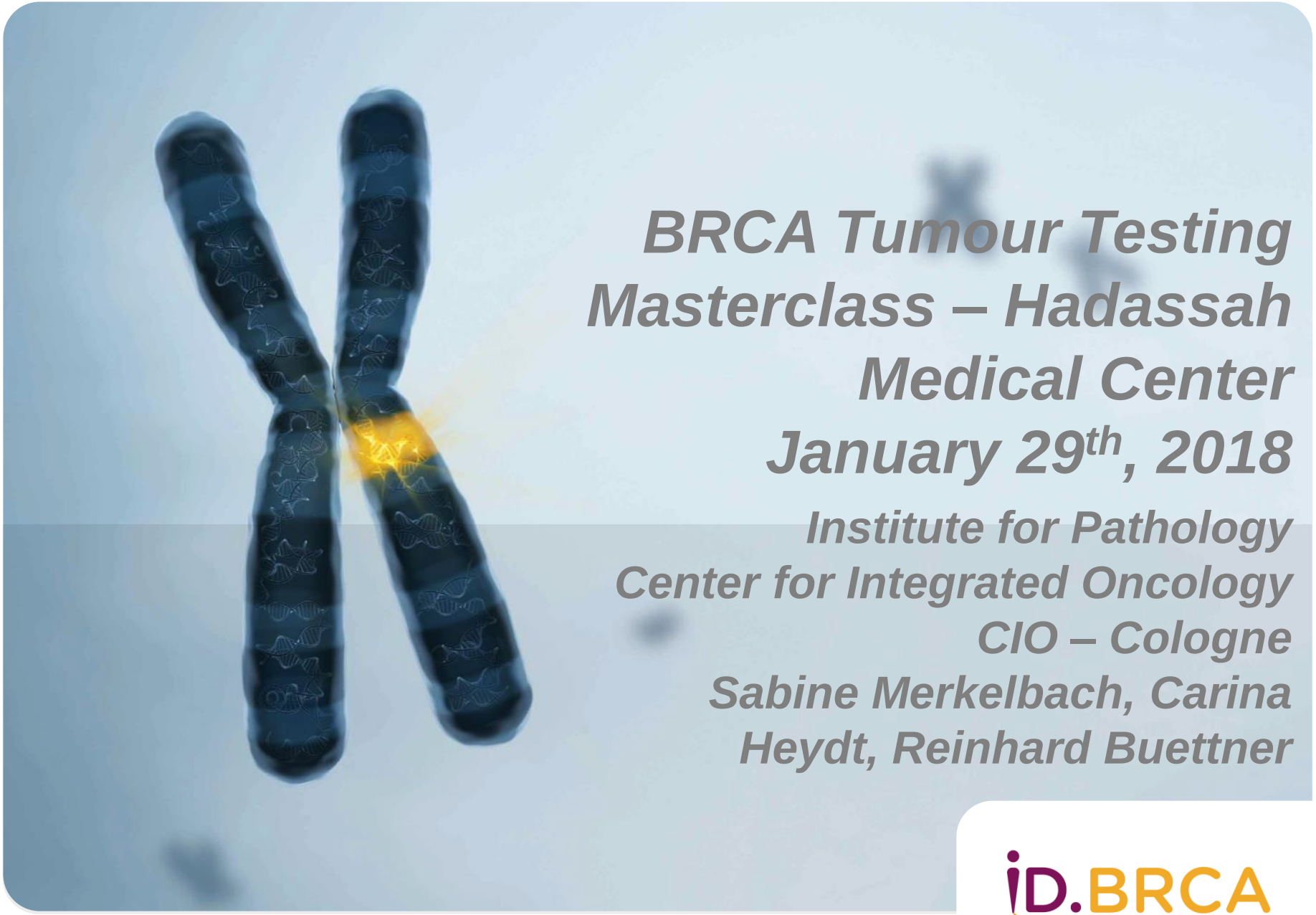

BRCA Tumour Testing Masterclass – Hadassah Medical Center January 29th, 2018

Institute for Pathology Center for Integrated Oncology CIO – Cologne

Sabine Merkelbach, Carina Heydt, Reinhard Buettner

iD.BRCA

AstraZeneca

Welcome!

Meeting Sponsorship AstraZeneca

Agenda

08:30-09:00 **Gathering & Breakfast**

09:00-09:30 **Introduction for sBRCA testing** - Prof. Reinhard Büttner

09:30-10:15 **Review of methodologies for tumour testing; highlighting experience from University Hospital, Cologne** - Dr. Carina Heydt

10:15-10:45 **gBRCA testing - classification of genomic variations and clinical implications**
Prof. Vardiella Meiner - Director of Center for Clinical Genetics

10:45-11:15 **Coffee break**

11:15-12:45 **Determining Pathogenicity & Interpretation of Results with the aid of the challenging samples from Cologn**
Group A - Dr. Sabine Merkelbach – Bruse
Group B - Dr. Carina Heydt

12:45-13:15 **Challenging case session from ISRAEL**
Dr. Yaniv Zohar - (Rambam medical center), Dr. Ariel Erental - (Hadassah medical center) and panel members

13:15- 14:15 **Lunch**

14:15- 14:45 **The Future: Panel testing** - Prof. Reinhard Büttner

14:45- 15:15 **Summary of key processes for tumour BRCA testing Q&A session**
Dr. Sabine Merkelbach – Bruse, Prof. Reinhard Büttner,
Dr. Carina Heydt & Prof. Eli Pikarsky (Hadassah medical center)

