Translating Data into Health:

Clinical Translational Research in the Digital Age

Prof. Dr. med. Christof von Kalle
Berlin
28.02.2020

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health
Charité & MDC
Turning Research into Health

The Paradigm Shift: Understanding each Individual Patient‘s Disease at the Cellular and Molecular Level

Translation Delivered...

1. ...in Obstetrics/Gynecology
2. ...in Gene Transfer and Gene Editing
3. ...in Cancer
4. ...as a Center
5. ...in the Digital Age
6. ...as a Society
7. ...@ BIH/Charité

1.

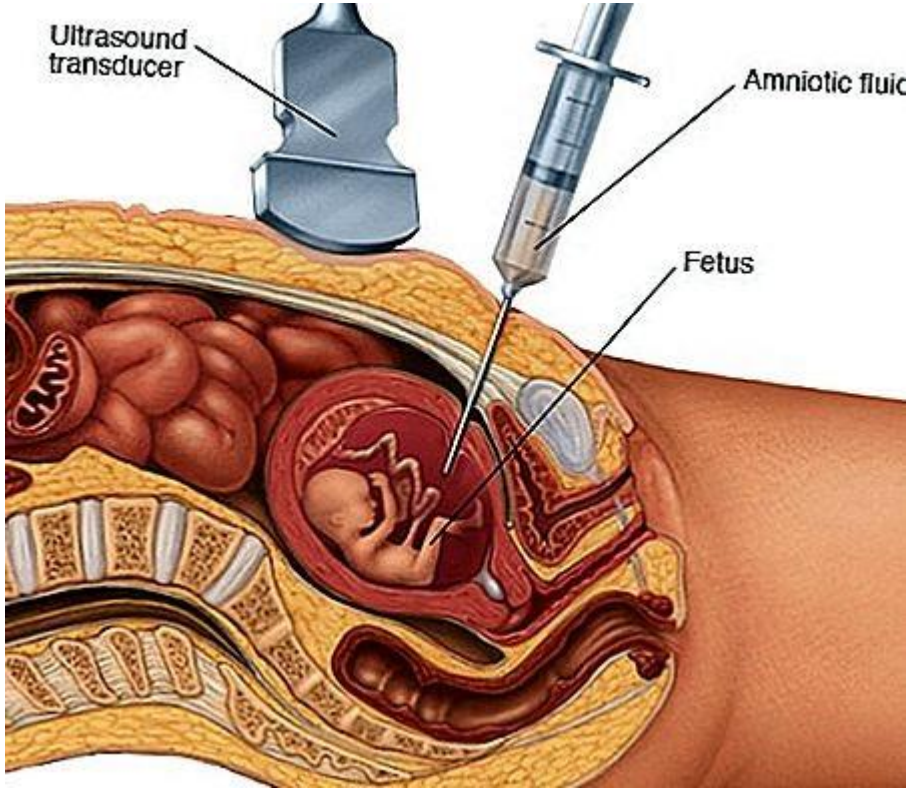
Translation Delivered…

…in Obstetrics/Gynecology

Problem Amniocentesis

- Complication rate of harvesting a fetal tissue sample with a needle stuck into mother and child kills approximately 1% of pregnancies

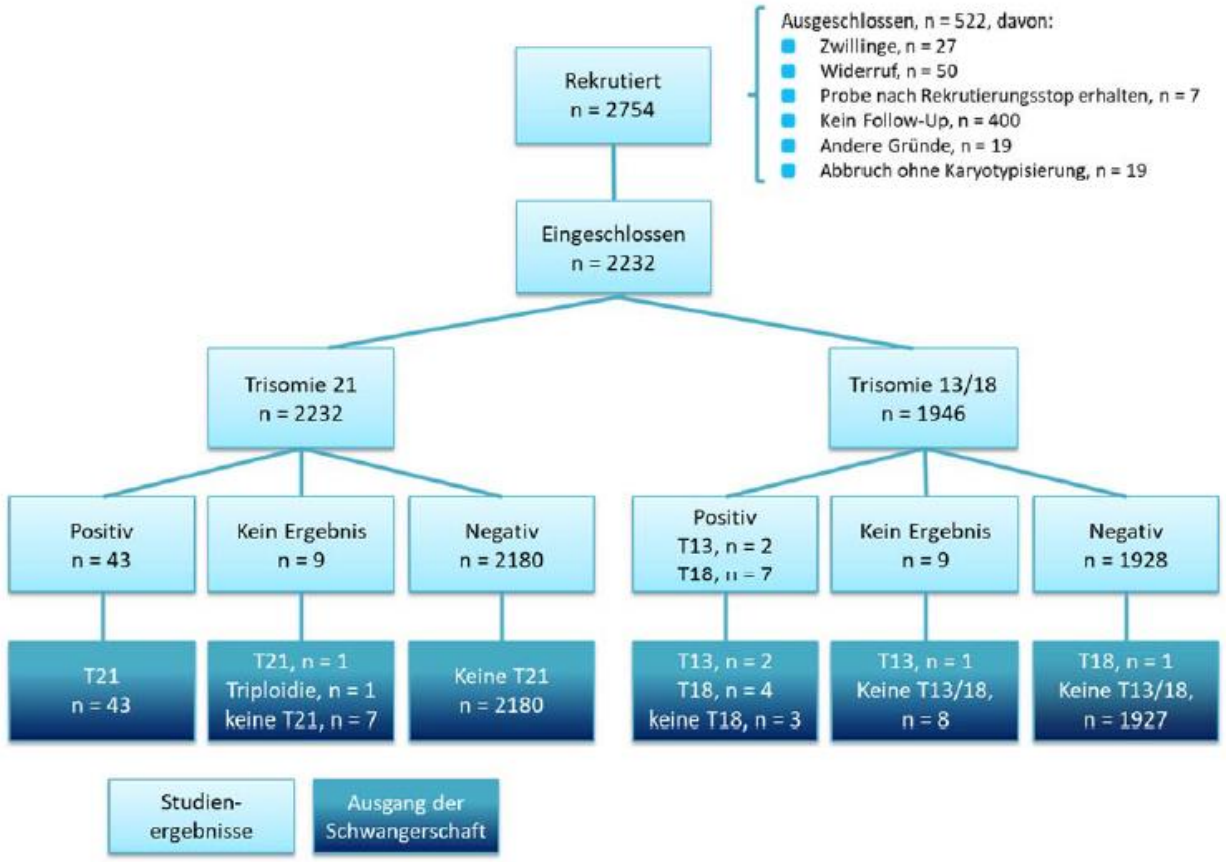
- 1% of 60.000 procedures per year is 600



Non-invasive Prenatal Testing
NIPT

- Detecting fetal DNA in the mother‘s bloodstream is feasible but expensive
  by high-throughput sequencing to enumerate Chr 21 reads

- Early-to-market approach has allowed undelayed access
  and bootstrapping of an innovative
- cost-efficient approach
  by PCR sequencing of differentially methylated alleles



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Mission accomplished

- It can be done!
- Scientists can do/need to do business
- 1% of 175.000 lives is 1.750 lives
- KMU is instrumental
- G-BA needs an overhaul:
  - our application from 2013 will
  - be passed in 2020

- How Germany forces its startups to sell to the foreign competition

„Bereits seit 2010 entwickelt LifeCodexx klinisch validierte, nicht invasive pränatale Tests. In 2012 wurde der PraenaTest® als Europas erster NIPT im Markt eingeführt. Bisher wurden knapp 175.000 Tests erfolgreich im LifeCodexx-Labor in Konstanz am Bodensee durchgeführt, davon zirka 105.000 von Proben aus Deutschland. LifeCodexx gehört seit Anfang 2018 zu Eurofins Scientific, eine international führende Laborgruppe.“

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

2.

Translation Delivered…

…in Gene Transfer and Gene Editing

Opportunity

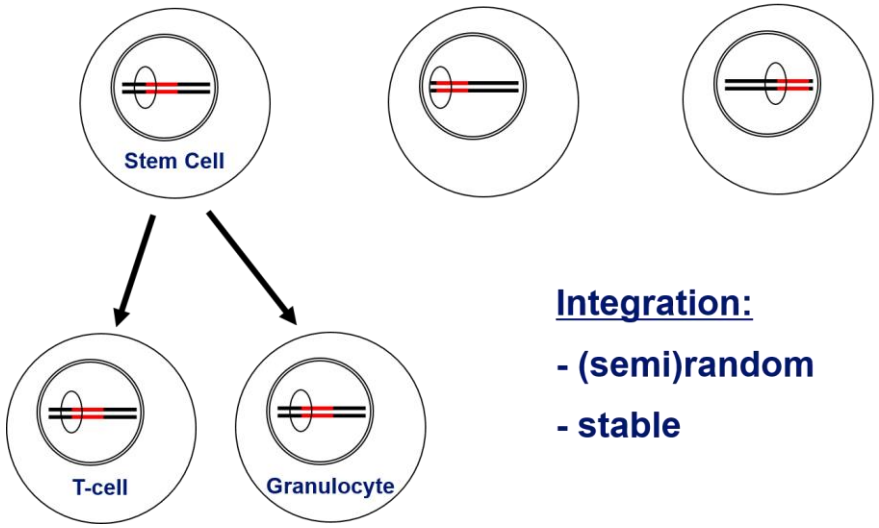
- Gene therapy and gene editing have come of age
- Rare disease treatment and cancer immunotherapy require innovative approaches at the therapeutic use of genetic information
- Pharmacokinetics and -dynamics of gene transfer and editing are an essential prerequisite of any clinical application

GeneWerk – Academic History

1996: Clonality of Hematopoiesis after Autologous Transplantation – Gammaretroviral Vector Gene Marking (CML; University Freiburg)

Clonal Marking by Integrating Vectors

- Dissect the Clonal Composition in Gene-Modified Hematopoiesis and Follow Cellular Fate -

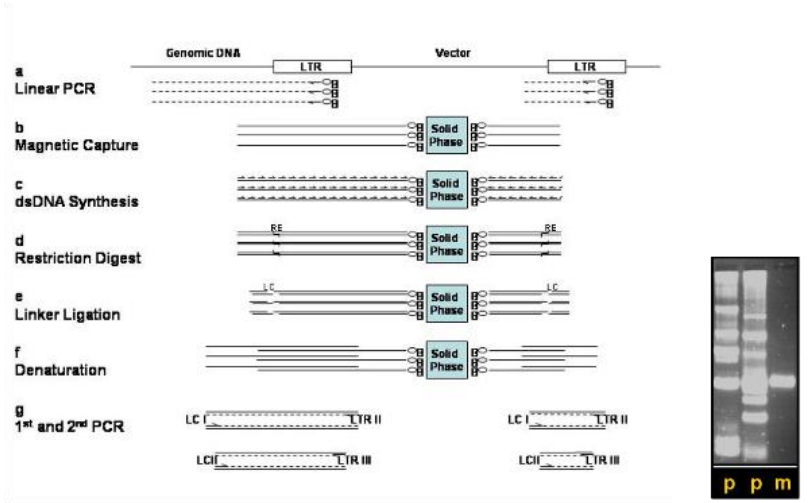


Integration:

- (semi)random

- stable

Integration Site Analysis by LAM-PCR



Schmidt M, et al, *Nat Methods*. 2007(12):1051-1057

GeneWerk – Academic History

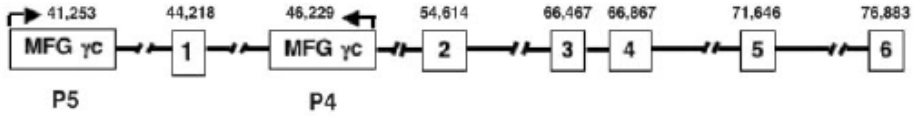
Gammaretroviral Gene Therapy: Severe Adverse Events

2003

LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1

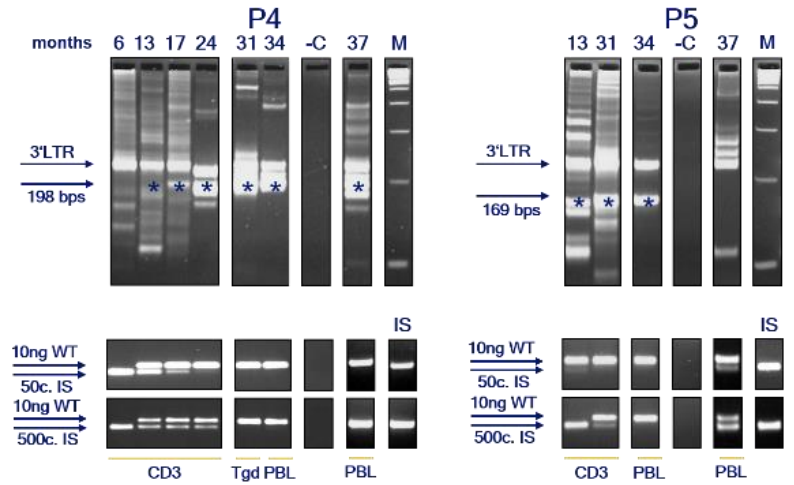
S. Hacein-Bey-Abina,[1,2*] C. Von Kalle,[6,7,8] M. Schmidt,[6,7] M. P. McCormack,[9] N. Wulffraat,[10] P. Leboulch,[11] A. Lim,[12] C. S. Osborne,[13] R. Pawliuk,[11] E. Morillon,[2] R. Sorensen,[19] A. Forster,[9] P. Fraser,[13] J. I. Cohen,[15] G. de Saint Basile,[1] I. Alexander,[16] U. Wintergerst,[17] T. Frebourg,[18] A. Aurias,[19] D. Stoppa-Lyonnet,[20] S. Romana,[3] I. Radford-Weiss,[3] F. Gross,[2] F. Valensi,[4] E. Delabesse,[4] E. Macintyre,[4] F. Sigaux,[20] J. Soulier,[21] L. E. Leiva,[14] M. Wissler,[6,7] C. Prinz,[6,7] T. H. Rabbitts,[9] F. Le Deist,[1] A. Fischer,[1,5]†‡ M. Cavazzana-Calvo[1,2]†

www.sciencemag.org SCIENCE VOL 302 17 OCTOBER 2003



LMO2-Activation in Oncoretroviral SCID-X1 Gene Therapy

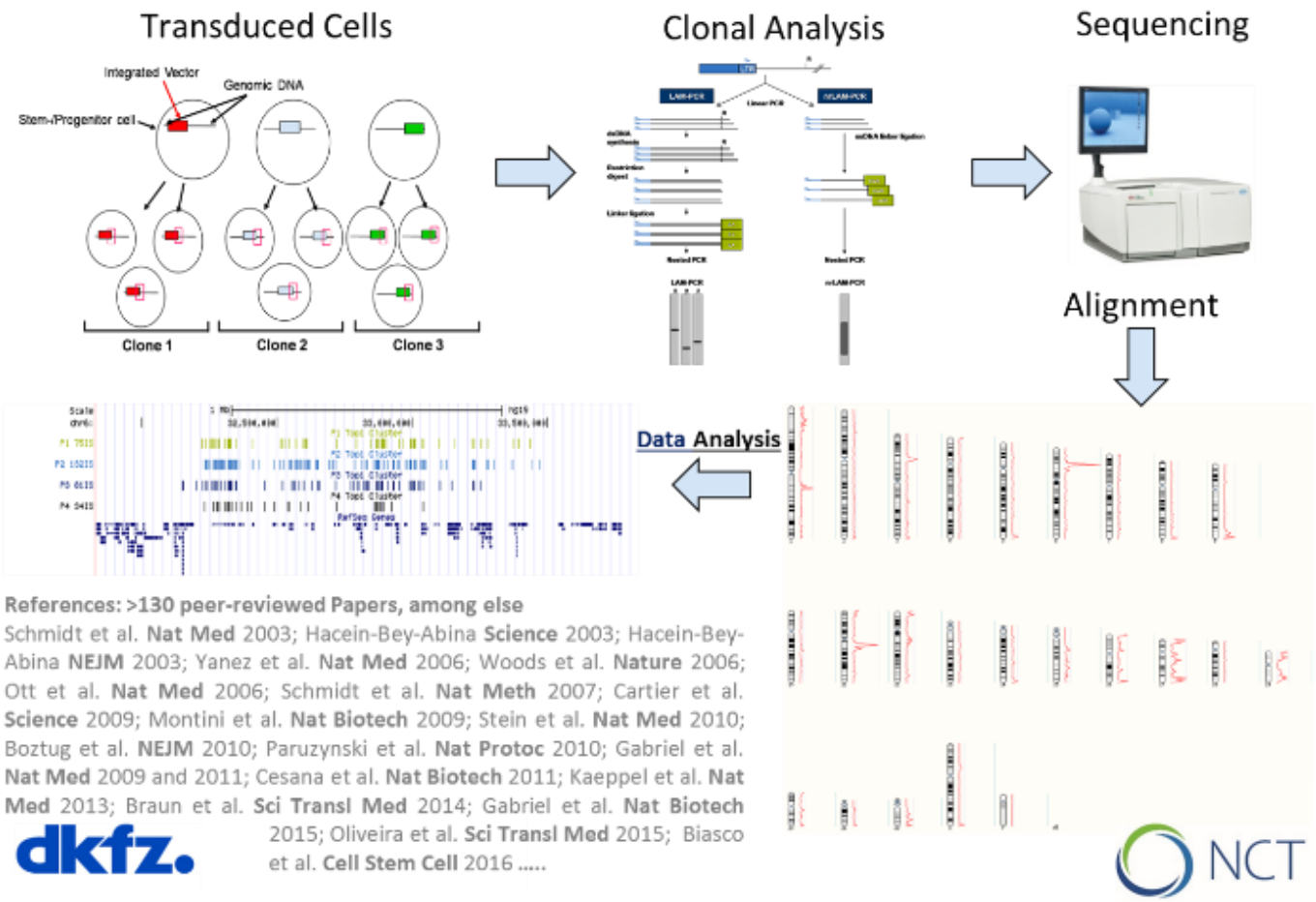
Cavazzana-Calvo et al., 2000: Clinical T-cell function restored



➢ Leukemia

Hacein-Bey-Abina S, et al, *Science*. 2003(5644): 415-419

Insertional Mutagenesis and Vector Safety Screen



References: >130 peer-reviewed Papers, among else

Schmidt et al. **Nat Med** 2003; Hacein-Bey-Abina **Science** 2003; Hacein-Bey-Abina **NEJM** 2003; Yanez et al. **Nat Med** 2006; Woods et al. **Nature** 2006; Ott et al. **Nat Med** 2006; Schmidt et al. **Nat Meth** 2007; Cartier et al. **Science** 2009; Montini et al. **Nat Biotech** 2009; Stein et al. **Nat Med** 2010; Boztug et al. **NEJM** 2010; Paruzynski et al. **Nat Protoc** 2010; Gabriel et al. **Nat Med** 2009 and 2011; Cesana et al. **Nat Biotech** 2011; Kaeppel et al. **Nat Med** 2013; Braun et al. **Sci Transl Med** 2014; Gabriel et al. **Nat Biotech** 2015; Oliveira et al. **Sci Transl Med** 2015; Biasco et al. **Cell Stem Cell** 2016 .....

dkfz.

NCT

Milestones:

- **First** IS analysis in gRV clinical samples (D Kohn: ADA-SCID)
- Dissection of **first** SAEs in mice and humans (C Baum: MDR; M Cavazzana-Calvo, A Fischer: XSCID)
- **First** IS Analysis in LV clinical samples (A Cartier, P Aubourg: ALD)
- IS analysis in **first** western GT drug product **Glybera** (AAV1, LPLD, uniQure)

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

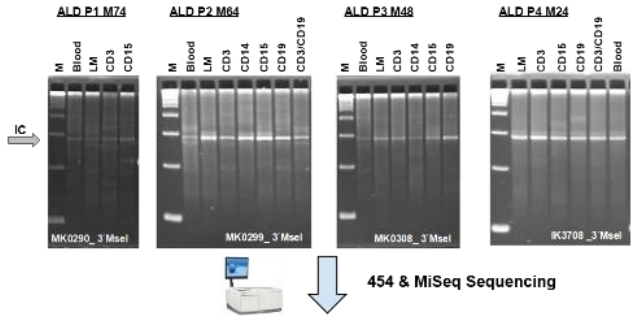
BIH Berlin Institute of Health Charité & MDC

GeneWerk – Academic History

Lentiviral Vector Gene Therapy: Efficiency and Safety

2009

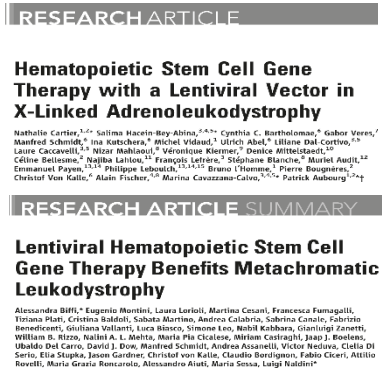
Stable Polyclonal Hematopoietic Repopulation in Lentivirus ALD Gene Therapy



	P1 [#]	P1 [%]	P2 [#]	P2 [%]	P3 [#]	P3 [%]	P4 [#]	P4 [%]
Unique exactly mappable IS	6372		17875		9449		5086	
IS in Refseq Genes	4458	69.96	12860	70.94	6625	70.11	3672	72.20

➢ Safe and Efficient

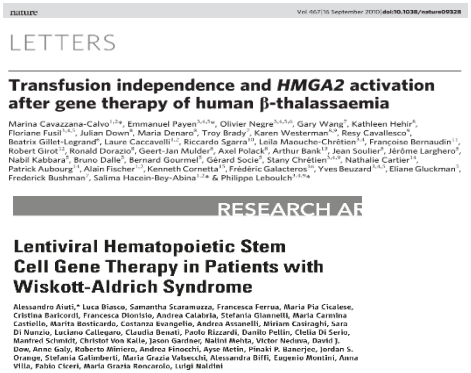
Cartier N, et al, *Science*. 2009(5954): 818-823


RESEARCH ARTICLE

Hematopoietic Stem Cell Gene Therapy with a Lentiviral Vector in X-Linked Adrenoleukodystrophy

RESEARCH ARTICLE SUMMARY

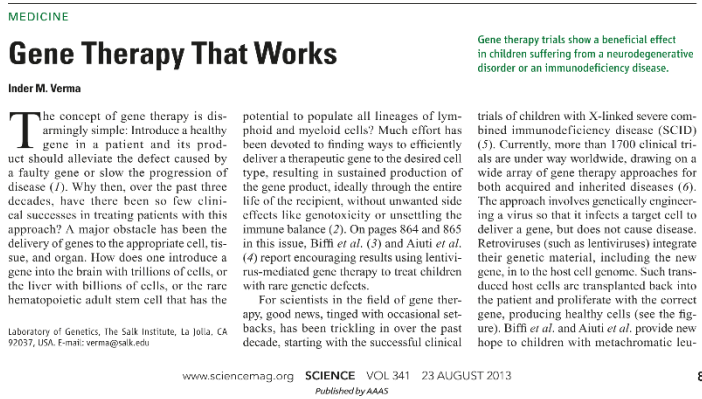
Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy


LETTERS

Transfusion independence and *HMGA2* activation after gene therapy of human β-thalassaemia

RESEARCH AR

Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome


MEDICINE

Gene Therapy That Works

Gene therapy trials show a beneficial effect in children suffering from a neurodegenerative disorder or an immunodeficiency disease.

