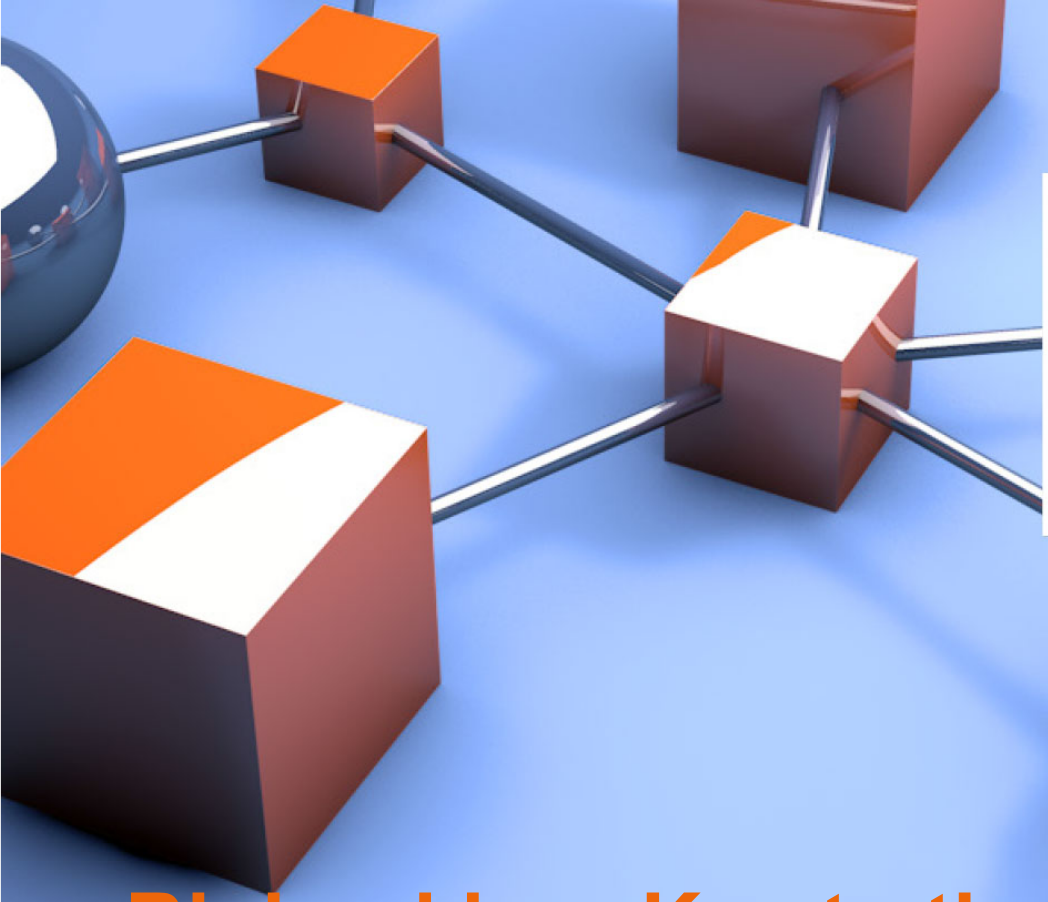

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Biobanking and
BioMolecular resources
Research Infrastructure
Austria

Biobanking: Key to the implementation of standards in personalized medicine

Kurt Zatloukal
Diagnostic and Research Center for Molecular Biomedicine,
Medical University Graz, Austria

Tackling Issues of in vitro Diagnostics
in Personalized Medicine
Brussels, 5.3.2019

