Genom-basierte Therapie-empfehlungen in der personalisierten Krebstherapie

Benedikt Brors
Abt. Angewandte Bioinformatik, DKFZ und NCT Heidelberg

DKTK German Cancer Consortium

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer

Personalisierte Onkologie

Die Personalisierte Onkologie (engl.: *precision oncology*) verwendet molekulare Informationen über einen Patienten, um Diagnose, Prognose, Behandlung und Prävention optimal anzupassen

- somatische Mutationen
- Transcriptomik
- Proteomik
- Metabolomik

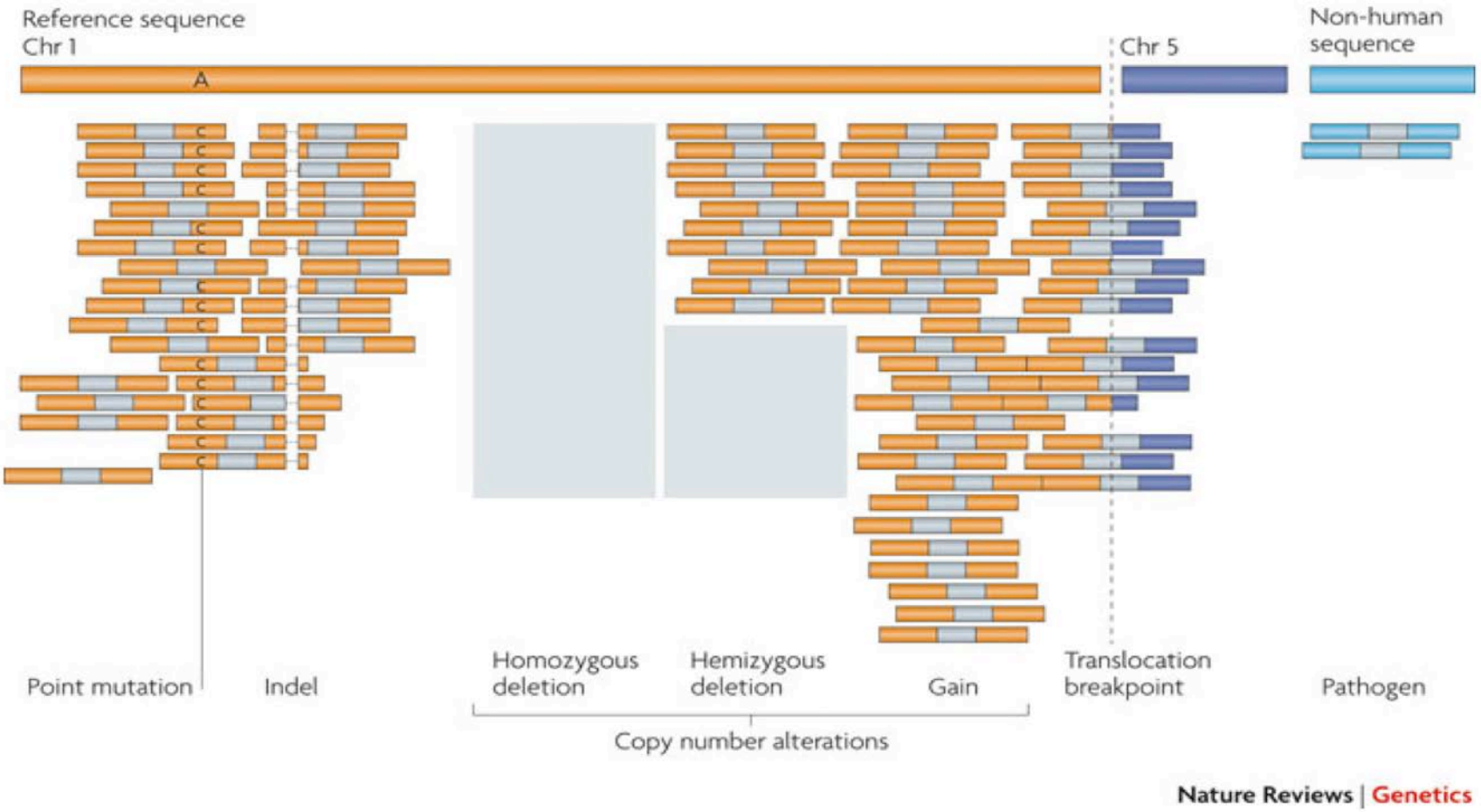
Krebs: eine erworbene genetische Erkrankung

- Onkogene werden durch genetische Veränderungen (Mutationen) aktiviert
- Tumor-Suppressor-Gene werden stillgelegt
- Diese Veränderungen werden (meist) nicht vererbt und entstehen zufällig
- Krebserzeugende Veränderungen werden durch evolutionäre Prozesse selektiert
- Risiko steigt mit dem Alter

Genomsequenzierung

- Viele 100 Millionen
  Basen)
- Mehr als 30-fache A
  Genoms

Cancer genome sequencing



Meyerson, Nat Rev Genet 2010

Capacity

The HiSeq X Ten contains 10 sequencing systems.