Inder M. Verma

The concept of gene therapy is disarmingly simple: Introduce a healthy gene in a patient and its product should alleviate the defect caused by a faulty gene or slow the progression of disease (*1*). Why then, over the past three decades, have there been so few clinical successes in treating patients with this approach? A major obstacle has been the delivery of genes to the appropriate cell, tissue, and organ. How does one introduce a gene into the brain with trillions of cells, or the liver with billions of cells, or the rare hematopoietic adult stem cell that has the potential to populate all lineages of lymphoid and myeloid cells? Much effort has been devoted to finding ways to efficiently deliver a therapeutic gene to the desired cell type, resulting in sustained production of the gene product, ideally through the entire life of the recipient, without unwanted side effects like genotoxicity or unsettling the immune balance (*2*). On pages 864 and 865 in this issue, Biffi *et al.* (*3*) and Aiuti *et al.* (*4*) report encouraging results using lentivirus-mediated gene therapy to treat children with rare genetic defects.

For scientists in the field of gene therapy, good news, tinged with occasional setbacks, has been trickling in over the past decade, starting with the successful clinical trials of children with X-linked severe combined immunodeficiency disease (SCID) (*5*). Currently, more than 1700 clinical trials are under way worldwide, drawing on a wide array of gene therapy approaches for both acquired and inherited diseases (*6*). The approach involves genetically engineering a virus so that it infects a target cell to deliver a gene, but does not cause disease. Retroviruses (such as lentiviruses) integrate their genetic material, including the new gene, in to the host cell genome. Such transduced host cells are transplanted back into the patient and proliferate with the correct gene, producing healthy cells (see the figure). Biffi *et al.* and Aiuti *et al.* provide new hope to children with metachromatic leu-

Laboratory of Genetics, The Salk Institute, La Jolla, CA 92037, USA. E-mail: verma@salk.edu

Published by AAAS

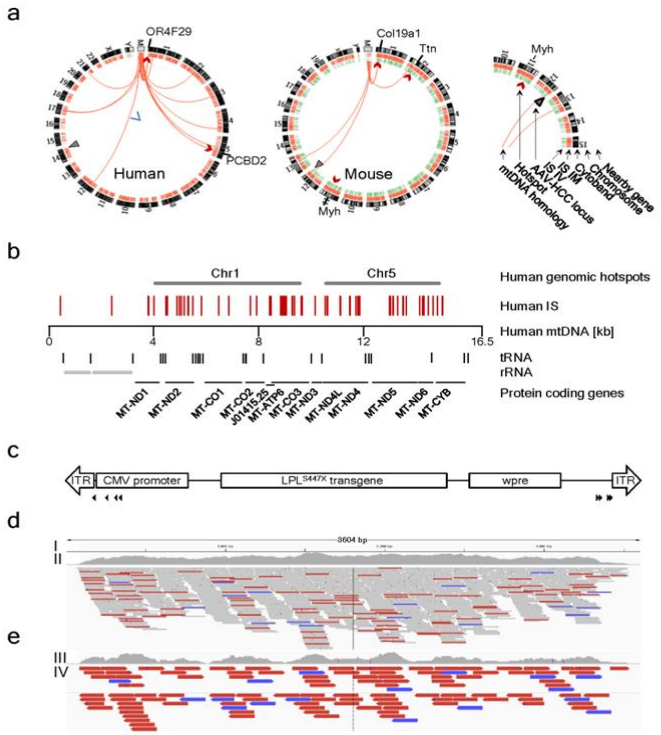
NCT dkfz. CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN BIH Berlin Institute of Health Charité & MDC

GeneWerk GmbH – Academic History

A largely random AAV integration profile after LPLD gene therapy

Kaeppel C, Beattie SG, Fronza R, van Logtenstein R, Salmon F, Schmidt S, Wolf S, Nowrouzi A, Glimm H, von Kalle C, Petry H, Gaudet D, Schmidt M. Nat Med. 2013 Jul;19(7):889-91. doi: 10.1038/nm.3230. Epub 2013 Jun 16.

Figure 1



ABSTRACT

The clinical application of adeno-associated virus vectors (AAVs) is limited because of concerns about AAV integration–mediated tumorigenicity. We performed integration-site analysis after AAV1-LPL^{S447X} intramuscular injection in five lipoprotein lipase–deficient subjects, revealing random nuclear integration and hotspots in mitochondria. We conclude that AAV integration is potentially safe and that vector breakage and integration may occur from each position of the vector genome. Future viral integration-site analyses should include the mitochondrial genome.

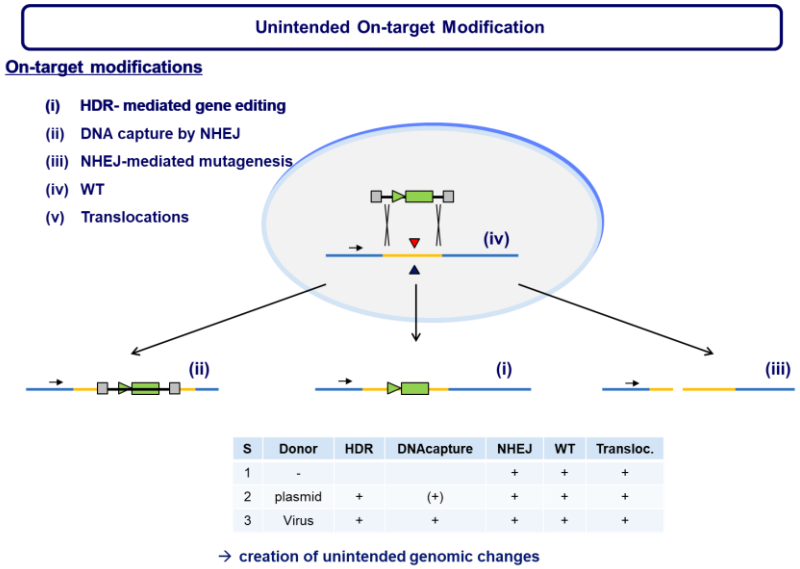
Figure 1 AAV1-LPL^{S447X} integration profile and persistence. **a,b,** AAV1-LPL^{S447X} integration preference in the mitochondrial (mt) DNA genome after intramuscular (IM) injection; IV, intravenous; IS, exact mappable integration site. (**a**) Circos Plots show the distribution of human and mouse IS on the nuclear and mtDNA genome (mtDNA genome is increased in size). HCC, hepatocellular carcinoma. (**b**) Detailed scheme of integrations within the 16,539 bp circular human mtDNA genome (shown in linear form). Chr, chromosome; MT-, mitochondrial genes. **c–e,** Direct AAV1-LPL^{S447X} vector sequencing of enriched mitochondrial (mt) DNA. (**c**) Scheme of the AAV1-LPL^{S447X} vector including LAM-PCR and used primer locations (indicated by the black triangles). ITR, inverted terminal repeats; CMV, cytomegalovirus; LPL, human lipoprotein lipase; wpre, woodchuck hepatitis virus post-transcriptional regulatory element. (**d**) Whole sequence reads on vector AAV1-LPL^{S447X}. Subpanel I: coverage information (maximum value = 67); subpanel II: mates alignment. Colored bars indicate reads that have a mate on mitochondria (blue bars) or on nuclear DNA (red bars). Gray bars indicate mates that are on the vector. (**e**) Selected sequence reads on vector AAV1-LPL^{S447X}. Subpanel III: coverage information (maximum value = 13); subpanel IV: mates that map on mtDNA (blue bars) and on nuclear DNA (red bars). Upper portion of the subpanel shows forward reads, whereas lower portion displays reverse reads.

AAV1-LPL^{S447X} ('Glybera') was developed to treat lipoprotein lipase deficiency (LPLD), an autosomal recessive disorder of lipid metabolism. AAV1-LPL^{S447X} was approved by the European Medicines Agency as the first gene therapy product in the Western world.

GeneWerk GmbH – BD & Milestones

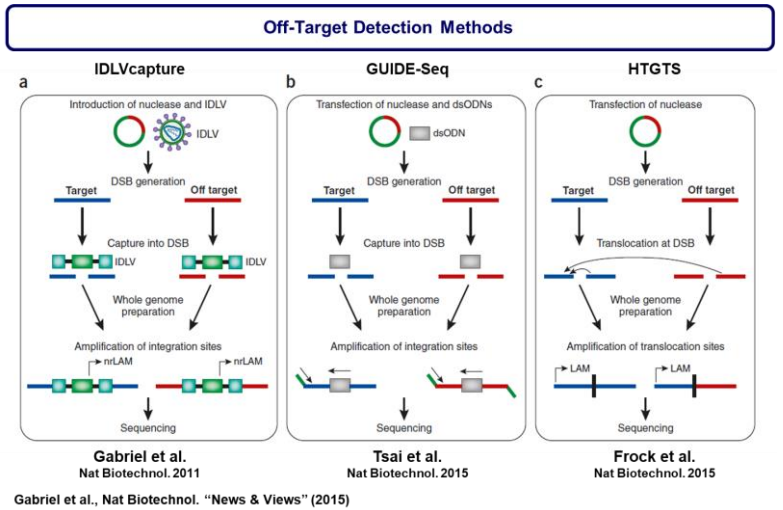
- Bootstrapping
- February 2020: 26 FTE
- GCP-compliant Quality Management System (QMS) that conforms to all relevant regulatory requirements
- Track record of successful on-site audits from clients
- Integration site monitoring in > 30 clinical studies
- IS studies in Kymriah samples
- IS / Vector safety studies as part of Zynteglo filing
- IS analysis wetlab validation completed 02/2020
- Preparation for building a subsidiary in the USA

Product Line 2 – Genome Editing On Off



S	Donor	HDR	DNAcapture	NHEJ	WT	Transloc.
1	-			+	+	+
2	plasmid	+	(+)	+	+	+
3	Virus	+	+	+	+	+

→ creation of unintended genomic changes



Gabriel et al., Nat Biotechnol. "News & Views" (2015)

Customized gene editing On and Off target analysis:

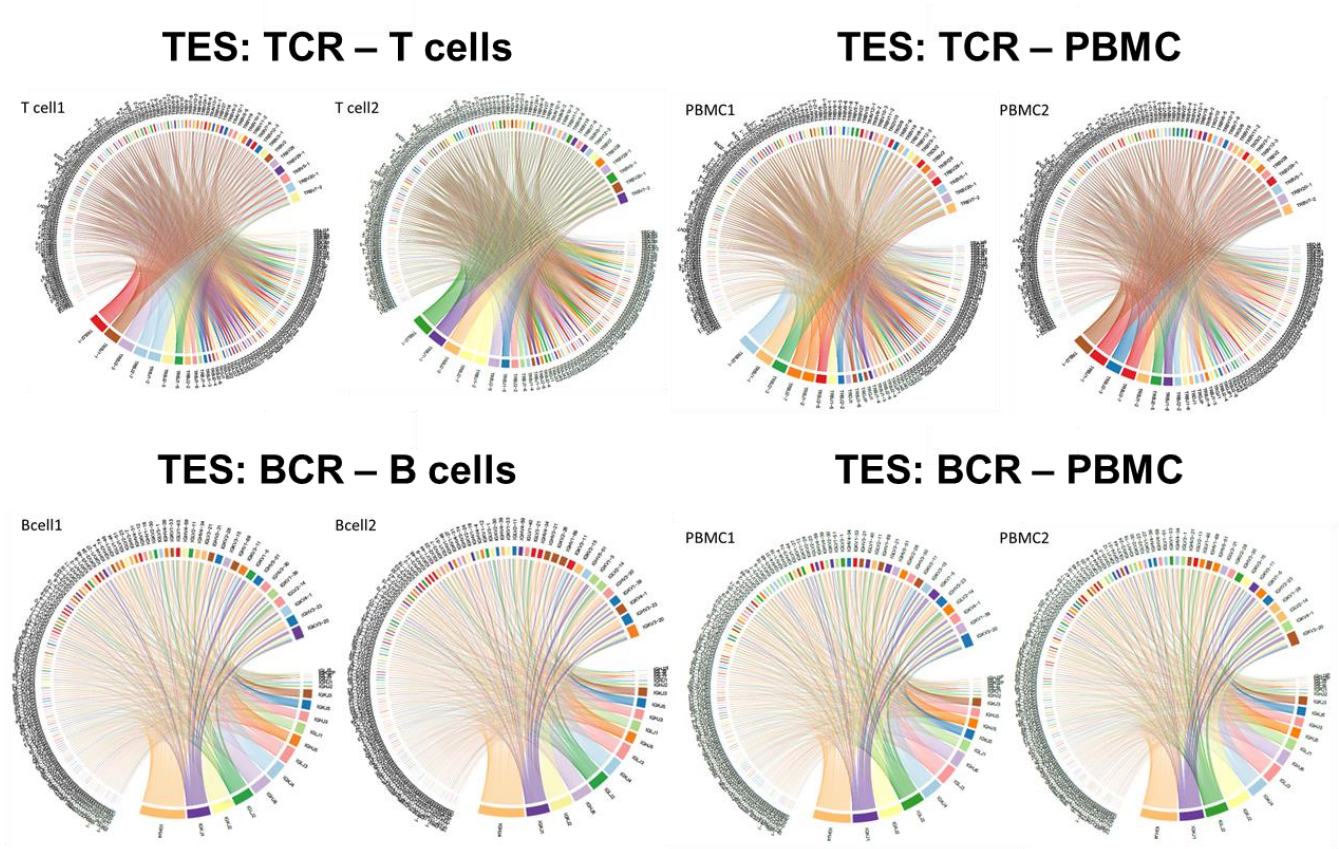
- Genome wide Off target sequencing
- In silico Off target prediction
- Bioinformatical Analyses
- **Assessing unintended On- and Off- target modifications**

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Product Line 3: Immune Repertoire

RACE-PCR or TES: T and B CELL RECEPTOR SEQUENCING

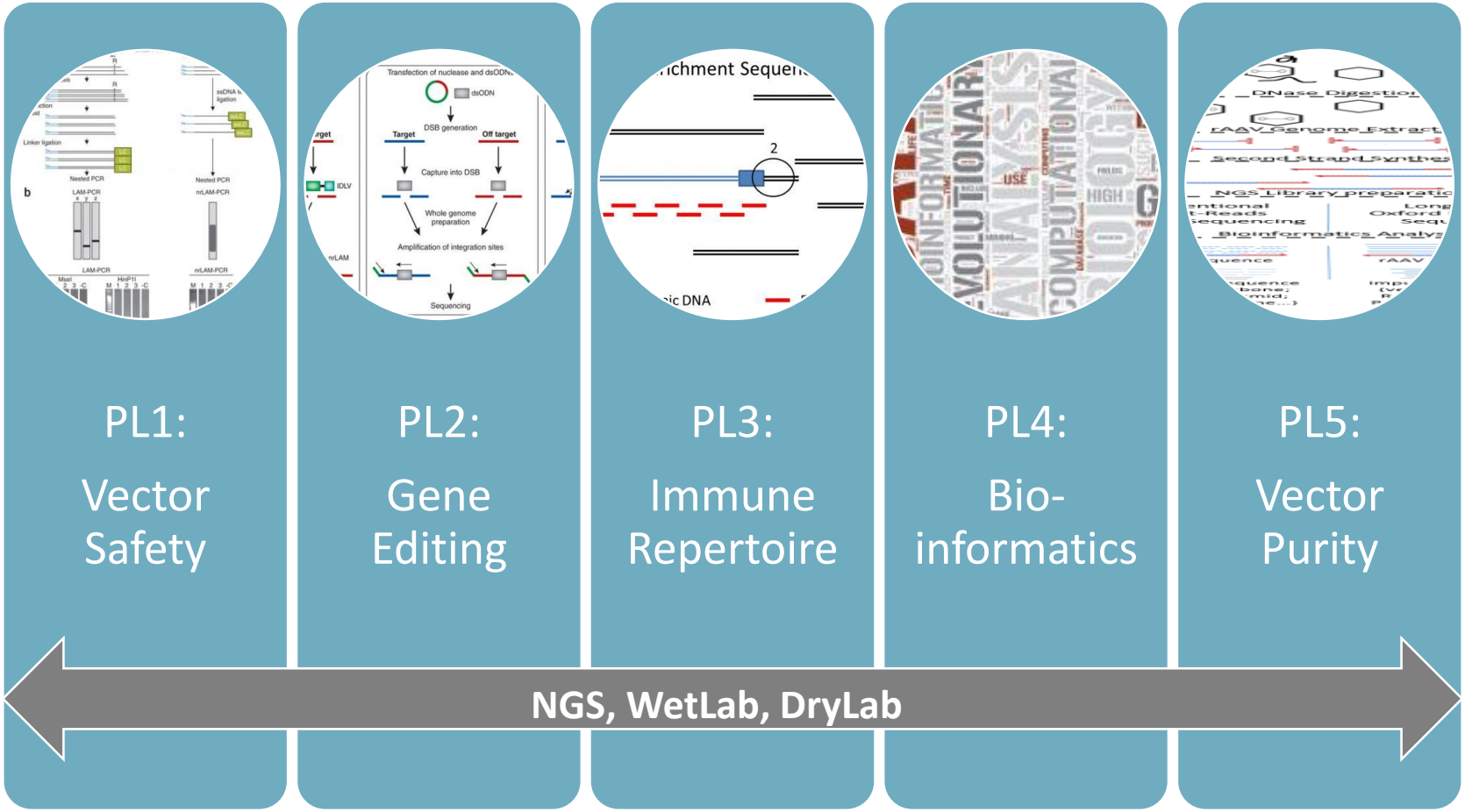


1. RNA/cDNA: 30-1000ng, 500k seq reads
2. Simultaneous sequencing of TCR: α, β, γ, δ and BCR: A, D, E, M, G; L, K

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

GeneWerk – Product Lines



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Mission accomplished

- Market access contribution to all major categories of gene therapy
- 90% of business outside of Germany
- 20% to 70% of market coverage
- The university technology transfer concept of the 90s needs an overhaul
- China issue?

3.

Translation Delivered…

…in Cancer

Every Second Citizen Gets Cancer at Some Point – One in Four of Us Will Die of It

Germany 2014

Total: 81,2 Mio.

Life Expectancy: 81 years

Prevalence: 1,6 Mio.

New cases p.a.: 0,48 Mio.

Mortality p.a.: 0,22 Mio.

Cancer patient

Cancer victim

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

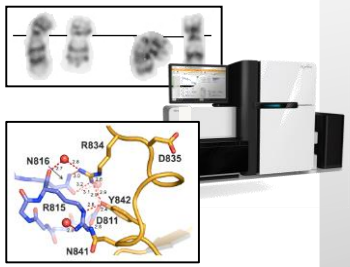
Shared Interest in Comprehensive Molecular Profiling as Starting Point

Molecular diversity and genetic taxonomy of cancer

Individual, “private” patterns of molecular lesions

Actionability of molecular lesions

Genetics



Clinical care

Comprehensive molecular stratification approaches that are able to capture the entire spectrum of

- Rare cancer drivers | NRG1 fusions
- Compound biomarkers | HR deficiency
- Newly emerging diagnostic, prognostic, and predictive parameters | T-cell-inflamed gene expression

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Eligibility and Methods

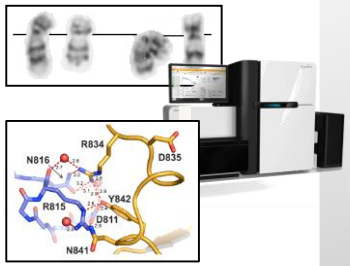
Molecularly **A**ided **S**tratification for **T**umor **E**radication **R**esearch

Molecular diversity and genetic taxonomy of cancer

Individual, “private” patterns of molecular lesions

Actionability of molecular lesions

Genetics



Clinical care

- Young adults with advanced-stage cancer
- Patients with rare tumors
- Fast-track exome and RNA sequencing
- DNA methylation profiling

Start: 06/2013

MASTER Registry Trial

Since 10/2016:
Genome sequencing (60x)

- Feasibility
- Diagnostic information
- Therapeutic opportunities

Molecularly stratified clinical trials

Horak et al. Int J Cancer 2017

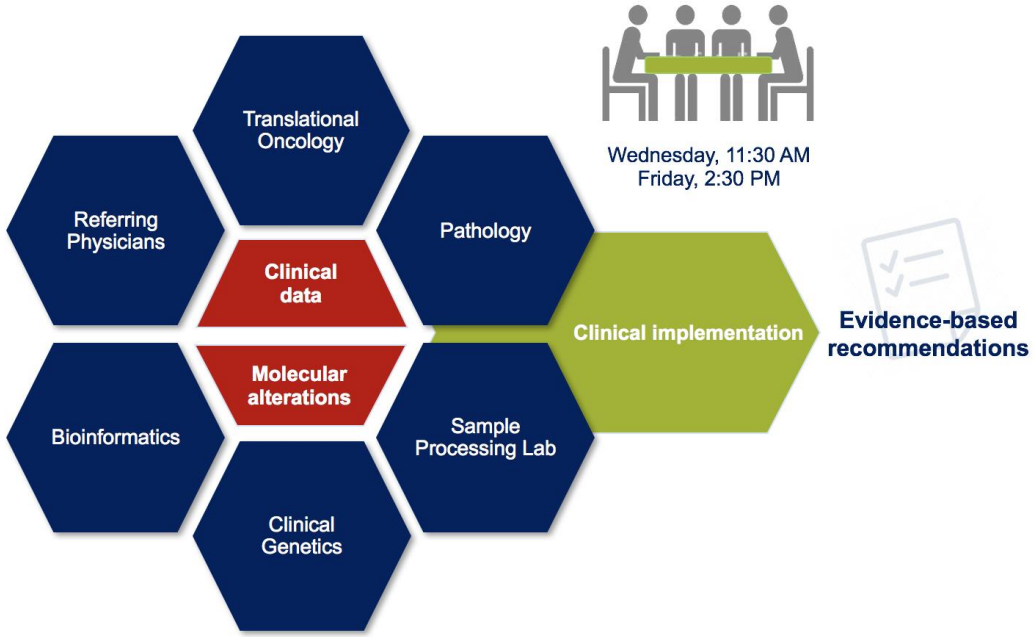
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Infrastructure and Governance

