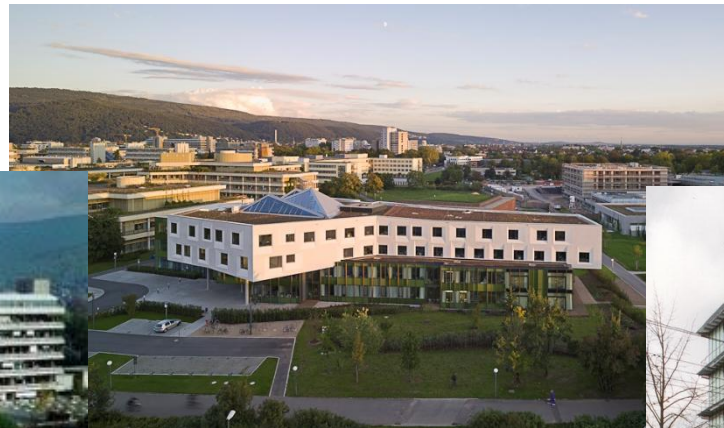
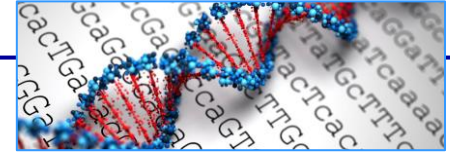


“Implementation of Genome-guided Concepts of Precision Oncology”

Peter Lichter

German Cancer Research Center, DKFZ



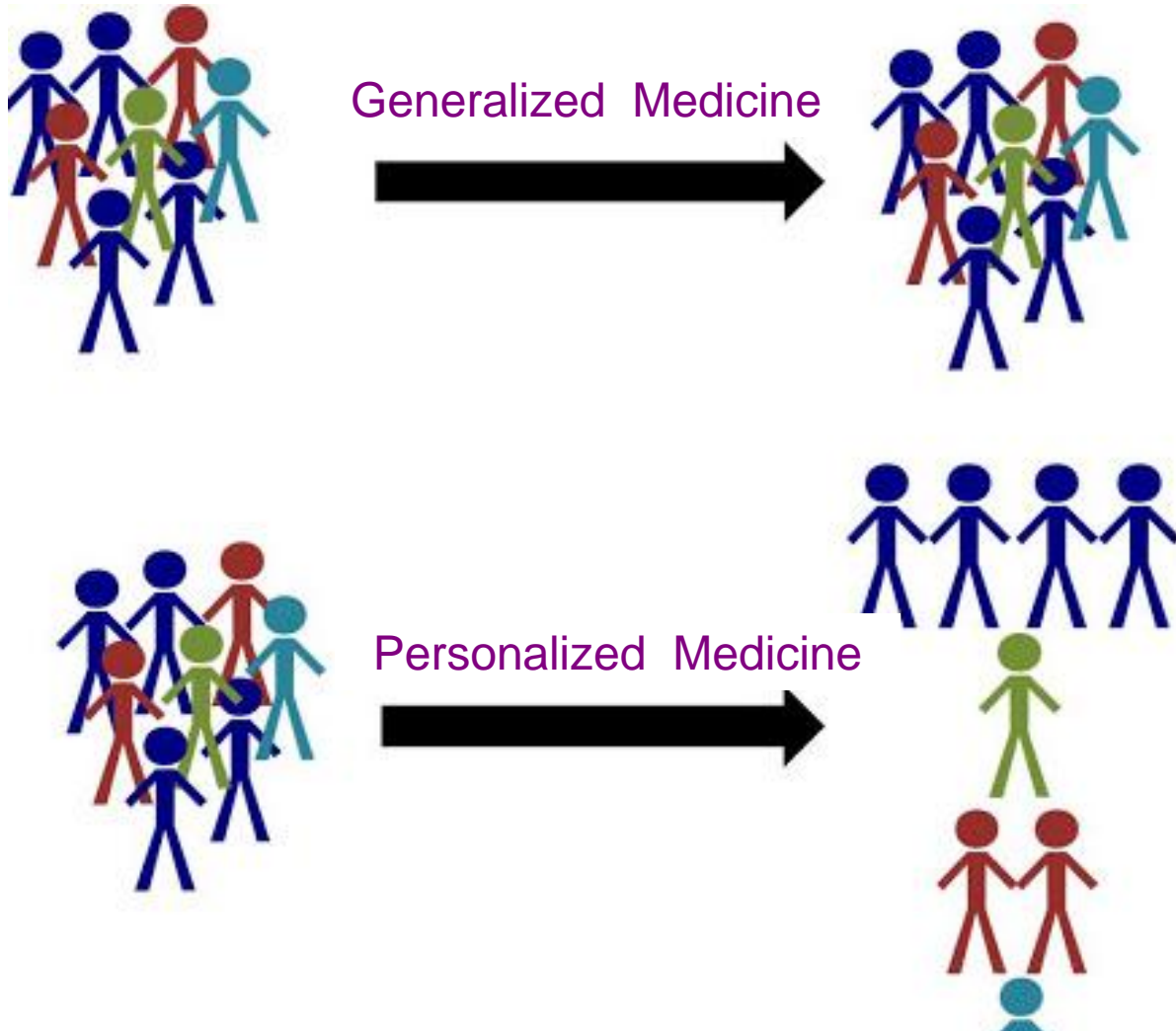
dkfz.

GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION



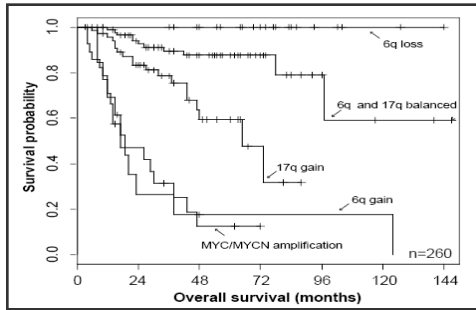
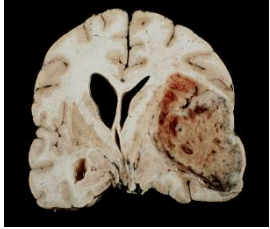
50 Years – Research for
A Life Without Cancer

Personalized Medicine

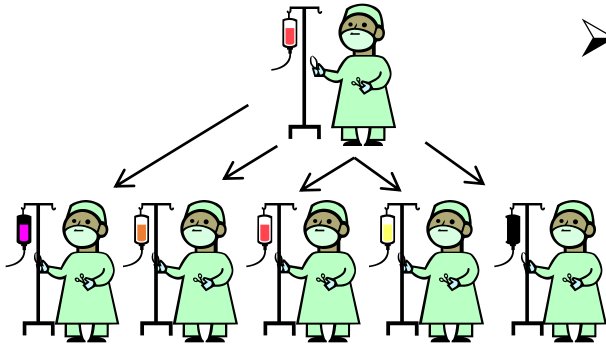


The Role of Genome Analysis

Aims of Cancer Genomics



- Identify **changes** in the genomes and epigenomes of tumors that drive cancer progression
- Validate **prognostic** potential of changes
- Potential to **predict** response to therapy
- Identify **new targets** for therapy
 - Select **drugs** based on **the genomic information** of the tumor