bmwfw
Bundesministerium für Wissenschaft, Forschung und Wirtschaft

Funded by
GZ 10.470/0016-II/3/2013

Research Data Reproducibility Crisis

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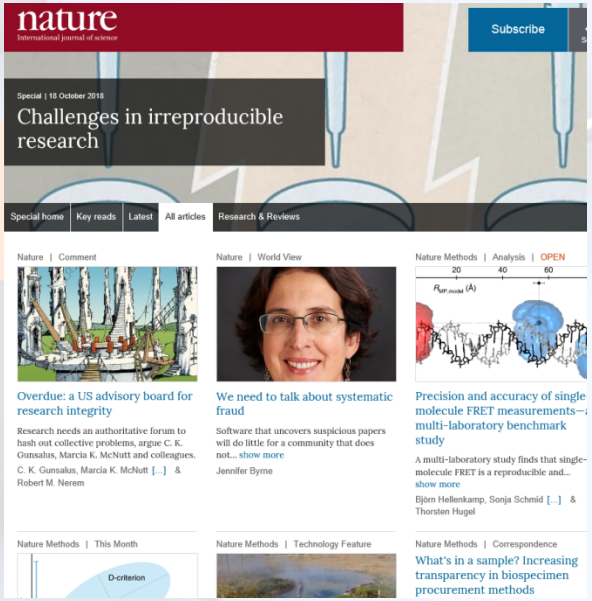


Reliability of 'new drug target' claims called into question

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.

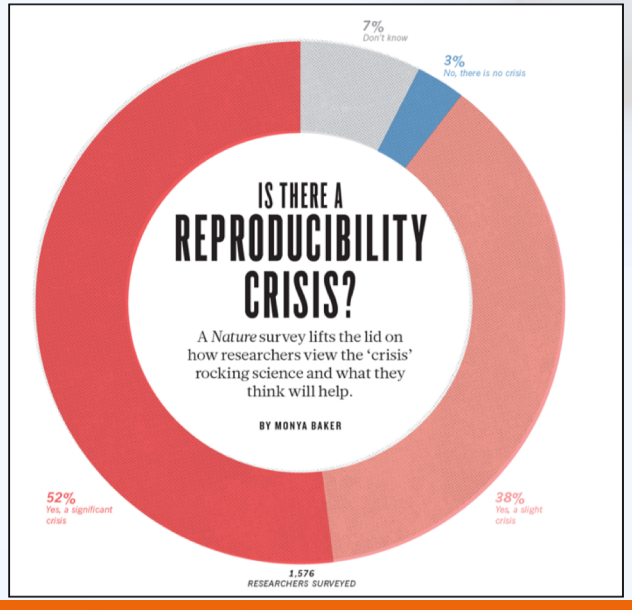
Asher Mullard

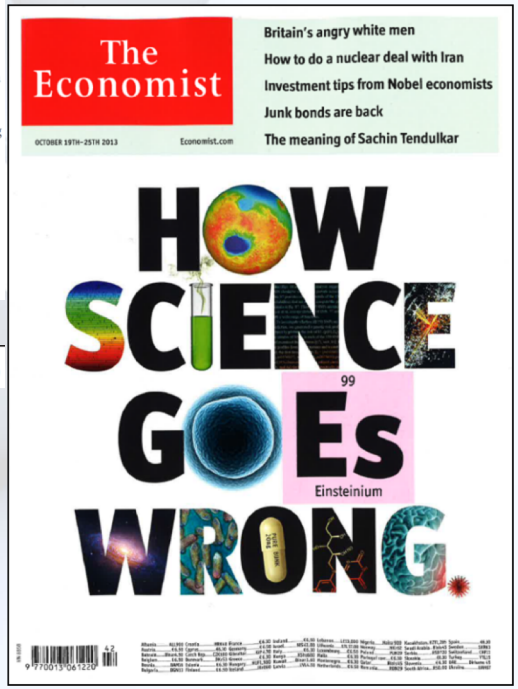
An unspoken industry rule alleges that at least 50% of published studies from academic laboratories cannot be repeated in an industrial setting, wrote venture capitalist Bruce Booth in a recent blog post. A first-of-a-kind analysis of Bayer's internal efforts to validate 'new drug target' claims now 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





