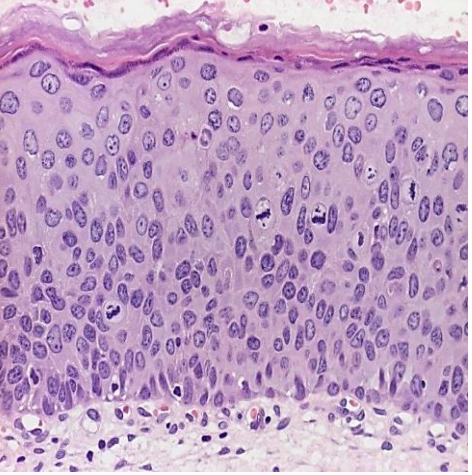
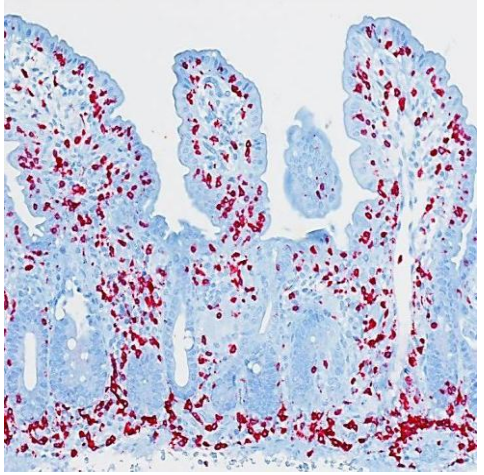
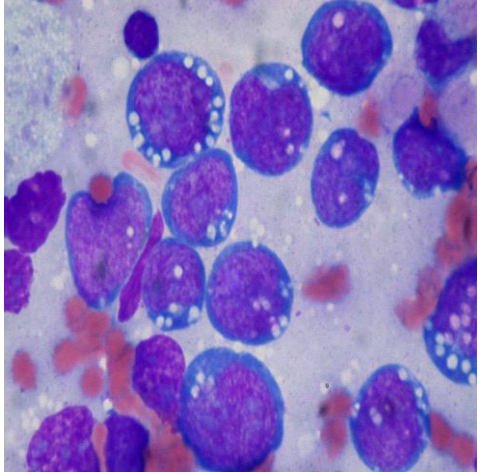
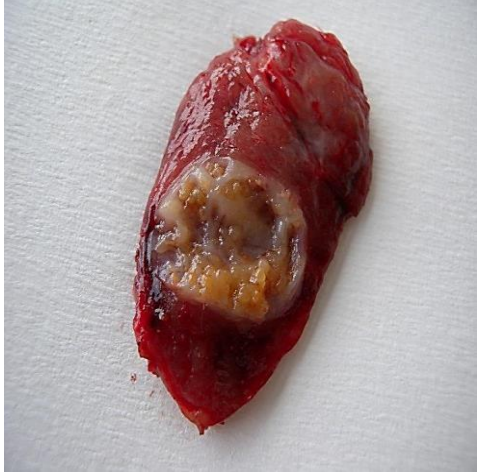
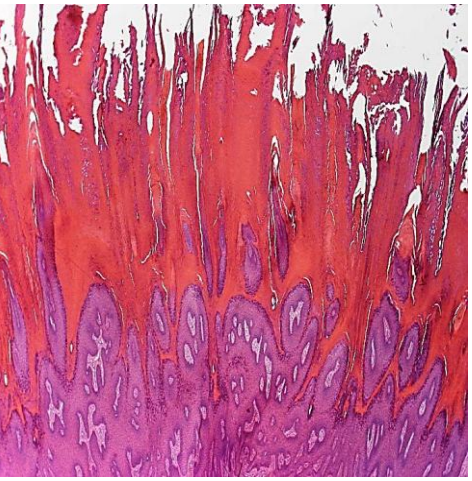
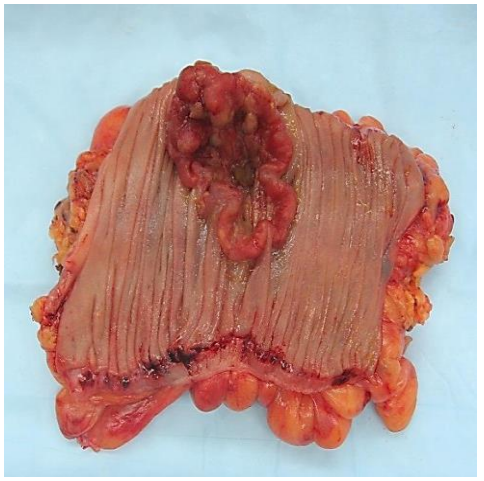
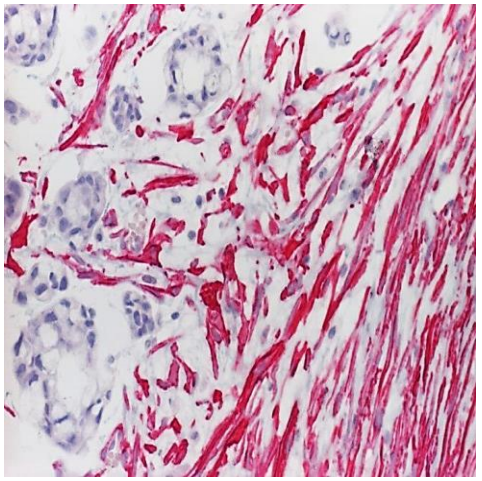
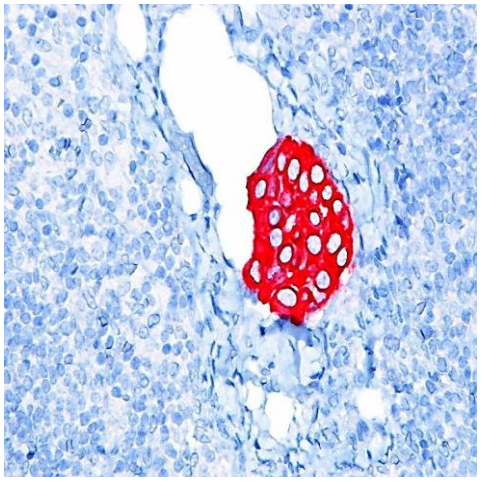
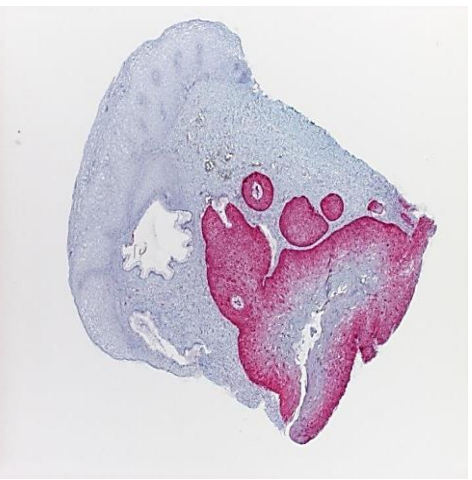
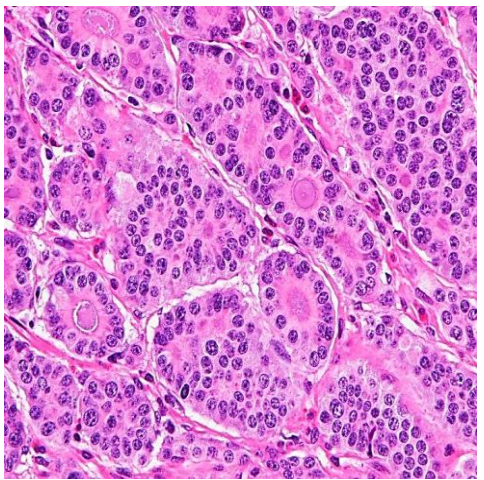
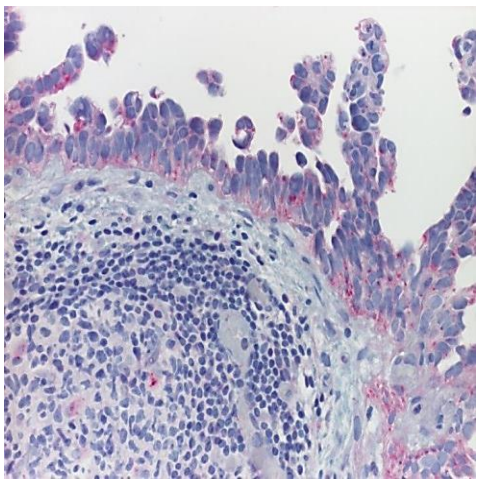
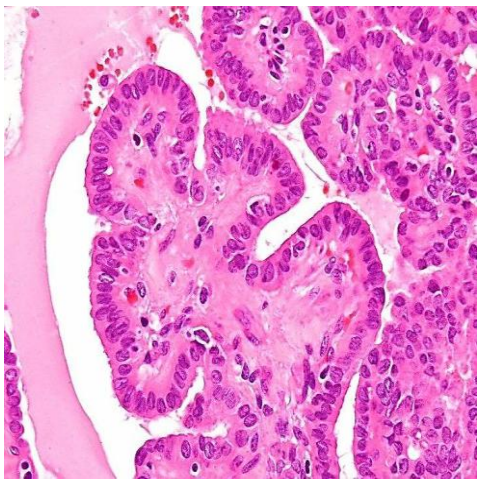

Molecular Med TRI-CON 2014

Driving Change and Shaping the Future of Medicine

February 9-14, 2014
Moscone North Convention Center
San Francisco, CA

Second Annual

Next Generation Pathology

New Perspective on Tissue: Converting Complexion into Action

Day 1 | **Day 2** | **Download Brochure** | **View TRICON Attendees**

Pathology studies structural and functional mechanisms of disease, making it the cornerstone of medical science. An array of innovative technologies is rapidly transforming the field of pathology and tissue analysis. Alongside these technological advances, we are also witnessing an expansion in pathology applications, both in the pharmaceutical industry and in the clinic. The second annual **Next Generation Pathology** symposium is designed to bring together pathologists and tissue analysis specialists working in the industry as well as in healthcare settings. The program will present solutions and case studies for various tissue analysis applications and will feature a broad array of novel technologies.

Monday, February 11

7:30 am Registration and Morning Coffee
8:25 Chairperson's Opening Remarks
Michael Roehrl, M.D., Ph.D., Associate Professor of Pathology, University of Toronto

NEXT GENERATION BIOSPECIMEN SCIENCE

8:30 Next Generation Biospecimen Sciences: Systems Pathology and Pushing the Frontier of Personalized Clinical Trials
Michael Roehrl, M.D., Ph.D., Associate Professor of Pathology, University of Toronto

2014 Brochure

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Quanterix

Molekularpathologie...

- Proteine (IHC): TTF-1, GATA3, CDX2, p53...
- Genamplifikationen: HER2
- Gentranslokationen: ALK-1, c-myc...
- Genmutationen: KRAS, BRAF...
- Genexpression: Mammaprint, Endopredict
- Gen-Methylierung: MLH-1
- Protein-Profiling (Proteomics): Melanom

Molekularpathologie
Technologische Revolution

Neues Verständnis der Tumorbiologie

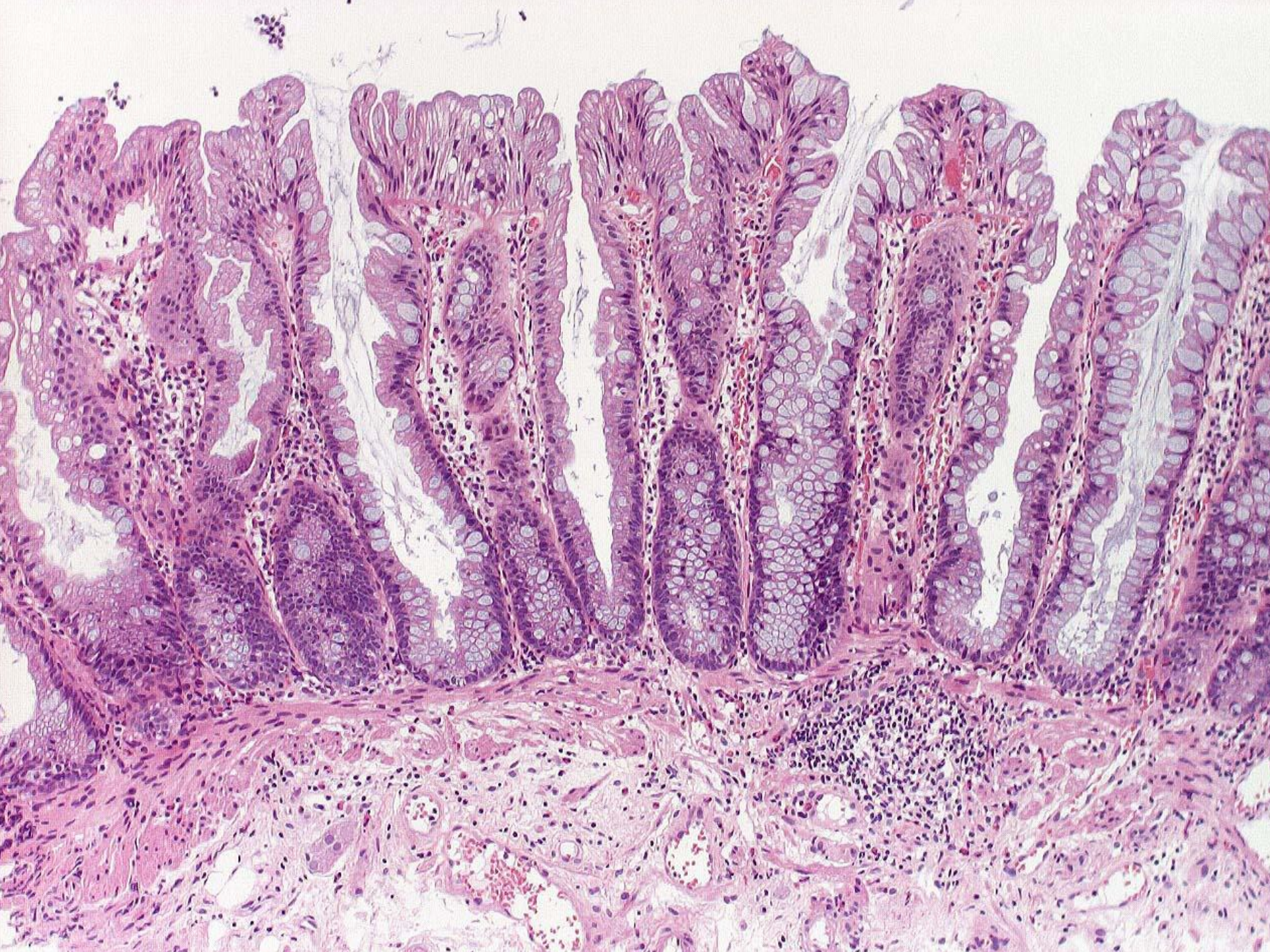
Neue Tumorklassifikationen

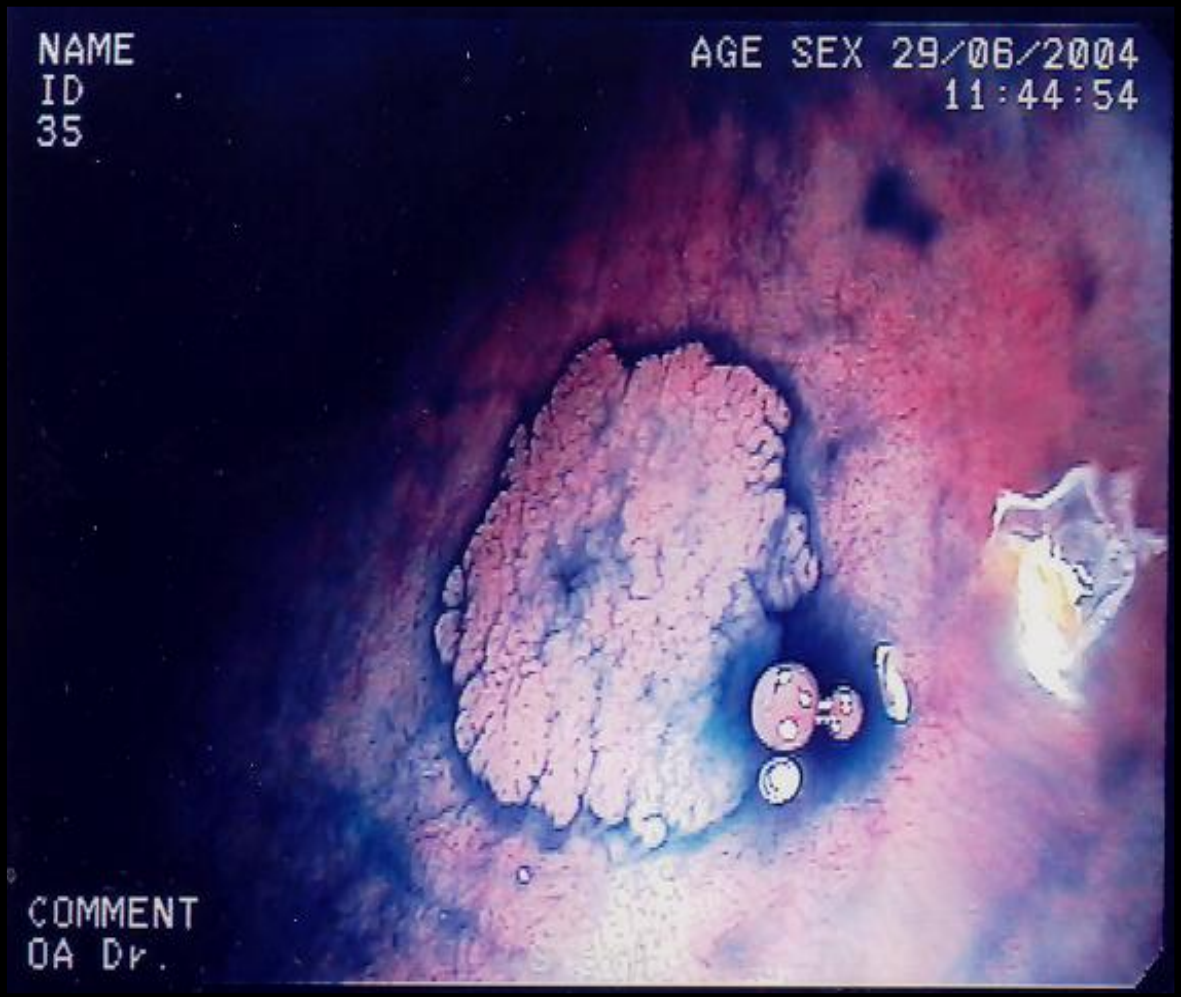
Neue Methoden der Tumordiagnostik

Prädiktion des Therapieansprechens

Monitoring des Therapieverlaufs

Neues Verständnis der Tumorbiologie
Neue Tumorklassifikationen

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ID
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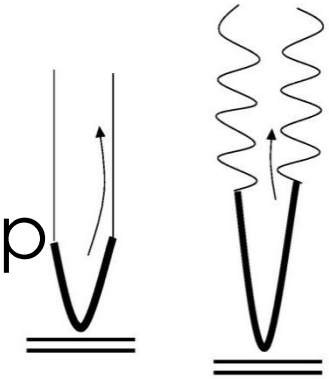
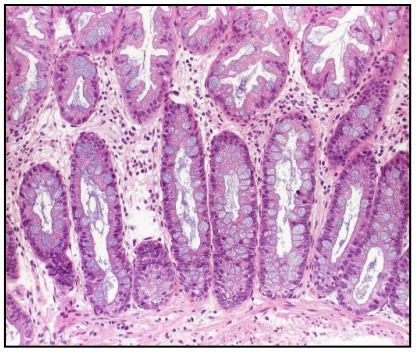
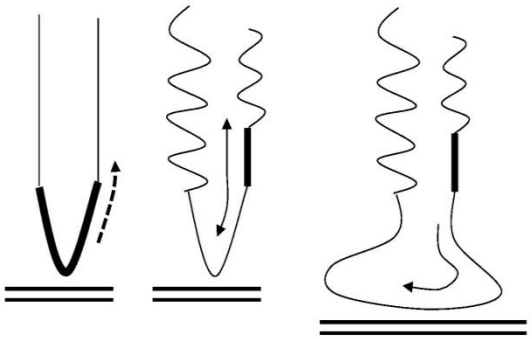
AGE SEX 29/06/2004
11:44:54
COMMENT
OA Dr.

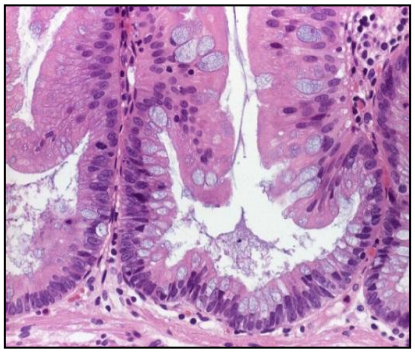
Hyperplastic polyp



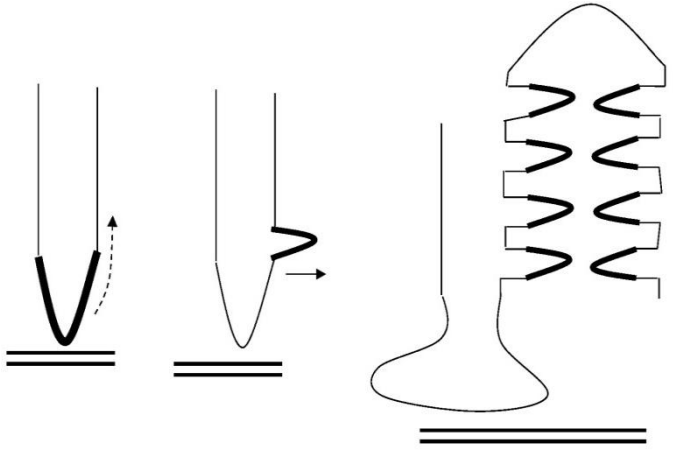


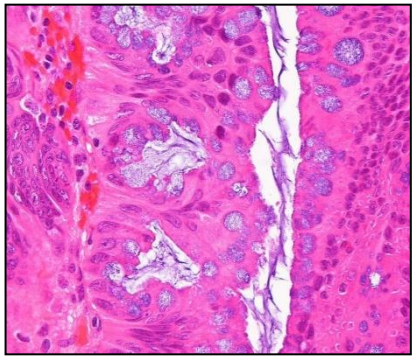
Sessile serrated adenoma



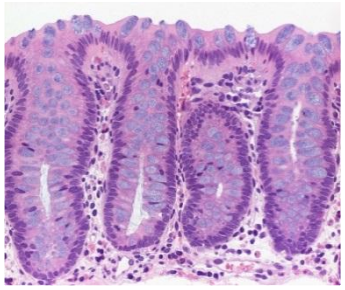


Traditional serrated adenoma





Snover et al. 2011

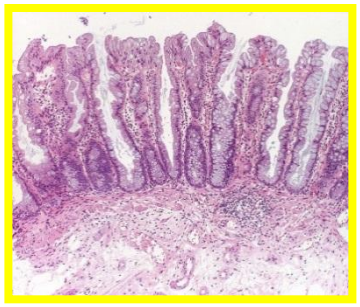


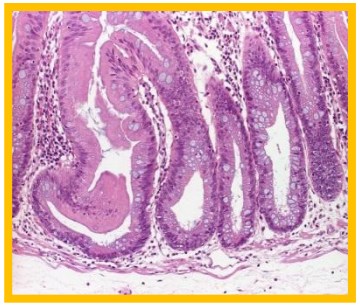
BRAF mutation+/-
methylation

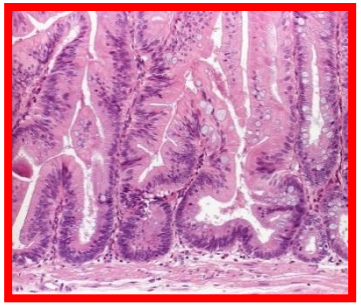
Methylation?

