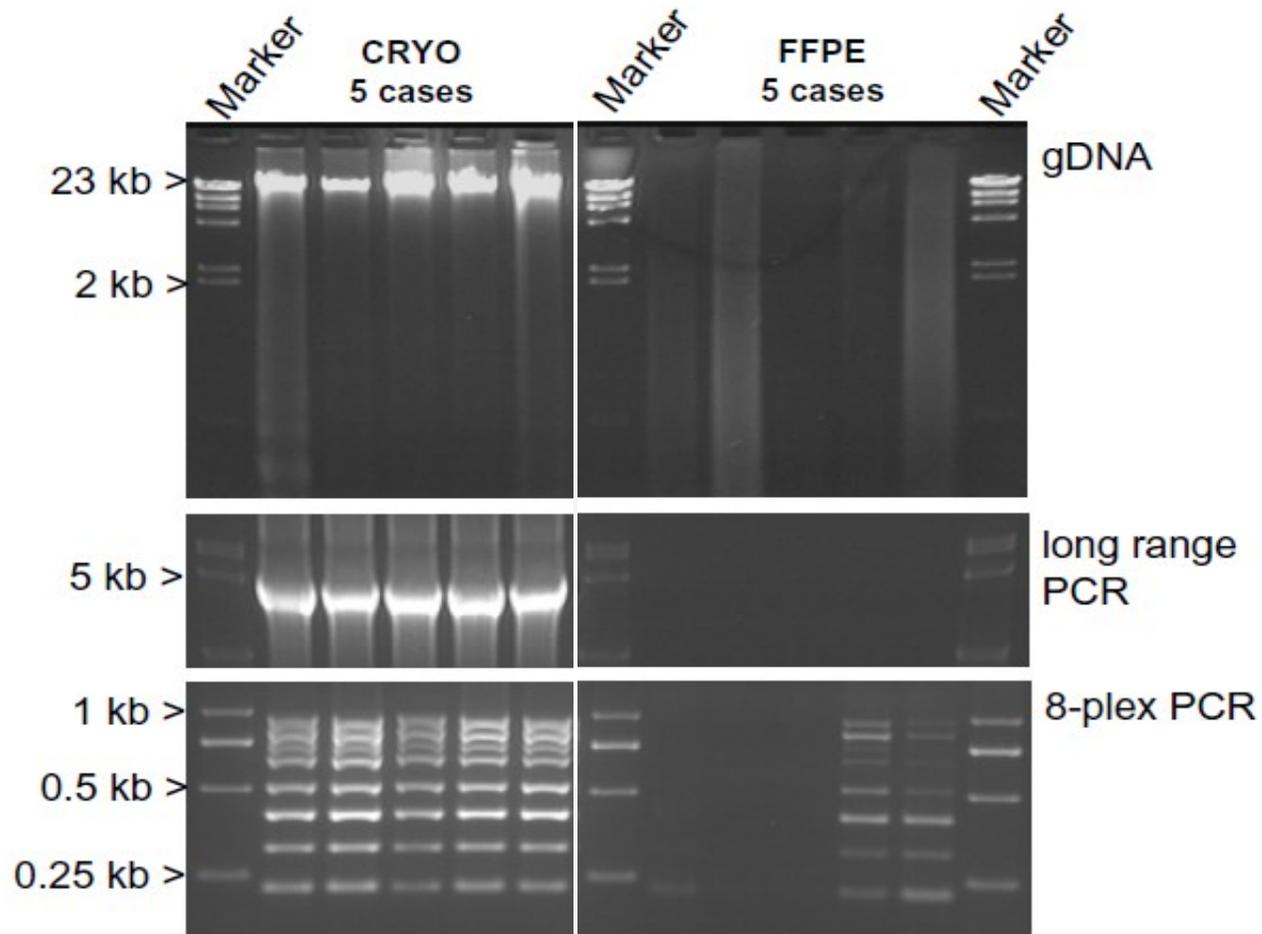
Standard buffered formalin solution

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

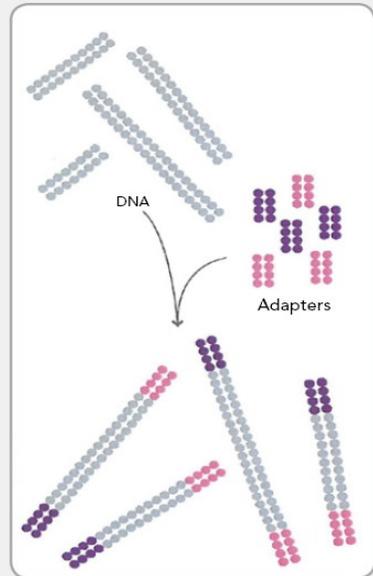
Fragmentation of Genomic DNA in FFPE



Massive Parallel Sequencing (MPS)

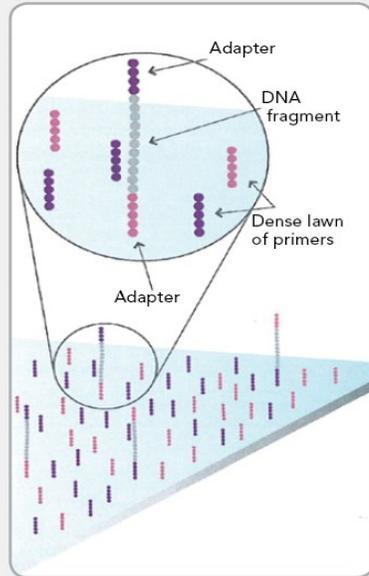
FIGURE 2: SEQUENCING TECHNOLOGY OVERVIEW

1. PREPARE GENOMIC DNA SAMPLE



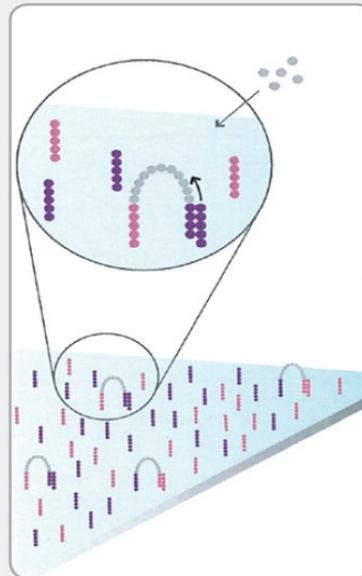
Randomly fragment genomic DNA and ligate adapters to both ends of the fragments.

2. ATTACH DNA TO SURFACE

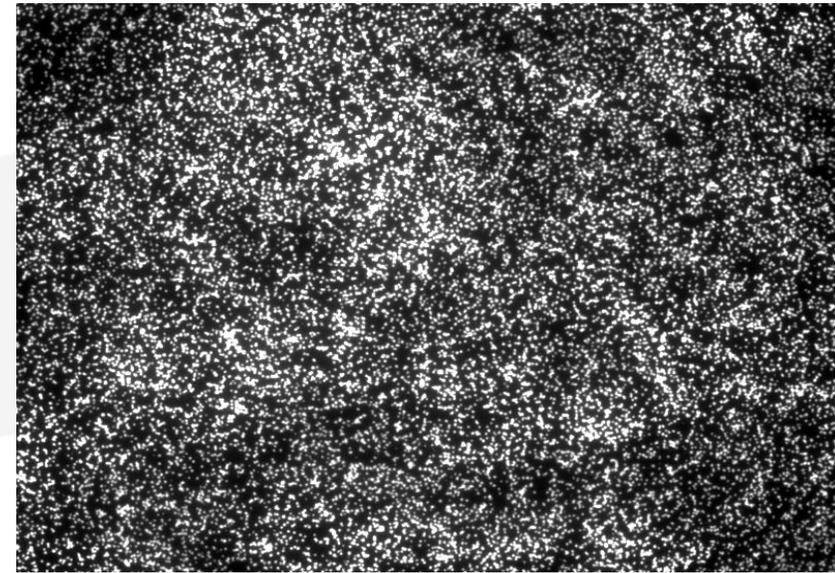


Bind single-stranded fragments randomly to the inside surface of the flow cell channels.