Biobanks:Quality-defined biosamples are the raw material for reproducible data

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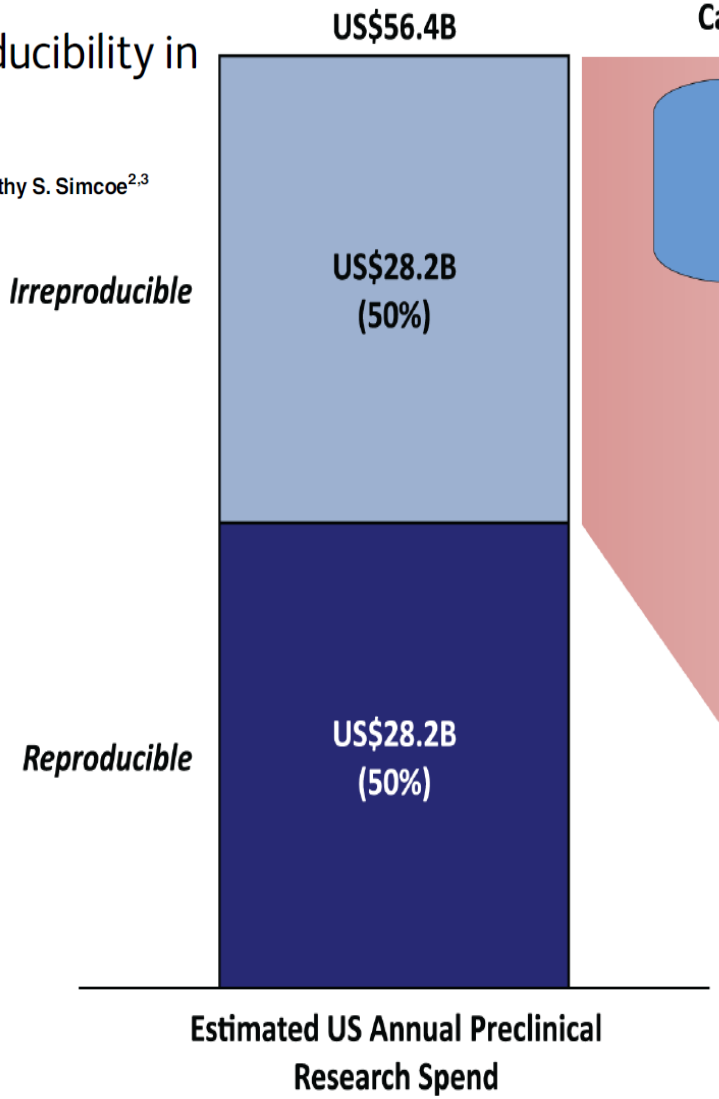
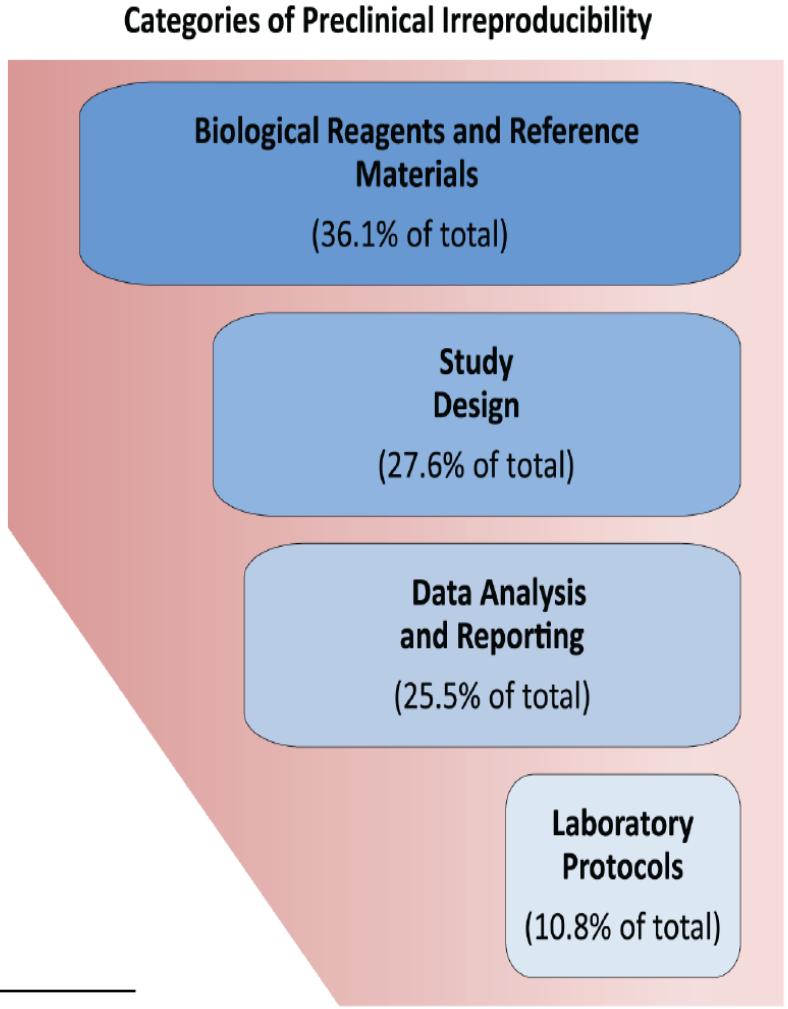
PLOS | BIOLOGY