HiSeq X™ Ten

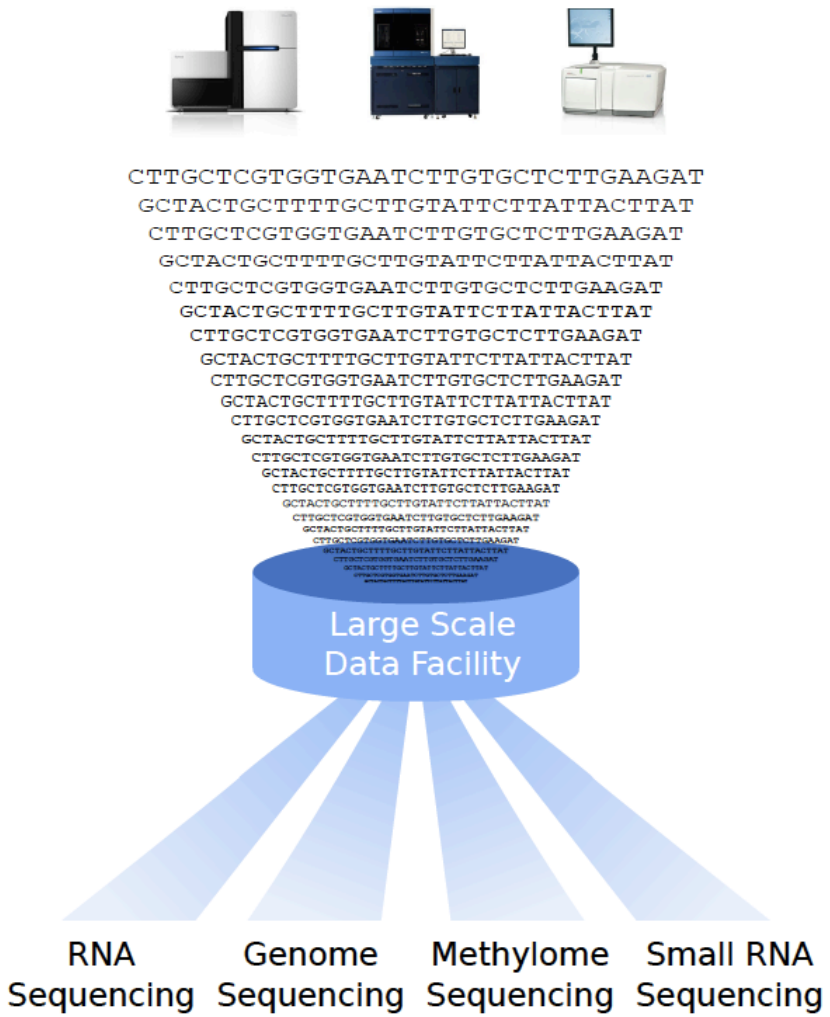
Population Power

Composed of 10 HiSeq X Systems, the HiSeq X Ten is the first sequencing platform that breaks the $1000 barrier for a 30x human genome. The HiSeq X Ten System is ideal for population-scale projects focused on the discovery of genotypic variation to understand and improve human health. It can rapidly sequence tens of thousands of samples at high genome coverage, delivering a comprehensive catalog of human variation within and outside coding regions.

- Tens of thousands of whole human genomes per year
- $1000 human genome, including depreciation, sample preparation, and labor

Capacity:	4.500 patients / year (120x Coverage)
Raw Data:	1,8 PB / year (5 TBytes per day)
Total Data including Analysis Data (approx. 2x overhead)	4 PB / year (11 TBytes per day)
Required growth of storage incl. mirror storagy for 2015-2018:	~ 10 PB per year

Big Data: Prozessierung

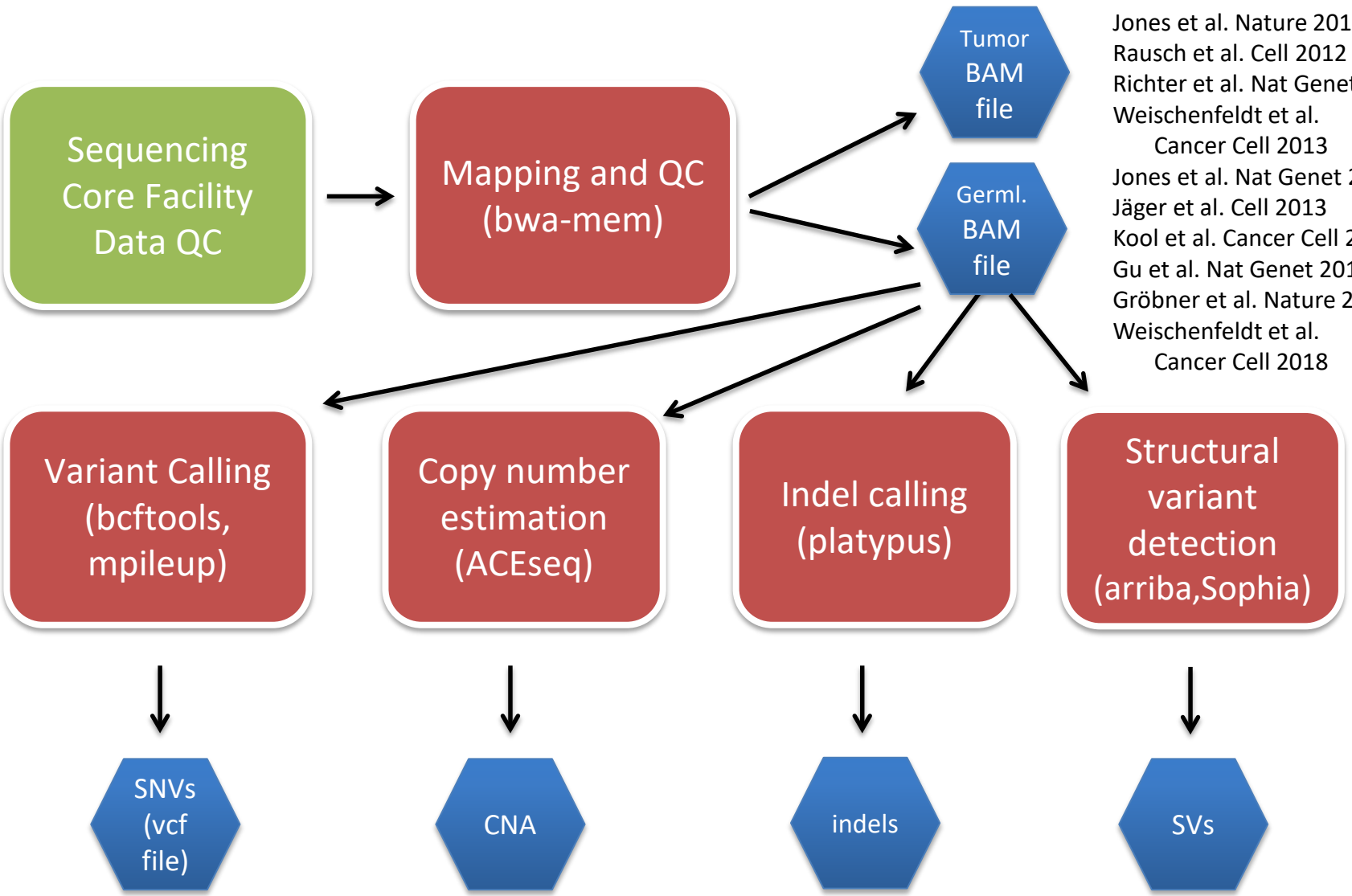


- Aktueller Zuwachs: ca. 3PB pro Jahr
- 4000 Prozessor-kerne
- Benötigt Hoch-geschwindig-keitsnetz (>10 Gbps)