The Human Genome

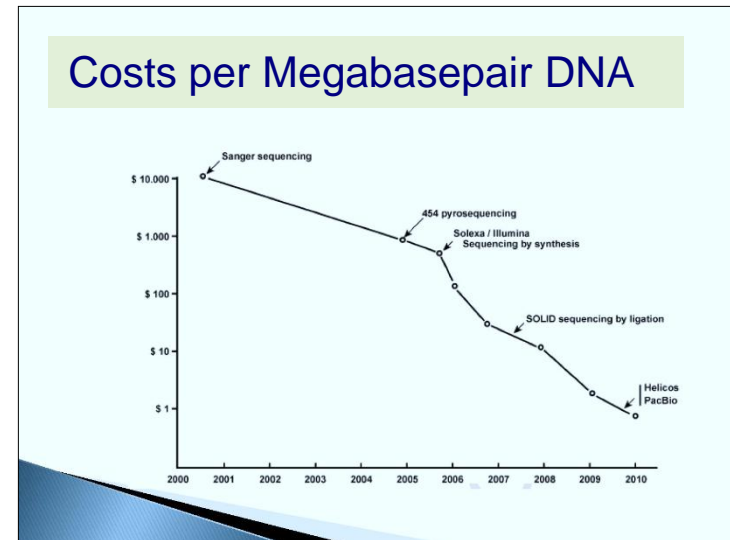
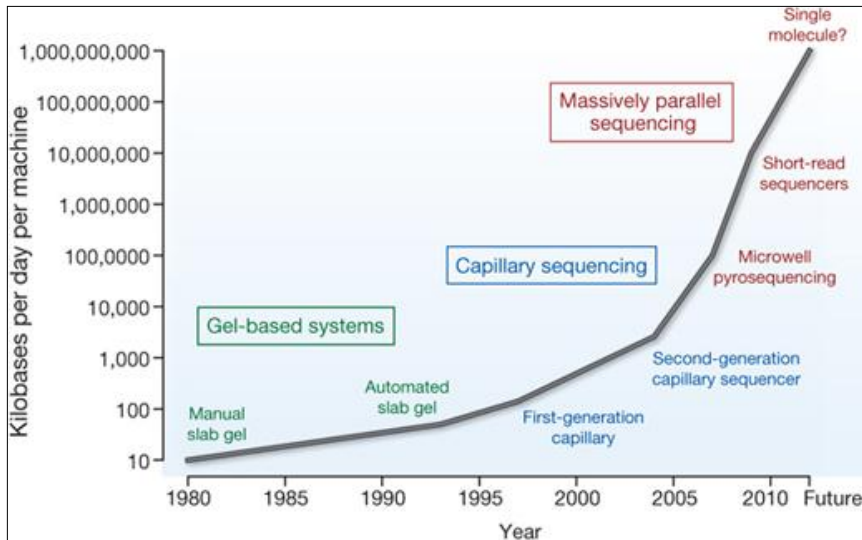


2001

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**~ 23,000 Genes
that code for Proteins**

The Technological Revolution



Performance per day
 → 24h for one genome is possible today
 („The“ human genome was done in 10 years)

Costs per genome
 → today < 5000 €
 („The“ human genome costed > 1.000.000.000 €)

DNA „Next Generation“ Sequencing:

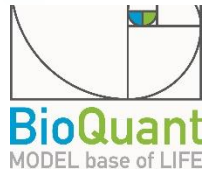


dkfz.





Data Storage



*Storage for
10 Petabyte*

Data Analysis

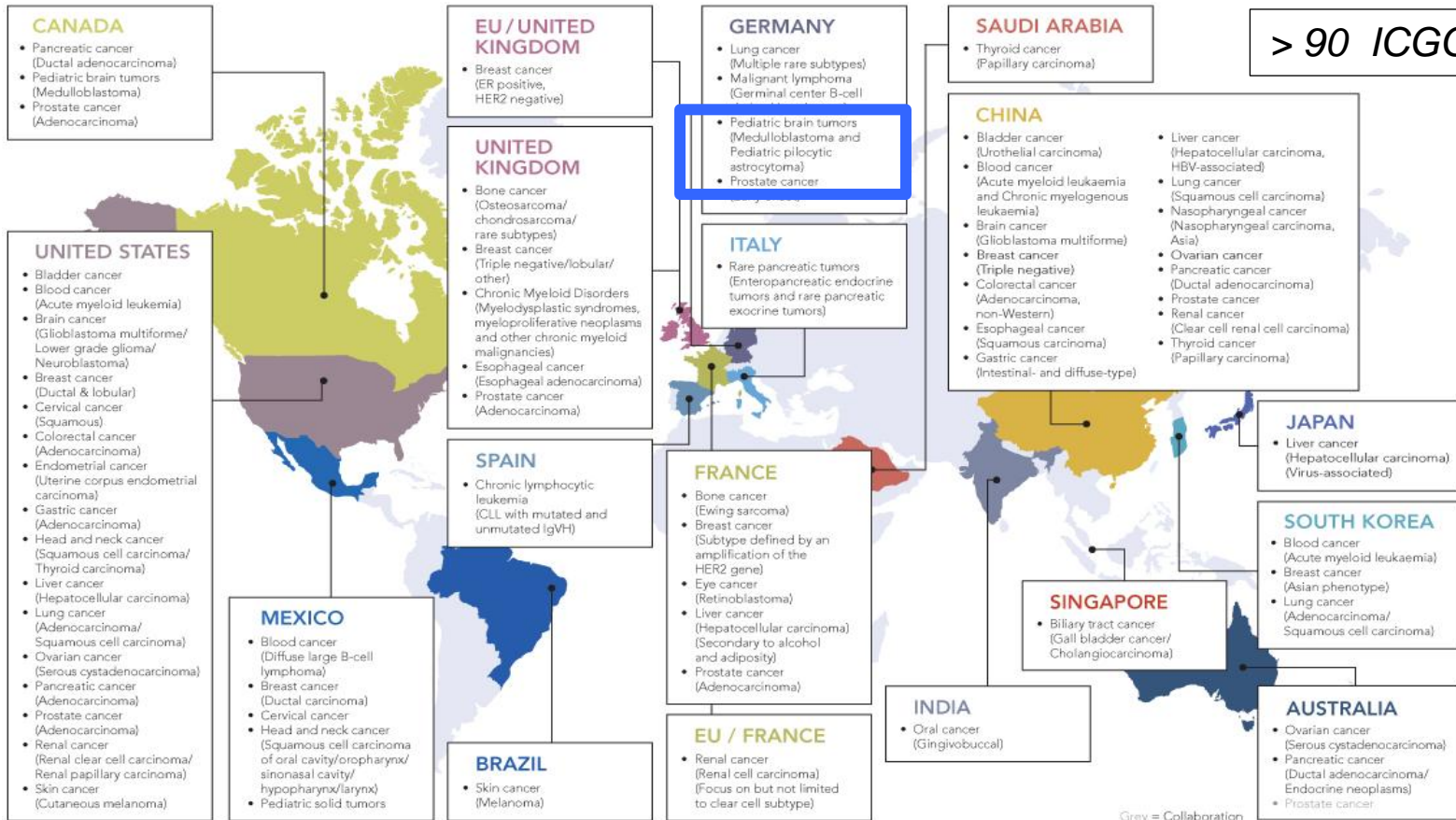


*Computer
Cluster*

International Cancer Genome Consortium



> 90 ICGC Projects



PedBrain Tumor (Pediatric Brain Tumors)

