

Big Data in Cancer: Curse or Cure ?

Roland Eils

International Cancer Genome Consortium

Brain Cancer

United States 

Breast Cancer

European Union / United Kingdom 

Breast Cancer

France 

Breast Cancer

United Kingdom 

Chronic Lymphocytic Leukemia

Spain 

Colon Cancer

United States 

Gastric Cancer

China 

Leukemia

United States 

Liver Cancer

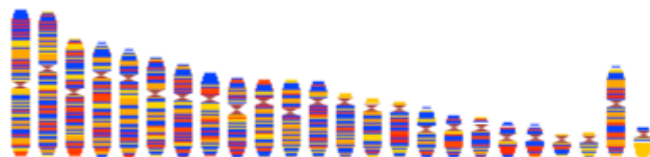
France 

Liver Cancer

Japan 

Lung Cancer

United States 



ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.

64 projects committed

Lung Cancer

United States 

Malignant Lymphoma

Germany 

Oral Cancer

India 

Ovarian Cancer

Australia 

Ovarian Cancer

United States 

Pancreatic Cancer

Australia 

Pancreatic Cancer

Canada 

Pediatric Brain Tumors

Germany 

Prostate Cancer

Canada 

Prostate Cancer

Germany 

Rare Pancreatic Tumors

Italy 

Renal Cancer

European Union / France 



International network of cancer genome projects. *Nature* **464**, 993-998 (15 April 2010)

[HTML](#)

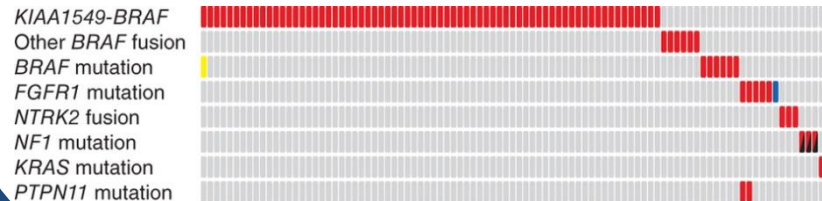
Fundamental insights into genomic principles

PedBrain Tumor

Jones, Jäger et al.: Dissecting the genomic complexity underlying medulloblastoma. **Nature 2012**

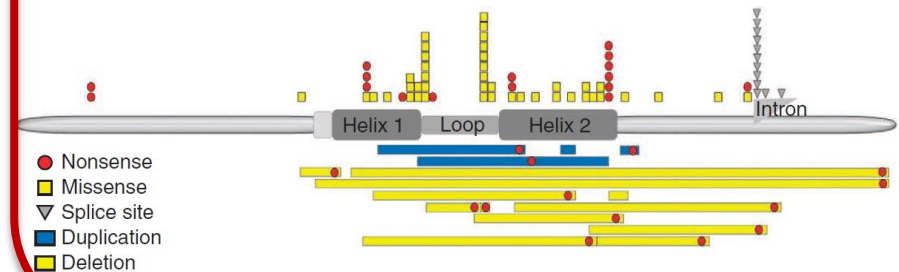


Jones, Hutter, Jäger et al.: Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma **Nature Genetics 2013**



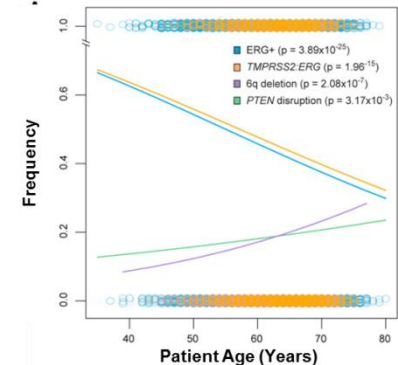
Malignant Lymphoma

Richter, Schlesner et al.: Recurrent mutation of the *ID3* gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing. **Nature Genetics 2012**



Early Onset Prostate Carcinoma

Weischenfeldt, Simon, Feuerbach, et al.:
Cancer Cell 2013
Gu et al., Epigenetic mechanism of prostate carcinoma;
Nature Genetics, 2015



Precision oncology program @ Heidelberg

NCT HEIDELBERG

- FIRST COMPREHENSIVE CANCER CENTER IN GERMANY
- JOINT VENTURE OF DKFZ AND UNIVERSITY HOSPITAL
- 10.000 CANCER PATIENTS ANNUALLY
- FOR A THIRD OF THEM CANCER GENOME SEQUENCING MIGHT BE AN OPTION

dkfz.