Daten pro Patient

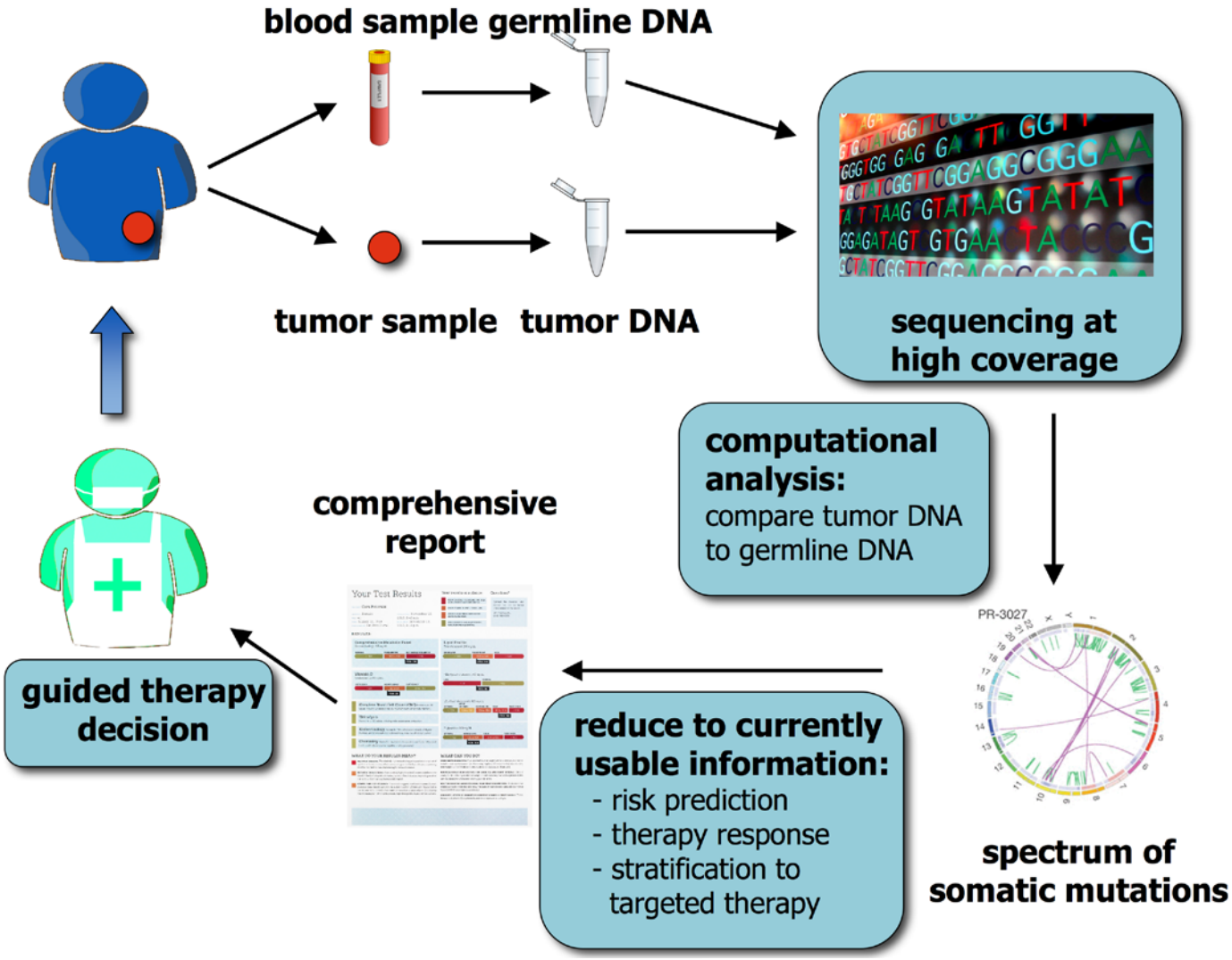
- pro Patient: 732 CDs
- pro 2 Wochen ein Stapel von der Höhe des Stuttgarter Funkturms

Pipelines zur Variantendetektion



Jones et al. Nature 2012
Rausch et al. Cell 2012
Richter et al. Nat Genet 2012
Weischenfeldt et al. Cancer Cell 2013
Jones et al. Nat Genet 2013
Jäger et al. Cell 2013
Kool et al. Cancer Cell 2014
Gu et al. Nat Genet 2015
Gröbner et al. Nature 2018
Weischenfeldt et al. Cancer Cell 2018

Genomic cancer medicine



Targeted therapeutics

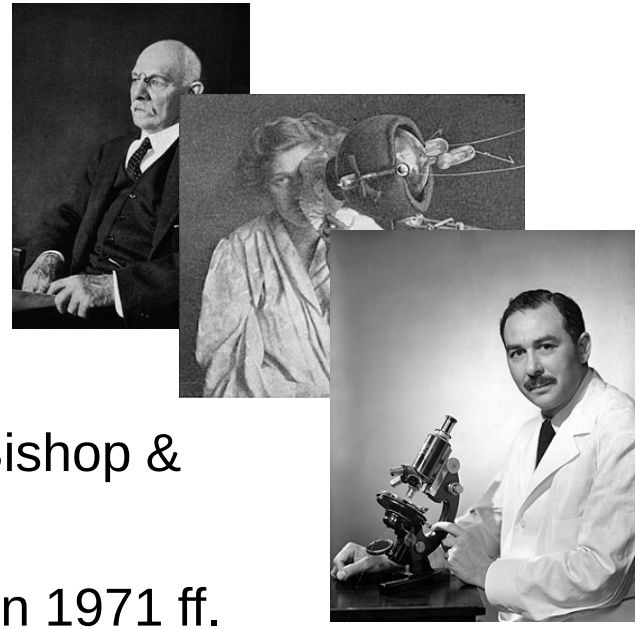
Table 1. Targeted Therapeutics in Cancer.*

Gene	Genetic Alteration	Tumor Type	Therapeutic Agent
Receptor tyrosine kinase			
EGFR	Mutation, amplification	Lung cancer, glioblastoma	Gefitinib, erlotinib
ERBB2	Amplification	Breast cancer	Lapatinib
FGFR1	Translocation	Chronic myeloid leukemia	PKC412, BIBF-1120
FGFR2	Amplification, mutation	Gastric, breast, endometrial cancer	PKC412, BIBF-1120
FGFR3	Translocation, mutation	Multiple myeloma	PKC412, BIBF-1120
PDGFRA	Mutation	Glioblastoma, gastrointestinal stromal tumor	Sunitinib, sorafenib, imatinib
PDGFRB	Translocation	Chronic myelomonocytic leukemia	Sunitinib, sorafenib, imatinib
ALK	Mutation or amplification	Lung cancer, neuroblastoma, anaplastic large-cell lymphoma	Crizotinib
c-MET	Amplification	Gefitinib-resistant non–small-cell lung cancer, gastric cancer	Crizotinib, XL184, SU11274
IGF1R	Activation by insulin-like growth factor II ligand	Colorectal, pancreatic cancer	CP-751,871, AMG479
c-KIT	Mutation	Gastrointestinal stromal tumor	Sunitinib, imatinib
FLT3	Internal tandem duplication	Acute myeloid leukemia	Lestaurtinib, XL999
RET	Mutation, translocation	Thyroid medullary carcinoma	XL184
Non–receptor tyrosine kinase			
ABL	Translocation (BCR-ABL)	Chronic myeloid leukemia	Imatinib
JAK2	Mutation (V617F), translocation	Chronic myeloid leukemia, myeloproliferative disorders	Lestaurtinib, INCB018424
SRC	Overexpression	Non–small-cell lung cancer; ovarian, breast cancer; sarcoma	KX2–391, dasatinib, AZD0530
Serine–threonine–lipid kinase			
BRAF	Mutation (V600E)	Melanoma; colon, thyroid cancer	SB-590885, PLX-4032, RAF265, XL281
Aurora A and B kinases	Overexpression	Breast, colon cancer; leukemia	MK-5108 (VX-689)
Polo-like kinases	Overexpression	Breast, lung, colon cancer; lymphoma	BI2536, GSK461364
MTOR	Increased activation	Renal-cell carcinoma	Temsirolimus (CCI-779), BEZ235
PI3K	PIK3CA mutations	Colorectal, breast, gastric cancer; glioblastoma	BEZ235
DNA damage or repair			
BRCA1 and *BRCA2*	Mutation (synthetic lethal effect)	Breast, ovarian cancer	Olaparib, MK-4827 (PARP inhibitors)

McDermott NEJM 2011

Hope in targeted treatments

Current main treatment modalities date to a time when the *mechanism* of cancer was not known



- radical surgery: 1870s (Halsted)
- radiotherapy: about 1900 (Grubbe)
- cytotoxic chemotherapy: 1940s (Farber)

- first oncogene (*Src*) discovered: 1970s (Bishop & Varmus)
- first tumor suppressor gene (*Rb*): Knudson 1971 ff.