3. BRIDGE AMPLIFICATION



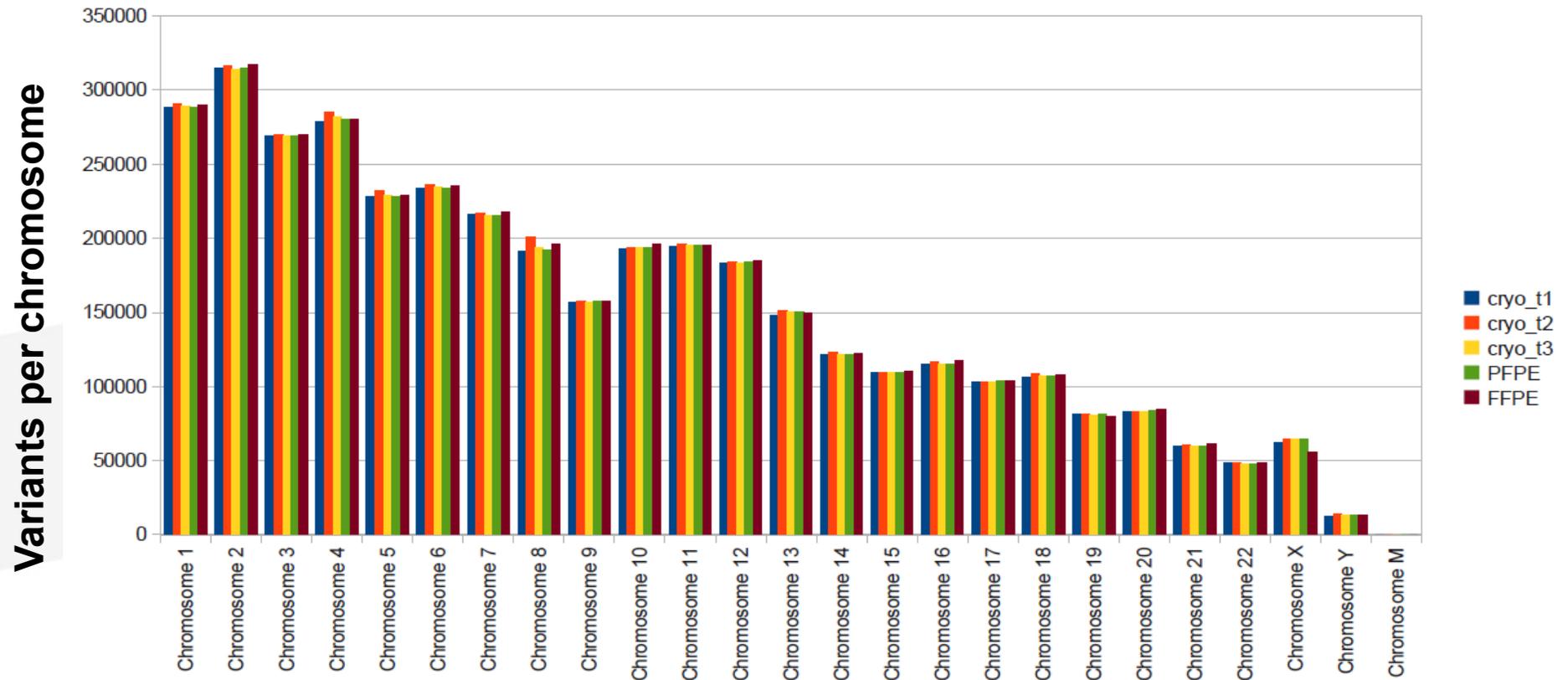
Add unlabeled nucleotides and enzyme to initiate solid-phase bridge amplification.



~ 40 mio clusters

The Good News: FFPE samples are suitable for MPS

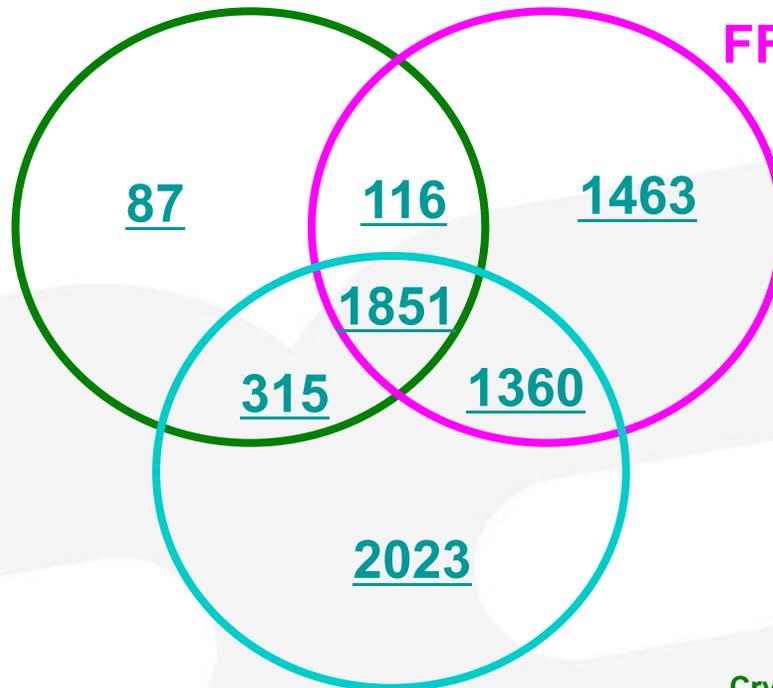
Illumina whole genome sequencing



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

Cryo1/2/3 (2369)

FFPE (4790)



PFPE (5549)

Cryo1/2/3: Intersection of the 3 cryos: 2369 positions (see previous slide)

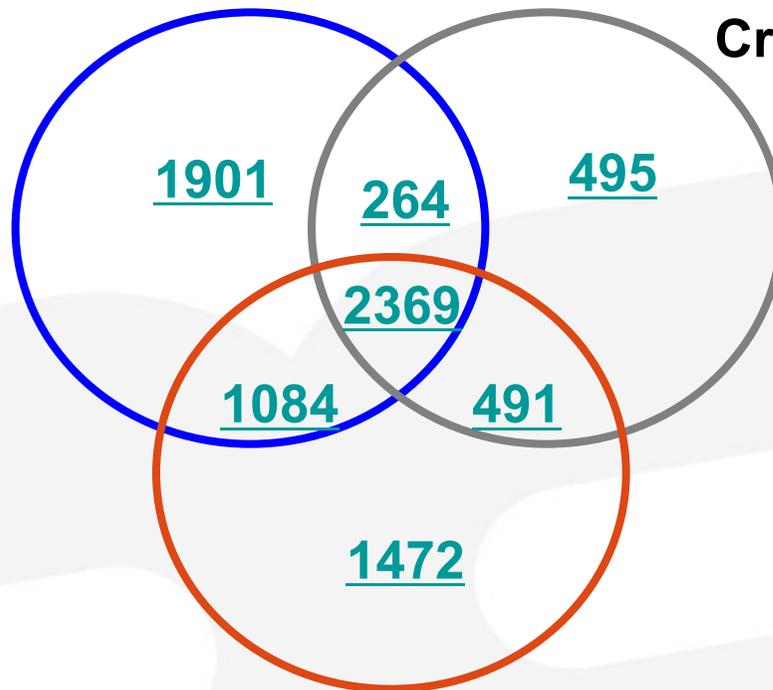
FFPE: 4790 positions passing som. filter

PFPE: 5549 positions passing som. filter

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

Cryo1 (5618)

Cryo2 (3619)



Cryo3 (5416)

Cryo1: 5618 positions passing som. filter

Cryo2: 3619 positions passing som. filter

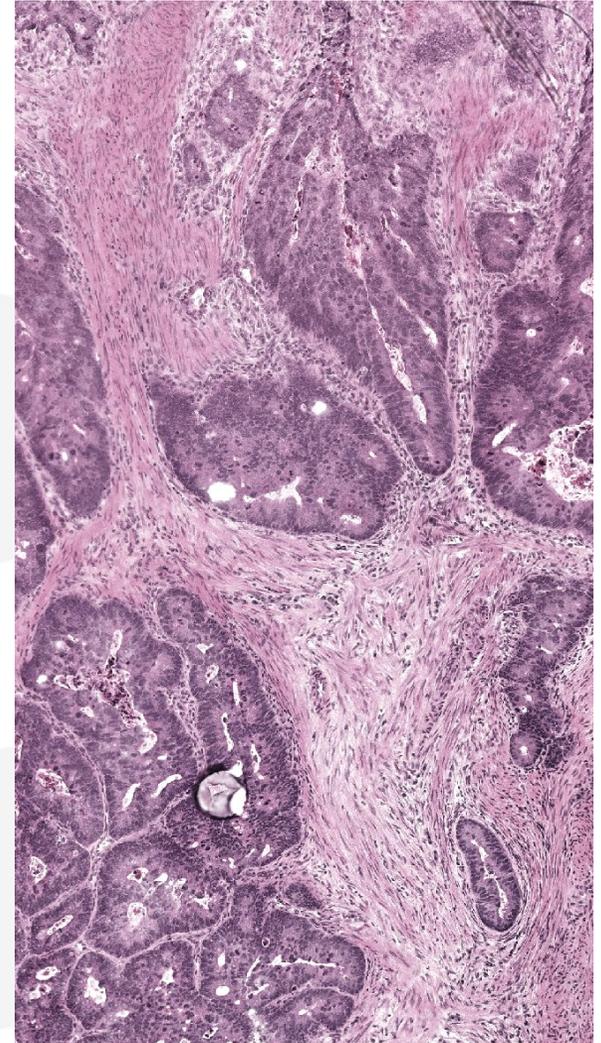
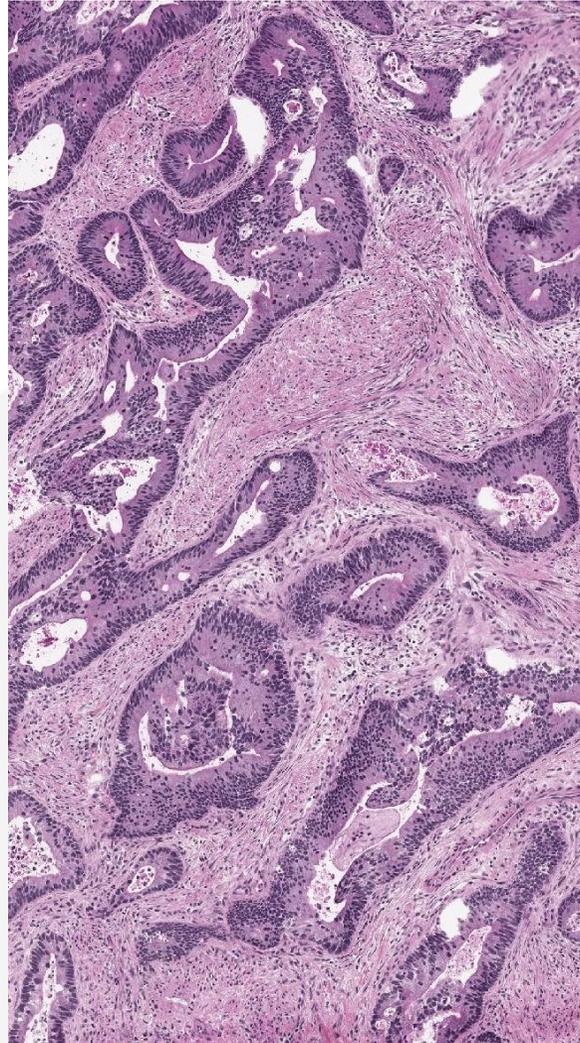
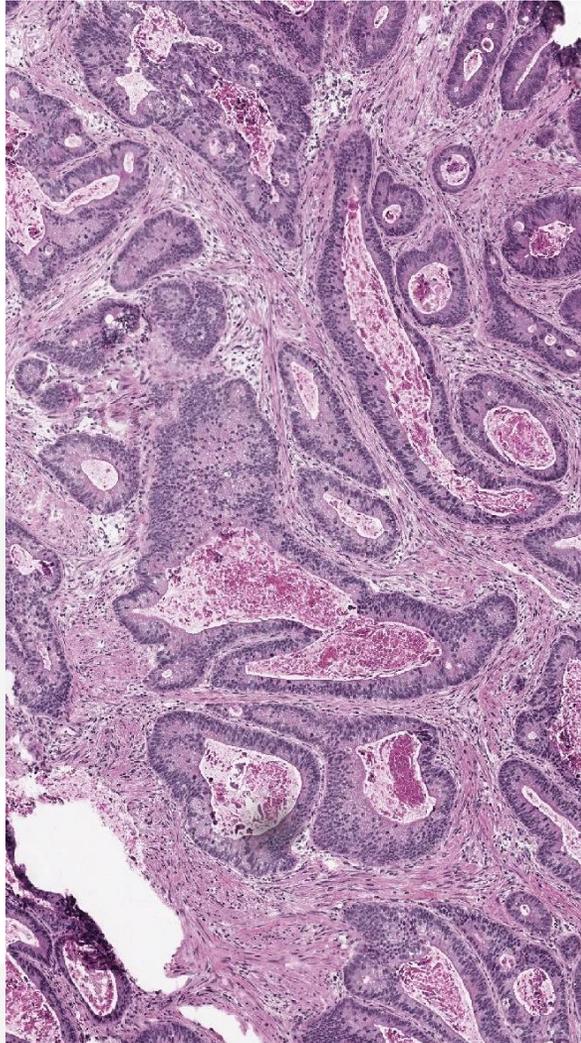
Cryo3: 5416 positions passing som. filter