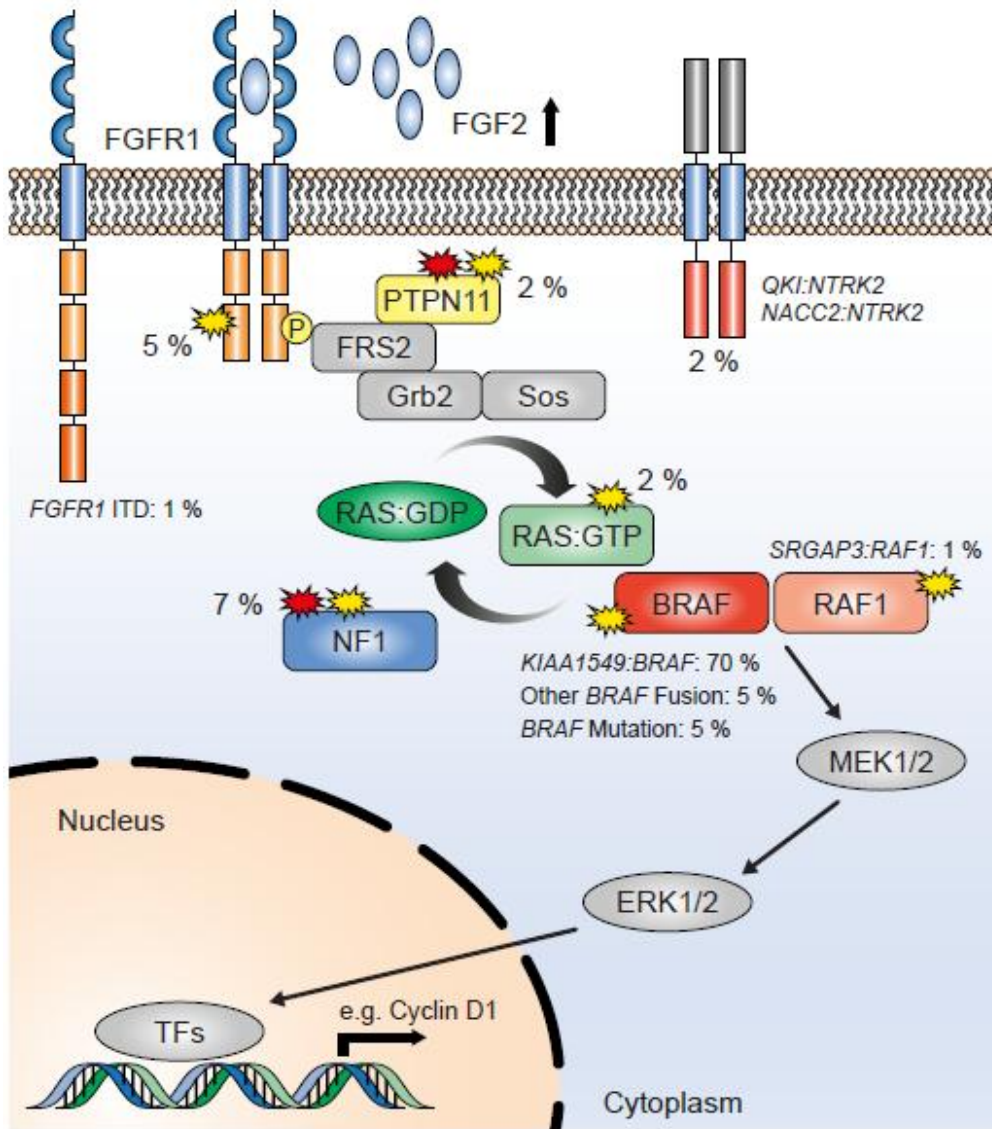


WGS, n > 550

=> Pilocytic Astrocytoma, Medulloblastoma, Glioblastoma, Ependymoma

=> Clinical Trial(s) in Oncology, the Heidelberg experience

Pilocytic Astrocytoma



n = 100

- Novel “actionable” targets
- Alterations in one pathway in 100% of cases
- Pilocytic Astrocytoma: a “single pathway” disease!

=> Therapy options

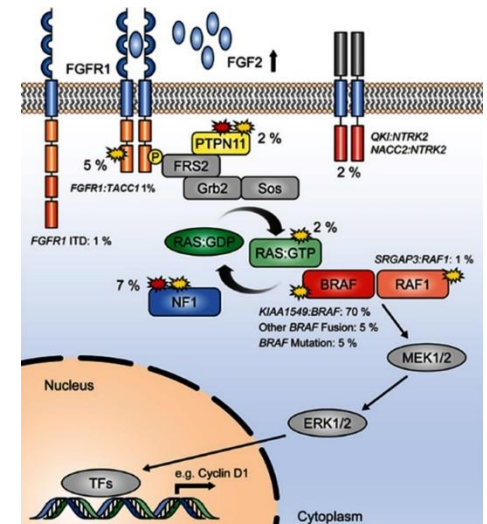
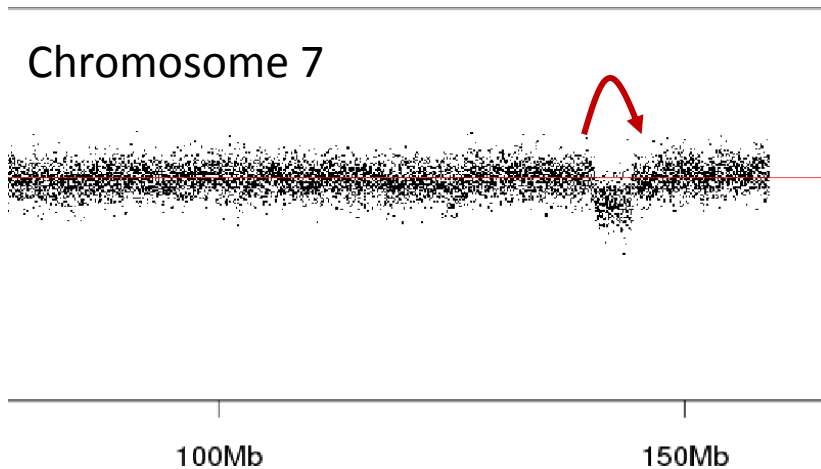