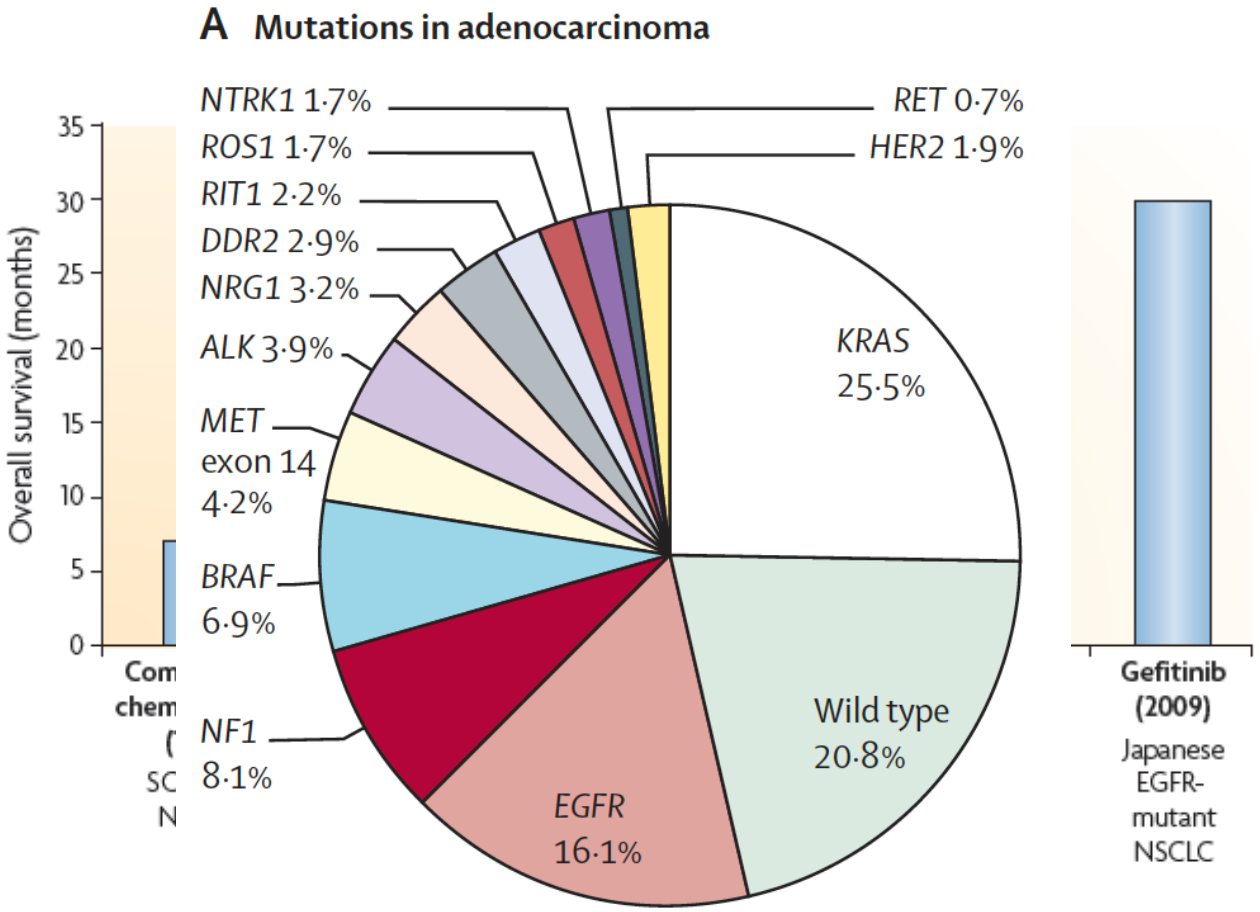
Inefficacy of traditional trial designs

- Gold standard: phase III randomized controlled trial
- Meta analysis: 62% of phase III trials in oncology failed (Gan et al. JNCI 2012)
  - 253 trials, 2005-2009

> “ These select 158 negative studies enrolled a total of 100 275 patients, with the subset of eight studies with statistically significant detriment enrolling 5287 patients. “

  - unselected population

Improvement in outcome for lung cancer

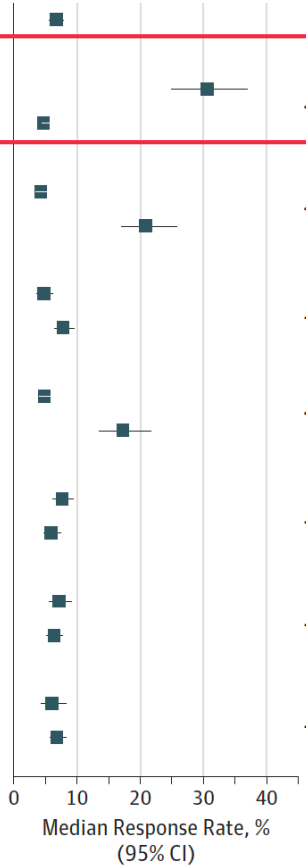


Pao & Chmielecki, Nat Rev Cancer 2010
Rosell & Karachaliou, Lancet 2016

Selected populations do better

B Response rate (meta-analysis)

Variable	No. of Arms	Median Response Rate, % (95% CI)	*P* Value
Overall	351	6.56 (5.57-7.72)	
Used a personalized strategy			
Yes	58	30.62 (25.0-36.90)	<.001[a]
No	293	4.89 (4.22-5.66)	
Tumor type			
Solid	272	4.25 (3.48-5.19)	<.001[a]
Hematologic	79	21.02 (17.0-25.71)	
Agent class			
Cytotoxic	117	4.72 (3.60-6.17)	.003
Targeted	234	7.84 (6.46-9.49)	
FDA/EMA approved			
No	267	4.83 (4.04-5.76)	<.001[a]
Yes	84	17.27 (13.60-21.69)	
No. of patients per arm			
≤30	182	7.67 (6.20-9.45)	.11
>30	169	5.94 (4.70-7.48)	
Administration route			
Oral	162	7.23 (5.68-9.16)	.41
Systemic	189	6.32 (5.13-7.76)	
No. of treating centers			
Single center	91	6.0 (4.3-8.2)	.48
Multiple centers	260	6.8 (5.7-8.2)	



