BBMRI
Biobanking and Biomolecular Resources Research Infrastructure

SPIDIA

CAPACITIES

BBMRI GA Nr. 212111
1.2.2008-30.04.2010

How to Improve Interoperability of Biobanks: Role of Standardization of Pre-anlytical Variables

K. Zatloukal
Medical University of Graz, Austria

Annual Biospecimen Research Network Symposium, March 24th 2010

Topics

- **Why interoperability**
- **The European Research Infrastructure approach to improve interoperability**
- **Interoperability in tissue sample management**
  - **Assessment of variables in tissue sample pre-analytics**
  - **Novel stabilization solutions**

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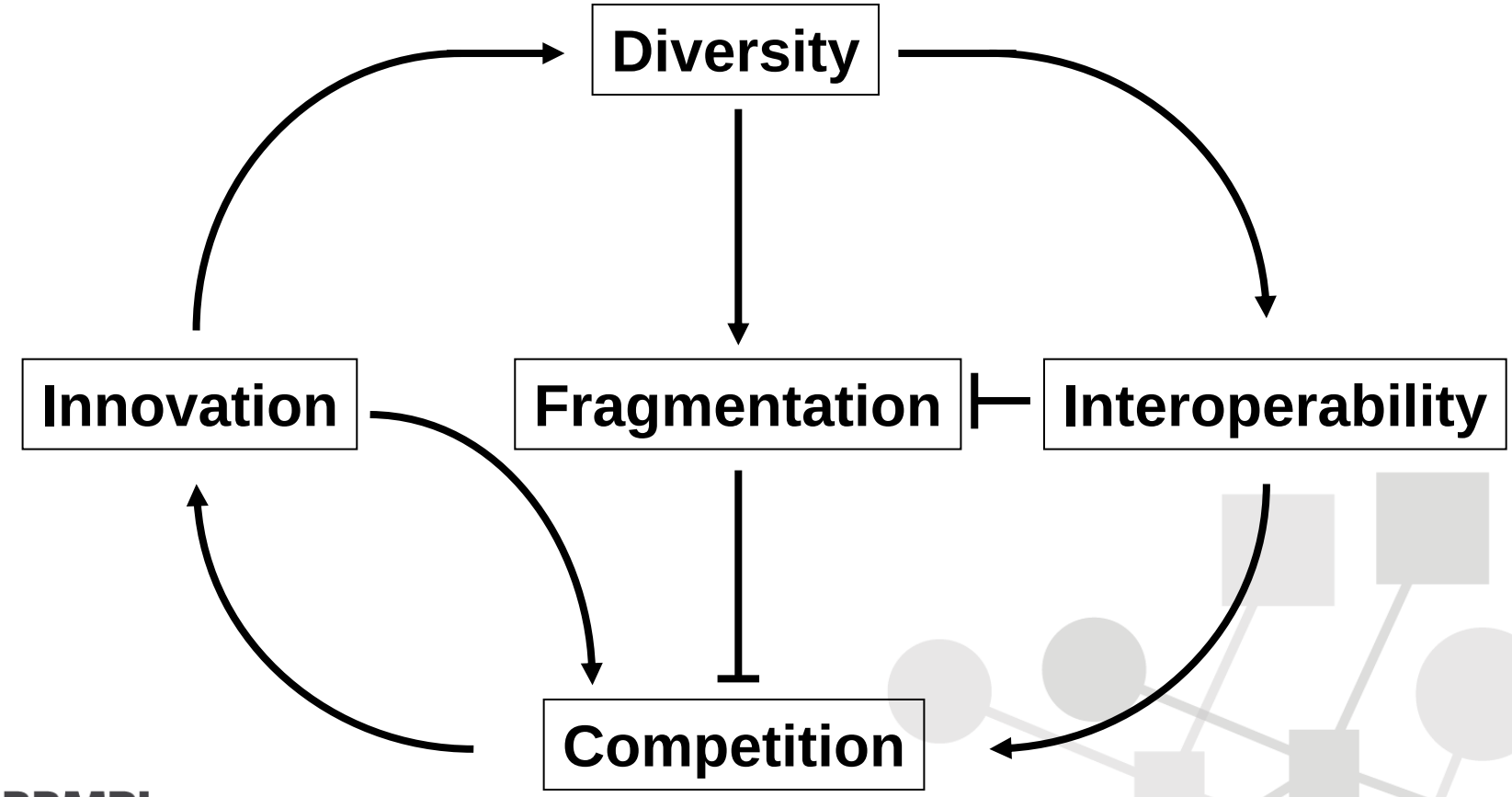
Competition as Driver of Innovation and Diversity



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Different Levels of Interoperability

- Ethical and legal frameworks
- Data management
- Sample management

⇒ Requires different solutions

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How to Measure Interoperability?

- Time from request to project start
- Number of samples analyzed
- Number of medical parameters
- Number of countries involved
- Scientific quality of outcome

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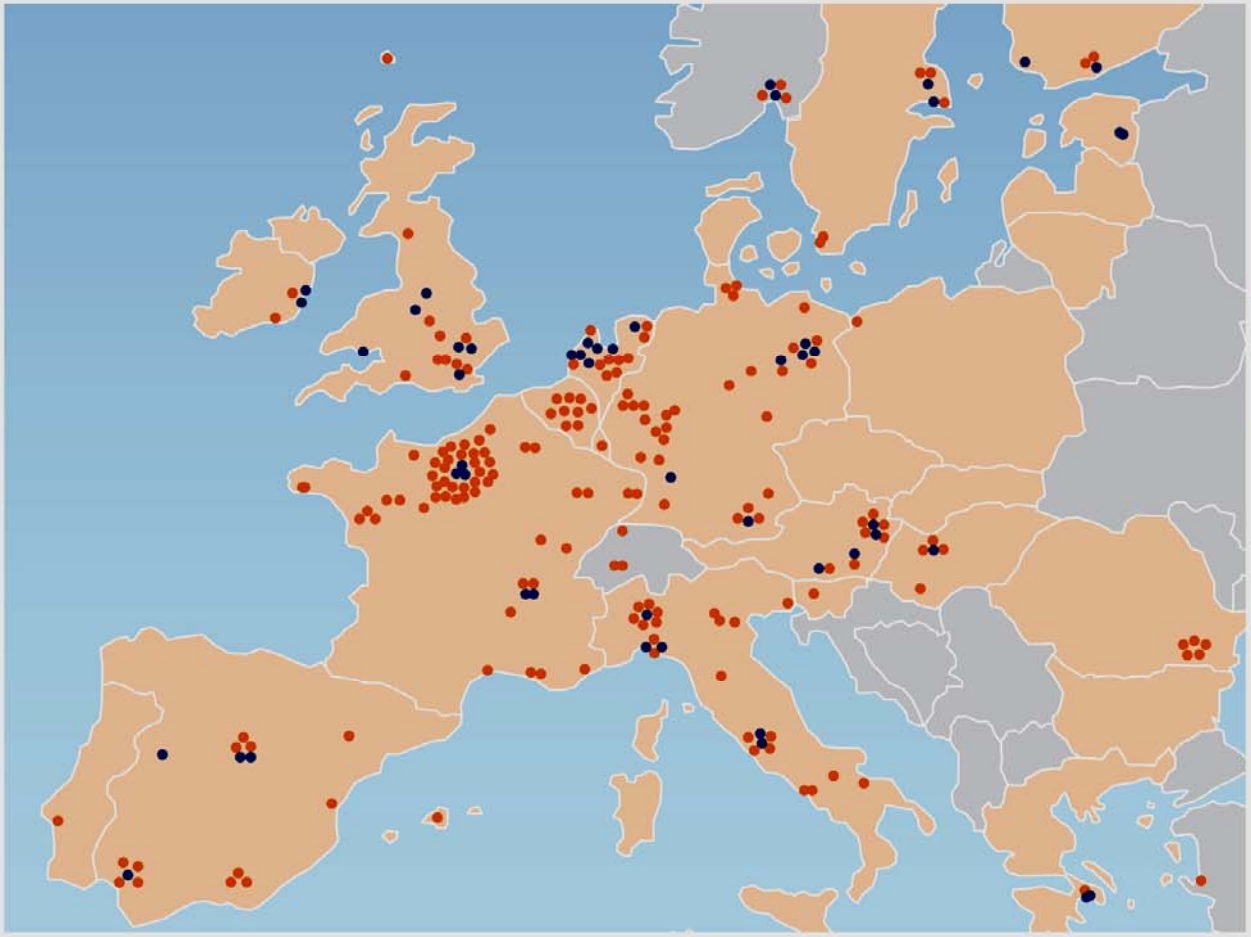
The Pan-European Research Infrastructure for Biobanking and Biomolecular Resources (BBMRI)