David Jones

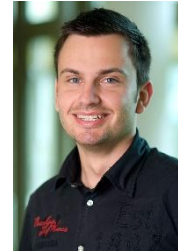
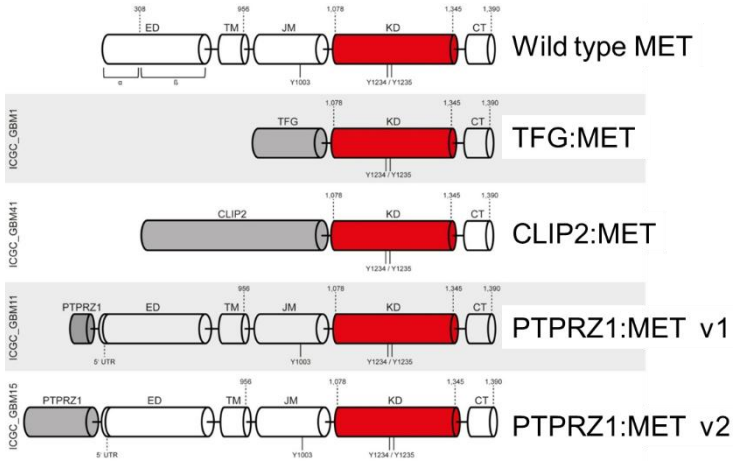
Patient example

*2008, female

- 11/2013: initial diagnosis **Anaplastic Astrocytoma (Grade III)**
treatment by standard protocol (radiotherapy & temozolomide)
- 11/2014: Tumor progress
- 12/2014: **sequence analysis: FAM131B:BRAF fusion**, typical for **Pilocytic Astrocytoma (Grade I)** => MAPK pathway activation
- Patient now treated with a **MEK-inhibitor (Trametinib)**
+ valproate + low-dose cyclophosphamide + chloroquine
- since 10/2015: **stable disease**



Pediatric Glioblastoma: Recurrent MET fusion gene



Sebastian Bender



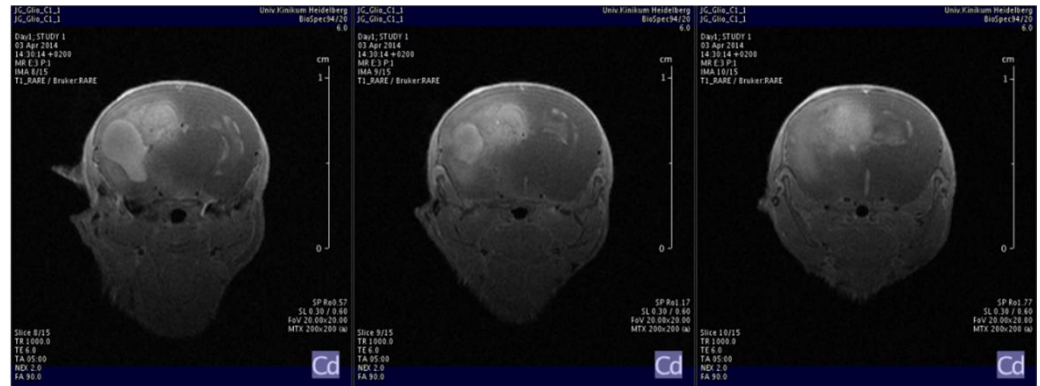
Jan Gronych



David Jones

*Bender, Gronych et al.
Nature Medicine 2016*

Preclinical model

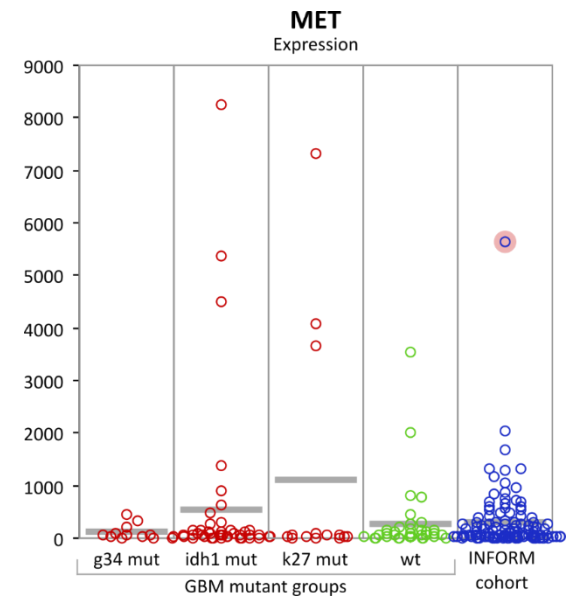
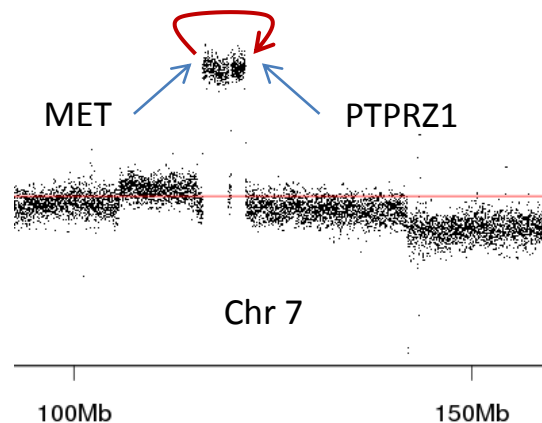
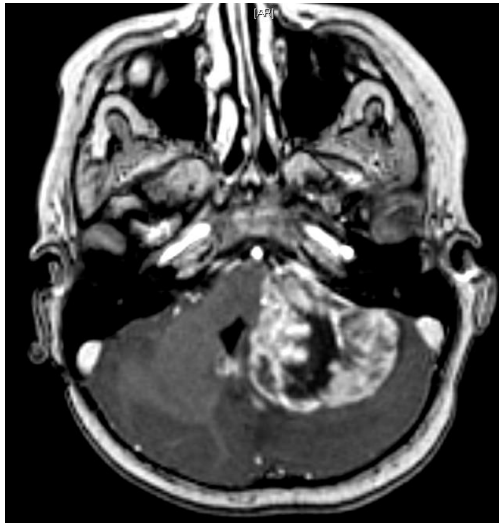


T1 RARE

Patient example

*2006, male

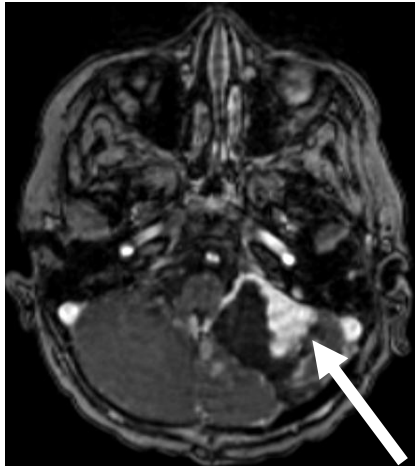
- 04/2011: initial diagnosis of a metastasized group 3 **Medulloblastoma** treatment by standard protocol (incl. craniospinal irradiation)
- 09/2014: massive tumor growth
- 10/2014: **sequence analysis: PTPRZ1-MET fusion** with **amplification** and **overexpression** of **MET** + **TP53** mutation (most likely radiation-induced **Glioblastoma**)



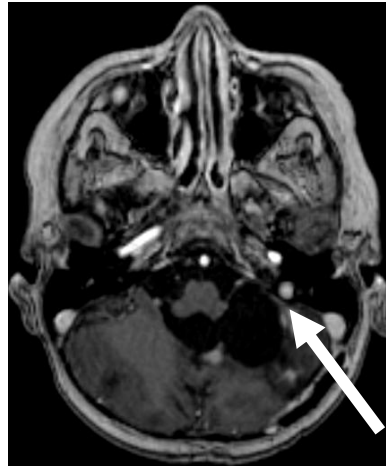
Patient example: Treatment response and resistance?