15:15- 16:00 **Meeting close & on demand private discussion on sBRCA testing**

AstraZeneca המפגש בחסות חברת

ISRAEL ASSOCIATION OF PATHOLOGISTS

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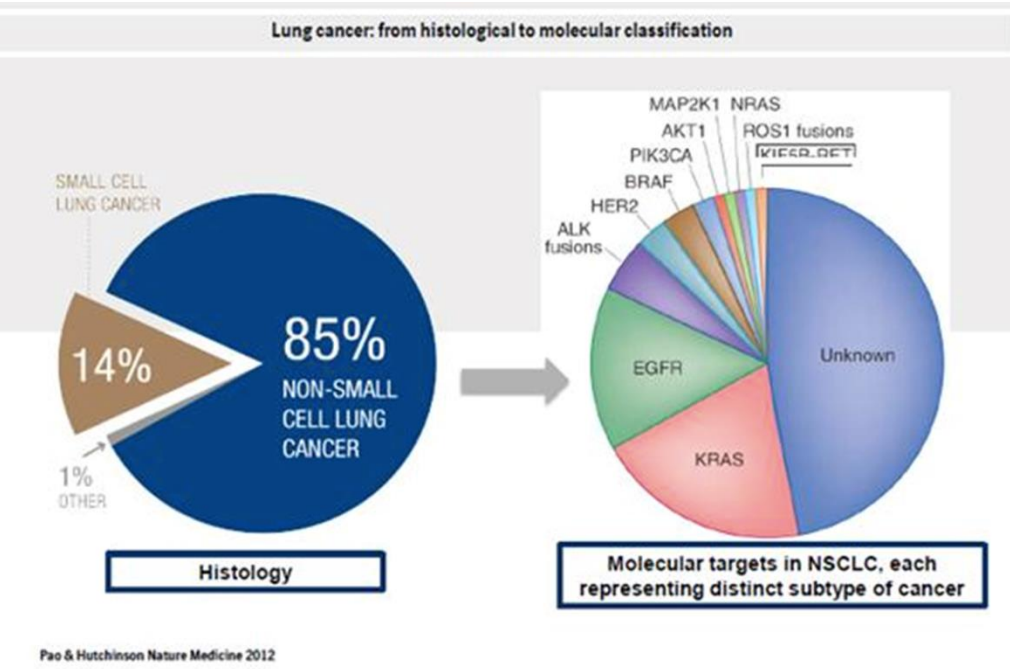
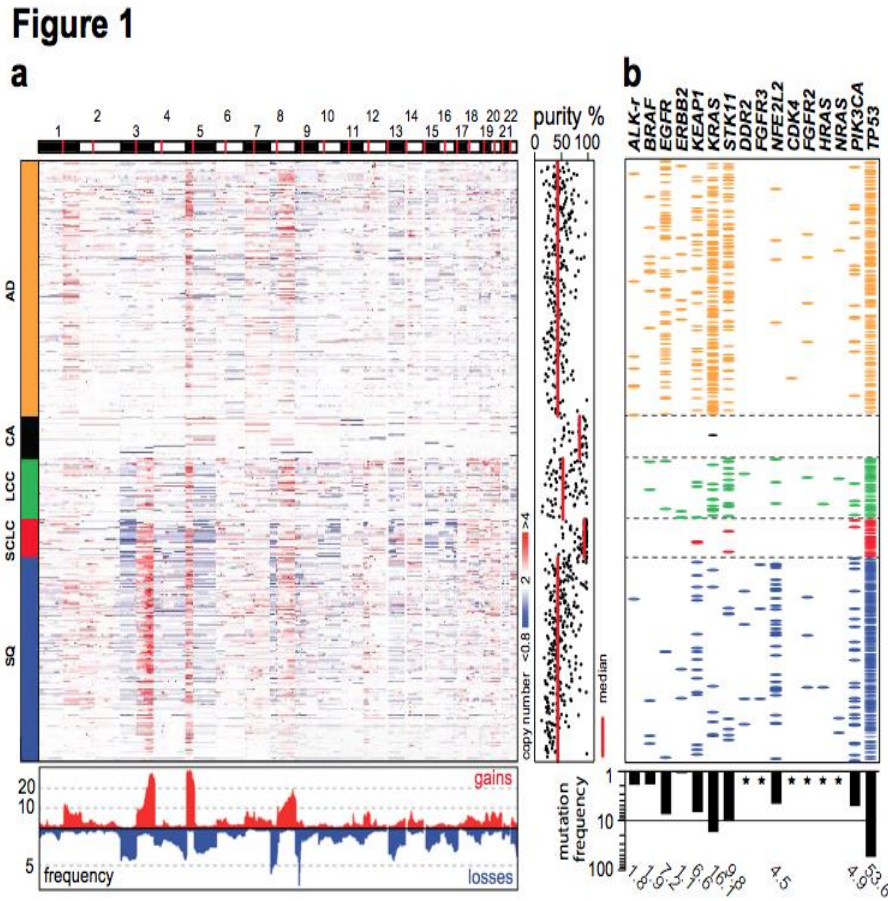
Molecular Classification of Cancer



Pao W, Nature Medicine 2012



Seidel D, Wolf J, Buettner R, Thomas RK: Science Transl Med Oct30th, 2013

~5,000 Lung Cancer Genomes connected to clinical data (NGM-L)

The Network Genomic Medicine NGM
A Platform for Molecular Diagnostics and Precision Medicine

www.ngm-cancer.com

Onkologisches Spitzenzentrum
seit 2008
Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

The Center for Integrated Oncology – CIO Köln Bonn

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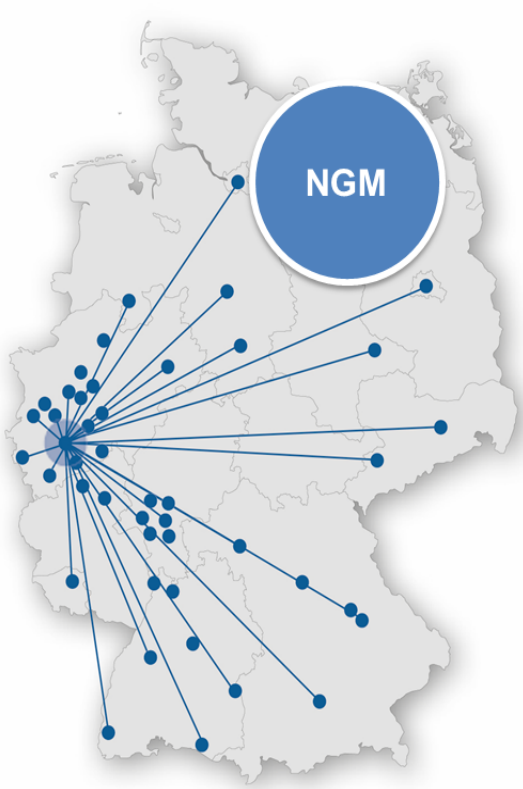
Reimbursement: Integrated Care Contract (ICC)

The Network Genomic Medicine



Public health insurances

AOK RH

First Integrated Care Contract (ICC) (§140a SGB V) in 2014

Further health insurances joined in 2015:
Barmer GEK; TK; BKK VBU; BKK NOVITAS and other private and public
→ over 42,4 Mio. insurants

NGS-based genotyping for **35 % of all German** annually newly diagnosed inoperable **lung cancer pts** is covered by the ICC

Gene panels: Multiplex PCR versus Hybrid Capture

Multiplex PCR panel

NGS_LUN4-QIAG_#39

Gen	Exon
ARAF	7, 10, 15
BRAF	11, 15
CTNNB1	3
DDR2	4 -19
EGFR	18 - 21
ERBB2/HER2	19,
FGFR2	8 - 1
FGFR3	7, 1(
KEAP1	2 - 6
KRAS	2 - 4
MAP2K1	2
MET	
NFE2L2	
NRAS	
PIK3CA	
PTEN	
TP53	