cnag

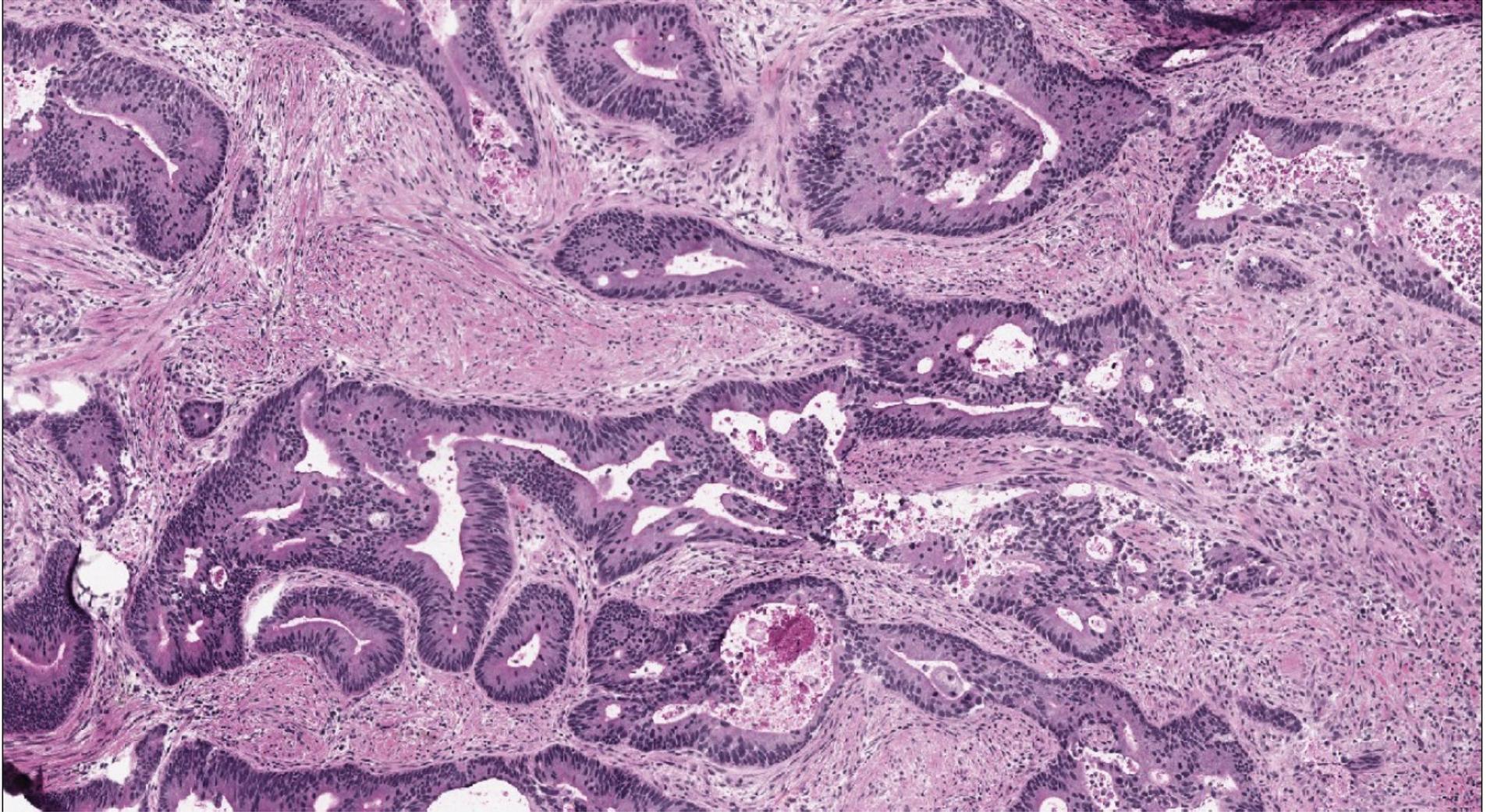
Ivo Gut



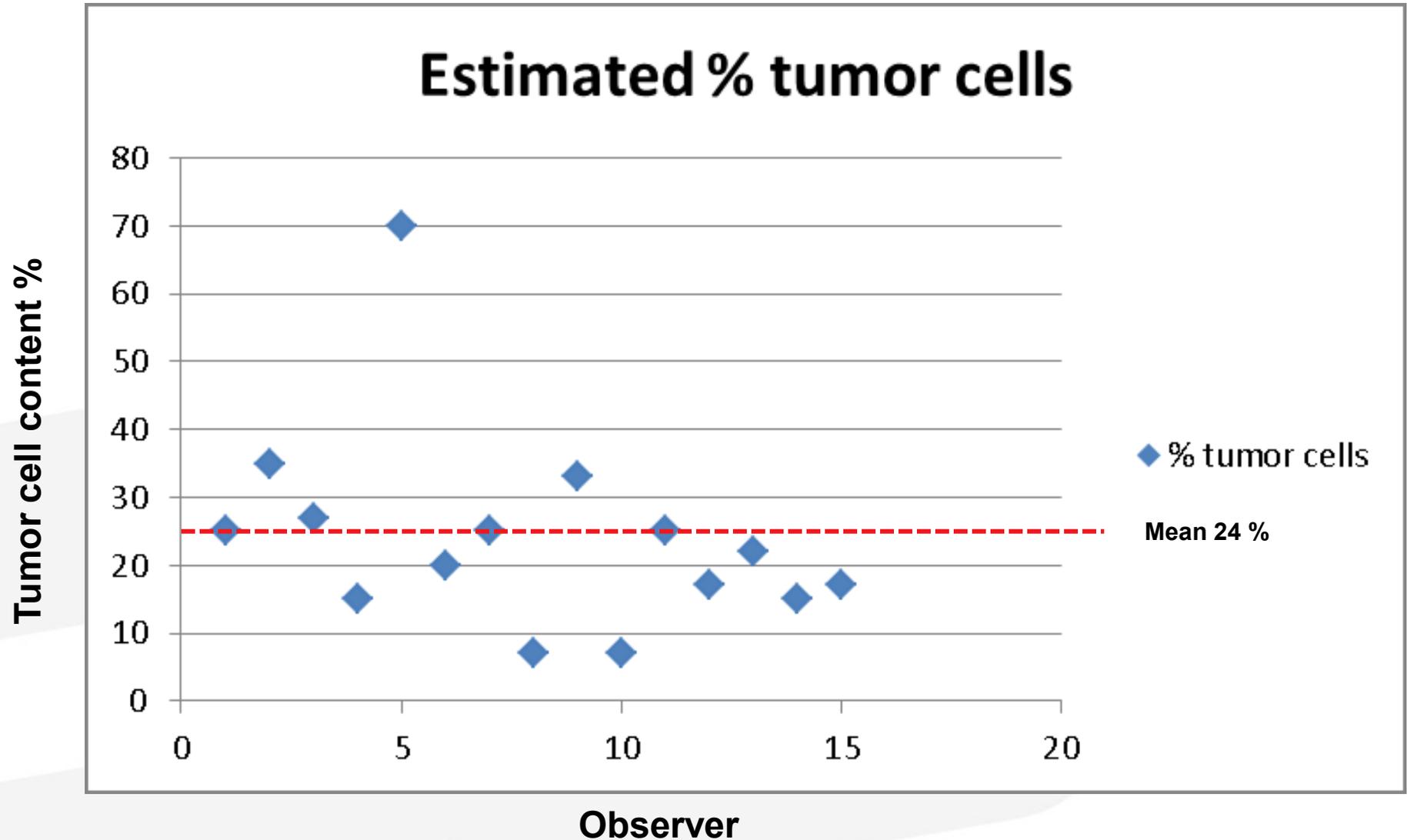
Tumor Heterogeneity in the 3 Related Cryo-preserved Samples