Methylation of
hMLH1

Mutation or
methylation of
other genes





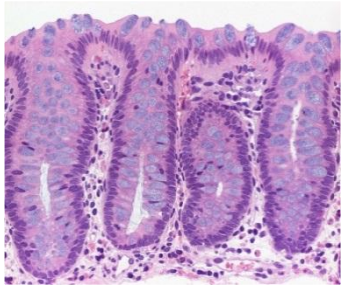


CA

HP

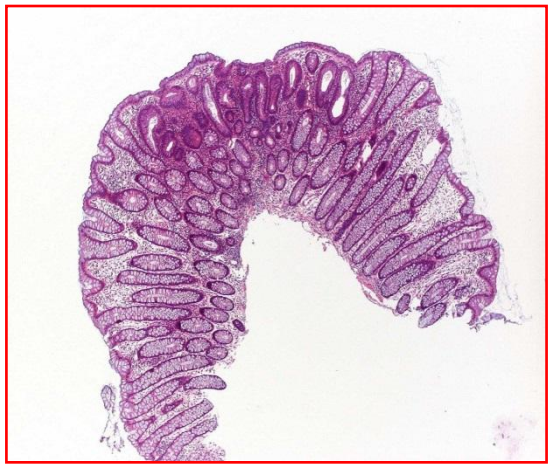
SSA

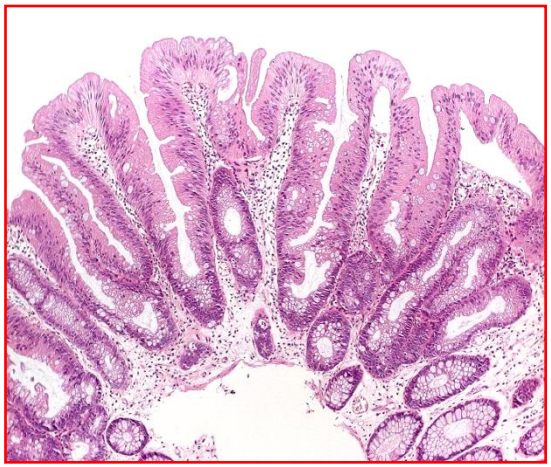
SSA with
cytological
dysplasia



BRAF mutation+/-
methylation

Snover 2011





Mutator Phenotype

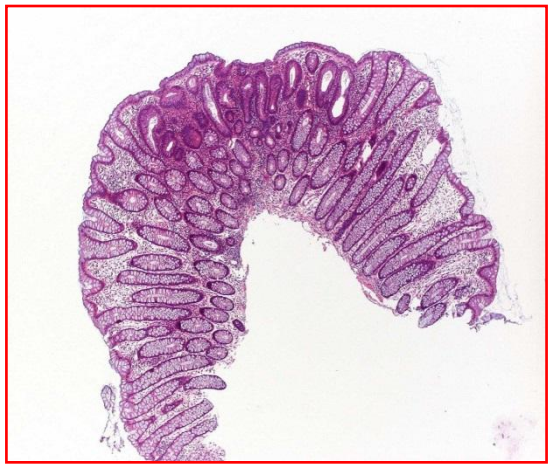
(APC, KRAS, p53)
Chromosomal Instability

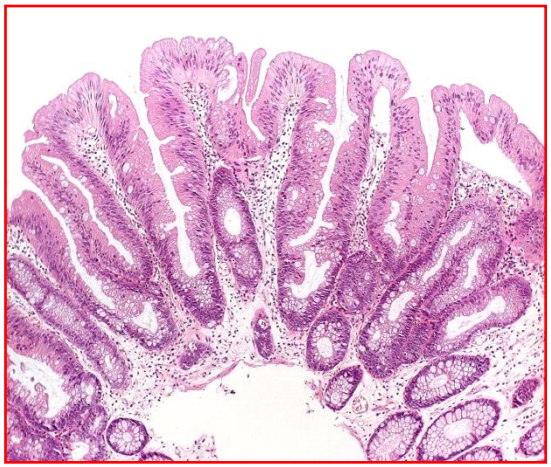
Methylator Phenotype

(BRAF, MLH1, MGMT)
Microsatellite Instability (+/-)

Genetic Instability

Colorectal Carcinoma





60%
of CRC

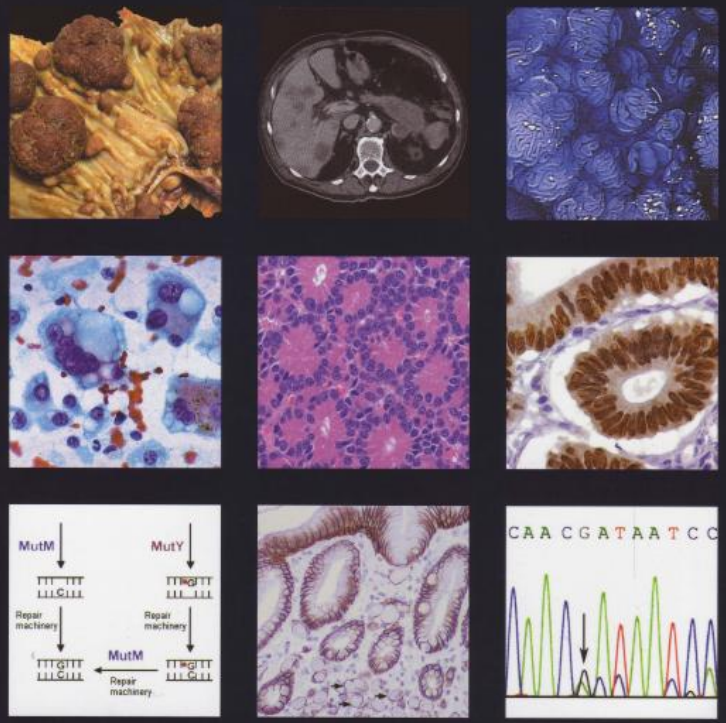
35%
of CRC

Genetic Instability

Colorectal Carcinoma

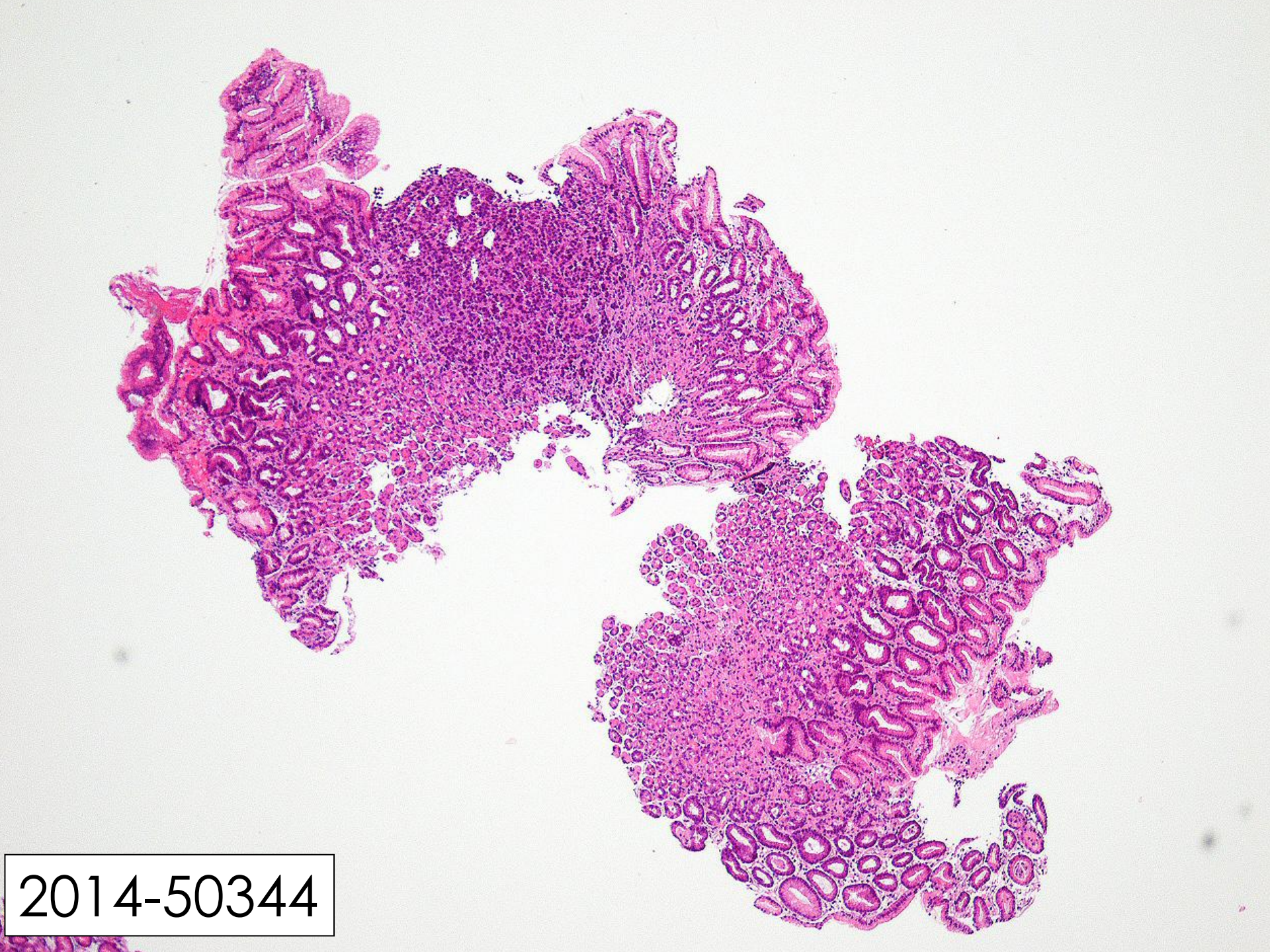
WHO Classification of Tumours of the Digestive System

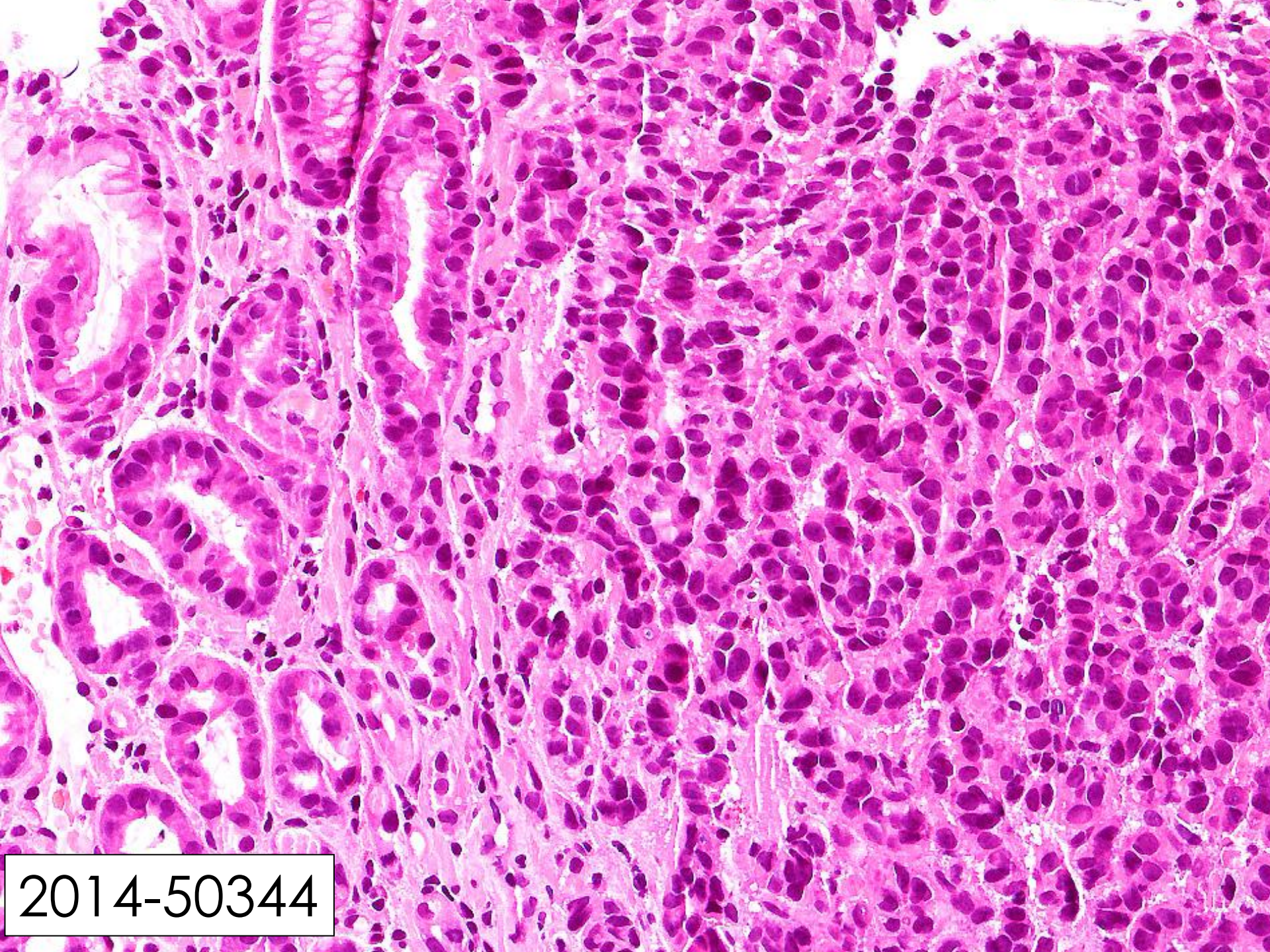
Edited by Fred T. Bosman, Fátima Carneiro, Ralph H. Hruban, Neil D. Theise



WHO

Neue Methoden der Tumordiagnostik


2014-50344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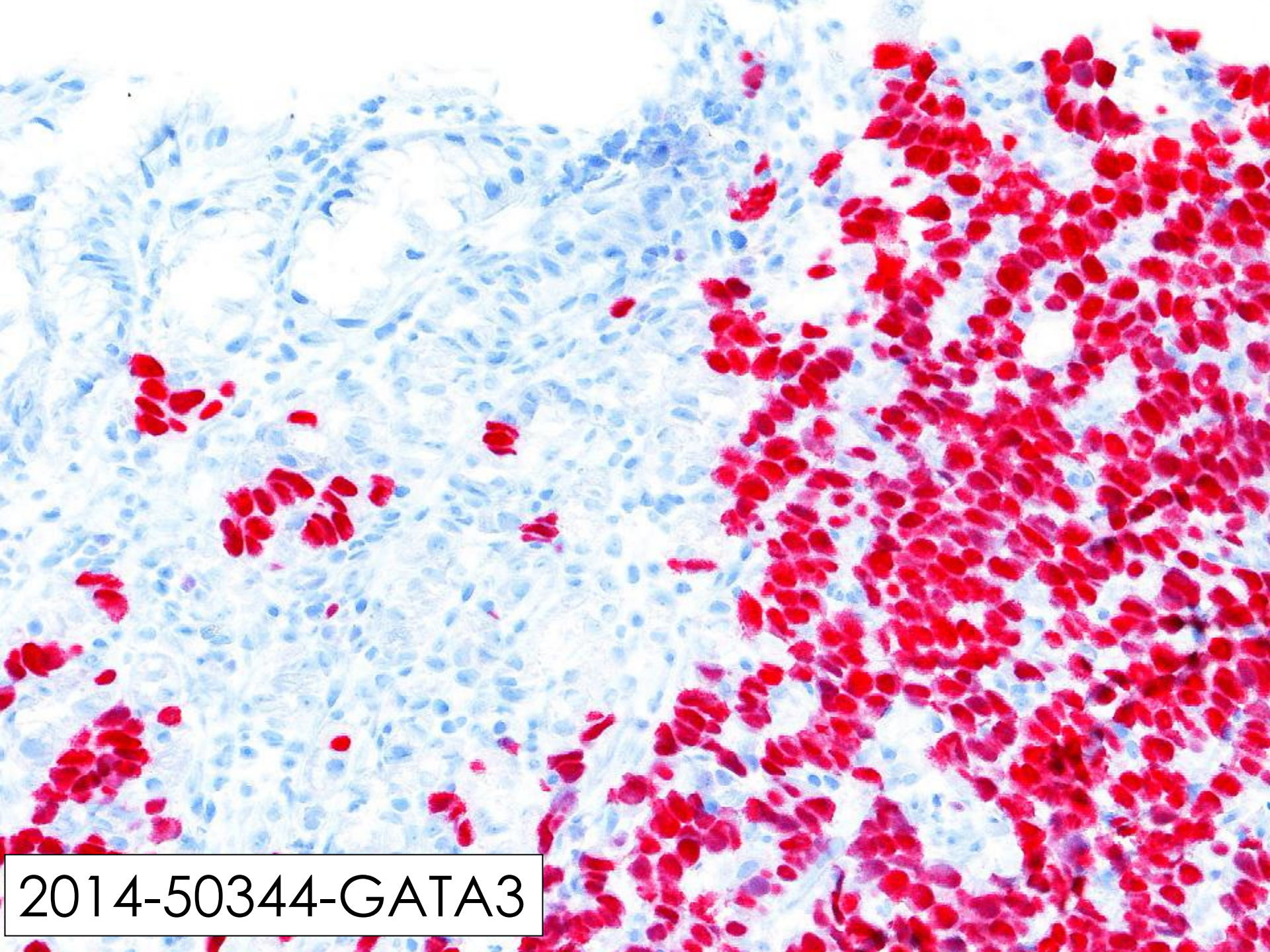
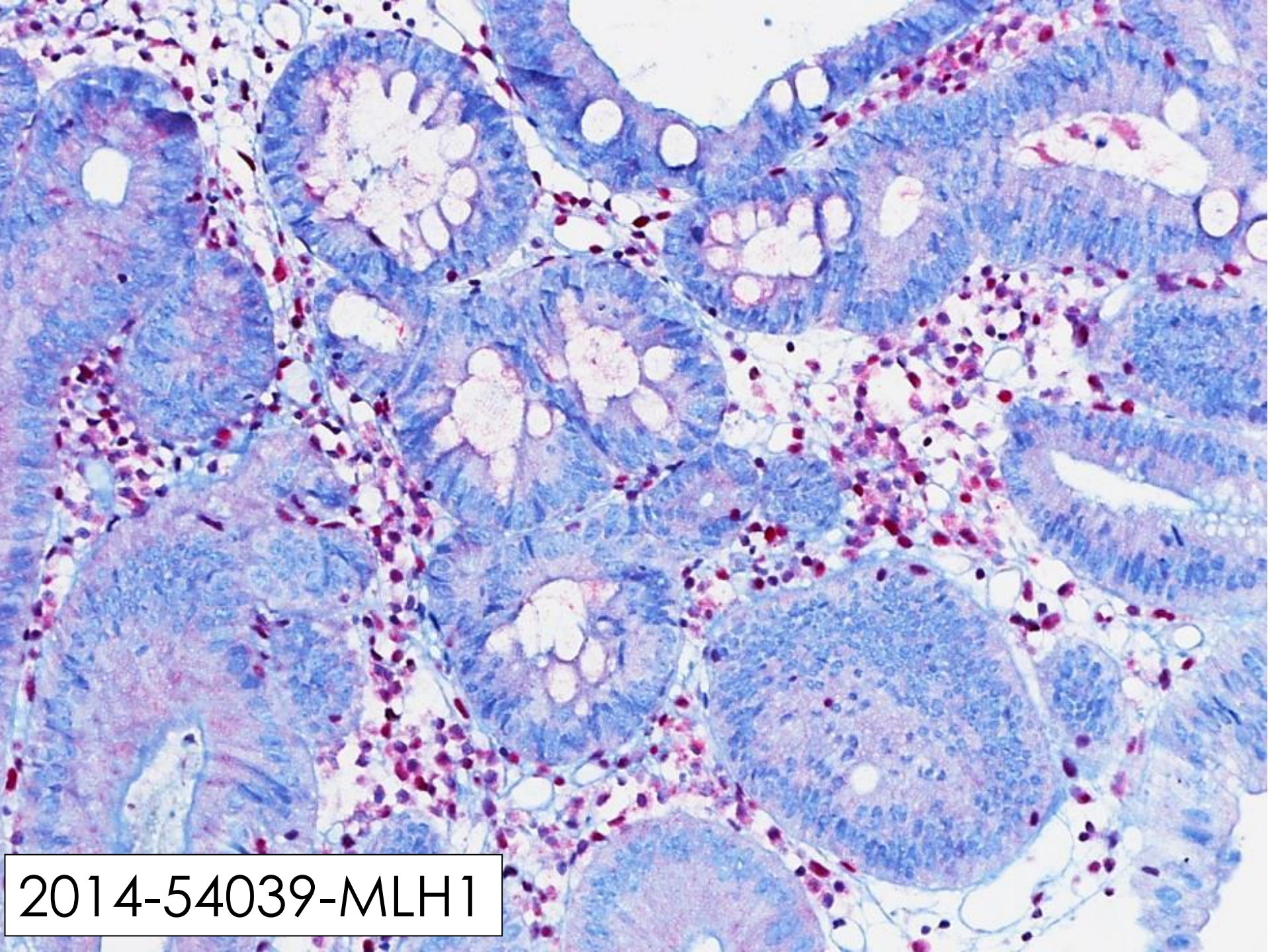
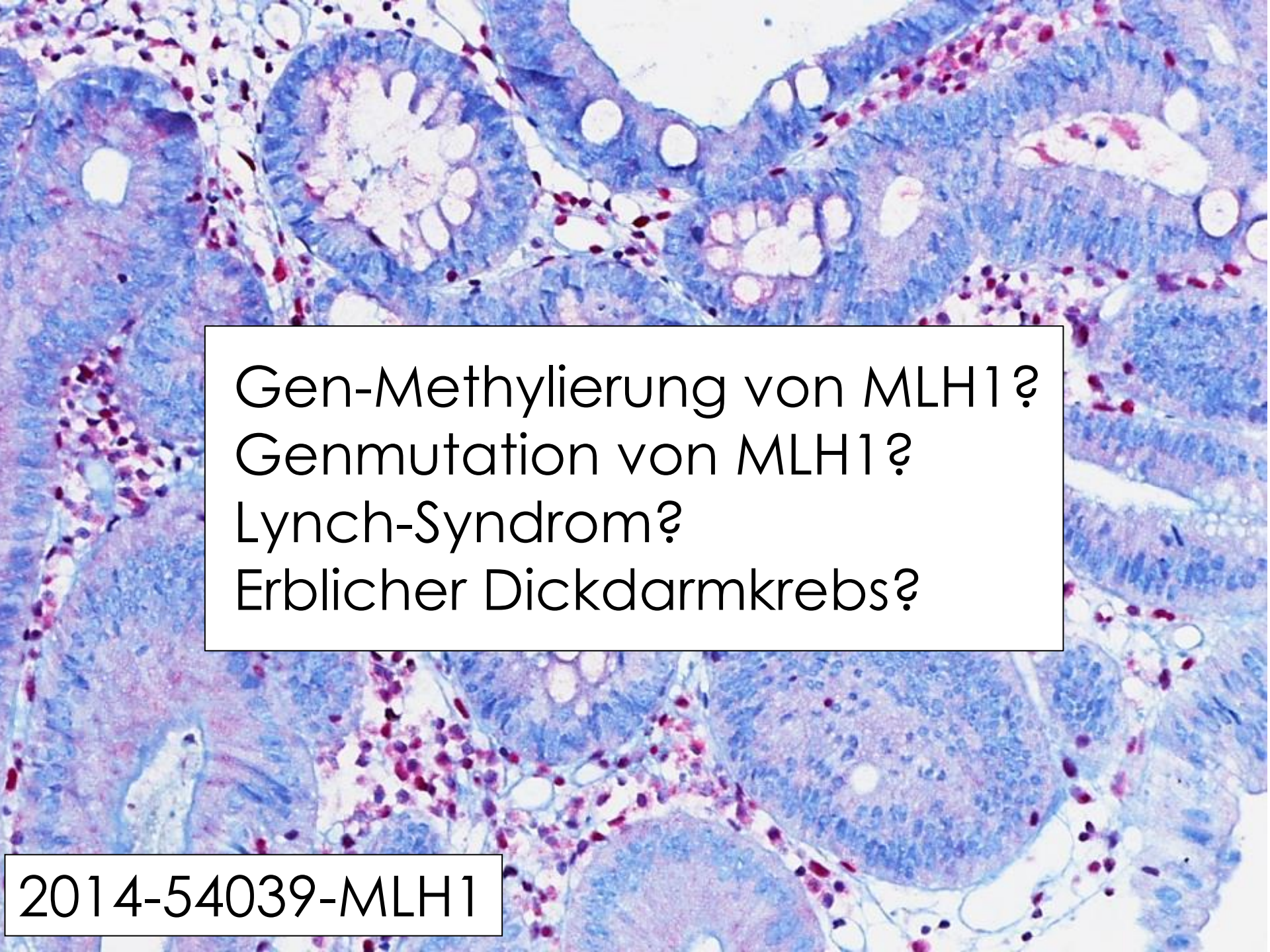