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

- 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)

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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

Companion Diagnostics (FDA-listed 2018)

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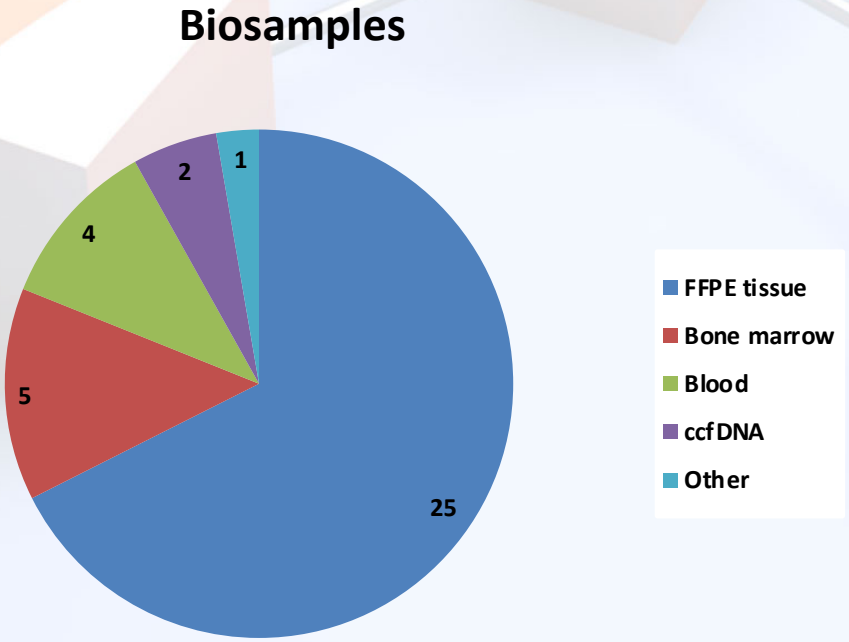

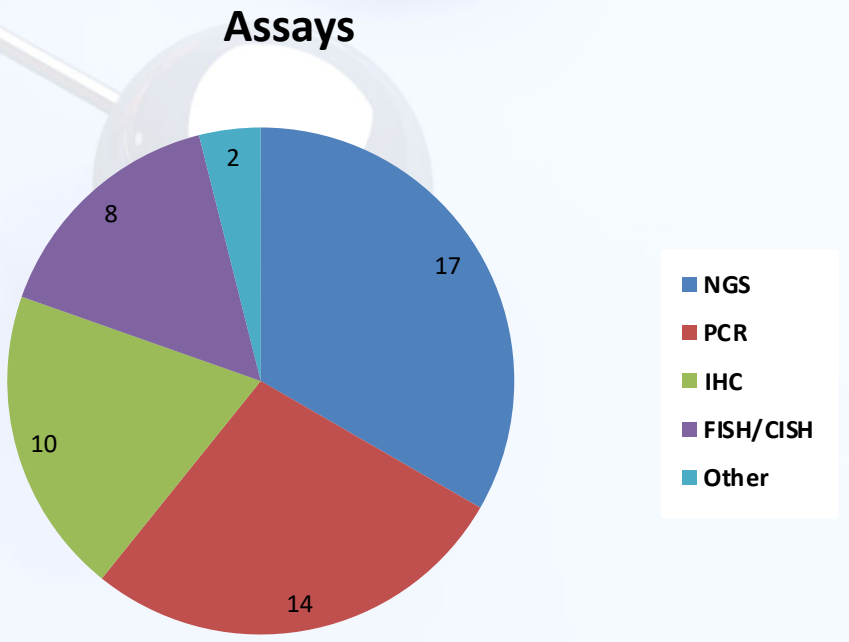

Stumptner et al. in Handbook for Biomarkers in Precision Medicine (in press)

