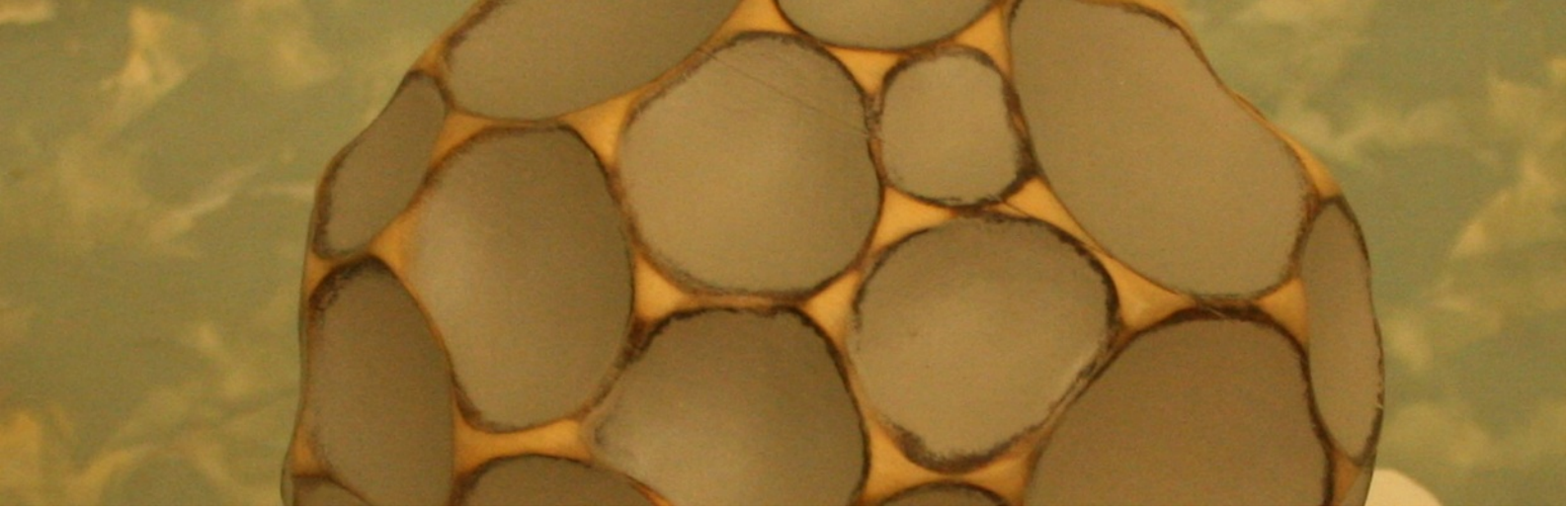


Understanding Cancer by Whole Genome Studies

Authors: Christof von Kalle
Submitted: 5. November 2016
Published: 5. November 2016
Volume: 3
Issue: 6
Keywords: cancer, whole genome studies, bioethics, symposium
DOI: 10.17160/josha.3.6.248

Understanding Cancer by Whole Genome Studies

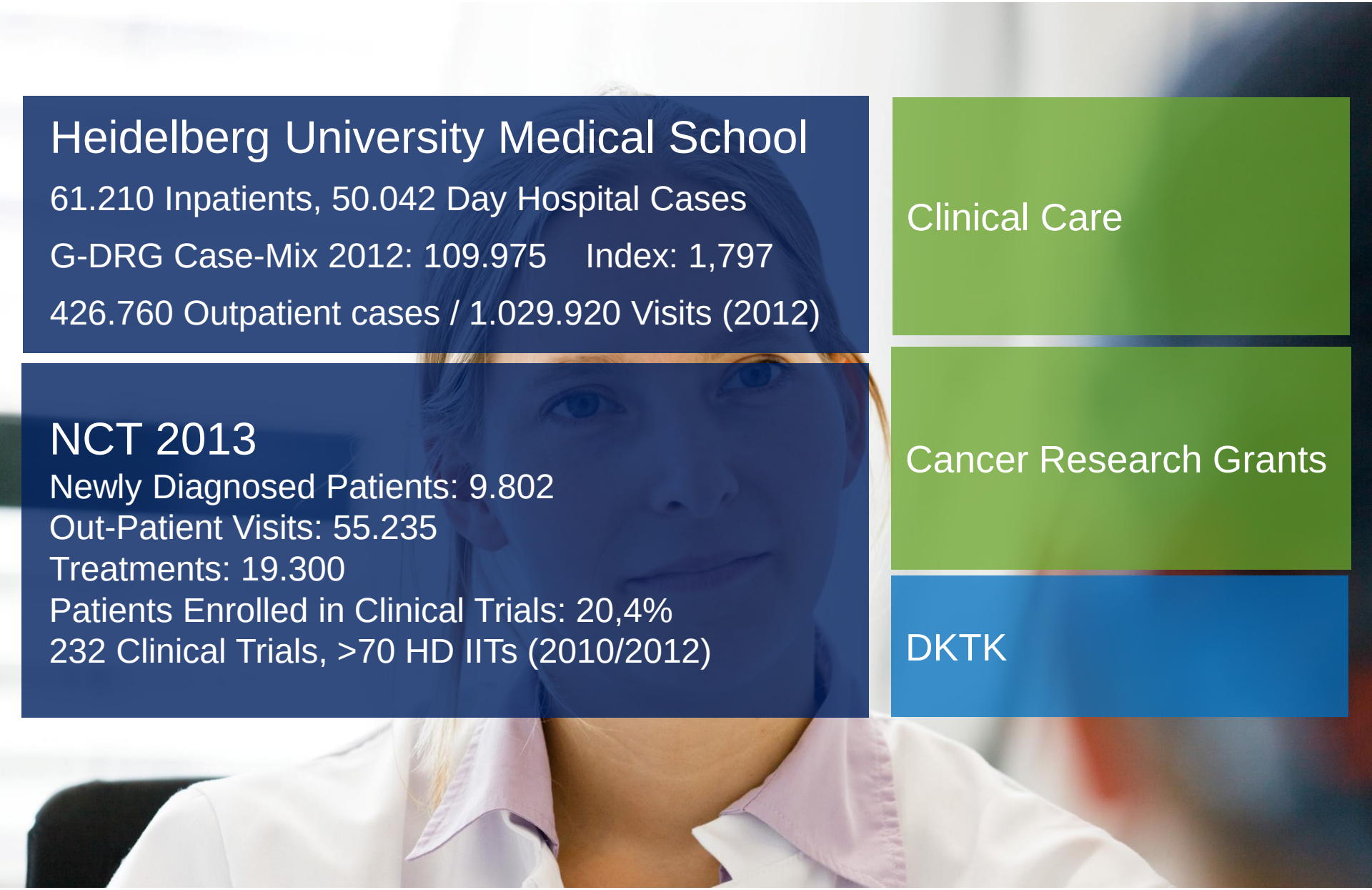
Christof von Kalle
NCT Heidelberg

Oncology – A Leading Topic in Heidelberg

EXCELLENCE in

- Clinical Translation and Basic Research
- Clinical and Translational Cancer Programs
- Interdisciplinary Patient Care

NCT - Interdisciplinary Patient Care



Heidelberg University Medical School

61.210 Inpatients, 50.042 Day Hospital Cases

G-DRG Case-Mix 2012: 109.975 Index: 1,797

426.760 Outpatient cases / 1.029.920 Visits (2012)

NCT 2013

Newly Diagnosed Patients: 9.802
Out-Patient Visits: 55.235
Treatments: 19.300
Patients Enrolled in Clinical Trials: 20,4%
232 Clinical Trials, >70 HD IITs (2010/2012)

Clinical Care

Cancer Research Grants

DKTK

NCT 1.0 – Principles & Practice

UniversitätsKlinikum Heidelberg

NCT

dkfz.

All
Clinical Departments with Oncological Activities

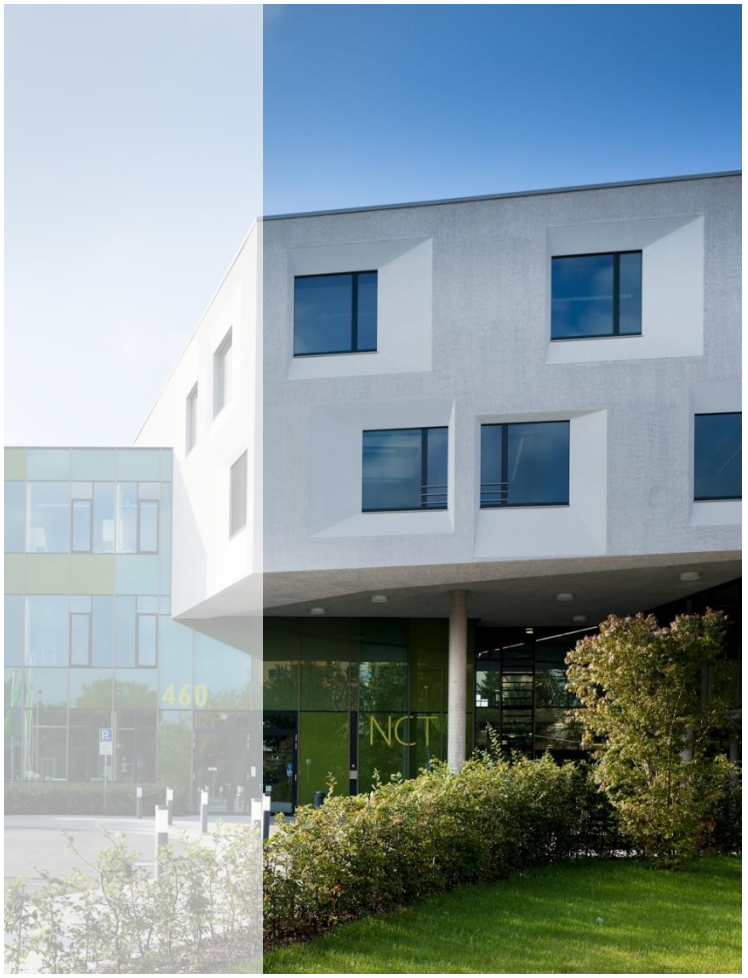
EVERY PATIENT

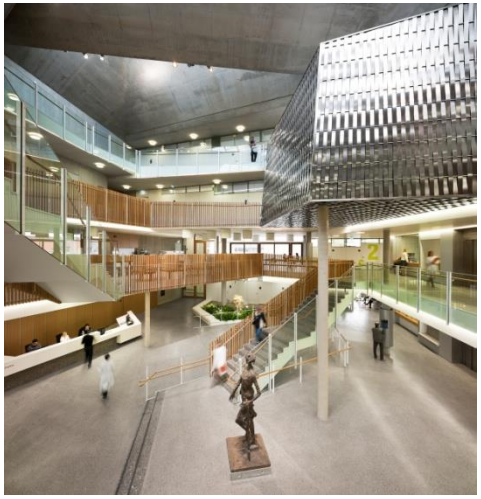
All
Translational Cancer Research Groups