2014-50344-GATA3

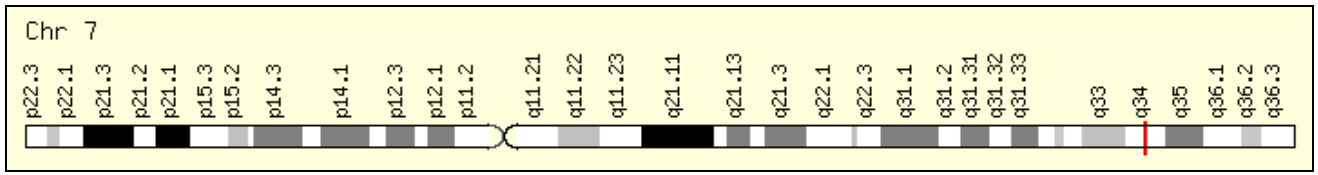
GATA3...

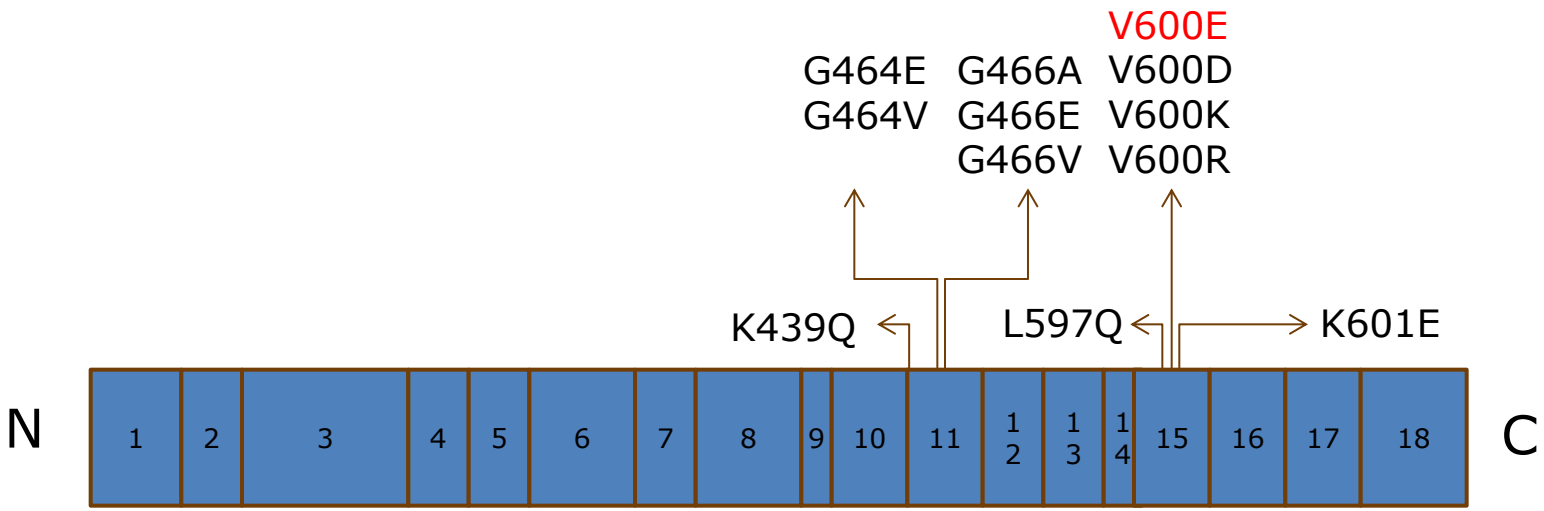
- Trans-acting T-cell specific transcription factor GATA3
- Kodiert durch GATA3 Gen
- Exprimiert in Mamma-Urothelkarzinomen
- Luminale Epithelzelldifferenzierung-Brust
- Luminal A Typ von Mammkarzinomen
- Prädictor
  - Insensitivität für Taxane
  - Insensitivität für Platin basierte Substanzen


2014-54039-MLH1


Gen-Methylierung von MLH1?
Genmutation von MLH1?
Lynch-Syndrom?
Erblicher Dickdarmkrebs?
2014-54039-MLH1

Location and mutations of the BRAF-gene





More then 60 BRAF mutations. 90% of all mutations are V600E

E-Nummer: 54039/2014 Material: Colon transversum
Teilresektion B

Histologischer Befund
Histologisch zeigt sich im Bereich des makroskopisch beschriebenen Tumors ein teils klassisches duktal kribriform strukturiertes Adenocarcinom. Zum Teil zeigt der Tumor allerdings auch eine ausgeprägte extrazelluläre Verschleimung mit flottierenden monozellulär verschleimenden Tumorzellen. Der Tumor durchbricht sämtliche Wandschichten und wächst in das pericolische Fettgewebe ein. Die untersuchten pericolischen Lymphknoten sind allseits tumorfrei.

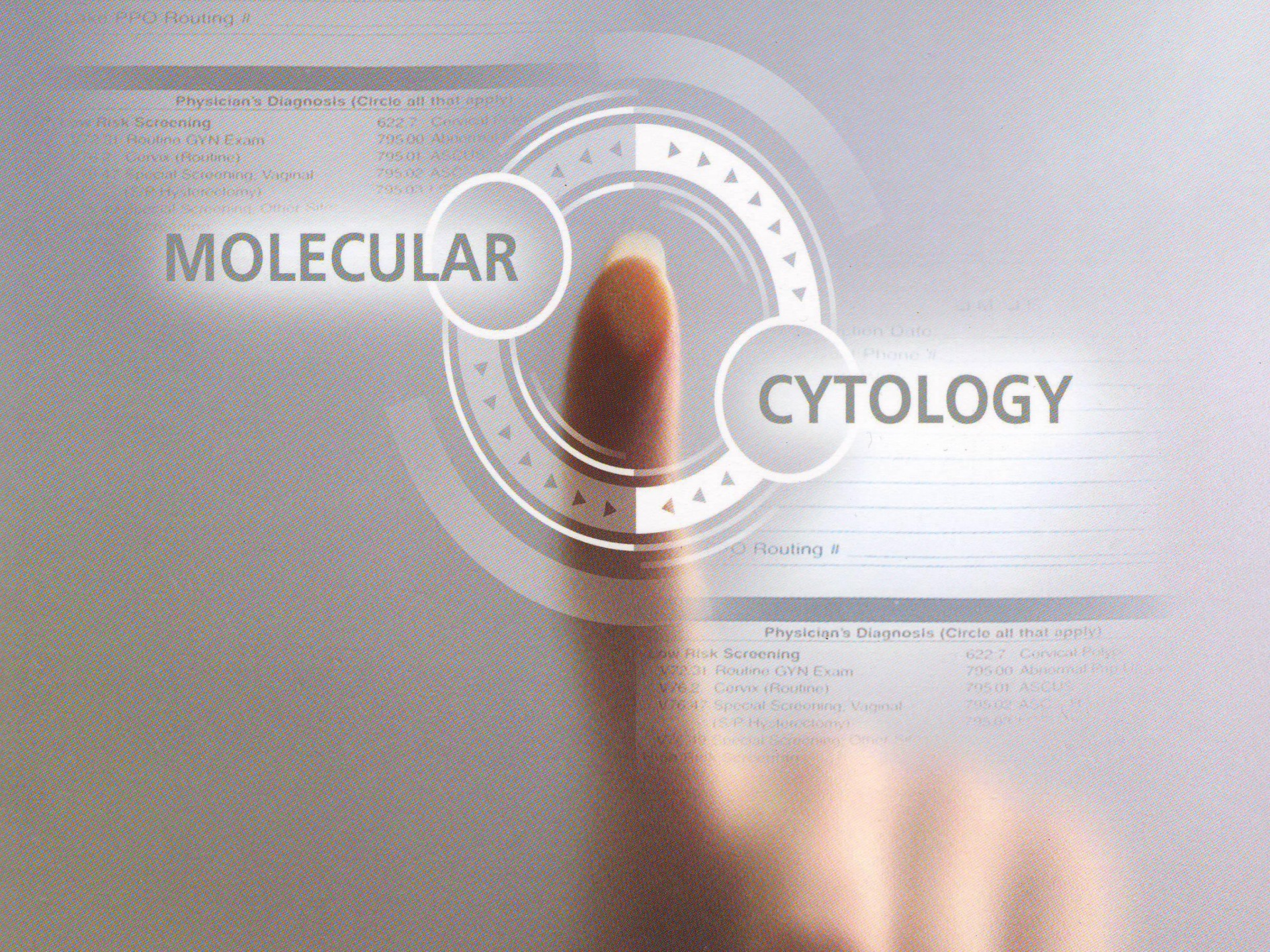
Immunhistologischer Befund
Immunhistochemisch zeigt sich ein Verlust der mismatch repair Proteins MLH-1. PMS-2, MSH-6 und MSH-2 sind erhalten.

Molekularpathologischer Befund
Molekularpathologisch wurde eine 1.17799T>A (p.V600E) - Mutation im Exon 15 Codon 600 des BRFAF-Gens nachgewiesen./c

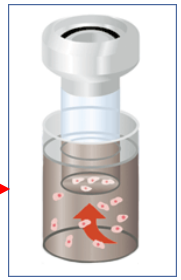
Abschlußdiagnose
Resektat des Colon transversum mit einem muzinösen Adenocarcinom des Colon.
Verlust des mismatch repair Proteins MLH-1 .
BRAF-Gen-Status: Mutation c.1799T>A (p.V600E) im Exon 15 Codon 600.
Einundzwanzig tumorfreie Lymphknoten.
pT3 **N**0 (0/21) **R**0

Kommentar
Die molekularpathologische Befundkonstellation spricht gegen das Vorliegen eines HNPCC, bzw. Lynch-Syndroms.

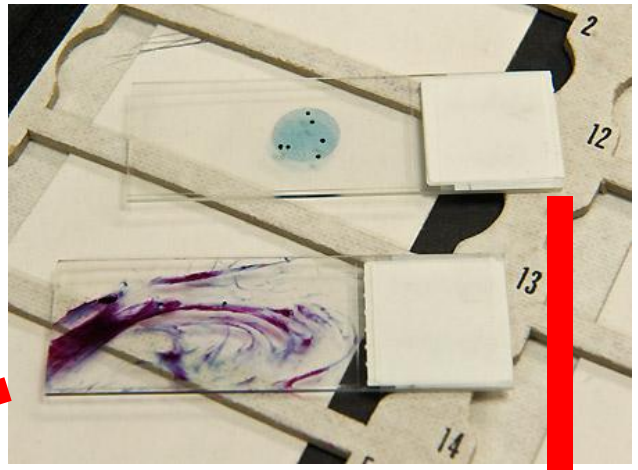
Abschlussdatum: 25.11.2014 **Befunder:** Prim. Univ.-Prof. Dr. Felix Offner
Vidit: Prim. Univ.-Prof. Dr. Felix Offner

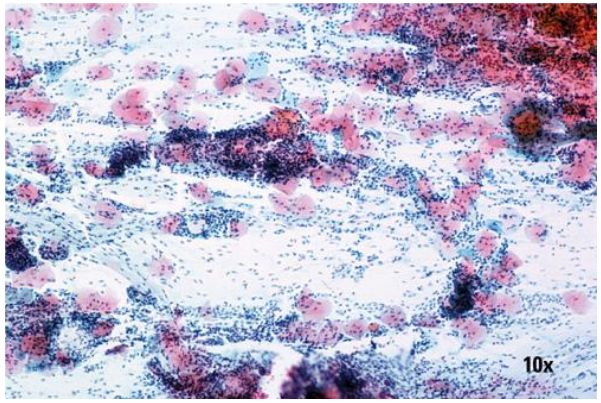

MOLECULAR
CYTOLOGY

Roboterassistierte Verarbeitung



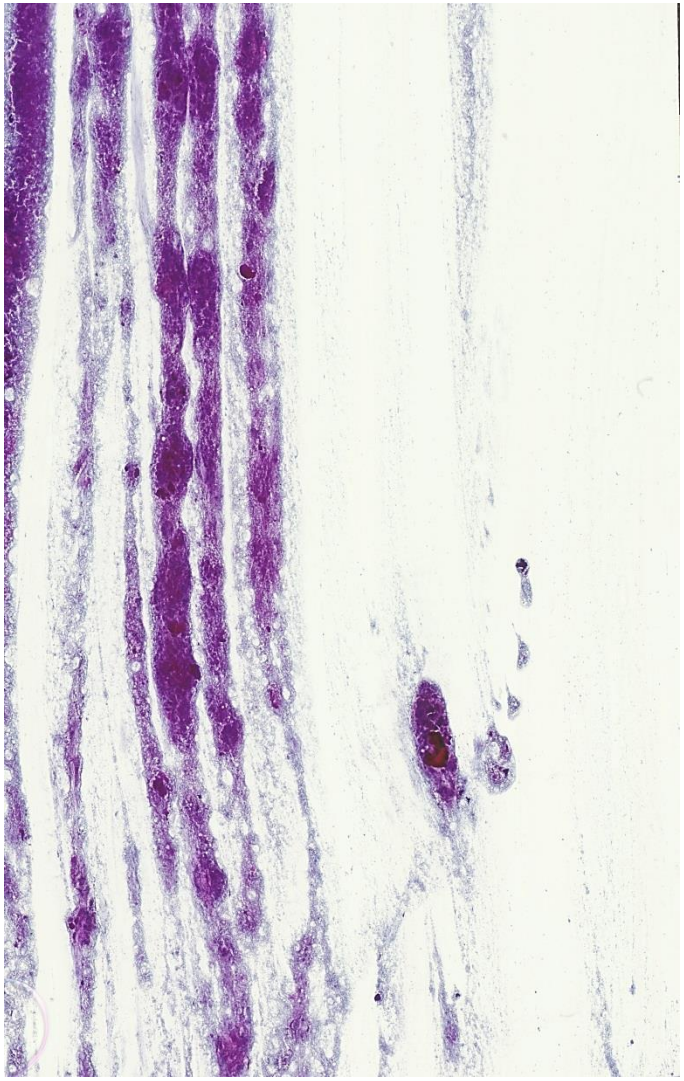
reduzierte Musterungsoberfläche



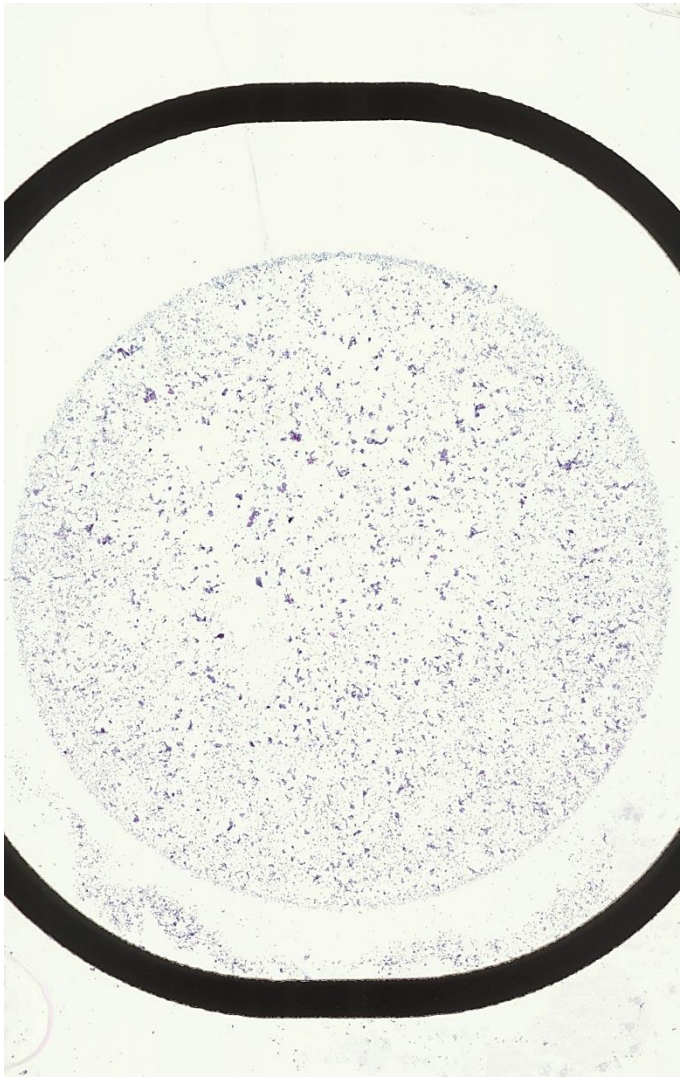


Konventionell: Überlagerungen, erschwerte Beurteilbarkeit

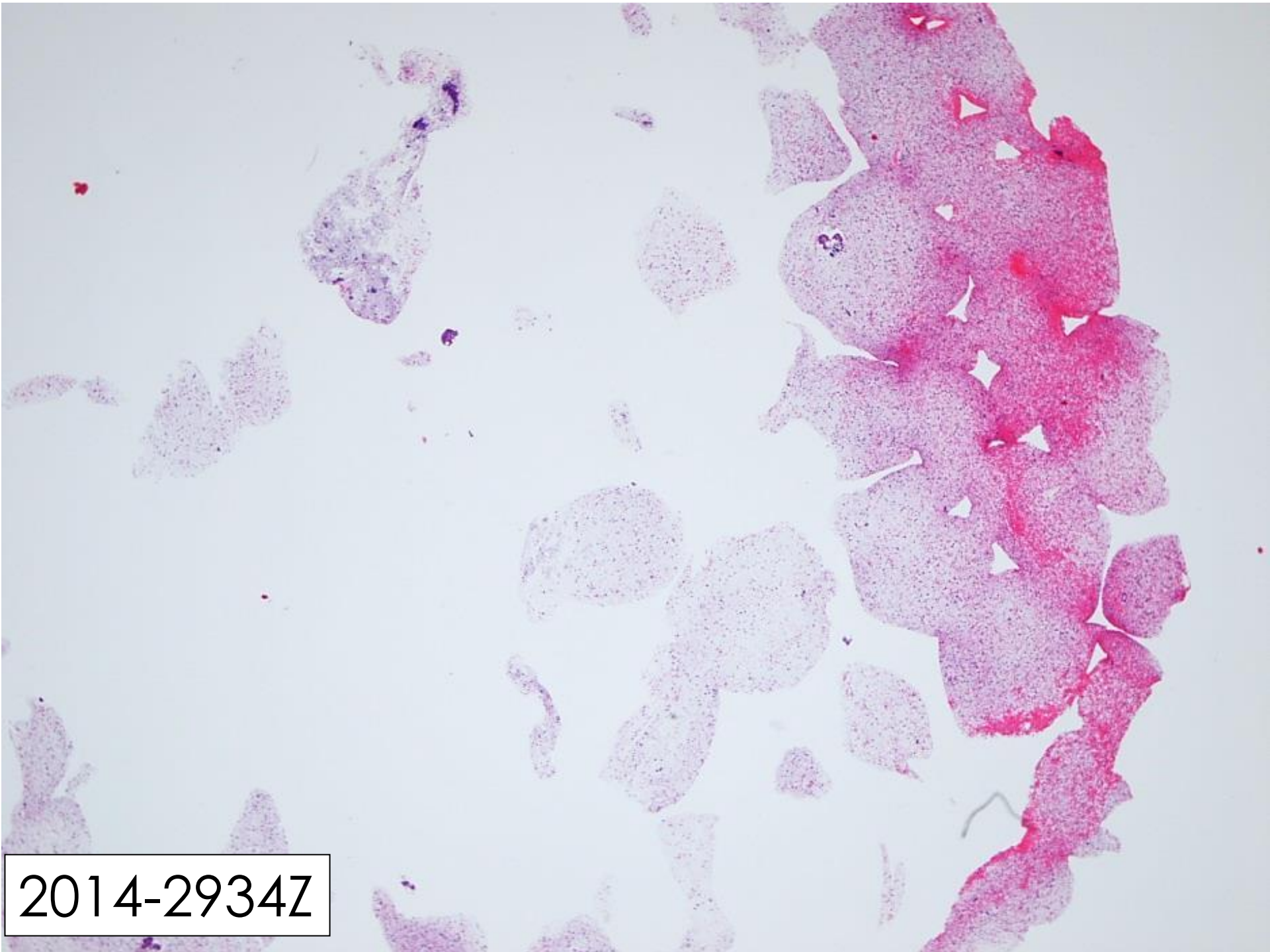
Dünnschicht: klares Bild, Möglichkeit für diagnostische Zusatztest