Preparatory phase 2008–2010
Funding 5 mio €

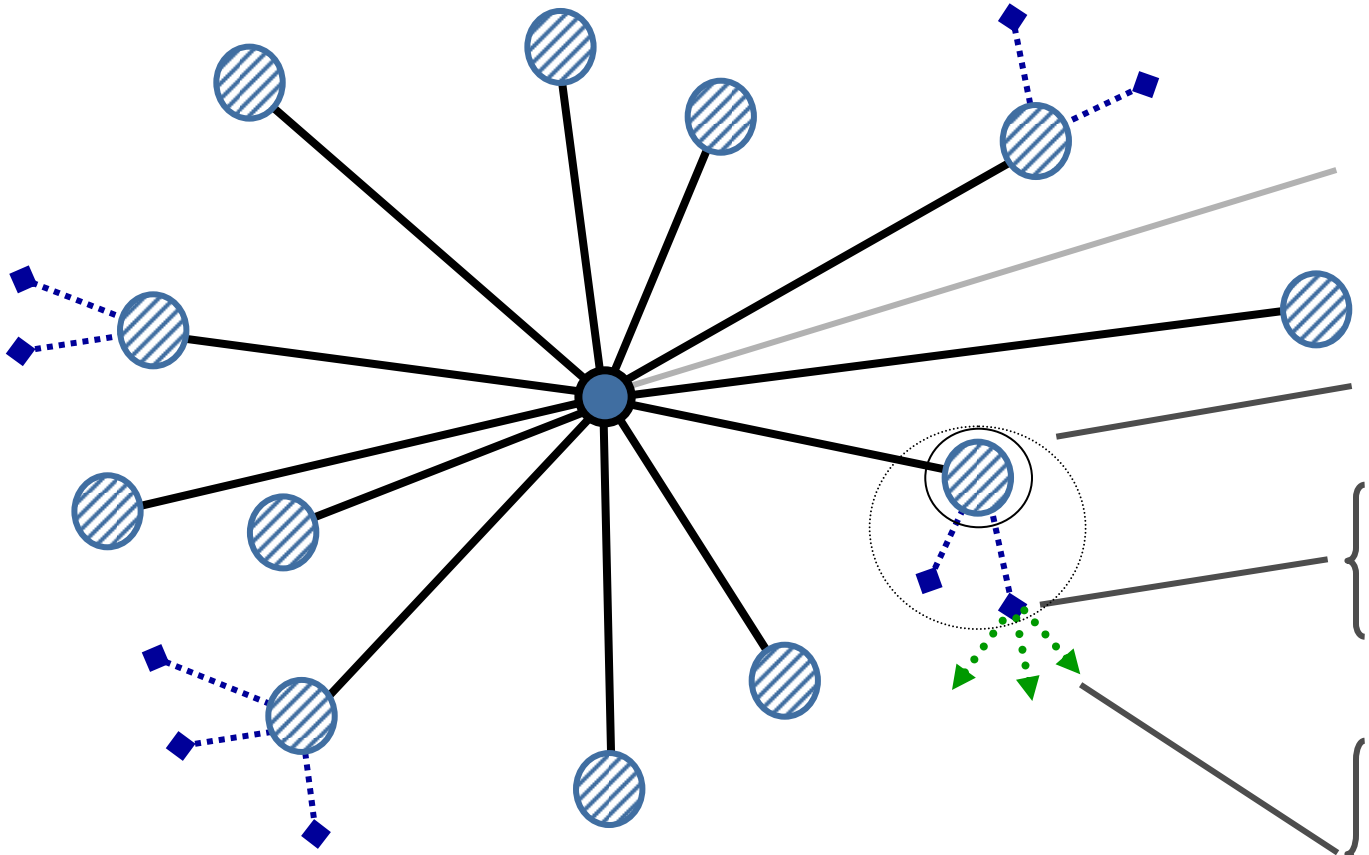
51
Participating Institutions

>200
Associated Organisations

30 Countries

ERIC as Possible Legal Structure of BBMRI

Distributed hub and spoke structure



Headquarter
(statutory seat)

National members

Biobanks
Biomolecular res.
Technology centers

Associated partners
Hospitals
Universities
Service providers ...

The ERIC Legal Framework

Establishement of operational sites in different Member States that operate under one legislation

In force since 28.8.2009

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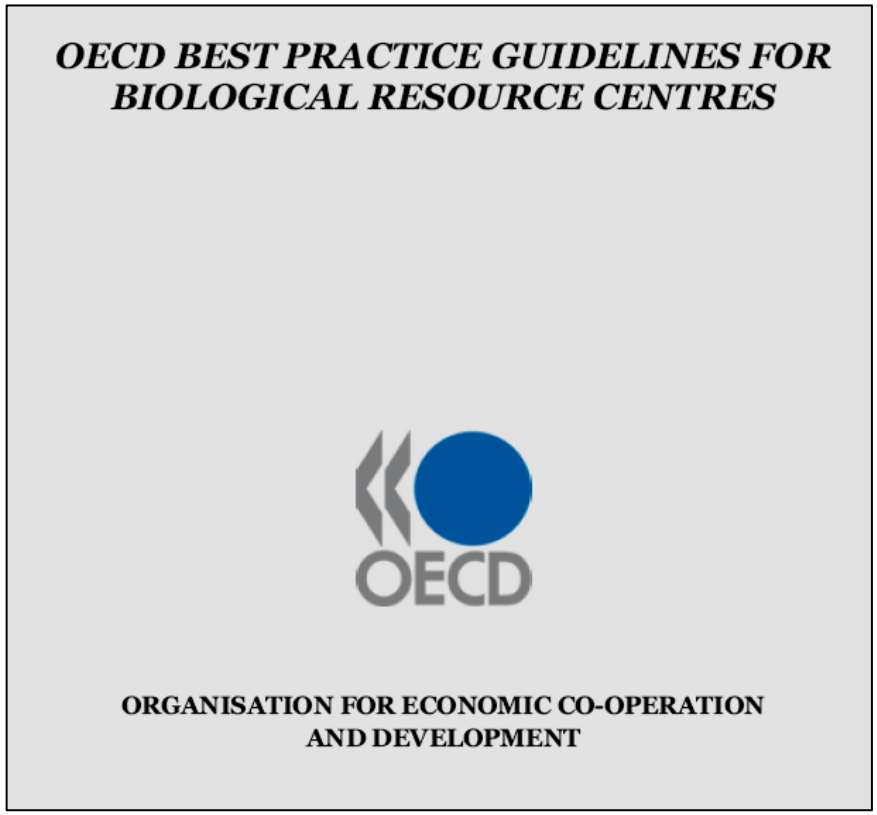
Human-Derived Material



Endorsed by CSTP in March 2007

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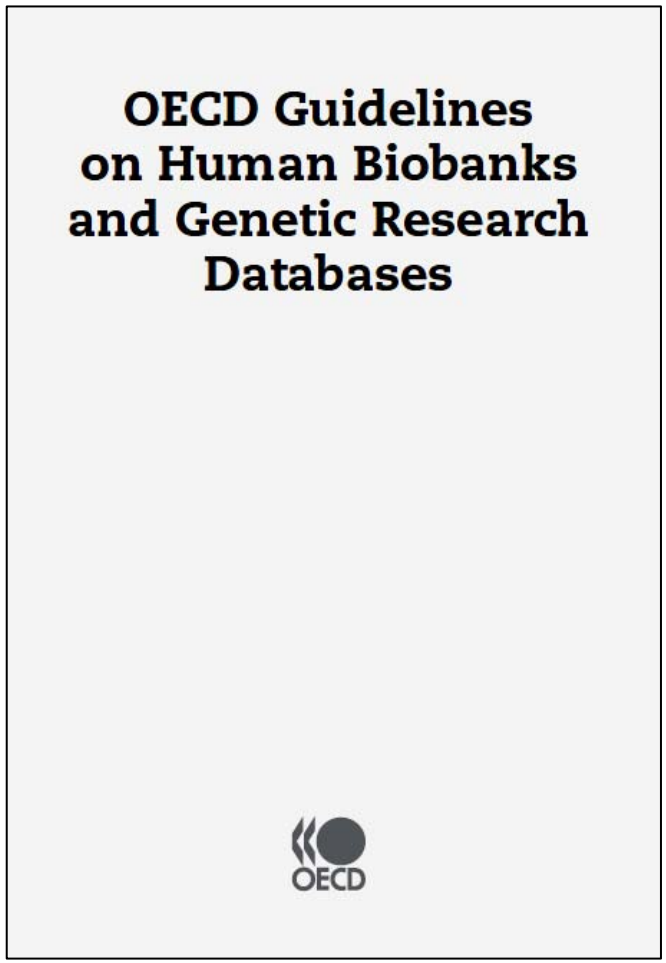
- Organisational requirements
- Staff-qualifications and training
- Premises
- Equipment
- Documentation
- Informatics
- Services
- Preparation of samples
- Accession of deposits
- Preservation
- Supply of biological material
- Quality audit and quality review



HBGRD

- Informed consent
- Governance
- Stakeholder
- Involvement of donors
- Data protection
- Change of scope
- (Old collections)