Strategic DKTK activity since March 2016

- Ethics approval at all sites
- Shared workflow for sample processing and molecular analysis
- Access to molecular data on all levels
- Joint clinical data repository
- Semiweekly molecular tumor board
- Bimonthly scientific board

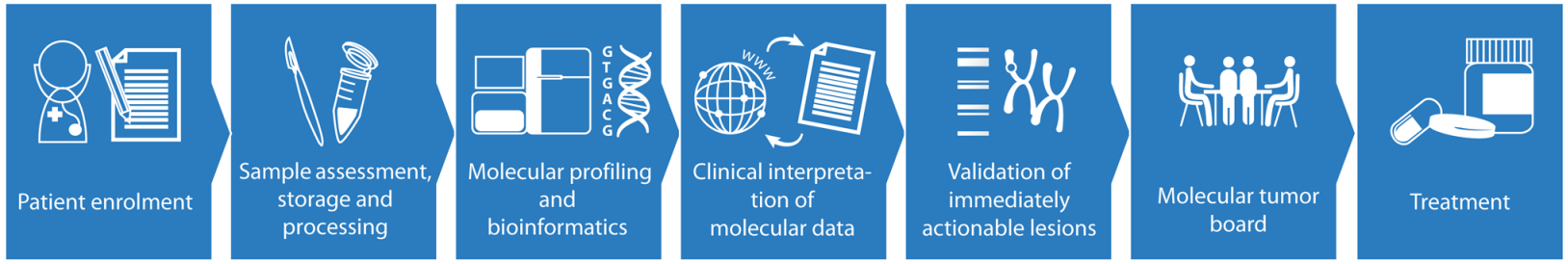


DKTK German Cancer Consortium

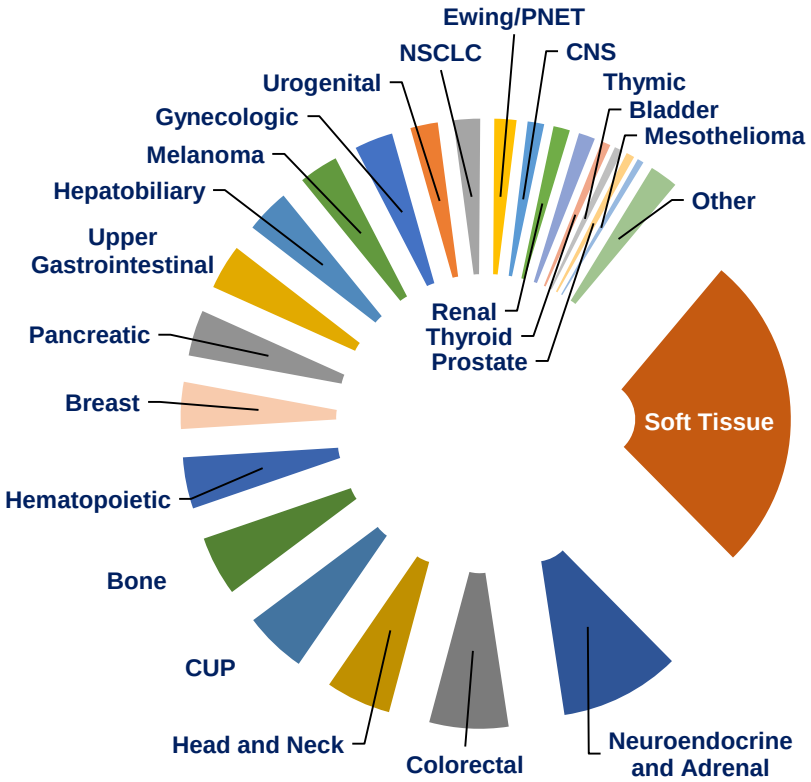
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

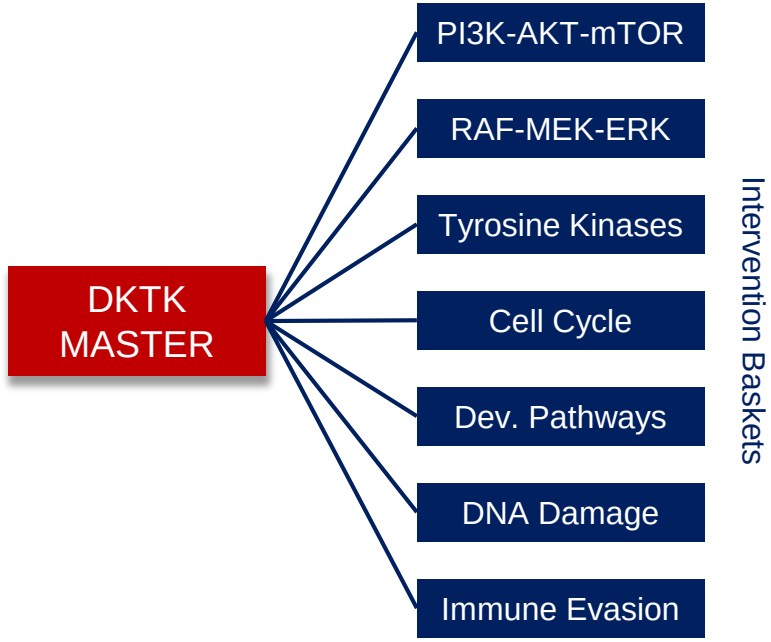
BIH Berlin Institute of Health Charité & MDC

Workflow and Accrual



Goal: 28 days





February 2020

- 1,986 patients
- 99 ICD-10 codes
- 262 ICD-O-3 codes

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Current Results

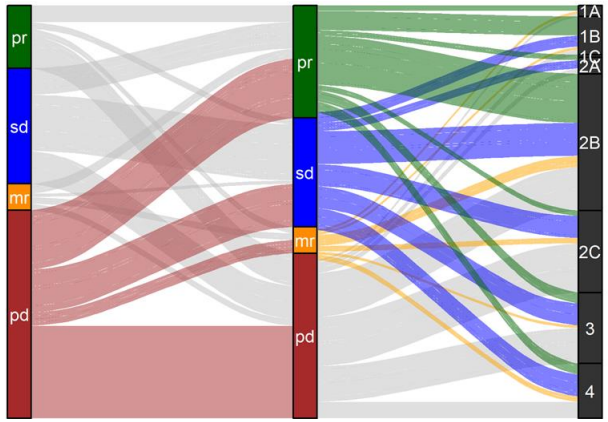
Clinical consequences and outcome

1,311 patients enrolled until October 2018

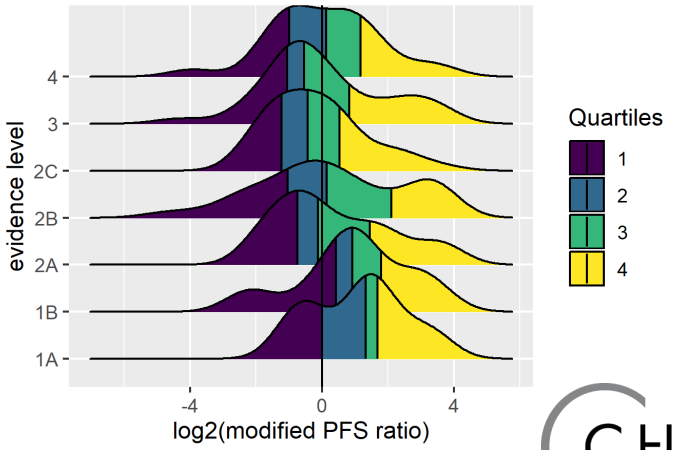
Median age, 45 years
Median overall survival, 12 months
Median follow-up duration, 6 months

• Diagnostic implication	4%
• Actionable germline alteration	11%
• Treatment recommendation	86% | 1,129 patients
• Treatment implementation	31% | Intention to treat, 27%
• Disease control rate	55% | Intention to treat, 15%
• Overall response rate	25% | Intention to treat, 7%
• PFS ratio ≥1.3	35% | Intention to treat, 9%

Prior therapy **Guided therapy** **Evidence level**



PFS ratio benefit across evidence levels



Mock et al. ESMO Open 2019

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Diagnostic Implications

Rationale for reevaluation of clinical diagnosis in 57 of 1,311 (4%) of cases

- Soft-tissue sarcoma, n=27
- Carcinoma of unknown primary site, n=19
- Close interaction with DKTK pathology network essential

Diagnosis	Mutation(s)	Differential Diagnosis	Potential Clinical Action
Soft-tissue sarcoma, not otherwise specified	CDK4/MDM2 amplification MYOD1 p.V125L/p.L122R PDGFRA p.D842V COL1A1-PDGFB TPM3-ALK	Liposarcoma Rhabdomyosarcoma GIST DFSP IMFT	CDK4/MDM2 inhibition CWS Guidance Crenolanib*, avapritinib* Imatinib* Crizotinib*
Synovial sarcoma	FUS-CREB3L2	LGFMS	Surgery
Hidradenocarcinoma	SS18-SSX2	Synovial sarcoma	Doxorubicin/ifosfamide
Neuroendocrine carcinoma	EWSR1-WT1	DSRCT	EWING 2008
Carcinoma of unknown primary site	RP3-388E23.2-NFIB FGFR2-WAC IDH1 p.R132H EWSR1-WT1 NUTM1-NSD3	ACC CCC CCC DSRCT NUT midline carcinoma	Vorinostat* FGFR inhibitor IDH1 inhibitor EWING 2008 BET inhibitor
Thymic carcinoma	NUTM1-BRD3	NUT midline carcinoma	BET inhibitor
Urothelial carcinoma	NUTM1-BRD4	NUT midline carcinoma	BET inhibitor

**Not approved for this indication in Germany*

Germline Predisposition

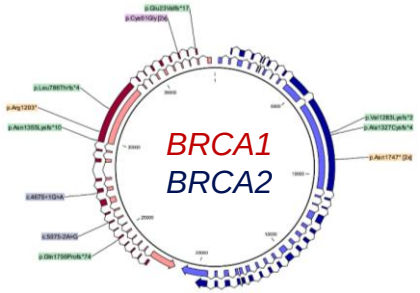
Clinical evaluation of rare germline variants in 180 tumor predisposition genes

- Pathogenic variants (ACMG Class 5) in 60 tumor predisposition genes (*BRCA1/2*, *PALB2*, *ATM*, *NF1*, *MEN1*, *RB1*, *APC*, *SDHB*, *PTEN*, *CDH1*, *MSH2*, etc.) in 11% of cases
- Carrier status for autosomal recessive disorders (Fanconi anemia, Bloom syndrome, xeroderma pigmentosum, etc.) in 4% of cases
- Implications for patients and family members (genetic counseling, predictive diagnostics, surveillance, prevention)
- Entry points for targeted therapies in individual patients (e.g. PARP inhibition in patients with pathogenic BRCA1/2 or PALB2 mutations)

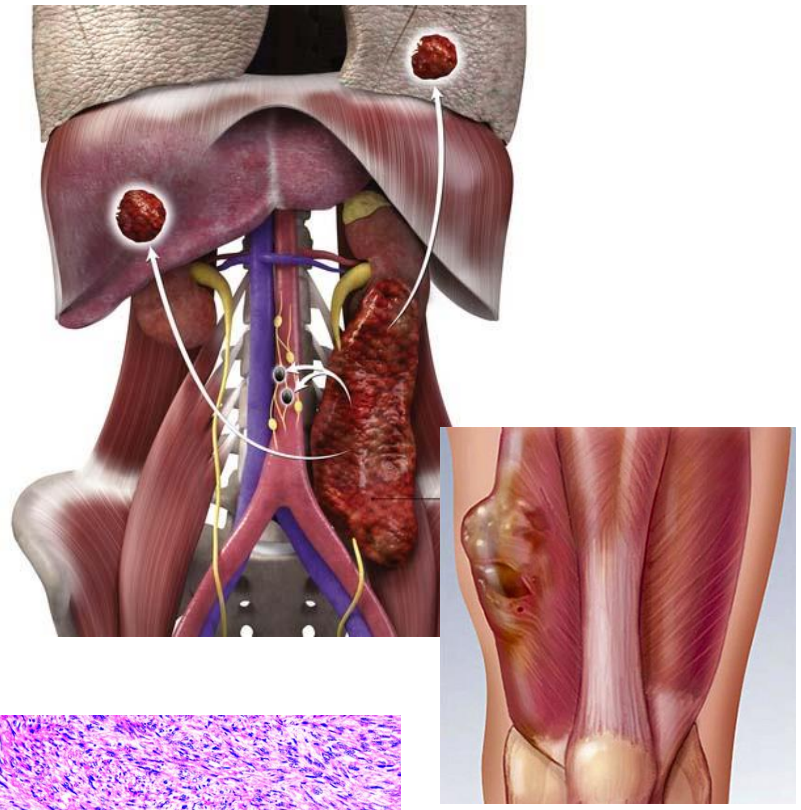
Evelin Schröck

Barbara Klink

Laura Gieldon



Genomic Analysis of Leiomyosarcoma



Chudasama et al. Nat Commun 2018

“BRCAness” als Angriffspunkt bei Leiomyosarcomen

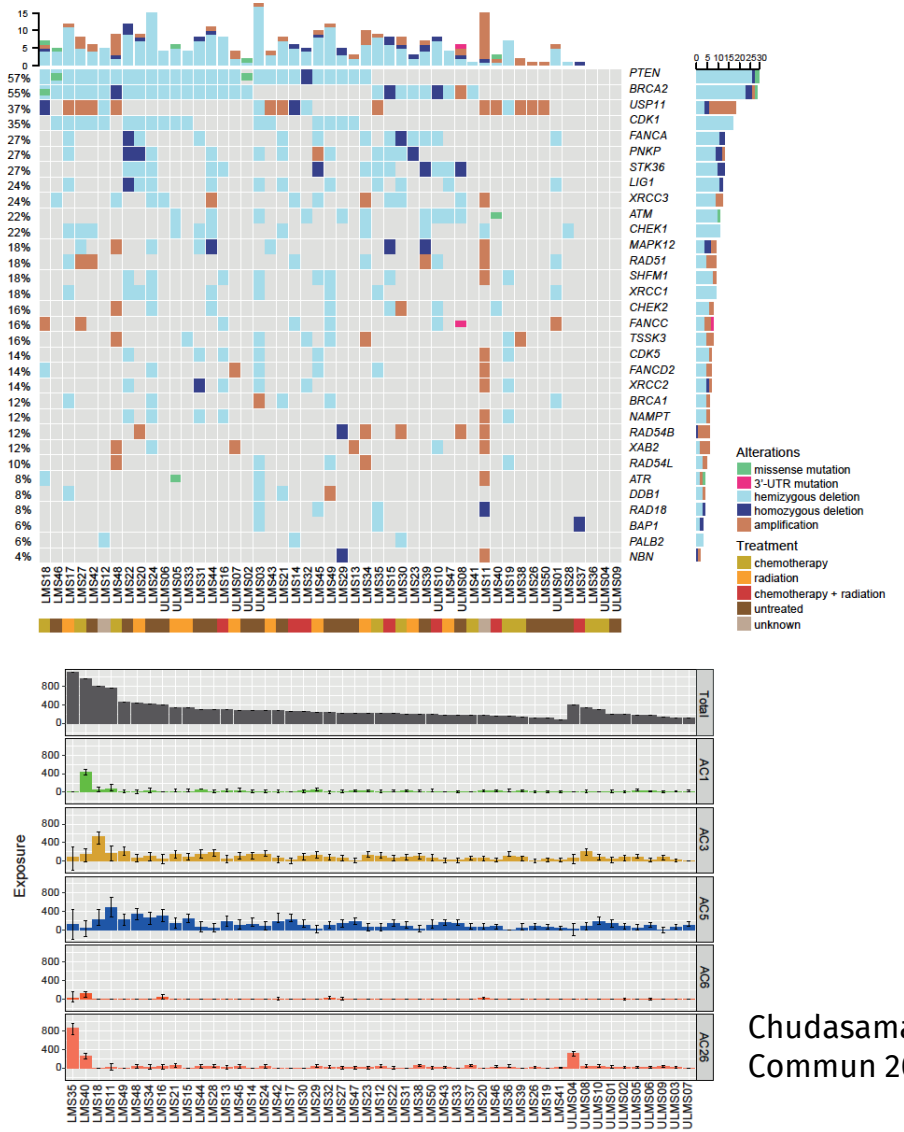
Lokalrezidive und/oder metastatische Erkrankung (*n* = 49)

Extrauterine und uterine Tumore

Gesamtexom- und RNA- Sequenzierung

- Mutationsheterogenität
- Fast durchgängige Inaktivierung von *TP53* und *RB1*
- Chromothripsis (35%)
- Gesamtgenom-Duplikation (51%)
- Alternative Telomerverlängerung (78%)
- Merkmale fehlerhafter DNA-Reparatur durch homologe Rekombination (“BRCAness”) in >90% der Fälle
  - Mutationen in Genen zur homologen DNA Reparatur
  - Umfassende Veränderung der DNA-Kopienanzahl
  - Signifikante Anreicherung der Alexandrov-COSMIC Mutationssignatur AC3

Genomic Analysis of Leiomyosarcoma



Chudasama et al. Nat Commun 2018

“BRCAness” als Angriffspunkt bei Leiomyosarcomen

Lokalrezidive und/oder metastatische Erkrankung (*n* = 49)

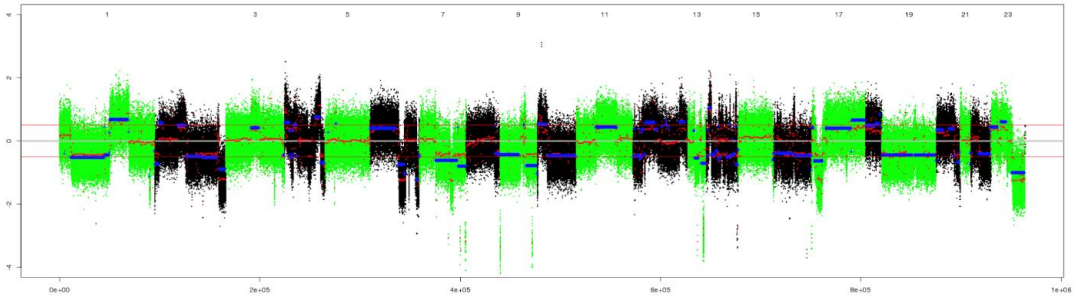
Extrauterine und uterine Tumore

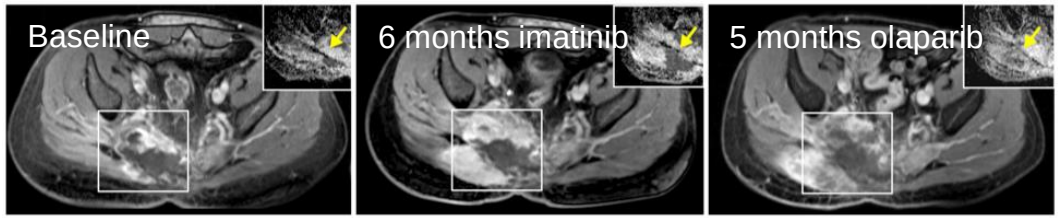
Gesamtexom- und RNA- Sequenzierung

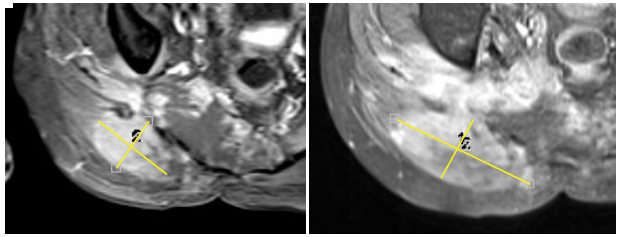
- Mutationsheterogenität
- Fast durchgängige Inaktivierung von *TP53* und *RB1*
- Chromothripsis (35%)
- Gesamtgenom-Duplikation (51%)
- Alternative Telomerverlängerung (78%)
- Merkmale fehlerhafter DNA-Reparatur durch homologe Rekombination (“BRCAness”) in >90% der Fälle
  - Mutationen in Genen zur homologen DNA Reparatur
  - Umfassende Veränderung der DNA-Kopienanzahl
  - Signifikante Anreicherung der Alexandrov-COSMIC Mutationssignatur AC3

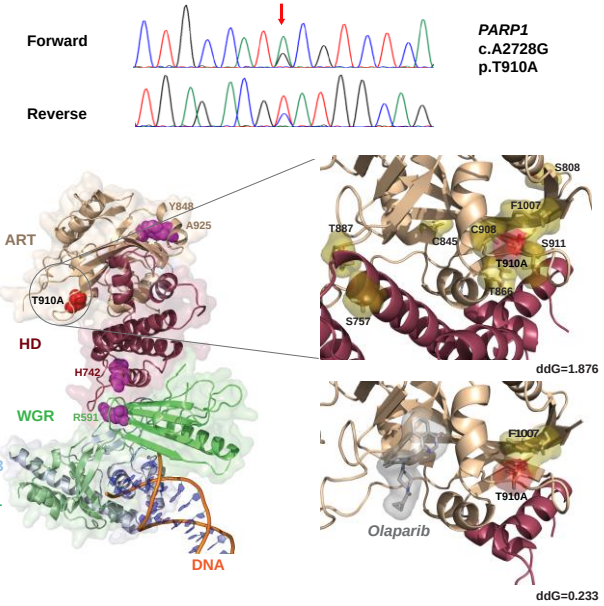
Homologous Recombination Deficiency

Clinical Trial
NCT PMO-1603









Defective homologous recombination (HR) in >90% of advanced leiomyosarcoma or chordoma

- Alteration of individual HR genes, genomic instability, Alexandrov-COSMIC mutational signature 3

Successful PARP inhibitor treatment of a patient with HR-deficient chordoma

- Partial response lasting 10 months

Newly acquired PARP1 p.T910A variant underlying secondary PARP inhibitor resistance

Chudasama, Mughal et al. Nat Commun 2018
Gröschel, Hübschmann et al. Nat Commun 2019