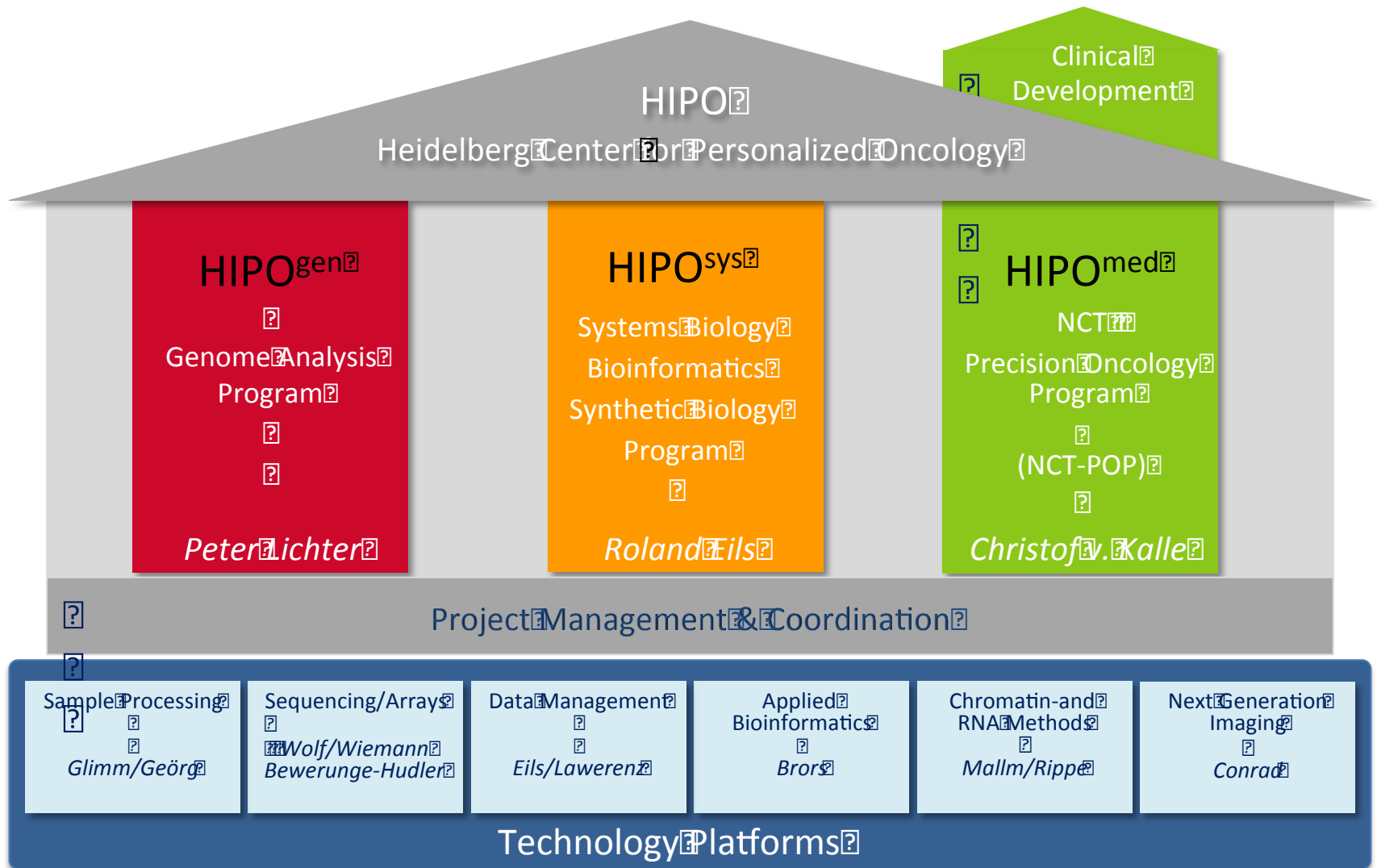


UniversitätsKlinikum Heidelberg

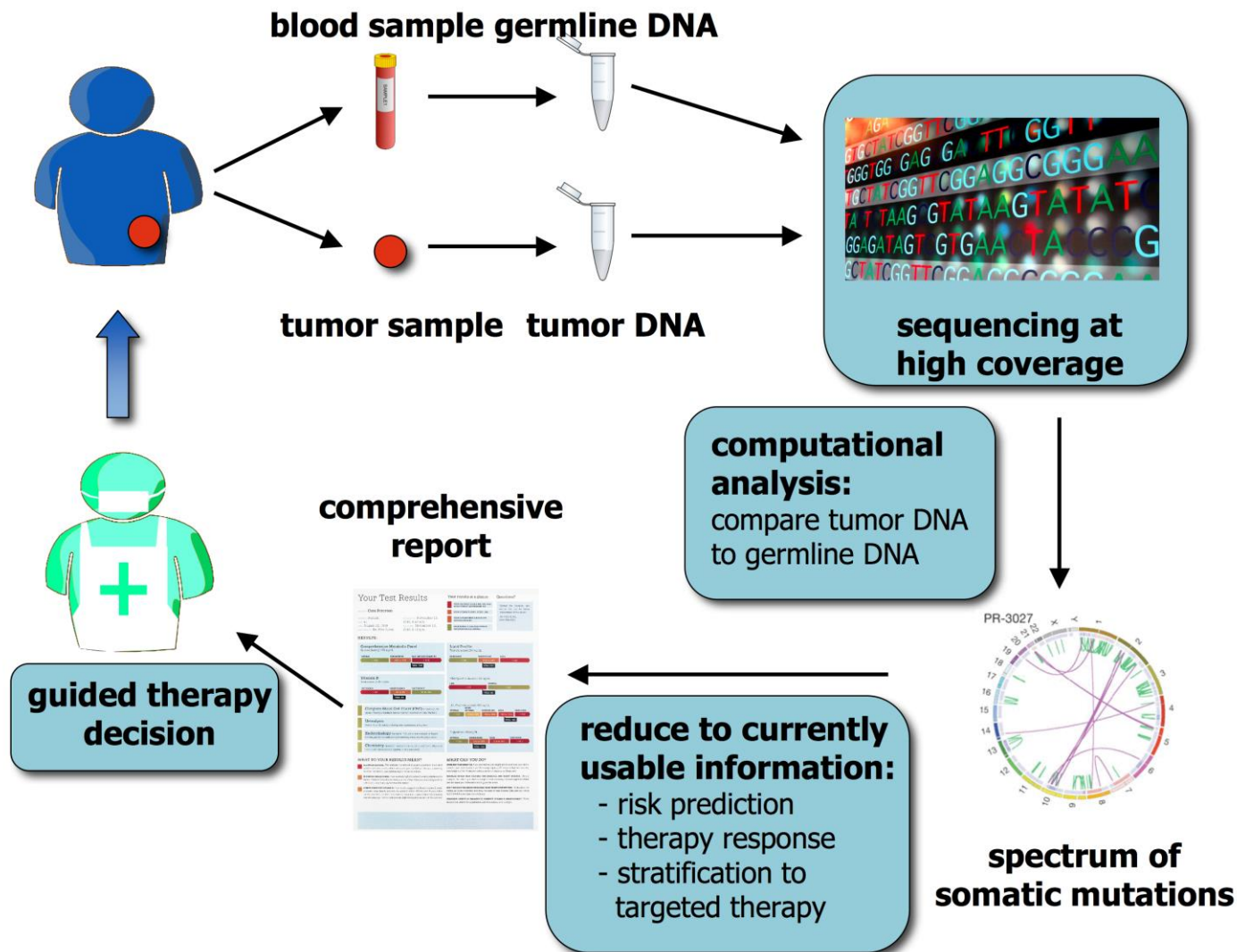
50 Jahre – Forschen für