Konventioneller Abstrich



Liquid Cytology - Thinprep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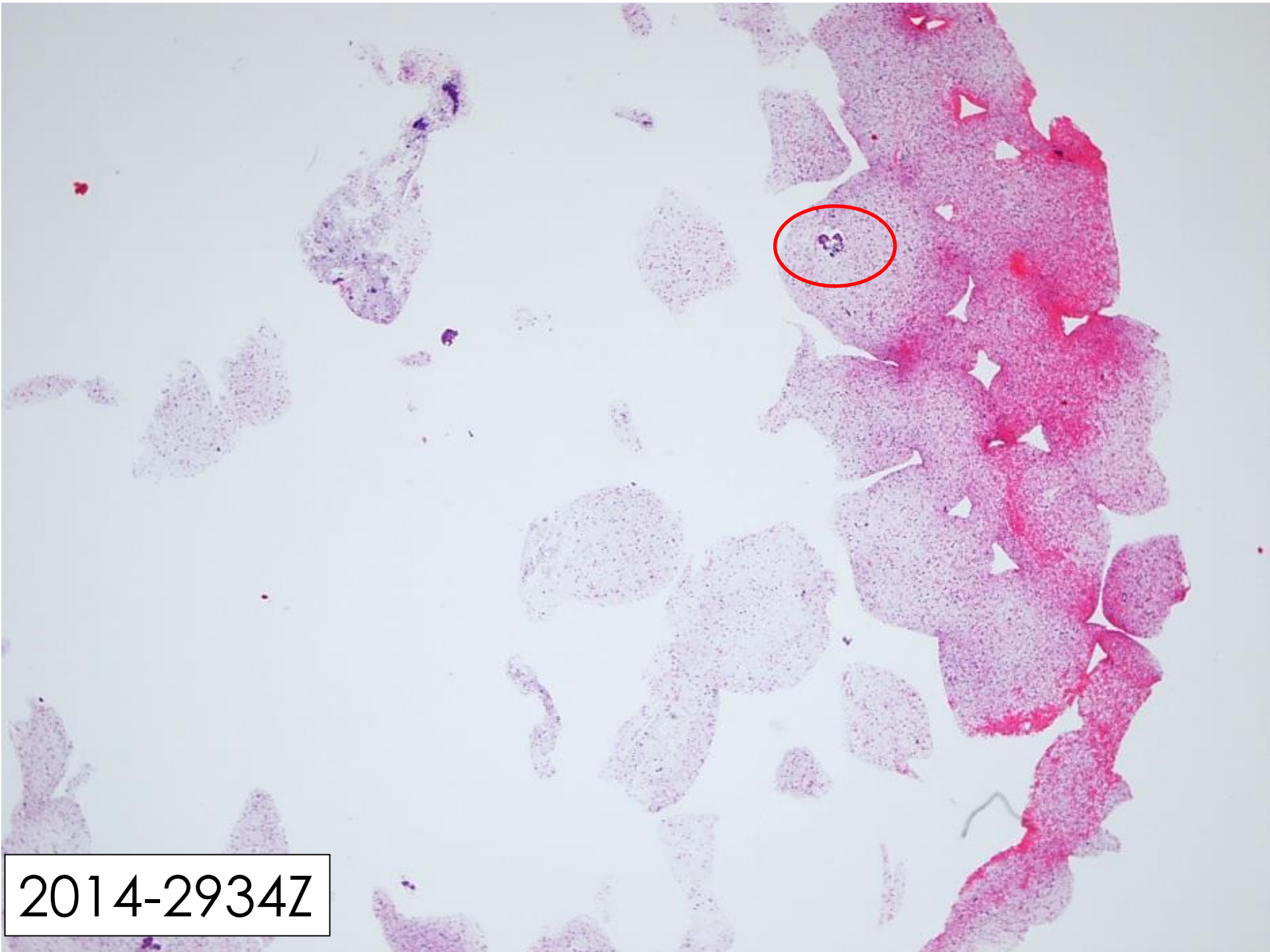
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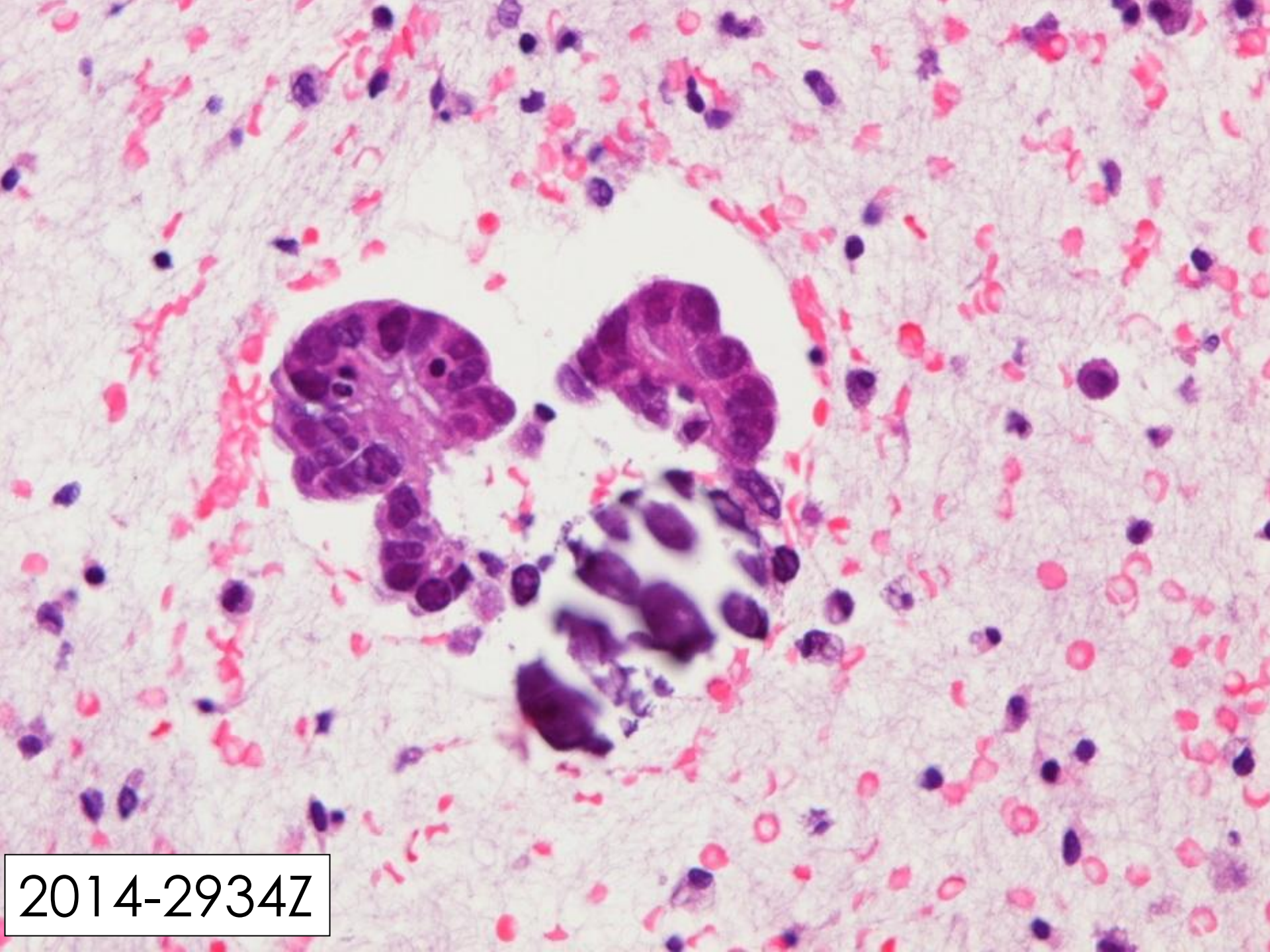
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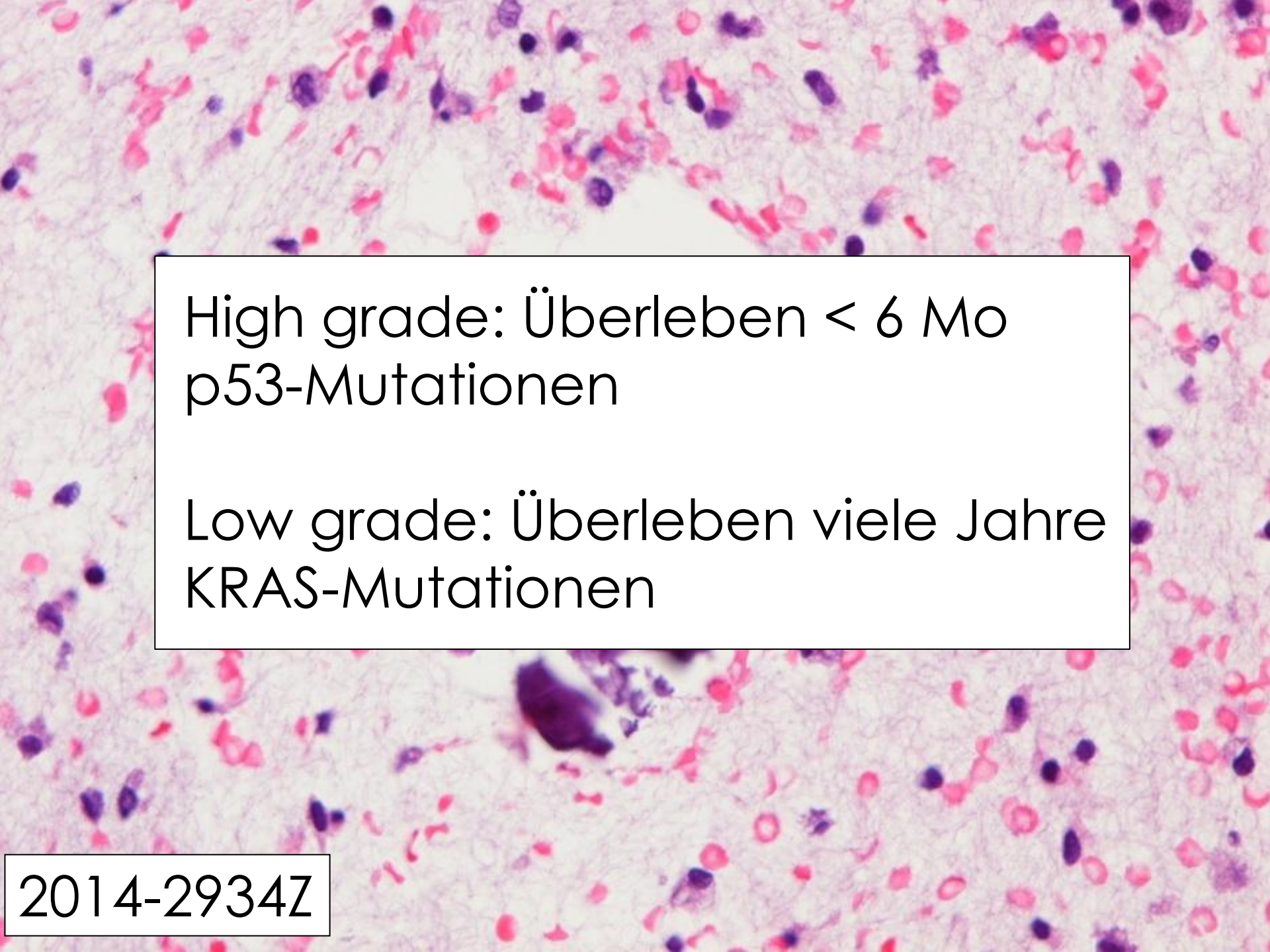
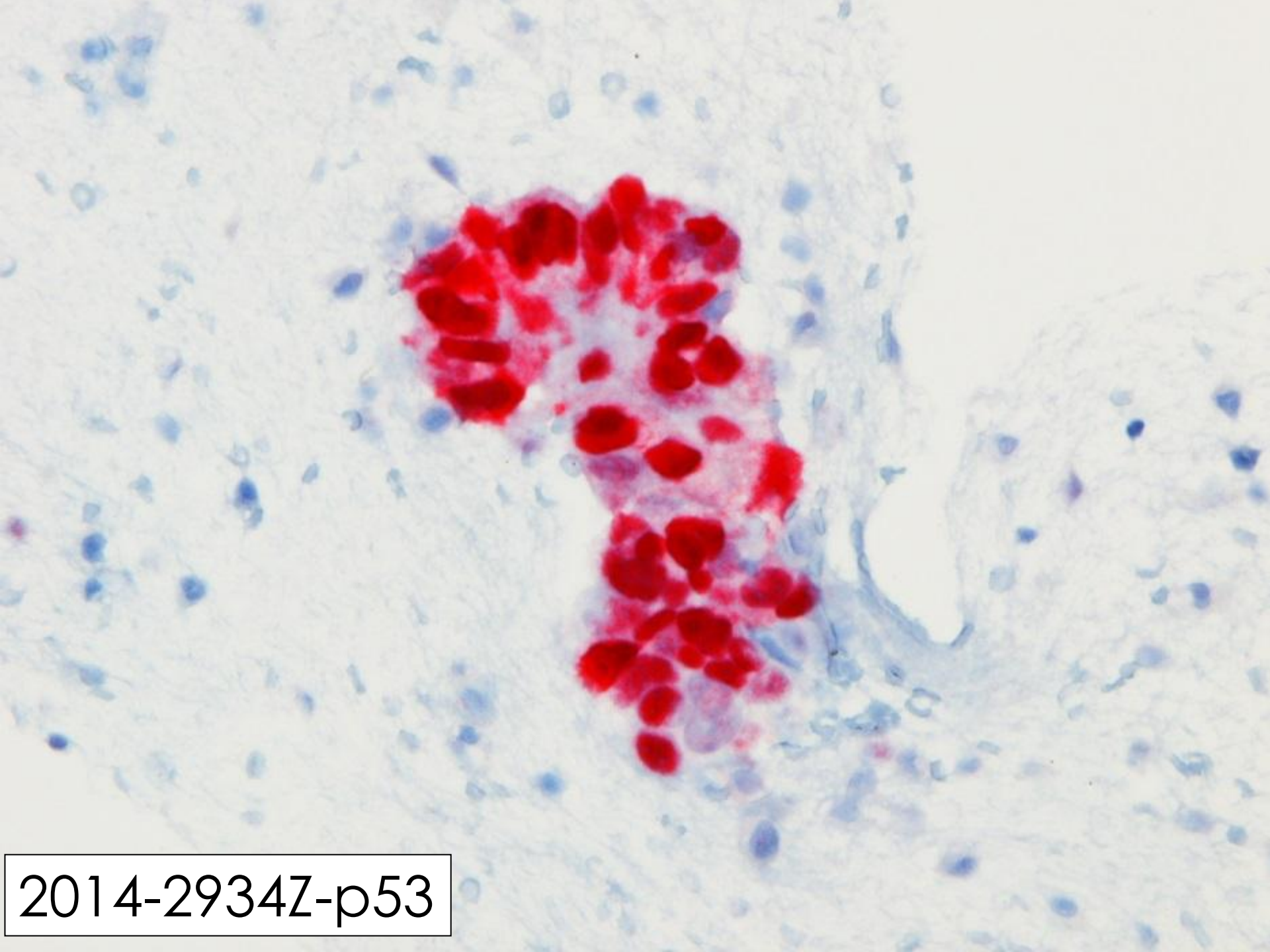
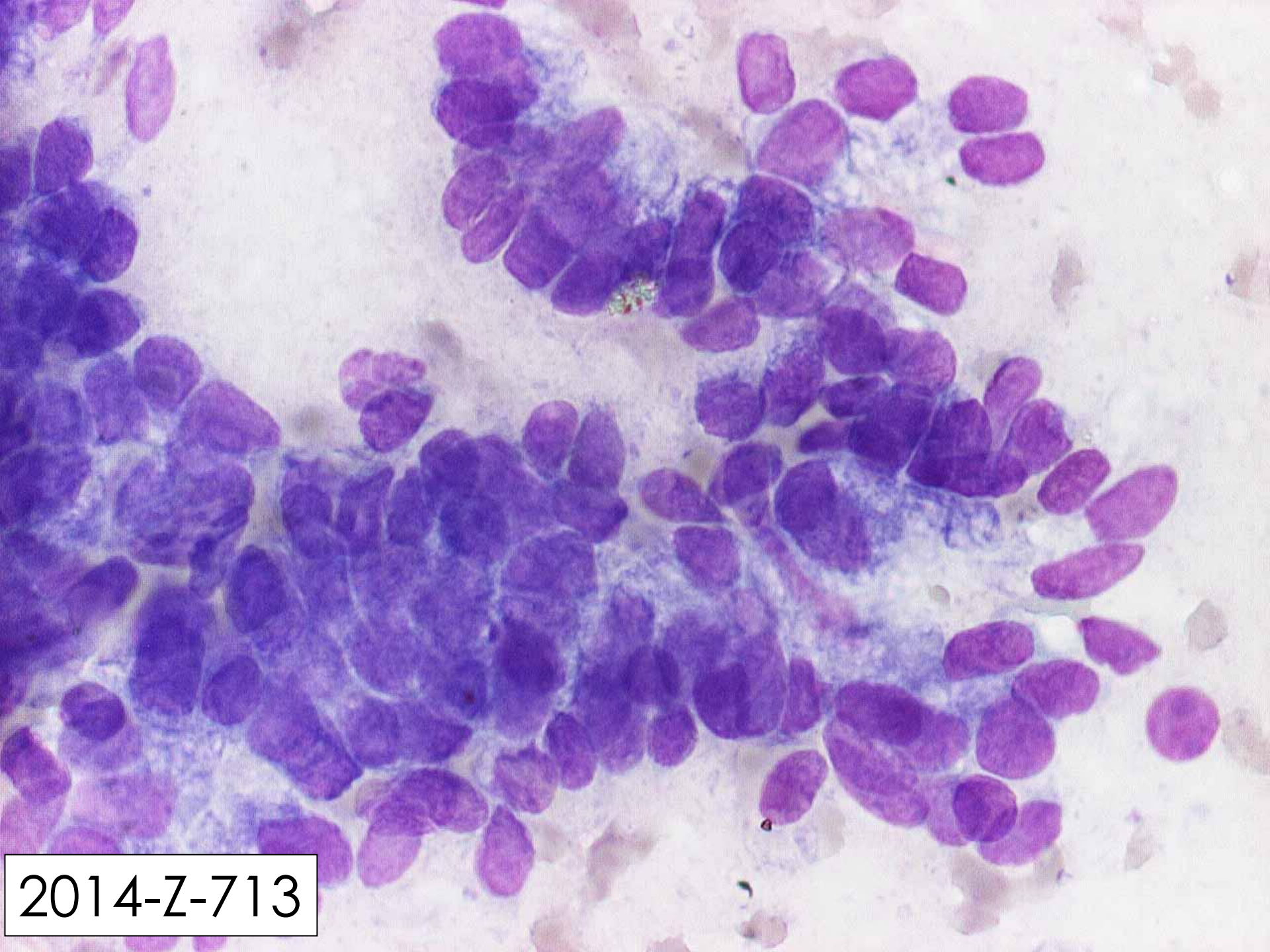
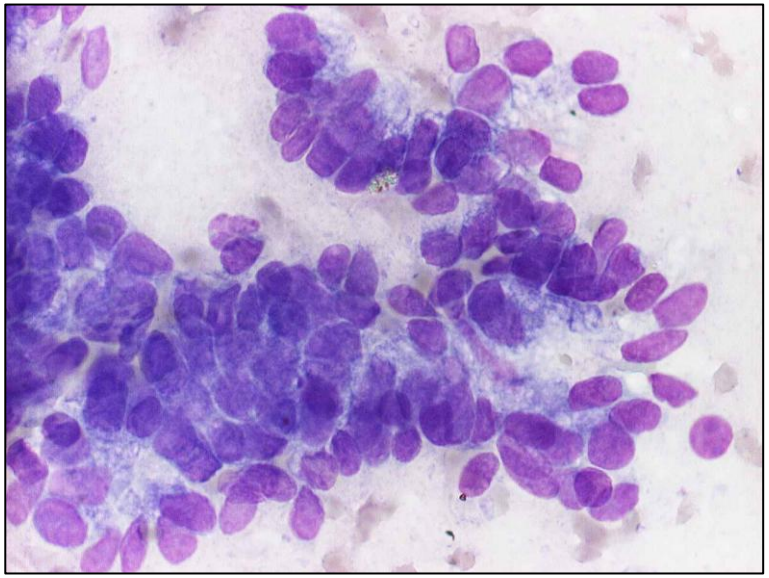
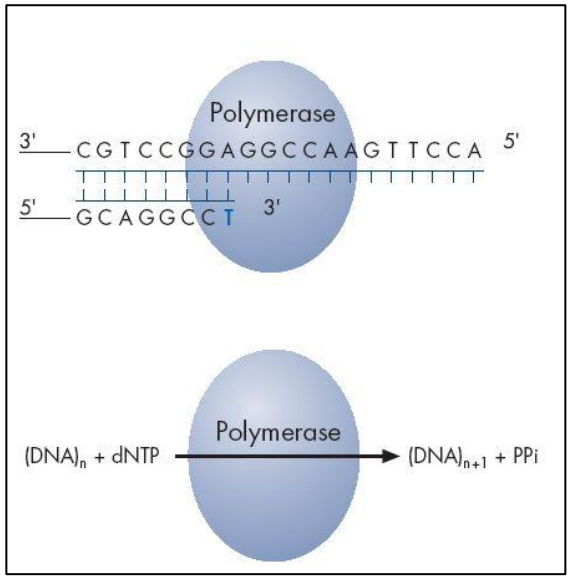