Treatment with a **MET-inhibitor (Crizotinib)**

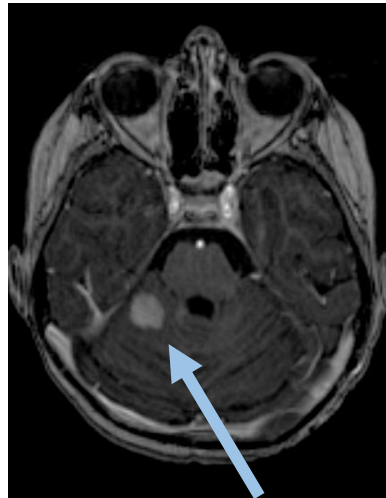
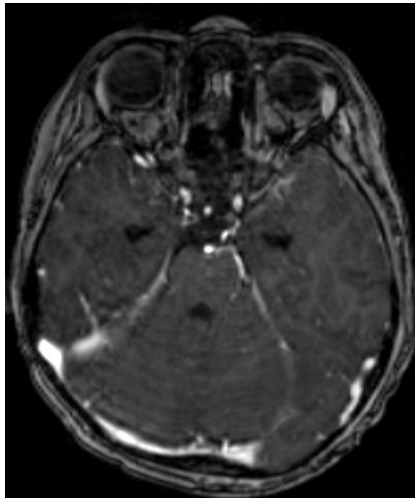
baseline post-OP



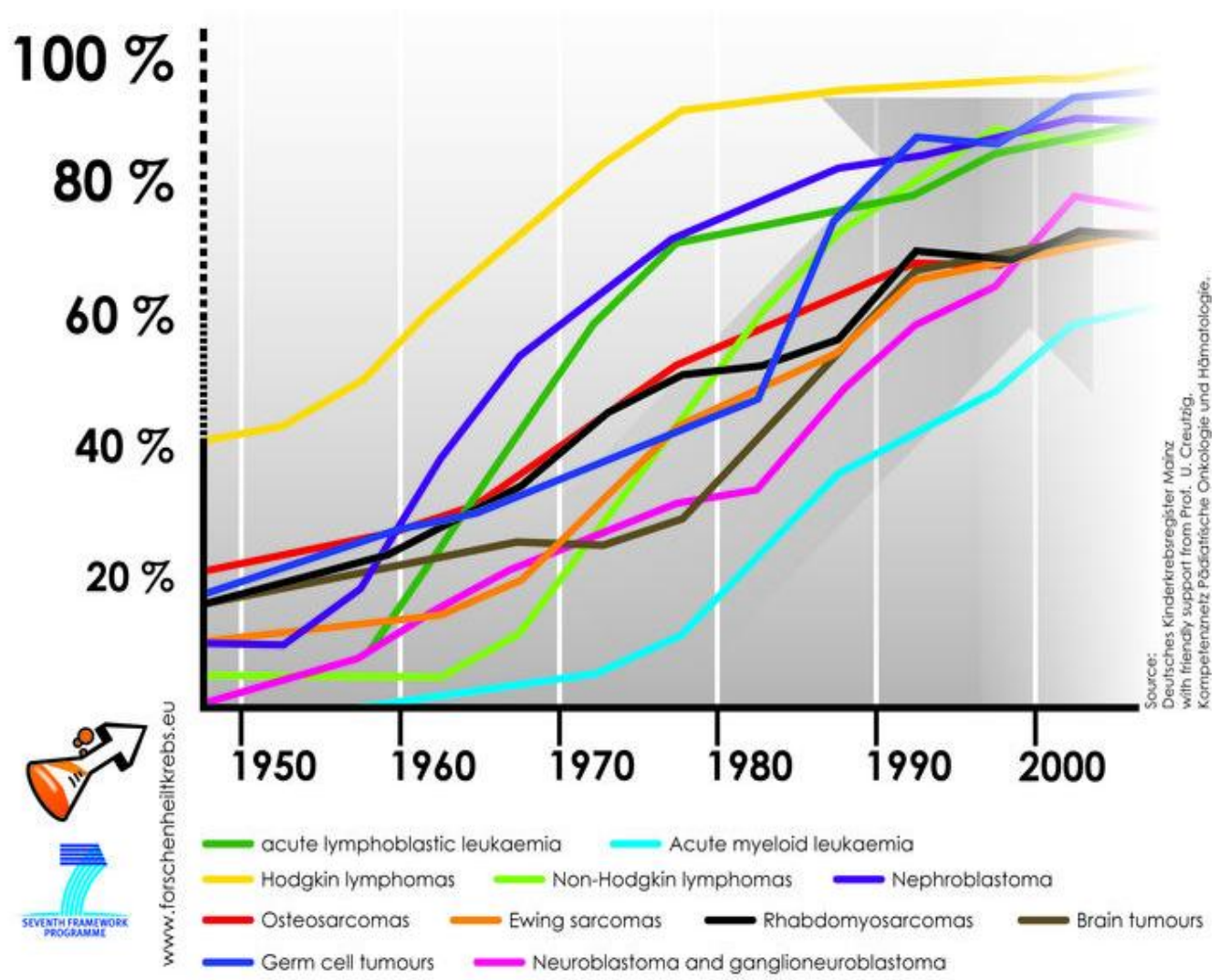
2 months Crizotinib



further 16 days Crizotinib



Survival rates of pediatric cancer patients

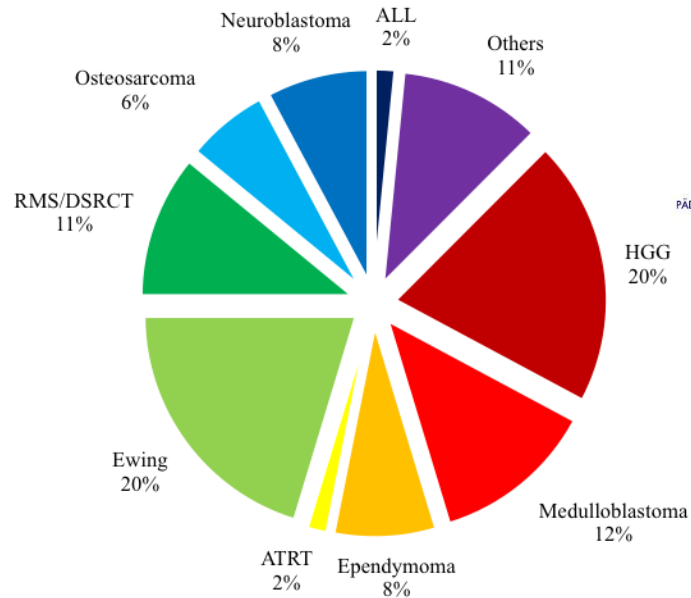


INFORM

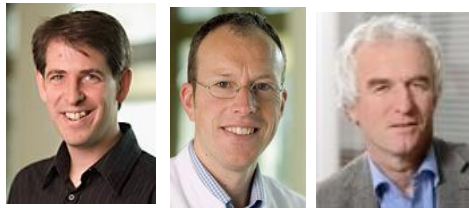
(*IN*dividualized therapy *FO*r *R*elapsed *M*alignancies in childhood)