- 346 trials 2011-2013
- ORR
  - not selected: 4.9%
  - selected: 30.6%
  - genomic biomarker: 42%
  - protein biomarker: 22.4%

Schwaederle et al. JAMA Oncol 2016

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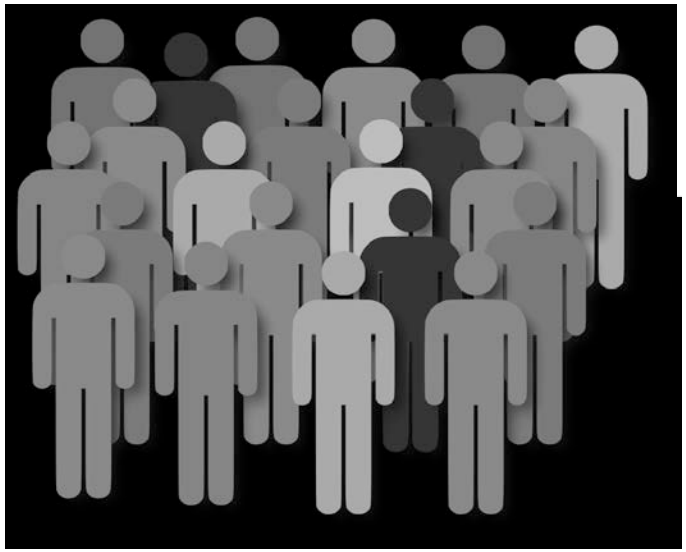
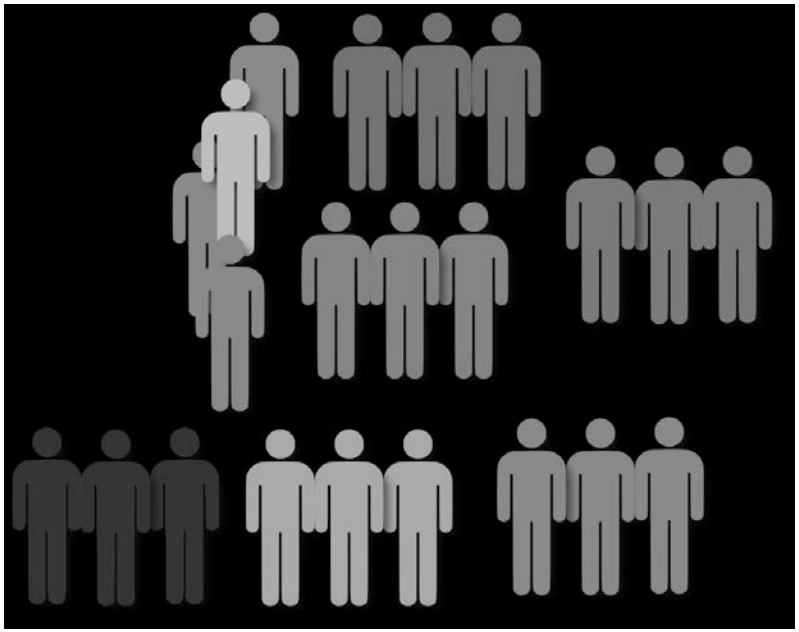
Personalisierte Medizin





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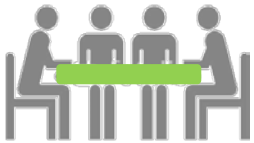
Molecular Tumor Board