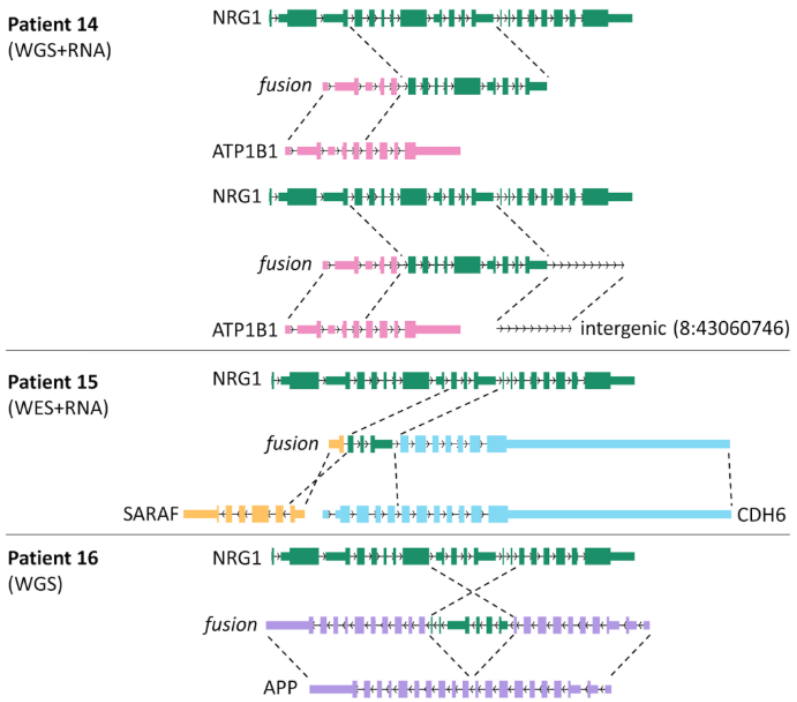
BRCAness

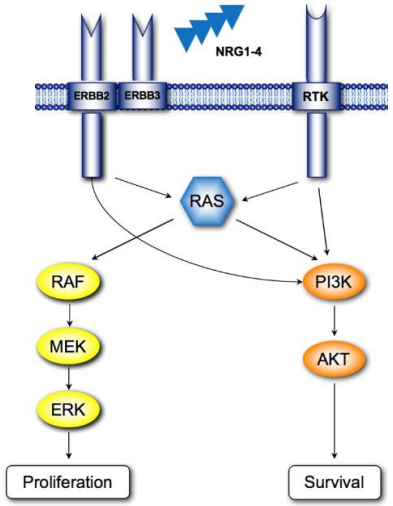
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

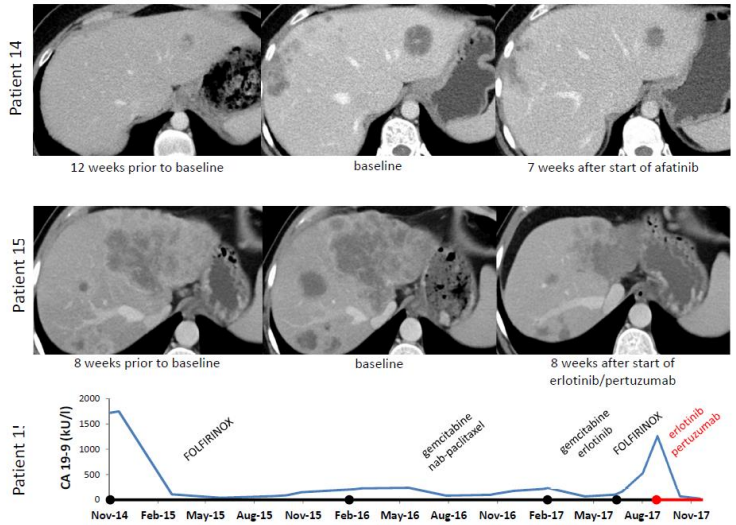
BIH Berlin Institute of Health Charité & MDC

NRG1 Fusions in Pancreatic Cancer

Clinical Trial
NCT PMO-1604







NRG1 fusion and wildtype KRAS in 3 of 17 patients with pancreatic ductal adenocarcinoma (PDAC)

- EGF-like domain retained in all cases
- Transforming activity in vitro and in vivo

Successful ERBB-directed treatment of patients with NRG1-rearranged PDAC

- Afatinib | Erlotinib/pertuzumab

KRAS testing in all patients with advanced PDAC

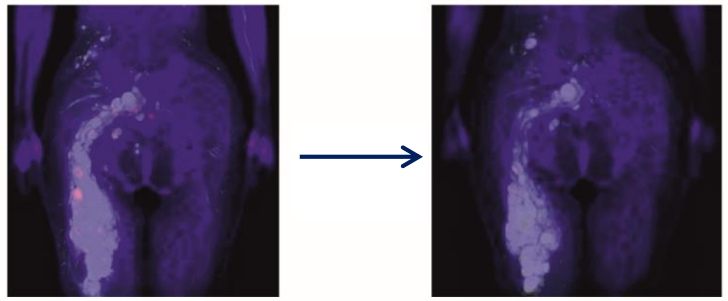
Heining, Horak, Uhrig et al. Cancer Discov 2018

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

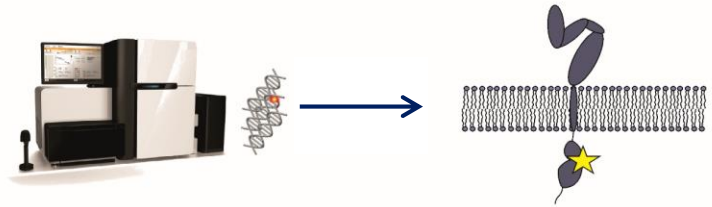
Mutant ERBB2 in Neurofibroma/Schwannoma Hybrid Nerve Sheath Tumors

Index patient



MASTER

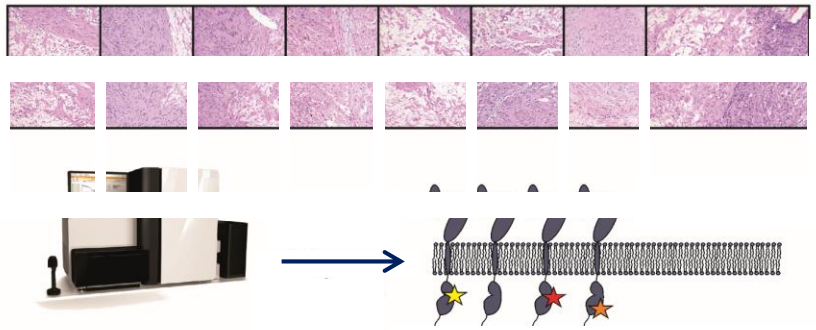
Lapatinib



Genetic analysis

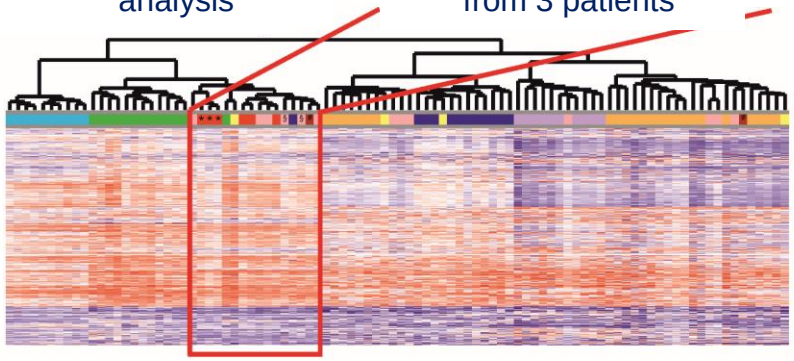
Activating ERBB2 mutation

Validation cohort (18 tumors)



Genetic & epigenetic analysis

5 ERBB2-mutant tumors from 3 patients



DNA methylation cluster with ERBB2-mutant tumors

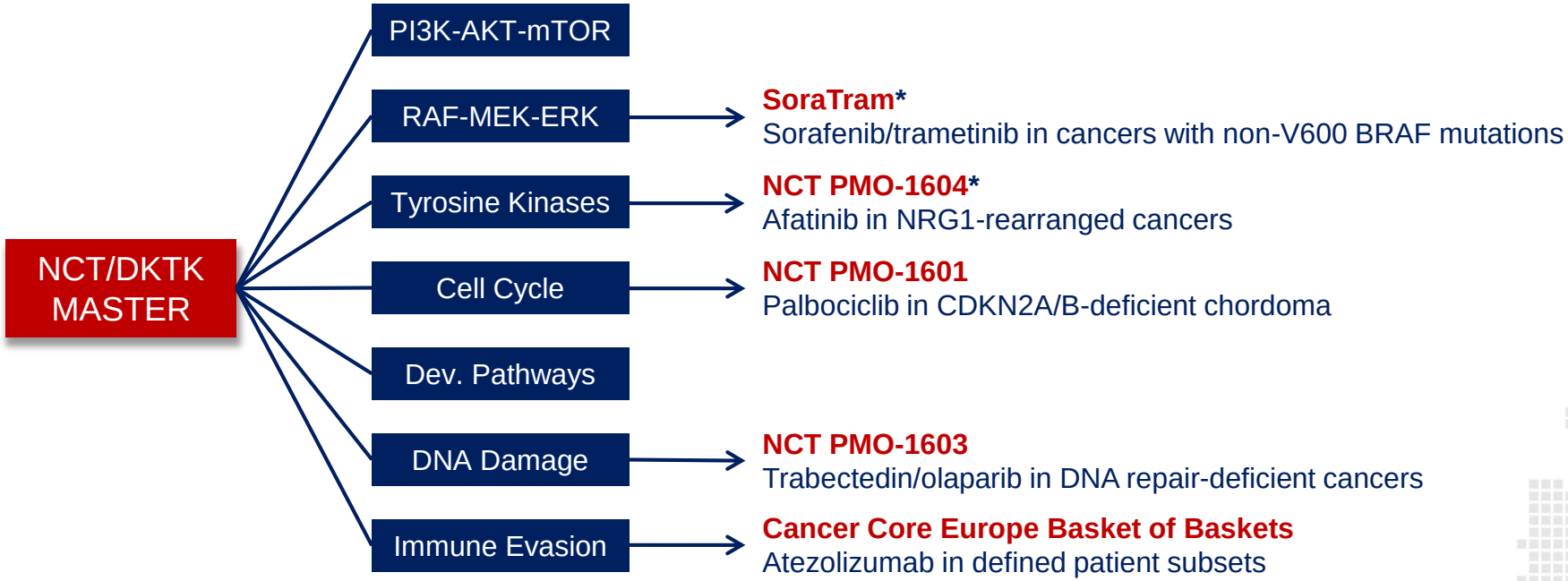
- Lasting (51+ months) response to lapatinib
- ERBB2 mutations only seen in the context of sporadic schwannomatosis (4 of 8 patients)

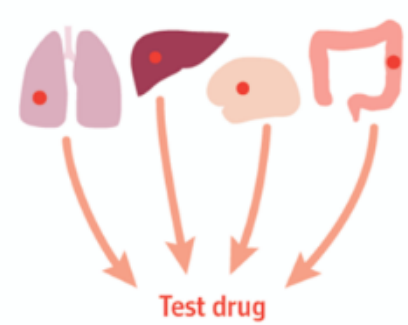
Ronellenfitsch et al. J Clin Invest 2020

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Stratified Clinical Trials





DKTK German Cancer Consortium

Eligibility
Advanced cancers in young adults | Advanced rare cancers or cancers from rare molecular subgroups of common cancers regardless of age | Actionable alteration, as determined in MASTER

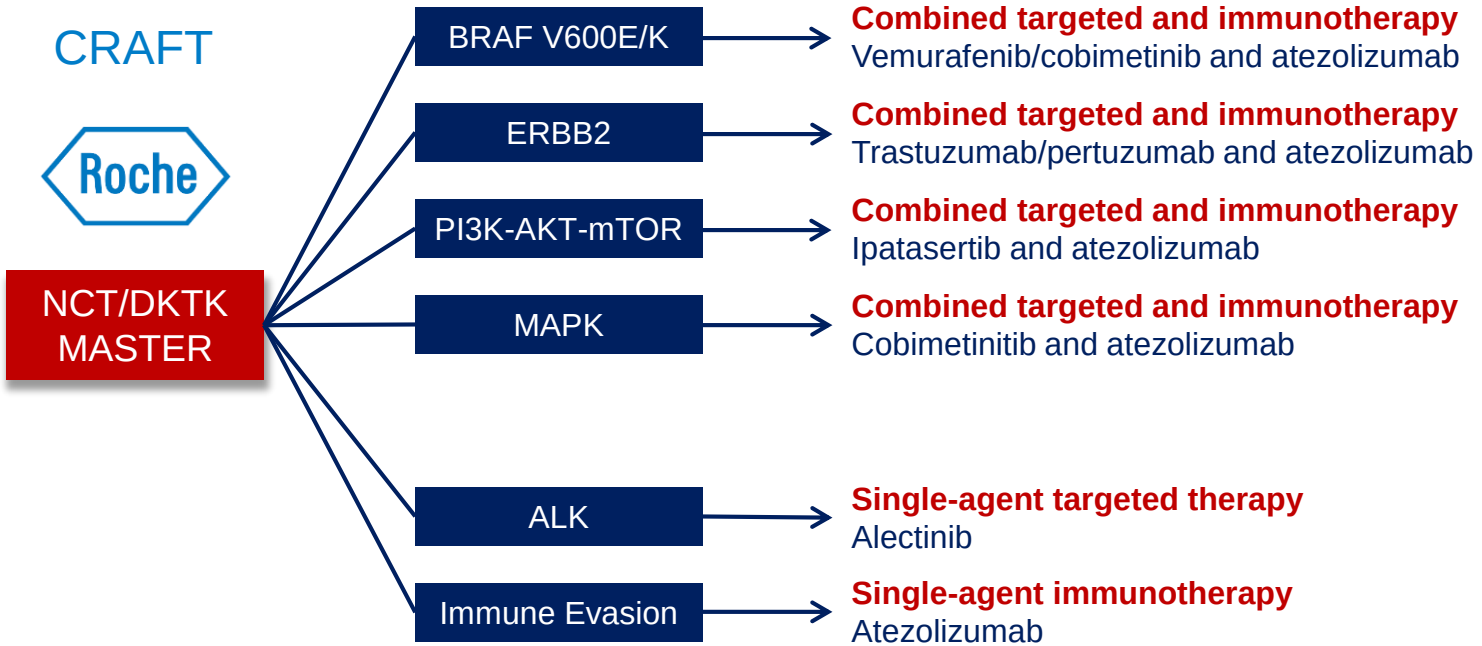
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

*DKTK Joint Funding

Stratified Clinical Trials

Clinical Trial
NCT PMO-1602



Eligibility
- Young adults with advanced cancers
- Patients with advanced rare cancers regardless of age
- Patients with advanced cancers from rare molecular subgroups of common cancers regardless of age
- Actionable molecular alteration, as determined in MASTER

Trial Level
- Safety surveillance
- Protocol and quality management
- Response evaluation
- Repeat and liquid biopsies

DKTK German Cancer Consortium

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

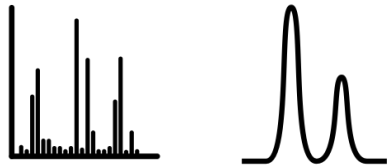
Scientific Output and Next Steps

Translational Research

- >25 multi-institutional projects
  - All partner sites
  - In part supported by DKTK Joint Funding
    - ImmuNeo MASTER*
    - MARRIAGE*
  - First patient-partnered research project
    - El PazoS
  - Modified PFS ratio as novel clinical endpoint
- >25 peer-reviewed publications

Additional layers of patient characterization

- DNA methylation profiling
- Proteomics (INFORM/MASTER-PRO)*
- Multiparameter imaging and radiomics
- Ex vivo drug sensitivity profiling



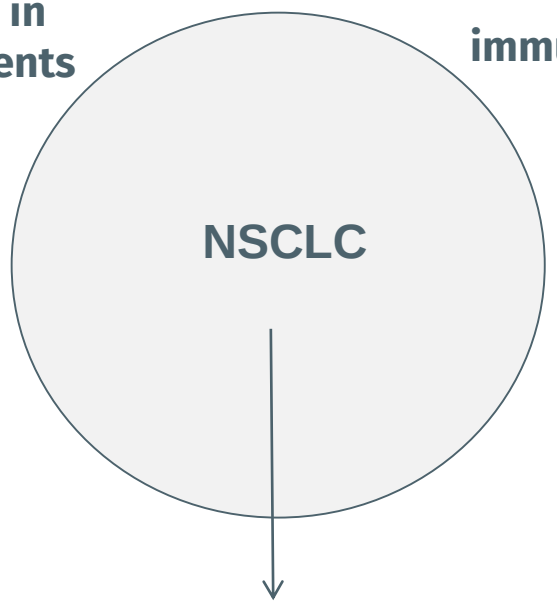
Treatment modalities beyond medical oncology

- Radiotherapy
  - MASTER-iRM

DKTK Joint Funding

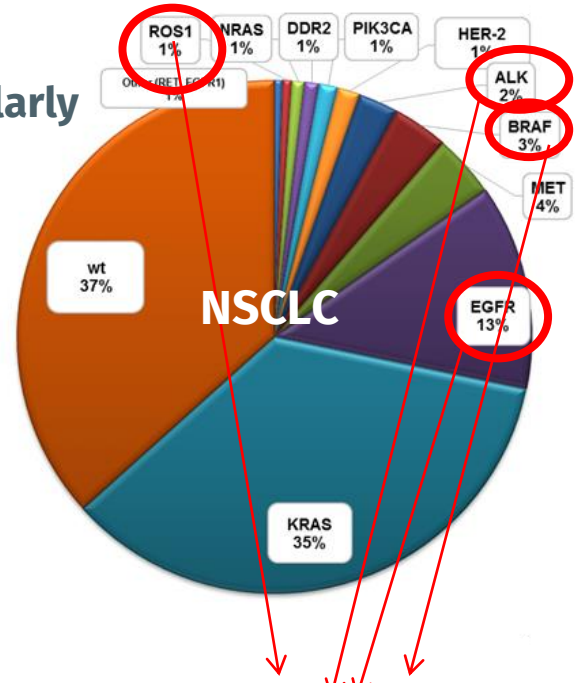
Systemic Cancer Therapy Turns into Personalized Therapy: NSCLC as Example

***10 years ago*:**
chemotherapy in unselected patients



response rate: 20-30%
med. survival: 1 year

today:
targeted therapy (and immunotherapy) in molecularly selected subgroups



response rates: 60-70%
med. survival 5 years and more
better tolerability

Molecular test rates are not acceptable in Germany

Nicht-Plattenepithel-Karzinom	HJ1 2016 (n=157)	HJ2 2016 (n=249)	HJ1 2017 (n=309)	HJ2 2017 (n=492)	HJ1 2018 (n=525)	Gesamt (n=1732)
Auf DrLTs getestet bei Erstlinie						
Yes	141 (89.8%)	232 (93.2%)	290 (93.9%)	464 (94.3%)	504 (96.0%)	1631 (94.2%)
DrLTs tested at 1st-line						
EGFR	117 (74.5%)	197 (79.1%)	233 (75.4%)	372 (75.6%)	396 (75.4%)	1315 (75.9%)
ROS-1	84 (53.5%)	141 (56.6%)	190 (61.5%)	333 (67.7%)	338 (64.4%)	1086 (62.7%)
PD-L1	31 (19.7%)	70 (28.1%)	162 (52.4%)	349 (70.9%)	391 (74.5%)	1003 (57.9%)
ALK	115 (73.2%)	183 (73.5%)	226 (73.1%)	369 (75.0%)	386 (73.5%)	1279 (73.8%)
BRAF	47 (29.9%)	74 (29.7%)	115 (37.2%)	258 (52.4%)	283 (53.9%)	777 (44.9%)

F Griesinger, AIO Herbstkongress 2018

A National Network Genomic Medicine Against Lung Cancer (nNGM)

nNGM | Nationales Netzwerk Genomische Medizin Lungenkrebs

- Countrywide implementation
- Access for all patients
- Collaboration on determining best results
- Quality control
- Real-world outcome as a tool for reimbursement

© Prof. J. Wolf, University Clinic Cologne

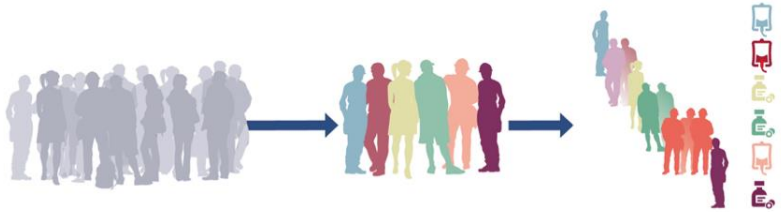
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

The Precision Medicine Paradigm Delivered

Molecular profiling based on whole-exome/genome and RNA sequencing in a multi-institutional clinical setting

- ✓ Is feasible
- ✓ Complements and advances routine molecular diagnostics
- ✓ Creates therapeutic opportunities
- ✓ Is particularly useful for detecting rare, complex, and newly emerging cancer drivers
- ✓ Needs to be evaluated within controlled clinical trials of genomics-guided therapies
- ✓ Is being integrated with additional layers of patient characterization
  - Proteomics
  - Epigenomics
  - Immune profiling
  - Functional profiling
  - Multiparameter imaging
- ✓ Will be extended to additional treatment modalities
  - Radiotherapy
  - Surgery



ESMO Precision Medicine Glossary 2017

4.

Translation Delivered…

…as a Center

NCT 1.0 – Principles & Practice

UniversitätsKlinikum Heidelberg

NCT

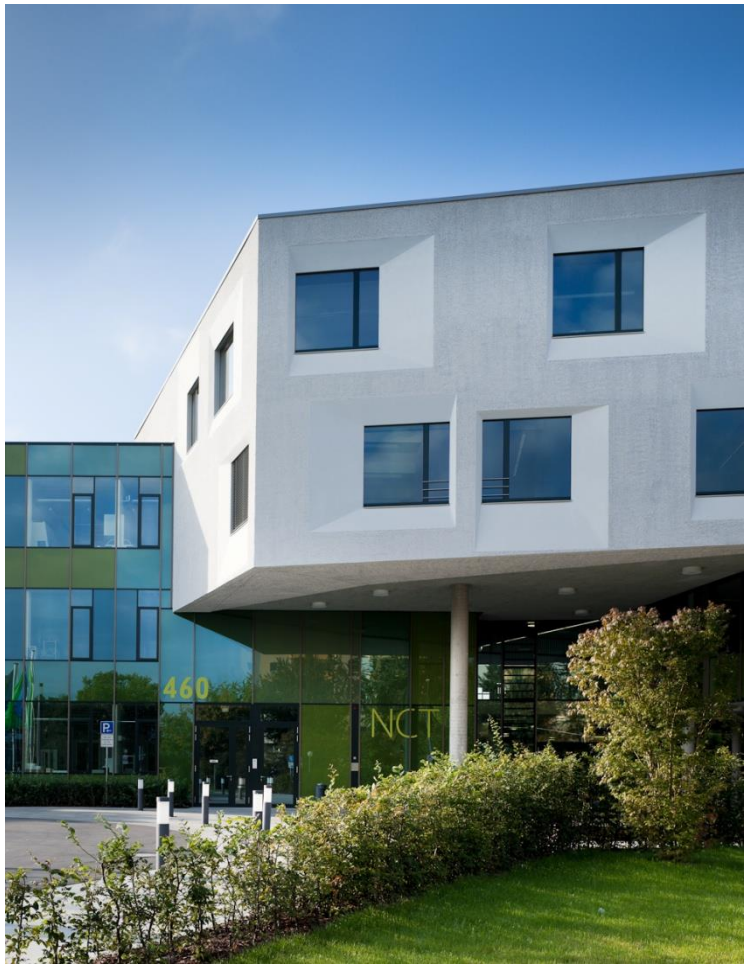
dkfz.