Endorced by OECD Council November 2009

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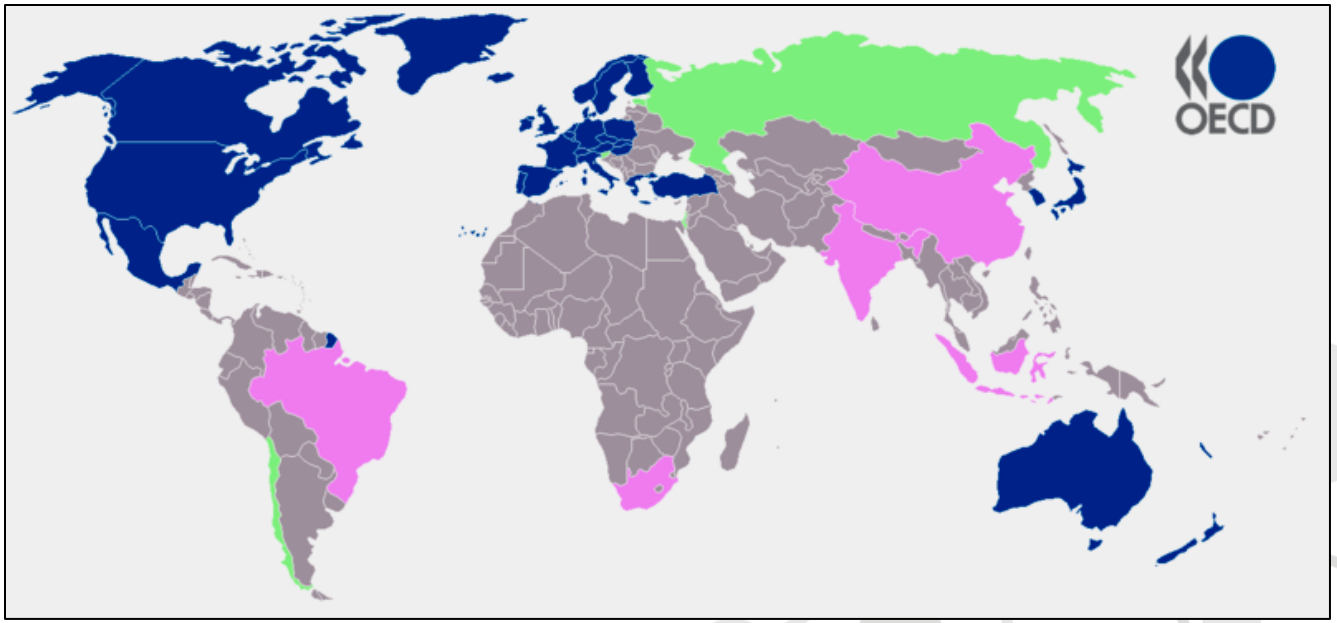
BBMRI: The European part of a human domain GBRCN

Phase 1: Establishment of planning consortium 2009

Phase 2: Identification of participants for pilot phase 2010

Phase 3: Pilot phase for implementation of 2011

OECD best practice guidelines



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Inventory of Biobanks in Europe

- **BBMRI questionnaires have been developed jointly with P^{3}G**
- **Detailed information on samples, data, access, governance, costs and funding**
- **Questionnaires from >260 biobanks evaluated**
- **Stored in a relational database system (http://www.bbmri.eu/index.php/catalog-of-european-biobanks)**

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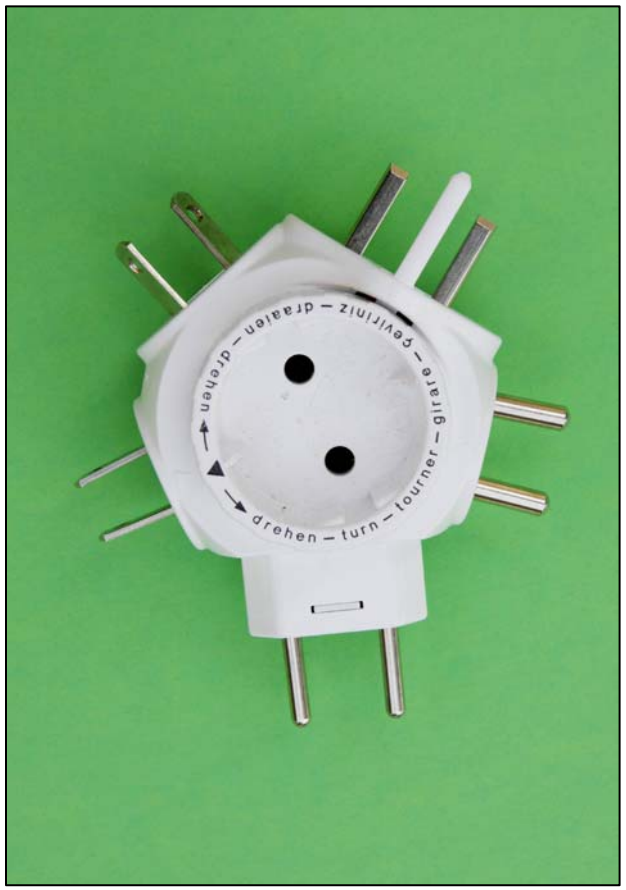
The Adaptor Approach of BBMRI to Achieve Interoperability



- Define criteria
  - Which samples and data can be combined?
  - Evidence-based quality indicators
- Develop tools
  - Data exchange
  - Intl. transfer of samples
  - Interoperability!

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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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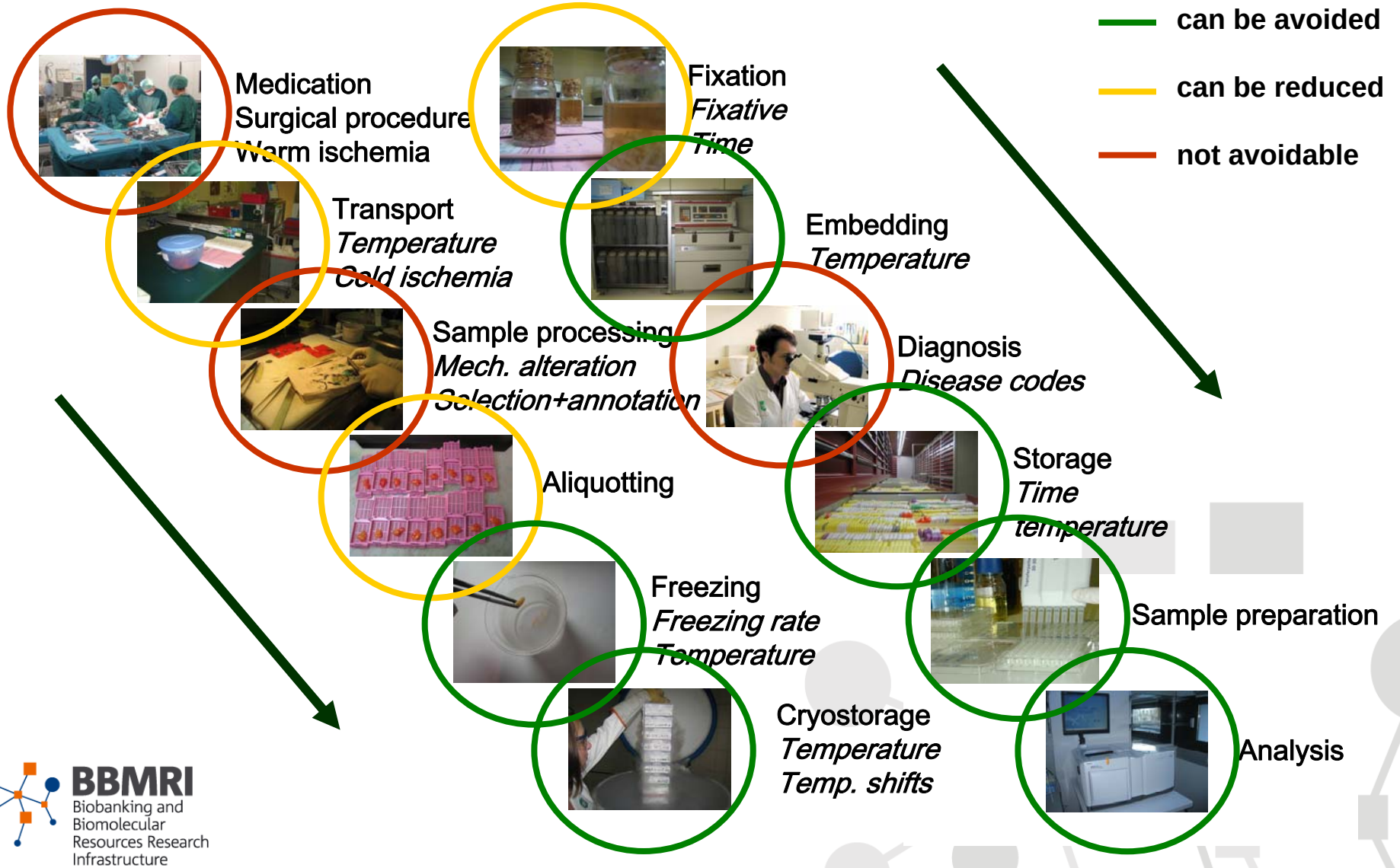
Sources of Diversity