EVERY TRIAL

Creating Interdisciplinarity

NCT 2.0 – New Building & Structures





IDENTITY & VISIBILITY

NCT 3.0 – The Next Level

DELIVER

Precision Oncology

EXCEL

Clinical and Translational Cancer Programs

GROW

Building

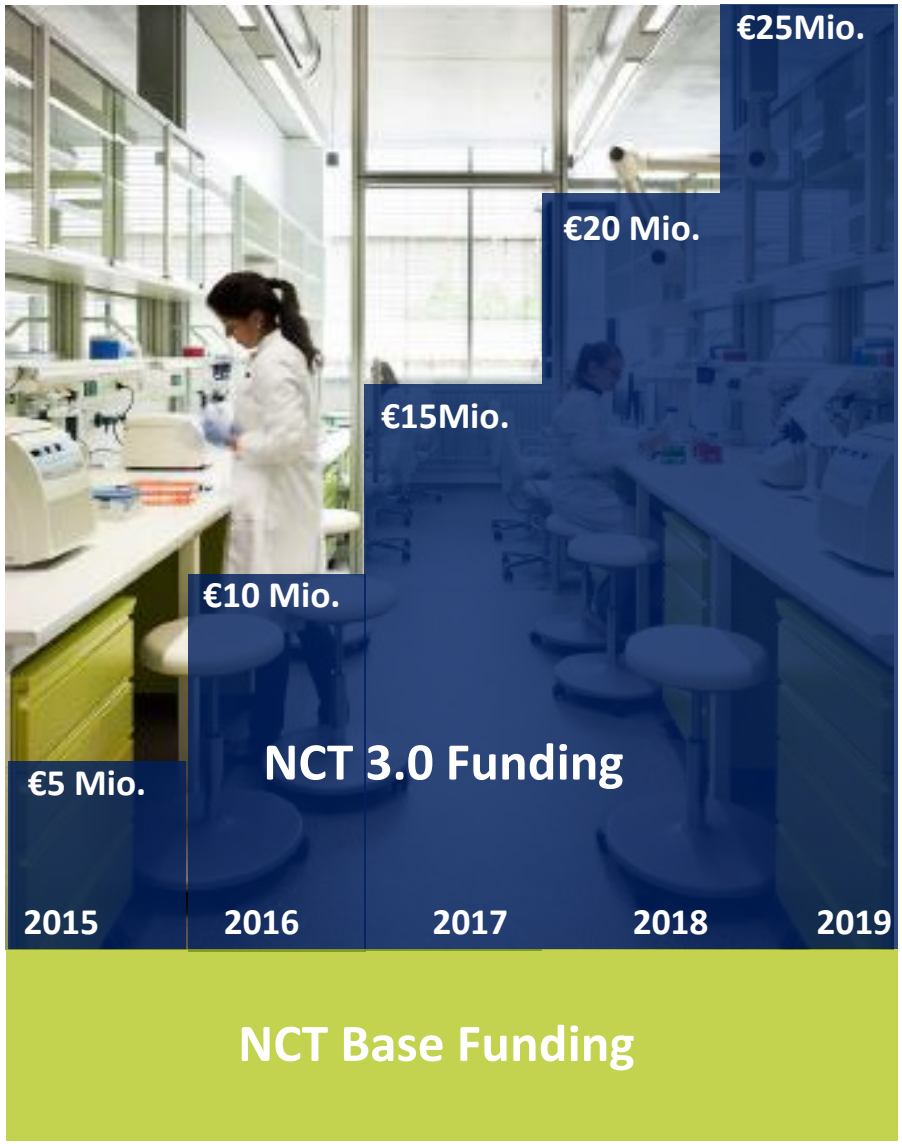
Partners

SCIENTIFIC & CLINICAL EXCELLENCE

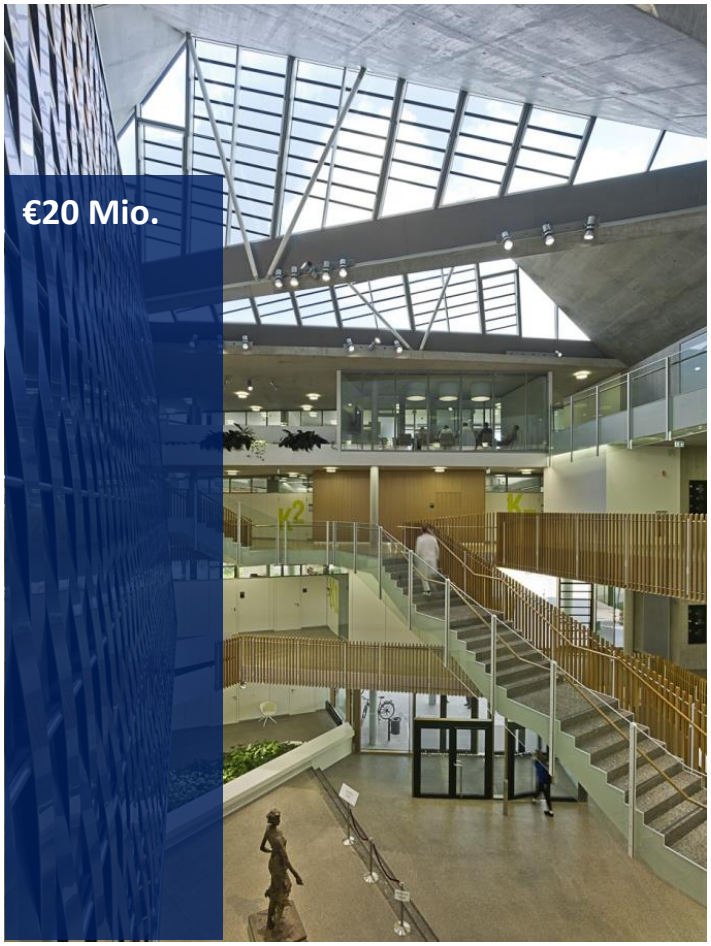
NCT 3.0 - Strategic Aims

- Position NCT as a Leading Comprehensive Cancer Center in Europe
- Expand NCT Precision Oncology Program
- Deliver at the Point of Care
  Translation – Personalization – Precision
- Expand Internationally Recognized Clincial Cancer Programs & Profile Areas
- Employ Novel, Innovative Treatment Concepts

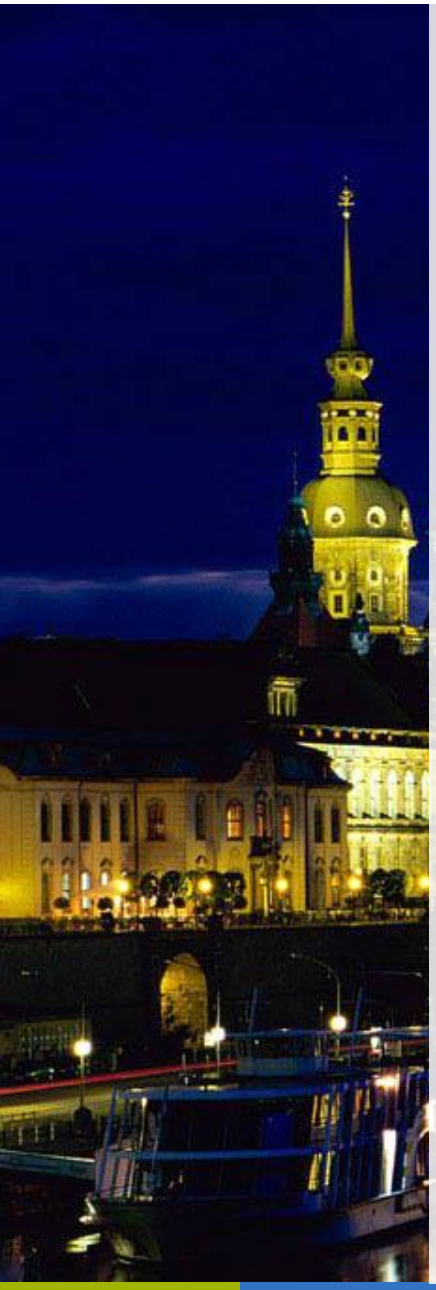
NCT 3.0 – Programmatic Funding



Building Extension



NCT Dresden



FUNDING

Up-to €15 Mio p.a. in 2019
New Research Building
CCC Building funded by DKH

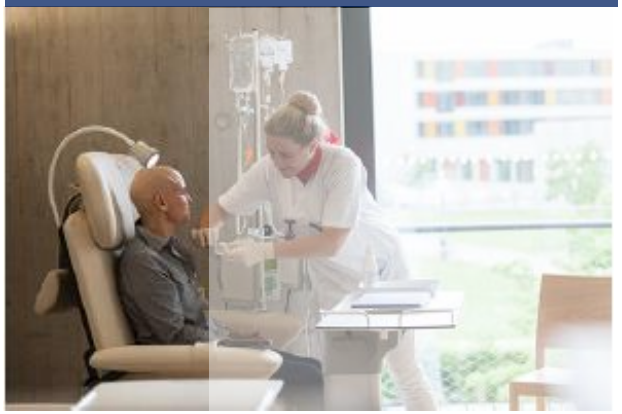
PROFILE AREAS / RECRUITMENTS

- Innovative Medical Oncology
- Translational Research
- Radioimaging
- Theragnostics
- Link-up DKFZ HIPO, NCT POP & NCT MASTER
- Immunotherapy
- Systems Biology
- Multidisciplinary Profile Areas

NCT 3.0 - Profile Areas to be Expanded

DELIVER

- NCT Precision Oncology
- Novel, Innovative Treatment Concepts
- Clinical Trials & Biobanking Infrastructure/Expertise

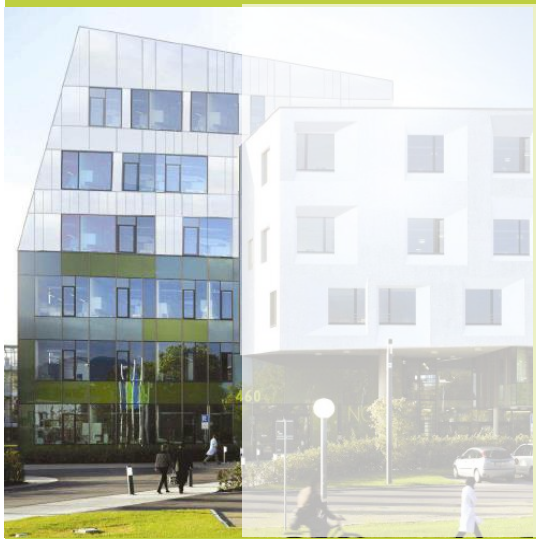


EXCEL

- Molecular Stratification
- Immunotherapy
- Profile Areas - Neurooncology Pancreatic Cancer, Radiooncology, Lung Cancer, Prostate Cancer
- NCT OncoCheck-Programm
- Innovative Oncological Imaging
- Molecular Tumor Pathology
- Biomarker Platform
- NCT DataThereHouse & Cancer Registry
- New Programs – CardiOncology, Palliative Oncology, Hematology
- NCT Basic Research Pipeline