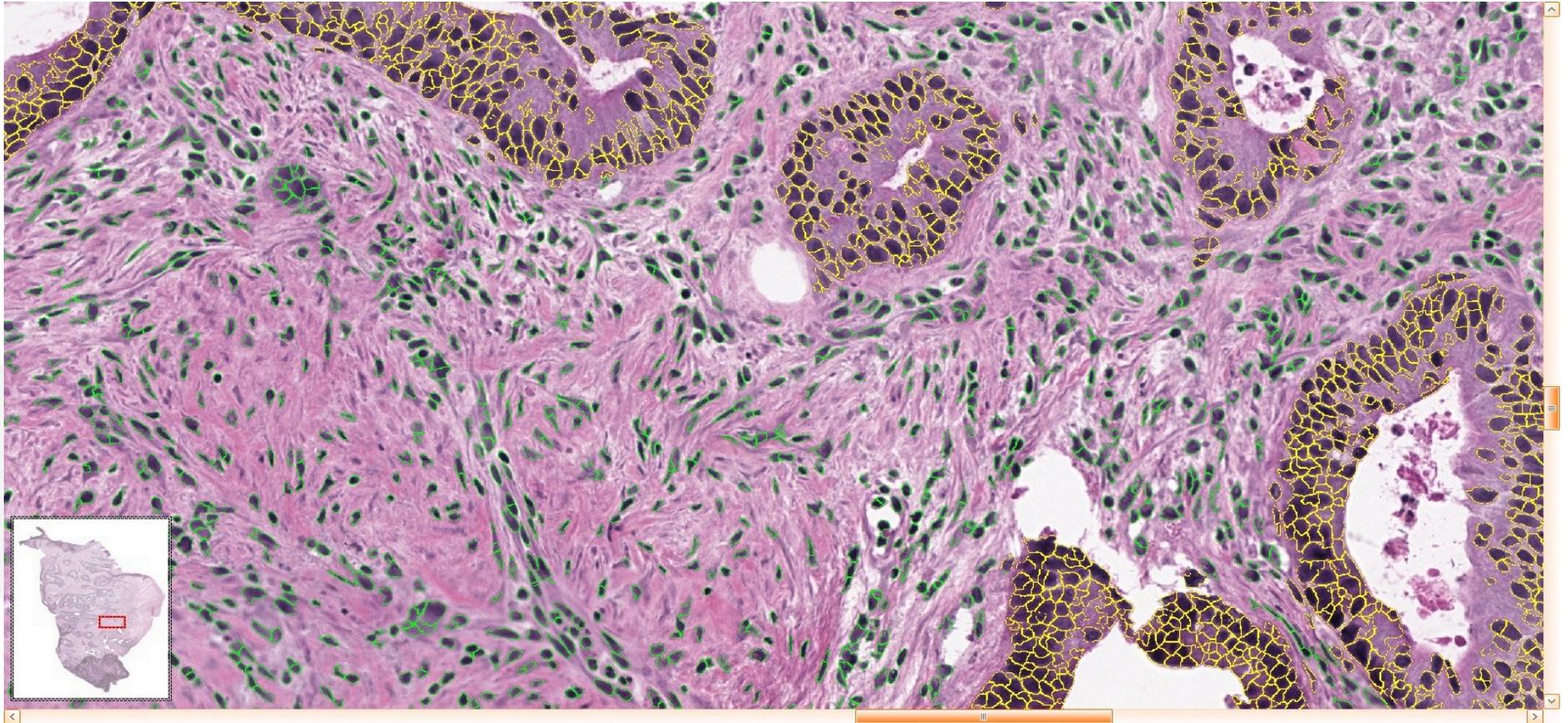
Evaluation of Tumor Content



Evaluation of Tumor Content



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



Morphometric Analysis of Epithelial and Stromal Tumor Components

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%

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)

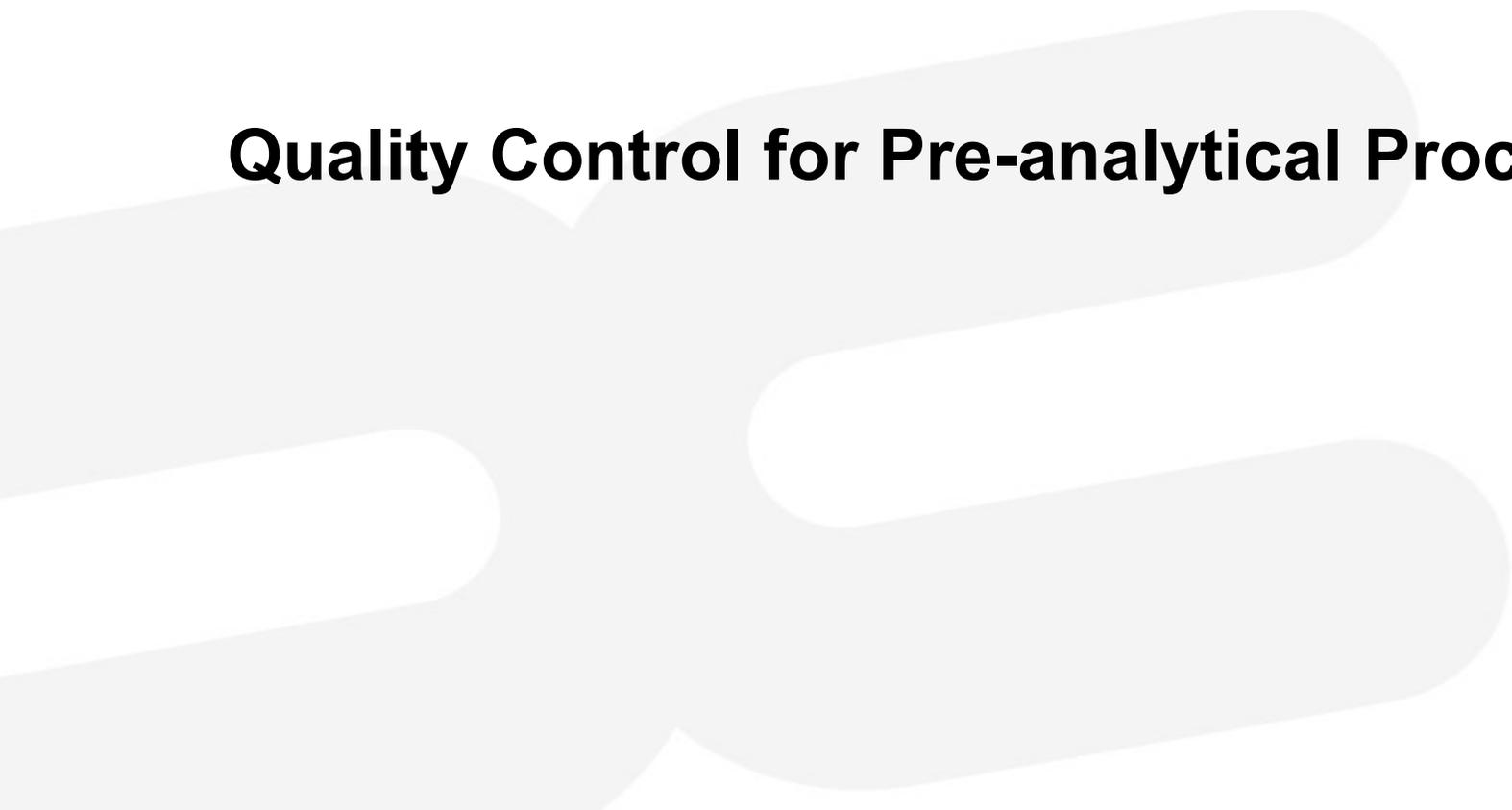
6.3 Evaluation of the pathology of the specimen and selection of the sample

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

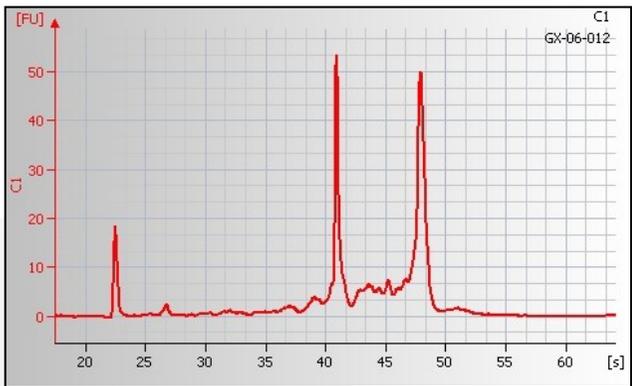
Where a histopathological characterization of the cellular composition and disease condition of the sample was not performed under 6.3, and is needed, it shall be performed at this stage to quantitatively assess the cellular composition and disease condition.