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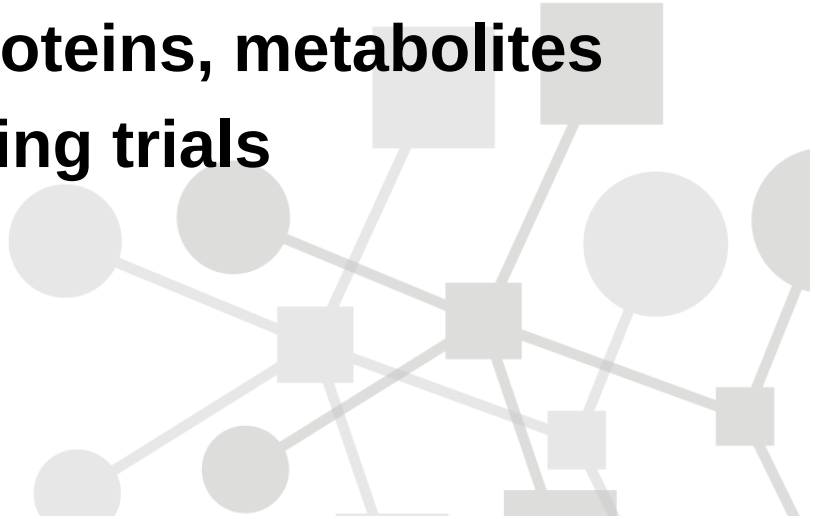
European FP 7
Large Integrated Project

- Evidence-based quality parameters
- New stabilization procedures
- New sampling procedures
- Evaluation of morphology
- Evaluation of antigenicity
- Evaluation of DNA, RNA, proteins, metabolites
- Validation in international ring trials
- European Norm (CEN)



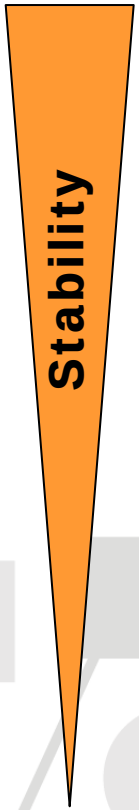
Parameters for Tissue-Based Analysis

Sample variables

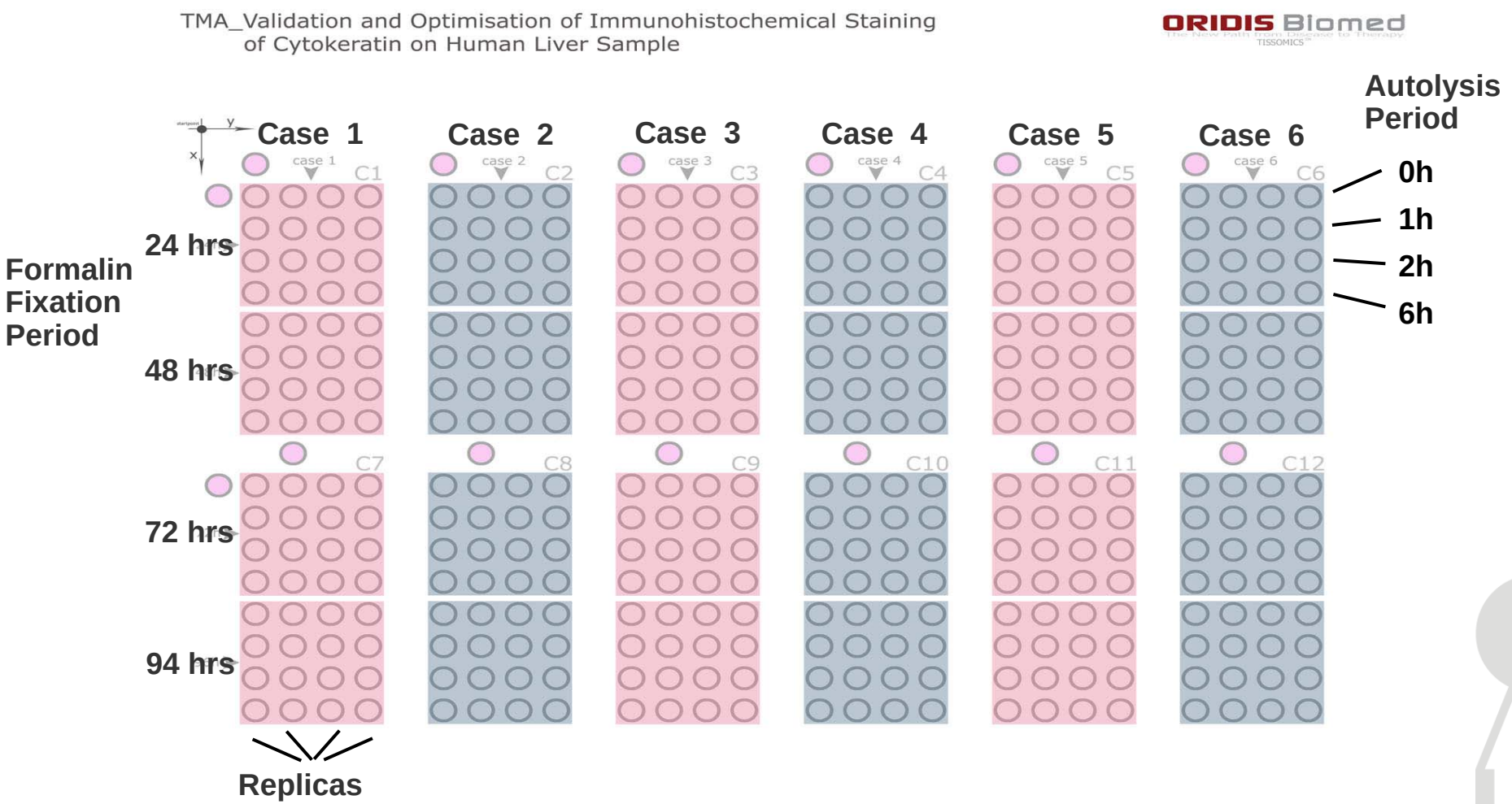
- Tissue type (organ)
- Diseased/normal
- Sample type (biopsy/surgery)
- Peri-operative effects
- Ischemia
- Processing
- Fixation
- Storage
- Analysis

Readout

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



TMA Design for Validation of Immunohistochemistry Protocols

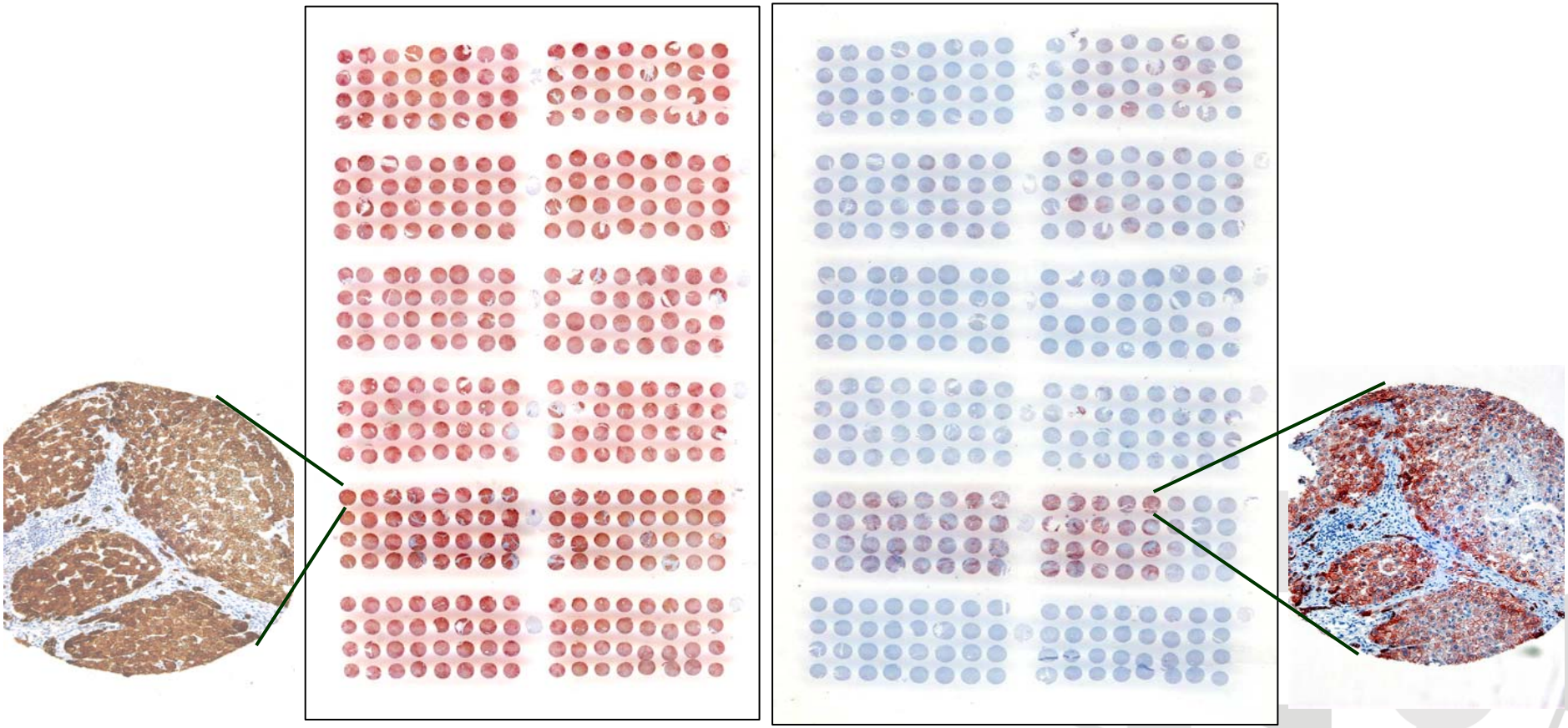


Variables Analyzed by TMA Protocol Validation

- 4x autolysis, 4x fixation, 6x cases, 4x replicas = 72 samples
- 5x antibodies, 3x concentrations, 4x retrieval, 2x detection systems =