GROW

- Partnerships
- Funding Programs
- Recruitments
- Talents
- Facilities



NCT Precision Oncology Program

STRATIFIED ONCOLOGY

CLINICAL EVALUATION & TRIALS

DATA INTEGRATION

TARGET EXPLOITATION

TARGET CHARACTERIZATION

TARGET IDENTIFICATION

NCT DataThereHouse

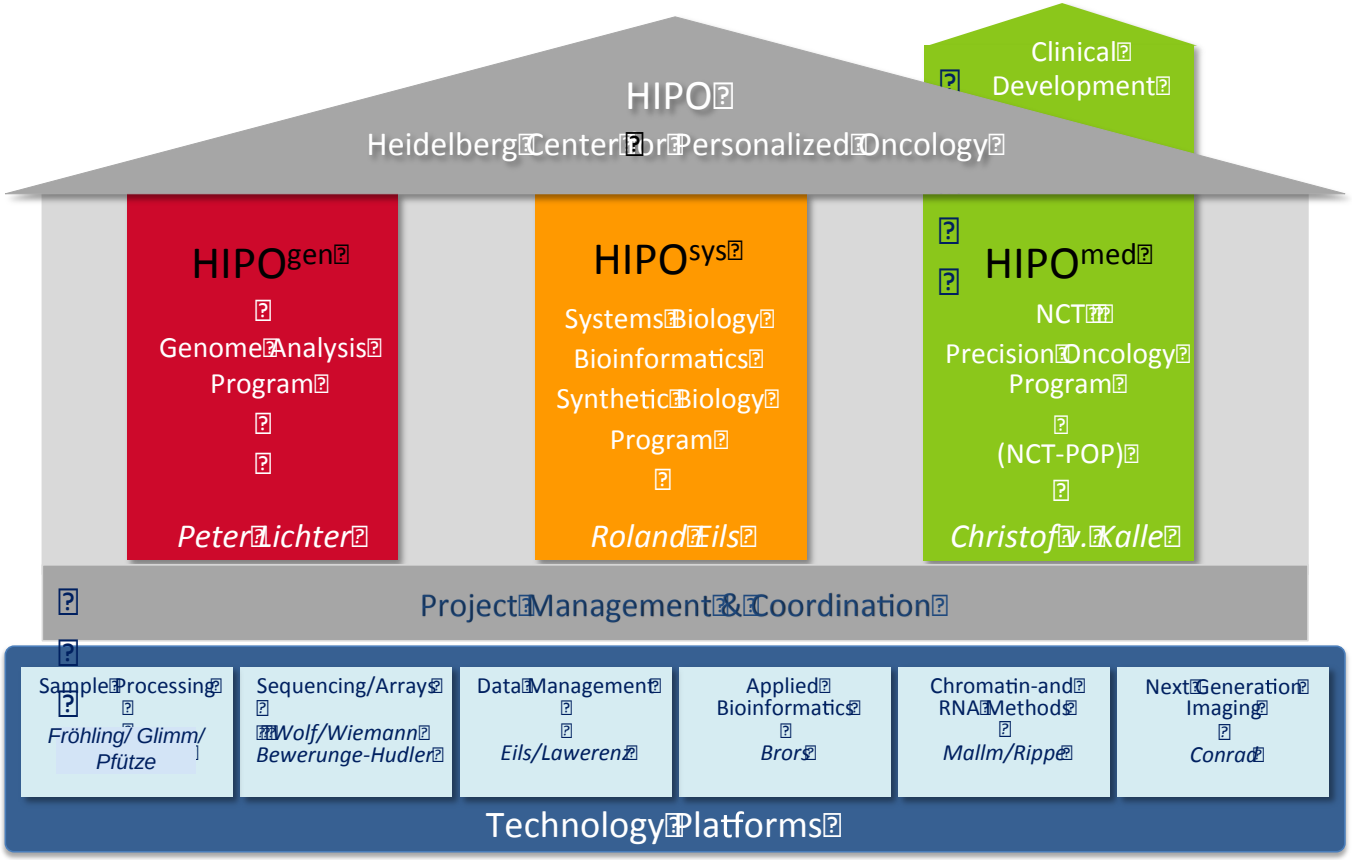
Organized in SAP HANA

NCT OMICS

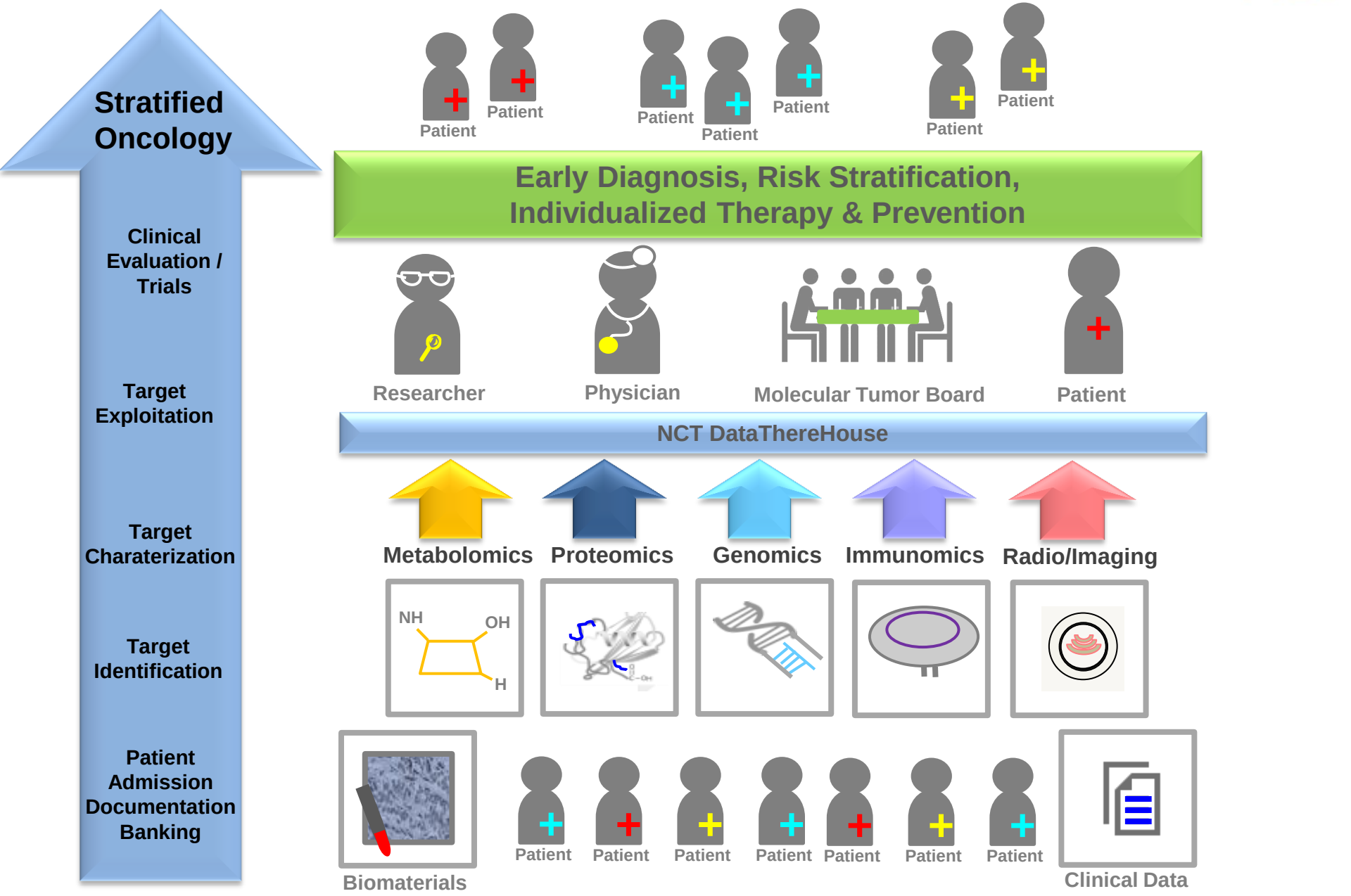
PATIENT ADMISSION – DOCUMENTATION - BANKING

The Paradigm Shift:
Imaging each Individual Patient‘s Cancer
At the Molecular Level

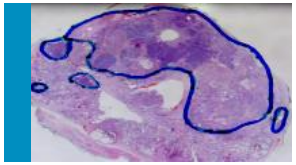
Heidelberg Center for Personalized Oncology

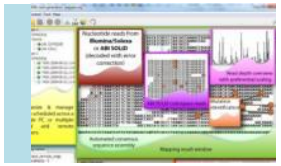


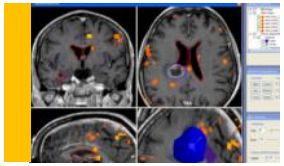
NCT Precision Oncology Program



NCT MASTER Workflow



PATIENT ADMISSION
ENROLLMENT
CLINICAL DATA

DIAGNOSIS &
SAMPLING

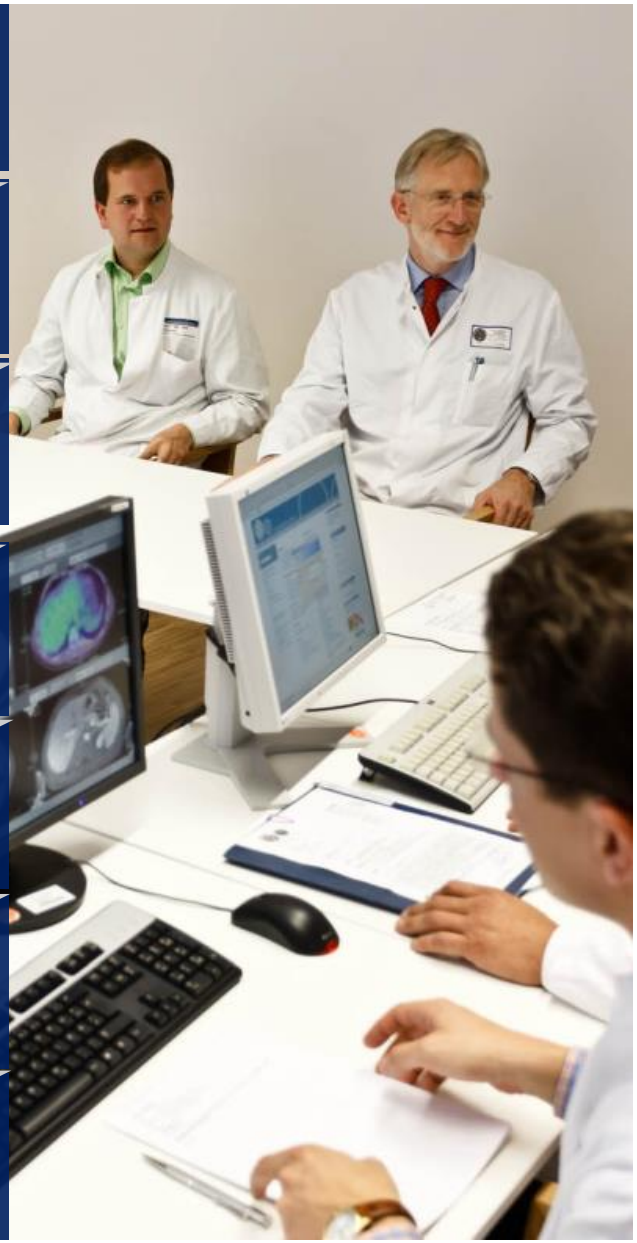
NCT OMICS

BIOINFORMATICS
CLINICAL REPORT

MOLECULAR
TUMOR BOARD

INDIVIDUALIZED
THERAPY &
TRIALS

RESPONSE
RESISTANCE
PREVENTION



NCT DataThereHouse (SAP HANA)