ein Leben ohne Krebs



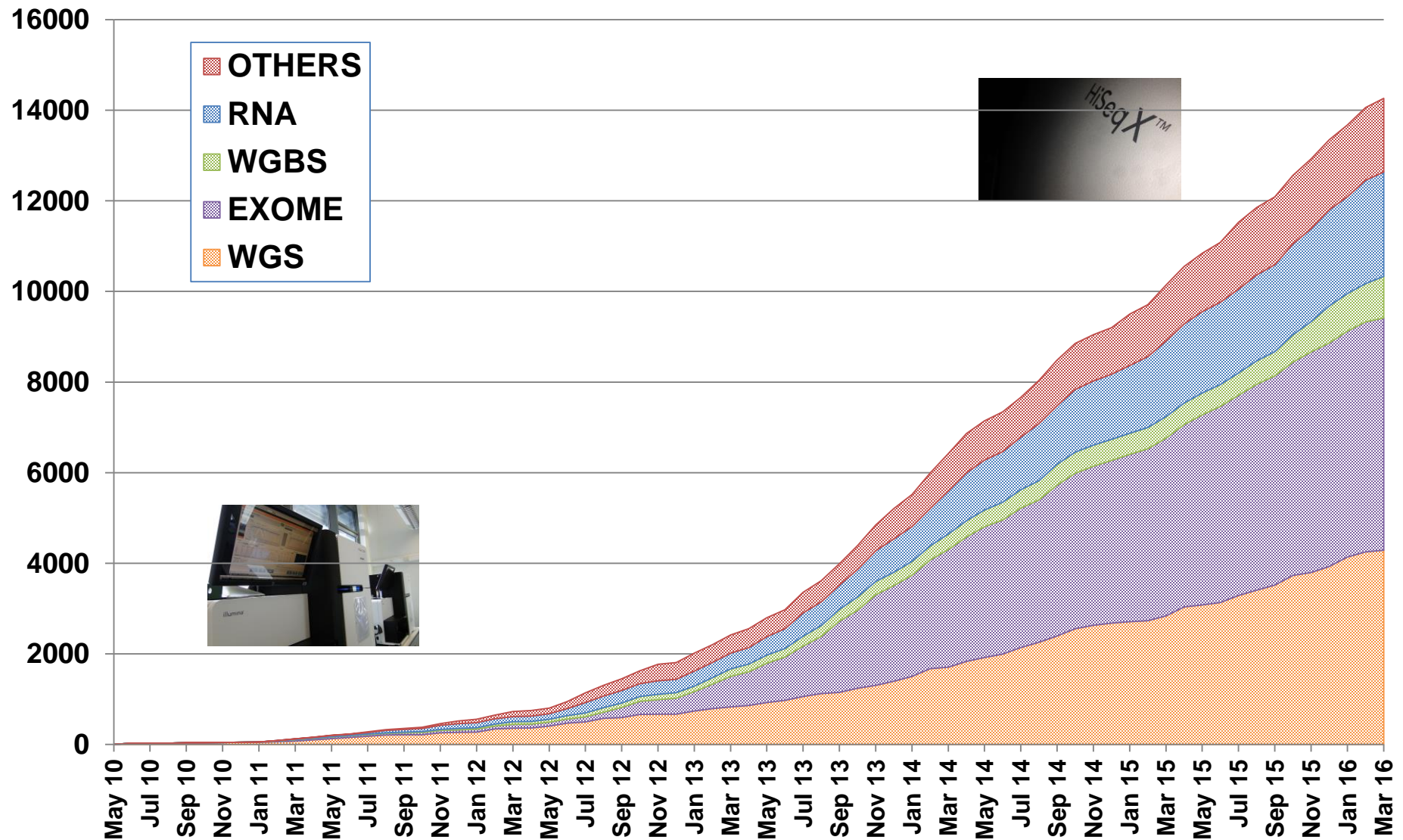
HIPO - THE HEIDELBERG CENTER FOR PERSONALIZED ONCOLOGY