Medical and Translational Oncology

Sequencing facility, sample processing lab

Pathology

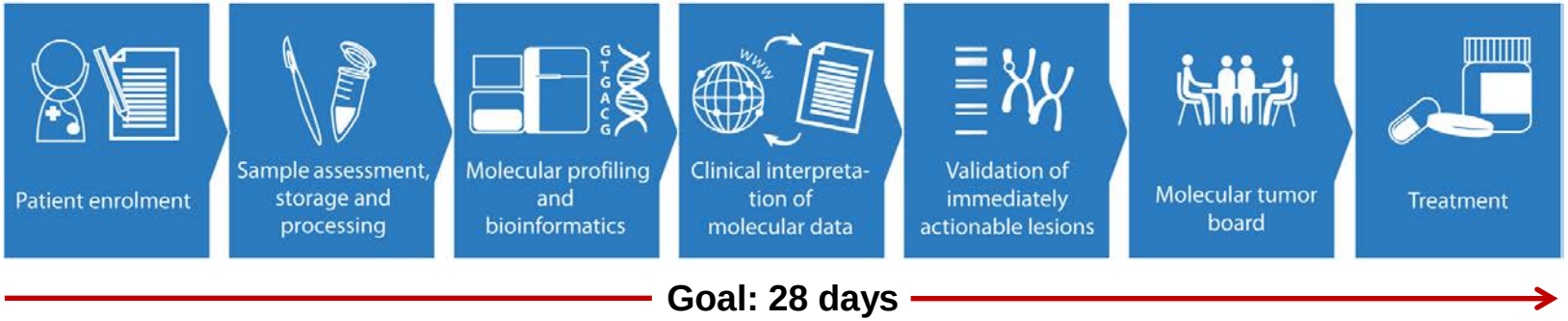
Wednesday 11.30 AM
Friday, 2:30 PM

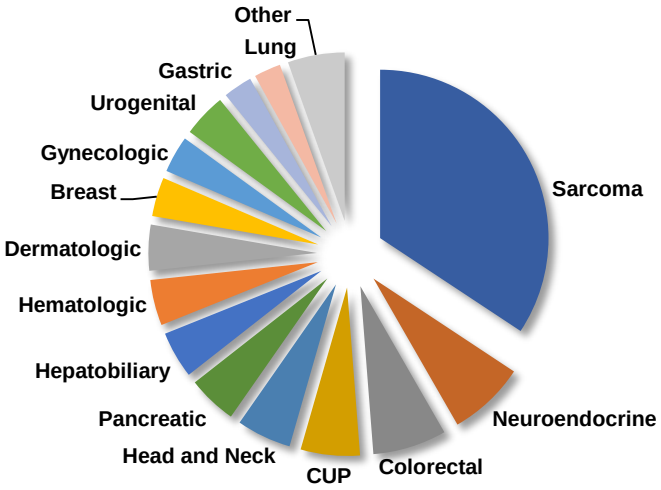
Bioinformatics

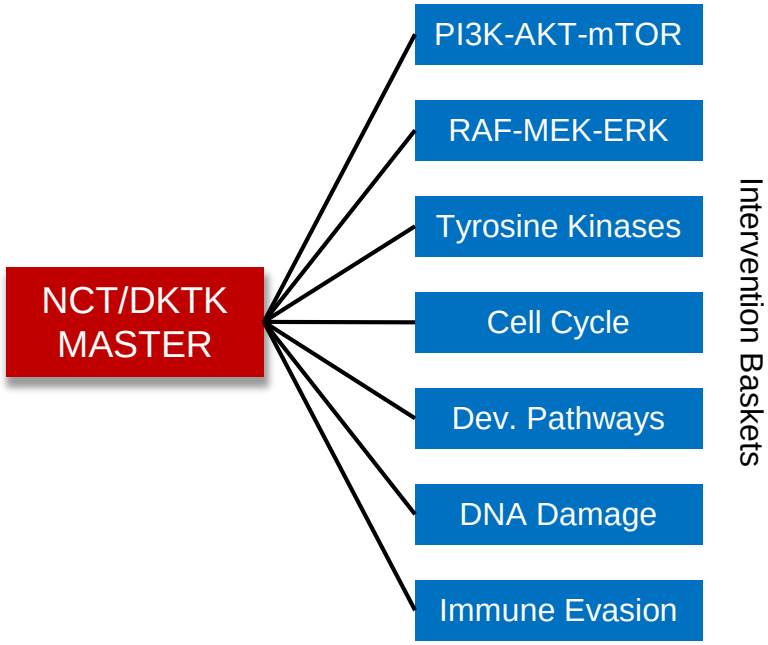
Referring physicians

Medical Genetics and Counseling

Workflow and Current Results







January 30, 2019

Molecular tumor board	1,382 patients
Management recommendation (Level 1-4)	~80%
Genomics-guided clinical management	~35%
Disease control rate (CR, PR, SD)	~40%
Progression-free survival ratio >1.3	~45% (MOSCATO 01: 33%)

courtesy of Stefan Fröhling

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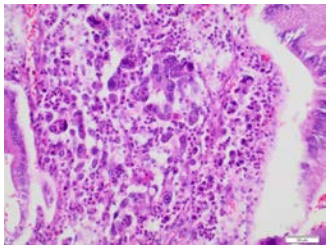
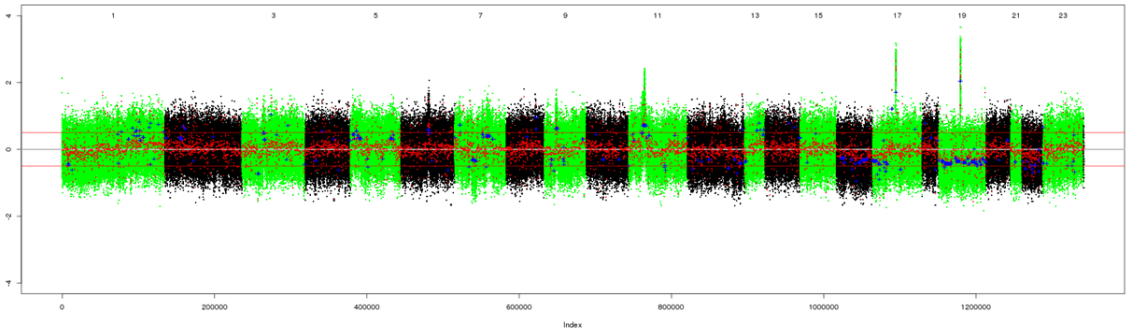
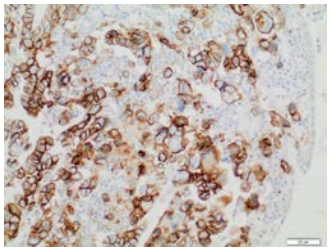
Response to Genomics-Guided Treatment



H&E





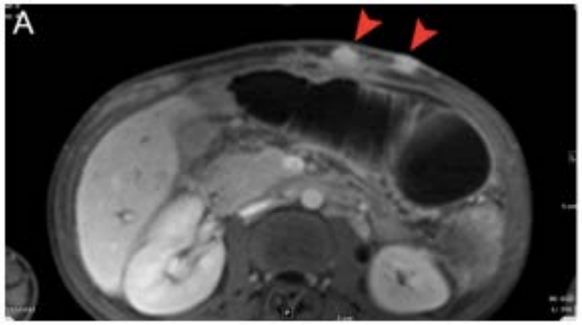
ERBB2

Metastatic gallbladder carcinoma

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

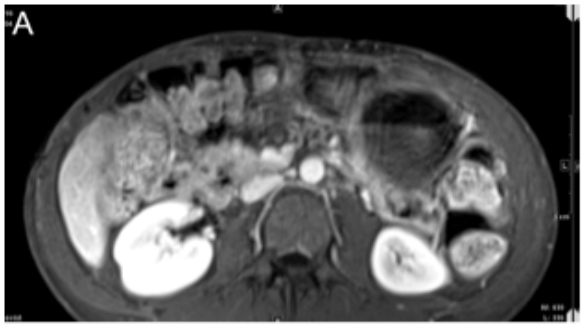
High-level amplification of chromosome 17q12, including *ERBB2*

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



Dual ERBB2 blockade:
trastuzumab/pertuzumab

Complete remission
(>12 months)



Czink et al., Z Gastroenterol 2016

NCT Evidenzbewertung

LoE		Explanation
m1A	Same entity	Predictive value of the biomarker or clinical effectiveness of the corresponding drug in a molecularly stratified cohort was demonstrated in a prospective study or a meta-analysis in the same tumor type.
m1B		Predictive value of the biomarker or clinical effectiveness of the drug in a molecularly stratified cohort was demonstrated in a retrospective cohort or case-control study in the same tumor type.
m1C		Case study or single unusual responder indicates the biomarker is associated with response to the drug in the same tumor type.
m2A	Different entity	Predictive value of the biomarker or clinical effectiveness of the corresponding drug in a molecularly stratified cohort was demonstrated in a prospective study or a meta-analysis in a different tumor type.
m2B		Predictive value of the biomarker or clinical effectiveness of the drug in a molecularly stratified cohort was demonstrated in a retrospective cohort or case-control study in a different tumor type.
m2C		Case study or single unusual responder indicates the biomarker is associated with response to the drug in a different tumor type.
m3	Preclinical	Preclinical data (in vitro, in vivo models or functional genomics studies) demonstrate that the biomarker predicts response to a specific drug treatment, supported by scientific rationale.
m4	Biological rationale	Biological rationale that associates the biomarker with altered signaling pathway activity or drug sensitivity without direct clinical or preclinical evidence for response to the drug.
Additional Modifiers	**is** several in situ data and studies on patient material (e.g. IHC, FISH) support the biomarker and the level of evidence. **iv** in vitro data **Z** Drug is approved for use with the specific biomarker (Z= EMA approval, Z(FDA)= FDA approval) **R** Biomarker predicts resistance to the drug.	