National High Throughput Sequencing Core Unit

Illumina
xten Cluster

2009 2010 2011 2012 2015

ICGC Sequencing

NCT Precision Oncology Program

ICGC

International Cancer Genome Consortium

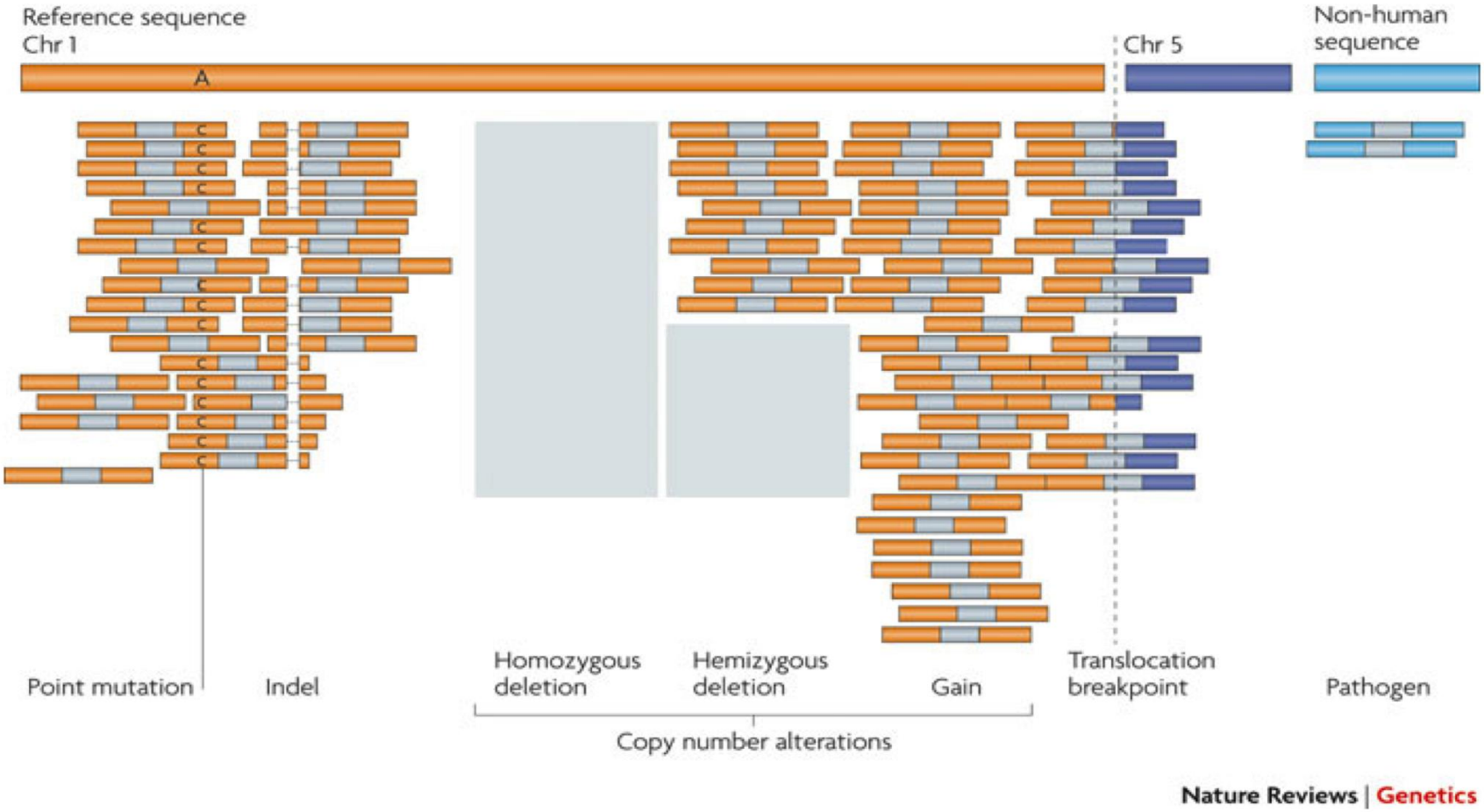
INFORM

hipo

Deutsches Konsortium für Translationale Krebsforschung

DNA Sequencing Methods Applied in Oncology

Cancer genome sequencing



Meyerson, Nat Rev Genet 2010

Applied Bioinformatics

Benedikt Brors

PRIMARY ANALYSIS

SECONDARY ANALYSIS

TERTIARY ANALYSIS: „INTERPRETATION“

OneTouchPipeline

RNA sequences

DNA sequences

fastq QC

alignment

duplicates

lane merging

calculate coverage

genotype matching

Pathogen integration

Ploidy prediction

INDELs

SNVs

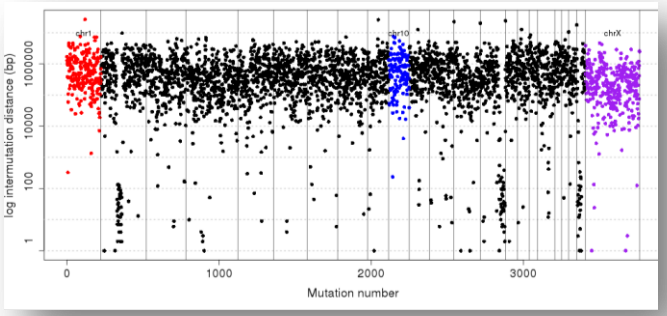
Copy number variants

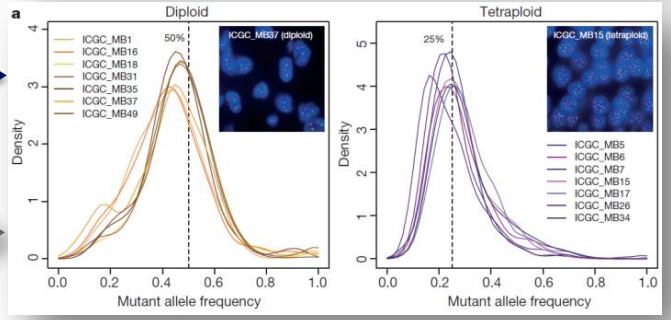
Structural Variants

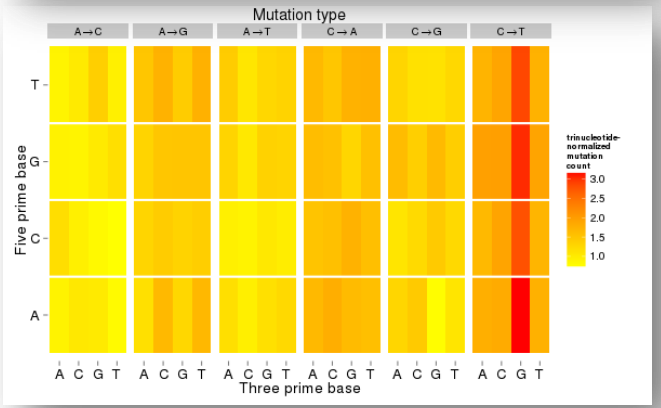
Alternative Splicing

Mutation in RNAseq?

Mutation annotation

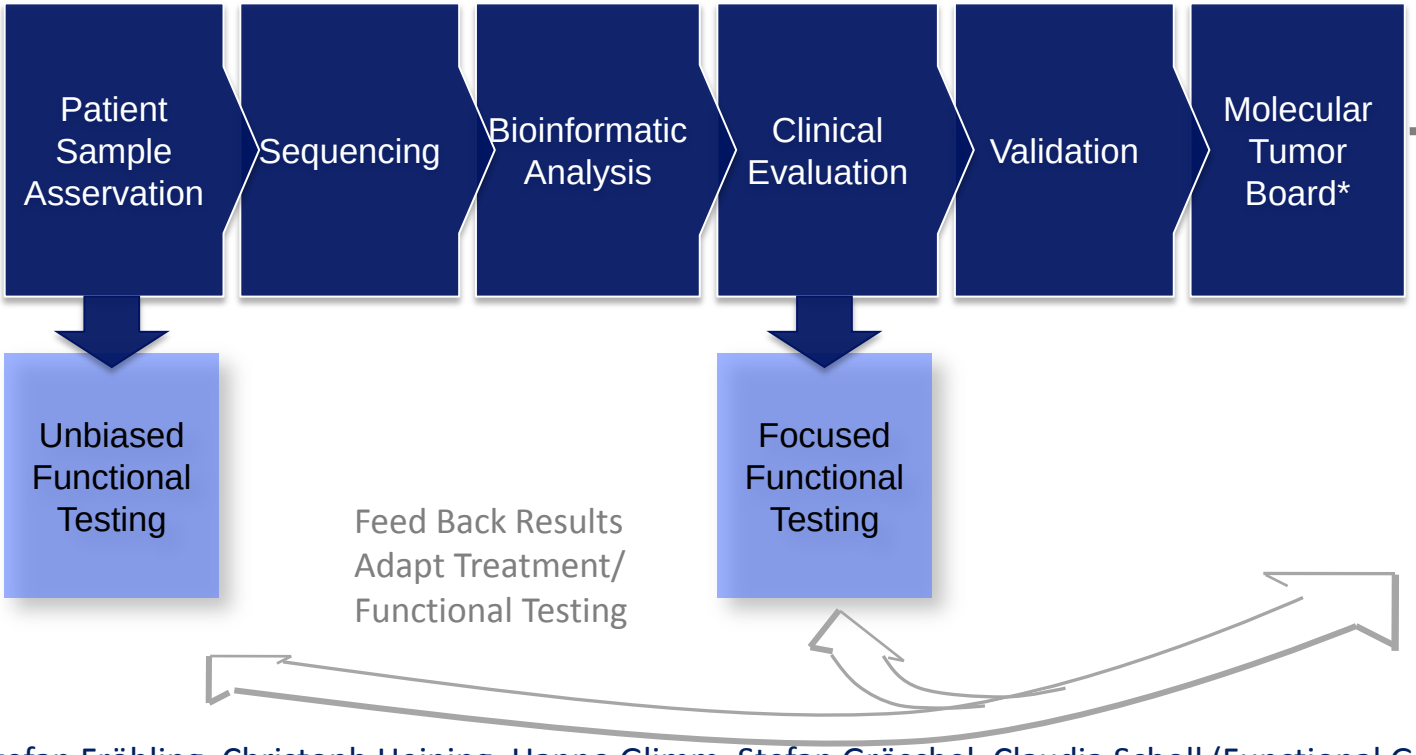






NCT MASTER – Registry & Interventional Trial

Hanno Glimm **Stefan Fröhling**

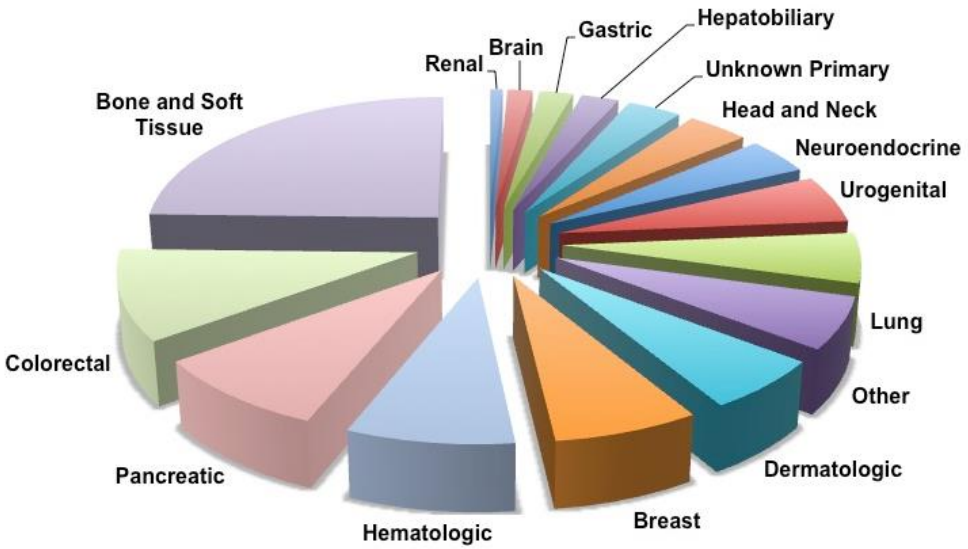


Stefan Fröhling, Christoph Heining, Hanno Glimm, Stefan Gröschel, Claudia Scholl (Functional Genomics)
DKTK – LMU München, Frankfurt, Dresden, Essen/Düsseldorf, Freiburg, Berlin

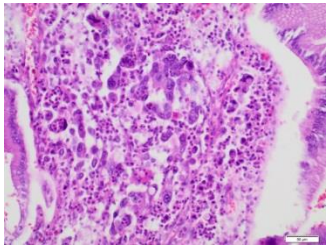
NCT MASTER – Registry & Interventional Trial

CURRENT STATUS

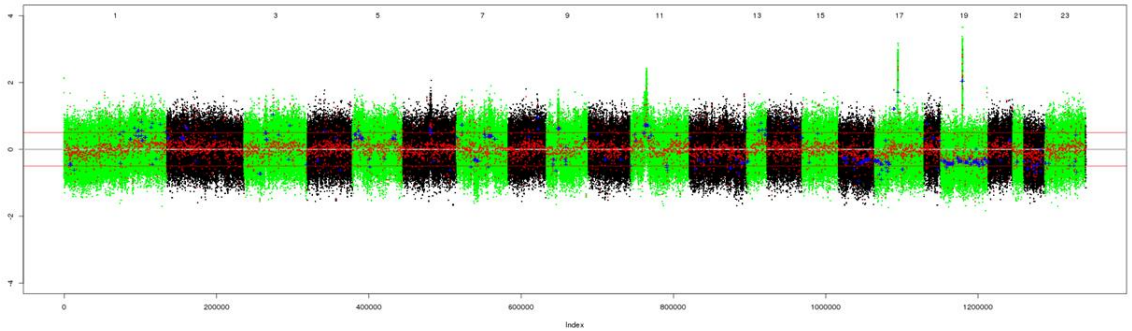
Entities

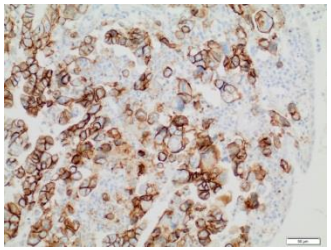


NCT MASTER – Case Report I)



H&E





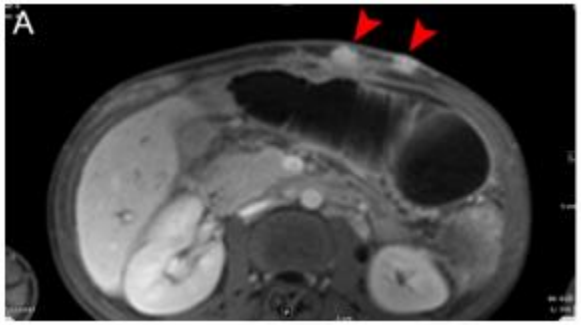
ERBB2

Metastatic gallbladder carcinoma

- **Peritoneal and cutaneous metastasis during adjuvant chemotherapy with oxaliplatin/gemcitabine**

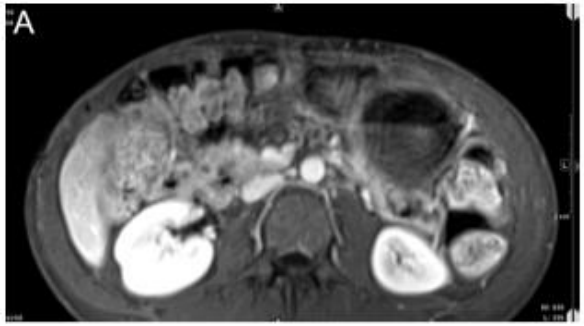
Amplification of chromosome 17q12, including *ERBB2*

- **Outlier *ERBB2* mRNA expression**
- **ERBB2 protein expression by immunohistochemistry (3+ according to ASCO guidelines)**