NCT CLINICAL CANCER PROGRAM



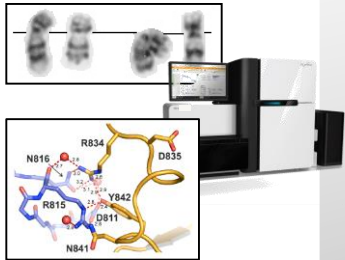
Number of Samples (> 14.000) sequenced in Heidelberg (clinical) sequencing program



Clinical Sequencing Program: Eligibility and Objectives



Genetics



Clinical care



Eligibility

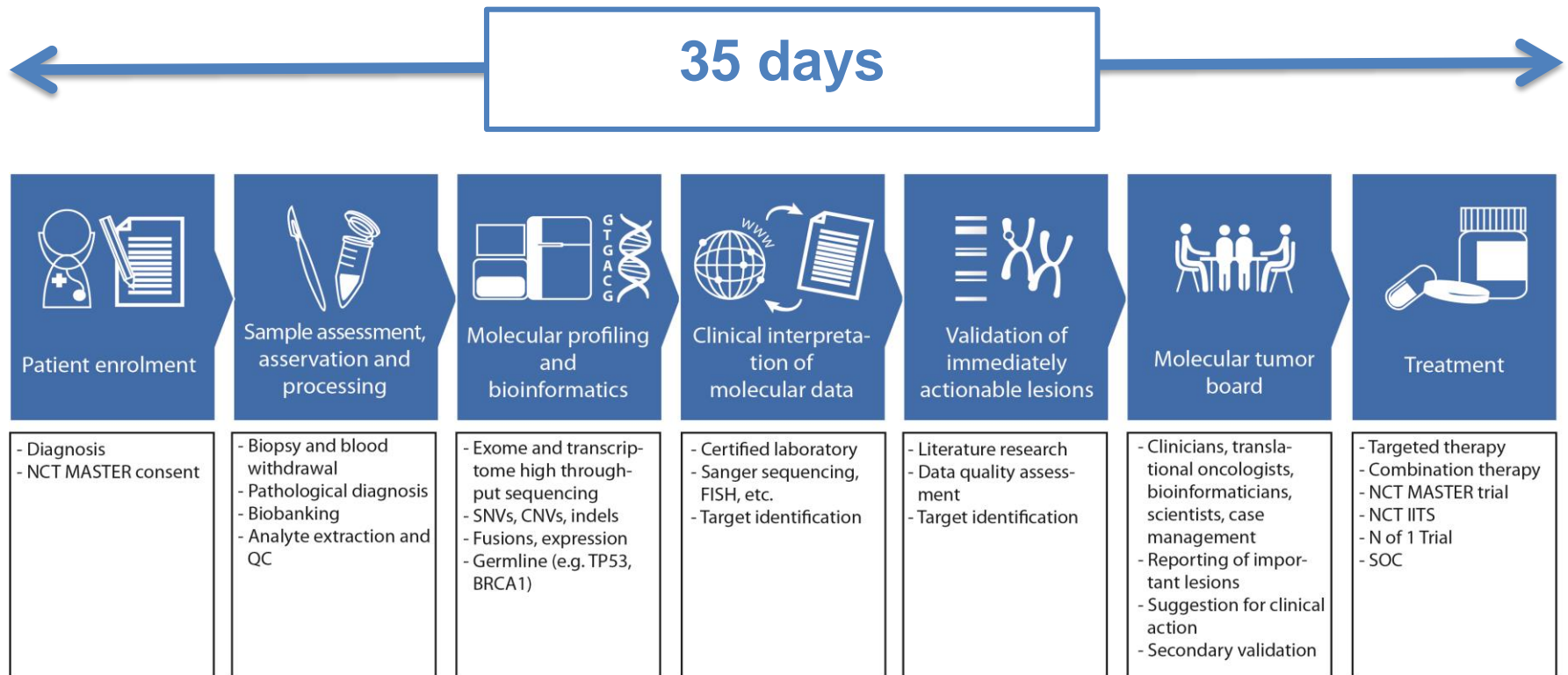
- Patients younger than 51 years
- Patients with rare cancers
 - *Incidence of less than 1/100,000 per year*
- Measurable disease activity
- No curative treatment available
- Karnofsky Performance Status of at least 70%
- Life expectancy of at least 6 months