High grade: Überleben < 6 Mo
p53-Mutationen
Low grade: Überleben viele Jahre
KRAS-Mutationen
2014-2934Z


2014-2934Z-p53


2014-Z-713



KRAS



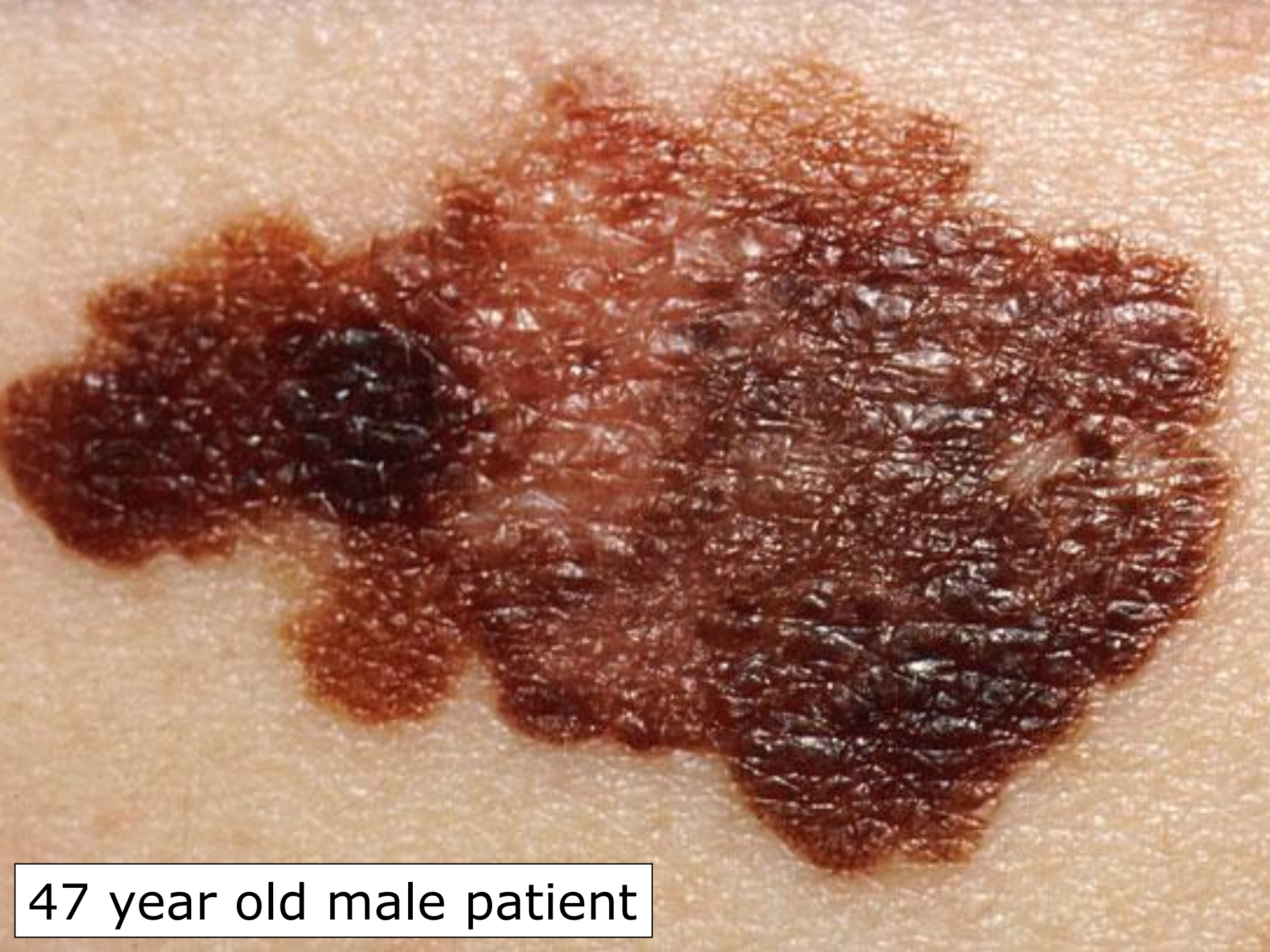
Mutation des KRAS-Gens
Somit epitheliale Tumorzellen

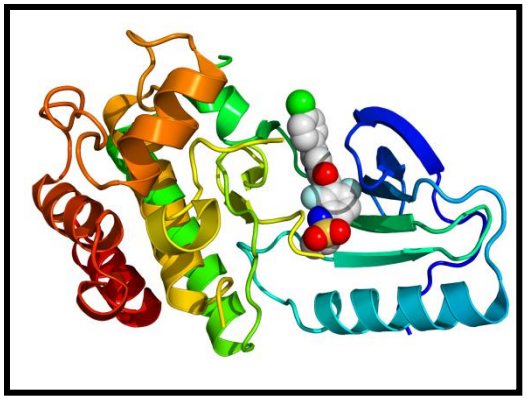
2014-Z-713

Genom-Analysen seit 2008...

- Dickdarmkarzinom: KRAS, NRAS, BRAF
- Lungenkarzinom: EGFR, KRAS, ALK, ROS, MET
- Plattenepithelkarzinom: HPV, p16, EGFR (p53)
- Magenkarzinom: HER2 (MET)
- Brustkrebs: HER2, (PI3K)
- Schilddrüsenkarzinom: BRAF
- Melanom: BRAF, c-KIT
- GIST: c-KIT, PDGFR
- Ovarialkarzinom: BRCA1, BRCA2

Prädiktion des Therapieansprechens
Monitoring des Therapieverlaufs

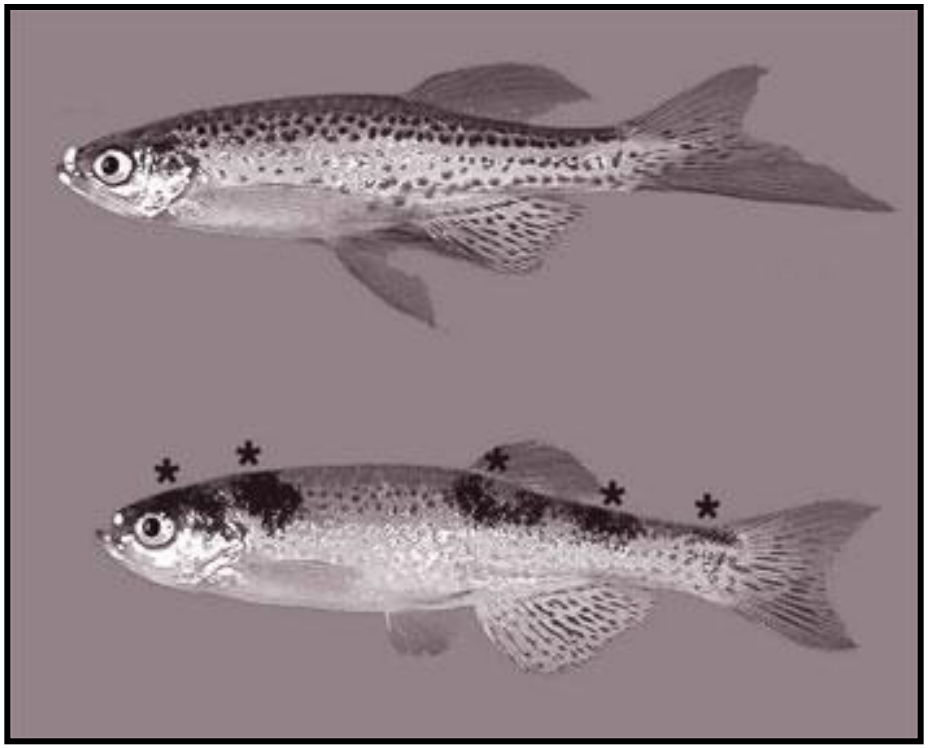

47 year old male patient



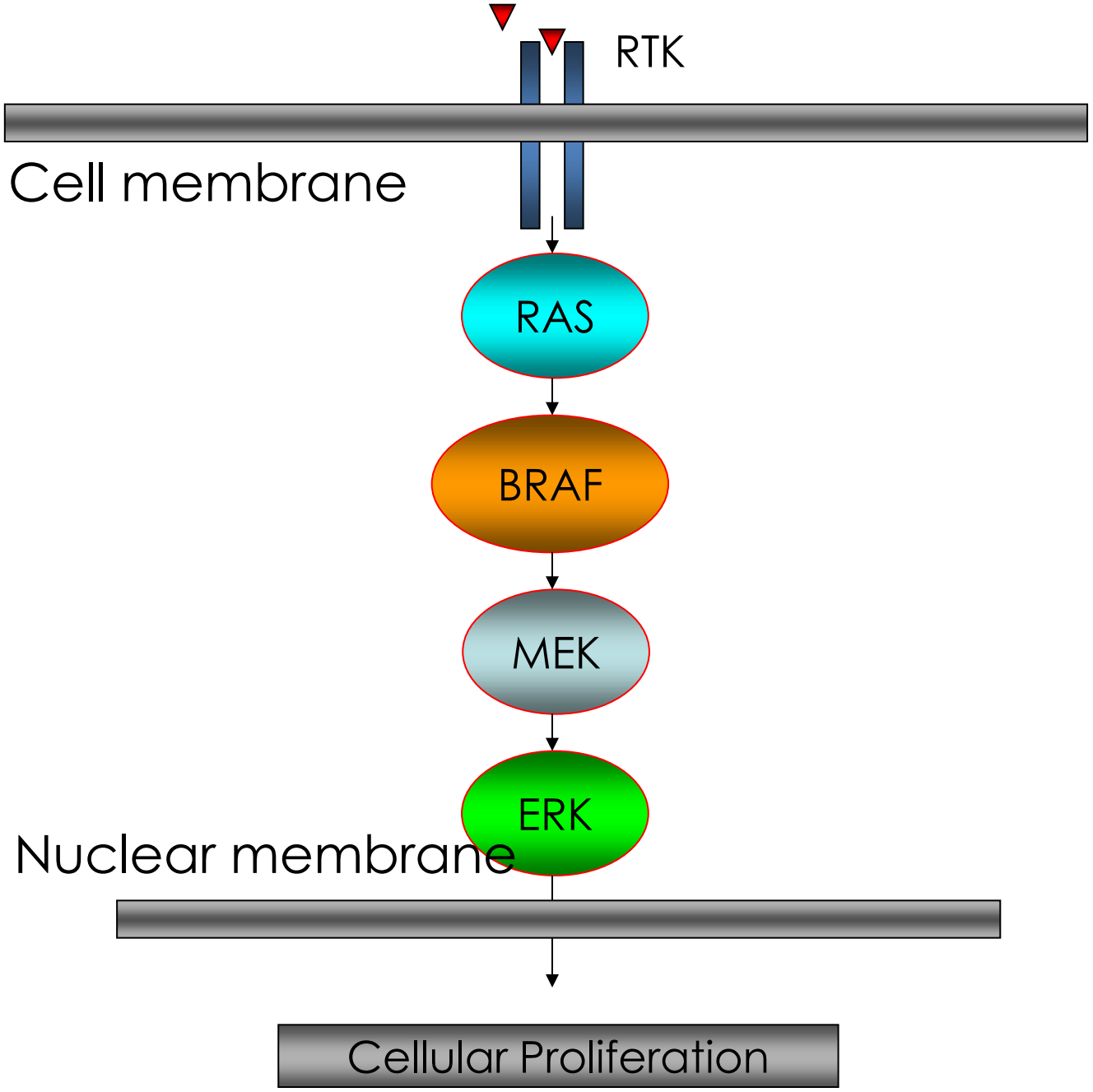
BRAF

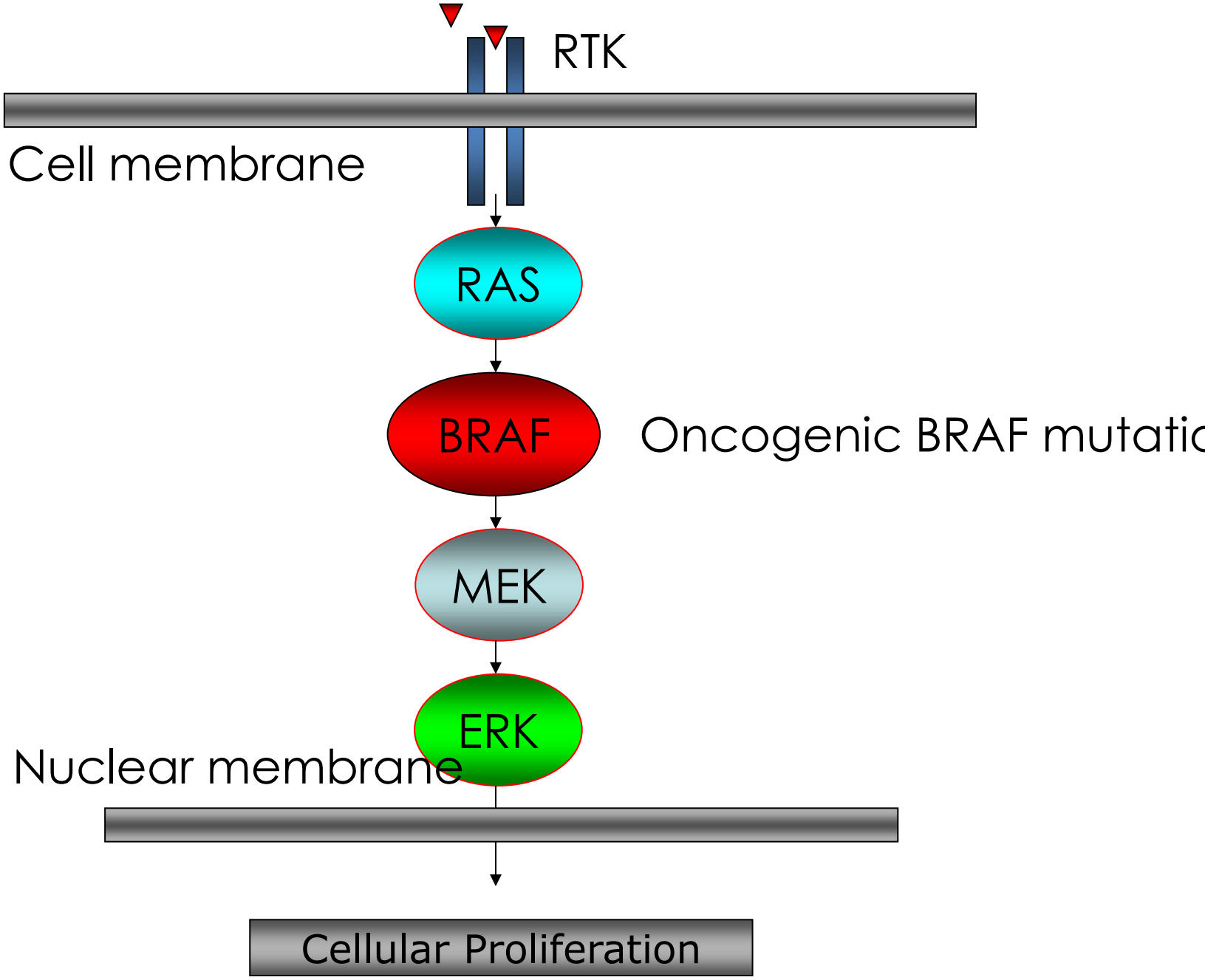
Zebra fish

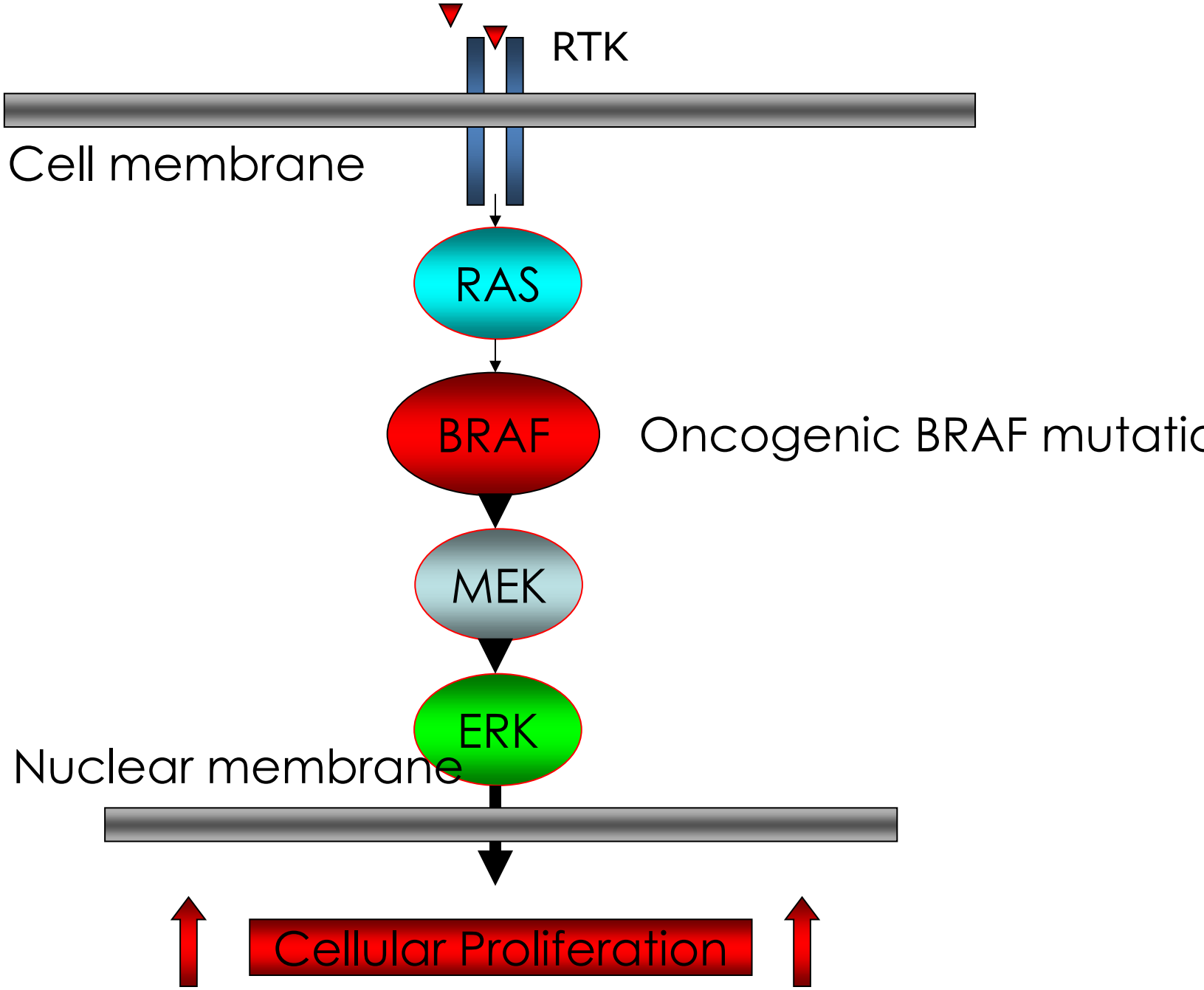
Transgenic
Zebra fish
Melanocyte-targeted
BARFV600E