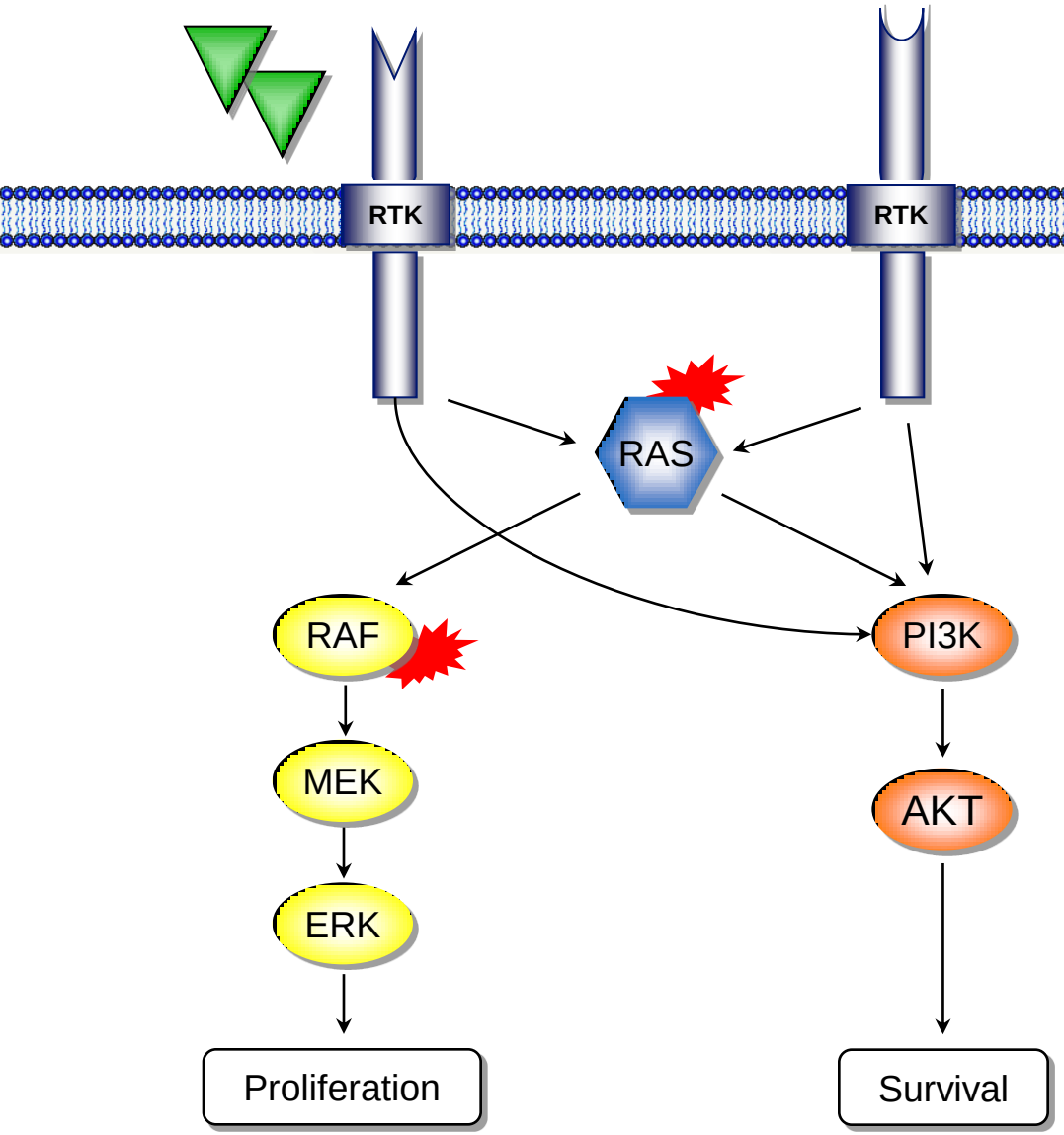
Dual ERBB2 blockade: trastuzumab/pertuzumab

Complete remission for >12 months



Czink et al. Z Gastroenterol 2016

NCT MASTER – Case Report II)



Rationale for Experimental Targeted Treatment

35-year-old patient with **bladder tumor**, bilateral **pulmonary masses**, enlarged hilar **lymph nodes**, and disseminated **bone lesions**
- Histology inconclusive
- Refractory to cyclophosphamide, doxorubicin, vincristine, and prednisone

Co-existence of **HRAS p.Q61R** and **BRAF p.F595L** within single clone

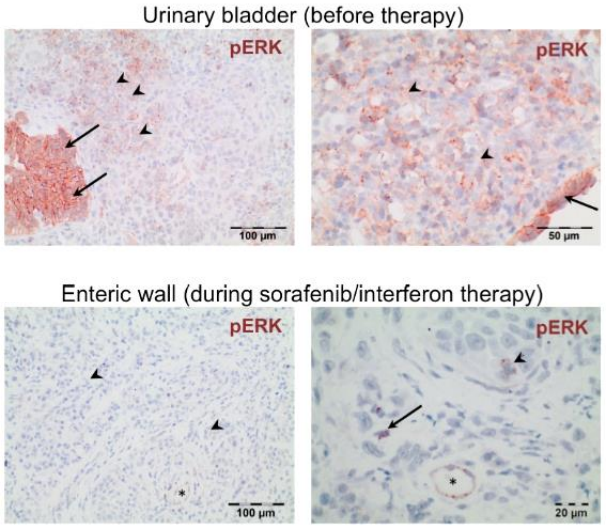
Mutational spectrum highly suggestive of **non-Langerhans histiocytosis**

Rationale for MAPK pathway blockade using **sorafenib** or **MEK inhibitor**

No rationale for vemurafenib or dabrafenib due to **risk of paradoxical MEK/ERK activation**

Kordes et al. Leukemia 2016

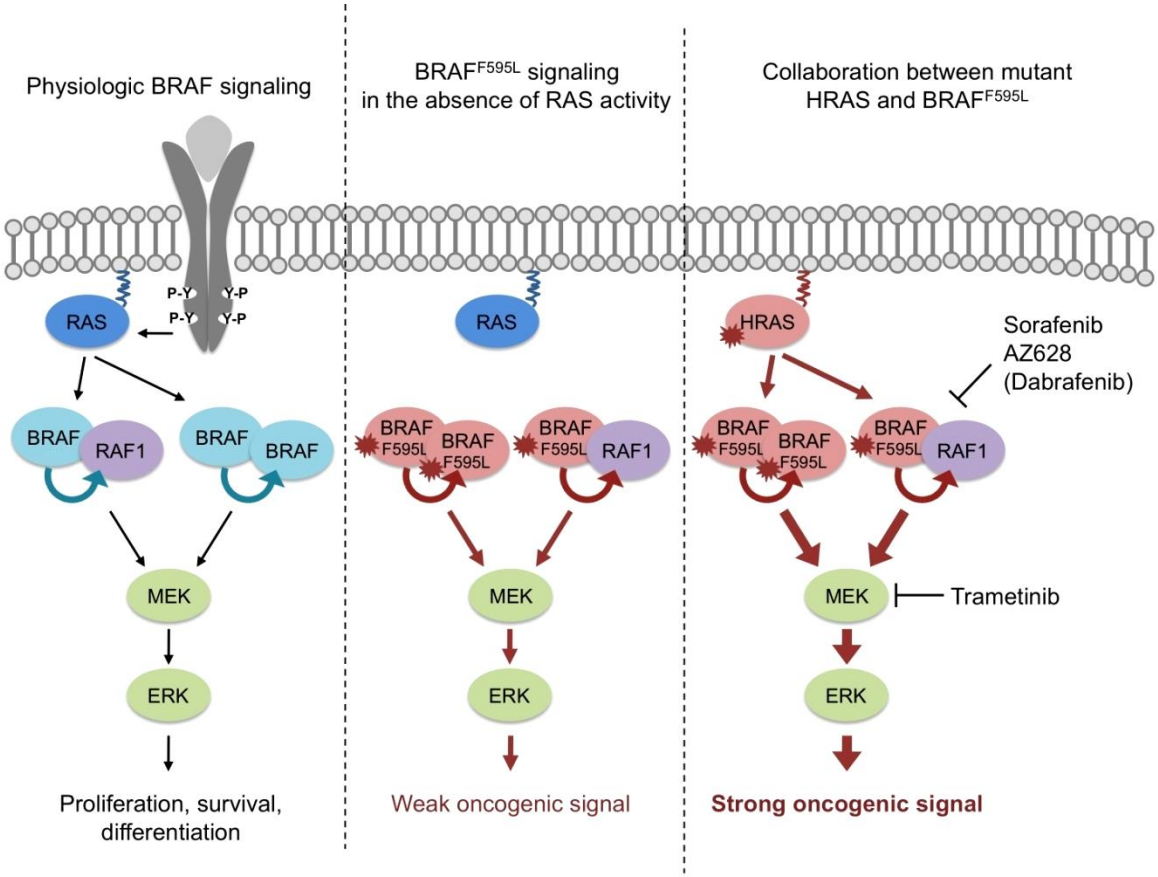
NCT MASTER – Case Report II)



Loss of phosphorylated ERK expression in tumor cells after 3 weeks of **sorafenib** and interferon alpha treatment

Frequent **coexistence of intermediate-activity BRAF mutations** and **oncogenic RAS** in various cancers
Wan et al. Cell 2004
COSMIC database

Rationale for Experimental Targeted Treatment

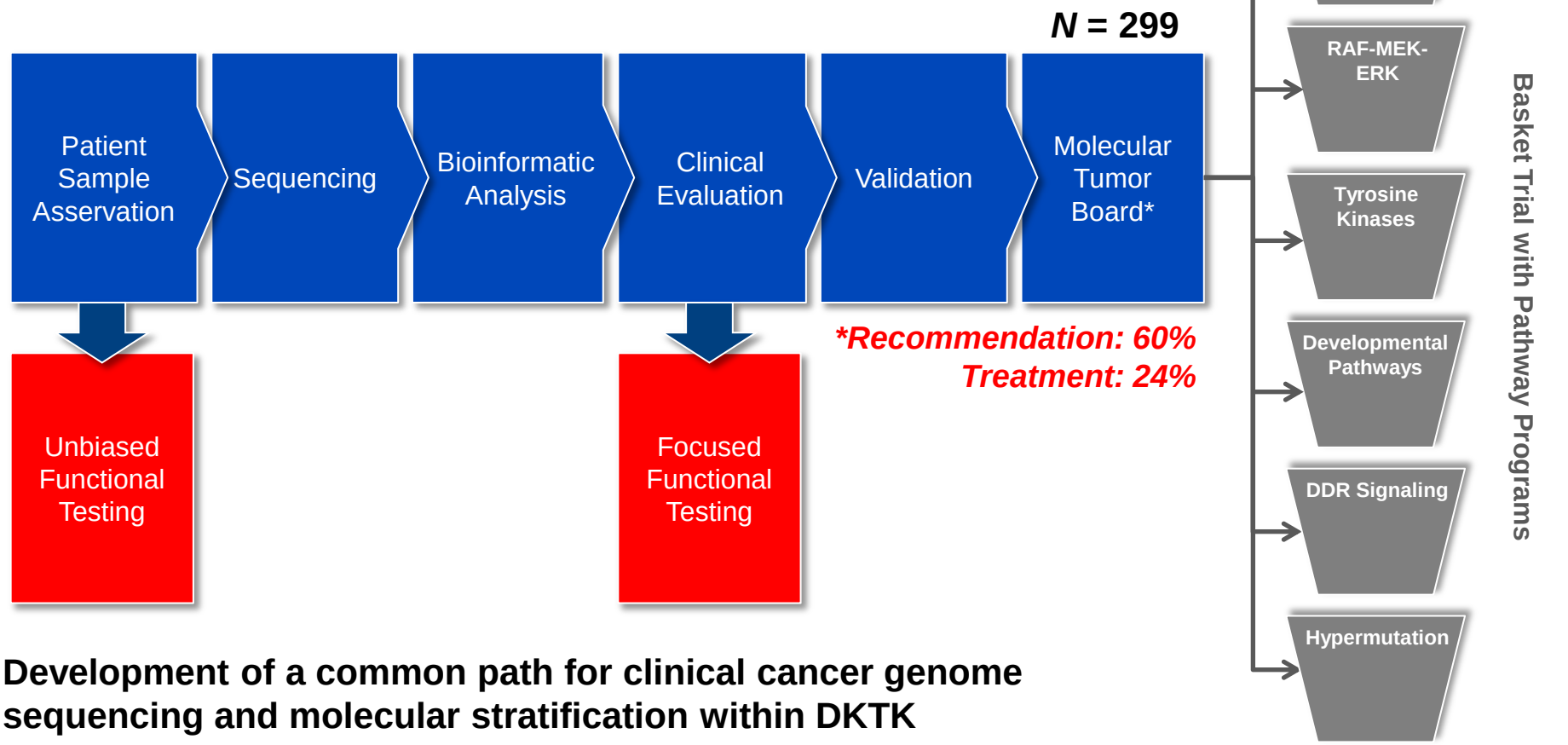


Cooperative activity of **BRAF p.F595L** and **HRAS p.Q61R** in aggressive histiocytic sarcoma