NGS_PROS-QIAG_#49

Gen	Exon
AR	1 - 8
ATM	2 - 63
CTNNB1	3
PIK3CA	1, 4, 7, 9, 20
PTEN	1 - 9
RAD51C	1 - 9
TP53	5 - 8

NGS_GCGC3-QIAG_#33

Gen	Exon	Codon
BRAF	15	582 - 612
DDR2	4 - 19	1 - 856
ERBB2/HER2	8, 19 - 21	302 - 338, 737 - 883
HRAS	2 - 4	1 - 93, 98 - 150
KEAP1	2 - 6	1 - 625
KRAS	2 - 4	1 - 73, 98 - 150
NFE2L2	2	16 - 104
NRAS	2 - 4	1 - 37, 41 - 92, 98 - 150
PIK3CA	1, 4, 7, 9, 20	58 - 117, 304 - 353, 418 - 468, 514 - 554, 980 - 1069
PTEN	1 - 9	1 - 404
RHOA	2, 3	1 - 92
TP53	5 - 9	126 - 331

NGS_MEL2QIAG_

Gen	Exor	
BRAF	11, 15	
CDK4	2	
CDKN2A	1, 2	
GNA11	5	
GNAQ	5	
HRAS	2, 3, 4	
IDH1	4	89 - 138
KIT	9, 11, 13, 17, 18	450 - 513, 550 - 591, 624 - 659, 784 - 824, 825 - 861
KNSTRN	1	1 - 38
KRAS	2 - 4	1 - 37, 41 - 92, 98 - 150
NRAS	2 - 4	1 - 37, 41 - 92, 98 - 150
OXA1L	1	1 - 77
PDGFRA	12, 14, 18	552 - 595, 632 - 667, 814 - 854
PIK3CA	9, 20	514 - 555, 980 - 1069
PTEN	1 - 7	1 - 26, 27 - 55, 56 - 70, 71 - 84, 85 - 164, 165 - 211, 212 - 267, 268 - 342, 343 - 404
RAC1	2	13 - 35
TP53	5 - 9	126 - 186, 187 - 224, 225 - 261, 262 - 306, 307 - 331

Hybrid Capture CAIO Panel

92 Gene und 14 MSI Marker

Gene	Target	Gene	Target	Gene	Target
ABL1	Exons	IDH1	Exons	RAC1	Exon 2
ALK	Breakpoints and Exons	IDH2	Exons	RAD50	Exons
APC	Exons	IGF2R	Exons	RAD51C	Exons
AR	Exons	JAK2	Exons	RB1	Exons
ARAF	Exons	KDR	Exons	RET	Breakpoints and Exons
ATM	Exons	KEAP1	Exons	RHOA	Exon 2,3
ATR	Exons	KIF5B	Breakpoints	RICTOR	Exons
BCL6	Exons	KIT	Exons	ROS1	Breakpoints and Exons
BRAF	Breakpoints and Exons	KNSTRN	Exon 1	RPTOR	Exons
BRCA1	Exons	KRAS	Exons	SMO	Exons
BRCA2	Exons	MAP2K1	Exon 2	STK11	Exons
CCND1	Exons	MET	Breakpoints and Exons	TERT	Exons
CCNE1	Exons	MSH3	Exons	TGFBR2	Exons
CD74	Breakpoints	MTOR	Exons	TMPRSS2	Breakpoints
CDK4	Exons	MYC	Exons	TP53	Exons
CDK6	Exons	MYCL1	Exons	TSC1	Exons
CDKN2A	Exons	MYCN	Exons	TSC2	Exons
CDKN2B	Exons	NF1	Exons	VHL	Exons
CTNNB1	Exons	NF2	Exons		
EGFR	Exons	NFE2L2	Exons		
EML4	Breakpoints	NOTCH1	Exons		
ERBB2	Exons	NOTCH2	Exons		
ERG	Breakpoints	NOTCH3	Exons		
FGFR1	Whole Gene	NR3C1	Exons		
FGFR2	Breakpoints and Exons	NRAS	Exons		
FGFR3	Whole Gene	NRG1	Whole Gene		
FLT1	Exons	NTRK1	Breakpoints and Exons		
FLT4	Exons	NTRK2	Breakpoints and Exons		
GNA11	Exons	NTRK3	Breakpoints and Exons		
GNA13	Exons	OXA1L	Exon 1		
GNAI2	Exons	PDGFRa	Breakpoints and Exons		
GNAQ	Exons	PDGFRb	Breakpoints and Exons		
GNAS	Exons	PIK3CA	Exons		
GNAT2	Exons	POLD1	Exons		
GNG2	Exons	POLE3	Exons		
HDAC2	Exons	PTCH1	Exons		
HRAS	Exons	PTEN	Exons		

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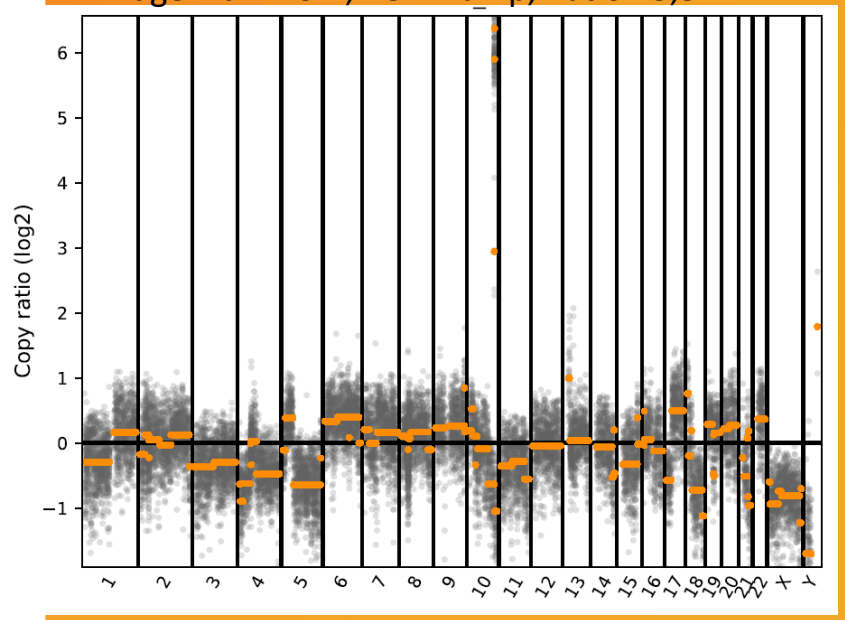
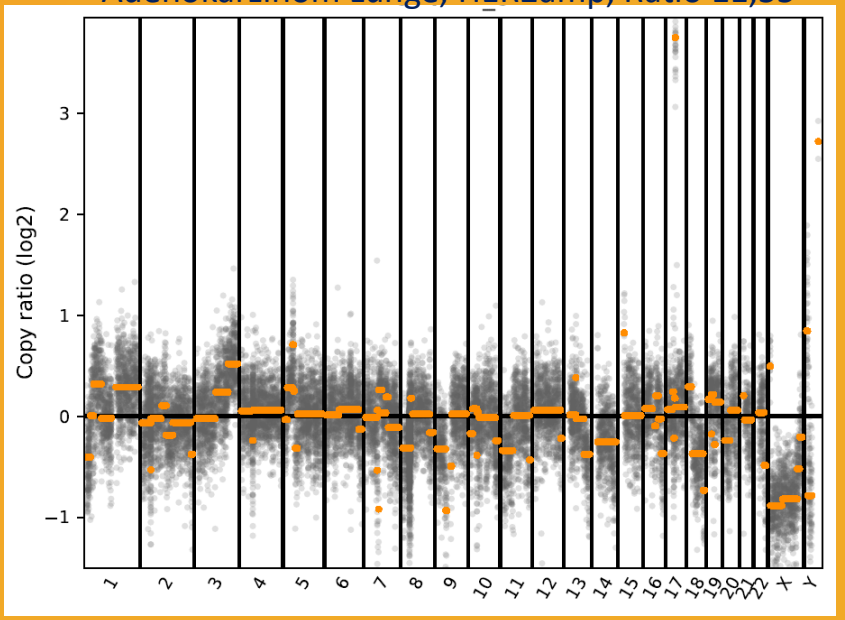
Amplificon Detection via Hybrid Capture Enrichment