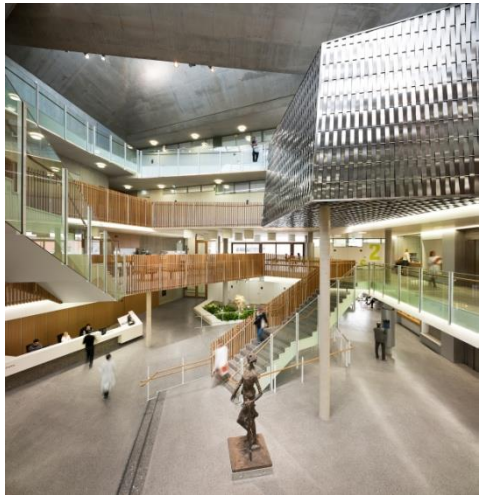
CREATING INTERDISCIPLINARITY

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

NCT 2.0 – New Building & Structures





IDENTITY & VISIBILITY

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

NCT 3.0 – The Next Level

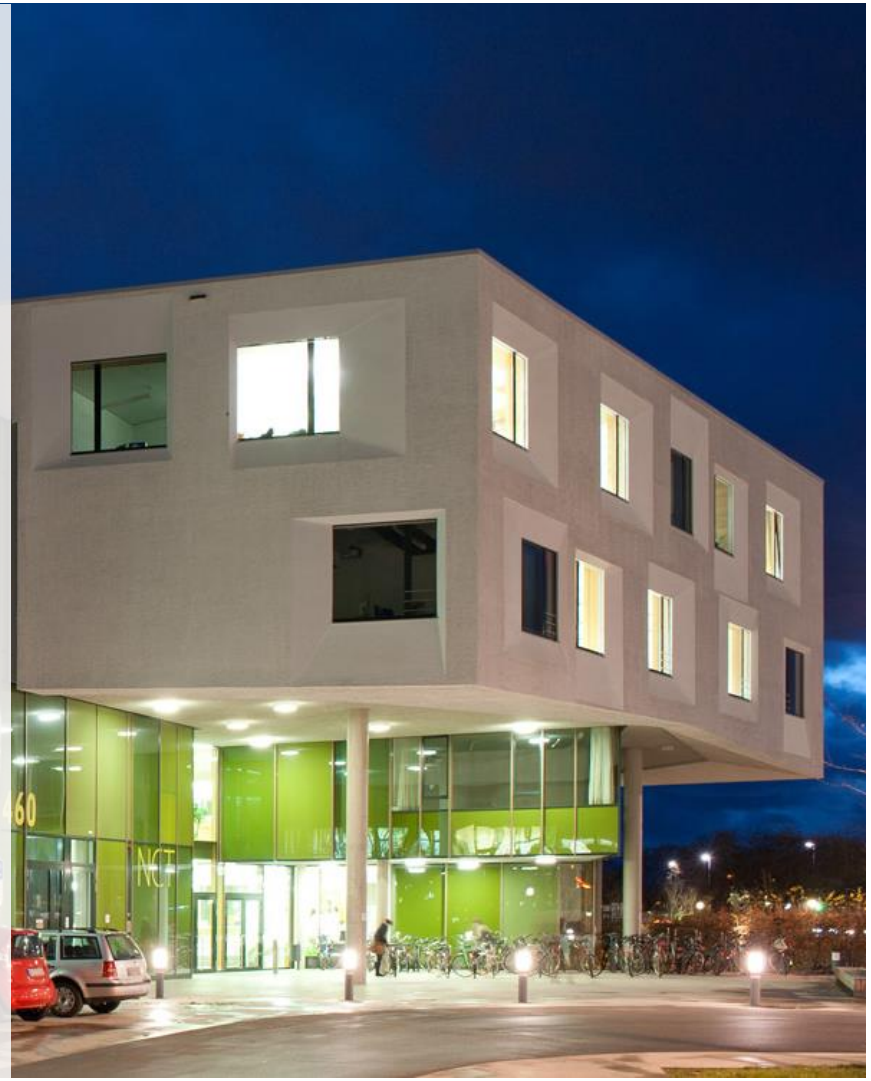
SCIENTIFIC & CLINICAL EXCELLENCE

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

NCT – Translation Delivered

- Internationally recognized profile areas and programs
- Comprehensive NCT core services & counselling and information services
- > 8.200 newly diagnosed and treated cancer patients
- >16.300 treated cancer patients
- > 6.700 second opinion
- Specialized interdisciplinary clinics, > 30 tumor boards & > 50 SOPs
- Overall research funding > 100 Mio. (2014-2016)
- > 580 clinical trials (2014-2016)
- More than 64% of all treated patients enrolled in clinical trials



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

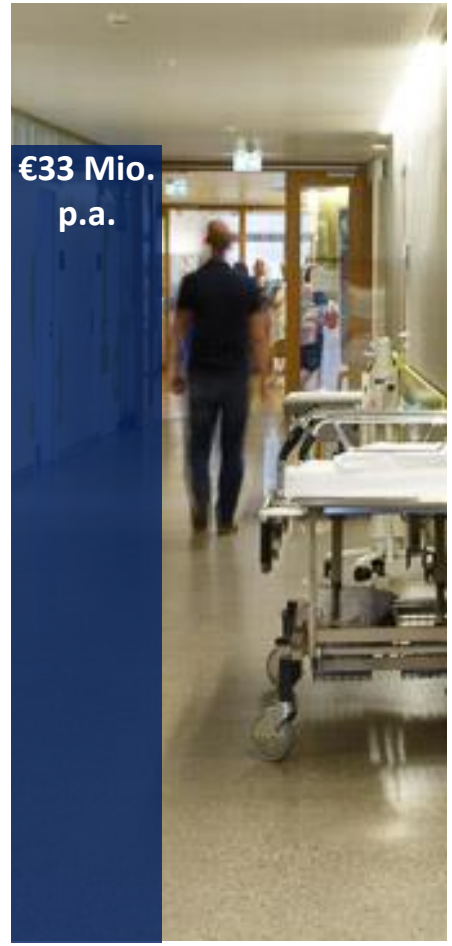
BIH Berlin Institute of Health Charité & MDC

NCT Extension Funding and Budget Beyond Certified CC

Extension funding for NCT (BMBF)

Building extension (federal state)

Budget beyond certified CC (local funding)



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

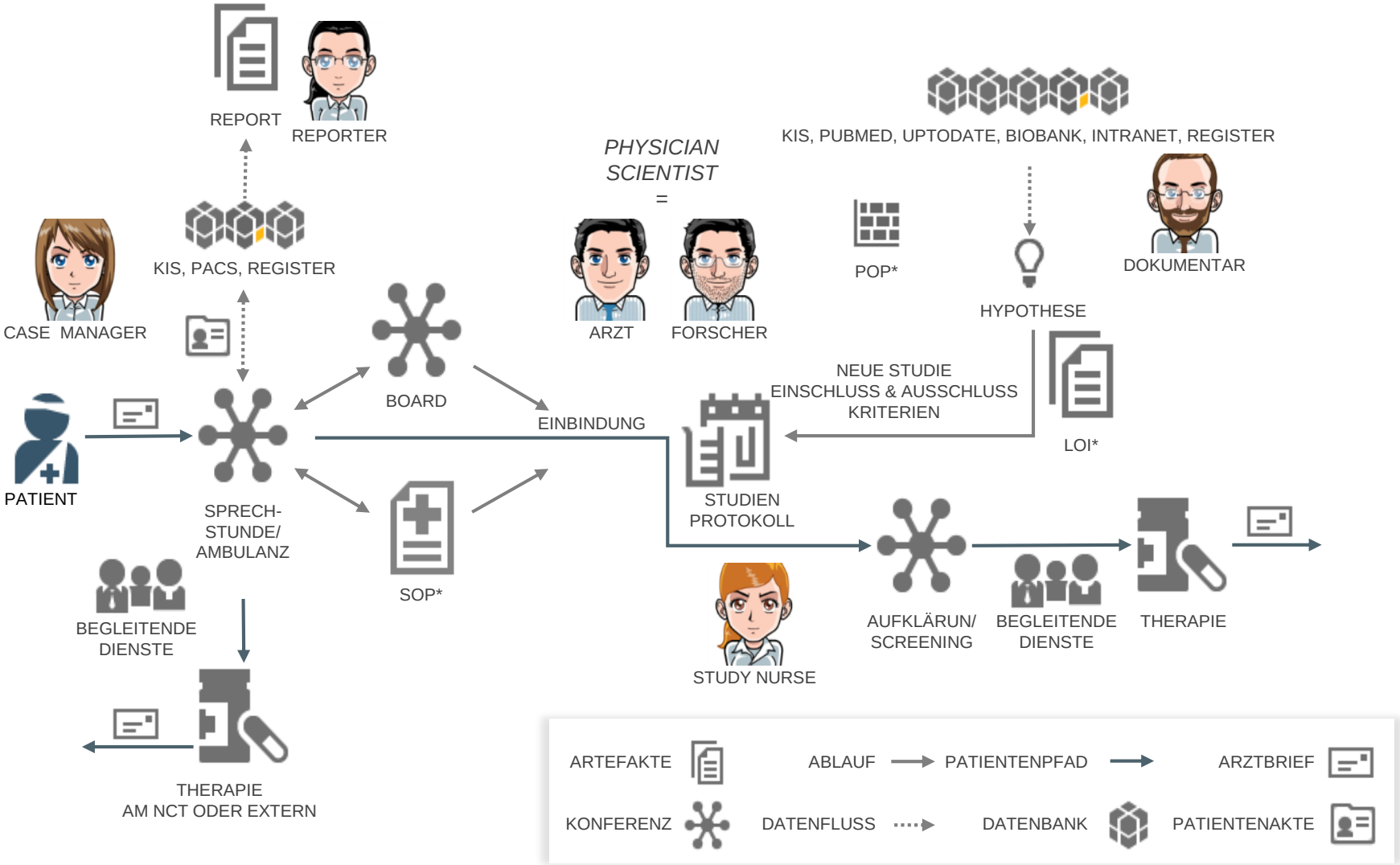
Next Step: NCT Annex

5.

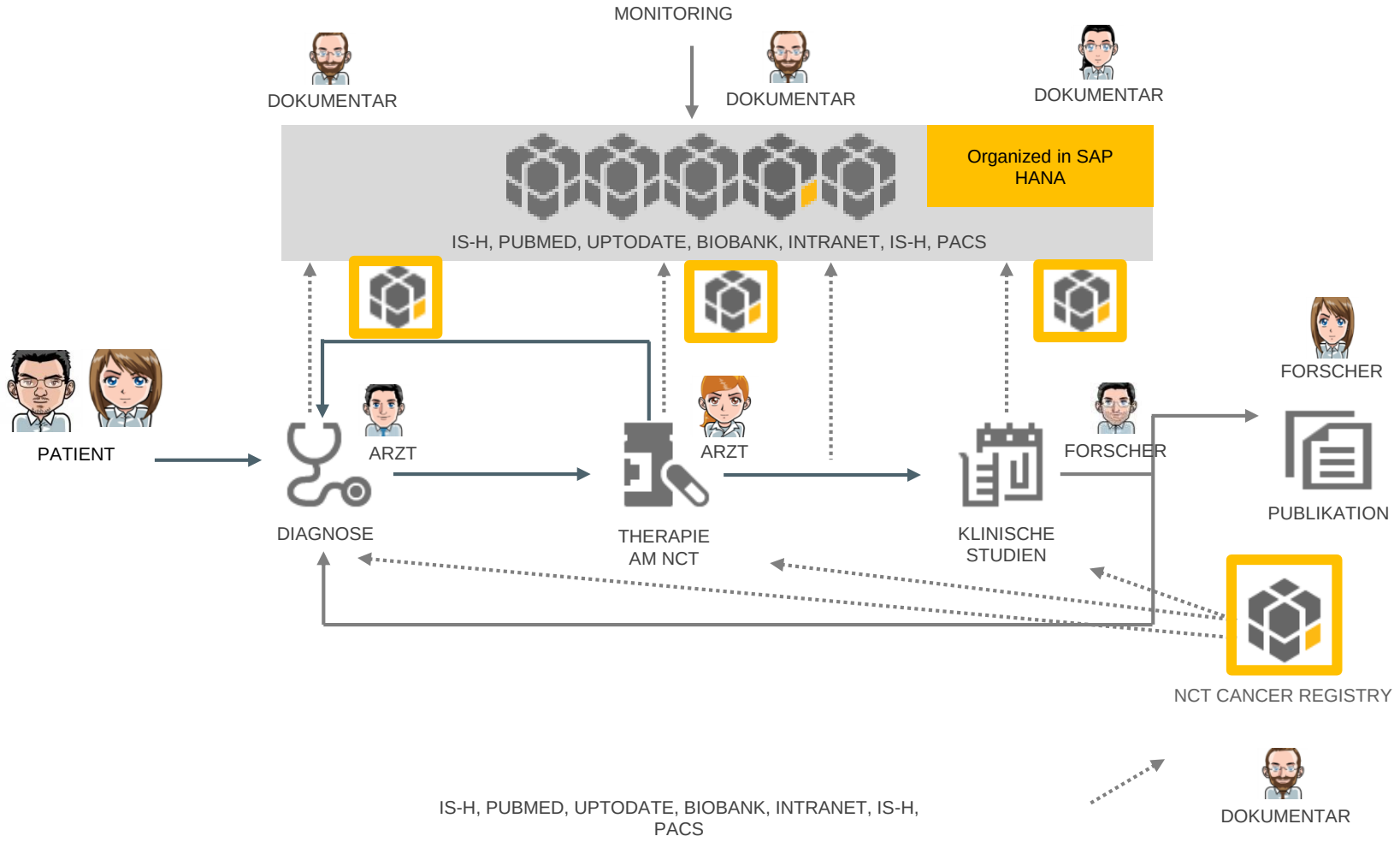
Translation Delivered…

…in the Digital Age

NCT DataThereHouse: Current Scenario



NCT DataThereHouse: NCT Clinical Development Strategy



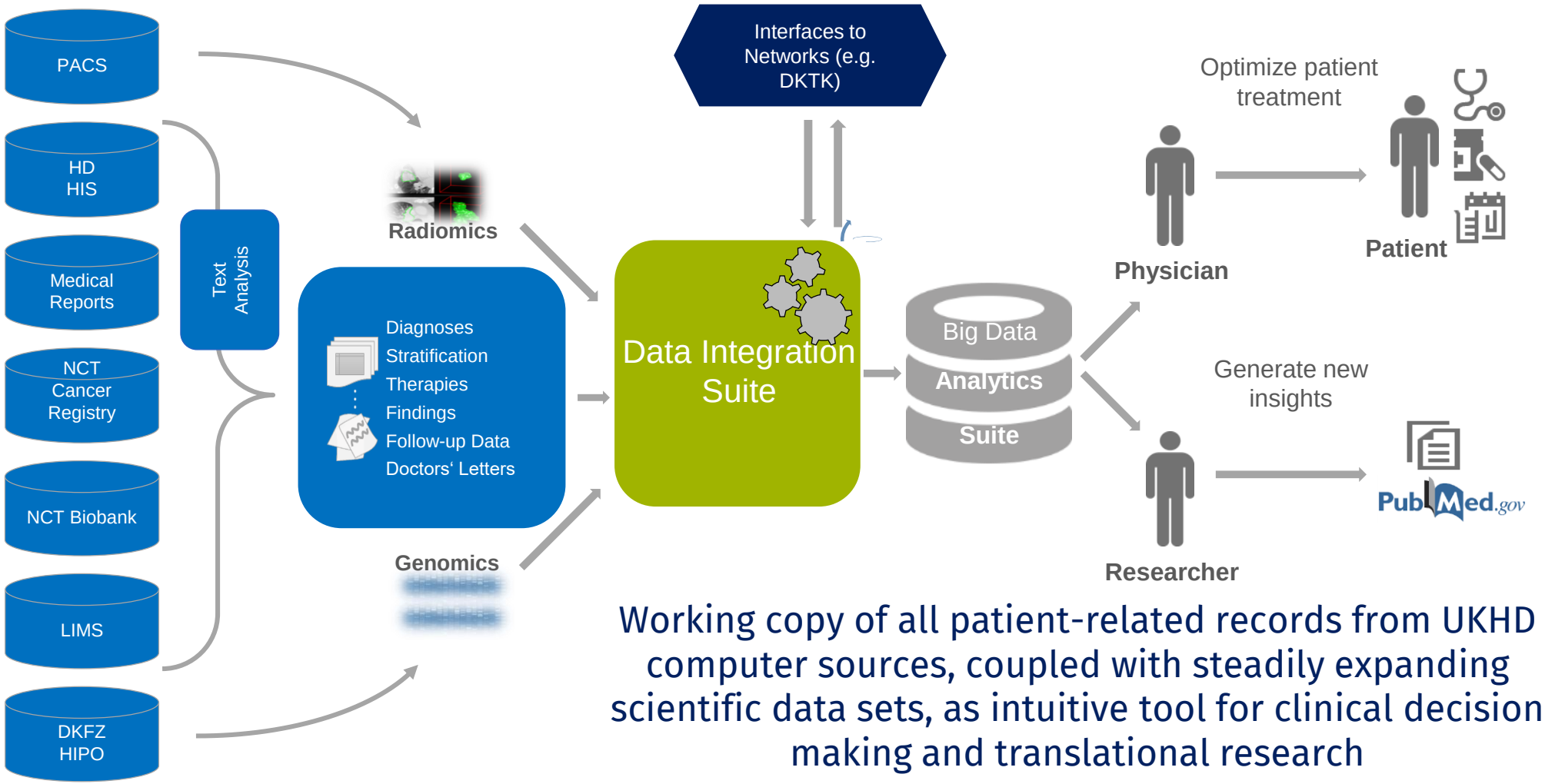
NCT DataThereHouse

Display data from various sources for a comprehensive overview of information relevant for personalized treatment

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

NCT DataThereHouse: Innovative Diagnostics and Therapies



Working copy of all patient-related records from UKHD computer sources, coupled with steadily expanding scientific data sets, as intuitive tool for clinical decision making and translational research

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

DataBox

- ✓ Structured, organized, complete
- ✓ Reliable and patient-centered
- ✓ Smart analysis concepts
- ✓ Innovative platform

SPONSORED BY THE
Federal Ministry of Education and Research

SIEMENS Healthineers

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

SAP

SAP Health

Supported by:
Federal Ministry of Health
on the basis of a decision by the German Bundestag

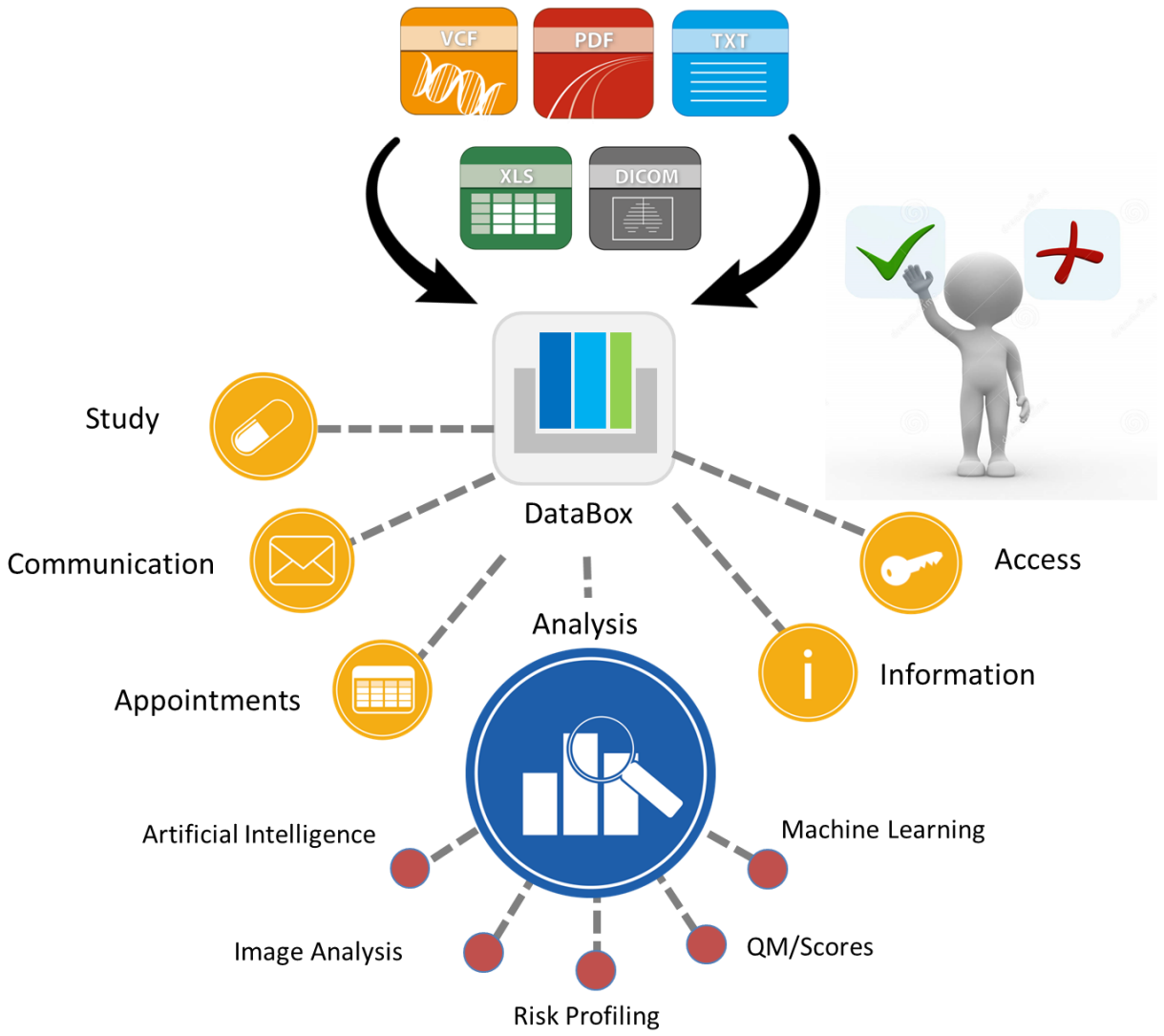
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Idea

Management of complex health data

- Patient-centered platform
- Different sources
- Integration of innovative big-data-analysis concepts
- Machine Learning (ML)
- AI approaches



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

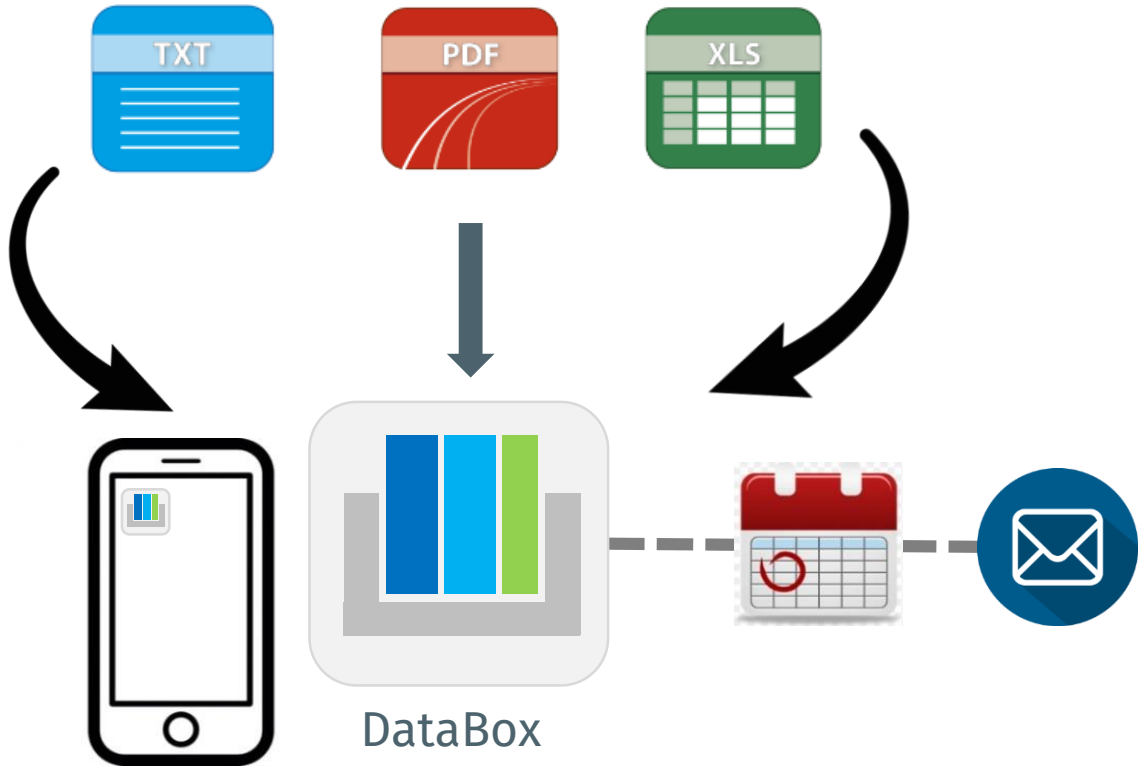
Solution

All data is available in one central database.