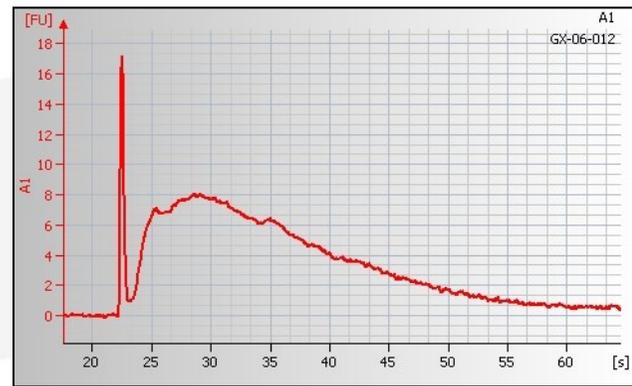
Quality Control for Pre-analytical Procedures

RNA Quality in Cryo-preserved and FFPE Tissues

Cryo-conservation

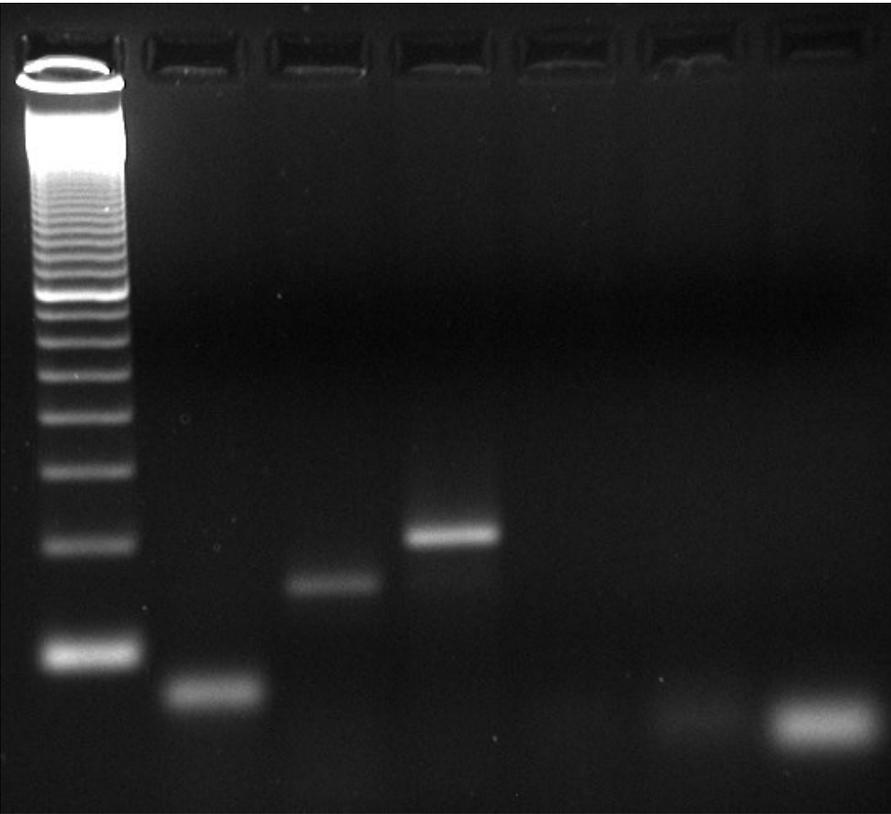


4% buffered formaldehyde



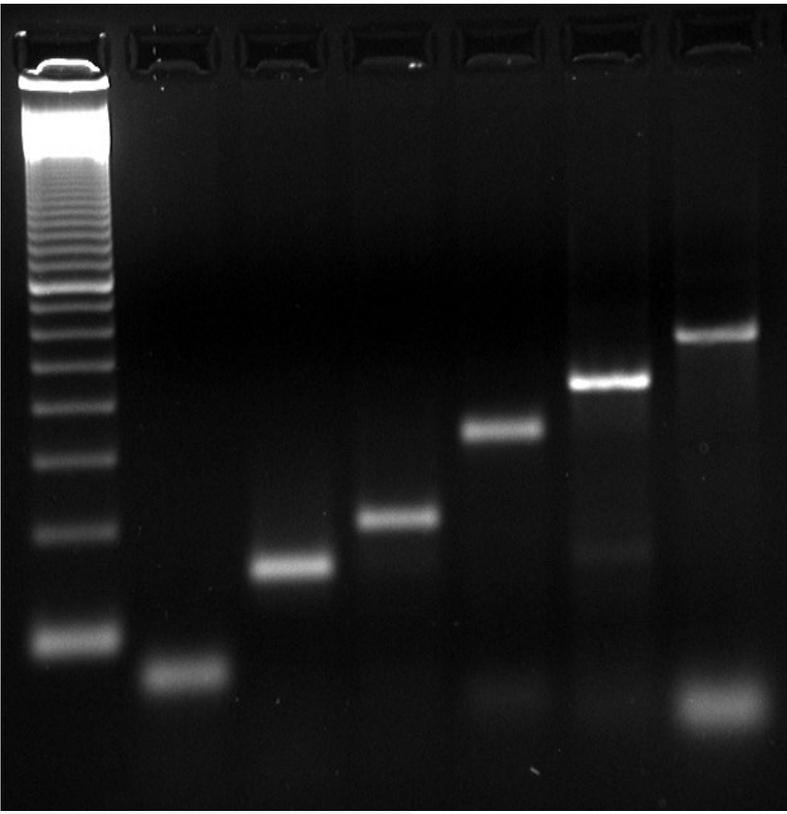
RT-PCR of RNA from FFPE Tissues

4% buffered formaldehyde



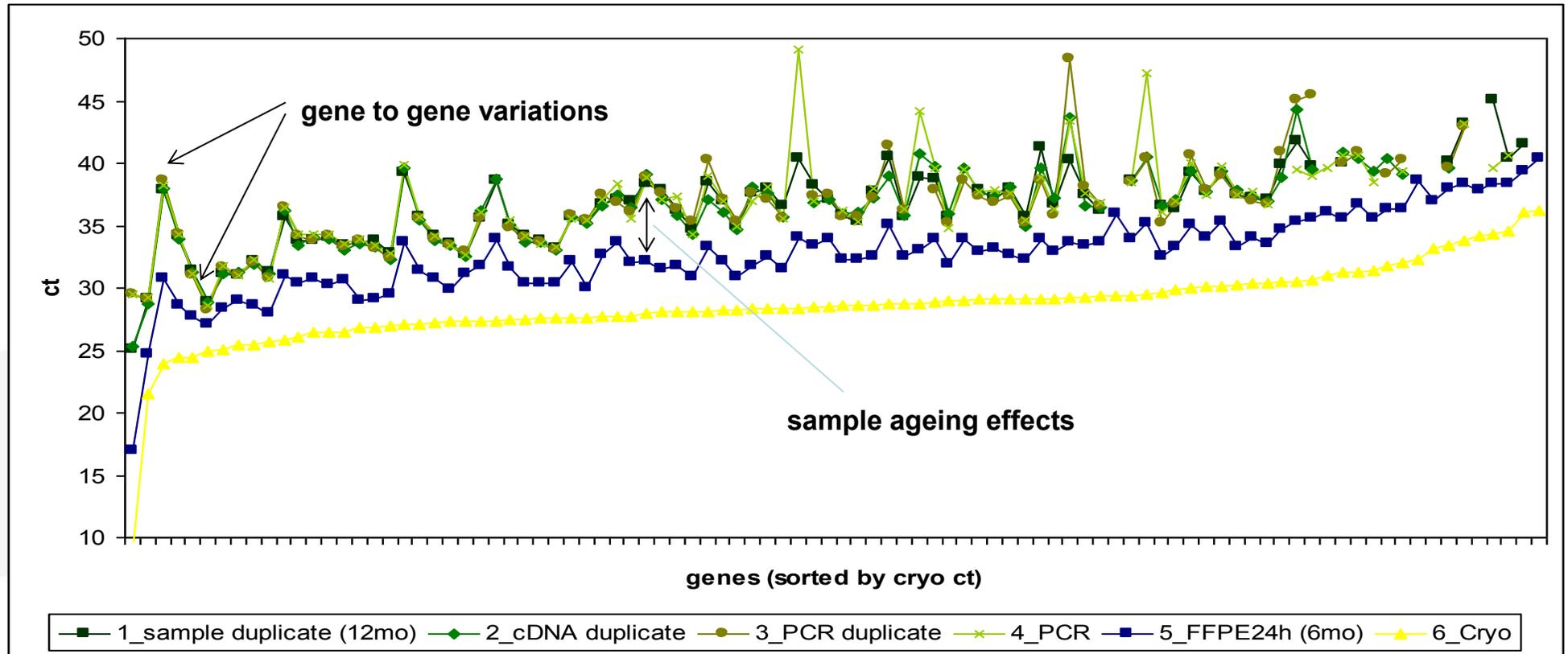