Kordes et al. Leukemia 2016

DKTK MASTER

Critical Next Steps



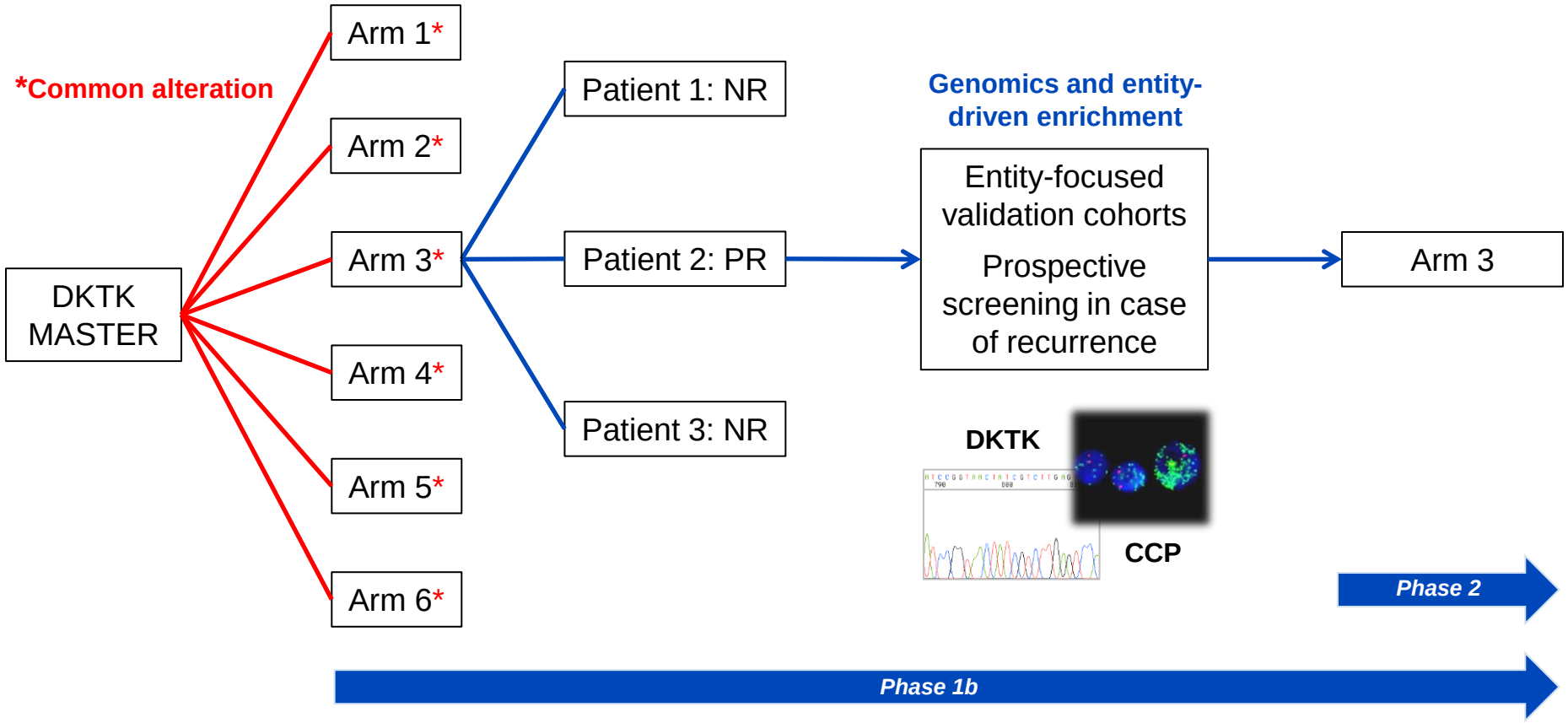
Development of a common path for clinical cancer genome sequencing and molecular stratification within DKTK

Further development of strategies for clinical translation

Refinement and expansion of strategies for functional annotation

Strategies for Clinical Translation

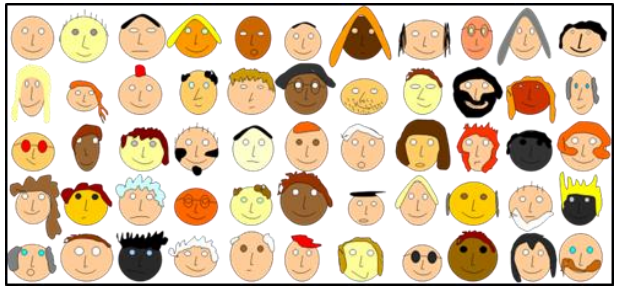
Continuous Reassessment with Flexible Extension – CRAFT



Study Arm Level
Responsible investigators, statistical planning/assessment, molecular pathology, prospective enrichment strategy, phase 1b/2a switch

Richard Schlenk (Ulm)
Meinhard Kieser (Heidelberg)

INFORM = INdividualized therapy FOr Relapsed Malignancies in childhood



Angelika Eggert

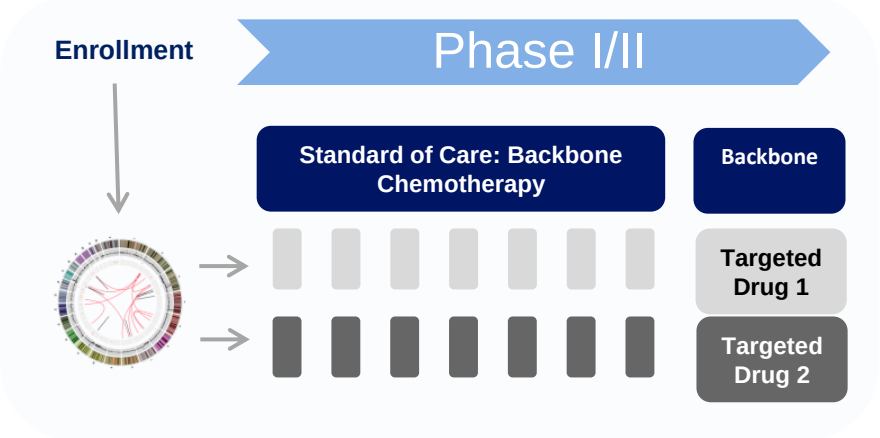
Olaf Witt

Peter Lichter

Stefan Pfister

Feasibility-Registry Study (Year 1+2)	
ALL	AML
HGG (incl. DIPG)	Medullo/Ependym.
Ewing Sarcoma	Neuroblastoma
NHL	Osteosarcoma
Rhabdomyosarcoma	Rhabdoid Tumors

Clinical Trial (Year 3-5)