Genome-based personalized treatment of children with relapsed tumors

- On average ~3 weeks from DNA/RNA preparation to tumor board
- ~ 60% “actionable” target molecules

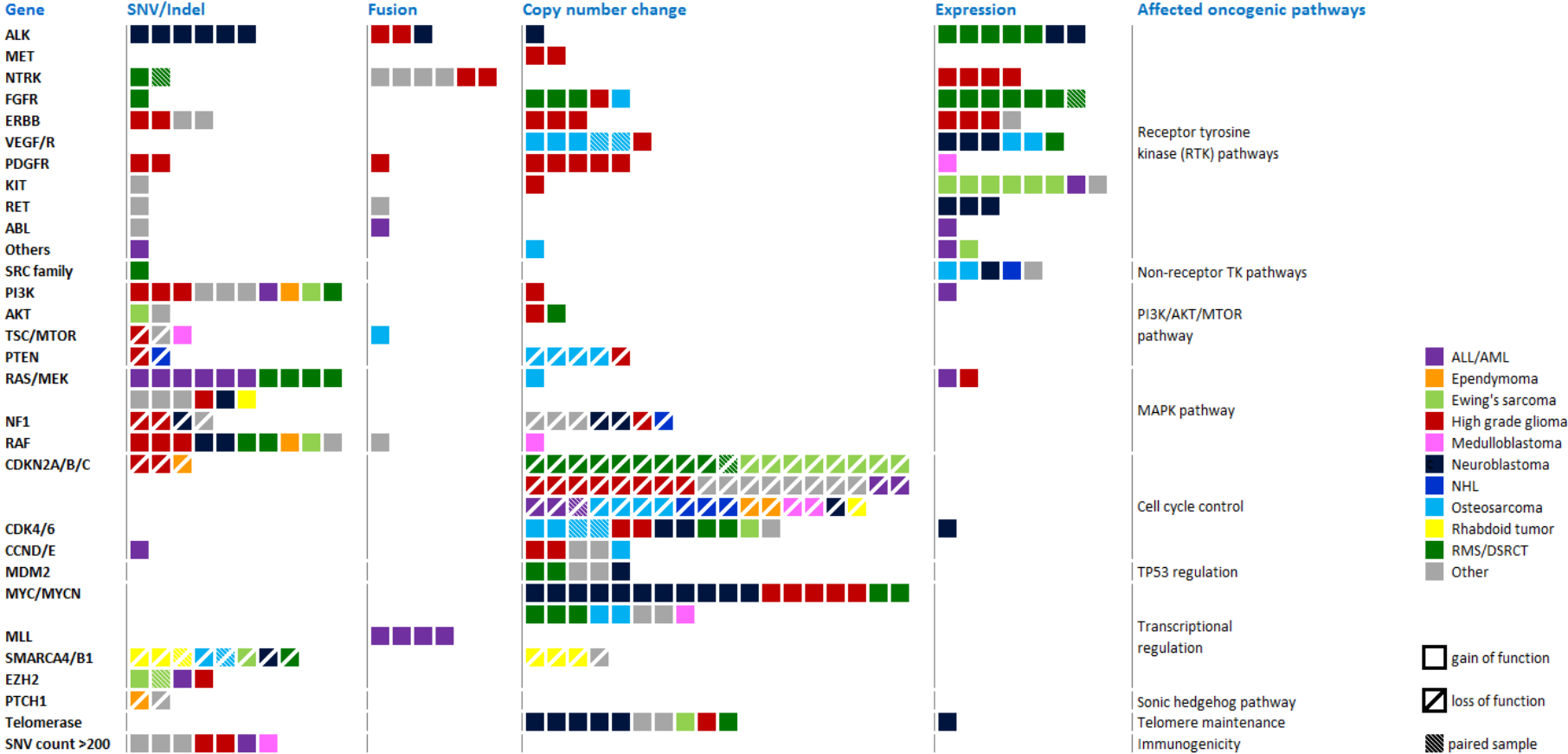


n > 300



S. Pfister, O. Witt, P. Lichter, A. Eggert & all of GPOH

INFORM: IDENTIFIED TARGET MOLECULES






Patient stratification based on molecular data

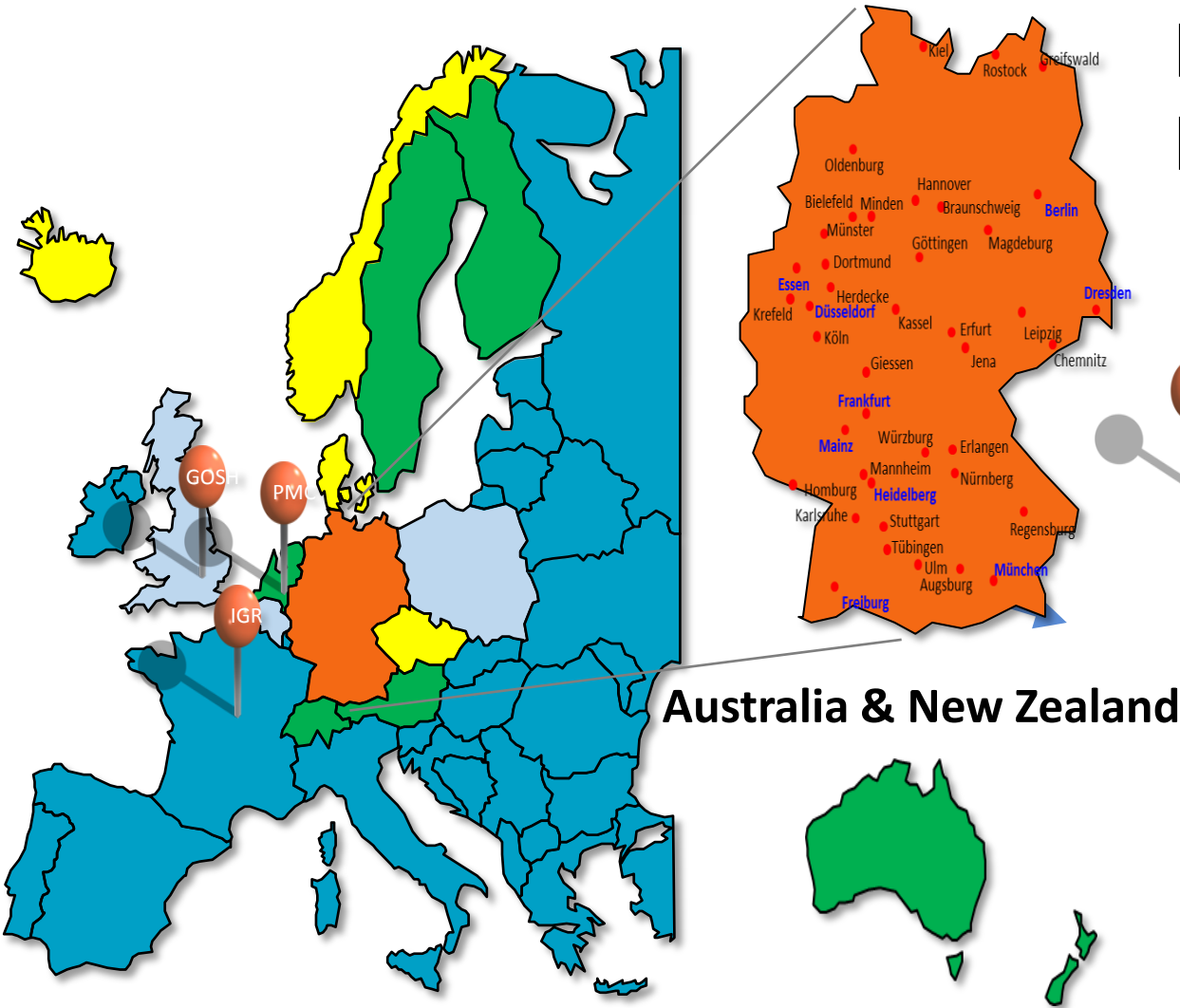
Worst et al. *Eur J Cancer*, 2016

International cooperation

European partners

DKTK + partners

-  Countries that have already joined
-  Countries that plan to join this year
-  Countries that are considering participation