71 153 200 323 413 530 nts

methyl-alcohol/polyethyleneglycol

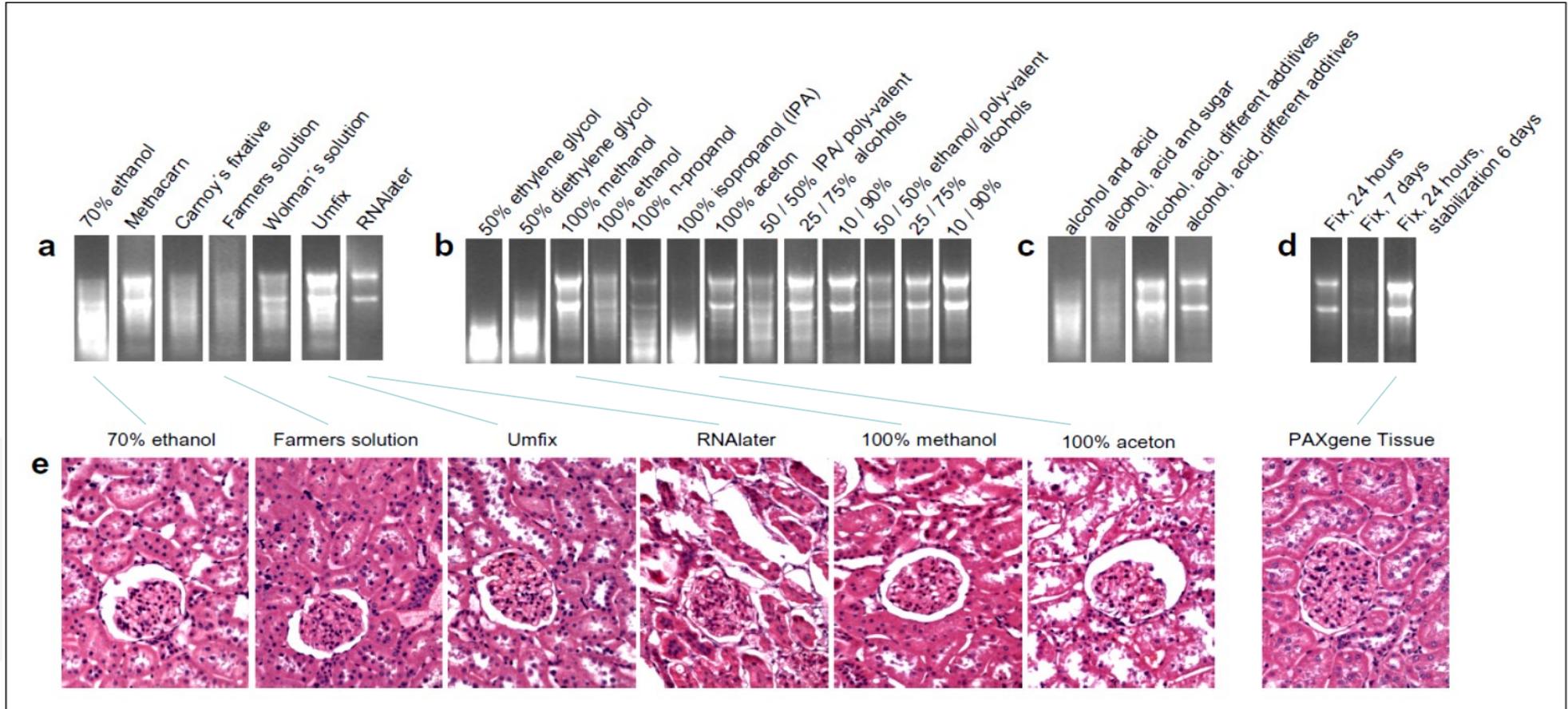


71 153 200 323 413 530 nts

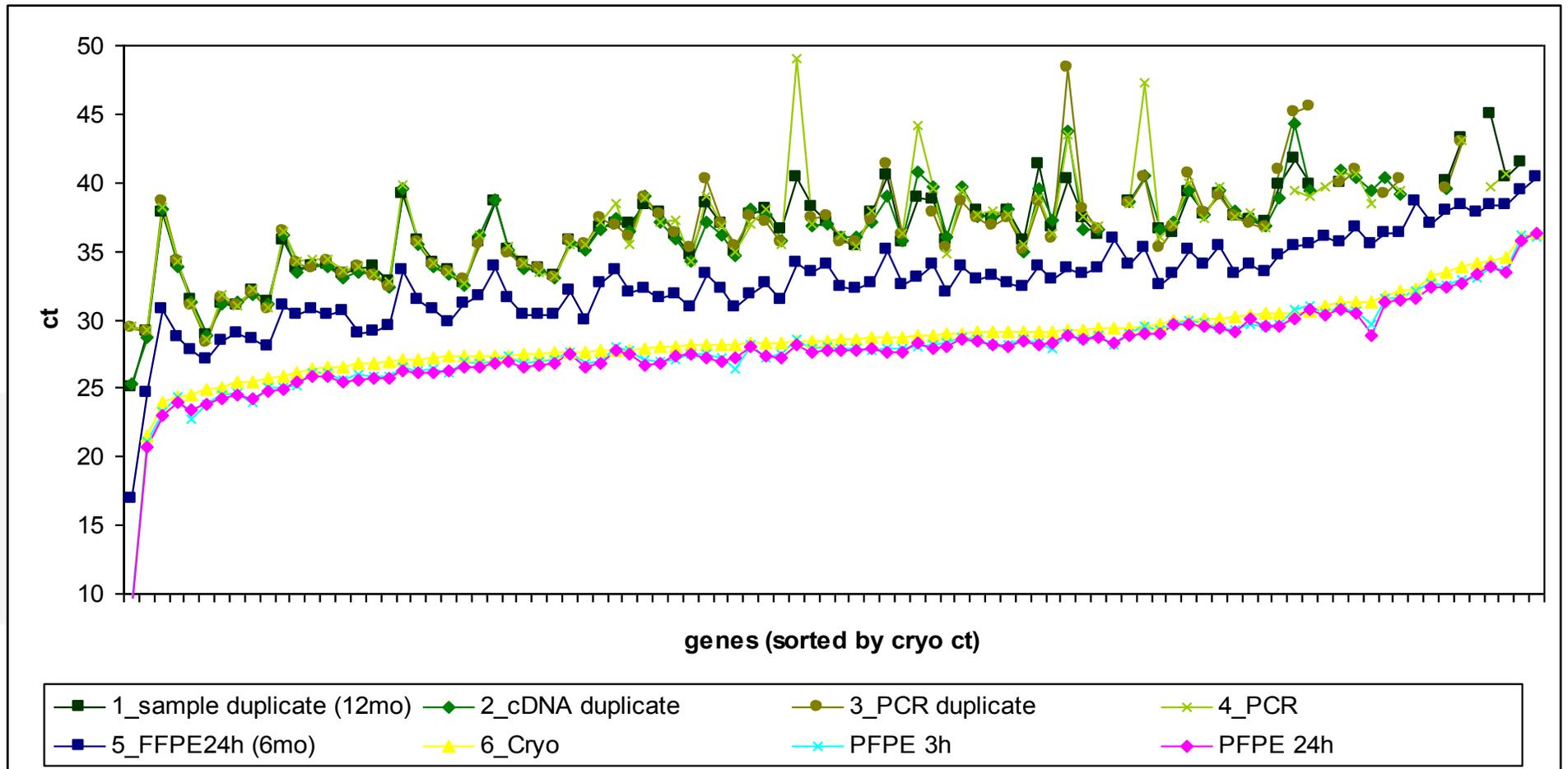
Formalin Fixation Interferes with qRT-PCR



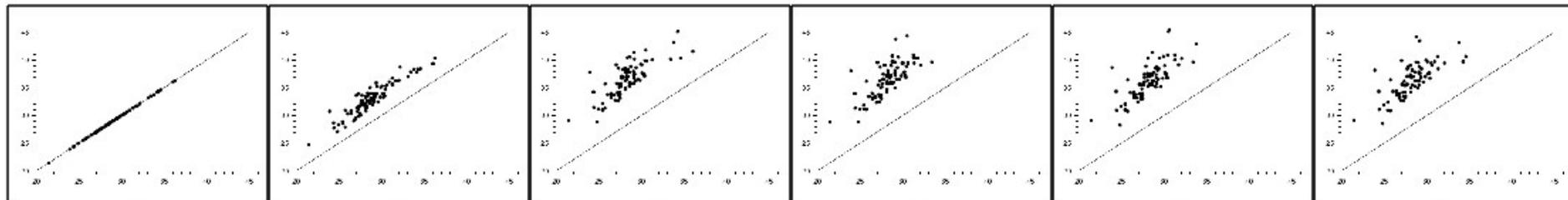
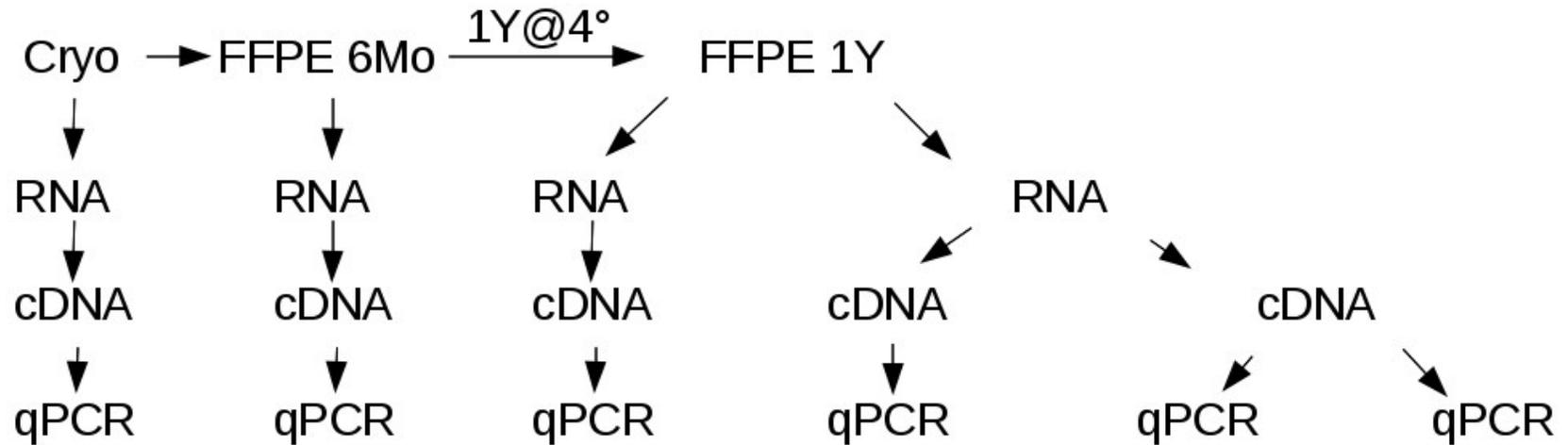
Impact of Fixation on Tissue Morphology and RNA Integrity