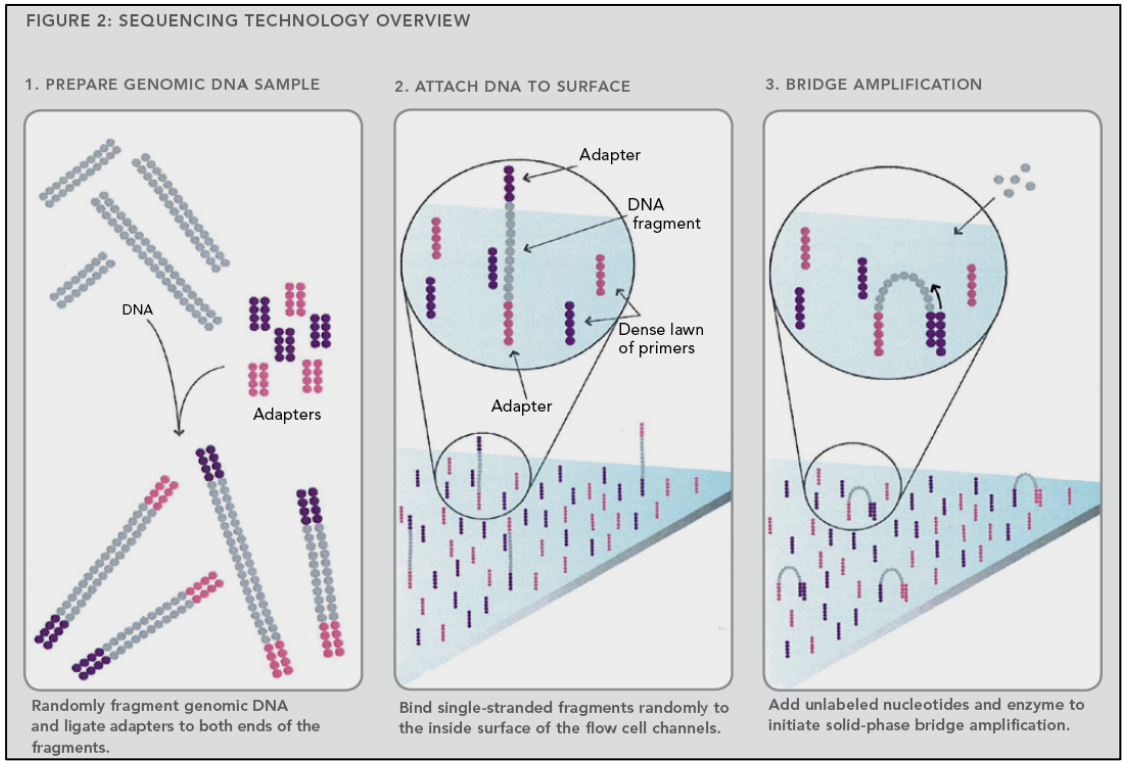
  120 IHC conditions
- **Total 8640 reactions for 1 antigen**

TMA Light Microscopy
(anti Keratin 8 and 18 staining)

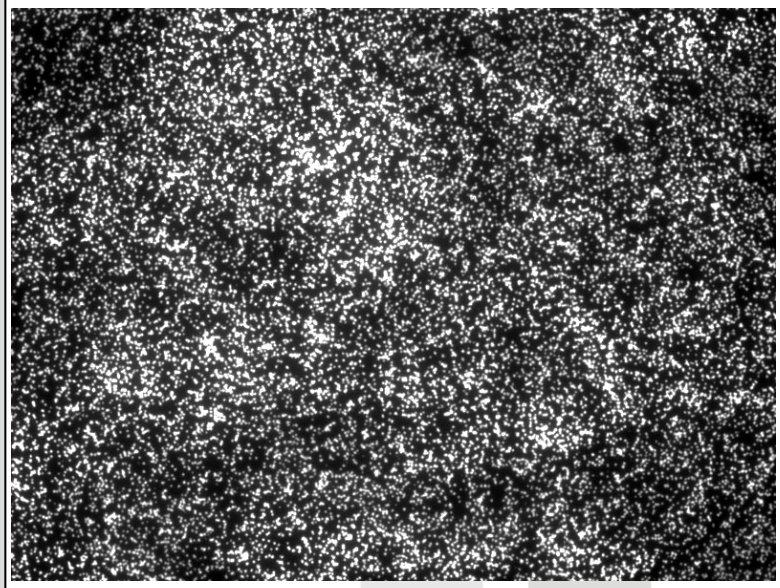


Robust protocol **Non-robust protocol**

Next Generation Sequencing



Illumina® Systems & Software



~ 40 mio clusters

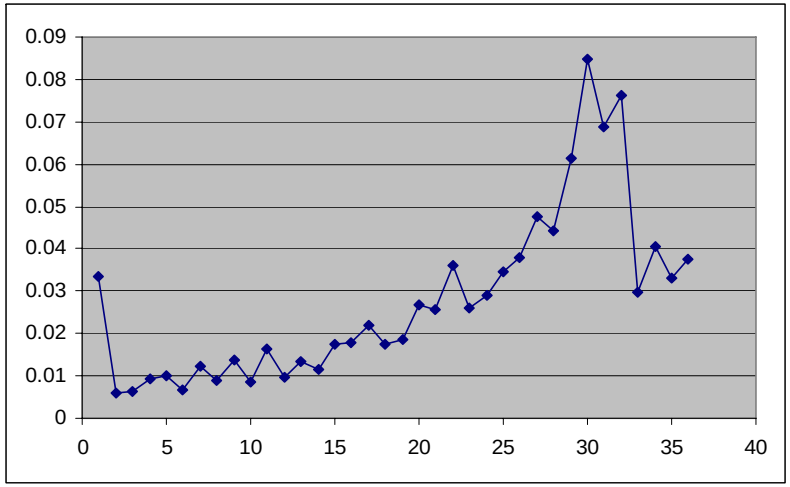
Evaluation of Parameters Affecting Sample Quality for Sequencing

Sample age (sample ID)	Fixation	Ischemia <20 min	Ischemia 60 min	Ischemia 3 hrs	Ischemia 6 hrs
1 year (ID1)	Snap frozen	+			
1 year (ID1)	24 hrs formaldehyde	+	+	+	+
1 year (ID1)	72 hrs formaldehyde	+	+	+	+
14 years (ID1202*)	Snap frozen	+			
14 years (ID1202)*	24 hrs formaldehyde	+			
18 years (ID 22)*	Snap frozen	+			
18 years (ID 22)*	24 hrs formaldehyde	+			