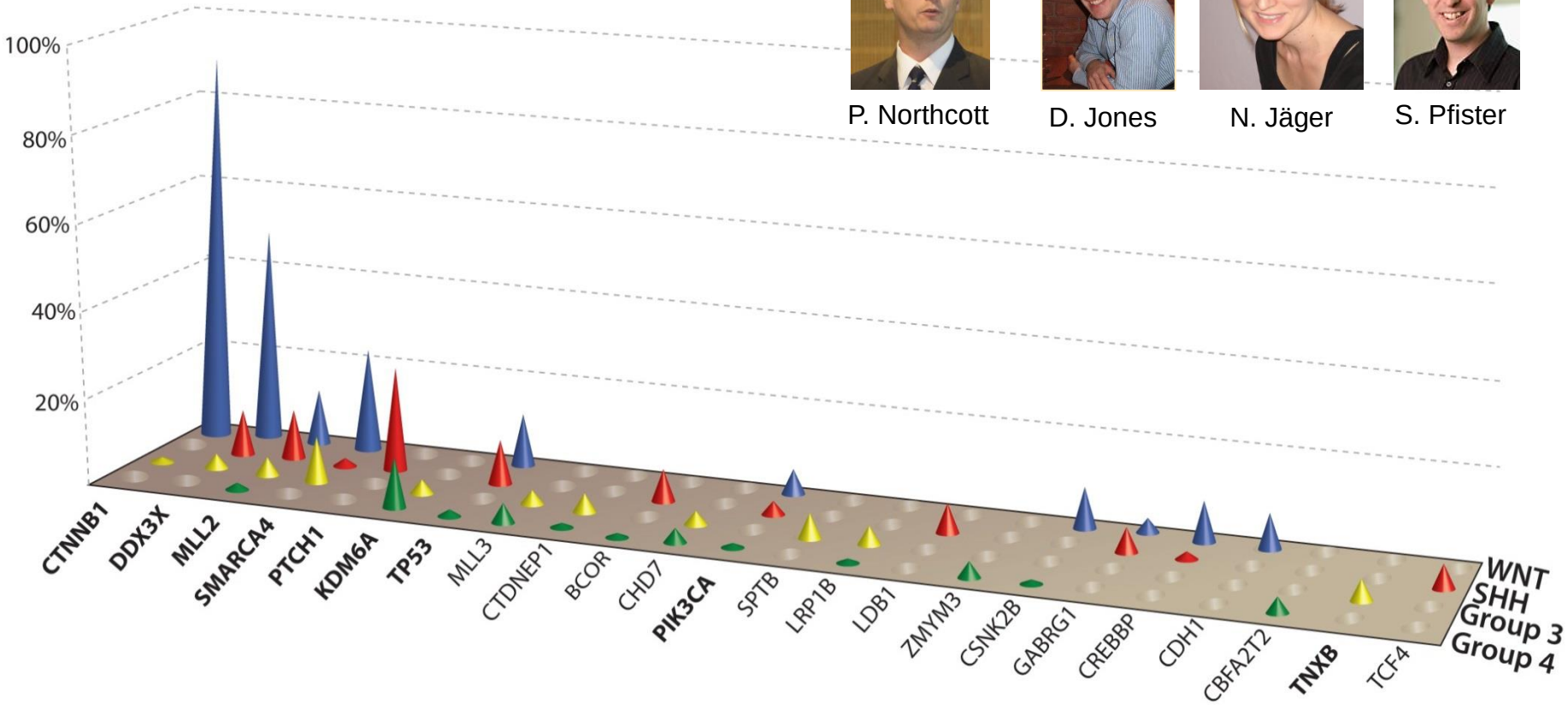
Somatic ‘drivers’ in medulloblastoma


P. Northcott


D. Jones


N. Jäger


S. Pfister



Northcott et al., Nature Reviews Cancer 2012

What else is out in the genome

ARTICLE

doi:10.1038/nature13379

Enh
onc Hi

Paul A. Nort

TERT Promoter Mutations in Familial

RESEARCH

RESEARCH ARTICLE

doi:10.1038/nature12477

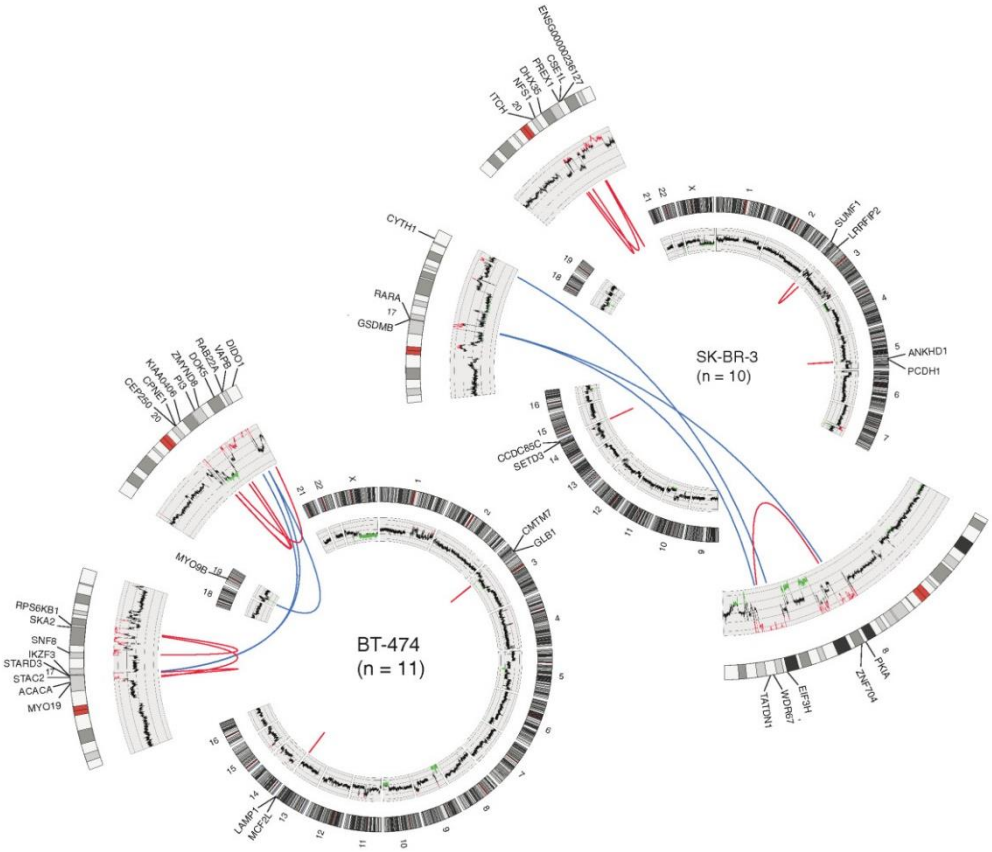
MOBILE DNA IN CANCER

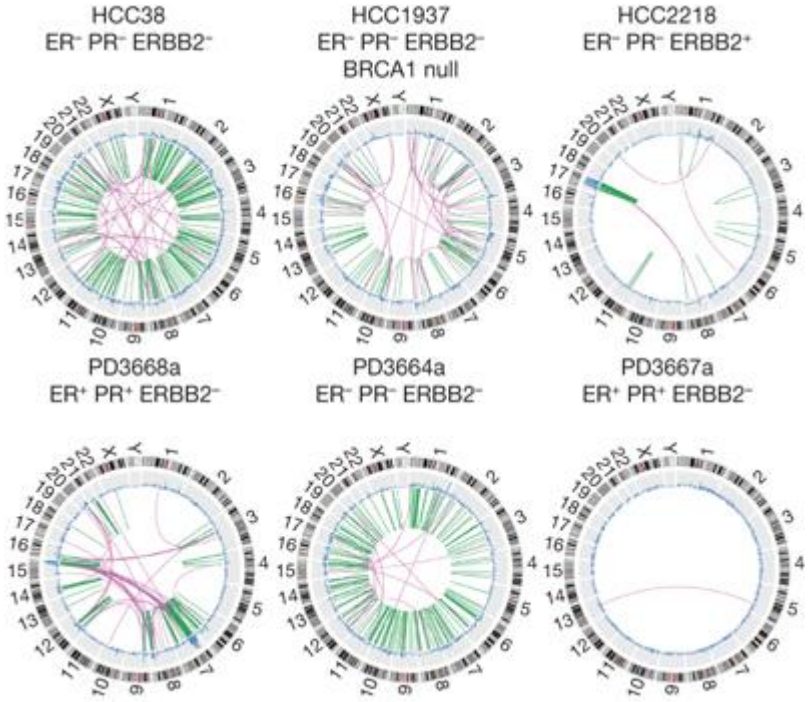
cesses in

Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes

Jose M. C. Tubio,[1] Yilong Li,[1]* Young Seok Ju,[1]* Inigo Martincorena,[1] Susanna L. Cooke,[1]

High abundance of fusion genes in breast cancer





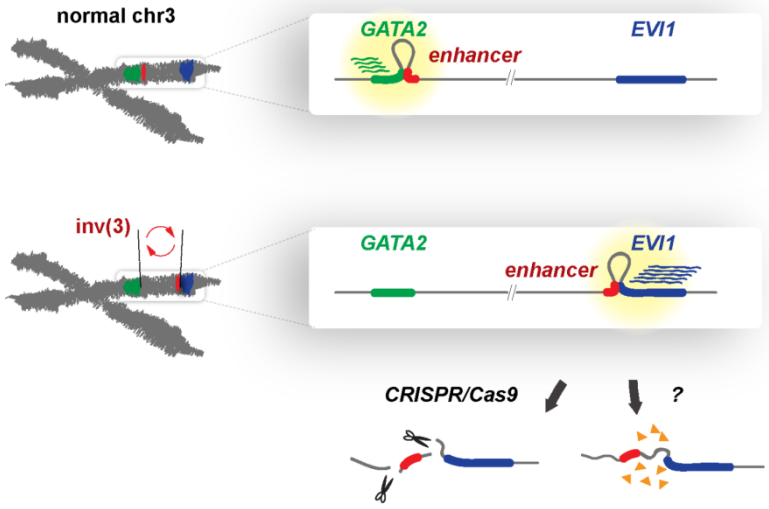
Edgren et al., Genome Biology 2011

Stephens et al., Nature 2009

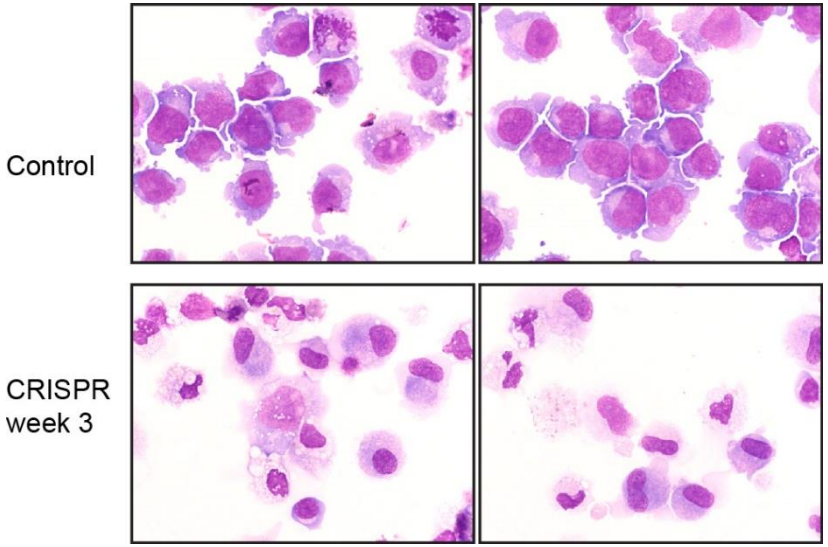
A Single Oncogenic Enhancer Rearrangement Causes Concomitant *EVI1* and *GATA2* Deregulation in Leukemia

Stefan Gröschel[1,2,9], Mathijs A. Sanders[1,9], Remco Hoogenboezem[1], Elzo de Wit[3], Britta A.M. Bouwman[3], Claudia Erpelinck[1], Vincent H.J. van der Velden[4], Marije Havermans[1], Roberto Avellino[1], Kirsten van Lom[1], Elwin J. Rombouts[1], Mark van Duin[1], Konstanze Döhner[2], H. Berna Beverloo[5,6], James E. Bradner[7,8], Hartmut Döhner[2], Bob Löwenberg[1], Peter J.M. Valk[1], Eric M.J. Bindels[1], Wouter de Laat[3], Ruud Delwel[1,]

Dual gene deregulation in inv(3) AML



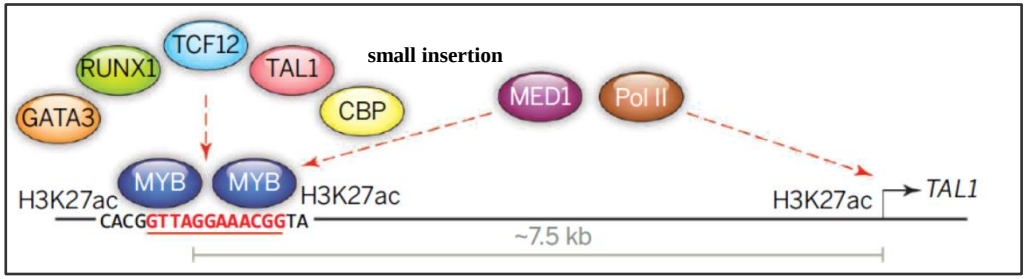
Monocyte/macrophage differentiation upon enhancer deletion



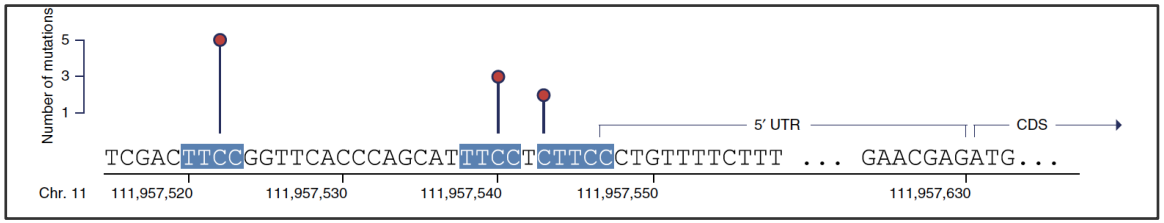
Gröschel et al., Cell, 2014

Examples of other NonCodingMutations:

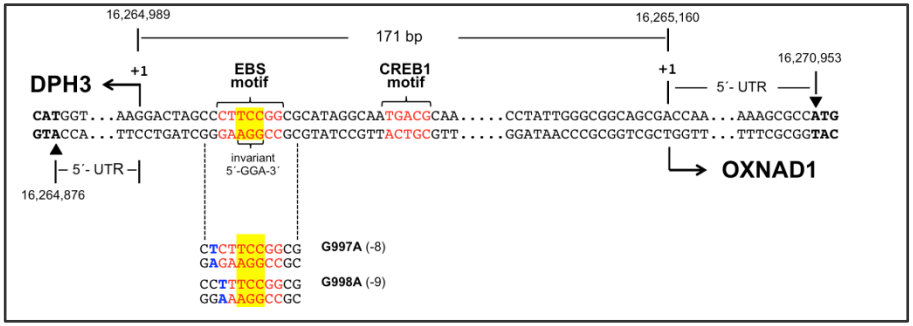
- **Mansour et al., 2014, Science 346, 1373: An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. (R. Young) (T-ALL)**



- **Weinhold et al., 2014, Nat. Genetics 46, 1160: Genome-wide analysis of noncoding regulatory mutations in cancer. (*PLEKHS1*, *WDR74*) (C. Sander) (Bladder Ca.)**



- **Denisova et al., 2015, Oncotarget 6, 35922: Frequent DPH3 promoter mutations in skin cancers (R. Kumar) (skin cancer: SCC, BCC)**

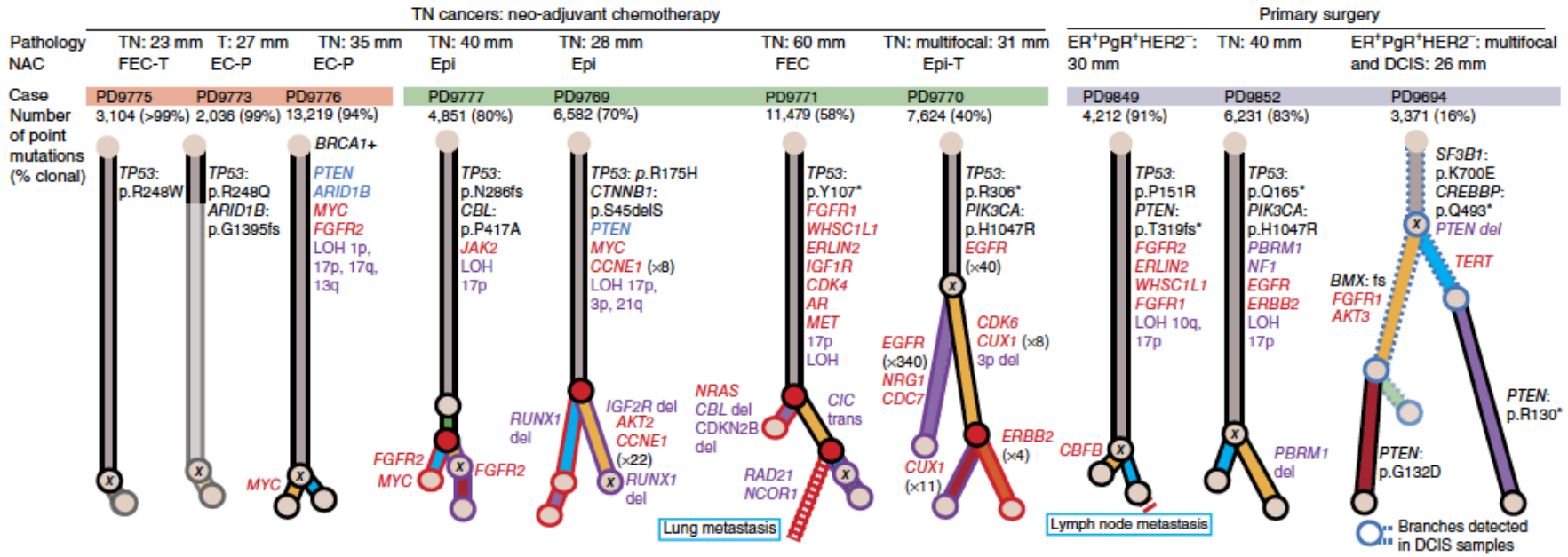


dkfz.