Data can be added and accessed via smartphone app or web tool.

- Available
- Structured
- Organized
- Functional
- Complete

Patient empowerment!



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

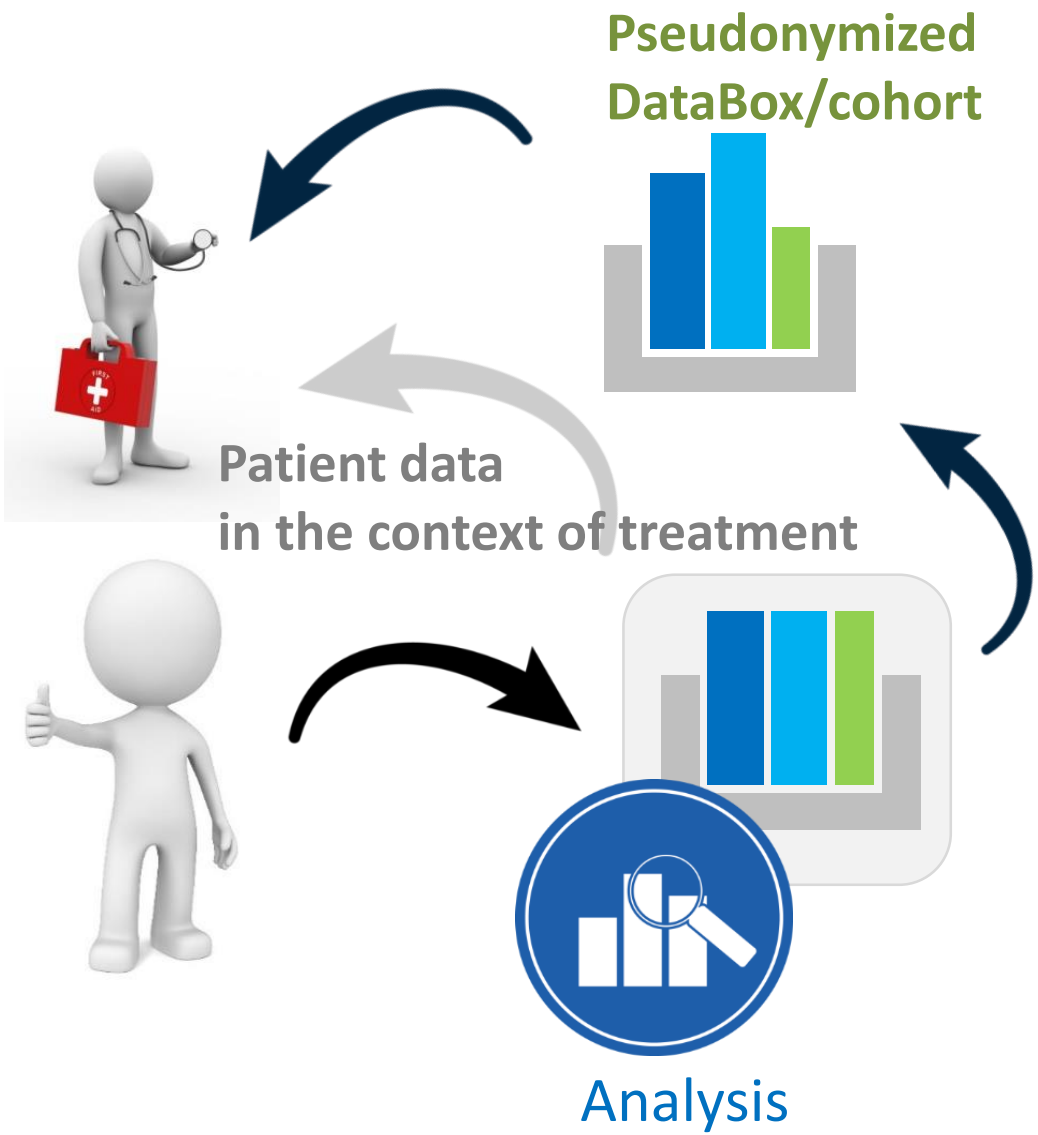
Smart Analysis Concepts

Physician-centered analysis

- Trans-sectoral and longitudinal data
- Molecular genetic analyses
- Scientific use
- Collectives of patients with rare cancer diseases

Patient-centered functions

- On-demand availability of data
- Patient empowerment through comprehensive information and transparency
- Prevents redundant examinations
- Improved treatments
- Higher range of aligned trials

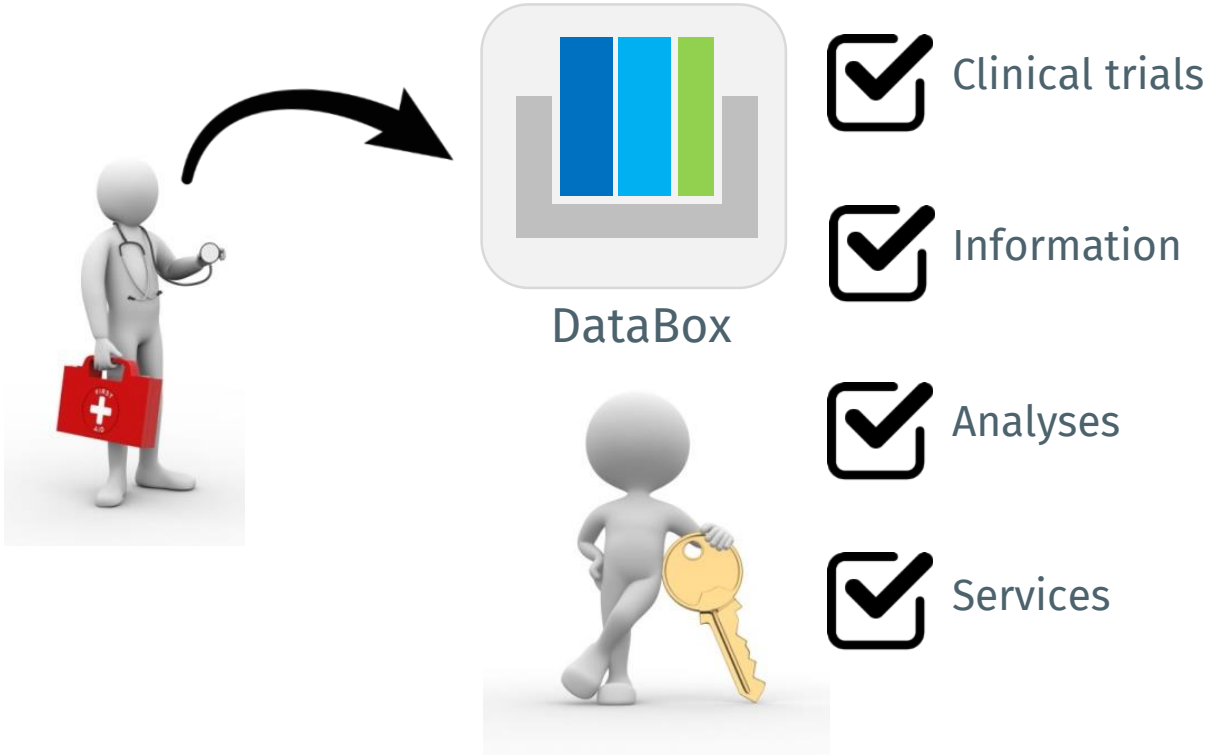


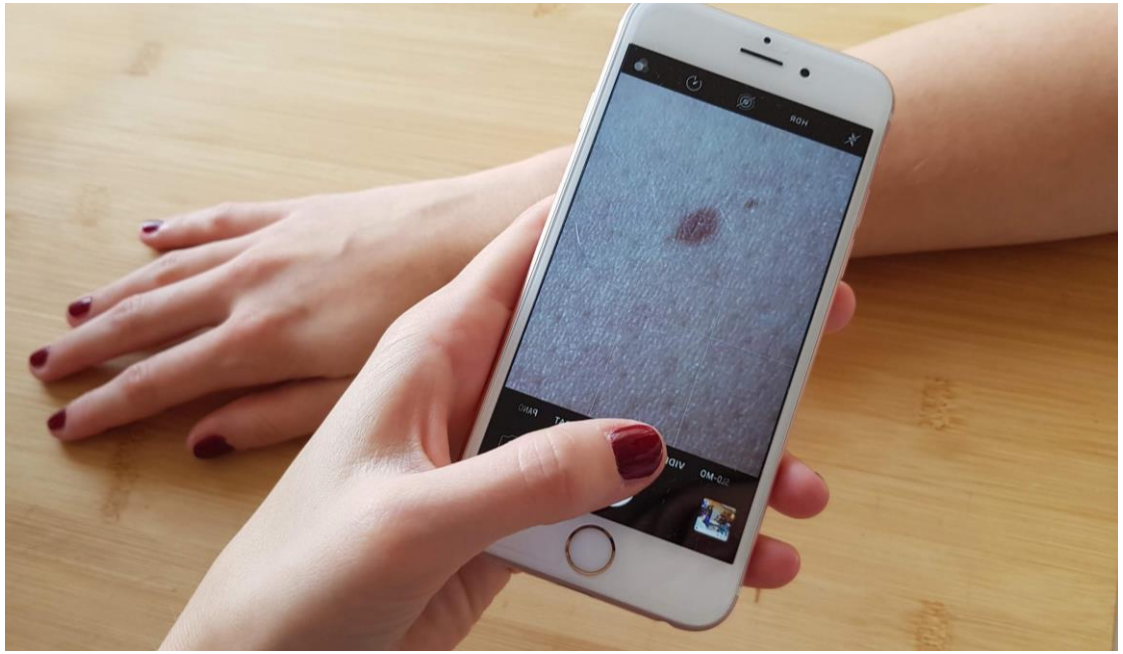
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Benefits

- Pseudonymized patient basic dataset for accredited, reliable institutions
- (e.g. to search for study participants)
- Information for patients on new trials or research projects (prior informed consent needed)
- Patients can share data upon request



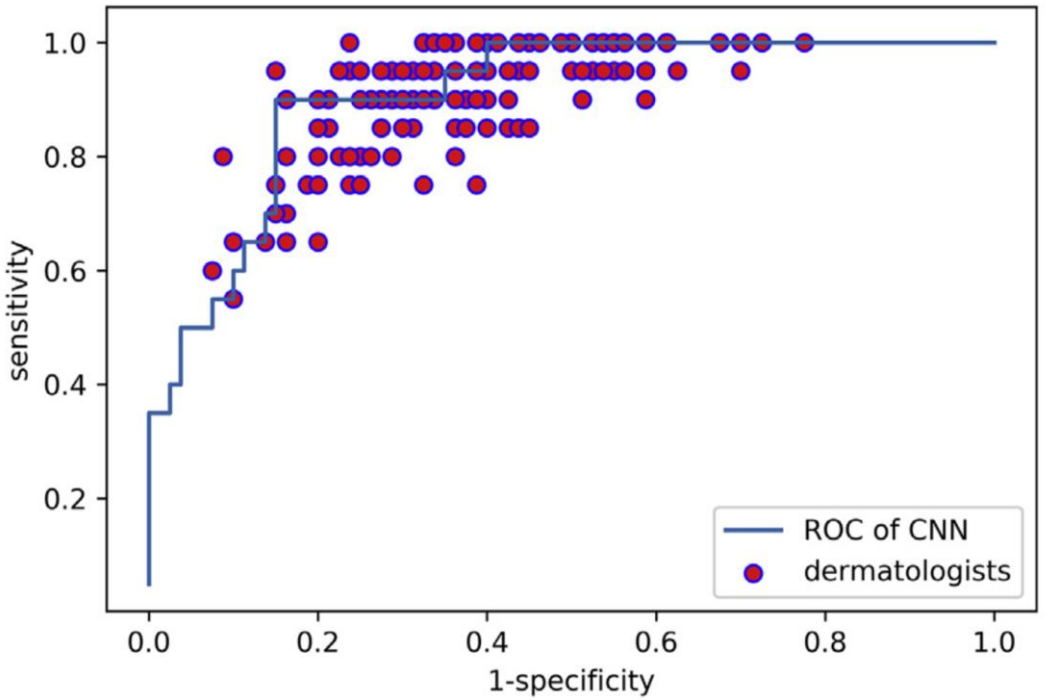


AI- & App-enhanced Cancer Diagnostics

1. AI as a tool to enhance
2. …the accuracy of clinical cancer diagnoses
3. …the accuracy of histopathologic diagnoses.
4. Apps as a tool to overcome barriers to catch cancer early
5. Two telemedicine apps currently treating patients:
6. Facemorphing Apps Smokerface & Sunface

Training with dermoscopic and testing with clinical images?

On par performance with 145 German dermatologists.



CNN performed as good as board-certified dermatologists on clinical images despite never receiving training on clinical images.

Brinker, Titus J., et al. "A convolutional neural network trained with dermoscopic images performed on par with 145 dermatologists in a clinical melanoma image classification task." European Journal of Cancer 111 (2019): 148-154.

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

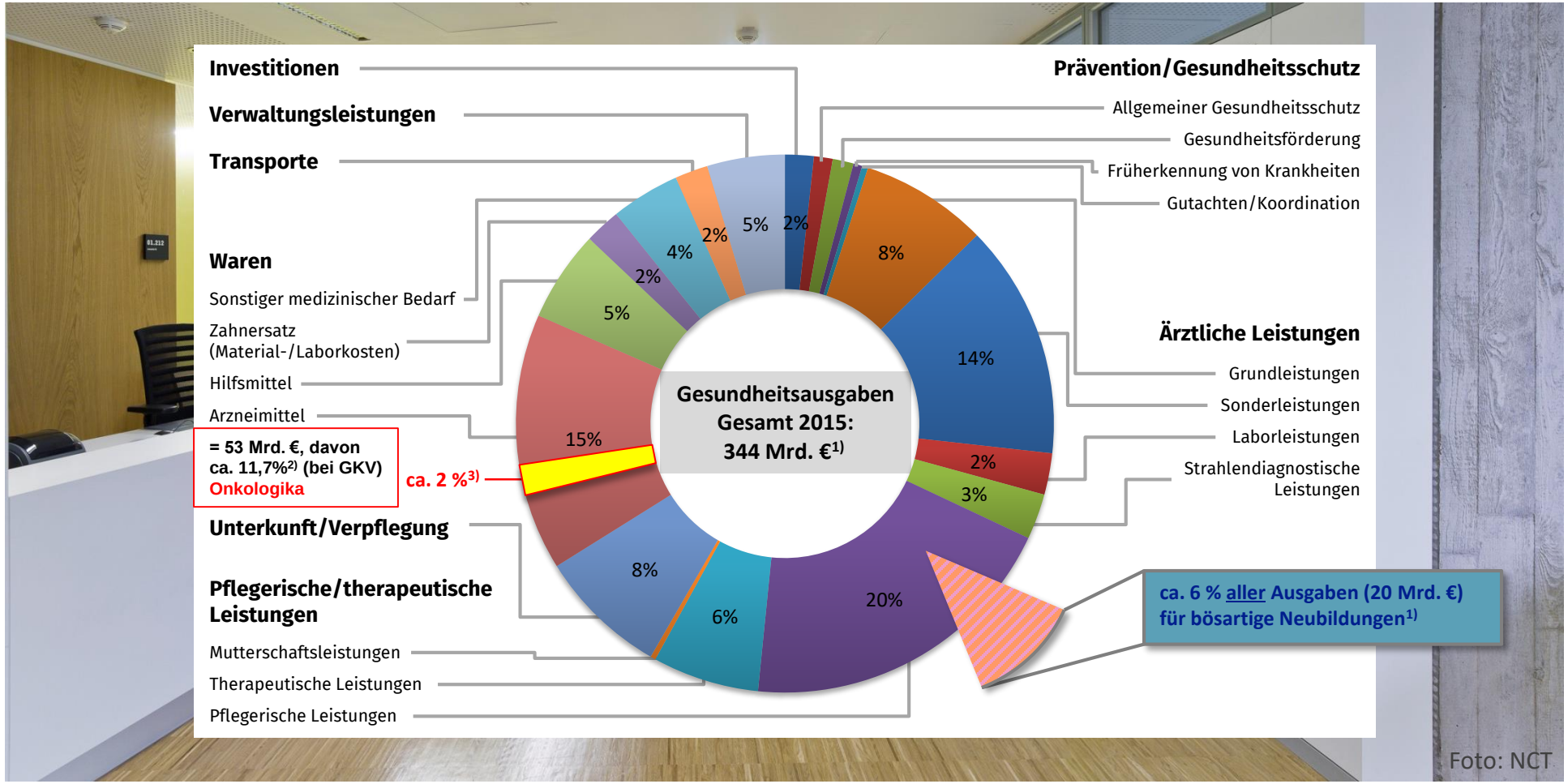
6.

Translation Delivered…

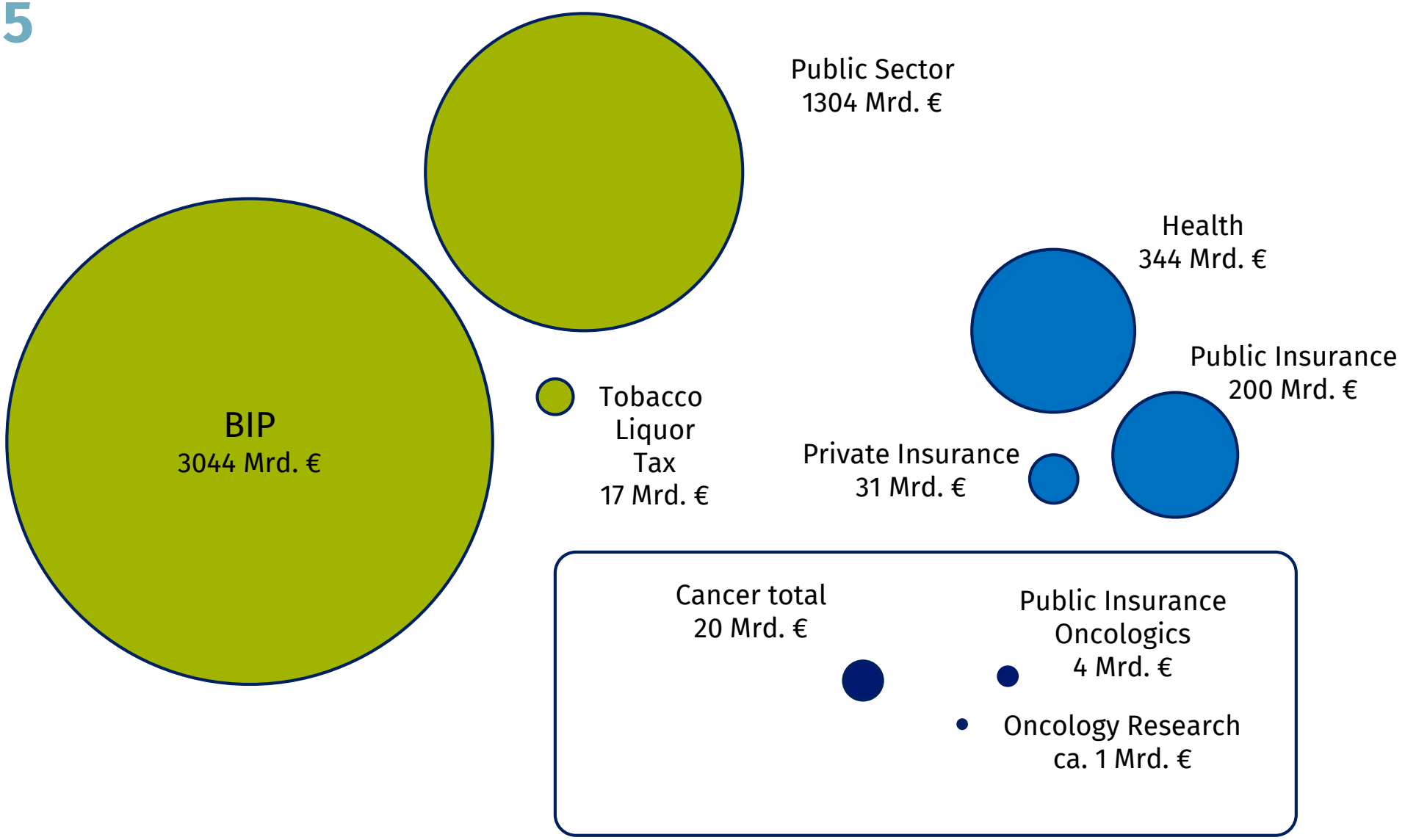
…as a Society

Taking Cancer Personal...