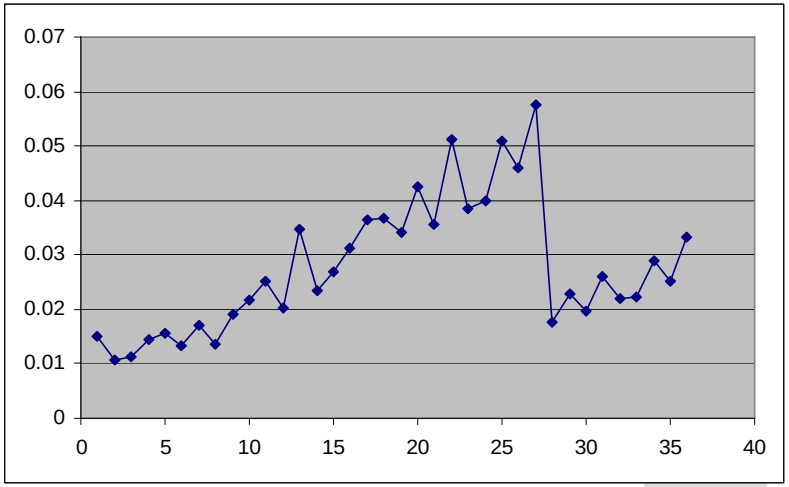
M. R. Schweiger et al., PLoS One 2009

Sequencing Efficacy: Read lenghts

Cryo



FFPE

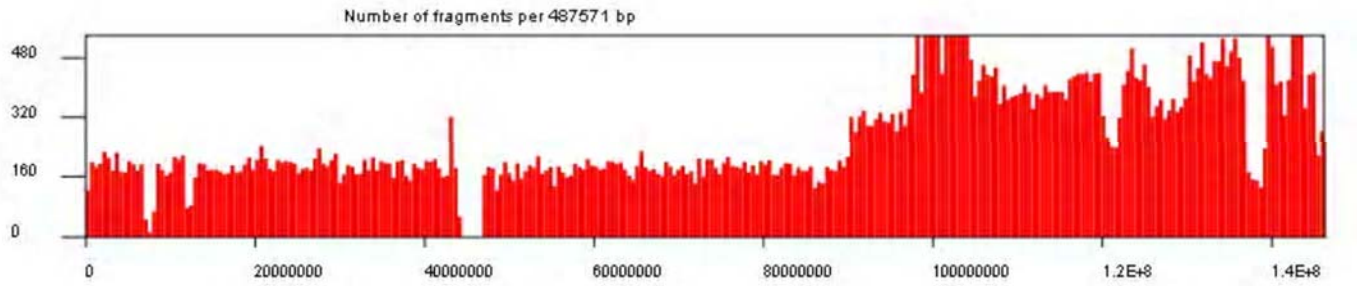


	lane	fragments	mismatches	
Cryo	070911_EAS12_0005_FC5999_1	1,068,015	622,989	cryo
FFPE	070911_EAS12_0005_FC5999_4	953,876	693,846	para