Need for Standardization of Whole Diagnostic Workflows

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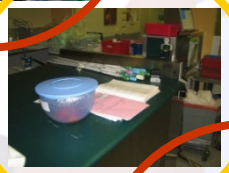
can be avoided

can be reduced

not avoidable

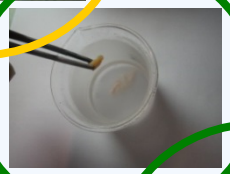
Medication
Surgical procedure
Warm ischemia



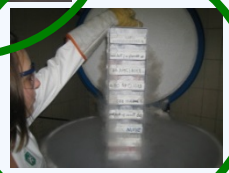
Transport
Temperature
Cold ischemia

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

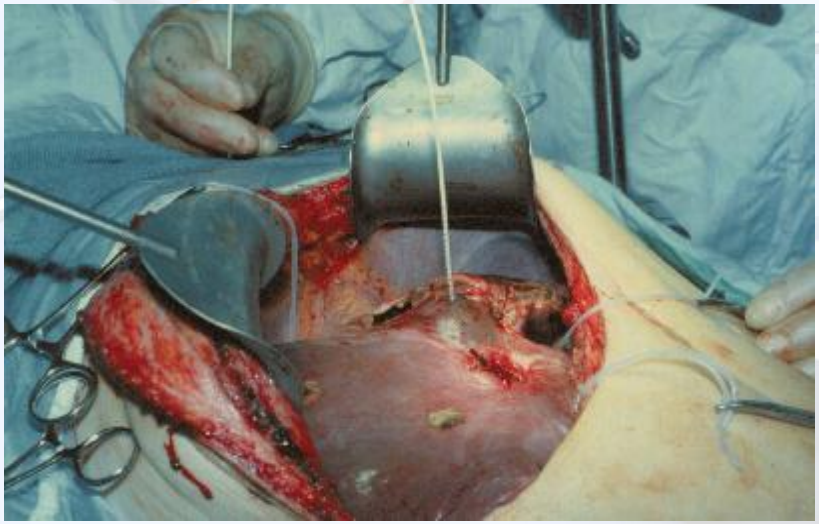
Sample preparation

Analysis

SPIDIA

Example: Role of Pre-analytics

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

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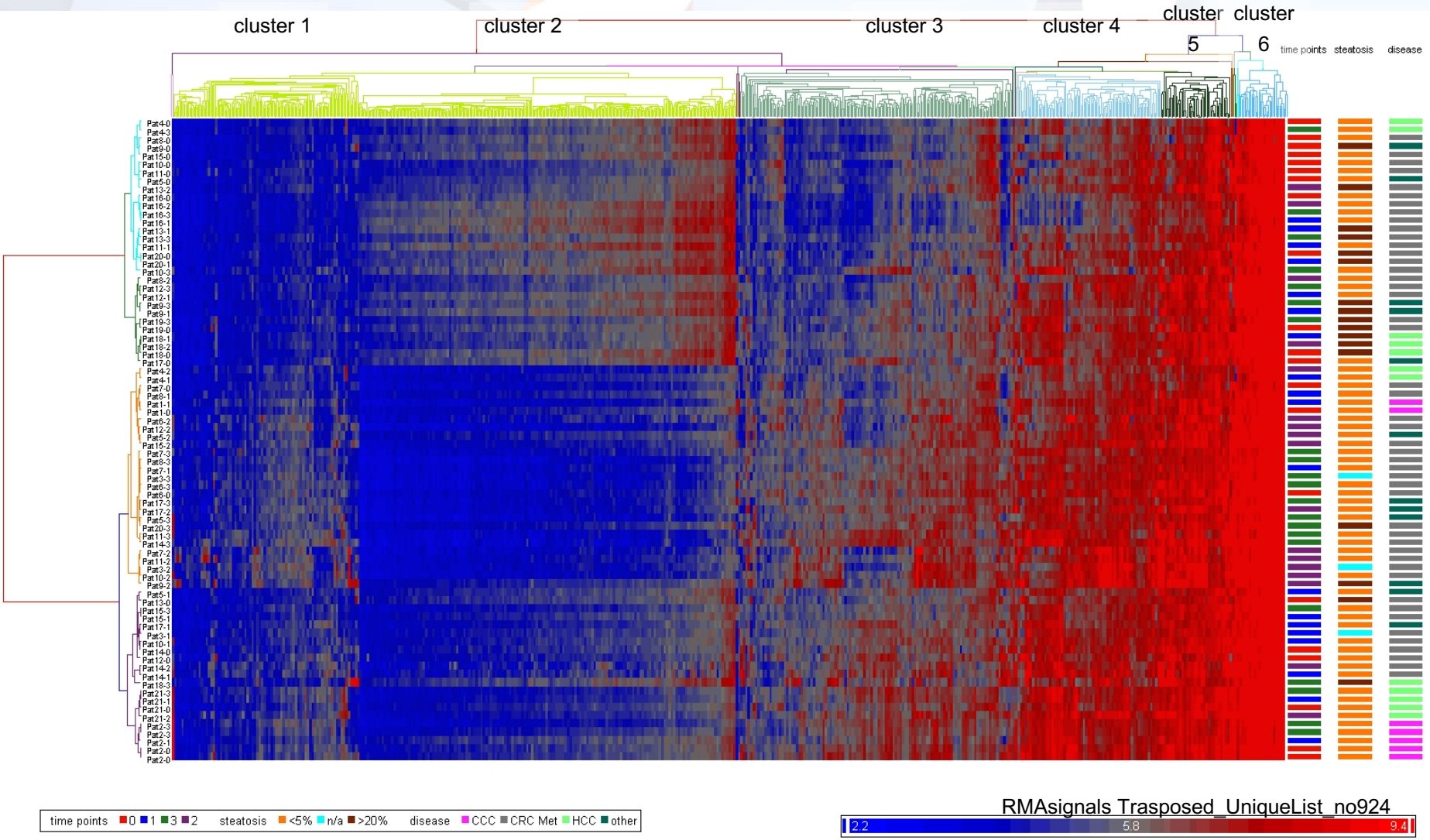
Affymerix HG-U219