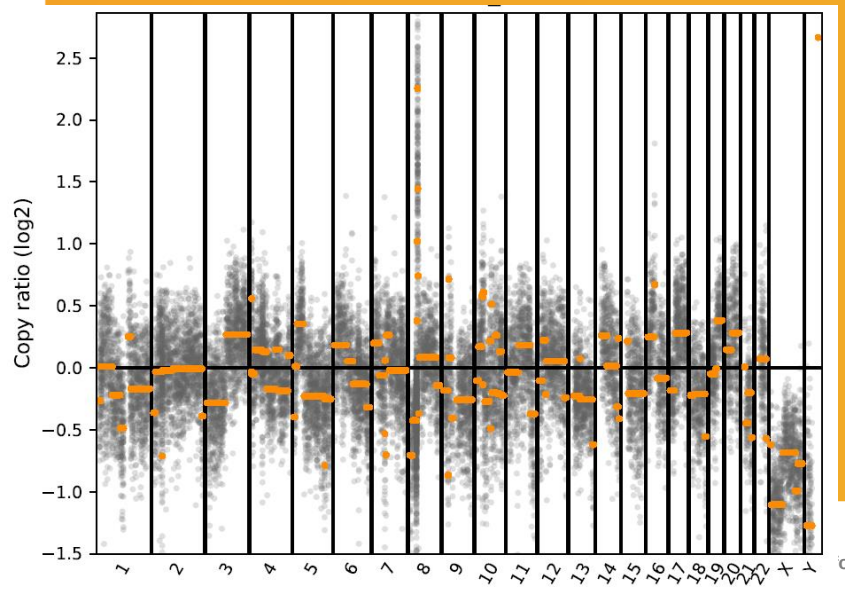
Magenkarzinom, FGFR2amp, Ratio 45,5



Adenokarzinom Lunge, HER2amp, Ratio 11,55



adenosquamöses Lungenkarzinom, FGFR1amp, Ratio 3,67



- analysed by CNVkit:
  https://cnvkit.readthedocs.io/en/stable/

- Reference: WT DNA from FFPE

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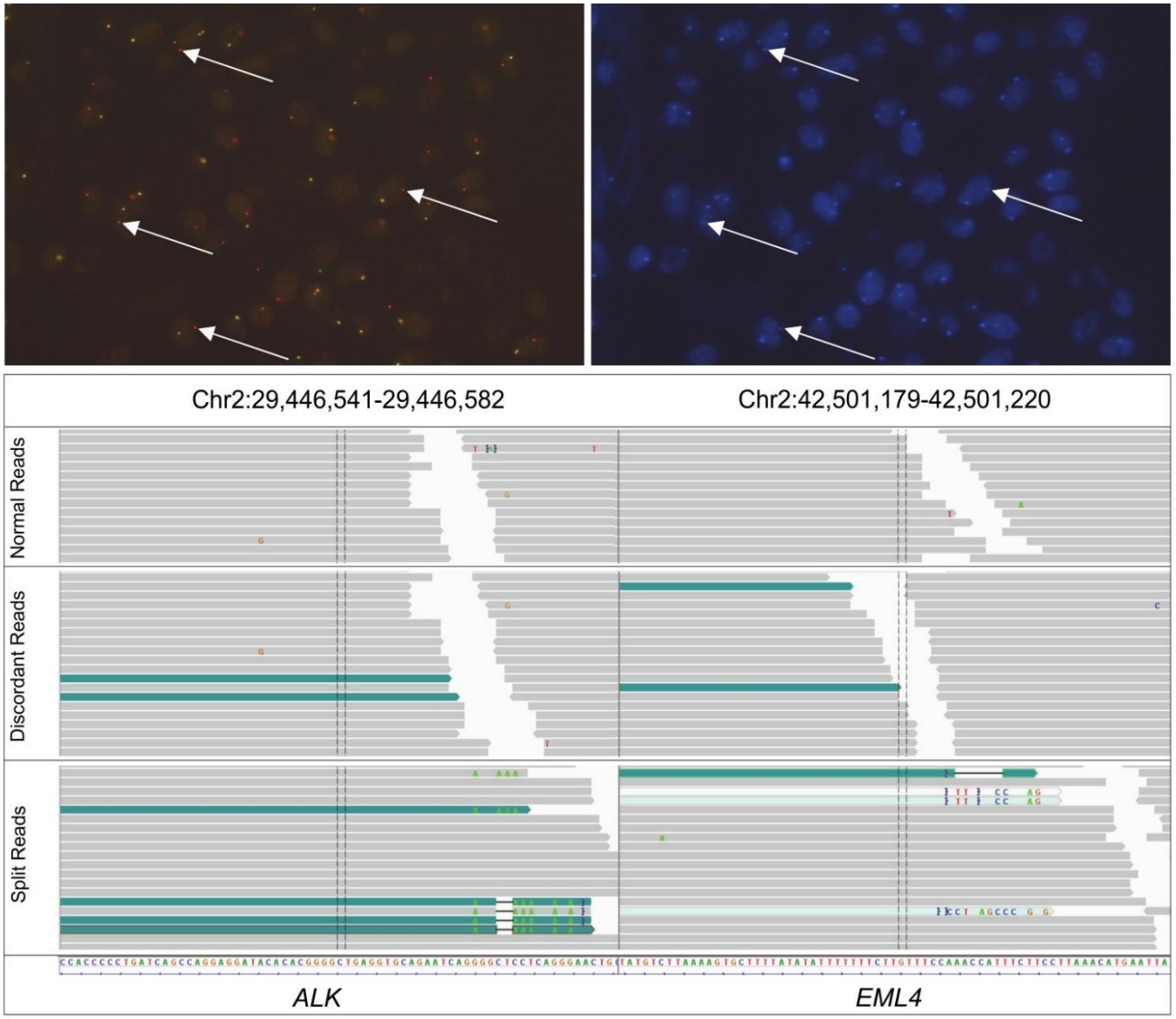
Detection of Gene Fusions by Hybrid-Capture