Own platform for molecular profiling:

IGR = Institut Gustave Roussy, Paris ('MAPPYACTS')

... in development:

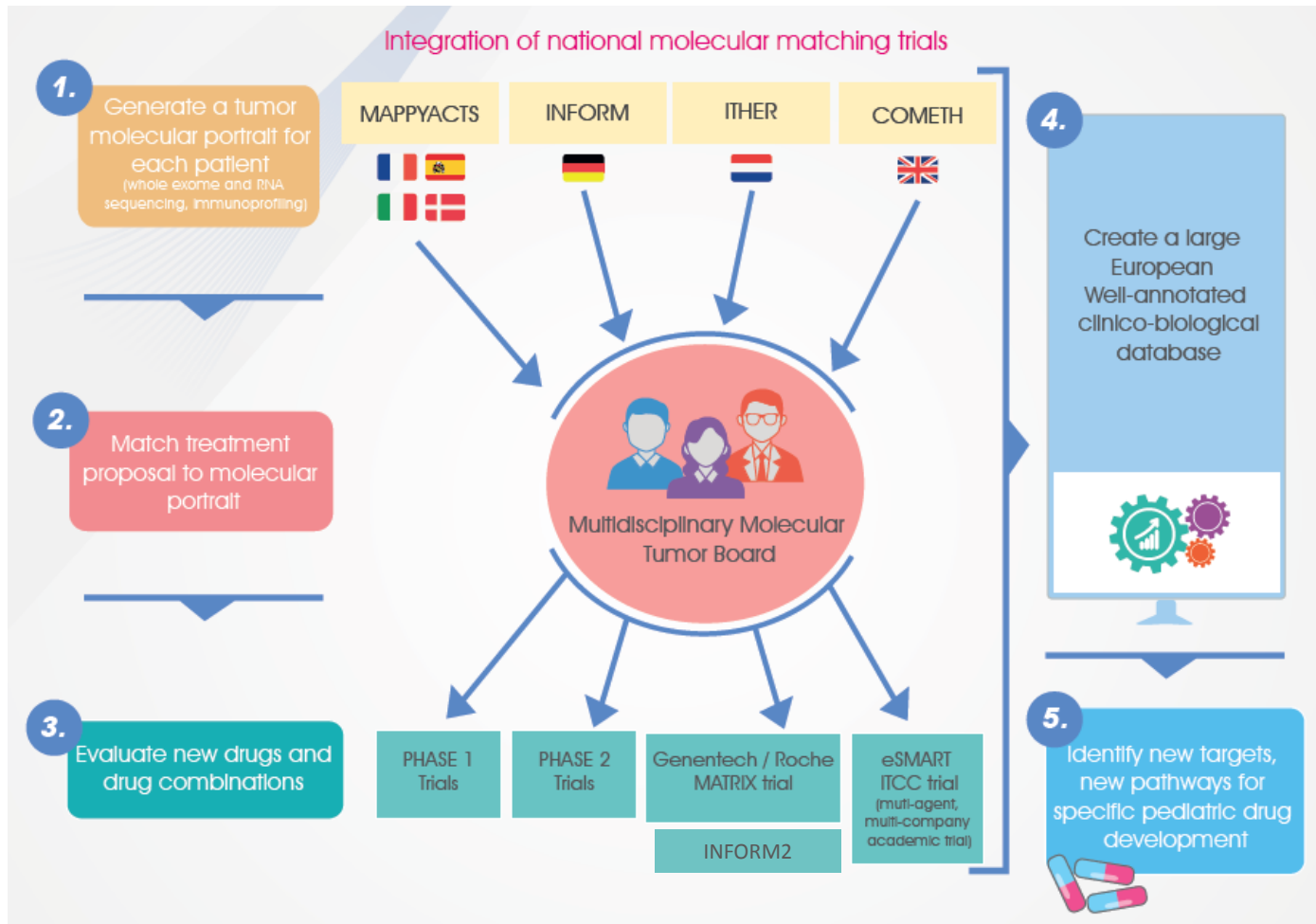
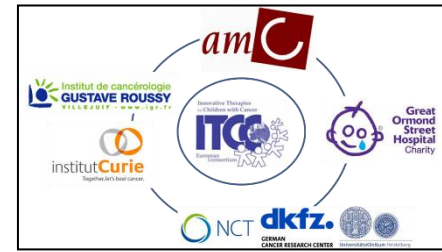
GOSH = Great Ormond Street Hospital, London ('SM-Paed')

PMC = Prinses Maxima Centrum, Utrecht ('iTHER')

Australia & New Zealand



European partners on clinical trials





HIPO-H021: The Individual Patient



NATIONAL CENTER
FOR TUMOR DISEASES
HEIDELBERG



German Cancer Consortium



S. Fröhling



H. Glimm

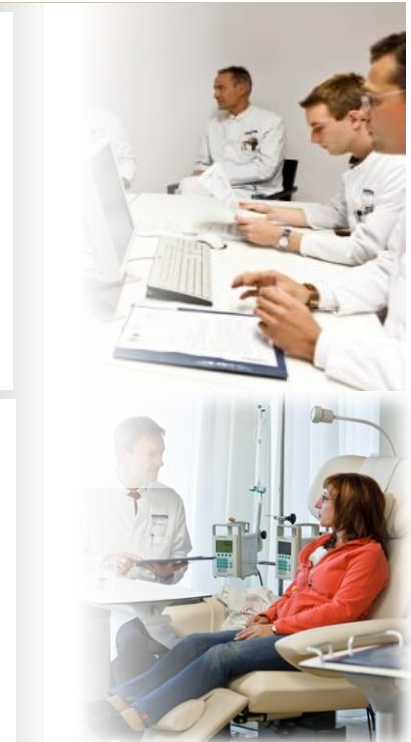
NCT/DKTK MASTER Molecular High-throughput Analysis