Objectives

- Prospective whole genome and transcriptome sequencing within clinical context
- Interdisciplinary evaluation and formulation of treatment recommendations
- Translation into individualized patient care



NCT CLINICAL CANCER PROGRAM: MOLECULAR SEQUENCING DIAGNOSTICS



Pilotphase on 2013 – December 2014 246 patients, success rate* 56%
 Ramp-up phase I: 2015 1.500 patients p.a. (120X)
 Ramp-up phase II: 2016 2.500 patients p.a. (120X)
 Ramp-up phase III: 2017 3.500 patients p.a. (120X)

* actionable mutations validated by certified diagnostics methods



NCT Master Match: basket trials based on molecular profiles (375*, Stefan Fröhling and Hanno Glimm)

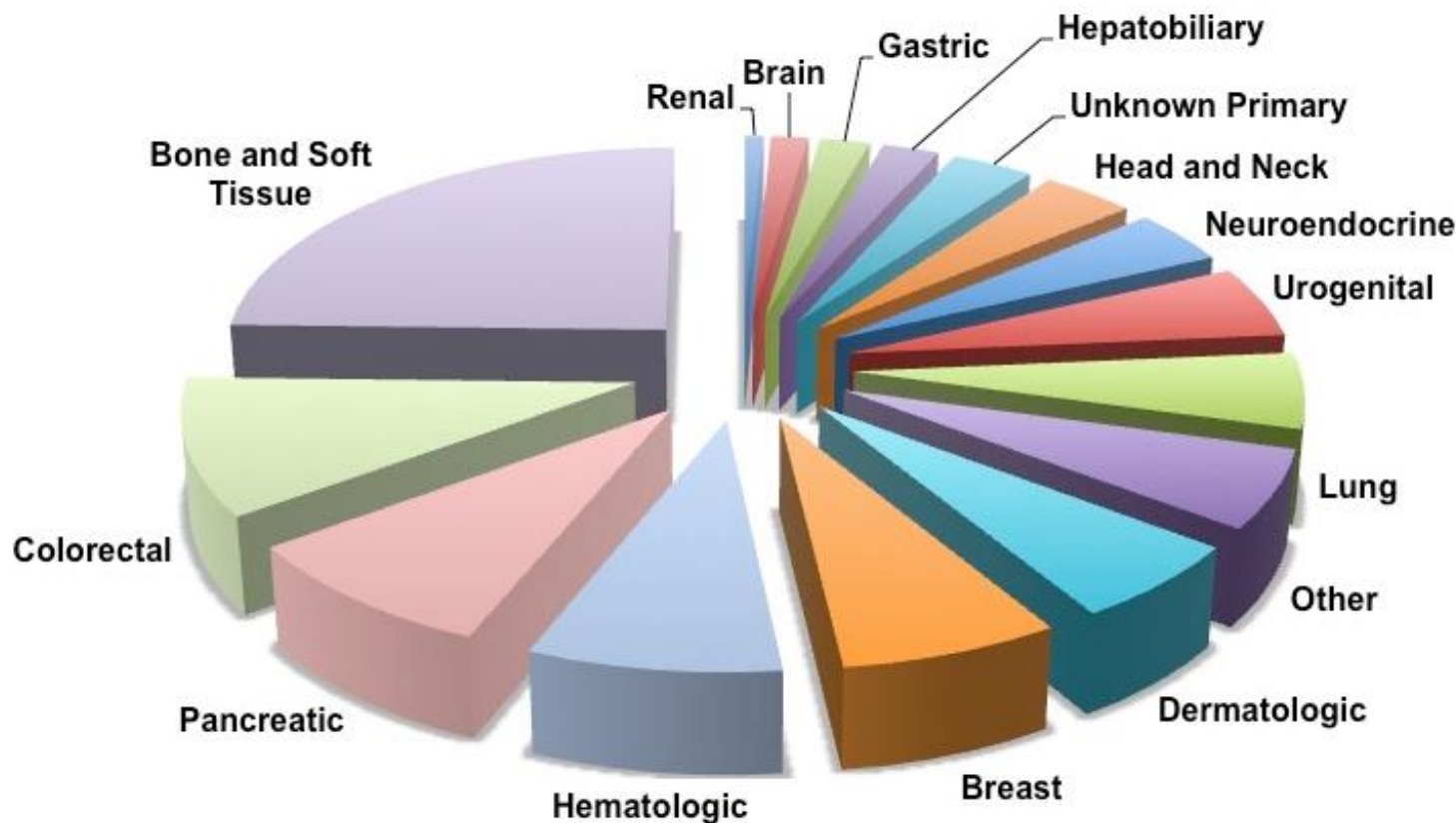
Regi

$N =$

Pati
Sam
Asser

Preli

- Re
- Genomics-guided treatment in 24% (51/213) of cases
- Response or disease stabilization in 45% (23/51) of cases



PI3K-AKT-
mTOR (1)

EK-
(2)

tor
ne
(3)

mental
ays

aling

(4)

Basket Trial with Pathway Programs

Wrap-up of first part on clinical cancer genomics

- Clinical sequencing has **strong impact on cancer diagnosis and treatment**
- **Success rate of 64%** in cancer at modest total cost for sequencing of < 5000€ per case
- **MAJOR LIMITATION:**
endpoint studies at time of disease

“Endpoint” vs. “longitudinal” bio-sampling and sequencing long before onset of disease

Environmental exposure



Städtisches Klinikum „St. Georg“ Leipzig
EIGENBETRIEB DER STADT LEIPZIG

PILOT STUDY: Tobacco smoke exposure during pregnancy



> 200 samples (including > 30 mother – child pairs)
Peripheral blood

Whole genome bisulfite sequencing
Coverage 30 - 50 fold

36th week
Cord blood

1-4
years

5-8
years

Differentially methylated regions (DMRs)