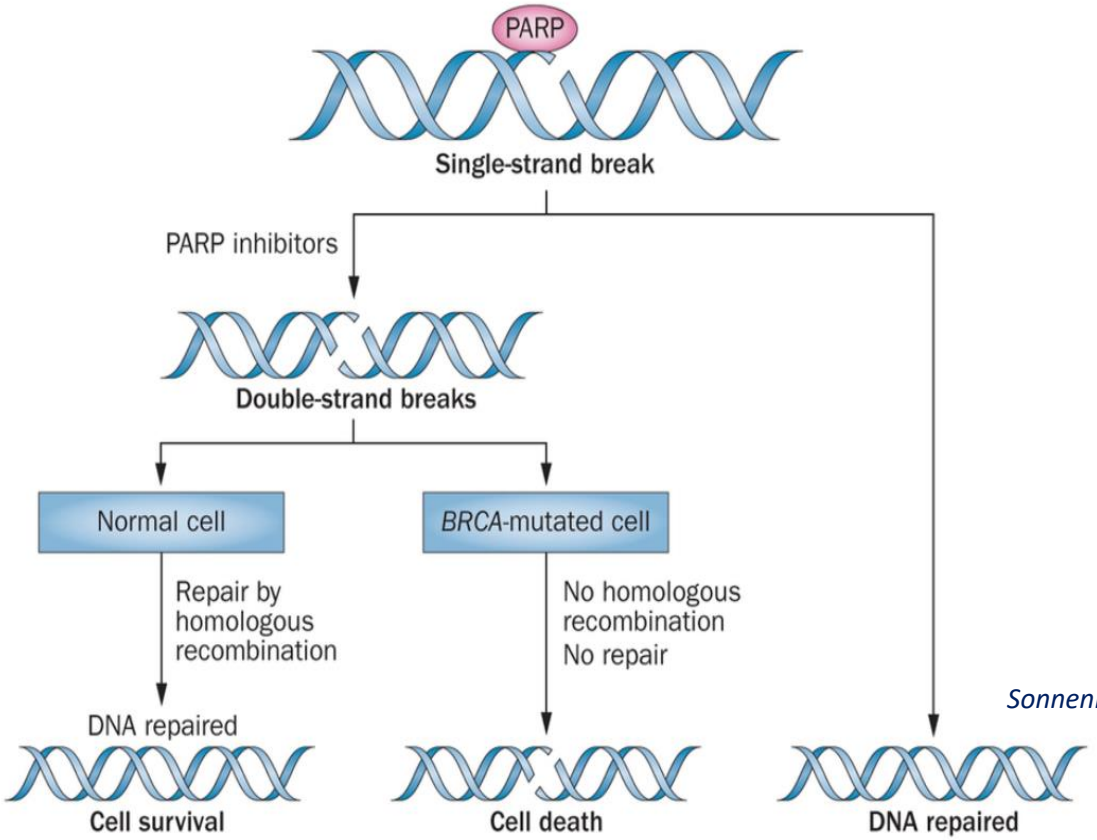
Heydt et al., Ann Oncol 2016

[Bärbel Söhlke | Facebook](https://de-de.facebook.com/barbel.sohlke)
https://de-de.facebook.com/barbel.sohlke
CIO-KölnBonn

BRCA-Diagnostics in Ovarian Carcinomas

- 2015: Approval of the first PARP-inhibitor (Olaparib) for *BRCA*-mutant, relapsed, Platinum-sensitive, serous HG carcinomas of ovary, Fallopian tube or peritoneum.
- in ~25-40% of *BRCA*-mutant ovarian carcinomas there is a somatic mutation (*Cancer Genome Atlas Research, Nature 2011; Hennessy BT et al., J Clin Oncol 2010*)

Mechanism of PARP-inhibition in BRCA-mutant tumors :