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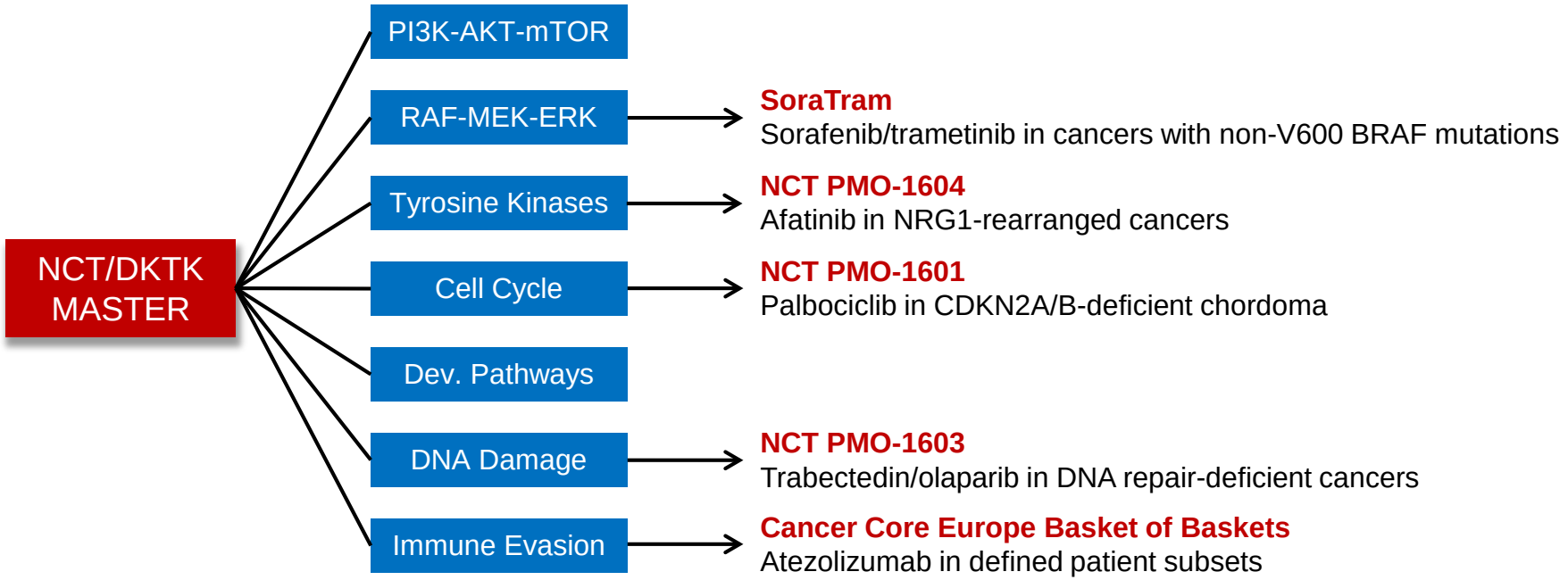
Basket trials



Eligibility

- Advanced-stage cancer
- Prior standard treatment
- Actionable molecular alteration, as determined by analysis within NCT/DKTK MASTER

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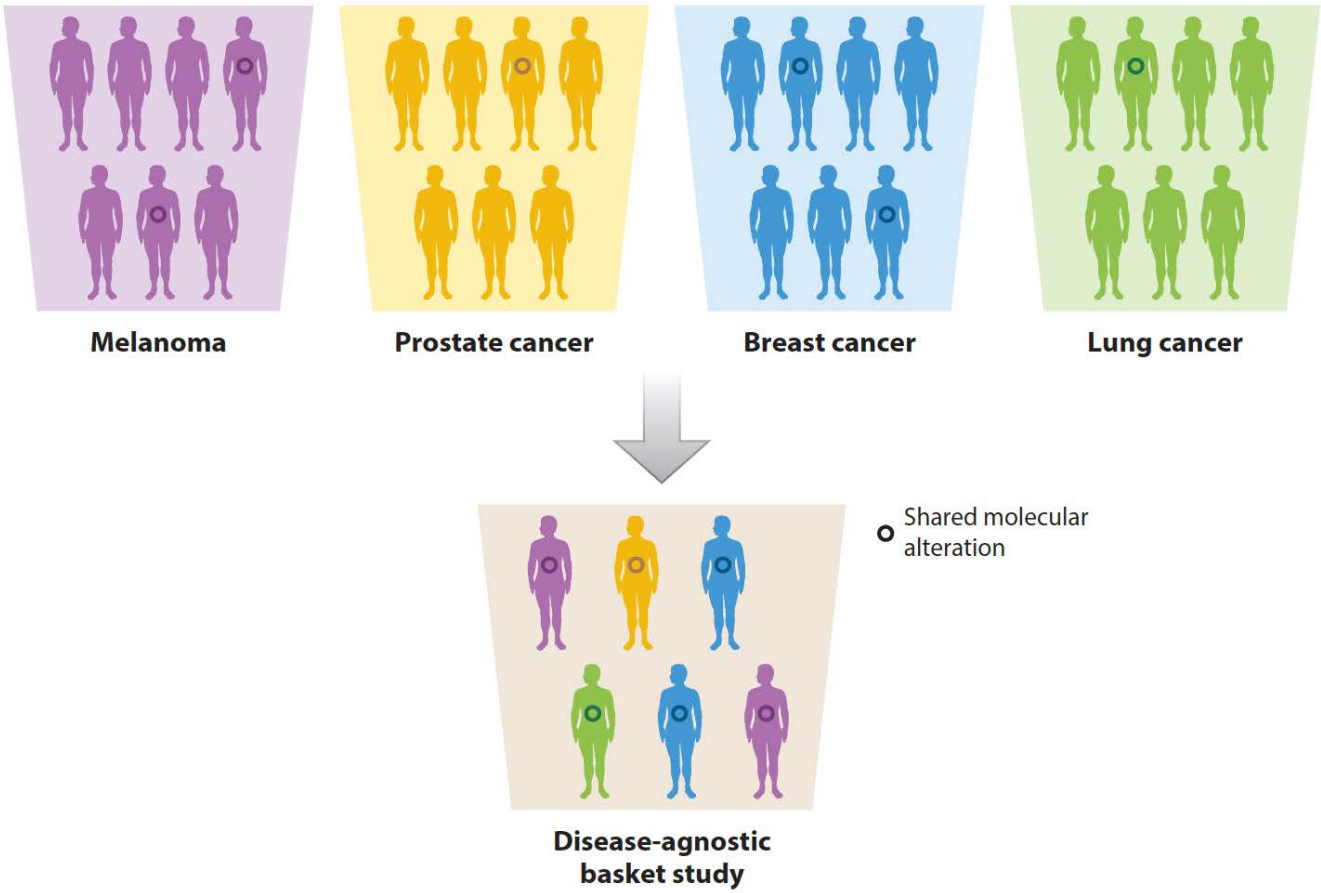
DKTK German Cancer Consortium