Epigenetic reprogramming

ChIP Seq 1-8 years

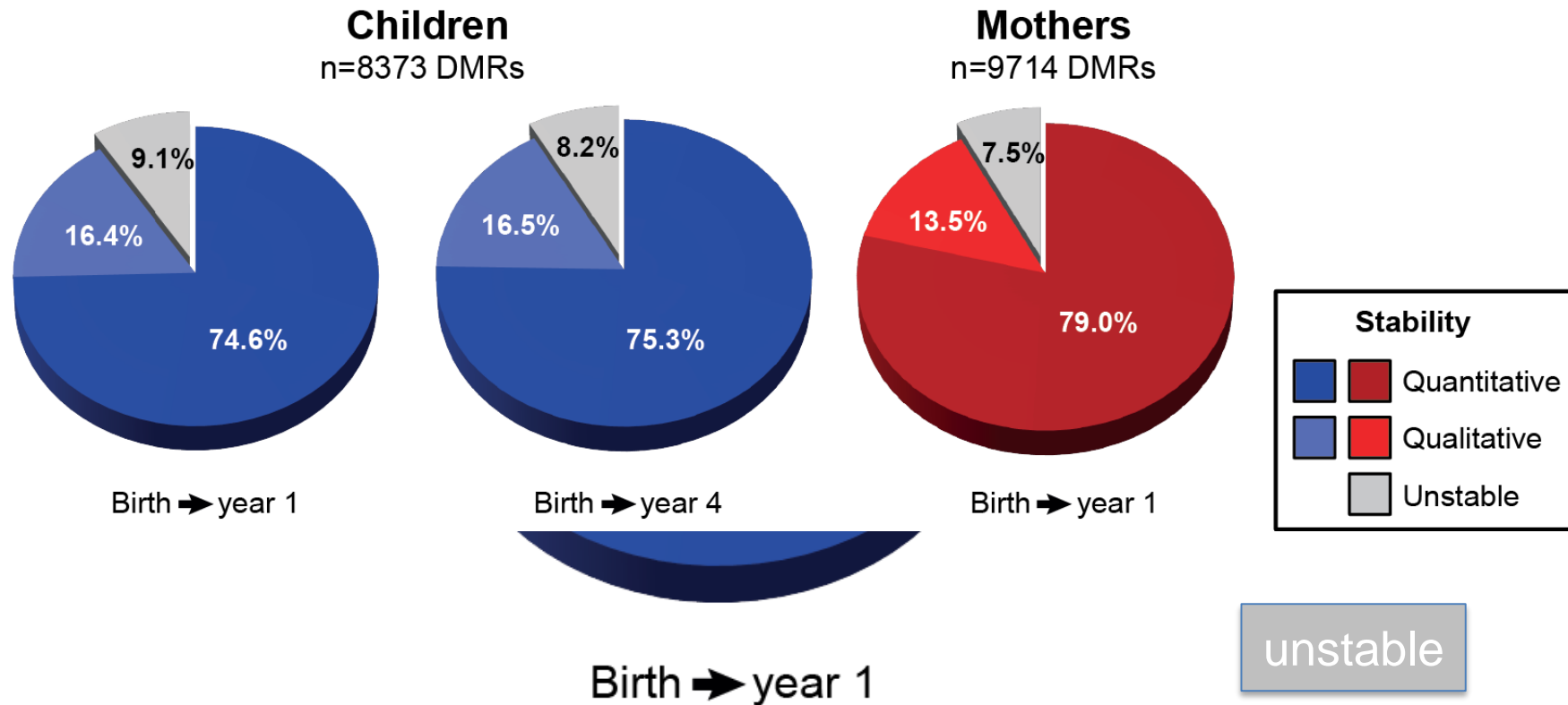
RNA Seq

Epigenetic regulators & Target genes

**Targeted validation
in two cohorts**

Disease phenotype (n=1000)

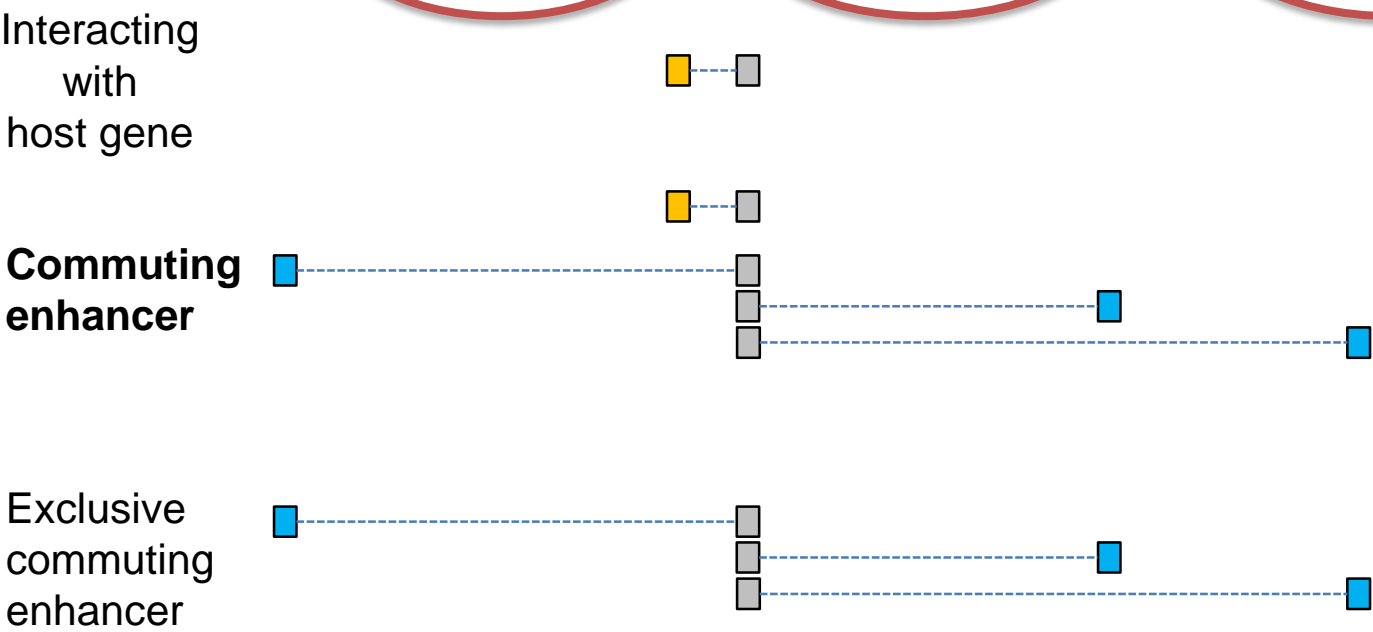
Epigenetic memory: DNA methylation is QUANTITATIVELY* highly conserved over years



*DMRs with <5% methylation difference over year 0 (1) and 4

DMRs are massively enriched in enhancers but not in promoters

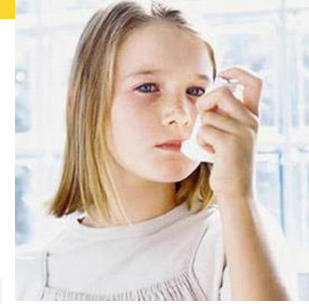
		TSS		TSS		TSS		
Genes	Total	Total	Intergenic	p-value	Intergenic	p-value	promoters	p-value
DMRS	Enhancers	Enhancers	enrichment	Enhancers	enrichment	TSS	enrichment	
Enhancer	8123	562	318	4.40E-08	244	1.41E-23	280	2.42E-02
Mothers	9743	616	248	3.37E-29	368	2.22E-22	292	1.78E-03