Deutsches Konsortium für Translationale Krebsforschung

Assessing heterogeneity/clonality/evolution

NATURE MEDICINE



- highly variable subclonal diversification
- no strict temporal order
- alterations in driver genes occurring early in some tumors and late in others
- resistance to therapy and invasive potential arose from subclones that were detectable in early lesions

=> Necessity to include subclonal and longitudinal analysis in clinical trials of primary breast cancer

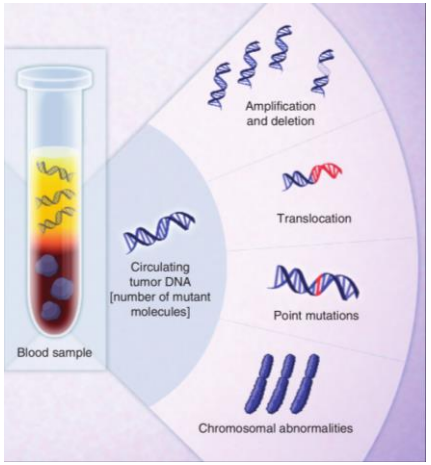
Yates et al. 2015

LIQUID BIOPSIES

Analysis of body fluids: Blood, Plasma, Sputum, Urine, Spinal Fluid

Focus on circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), for

- Prognosis
- Prediction
- Molecular Heterogeneity
- Identification of drug targets
- Monitoring of therapy response
- Monitoring of resistence mechanisms

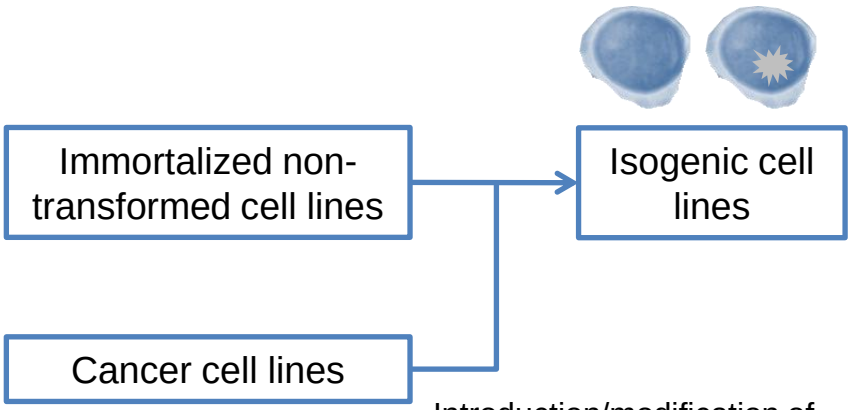


Haber et al. *Cancer Discov* 2014

"non"-invasive approach to generate genetic tumor profiles

Functional Genomics

Development of experimental systems for functional validation

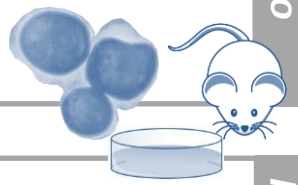


Introduction/modification of genetic alterations by lentiviral gene or shRNA transfer or CRISPR/Cas9 technology

1 Functional annotation of molecular lesions

In vitro

- Viability/proliferation
- Apoptosis/cell cycle
- Anchorage independence
- Invasion/migration
- Pathway activation
- Others



In vivo

- Tumorigenicity (mouse, CAM)

2 Unbiased identification of functional dependencies

In vitro

- Genome-wide or targeted shRNA screens
- Genome-wide or targeted CRISPR/Cas9 screens

Stefan Fröhling, Claudia Scholl, Michael Boutros (NCT Heidelberg/DKFZ) and Frank Buchholz (NCT Dresden)

NCT DataThereHouse

Display Data from Various Sources for a Comprehensive Overview of Information Relevant for Personalized Treatment

SEQUENCING DATA

ARRAY DATA

CLINICAL PATHWAYS

UNSTRUCTURED DATA

INDIVIDUALIZED TREATMENT PLAN

DOCTOR'S LETTER

STRUCTURED DATA

PHYSICIAN

SCIENTIST

TUMOR BOARD

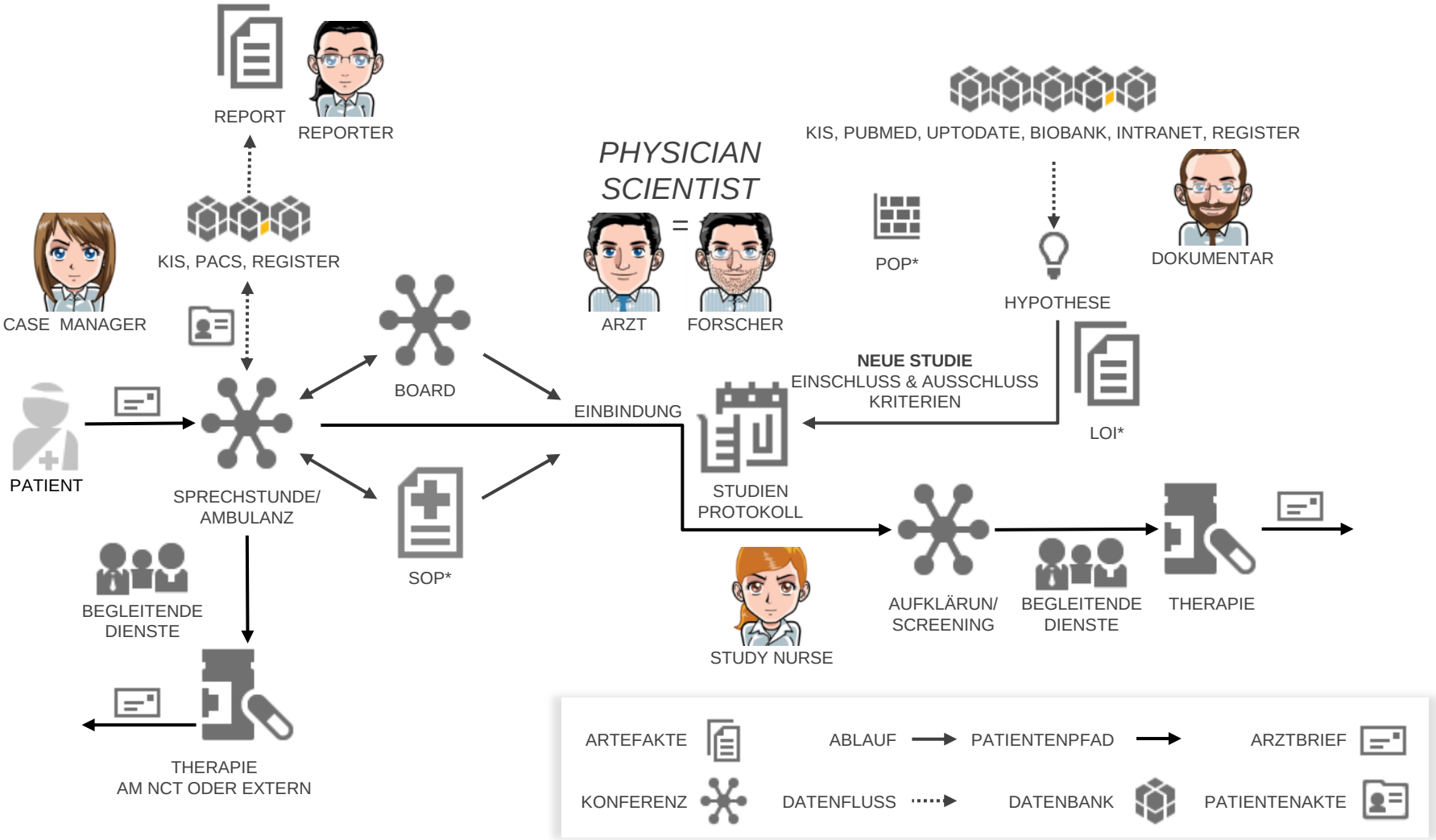
CASE MANAGER

STUDY NURSE

DOCUMENTALIST

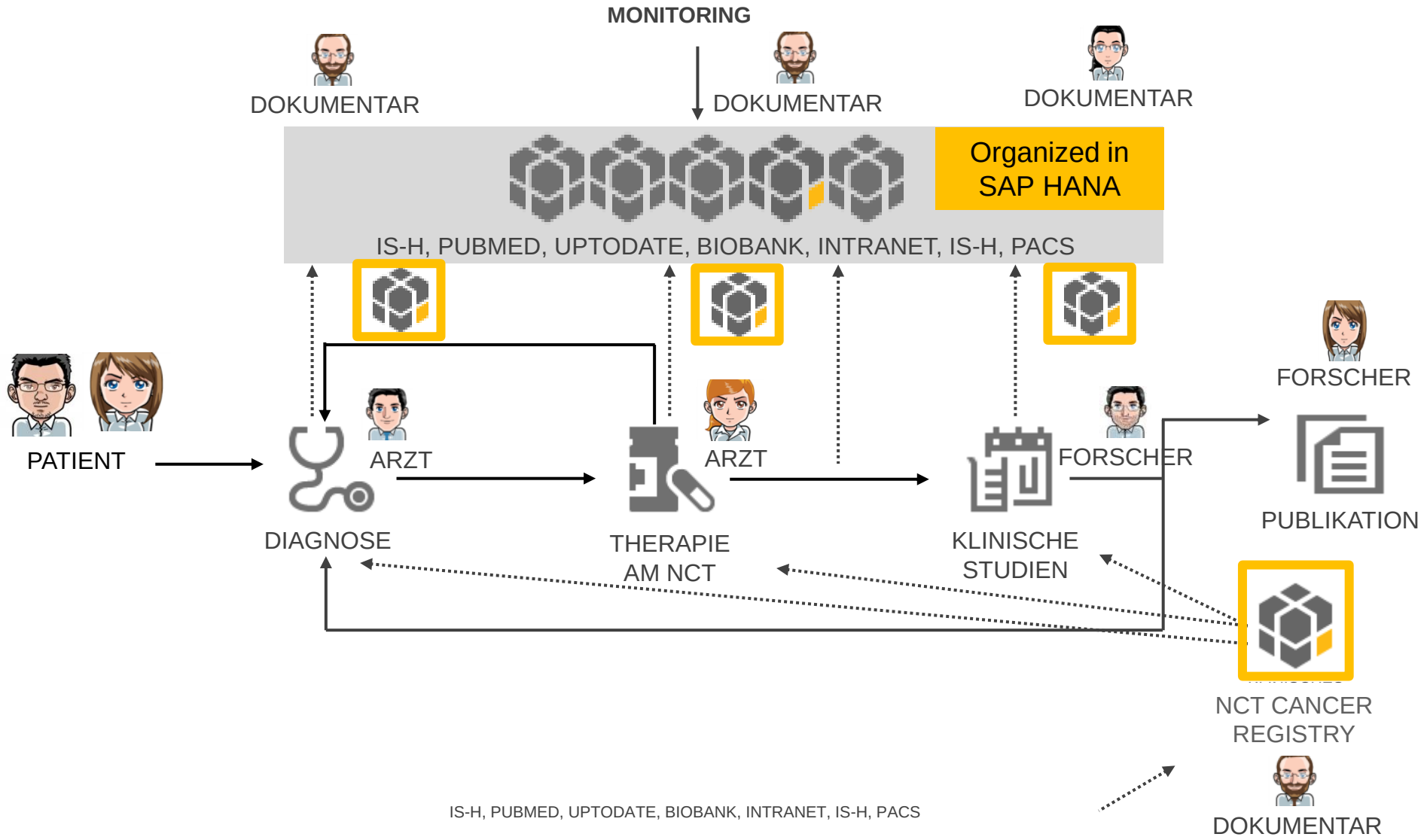
NCT DataThereHouse

Current Scenario



NCT DataThereHouse

NCT Clinical Development Strategy



Translational Oncology…

- needs to RETHINK the old & the new
- needs SMART Data
- is a TEAM Effort

NCT Partnerships

Academic Collaboration

iMed HELMHOLTZ ASSOCIATION

EMBL

DKFZ-ZMBH ALLIANCE

Joint Industry-Academia Collaboration

Roche

BAYER

SAP

Cancer Core Europe Consortium Centers

dkfz.

NCT

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

NKI-AVL The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital

Karolinska Institutet

VHIO

NATIONAL CENTER FOR TUMOR DISEASES

NCT HEIDELBERG

THANK YOU

dkfz.

NCT

UniversitätsKlinikum Heidelberg

50 Jahre – Forschen für ein Leben ohne Krebs