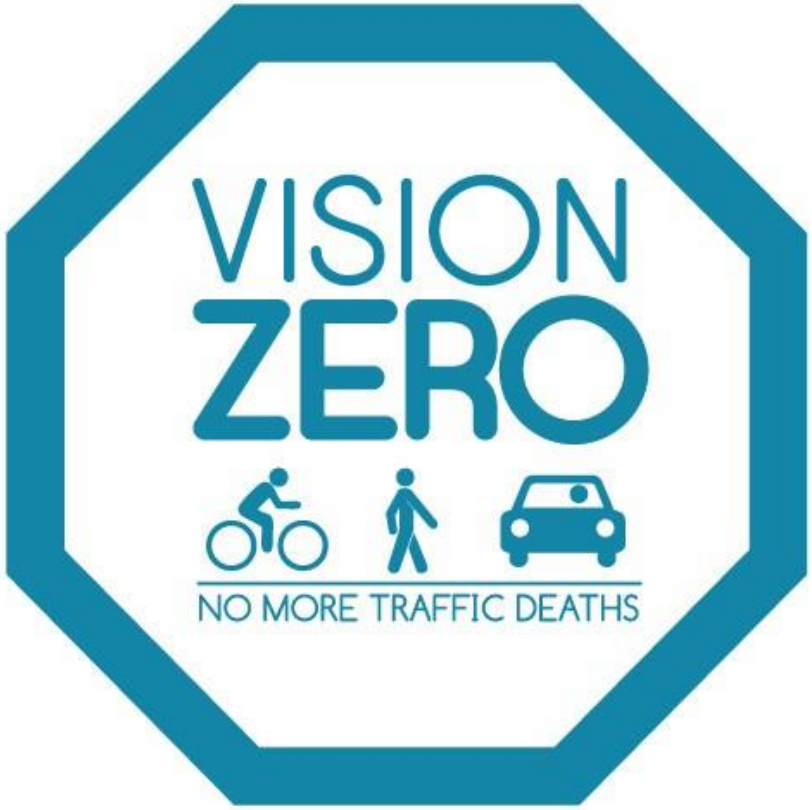
We Are Spending What???

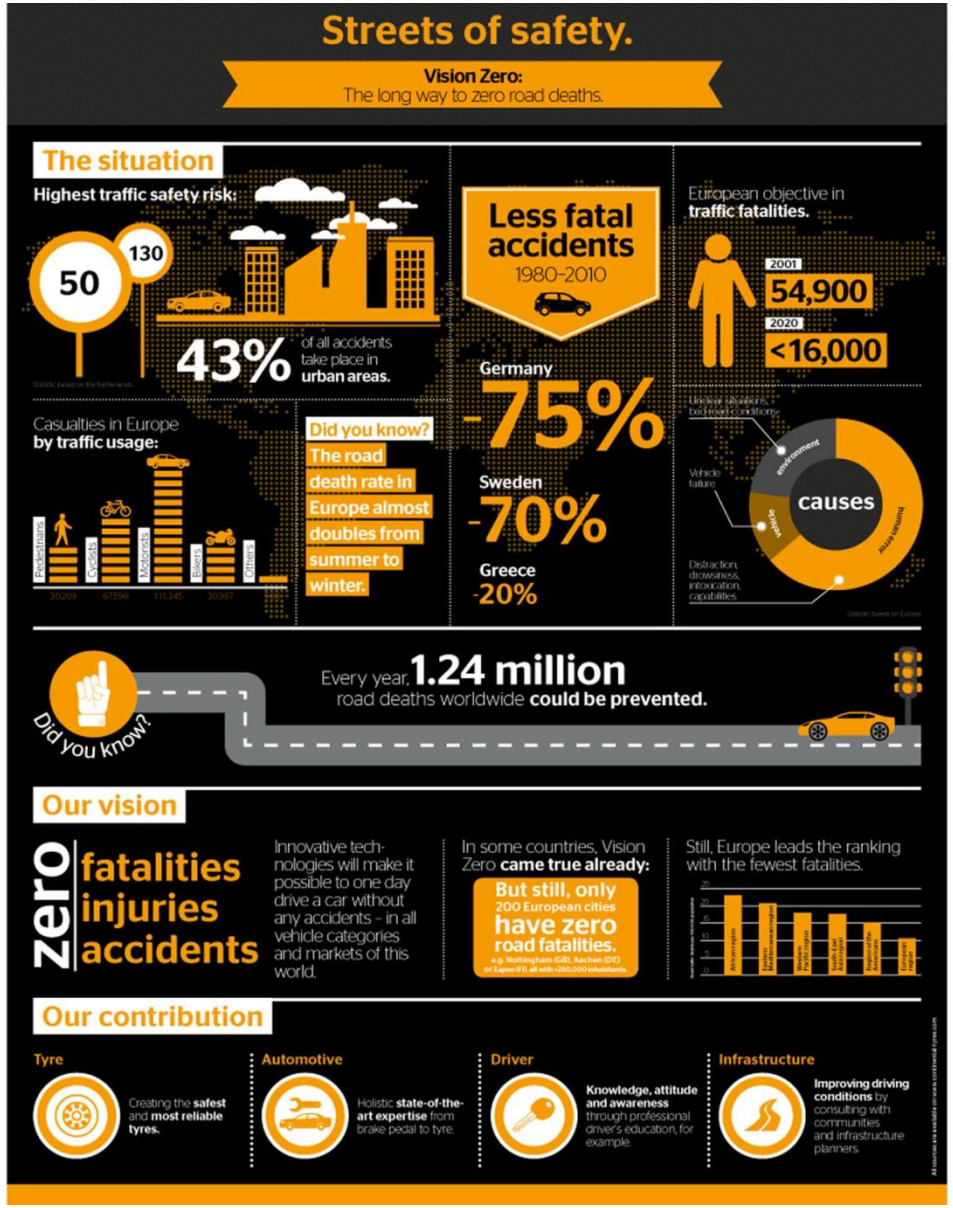


Cost 2015


Public Sector
1304 Mrd. €
BIP
3044 Mrd. €
Tobacco
Liquor
Tax
17 Mrd. €
Health
344 Mrd. €
Public Insurance
200 Mrd. €
Private Insurance
31 Mrd. €
Cancer total
20 Mrd. €
Public Insurance
Oncologics
4 Mrd. €
Oncology Research
ca. 1 Mrd. €

Vision Zero



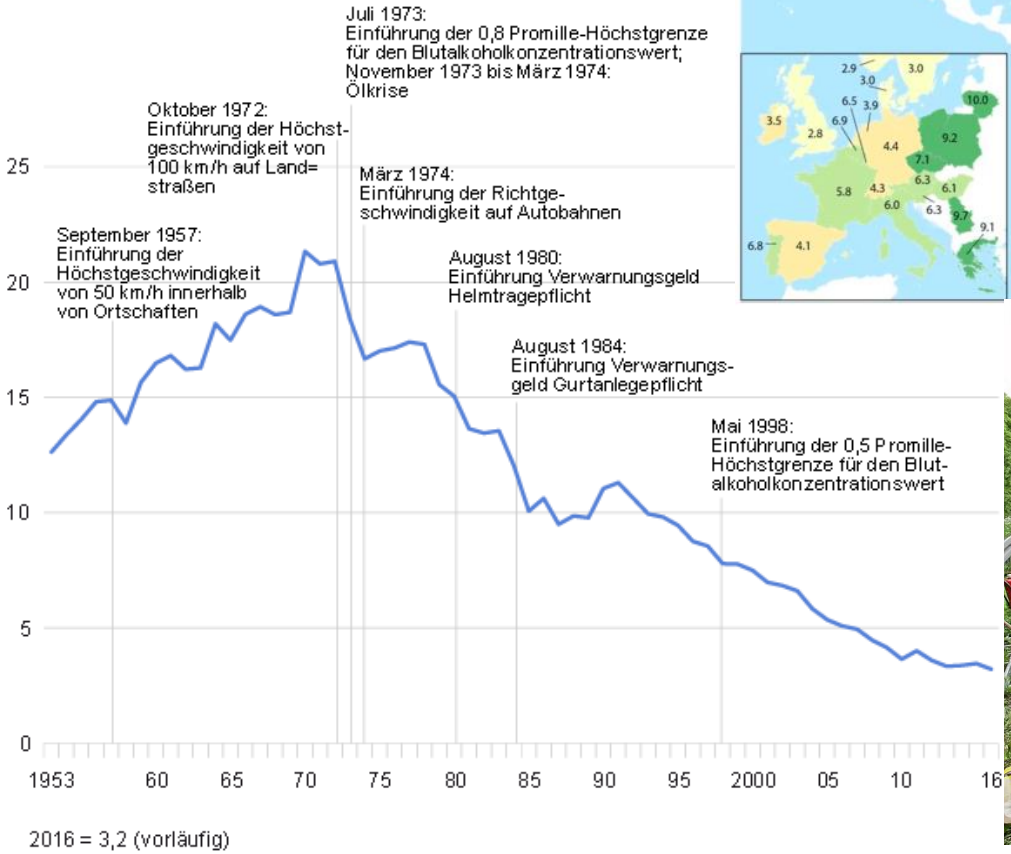


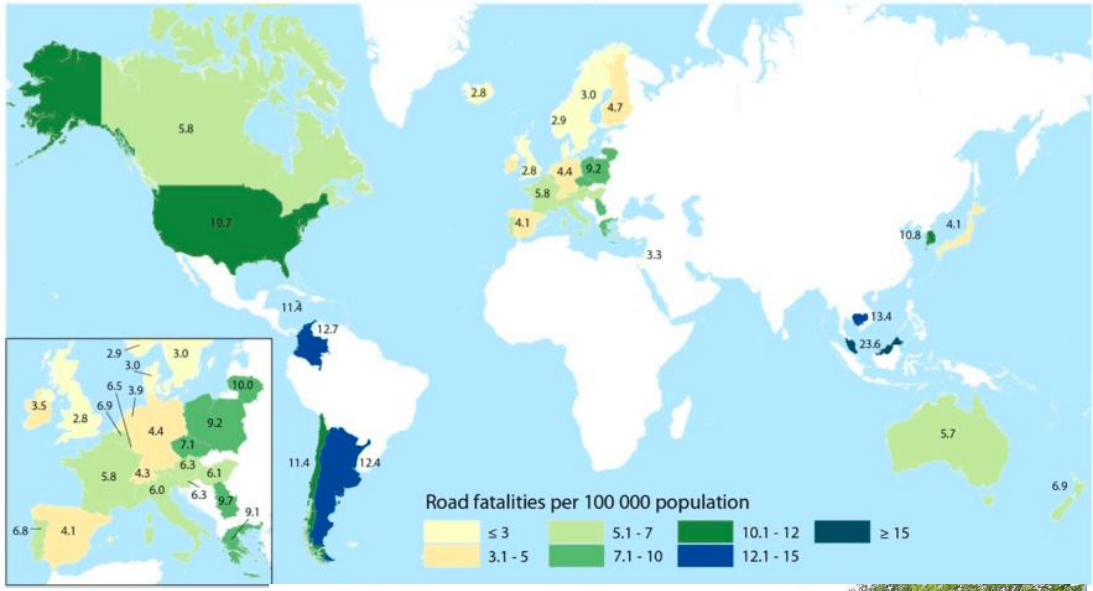
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

An All-out Fight Against Other Causes of Death…

Development of the number of traffic fatalities
(Germany, in thousands)





© Statistisches Bundesamt (Destatis), 2017

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Vision Zero

- Focus on fatalities and serious injuries
- Flaws in the transportation system identified as cause of collisions
- Focus on perfecting road system for imperfect human behavior
- Safety initiatives reduce societal costs

Traditional thinking

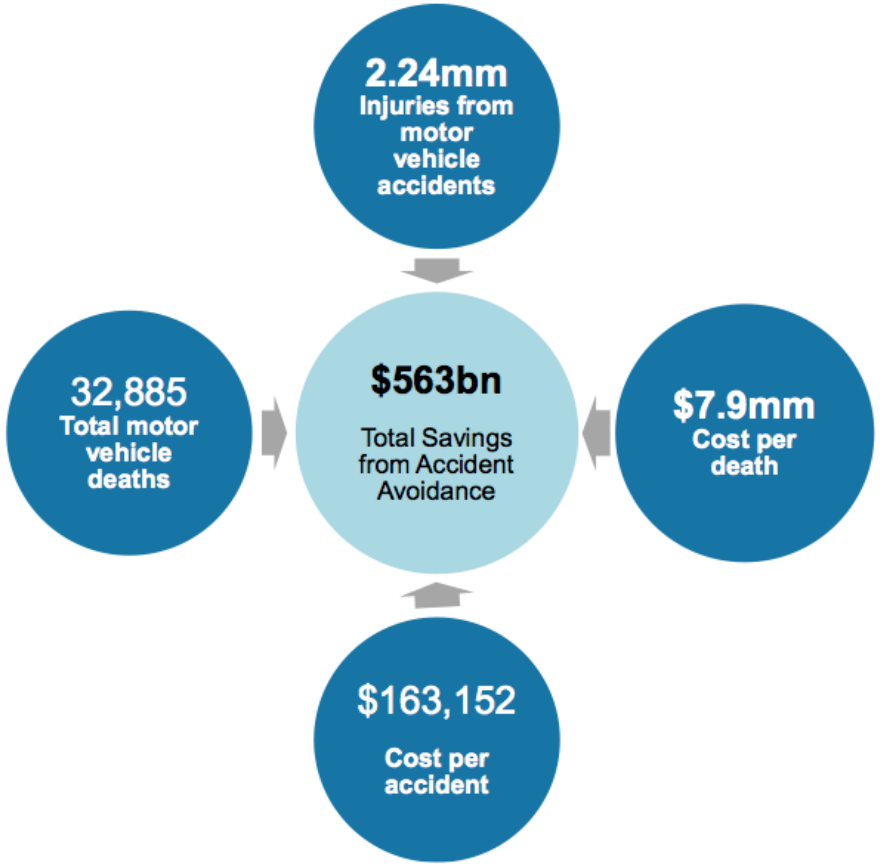
- Focus on overall collision rates
- Human error identified as cause of collisions
- Focus on perfecting human behavior on an imperfect road system
- Safety initiatives are costly

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Expensive Prevention is Very Cheap...

US data



Source: US Department of Transportation, National Highway Traffic Safety Administration, Federal Highway Administration, EPA, FDA, AAA, Morgan Stanley Research

Models with the highest and lowest rates of driver deaths

Lowest rates of driver deaths
Fewer than 6 driver deaths per million registered vehicle years, 2011 and equivalent earlier models, 2009-12

			Overall	MV	SV	SV roll
Audi A4 4WD	luxury car	midsize	0	0	0	0
Honda Odyssey	minivan	very large	0	0	0	0
Kia Sorento 2WD	SUV	midsize	0	0	0	0
Lexus RX 350 4WD	luxury SUV	midsize	0	0	0	0
Mercedes-Benz GL-Class 4WD	luxury SUV	large	0	0	0	0
Subaru Legacy 4WD	4-door car	midsize	0	0	0	0
Toyota Highlander hybrid 4WD	SUV	midsize	0	0	0	0
Toyota Sequoia 4WD	SUV	large	0	0	0	0
Volvo XC90 4WD	luxury SUV	midsize	0	0	0	0
Honda Pilot 4WD	SUV	midsize	2	0	2	0
Mercedes-Benz M-Class 4WD	luxury SUV	midsize	3	3	0	0
Ford Crown Victoria	4-door car	very large	4	4	0	0
GMC Yukon 4WD	SUV	large	4	0	4	0
Acura TL 2WD	luxury car	midsize	5	5	0	0
Chevrolet Equinox 2WD	SUV	midsize	5	3	2	0
Chevrolet Equinox 4WD	SUV	midsize	5	5	0	0
Ford Expedition 4WD	SUV	large	5	5	0	0
Ford Flex 2WD	SUV	midsize	5	0	5	0
Mazda CX-9 4WD	SUV	midsize	5	0	5	5

Highest rates of driver deaths
More than 46 driver deaths per million registered vehicle years, 2011 and equivalent earlier models, 2009-12

			Overall	MV	SV	SV roll
Kia Rio	4-door car	mini	149	96	54	15
Nissan Versa sedan	4-door car	small	130	44	87	51
Hyundai Accent	4-door car	mini	120	65	53	16
Chevrolet Aveo	4-door car	mini	99	65	31	10
Hyundai Accent	2-door car	mini	86	43	48	20
Chevrolet Camaro coupe	sports car	large	80	19	60	25
Chevrolet Silverado 1500 Crew 4WD	pickup	large	79	40	36	17
Honda Civic	2-door car	small	76	46	29	10
Nissan Versa hatchback	4-door car	small	71	37	33	20
Ford Focus	4-door car	small	70	55	13	5
Nissan Cube	station wagon	small	66	38	29	6
Chevrolet HHR	station wagon	small	61	34	25	9
Chevrolet Suburban 1500 2WD	SUV	very large	60	31	28	9
Chevrolet Aveo	station wagon	mini	58	58	0	0
Mercury Grand Marquis	4-door car	very large	57	33	25	0
Jeep Patriot 2WD	SUV	small	57	44	9	3
Mazda 6	4-door car	midsize	54	34	17	3
Dodge Nitro 2WD	SUV	midsize	51	7	50	40
Honda Civic	4-door car	small	49	28	21	8

KEY:
overall: driver deaths per million registered vehicle years
mv: driver death rate in multiple-vehicle crashes
sv: driver death rate in single-vehicle crashes of all types
sv roll: driver death rate in single-vehicle rollovers (subset of sv)
2WD: 2-wheel drive | **4WD:** 4-wheel drive

Vision Zero is im.....POSSIBLE!

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

22,000 Deaths per Year. Sounds Familiar?

3.5 Colon and rectum

Table 3.5.1
Overview of key epidemiological parameters for Germany, ICD-10 C18–C21

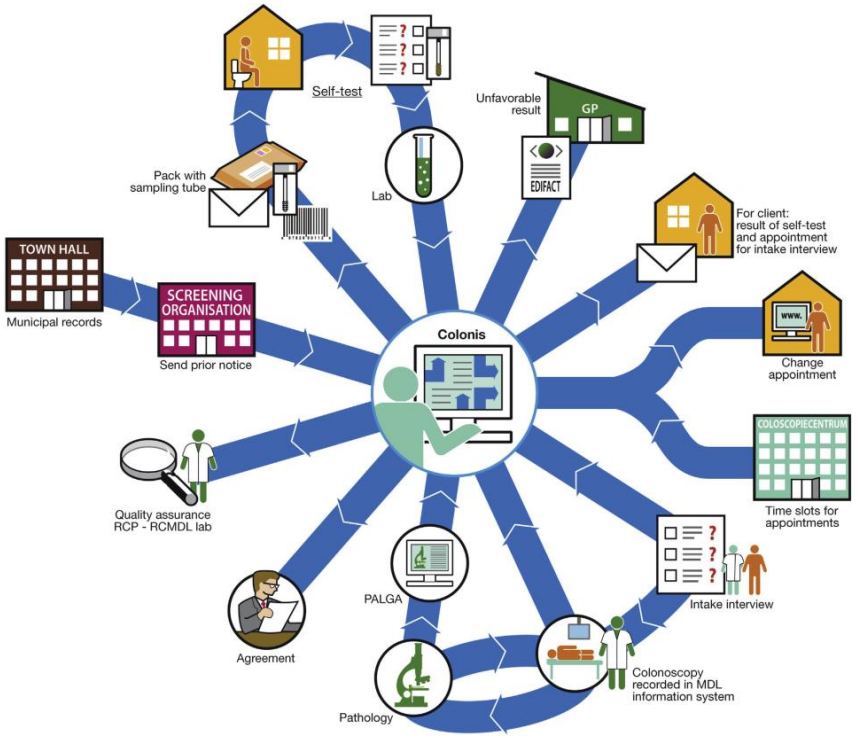
	2011		2012		Prediction for 2016	
	Men	Women	Men	Women	Men	Women
Incident cases	34,460	29,330	33,740	28,490	33,400	27,600
Crude incidence rate[1]	88.0	71.4	85.8	69.3	83.5	66.6
Standardised incidence rate[1,2]	59.5	37.9	57.1	36.8	52.7	33.9
Median age at diagnosis	71	75	72	75		
Deaths	13,863	12,439	13,772	12,200		
Crude mortality rate[1]	35.4	30.3	35.0	29.7		
Standardised mortality rate[1,2]	23.2	13.7	22.4	13.3		
5-year prevalence	117,700	98,800	116,200	97,200		
		after 5 years		*after 10 years*		
Absolute survival rate (2011–2012)[3]	52 (50–55)	52 (49–56)	38 (35–42)	40 (37–44)		
Relative survival rate (2011–2012)[3]	63 (60–66)	63 (58–68)	58 (55–61)	61 (54–70)		

[1] per 100,000 persons [2] age-standardised (European standard) [3] in percentages (lowest and highest value of the included German federal states)

A sound Investment into long-Term Happiness :

Laureate of the Felix-Burda Award 2017:
Ernst J. Kuipers and team
(Erasmus University of Rotterdam)

- FIT send out to a cohort of
  > 850,000 individuals (> 55 y)
  including a prepaid return envelope
  (ca. 10 € / test)
- Analysis in central laboratory
  (ca. 10 € / analysis)
- ✓ **> 70% participation rate**
- ✓ **> 20,000 malignancies** potentially **avoided**



In Germany:

ca. **20 Mio.** individuals are qualified for CRC screening

- Total ca. **350 Mio € /** 5 **years (0.022% of 1600 Billion € total Health Cost)**
- Potentially **life saving** in almost **500,000 individuals**
- **Consider: Tobacco + Alcohol Tax €17 Billion, Meat Production € 41 Billion**

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

7.