FC1,5_p0,05 924 genes

Alterations in Gene Expression are an Active Respose

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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

Tissue Quality Marker (qRT-PCR Verification)

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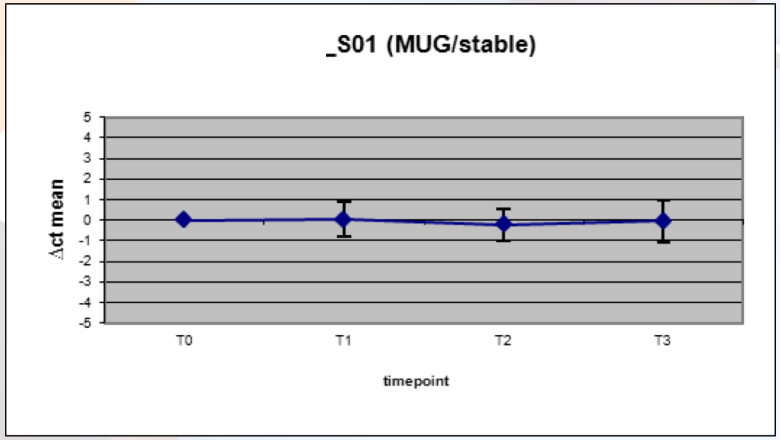
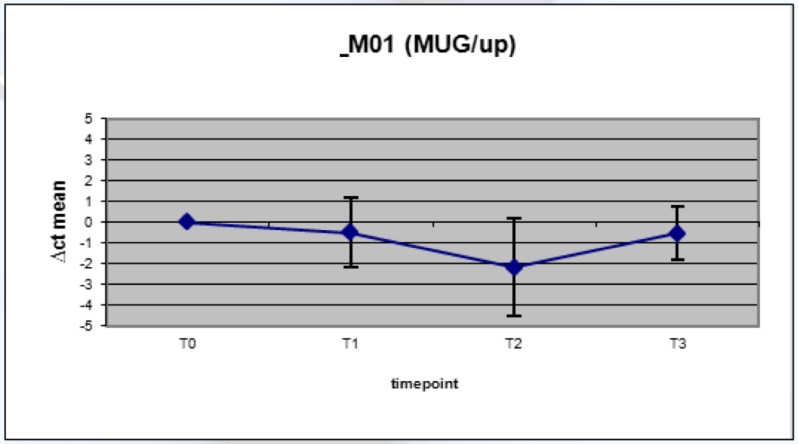
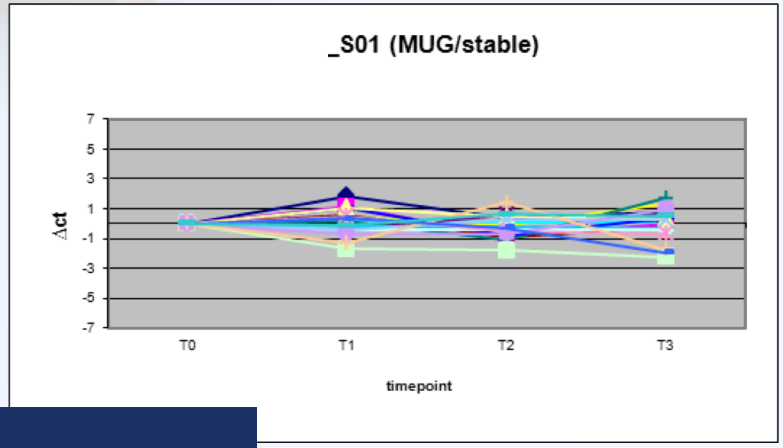
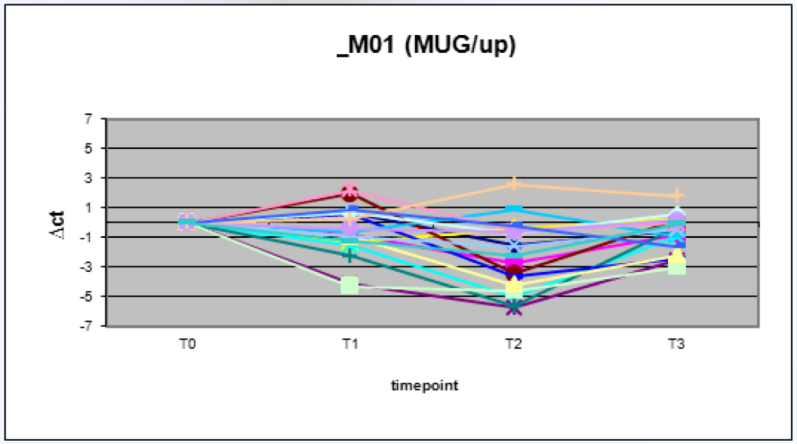
stable

unstable









128-fold individual variation

Sample Quality: a Legal Requirement

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EN Official Journal of the European Union

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

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

Roadblocks for Improving Pre-analytics

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A classical change management issue

- New standards do not fit with current processes
- Additional costs
- Unknown risks in regulatory affairs

Roadblocks for Improving Pre-analytics

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A classical change management issue

- New standards do not fit with current processes
- Additional costs
- Unknown risks in regulatory affairs

→ Improving health outcomes