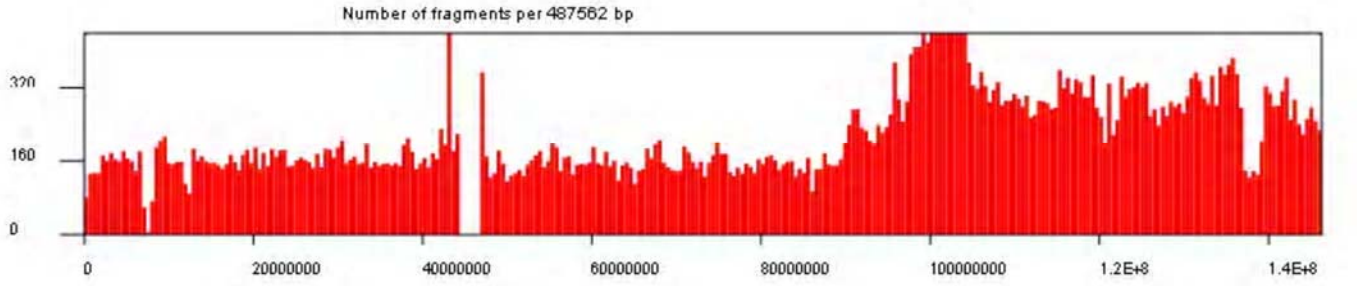
h

Quantitative Results: CNVs/Amplifications

Cryo

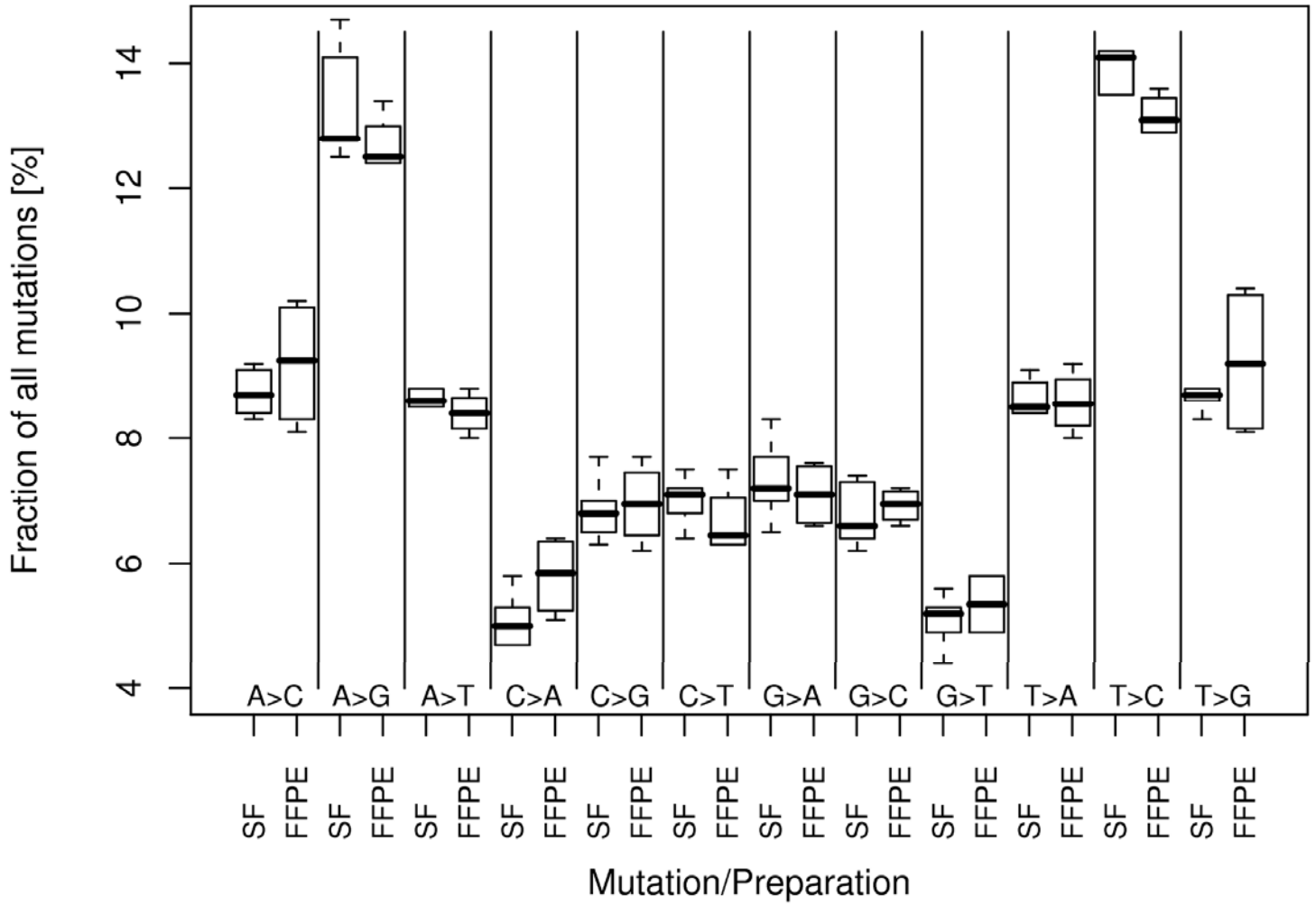


FFPE



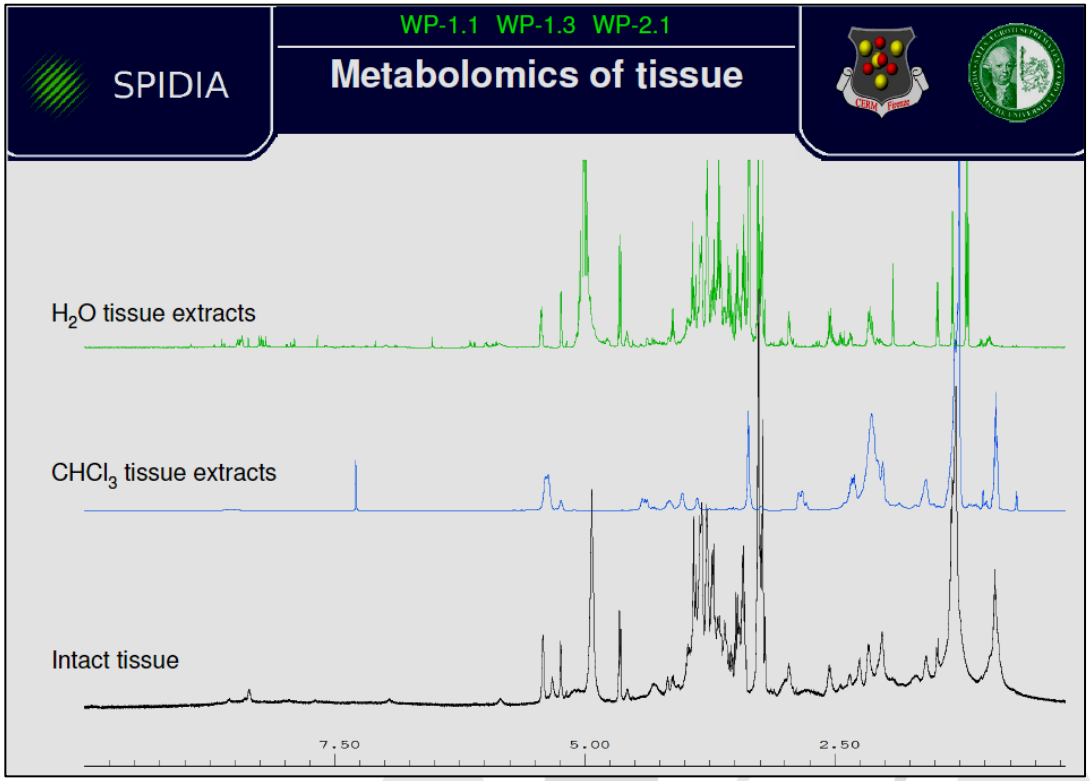
Chromosome 8

Qualitative Results: SNPs/Mutations

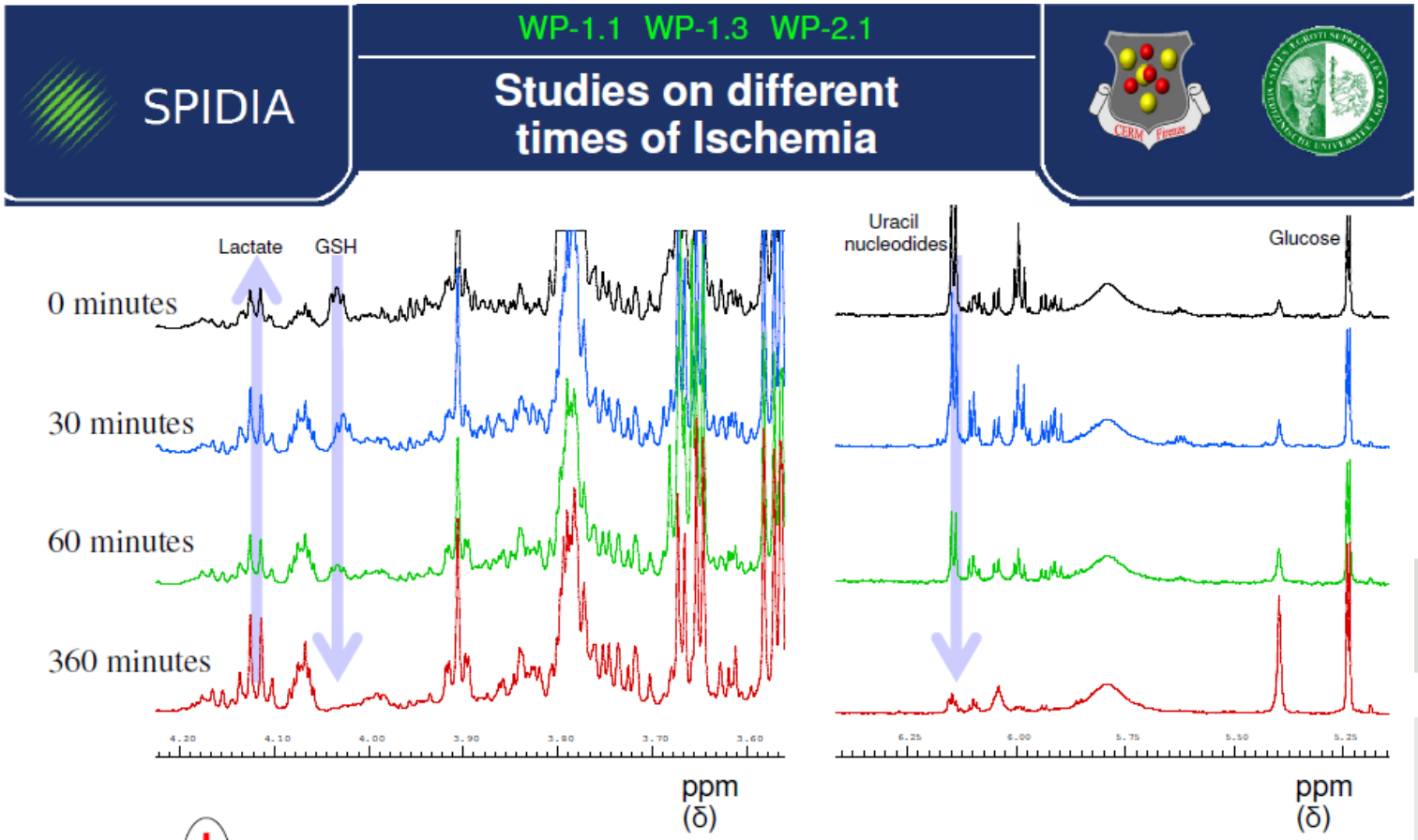


NMR-Based Metabolomics

CERM Univ. Florence



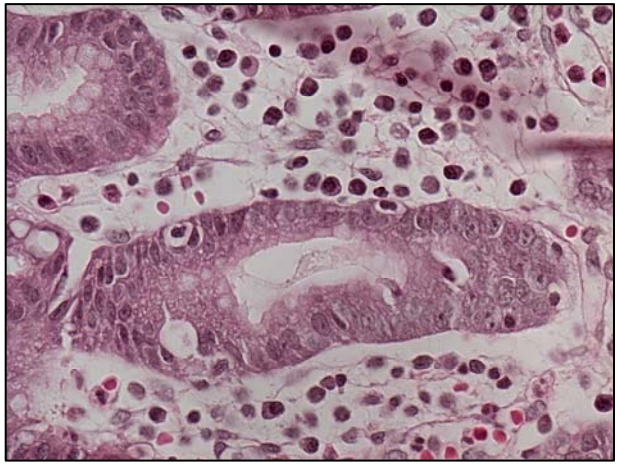
Ischemia - Induced Alterations



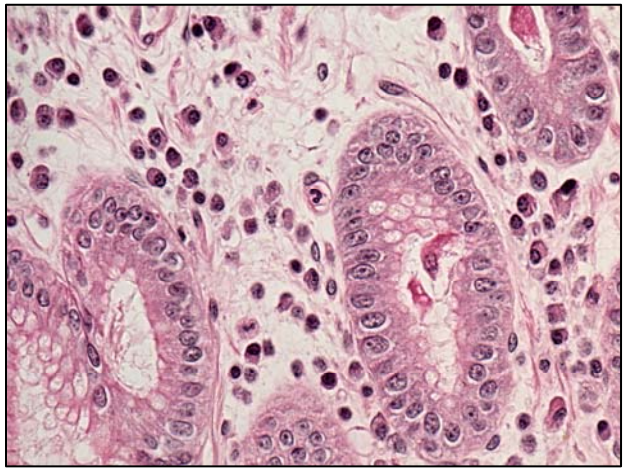
New Stabilization Solutions for Multimodal Biomarkers

- **PaxGene^{R} (Qiagen)**
  - **Morphology**
  - **Antigenicity**
  - **DNA**
  - **RNA**
  - **Proteins**

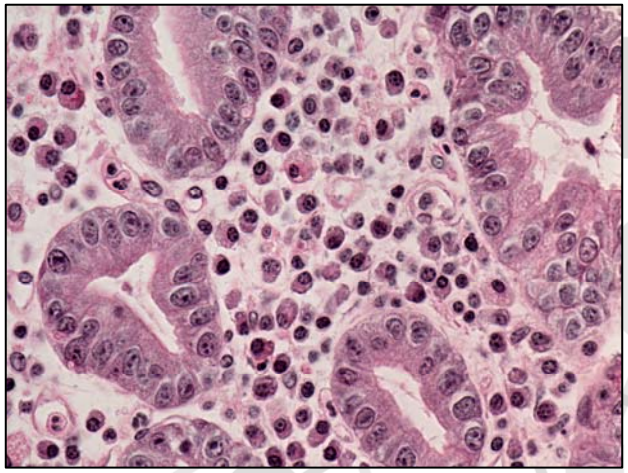
Preservation of Morphology



501StomachFF24h_60x

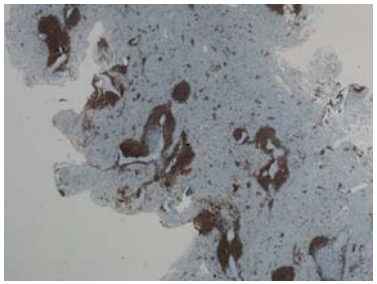


502StomachPG3h_60x

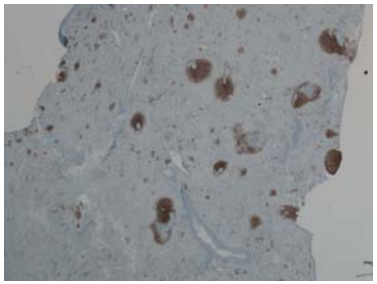


503StomachPG24h_60x

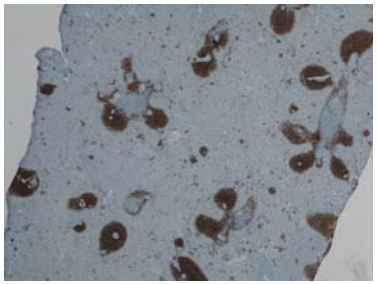
Preservation of Antigenicity
(Spleen CD20 with Ag retrieval)