Sonnenblick et al., Nat Rev Clin Oncol 2015

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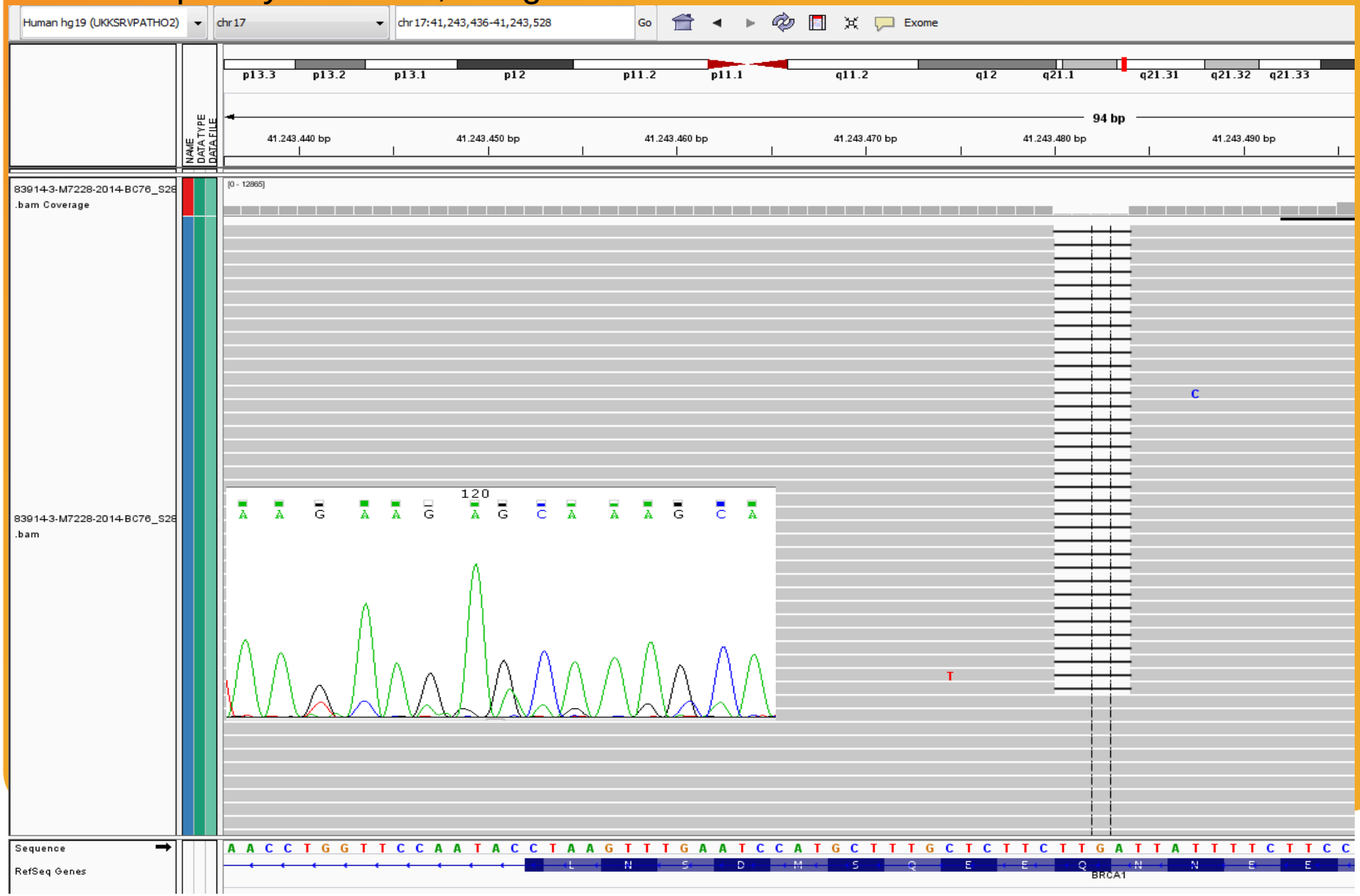
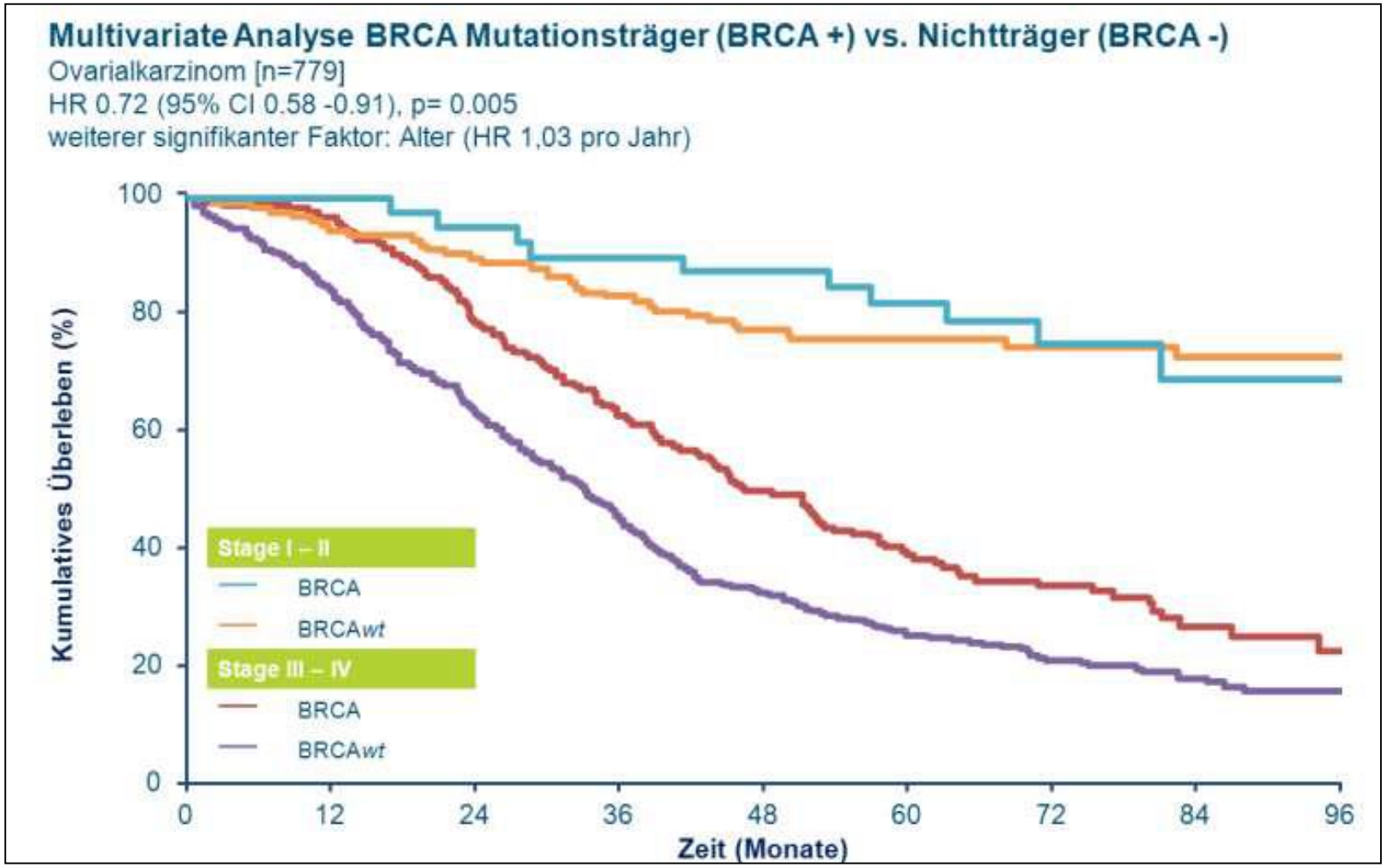
***BRCA1* Mutation** in Ovarian Cancer (Run 5): **Sample 7228_14**