BBMRI-ERIC's Role and Contribution

- Proactive role in standard development
  - Member of SPIDA4P, ASI, CEN, ISO, standard project leader
- Raising awareness at biobanks
- Developing tools (self assessment)
- Education and training programs
- Promoting biobanks to provide access to quality-defined samples meeting requirements of ISO standards and IVDR
- Raising awareness at user side
  - Academia, industry, health care

Thank You for Your Attention

Medizinische Universität Graz

SPIDIA4P

Grant agreement no. 733112

SPIDIA

Grant agreement no. 222916

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Biobanking and BioMolecular Resources Research Infrastructure

ADOPT BBMRI-ERIC
gateway for health

Grant agreement no. 676550

BioBank GRAZ

Bridging the gap ... CORBEL

QIAGEN

B3 Africa
BRIDGING BIOBANKING AND BIOMEDICAL RESEARCH ACROSS EUROPE AND AFRICA

Christian Doppler Forschungsgesellschaft

BBMRI.AT
Biobanking and BioMolecular Resources Research Infrastructure Austria

CBmed
BIOMARKER RESEARCH

GEN-AU
GENOMFORSCHUNG IN ÖSTERREICH

CAPACITIES

BBMRI GA Nr. 212111
1.2.2008-30.04.2010

European Commission

bbmri-lpc
BBMRI – Large Prospective Cohorts

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