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



Sources of Variations in FFPE Tissue

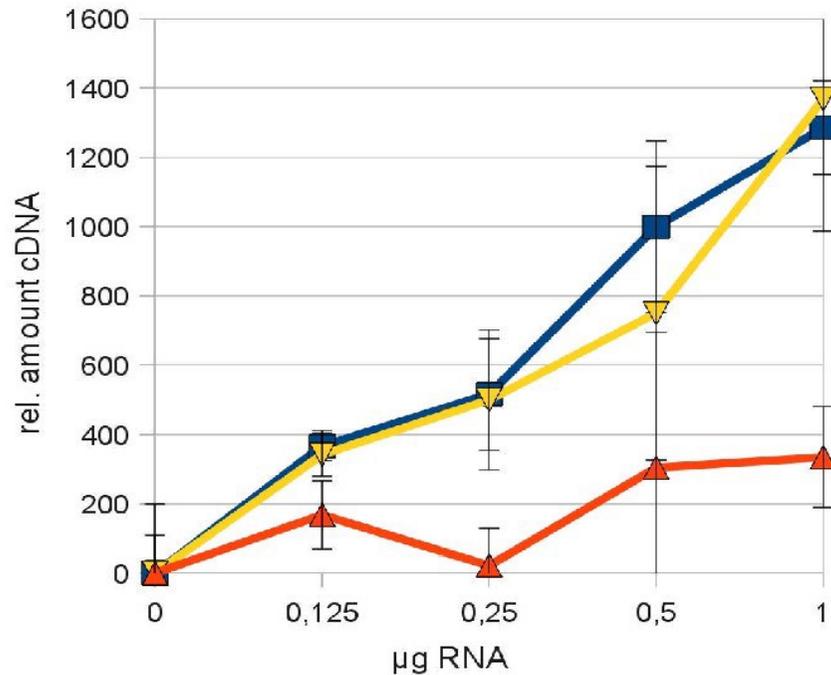


Pearson	1,0000	0,9411	0,7944	0,7462	0,6454	0,6040
Avg. dCt	0,0000	3,9952	8,0566	8,0446	8,0676	8,1876

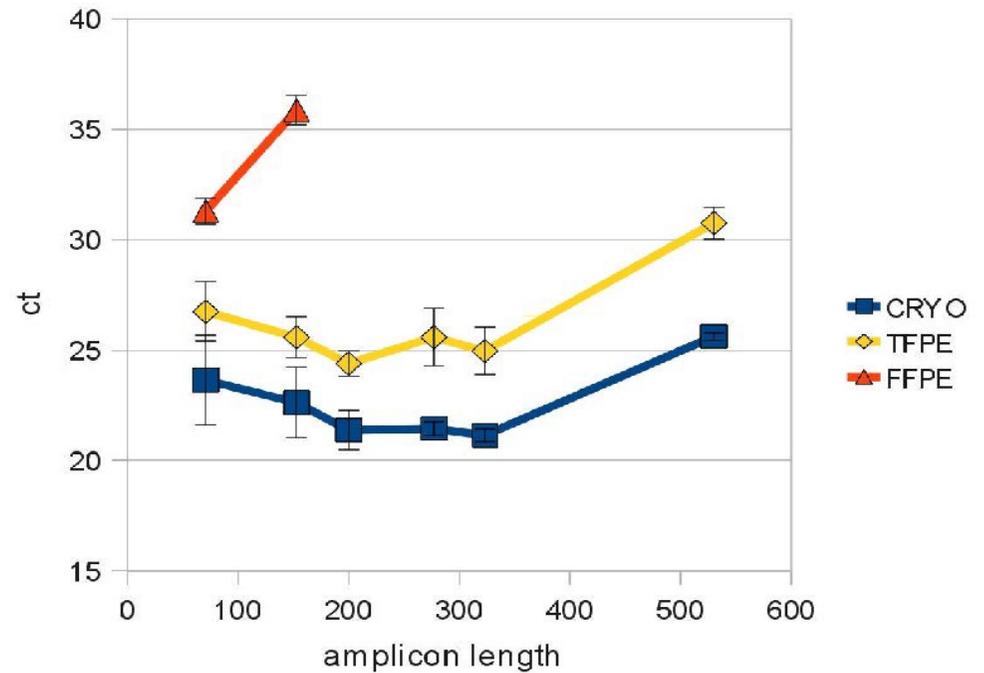
TaqMan Array Gene Signature Plate

Formalin Fixation Reduces cDNA Synthesis and Amplification Efficiency

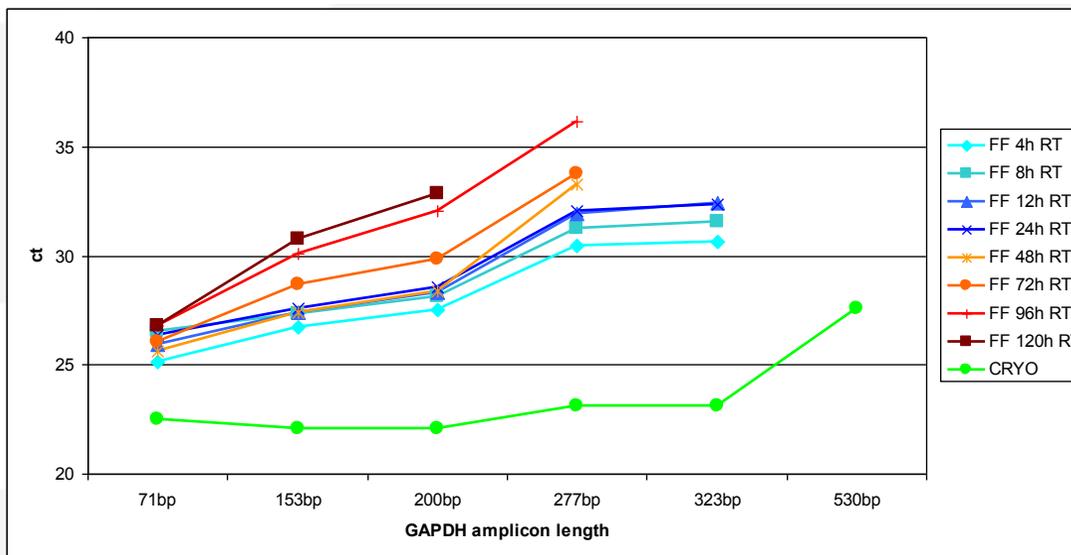
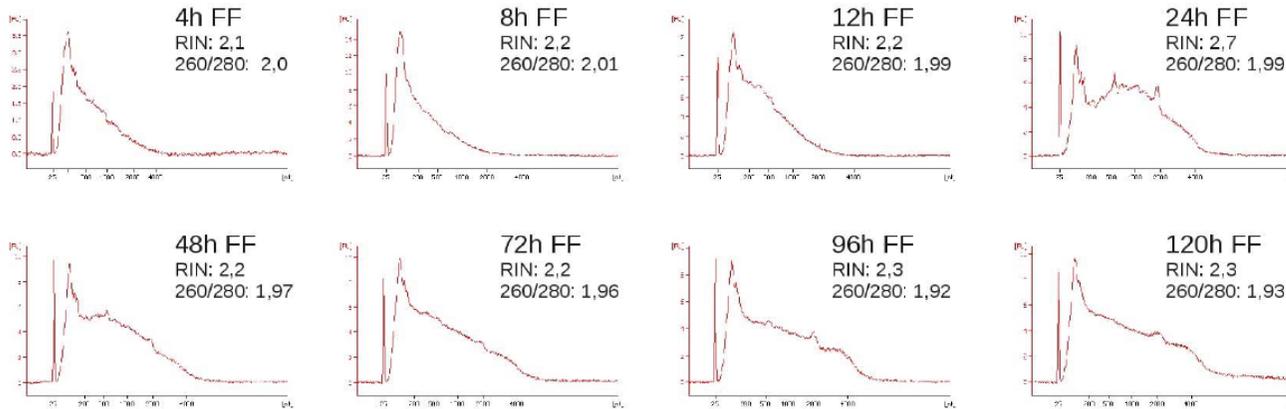
A