NCT MASTER
Registry Study

- All NCT Patients < 50 Jahre, Rare Tumors
- Molecular Profiling
- Clinical Analysis and Interpretation
- Therapy Recommendation

NCT MASTER
Interventional
Studies

- Clinical Intervention
- Basket Trials
- Multiple Treatment Arms



DKTK MASTER TRIAL

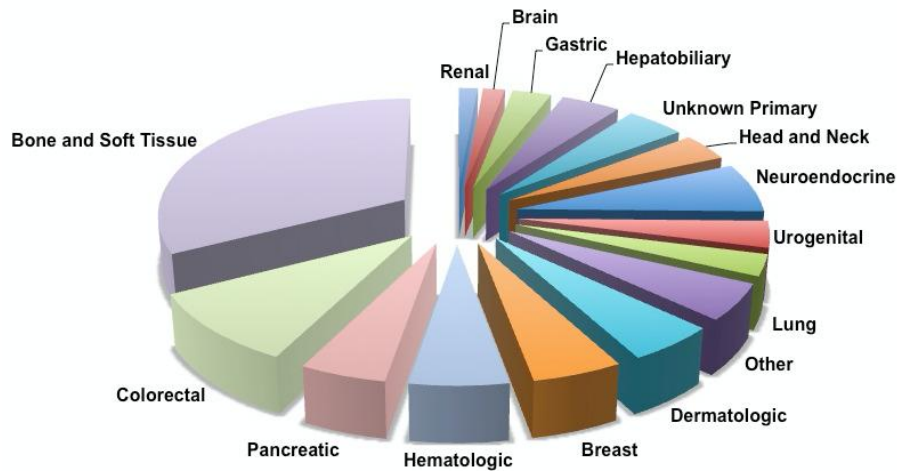
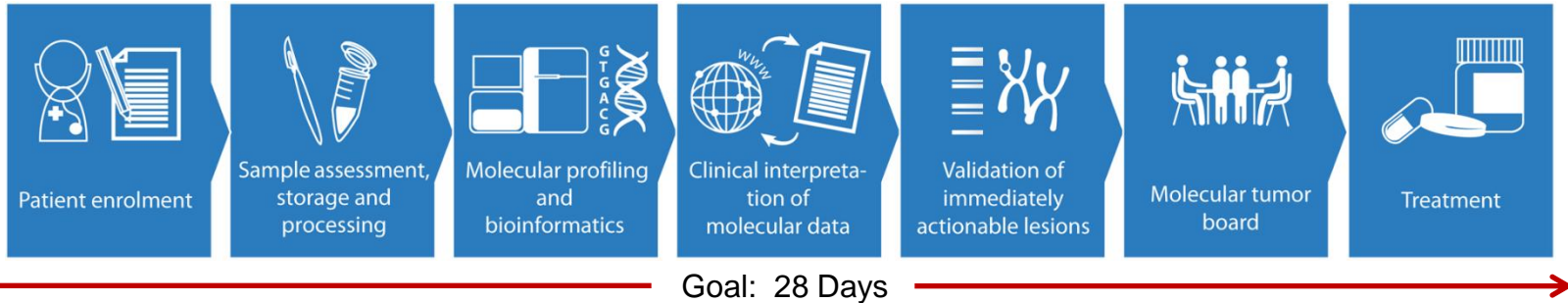
(young adults, rare tumors)



S. Fröhling



H. Glimm



NCT/DKTK MASTER

- PI3K-AKT-
- RAF-MEK-ERK
- Tyrosine
- Cell Cycle
- Dev. Pathways
- DNA Damage
- Immune

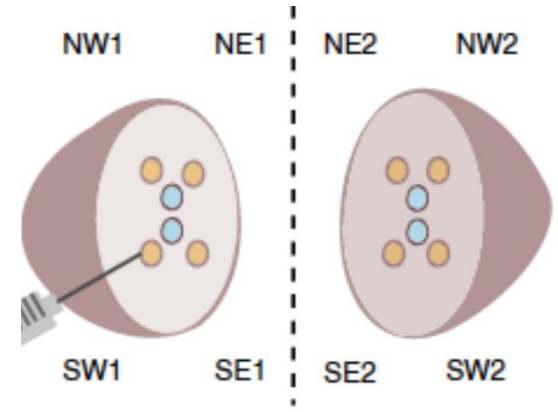
Intervention Baskets

October, 2017
 Molecular Tumor Board
 Management recommendations (Level 1-4)
 Genome-based clinical management

793 patients
 ~75% (05/2016: ~60%)
 ~30% (05/2016: ~25%)

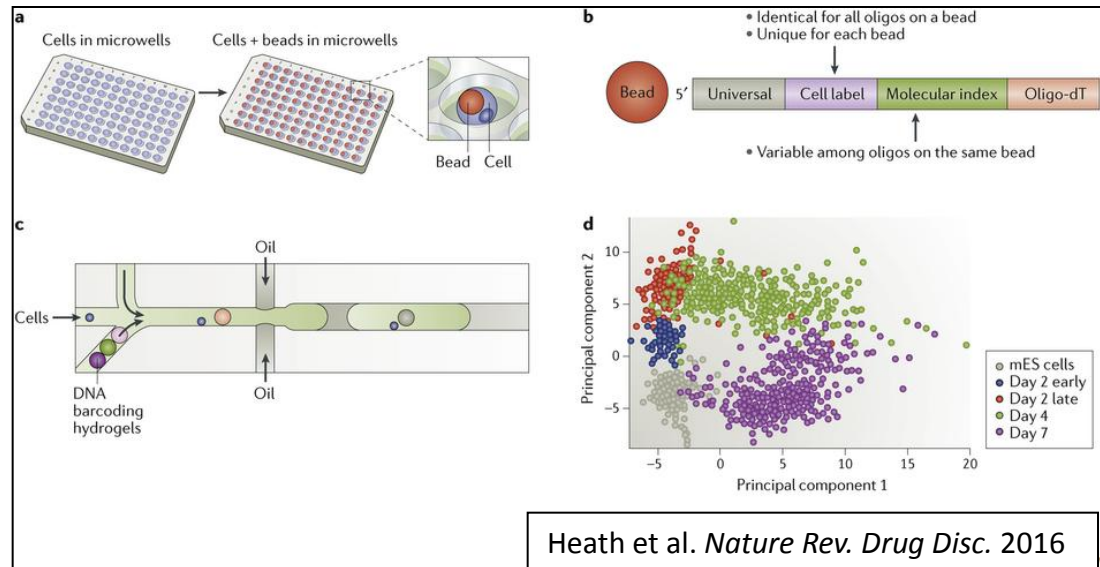
Genetic Heterogeneity: tumors may consist of subclones

Diagnosis on multiple biopsies



Yates et al. *Nature Medicine* 2015

Diagnosis based
on single cell
sequencing?



Heath et al. *Nature Rev. Drug Disc.* 2016

Thank you for the
attention!