COMMUTING enhancers account for $\approx 90\%$ of all interactions

Interactions determined by ChIA-PET data

Demethylation of the JNK2 enhancer increases the risk for lung diseases

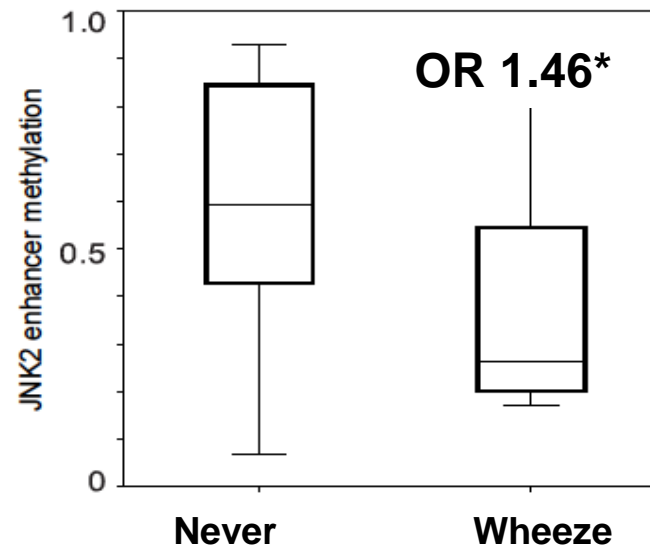


Wheeze Whistling sound produced in the airways during breathing
Early sign for lung dysfunction

**Methylation at birth
(N=475)**



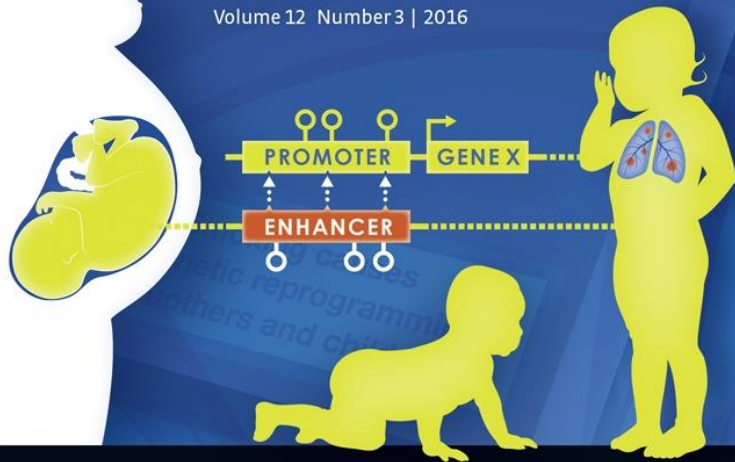
**Validation cohort (LISA)
(N=350)**



* Risk increase per 10% methylation loss
4 x increased risk for children with fully unmethylated enhancer

molecular systems biology

Volume 12 Number 3 | 2016



**Smoking causes
epigenetic reprogramming
in mothers and children**

 **EMBO**press

- **Genome-wide epigenetic reprogramming, particularly of *commuter enhancers***
- ***Epigenetic memory* persistent over years in both mothers and their children**
- ***GWAS risk SNPs* should be reconsidered given epigenetic background**

Bauer et al., Mol Syst Biol 2016

Summary

- Clinical sequencing has **strong impact on cancer diagnosis and treatment**
- **Success rate of 64%** in cancer at modest total cost for sequencing
- **Longitudinal sequencing** required to understand onset and persistence of disease
- **Enhancers primary targets** of variety of diseases

Acknowledgment



GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

50 Years – Research for
A Life Without Cancer

Matthias Schlesner, Tobias Bauer, Matthias Bieg,
Naveed Ishaque, Zuguang Gu, Lei Gu, Qi Wang,
Matthias Schlesner, Chris Lawerenz, Carl Herrmann

Stefan Wolf, Michaela Schanne, Nicolle Diessl
Genome sequencing Core facility

Christoph Plass, Dieter Weichenhan,
Division of Epigenomics and Cancer Risk Factors

Philipp Malm, Karsten Rippe
Genome Organization and Function

Christina Geörg
Sample Processing Lab

Stefan Fröhling, Hanno Glimm
NCT

Medical Centre, Radboud University Nijmegen
Henk Stunnenberg



**HELMHOLTZ
CENTRE FOR
ENVIRONMENTAL
RESEARCH – UFZ**

**Department of
Environmental Immunology**

Irina Lehmann

Saskia Trump

Stefan Röfer

Loreen Thürmann

Melanie Novak

Gunda Herberth Anne Hain

Tobias Polte

Beate Fink

Mario Bauer

Marita Reiprich

Kristin Weiße

**Municipal Hospital “St. Georg”
Children`s Hospital, Leipzig**

Michael Borte

Ulrike Diez

Cornelia Dorn





eis labs

eis labs