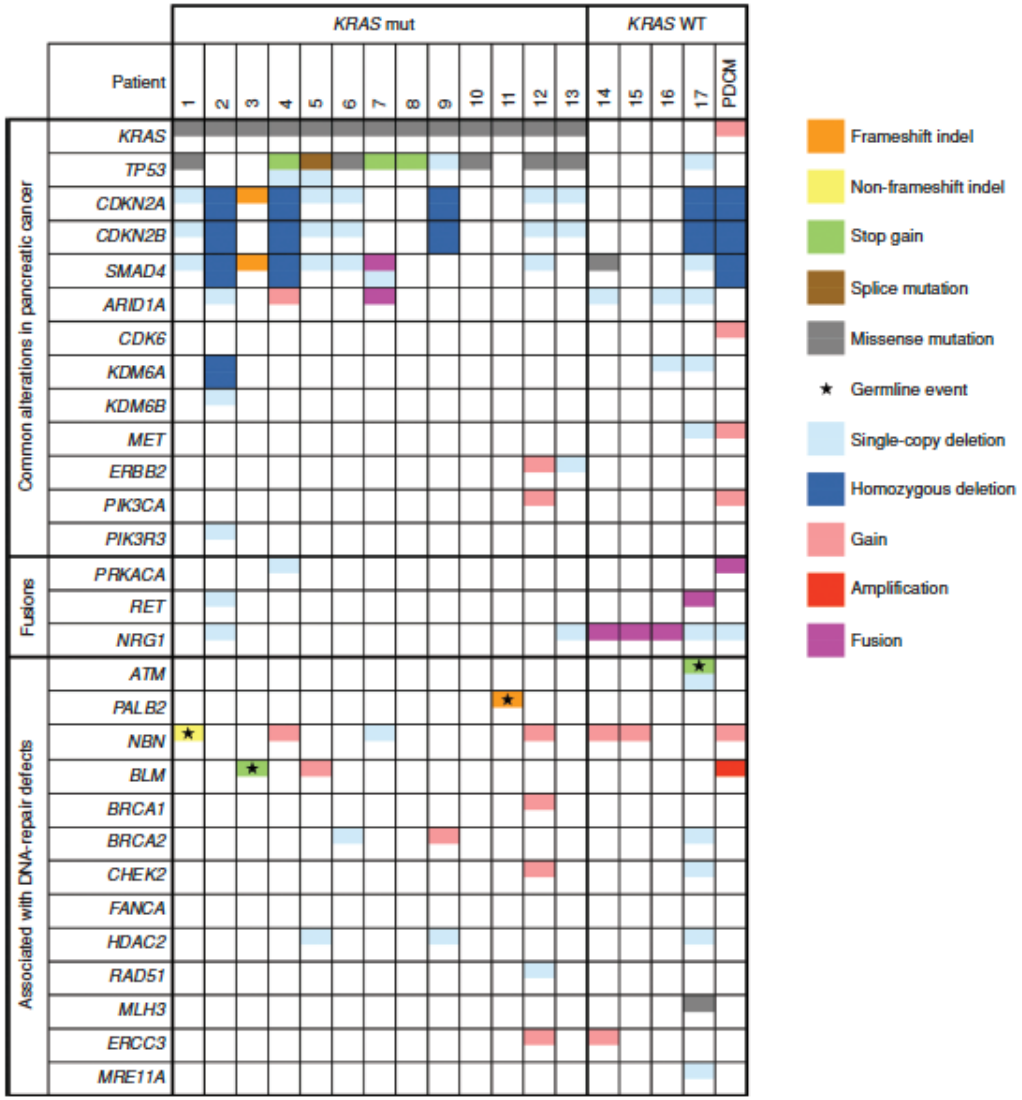
courtesy of Stefan Fröhling

Konzept: Basket-Studien



Tao et al. Ann Rev Med 2018

Seltene Subgruppen: Pankreaskarzinom



Heining, Horak, Uhrig et al. Cancer Discov 2018

Komplexe Biomarker

- „BRCAness“: Defekte im Mechanismus der DNA-Reparatur durch homologe Rekombination (HRD)
  - Zuerste beschrieben in Patienten mit Mutationen in BRCA1/2
  - hat synthetische Lethalität bzgl. PAPR-Inhibitoren zur Folge
  - Kennzeichen:
    - Funktionsverlust von DNA-Reparatur-Genen
    - hohe Anzahl genomischer Bruchpunkte, stark variierende Kopienzahlen
    - Mutationssignatur für HR-Defizienz (COSMIC Signatur 3)
- Vorhersage des Ansprechens auf Immun-Checkpointinhibitoren
  - Gesamtmutationslast bzw. Neoepitop-Spektrum
  - Expression van PD1, PDL1, CTLA4 (und/oder Amplifikation)
  - Dekonvolution der Zelltypen in der Immun-Mikroumgebung

Zukünftige Entwicklungen

- Mehr klinische Studien in Erst- und Zweitlinie
- Resistenzen überwinden
  - Kombinationstherapien
  - mit intra-Tumor-Heterogenität umgehen
  - bessere Strategien zur Vorhersage wirksamer Interventionen (einschl. epigenetischer Therapien und Immunonkologie)
- Verstehen der Interaktion von Tumorzellen mit dem Immunsystem, Vorhersage des Ansprechens auf Immuntherapien
- Translation der Erkenntnisse über Relevanz von Veränderungen außerhalb kodierender Genombereiche (z.B. Northcott et al., Nature 2014)

Zukunft der Präzisionsmedizin

- Benötigt Daten von sehr großen Kollektiven (> 10.000)
  - z.B. *ICGC-ARGO, 200.000 Patienten*
- Bessere Erfassung der klinischen Daten („Real World Evidence“)
  - Diagnose
  - Pathologischer Befund
  - Behandlung
  - Nachverfolgung
  - Lebensqualität
- Für zielgerichtete Therapien: Verfügbarkeit von Medikamenten kritisch (→ klinische Studien, entitätsübergreifende Zulassung)
- Abrechnung der Diagnostik im Gesundheitssystem

NCT/DKFZ

Translational Oncology

Christoph Heining, Stefan Gröschel, Hanno Glimm

Medical Oncology

Dirk Jäger and Team

NCT POP/DKFZ-HIPO

Sample Processing/Coordination

Christina Geörg, Katrin Pfütze and Team, Katja Oehme, Daniela Richter, Karolin Willmund, Katja Beck

Board of Directors

Peter Lichter, Roland Eils, Christof von Kalle

DKFZ

Sequencing Core Facility

Stephan Wolf and Team

Applied Bioinformatics

Barbara Hutter, Martina Fröhlich, Daniel Huebschmann, Prakash Balasubramanian, Benedikt Brors

Heidelberg University

Molecular Pathology

Volker Endris, Roland Penzel, Stephan Singer, Felix Lasitschka, Albrecht Stenzinger, Peter Schirmacher

DKFZ-HIPO

NCT POP
Precision Oncology Program

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Frankfurt/Mainz
Christian Brandts, Nicola Gökbuget, Thomas Kindler, Hubert Serve, Joachim Steinbach, Matthias Theobald

Munich
Katharina Götze, Volker Heinemann, Wolfgang Hiddemann, Ulrich Keller, Thomas Kirchner, Lars Lindner, Klaus Metzeler, Katja Specht, Karsten Spiekermann, Wilko Weichert

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Düsseldorf/Essen
Sebastian Bauer, Martin Schuler

Freiburg
Melanie Börries, Nikolas von Bubnoff, Hauke Busch, Justus Duyster, Silke Lassmann, Christoph Peters, Martin Werner

Berlin
Ulrich Keilholz, Marianne Pavel, Reinhold Schäfer

Deutsches Konsortium für Translationale Krebsforschung

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50 Years – Research for
A Life Without Cancer