Exon 11: **c.4065_4068del** leads to frameshift mutation p.N1355Kfs*10

Allele frequency: 82.32%, Sanger validated

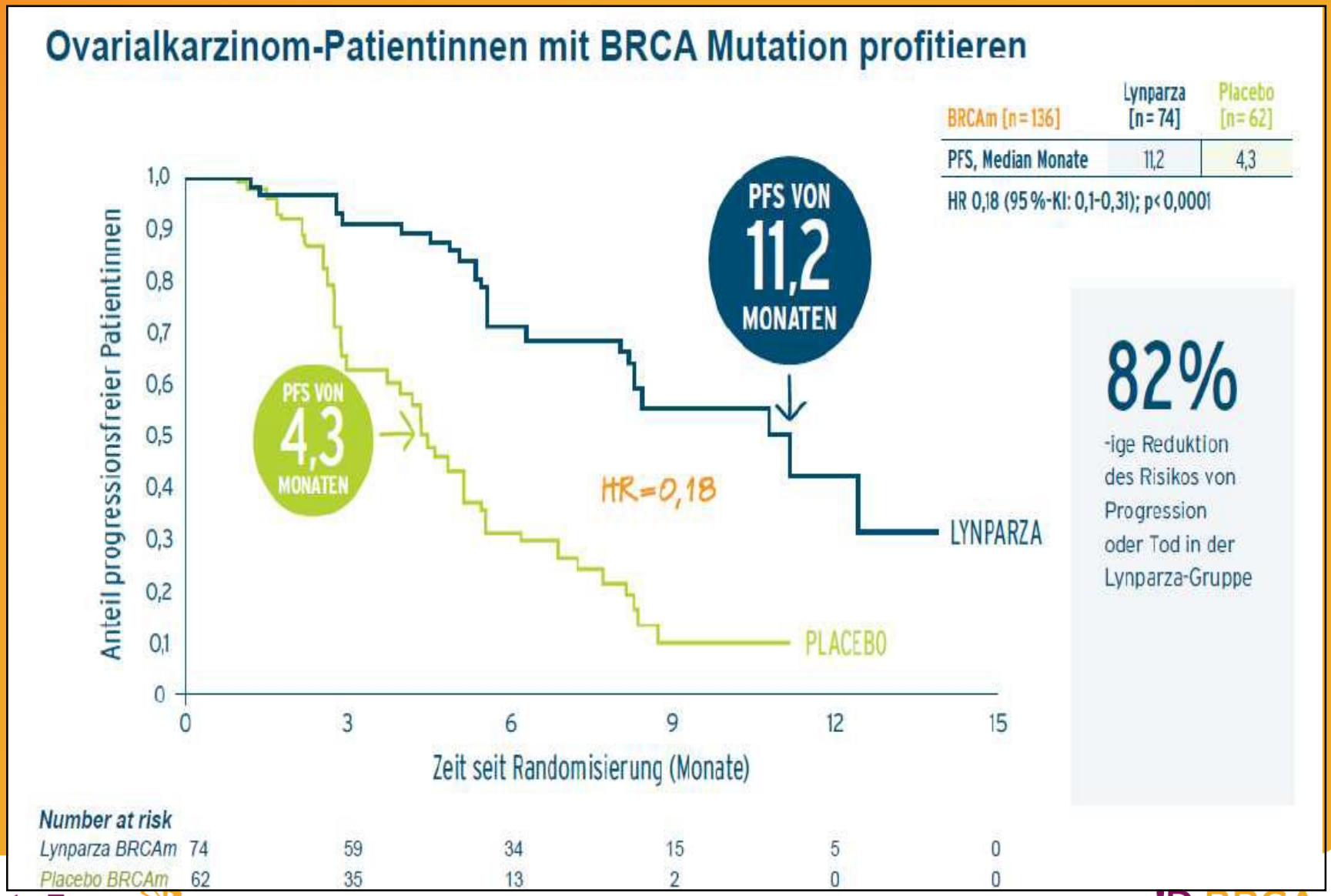


BRCA mutations influence OS of patients with ovarian cancer



Modifiziert nach: Chetrit, A. et al. J Clin Oncol; 26:20-25 2008

Olaparib perlongs PFS in stage IV ovarian cancer patients with BRCA mutations



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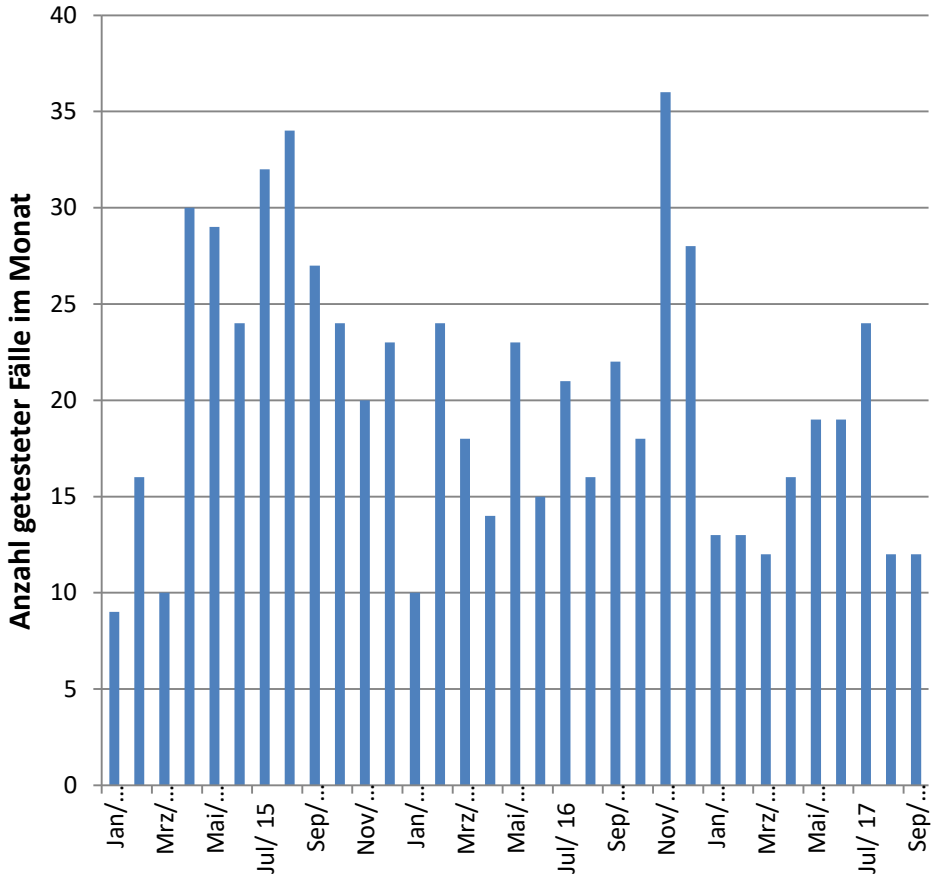
Results of BRCA testing in Cologne, first 21 months:

Cases	N =	%
Total	668	100,0
n.a.	26	3,9
Wild-type	474	72,4
Mutant	168	25,6
all Categories 4/5 (based on databases)	114	17,4
Categories 4/5	80	12,2
Categories 5 (truncating muts))	34	5,2
Category 3	51	7,8



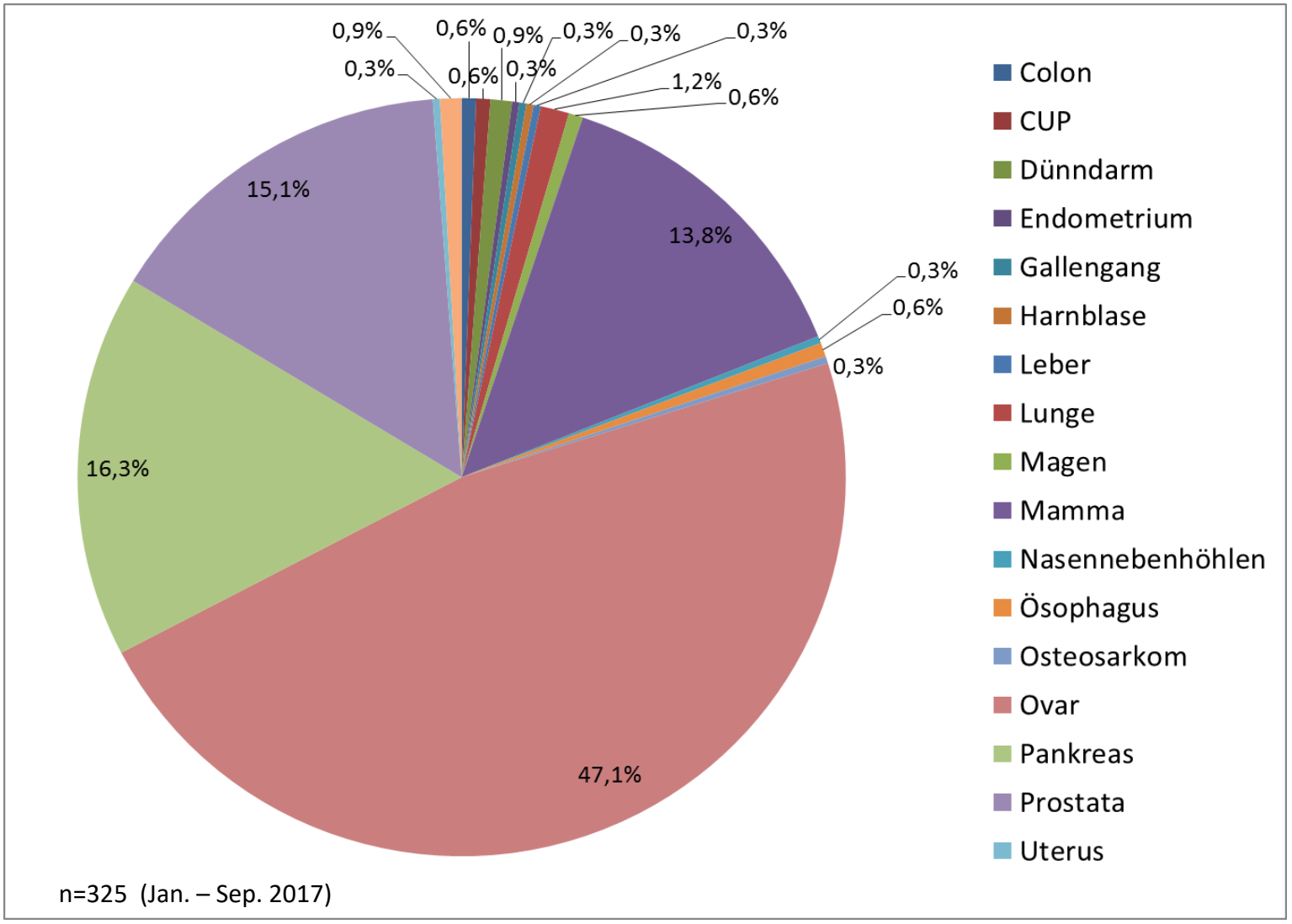
Stand 19.10.2017

Kategorie 1: neutral
Kategorie 2: wahrscheinlich neutral
Kategorie 3: unklare Signifikanz
Kategorie 4: wahrscheinlich pathogen
Kategorie 5: pathogen

Datenbanken (DB):
UMD-DB
ARUP-DB
LOVD-DB
ClinVar-DB
BRCA Exchange

BRCA-diagnostics at Cologne Inst. Pathology (2017)

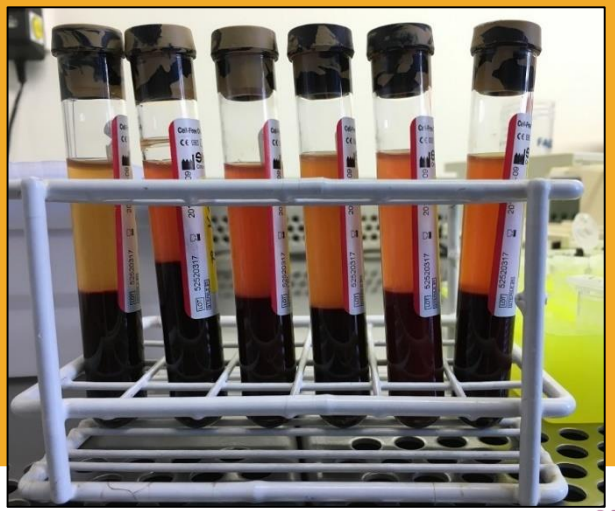
Entities:



n=325 (Jan. – Sep. 2017)

What materials are being tested ?

- FFPE blocks
- Cytology specimens
- Plasma / Blood



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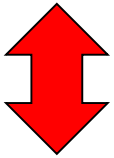
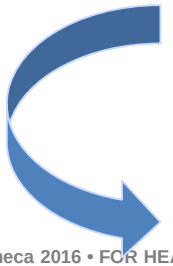
Intention Therapy

Gyn Onkology

Platin-sensitive OvCA, stage III-IV



Institute for Pathology
Tumor Board
CIO-Oncology

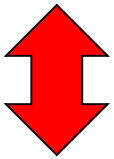


Tumorbezogene Biomarkertestung
Molekulare Pathologie
Klinisches Tumorboard

Intention Genetic Consulting

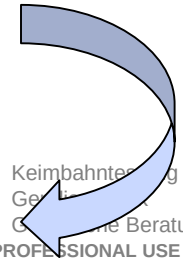
Primary tumor, Fam+

Risc-Surveillance-Prevention



National Center for Familial Tumors
NCFT Board

Surveillance Plan
Preventive Surgery
Family screening



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