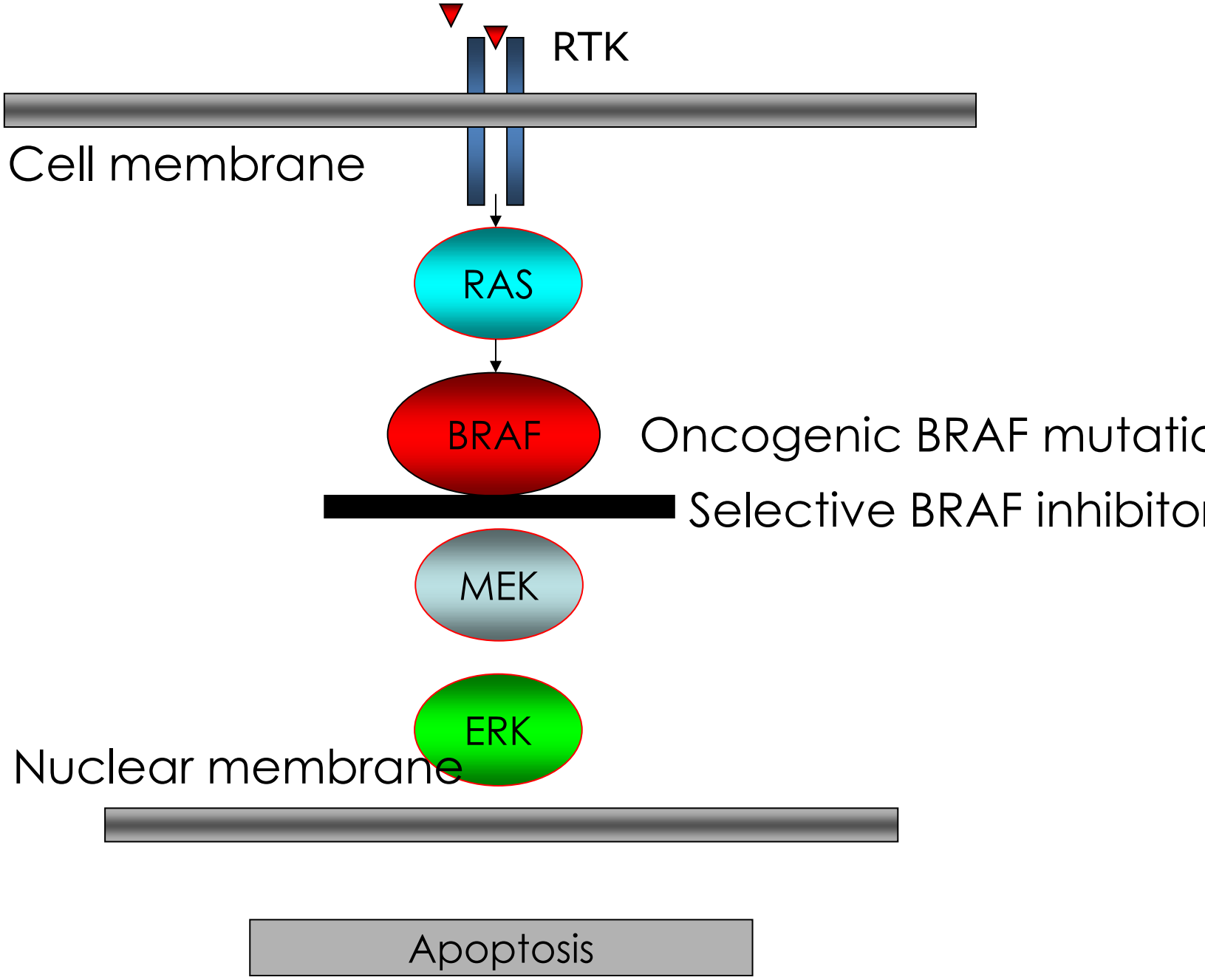


Patton et al. 2005


RTK
Cell membrane
RAS
BRAF
MEK
ERK
Nuclear membrane
Cellular Proliferation


RTK
Cell membrane
RAS
BRAF
Oncogenic BRAF mutatio
MEK
ERK
Nuclear membrane
Cellular Proliferation


RTK
Cell membrane
RAS
BRAF
Oncogenic BRAF mutatio
MEK
ERK
Nuclear membrane
Cellular Proliferation


RTK
Cell membrane
RAS
BRAF
Oncogenic BRAF mutatio
Selective BRAF inhibito
MEK
ERK
Nuclear membrane
Apoptosis

LANDESKRANKENHAUS FELDKIRCH
Akademisches Lehrkrankenhaus
Institut für Pathologie
Vorstand: Prim. Univ.-Doz. Dr. Felix Offner

007175 / 4

IPF

Begleitschein - Histopathologie: Leber, Magen, Darm

4F

Krankenhaus, Abteilung:
Krankenhaus Dornbirn / **Interne Ost**

Operierende(r) Ärztin/Arzt:
Prim.Dr. Guntram Winder

Telefon: **05572 303 2600**

Pat.-Ident.:

Fallzahl: **12002220**
Patient: [redacted]
Vers. Nr.: **6909** Geb. Dat.: **15.01.1971**
Klasse: **AKL**

Untersuchungsmaterial und Abnahmezeitpunkt:

- ☐ ZangenBiopsie
- ☐ Resektat
- ■ Stanzbiopsie
- ☐ Polypektomie
- ☐ Mucosektomie

Sonstiges:

Datum, Uhrzeit:
10.02.2012 09:19

Gewünschte Untersuchungsart:

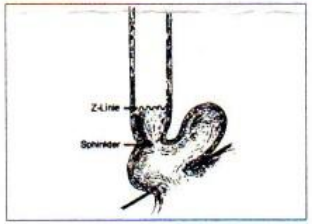
- ■ Standardbearbeitung
- ☐ Expressbearbeitung
- ☐ Gefrierschnittuntersuchung

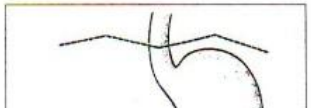
Anamnese, Klinische Diagnose, Lokalisationsangabe und Fragestellung:

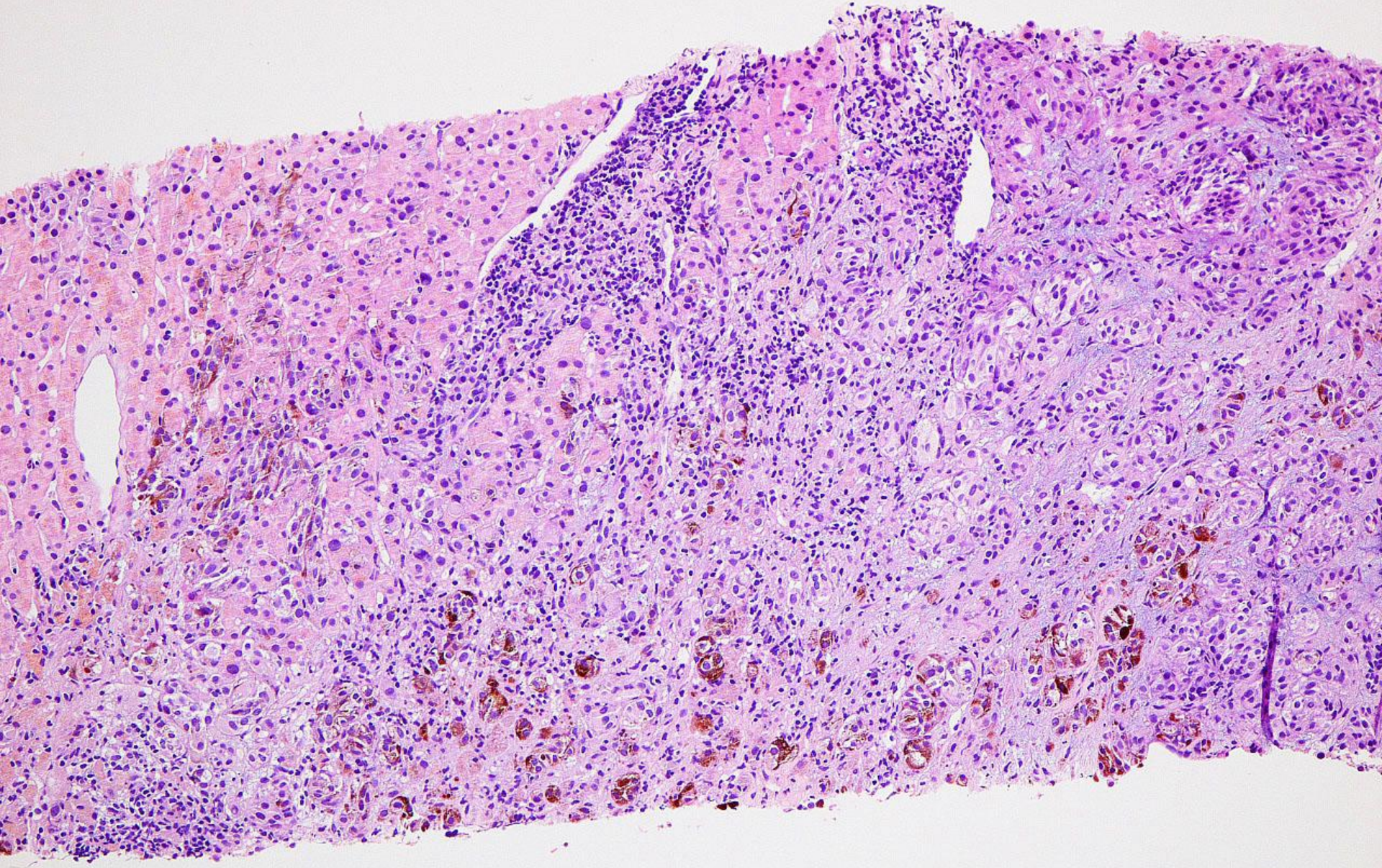
bek. metast. Melanom (Primum Iris)

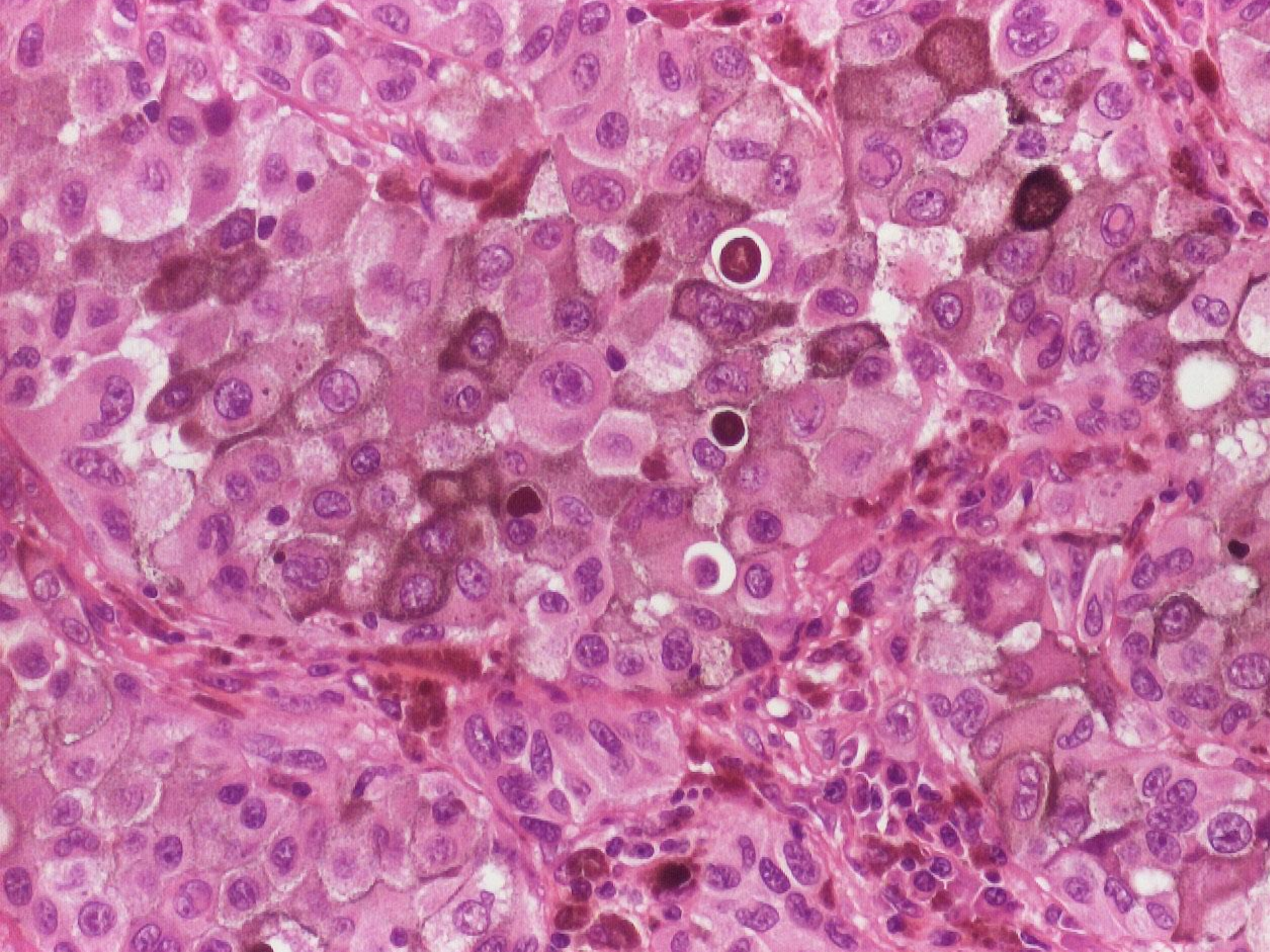
aktuell Leberbiopsie

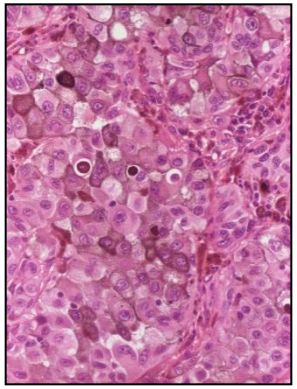
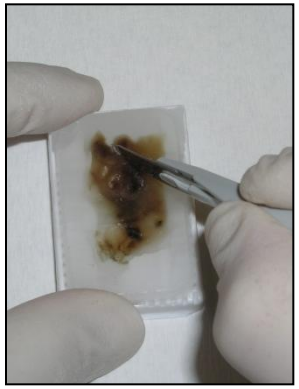
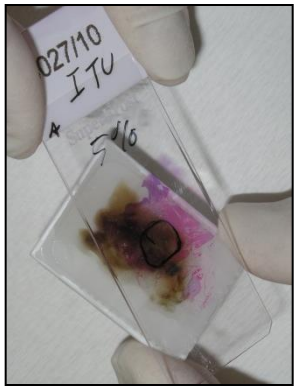
1. histologische Bestätigung
2. BRAF- Mutationsanalyse erbeten





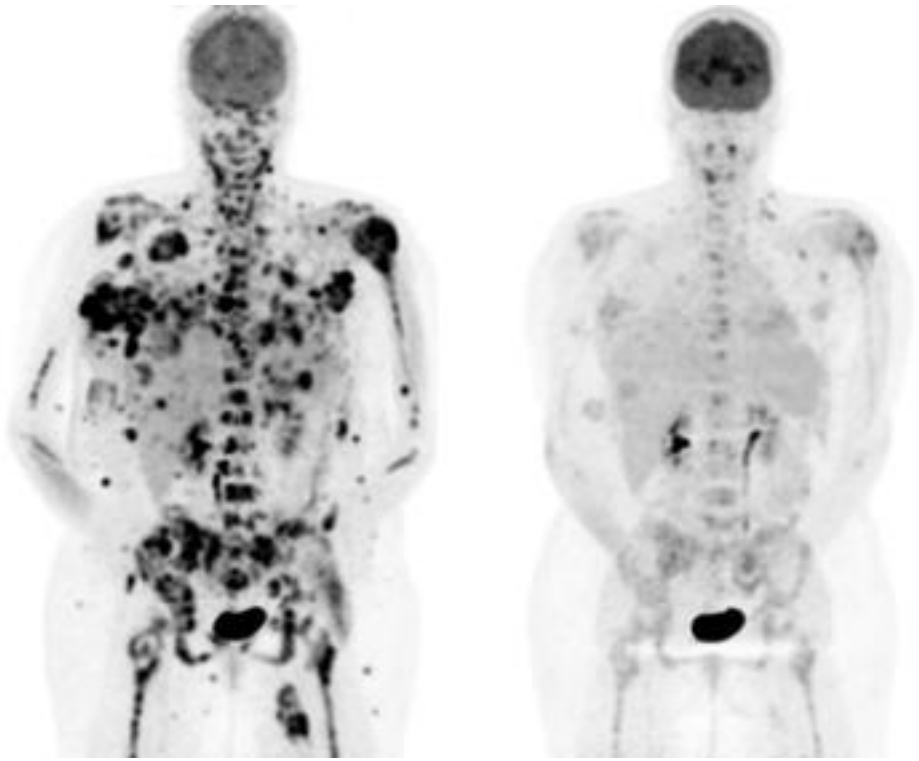






- Macrodissection
- DNA extraction
- 10ng genomic DNA
- BRAF Q24 Kit (Qiagen)
- Pyroseqencing



2 weeks of Vemurafenib (PLX 4032)

Merck Serono

MERCK

Wichtige sicherheitsrelevante Information für Angehörige medizinischer Heilberufe

hinsichtlich der Bedeutung des Nachweises des *Ras*-Wildtyp-Status (Exons 2, 3 und 4 von *K-Ras* und *N-Ras*)

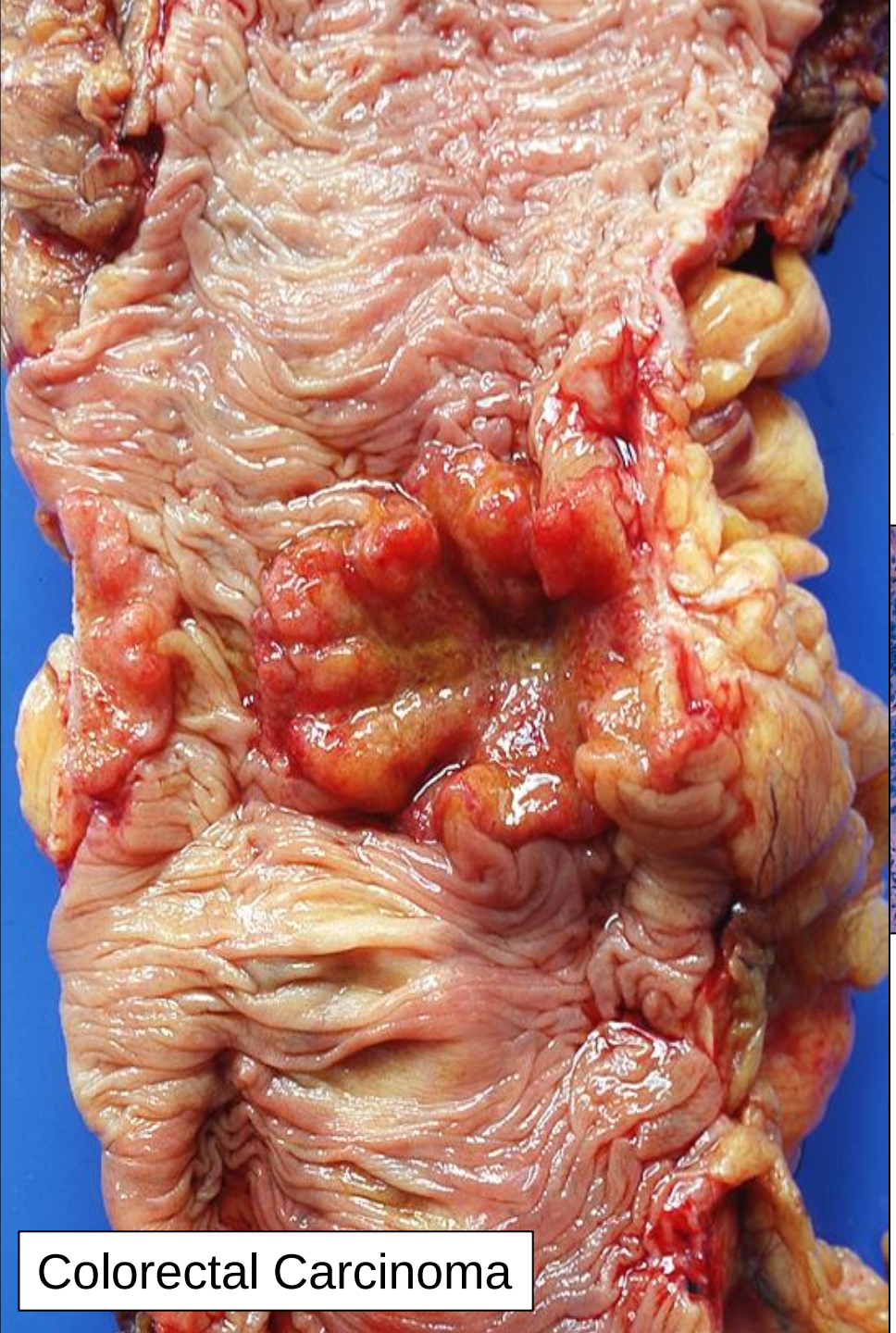
vor der Behandlung mit Erbitux® (Cetuximab)

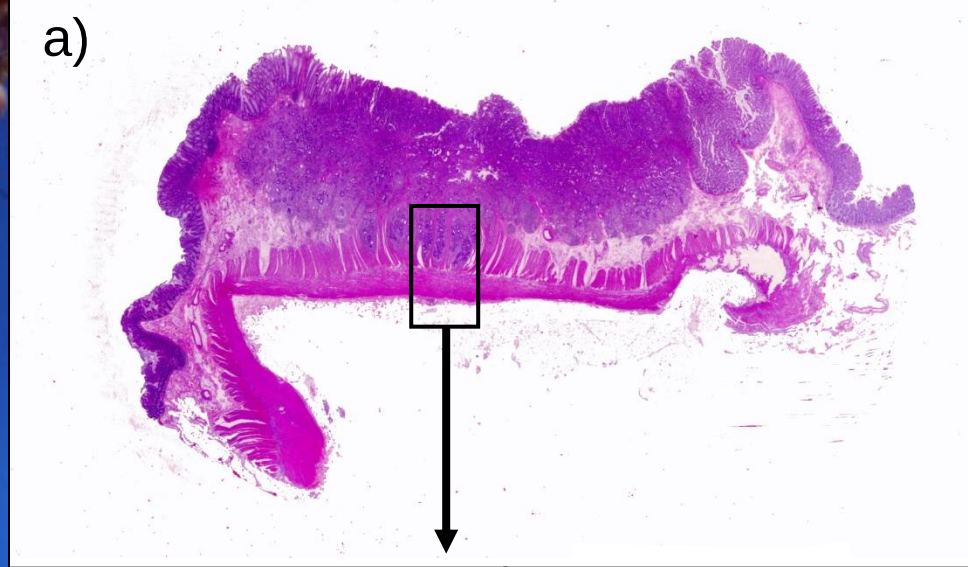
Zusammenfassung

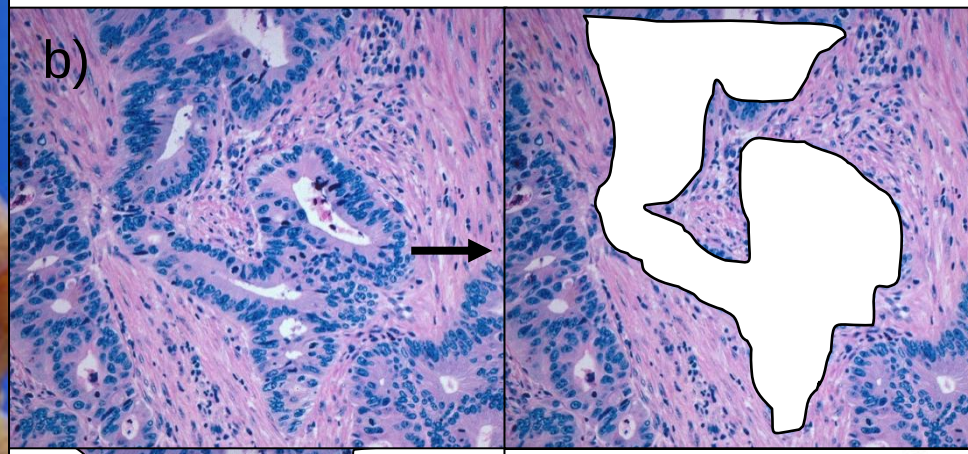
- Der Nachweis des *Ras*-Wildtyp-Status (Exons 2, 3 und 4 von *K-Ras* und *N-Ras*) ist vor Beginn der Behandlung mit Erbitux erforderlich.