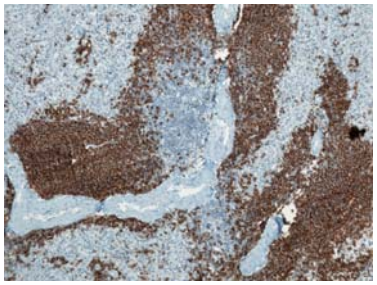
SpleenFF24h_CD20(2x)



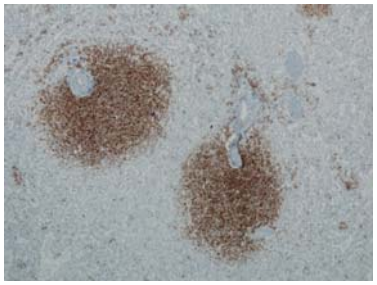
SpleenPG3h_CD20(2x)



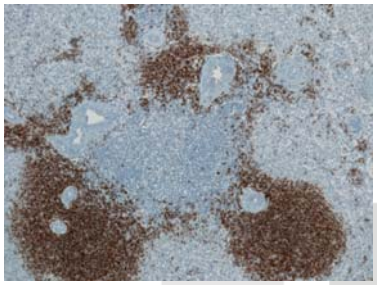
SpleenPG24h_CD20(2x)



SpleenFF24h_CD20(10x)



SpleenPG3h_CD20(10x)



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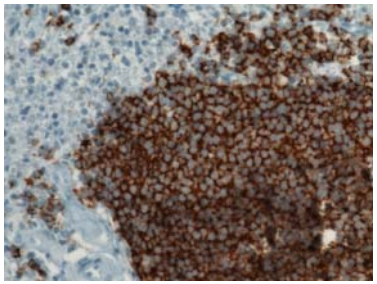

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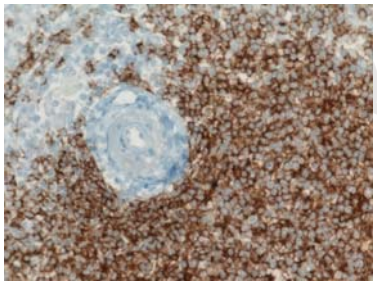
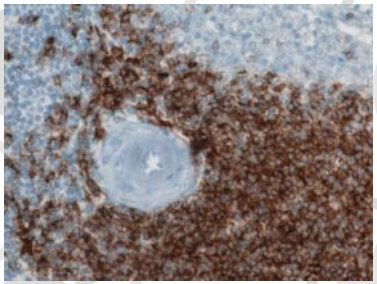
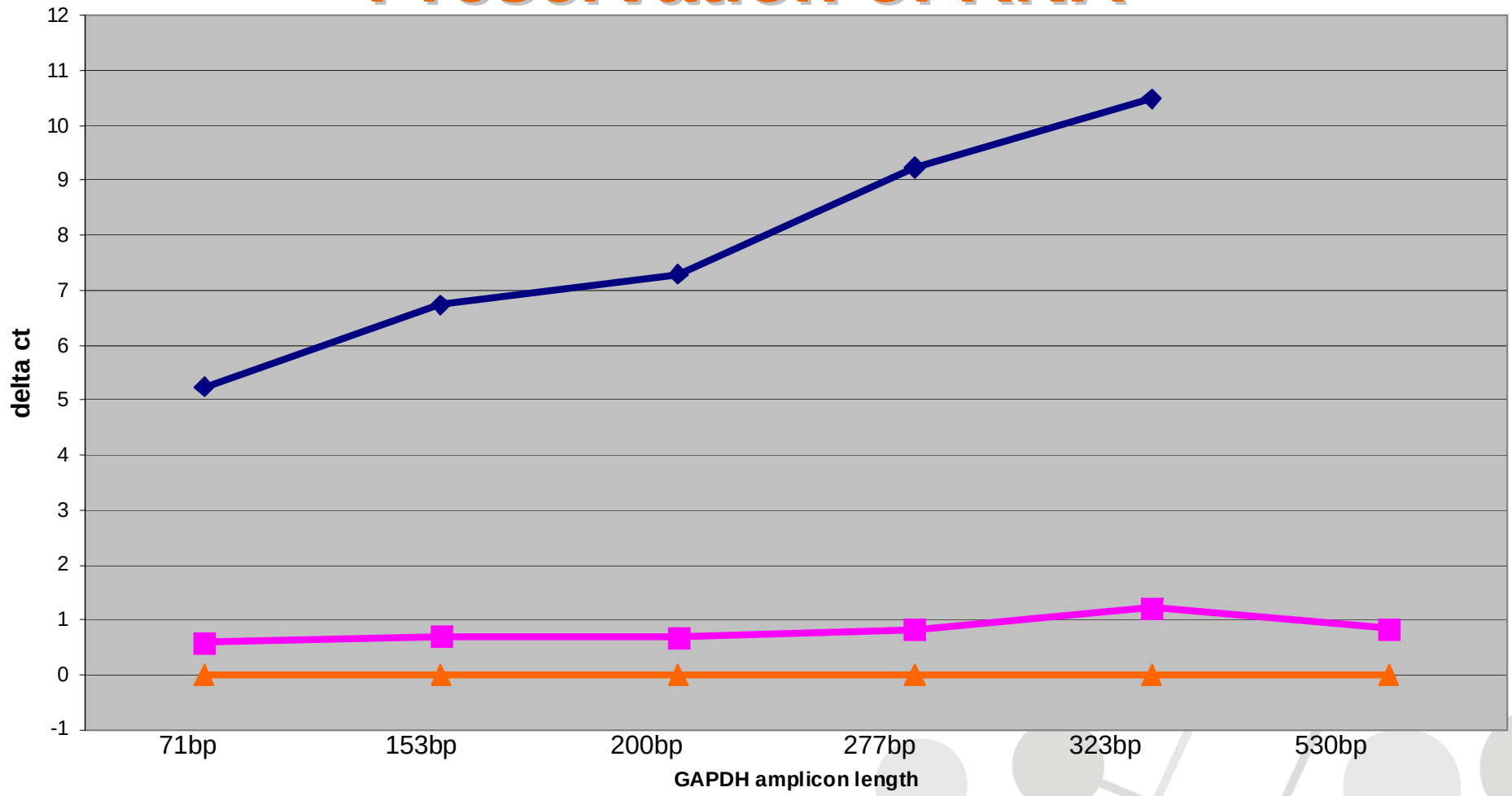


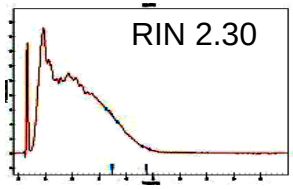
SpleenPG3h_CD20(40x)

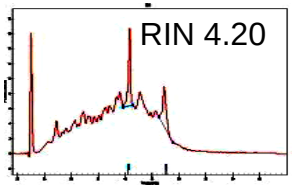


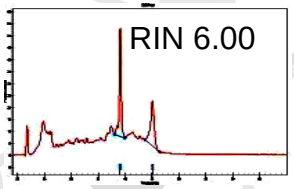
SpleenPG24h_CD20(40x)

Preservation of RNA









The BBMRI Team: WP Leaders and Chairs

Coordination/Executive Mgmnt.	K. Zatloukal, AT; E. Vuorio, FI
	M. Yuille, UK; M Pasterk, FR
Population-based Biobanks:	L. Peltonen+, FI/UK; A. Metspalu,EE
Disease-oriented Biobanks:	E. Wichmann, GER, T Meitinger, GER
Biomolecular Resources:	U. Landegren, SE; M. Taussig, UK
Databases & Biocomputing:	J-E Litton, SE
Ethical, Legal and Societal Issues:	A. Cambon-Thomsen, FR
Funding and Financing:	G. Dagher, FR; J. Ridder, NL
	C. Brechot, FR;
Governance Council Chair:	L. Peltonen, FI
Advisory Board Chair:	G-J van Ommen, NL
Coordination Board Chair:	K. Zatloukal, AT
Stakeholder Forum Chair:	M. Griffith, IR

51 Participants (6 Ministries, 18 Funding Organizations)

210 Associated Organizations 30 Countries

SPIDIA Partners

Medical University of Graz Austria:

Christian Viertler

Daniela Pabst

Nicole Kurzmann

Monika Moser

CREM University of Florence Italy:

Ivano Bertini

Paola Turano

Qiagen, Hilden Germany:

Uwe Oehlmueller

Ralf Wyrich

Max Planck Institute for Molecular Genetics, Berlin Germany:

Hans Lehrach

Michal Schweiger

Thank you

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SEVENTH FRAMEWORK
PROGRAMME

GEN-AU
GENOMFORSCHUNG IN ÖSTERREICH