B



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



Conclusions and Recommendations

- Different pre-analytical 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

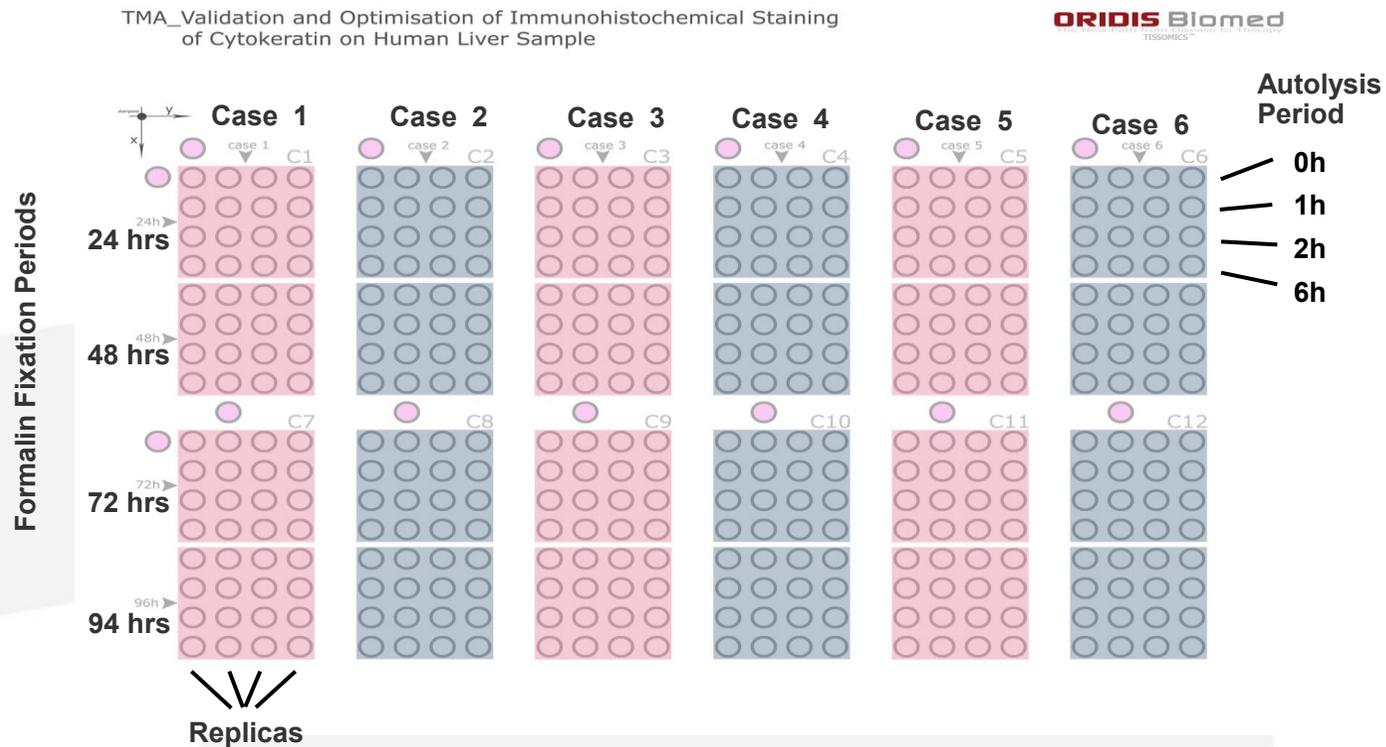
Molecular *in vitro* diagnostic examinations –
Specifications for pre-examination processes for
formalin-fixed and paraffin-embedded (FFPE)
tissue for *in situ* detection techniques”

Companion Diagnostics for Cancer Therapy (Examples FDA listed)

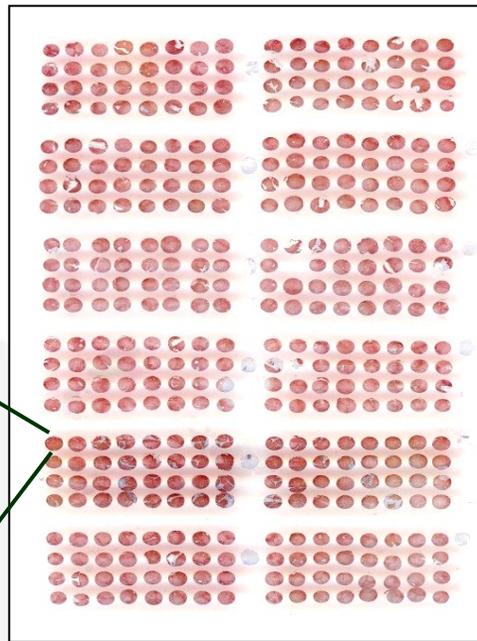
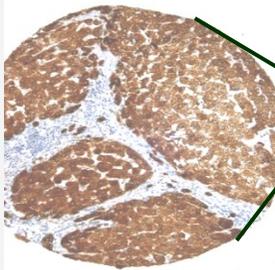
DRUG	DISEASE	TARGET	ASSAY	TECHNOLOGY
Afatinib	NSCLC	EGFR	RT-PCR	Rotor-Gene
Brentuximab Vedotin	Hodgin Lymph., sALCL	CD30	IHC	
Cetuximab (1)	CRC	EGFR	IHC	
Cetuximab (2)	mCRC	KRAS	RT-PCR	Rotor-Gene
Crizotinib	NSCLC	ALK	FISH	
Dabrafenib	Melanoma	BRAF	PCR	ABI 7500
Denileukin Diftitox	cut TCL	CD25	IHC	
Erlotinib	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-PDGFR α	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

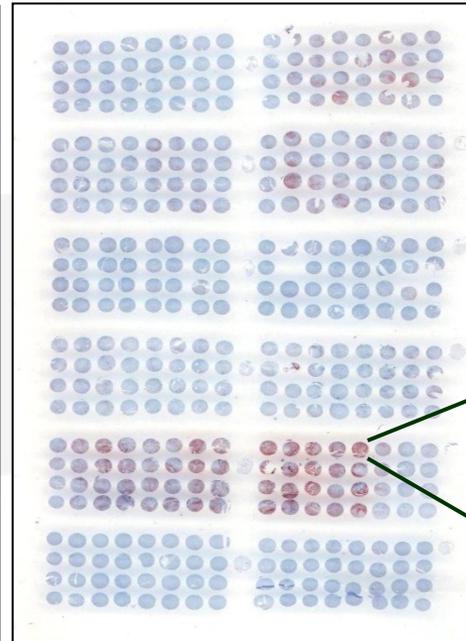
Example: Immunohistochemistry Protocols



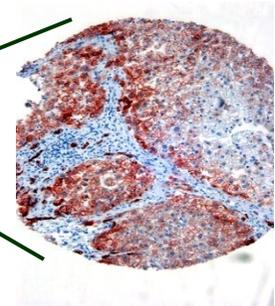
Differences in Protocol Robustness



Robust protocol



Non-robust protocol

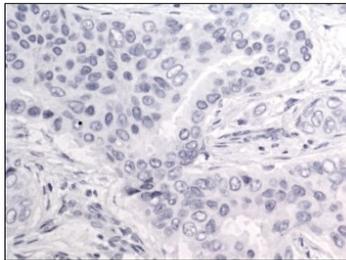


Sample pre-analytics and Antigen Retrieval

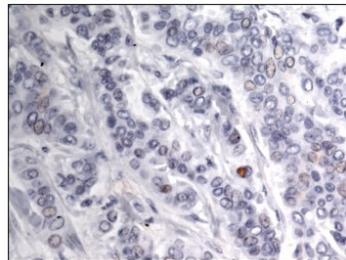
P53_H853_Mamma TU_72h_40x

Formalin

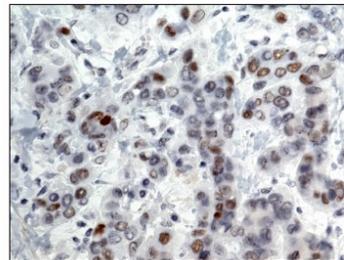
pH 6 MW 30



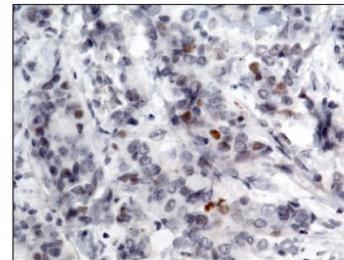
pH 6 MW 40



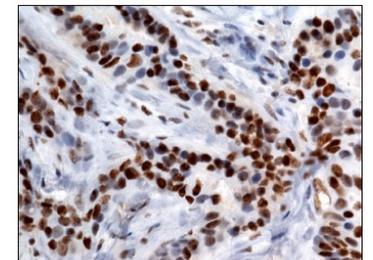
pH 9 MW 30



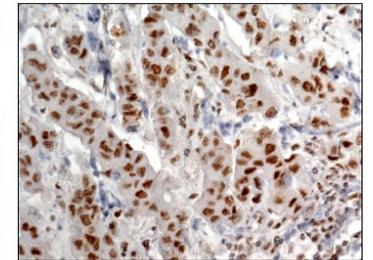
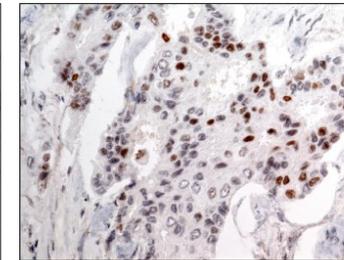
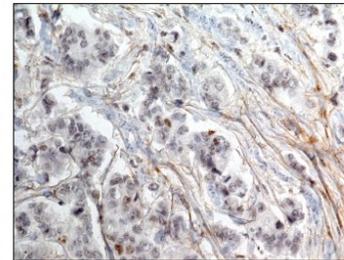
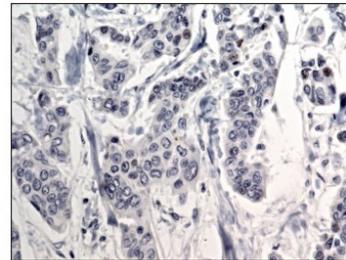
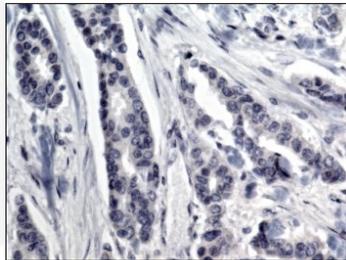
pH 9 MW 40



pH 9,5 MW 40



PAXgene



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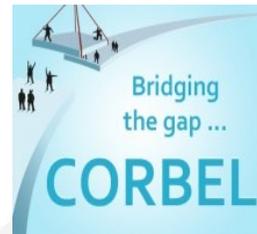
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BBMRI.at consortium
HRSM Digital Pathology Consortium
SPIDIA consortium
Biobank Graz

Thank You for Your Attention



Medizinische Universität Graz



BBMRI GA Nr. 212111
1.2.2008-30.04.2010