- Der *K-Ras*-Mutationsstatus (Exons 2, 3 und 4 von *K-Ras* und *N-Ras*) sollte durch ein erfahrenes Labor mittels einer validierten Prüfmethode bestimmt werden.

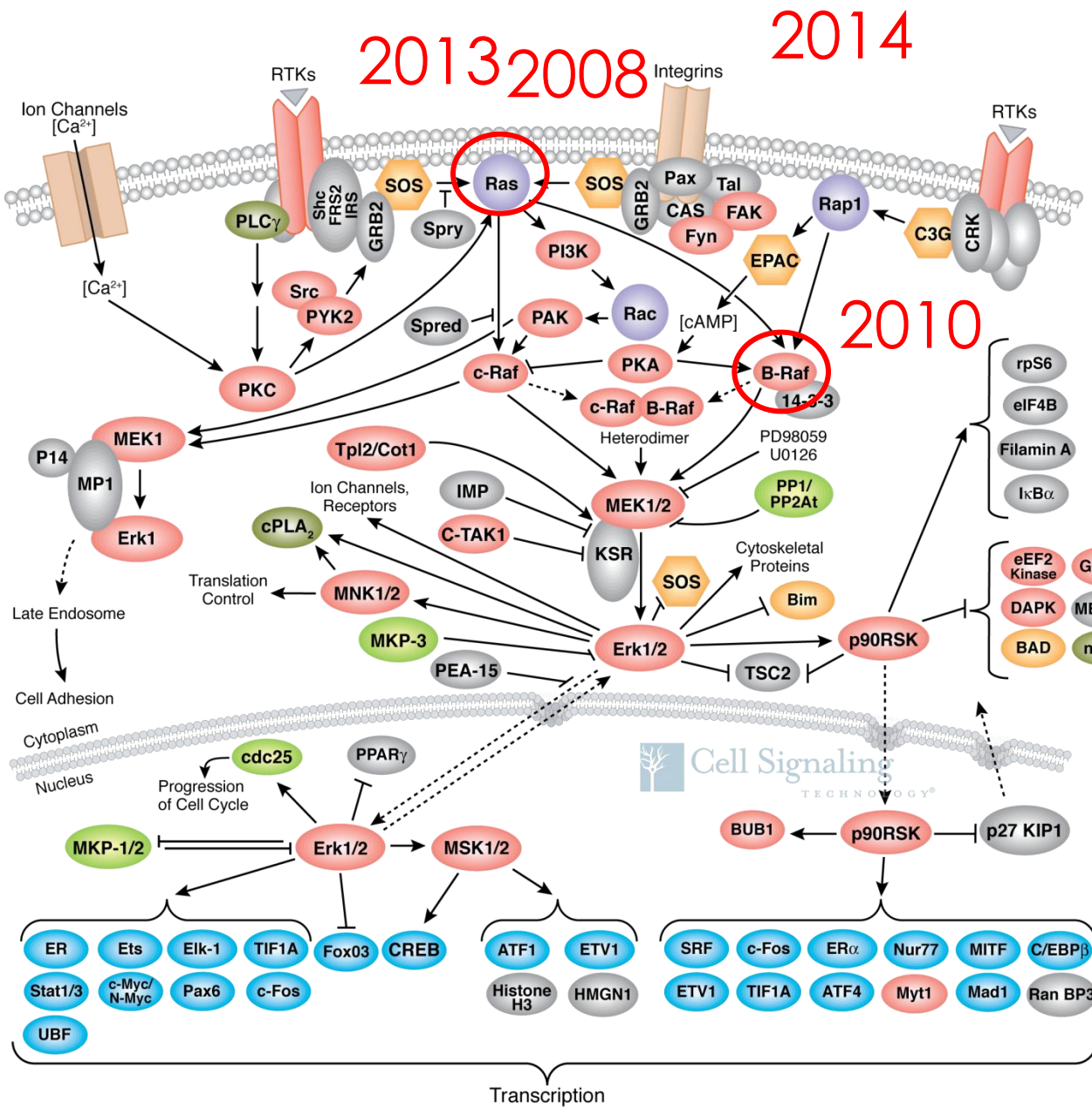
Merck Serono GmbH


Colorectal Carcinoma


a)


b)


c)
TheraScreen
TheraScreen
TheraScr



KRAS
3 Codons
+
3 Codons

NRAS
3 Codons
+
3 Codons

Kolonkarzinom

MP MOLEKULARPATHOLOGISCHER BEFUND Feldkirch, am 21.07.2015

Ergänzende klinische Angaben: H-Nr. 32446/15 - Colorektales Adeno Ca T3 N0 G2 R0

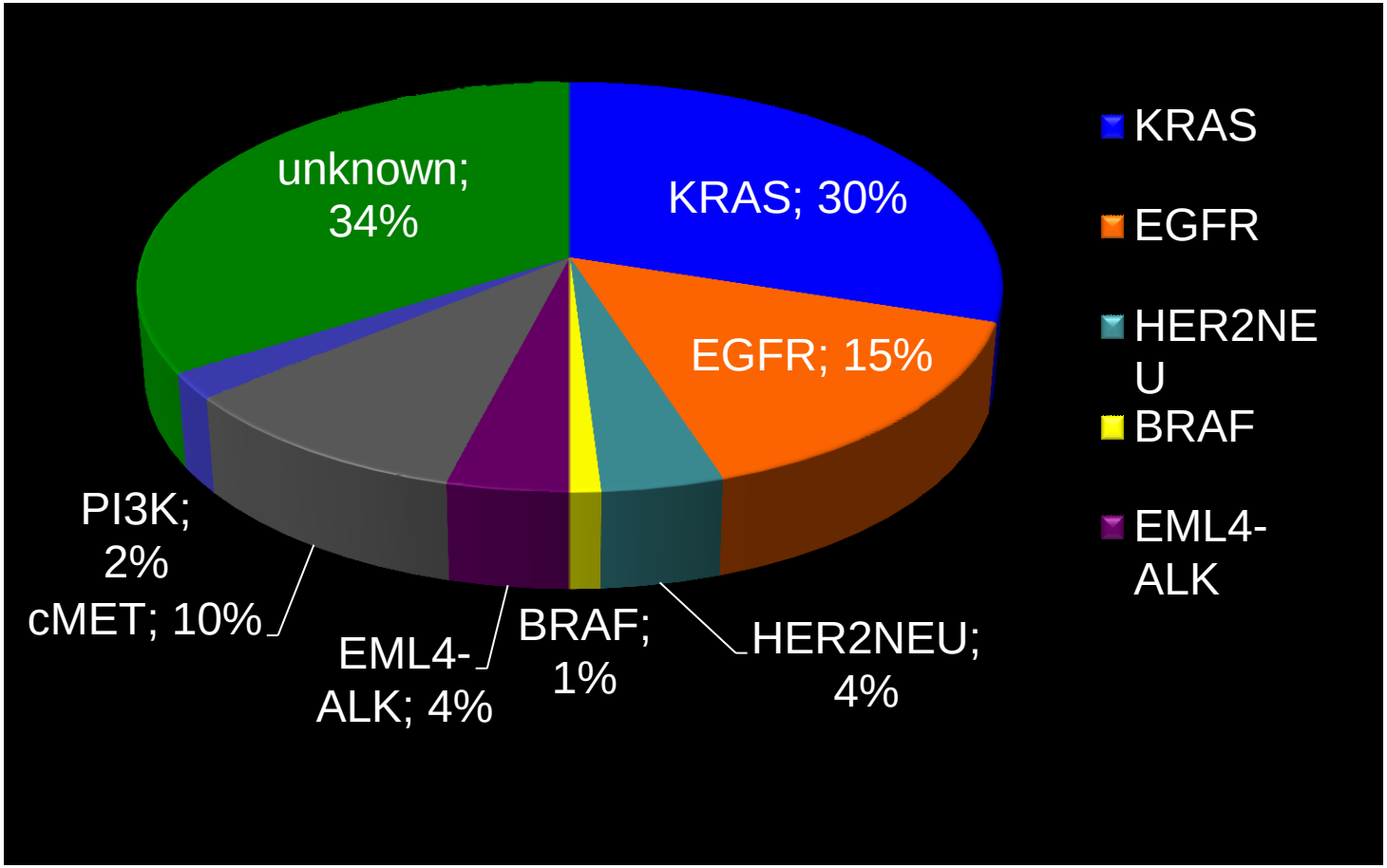
E-Nummer: 4975/2015 / Material: FFPE / Entn. Datum: 02.07.2015 10:16; Tumorzellzahl (%): 30 ; DNA-Menge (ng/µl): 11,0

Parameter	Methode	Ergebnis	Lokalisation	COSMIC-ID
KRAS Exon 2	PYRO	KEINE MUTATION	Wildtype	
KRAS Exon 3	PYRO	KEINE MUTATION	Wildtype	
KRAS Exon 3 Extension	PYRO	KEINE MUTATION	Wildtype	
KRAS Exon 4 Extension	PYRO	KEINE MUTATION	Wildtype	
NRAS Exon 4 Extension	PYRO	KEINE MUTATION	Wildtype	
NRAS Exon 3 Extension	PYRO	KEINE MUTATION	Wildtype	
NRAS Exon 2	PYRO	KEINE MUTATION	Wildtype	
NRAS Exon 3	PYRO	KEINE MUTATION	Wildtype	

Beschreibung: COSMIC-ID= Catalogue of Somatic Mutations in Cancer

Methode: Es wird auf Mutationen in den Codons 12, 13 und 61 des KRAS-Onkogens mittels Pyrosequenzierung (PyroMark KRAS v2.0, Qiagen) untersucht.
Die DNA-Extraktion erfolgt mit QIAmp DNA FFPE-Kit (Qiagen).

Gen-Mutationen bei Adenokarzinomen der Lunge




NDC 50242-060-01
List No.:15734
100 mg
25 mg/mL
AVASTIN™
(bevacizumab)
For Intravenous Use
4 mL SINGLE-USE VIAL
NO PRESERVATIVES.
DISCARD UNUSED PORTION.
Genentech
100 mg
25 mg/mL
AVASTIN
(bevacizumab)
For Intravenous Use


IRESSA® 250 mg
filmdragerade tabletter/
kalvopäällysteiset tabletit/
õhukese polümeerikattega tabletid
gefitinib
Oral användning
Suun kautta
Suukaudseks manustamiseks
30


Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Dispense in tight containers (USP).
DOSAGE AND USE
See accompanying prescribing information.
Each capsule contains 250 mg crizotinib.
Manufactured by
Pfizer Ireland Pharmaceuticals
Dublin, Ireland
Pfizer
NDC 0069-8140-20
XALKORI®
(crizotinib) capsules
250 mg
60 Capsules
Rx only
N 3 0069-8140-20 1
Distributed by Pfizer Labs
Division of Pfizer Inc, NY, NY 10017
MADE IN IRELAND
413 156
4152


© Alamy

CERTIFICATE OF PARTICIPATION

IN THE 2012 EXTERNAL QUALITY ASSESSMENT SCHEME FOR *KRAS*

Molekularpathologisches Labor
Institut für Pathologie
Landeskrankenhaus Feldkirch
Feldkirch, Austria

European Society of Pathology

EQA
European Society of Pathology

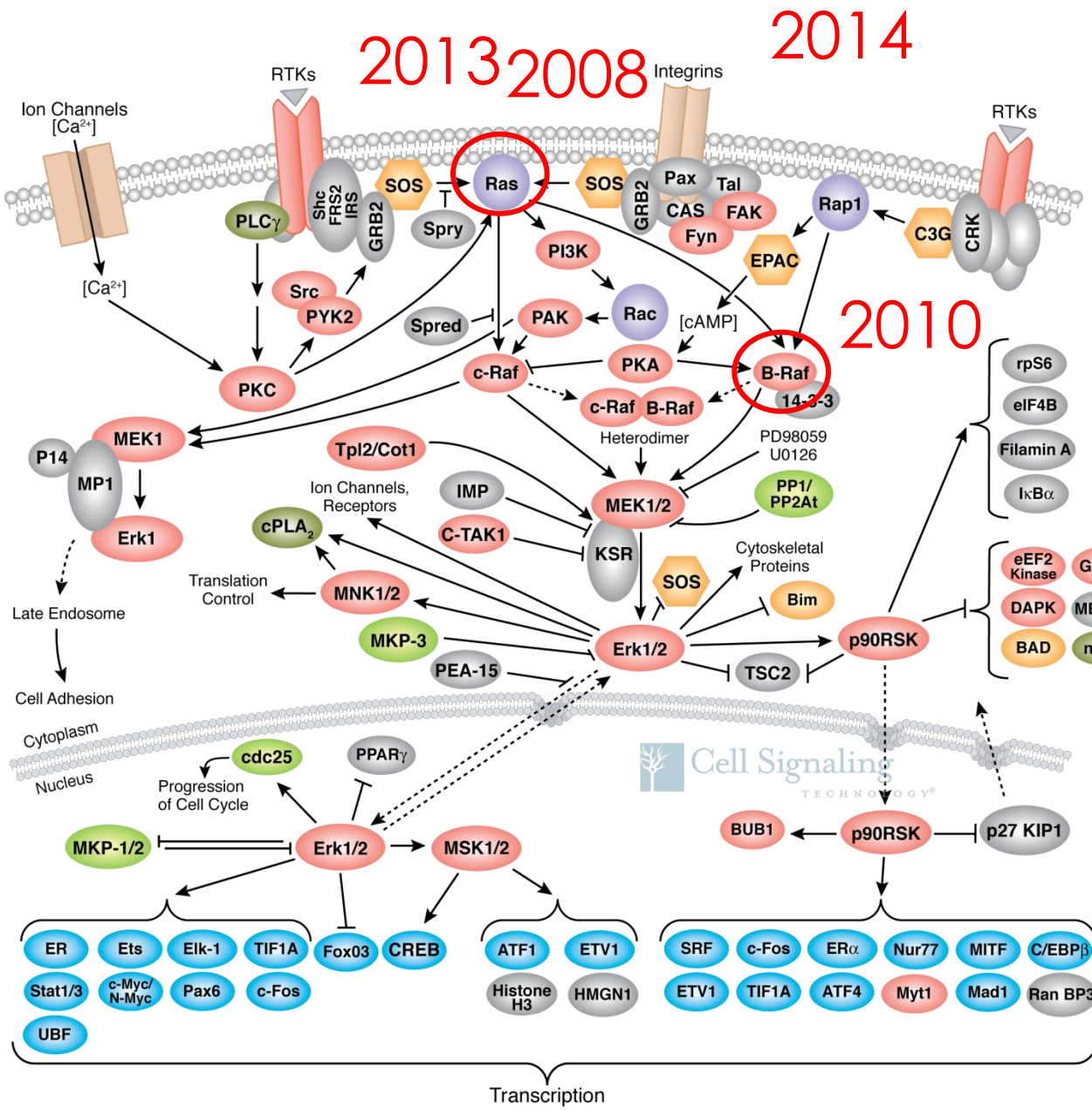
Genotype score: 20/20
Average genotype score: 18.97/20
Average genotype score (subscheme): 19.21/20
Successful participation

Report score: 3,75/4
Average report score: 2.93/4

Prof. Dr. E. Dequeker 10/05/13

Prof. Dr. H. Van Krieken 10/05/13

The ESP KRAS EQA scheme is coordinated by
the Biomedical Quality Assurance Research Unit of the KU Leuven, Belgium



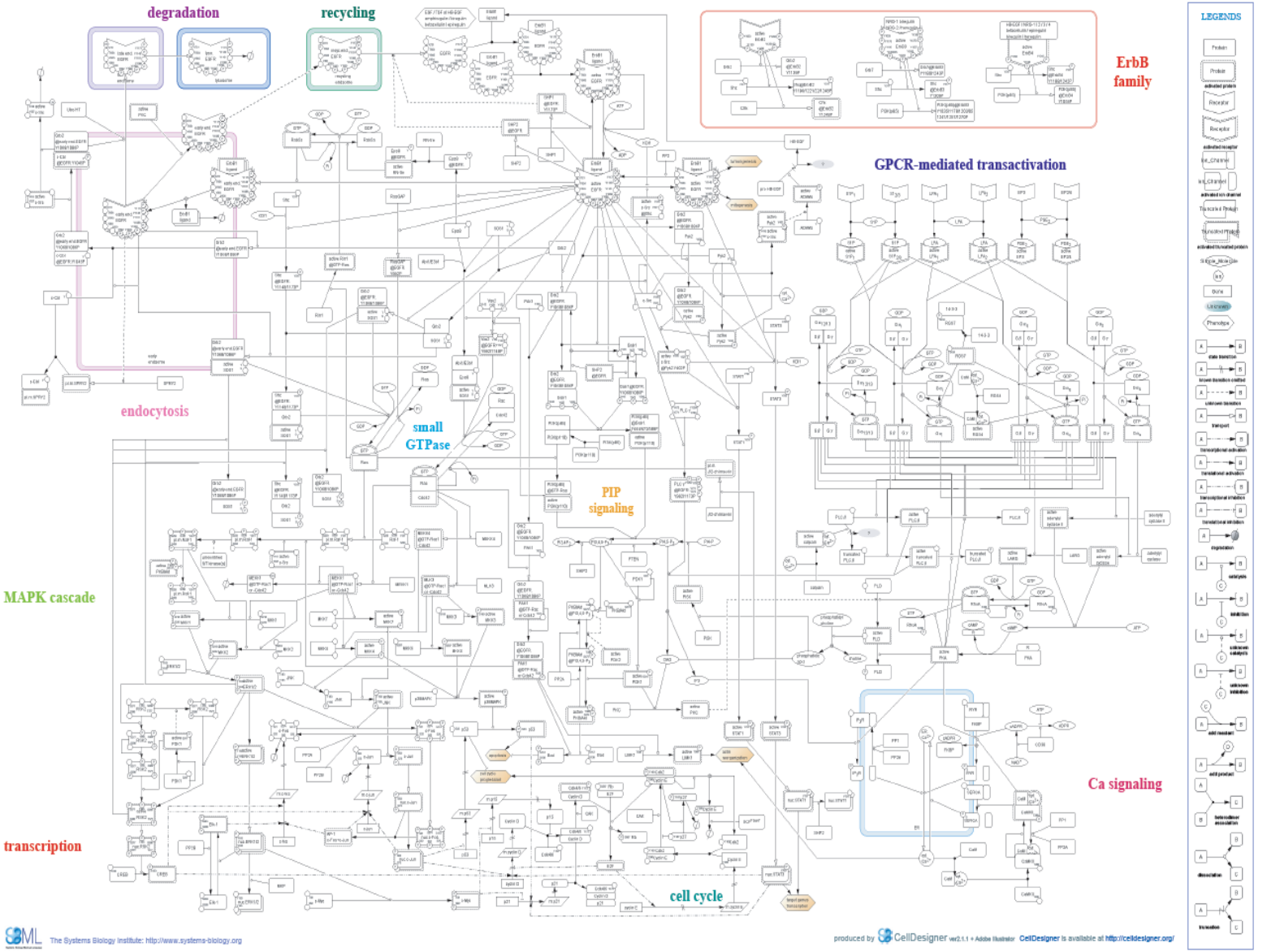
KRAS
3 Codons
+
3 Codons

NRAS
3 Codons
+
3 Codons

Kolonkarzinom

Epidermal Growth Factor Receptor Pathway Map

Kanae Oda (1,2), Yukiko Matsuoka (2), Hiroaki Kitano (1,2,4)
(1) The Systems Biology Institute (2) Department of Computational Biology and Medical Sciences, Tokyo University
(3) ERATO-SORST Kitano Symbiotic Systems Project, Japan Science and Technology Agency, (4) Sony Computer Science Laboratories, Inc.



The Systems Biology Institute: http://www.systems-biology.org
produced by CellDesigner ver2.1.1 + Adobe Illustrator CellDesigner is available at http://celldesigner.org/

Next Generation Gene Sequencing (NGS)

112-150.000 Euro

illumina®

TruSight® Tumor Panel (15 Genes)

Amplicon coverage of 15 consequential genes using a PCR-based method for highly sensitive detection of low-frequency somatic variants from FFPE solid tumor samples.

Highlights

- **Gene Content Guided by Oncology Community**
  Relevant genes for solid tumors selected from industry guidance given by CAP, NCCN, and late-stage clinical pharmaceutical studies
- **Highly Sensitive, Low-Frequency Variant Detection**
  Accurate somatic variant detection of 5% allele frequency at minimum 500× coverage
- **Compatibility With Low-Input and Degraded Samples**
  Optimized for 20 ng DNA from FFPE tissue samples
- **Rapid Turnaround Time**
  DNA-to-data workflow includes extraction recommendations, sample QC recommendations, and analysis tools providing results < 40 hours after extraction

Introduction

Table 1: Genes Assessed by the TruSight Tumor Panel (15 Genes)

AKT1	*GNA11*	*NRAS*
BRAF	*GNAQ*	*PDGFRA*
EGFR	*KIT*	*PIK3CA*
ERBB2	*KRAS*	*RET*
FOXL2	*MET*	*TP53*

Accurate, Low-Frequency Variant Detection

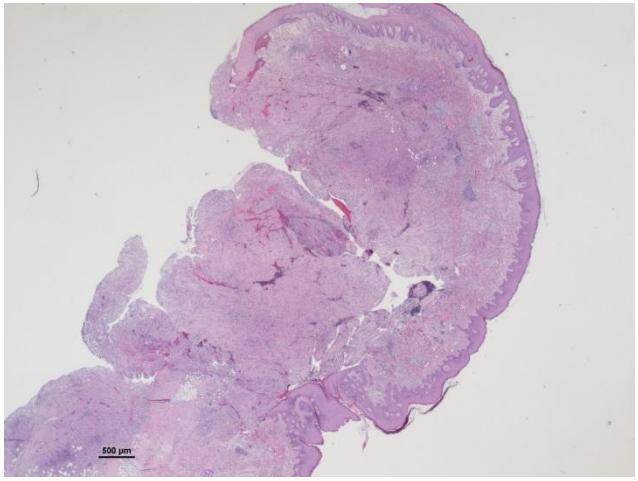
Deep sequencing using NGS can reveal somatic variation in tumor subpopulations across a panel of genes. The TruSight Tumor Panel (15 Genes) analyzes down to 5% variant allele frequency from FFPE samples. When combined with the industry-leading accuracy of the MiSeq® System, the assay provides uniform coverage of target regions, delivering > 500× coverage and highly accurate calls of low-frequency cancer-related variants (Table 2). This sensitivity provides the accuracy and confidence needed to identify low-frequency variation from FFPE tumor samples (Table 3).

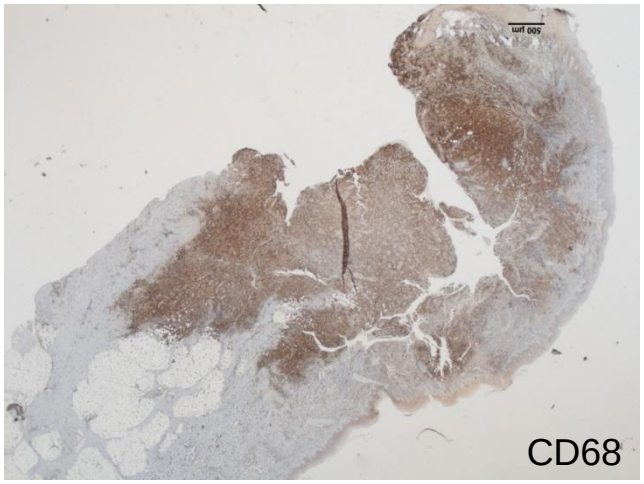
NGS an Pathologie Instituten...

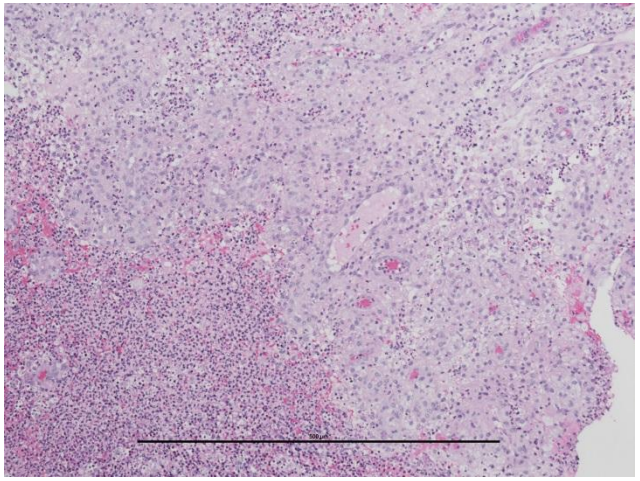
- Uni-Zürich, Basel, Bern, Genf, Lausanne, Graz, Wien, Salzburg
- KS- Luzern
- KS- Basel-Land
- KS- Locarno
- KS- Aarau
- KH-Mistelbach

Case 3

8 yrs. male
Soft tissue tumor, presternal extending into thorax; surgical removal
Histopathological diagnosis: Inflammatory pseudotumor; no malignancy







Consensus Lineage	S.BC01	AS.BC01	#OTU ID
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	747		22
k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Pasteurellales;f__Pasteurellaceae;g__Aggregatibacter;s__actinomycetemcomitans	15922		48
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	5922		88
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__		6142	125
k__Bacteria;p__Proteobacteria;c__Epsilonproteobacteria;o__Campylobacterales;f__Campylobacteraceae;g__Campylobacter	4252		130
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	1077		135
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	2901		155
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	522		173
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	1817		217
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	540		218
k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Pasteurellales;f__Pasteurellaceae;g__Aggregatibacter		2672	227
k__Bacteria;p__Fusobacteria;c__Fusobacteria;o__Fusobacteriales;f__Fusobacteriaceae;g__Fusobacterium;s__	101977		234
k__Bacteria;p__Actinobacteria;c__Actinobacteria;o__Actinomycetales;f__Actinomycetaceae;g__Parascardovia;s__	2198		244
k__Bacteria;p__Proteobacteria;c__Epsilonproteobacteria;o__Campylobacterales;f__Campylobacteraceae;g__Campylobacter;s__rectus		1580	251

53% Fusobacterium nucleatum

23% A. actinomycetemcomitans

12% Campylobacter rectus*

* not found in culture

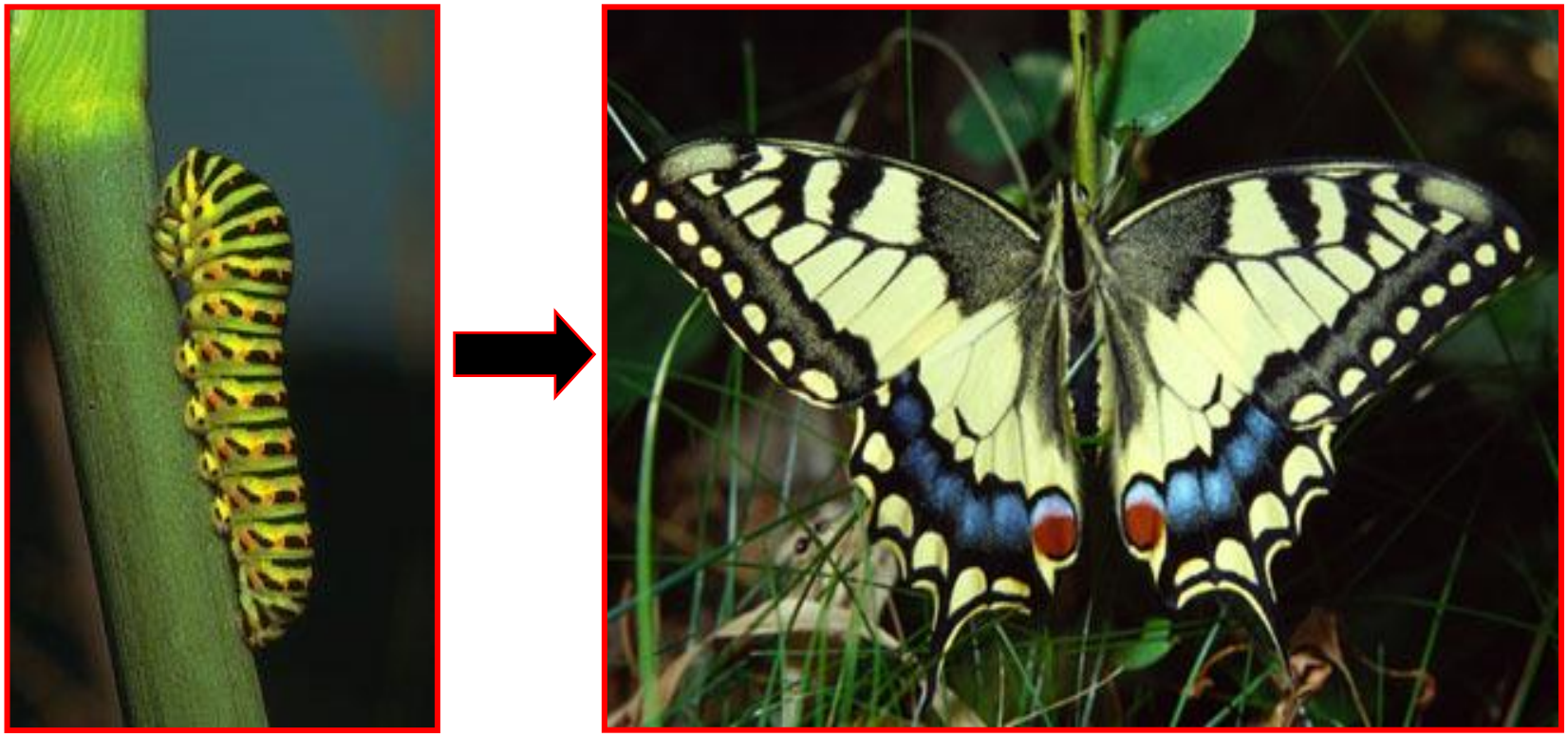
Lemierre-Syndrome: Oral translocation of bacteria (parodontitis); polymicrobial infection

APPLICATIONS OF NEXT-GENERATION SEQUENCING

Transforming clinical microbiology with bacterial genome sequencing

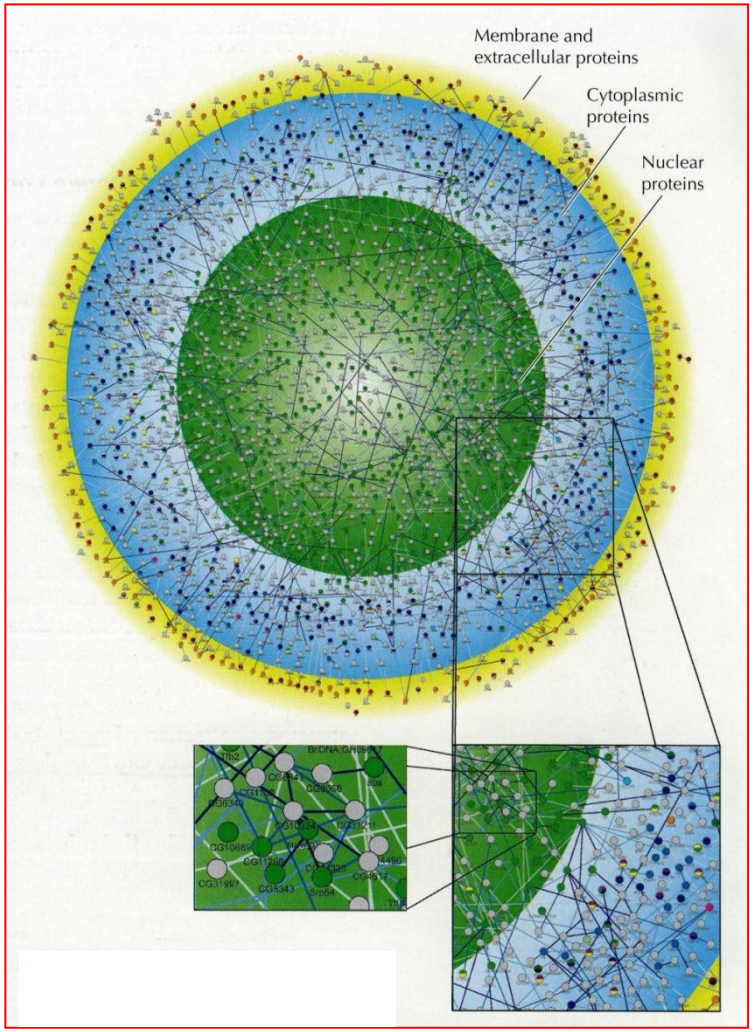
Xavier Didelot[1], Rory Bowden[1,2,3], Daniel J. Wilson[2,4], Tim E. A. Peto[3,4] and Derrick W. Crook[4,3]

Abstract | Whole-genome sequencing of bacteria has recently emerged as a cost-effective and convenient approach for addressing many microbiological questions. Here, we review the current status of clinical microbiology and how it has already begun to be transformed by using next-generation sequencing. We focus on three essential tasks: identifying the species of an isolate, testing its properties, such as resistance to antibiotics and virulence, and monitoring the emergence and spread of bacterial pathogens. We predict that the application of next-generation sequencing will soon be sufficiently fast, accurate and cheap to be used in routine clinical microbiology practice, where it could replace many complex current techniques with a single, more efficient workflow.



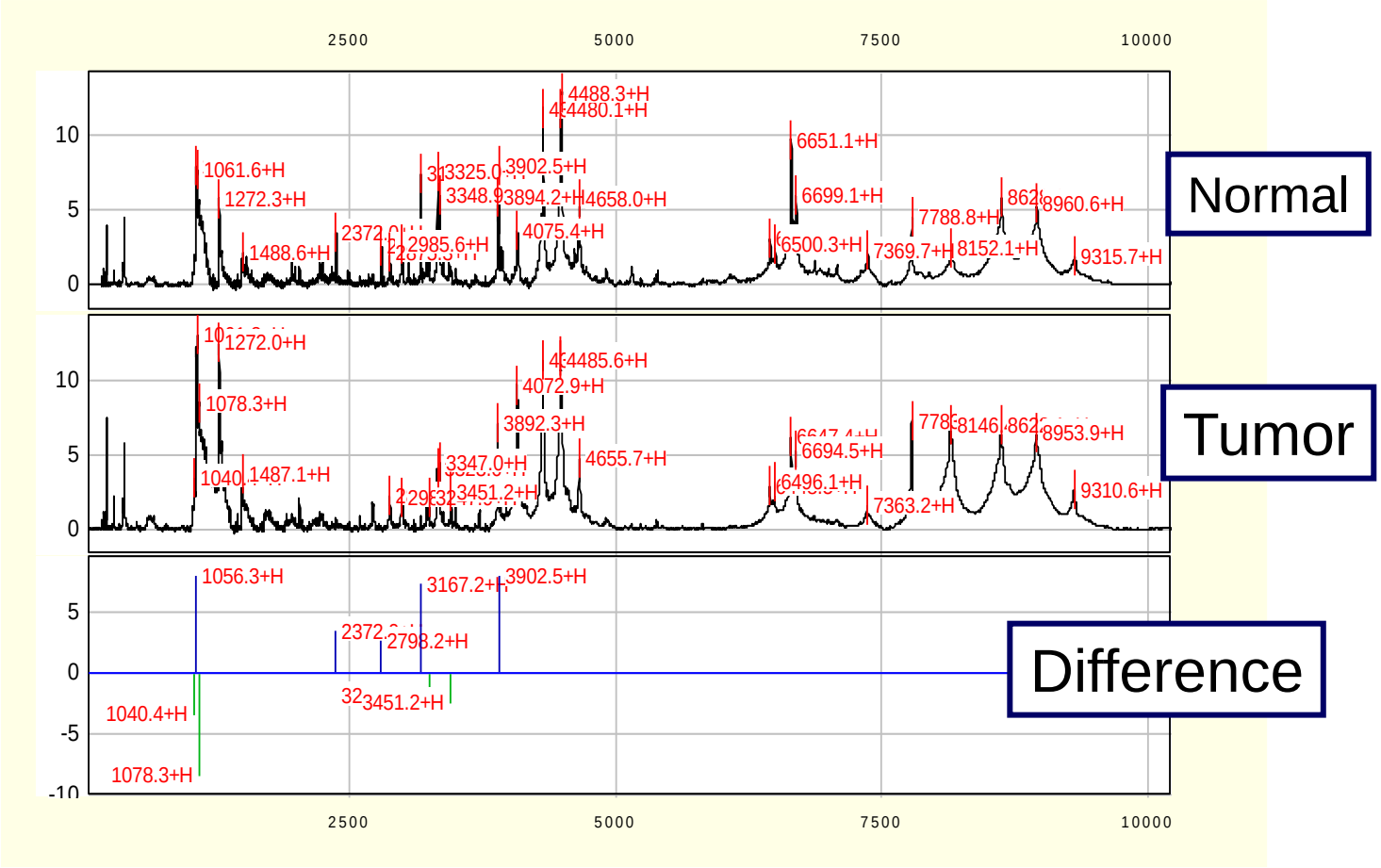
Morphology matters!

Proteins - Interactions - Complexity

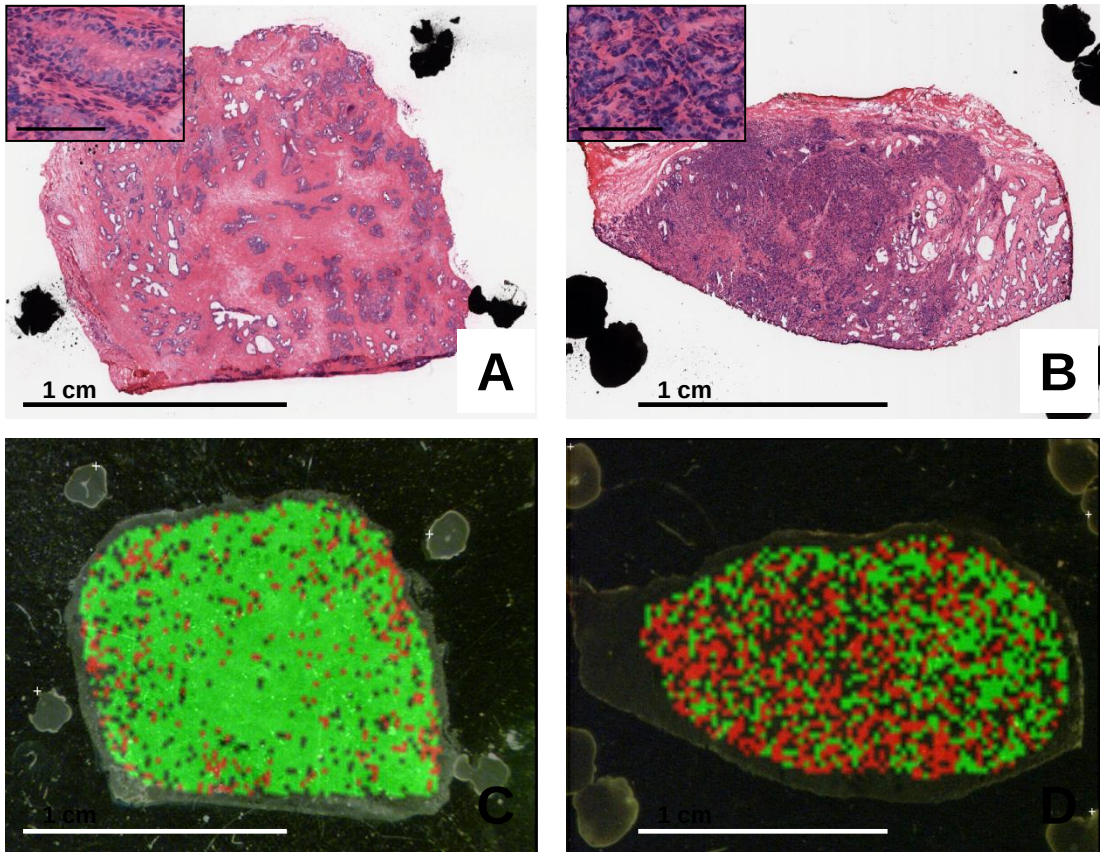


Giot L et al. Science 302:1727 (2003)

MALDI-Analysis
Different Expression of Proteins



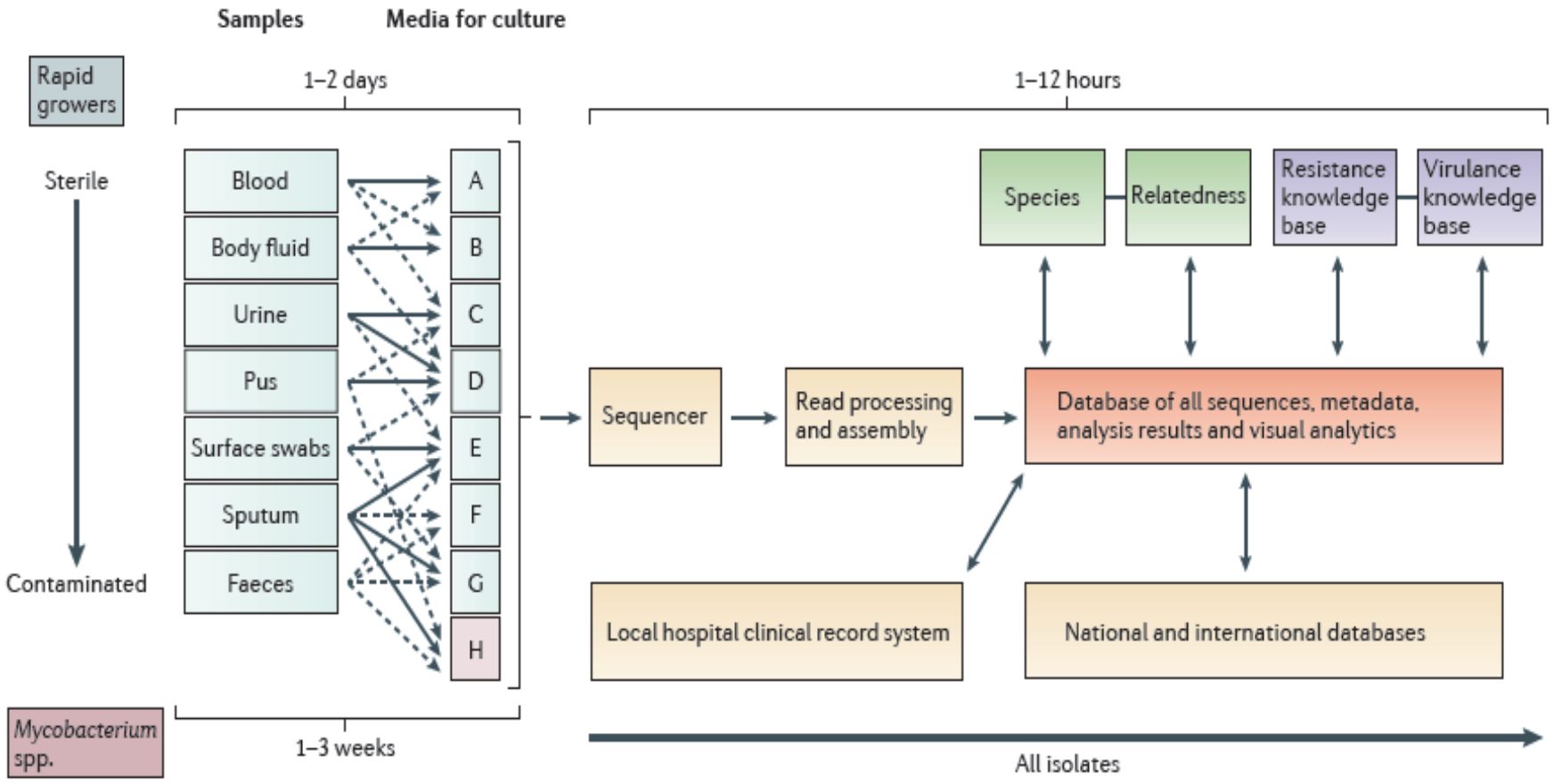
MALDI-Imaging



Normal Prostate Prostate Cancer

INSTITUT FÜR PATHOLOGIE-FELDKIRCH

NGS in der Mikrobiologie



Didelot X, Bowden R, Wilson DJ, Peto TE, Crook DW. **Transforming clinical microbiology with bacterial genome sequencing.** *Nat Rev Genet.* 2012 Sep;13(9):601-12.