@ BIH/Charité

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Chances

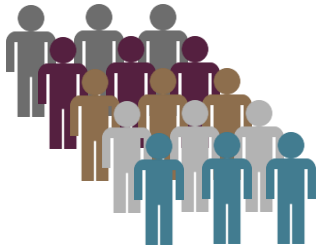
New Disruptive Technologies Meet Personalized Medicine

Precision Medicine

Optimized Therapy for Individuals

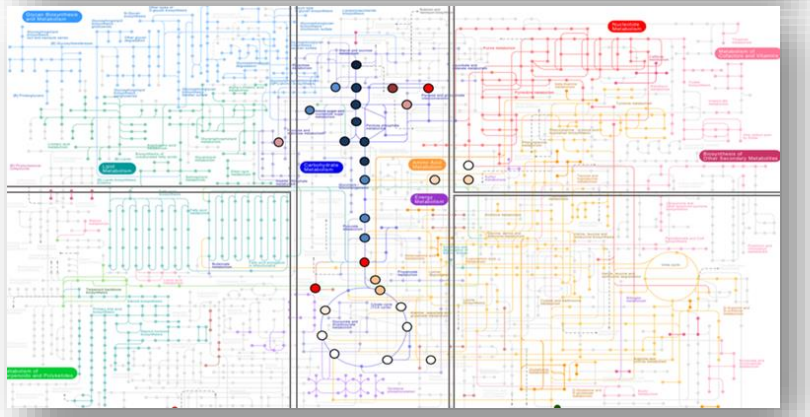
instead of

Blockbusters for Everyone

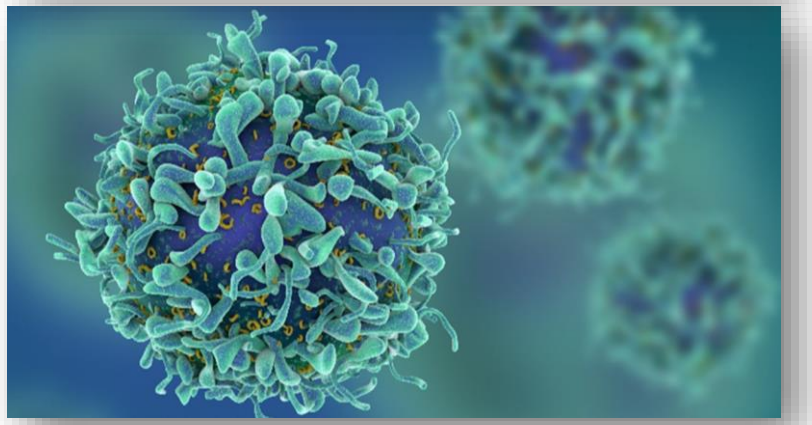


Digital Medicine

Omics

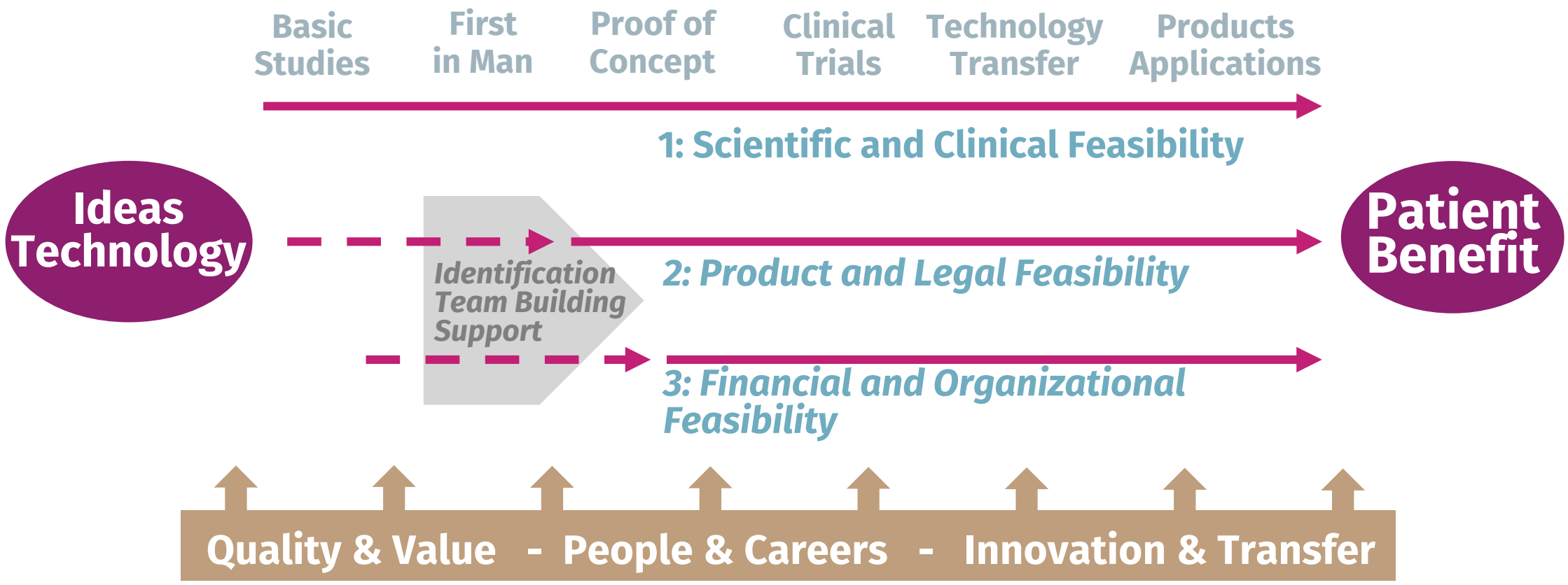


Cell Engineering



Translational Ecosystem

Innovation Enablers: Addressing the Value Chain



CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

BIH: Core Principles

Full Circle	Building a comprehensive translational Value-Chain From Bench to Clinical Reality ⟷ Clinical Challenges to Bench
Campus	One place to bring actors, institutions, clinics and infrastructure together
Multisector	Community includes basic and clinical scientists, data scientists, technology expert, innovators, entrepreneurs and transfer experts
Partnering	Cooperation with external partners from science an industry wherever needed
Value	New mechanisms to ensure quality, value and robustness of processes and results

Translational Ecosystem
Innovation Enablers: Approaches and Incentives

BIH-Academy	*People*	Task Approach Incentives	Establish a faculty skilled in medical translation Support personal development and careers BIA - Career Support Initiatives
QUEST	*Quality*	Task Approach Incentives	Assure optimal use of material and human resources Define and assure value of research Value-Incentives *(VoM)*
BIH-Accelerator	*Support*	Task Approach Incentives	Increase speed and probability-of-success in translation Bridge gaps in the translational process Translation-Incentives (*ToM*)
BIH-Innovation	*Transfer*	Task Approach Incentives	Increase effectivity of innovation transfer Provide structures and support for effective transfer Innovation-Incentives (*IoM*)

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Translational Ecosystem
Translation Clusters: Technology and Faculty

	Clinical Studies	*Clinical Study Center* *Clinical Research Units*	*Medical Informatics* *Biostatistics* *BeLOVE*
Digital Medicine	*Data*	*High Performance Computing* *Health Data Platform*	*Artificial Intelligence* *Simulation / Digital Twins* *Big Data*
Omics	*Information*	*Next Generation Sequencing* *Mass Spectrometry* *Metabolomics*	*Biobanking* *Single Cell Approaches*
Cell Engineering	*Targeted Cells*	*Gene Editing* *Stem Cells* *ATMP / GMP*	*'Human on a Chip'* *Organoids*

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Translational Ecosystem
Focus Areas: Address Burning Questions

Vascular Biomedicine		**(Micro-)vascular dysfunction is a cross-cutting patho-mechanism contributing to many diseases in all major organ systems**
Single Cell Approaches	***Flagship Project 'Life Time'***	**Cells of a given cell type exhibit individual properties and fates – analysing and addressing that offers fundamentally new medical options**
Regenerative Therapies	***Flagship Project 'RESTORE'***	**Advanced therapies and 'living drugs' will replace and supplement approaches to allow true regeneration**
Excellence Fund		**Dynamic mechanism to support initiatives with high translational potential**

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Clinical Translational Research @ Charité & BIH

Current challenges / improvement opportunities:

- Structure, coherence and governance
- Education and career development
- Clinical data management model

Strategic Aims Supported by the CSC

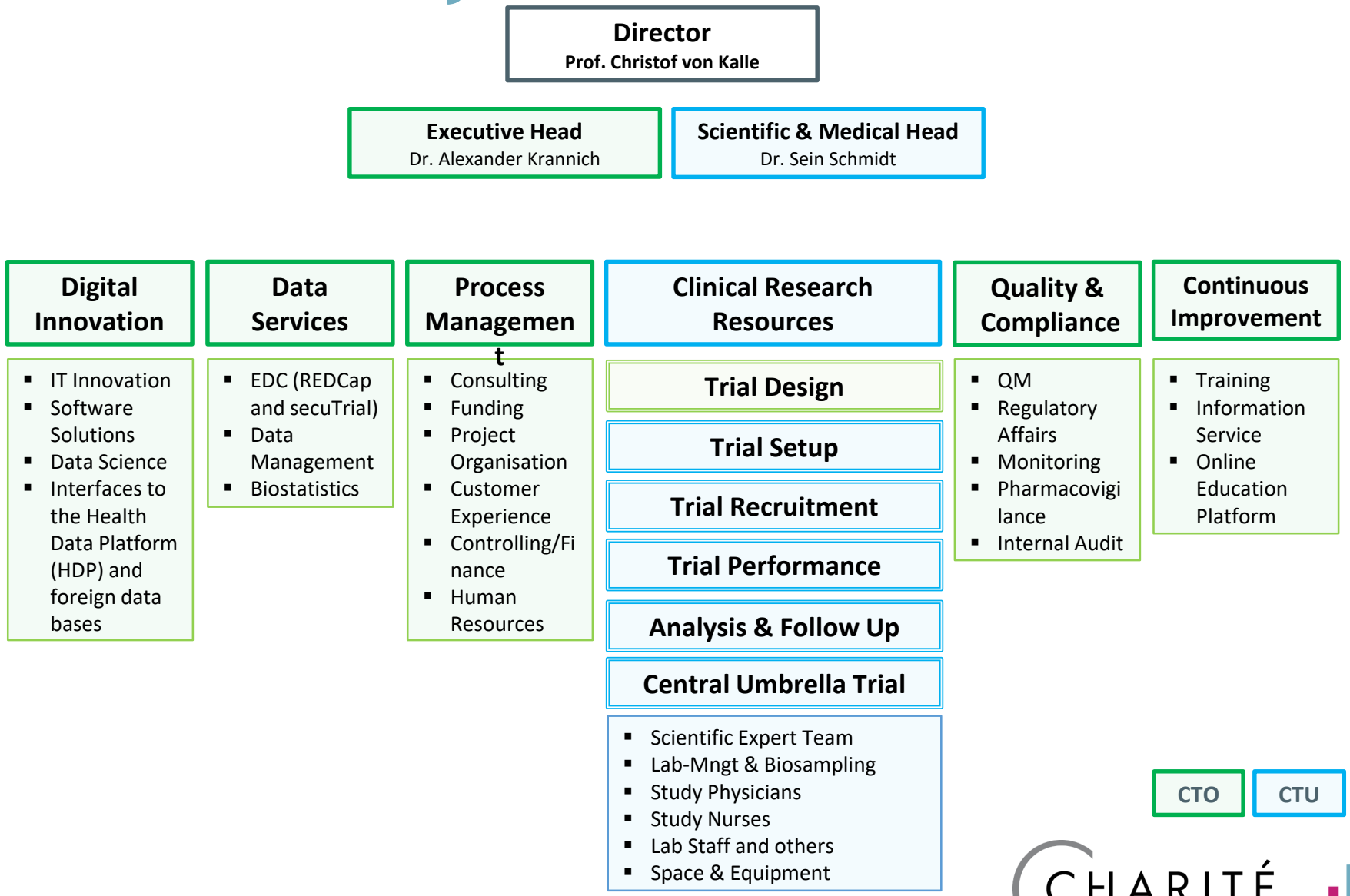
Strategic aims:

- Turn the Berlin health care environment into a learning system embodying a patient centered ‘bedside to bench to bedside’ approach
- Sophisticated diagnostics and innovative research
- Provide trial, intervention and prevention opportunities
- Maximal patient involvement
- Role in / Contribution to national programs in Germany

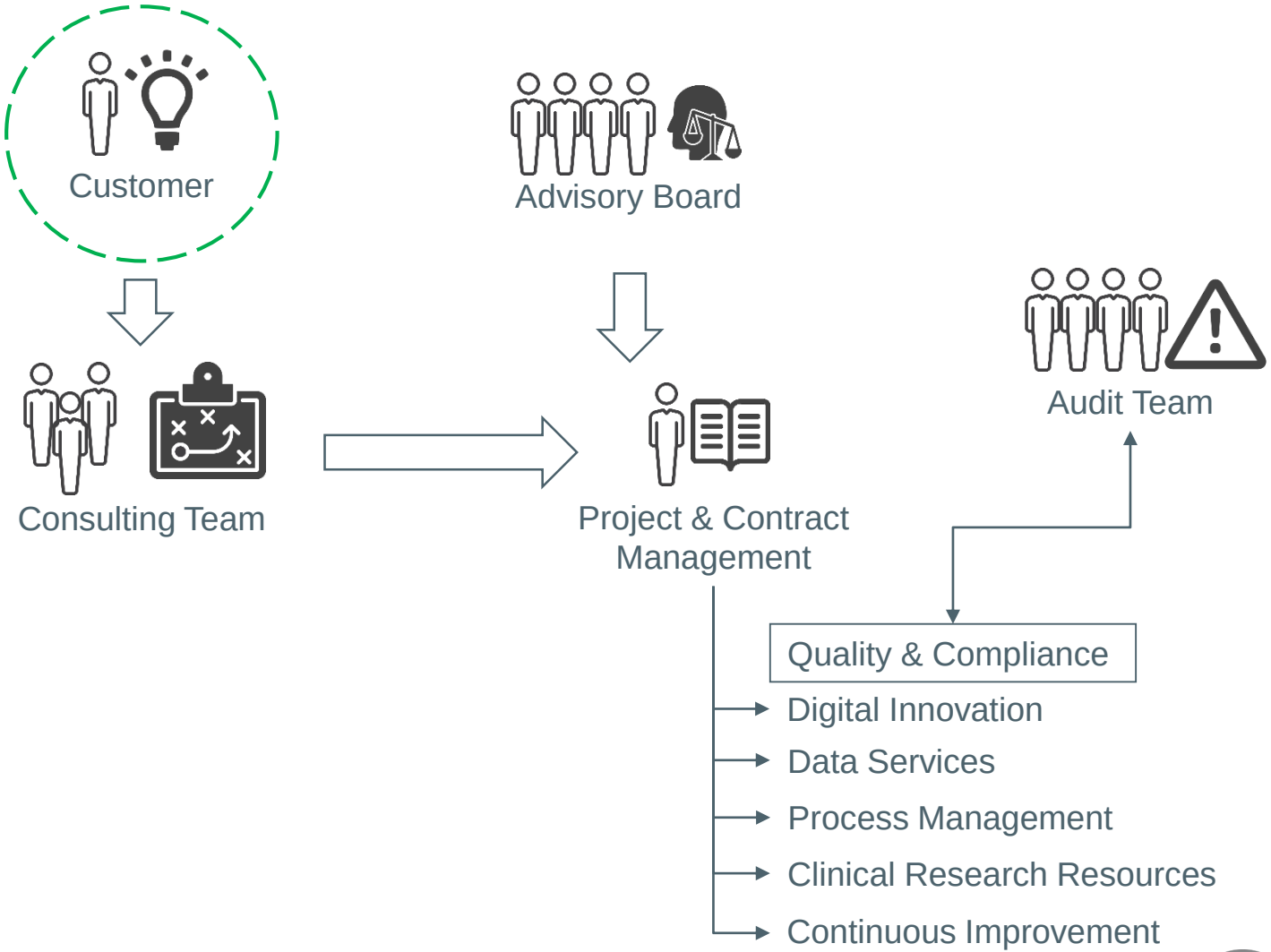
Strategic Vision to Tactical Steps
Herding the Cats

- Visions, wants and needs
- SWOT analysis – esp. strengths and weaknesses
- Gap analysis – operational gaps – strategic gaps
- **Define clinical and translational research as an end-to-end process**
- **Tracer Analysis (!)**
- Create/enhance transparency
- Feedback and consensus building
- Lateral leadership to get there

Charité BIH Clinical Study Center



Reducing Complexity: One-stop Shop



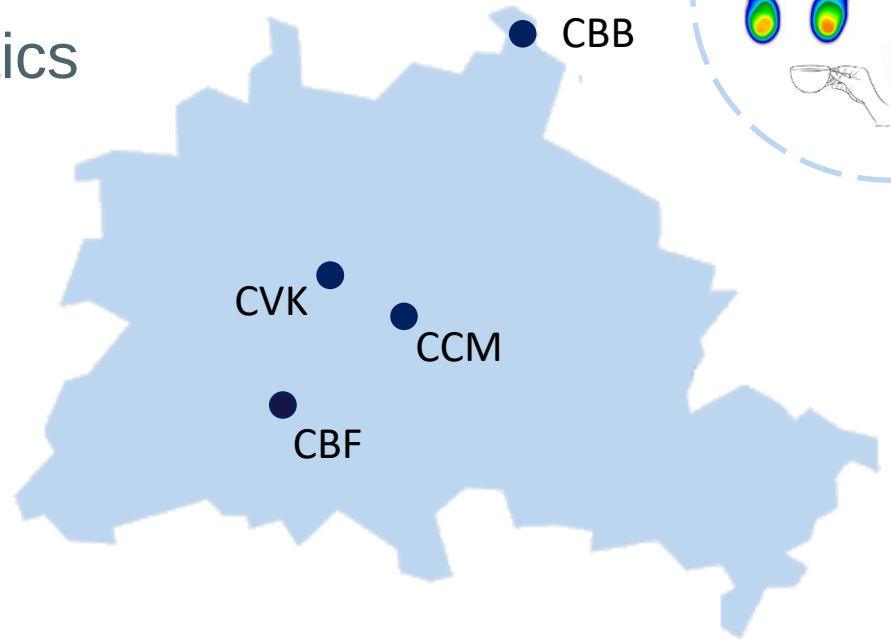
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Clinical Research Resources

Expertise, Space, Physicians, Nurses, Lab Staff, Equipment

- **The Charité Umbrella Trial, developing a central umbrella-consent registry at the Charité**
- Backbone and deep phenotyping
- Kinetics and kinematics
- Physical Status
- Activity profile
- Trial setup
- Recruitment
- Performance
- Follow-up

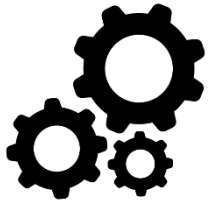


CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Data Services

- **Electronic data capture:** Harmonization and professionalization of both systems with common SOPs



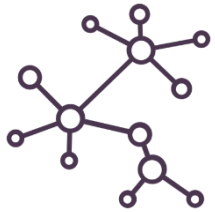
- **Data management**: Automation through standardization vis interfaces and coding to speedup processes

- **Biostatistics planning:** Close cooperation to iBikE with 3 statisticians under CSC payment as well as disciplinary leadership

Digital Innovation

- **Data science:** Machine learning pipeline as regular service for supervised prediction and unsupervised pattern detection within studies

- **Software solutions**: Establishment of electronic clinical trial management, monitoring, pharmacovigilance, document management and trial master file solutions



- **Interfaces:** Linking study data to the health data platform (HDP) and foreign data bases

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

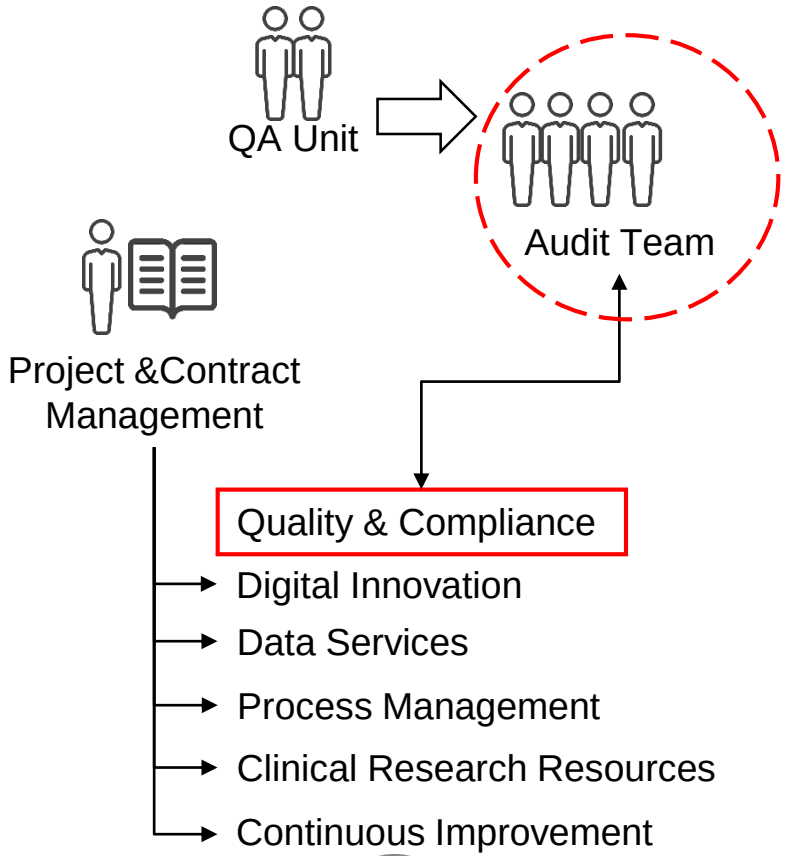
BIH Berlin Institute of Health Charité & MDC

Quality & Compliance and Continuous Improvement

Service driven compliance, QM and training structures:

- **Quality management**
- **Internal audit**

- Online education platform
- Regulatory affairs
- Monitoring
- Pharmacovigilance
- Training
- Information service



First Results

- Relocation of about thirty employees from four places (CVK, CBF, Reinickendorfer Str., Hessische Str.,) to the main CSC offices at CCM
- Unification and reorganization of all employees of CRU, KKS and CTMU in a new structure of five departments within a one-stop-shop model
- Initiation of a process to create new identity, services, cost models, procedures and SOPs with final certification
- Establishment of a quality and audit team to support studies to achieve inspection readiness
- Lead of Task Force Clinical Research Governance for drug and medical product studies to handle LAGeSo and BFARM requests
- Joint development of the quality guidelines and the central SOPs for clinical studies at the Charité together with the QA unit
- Establishment of an audit series to support all Charité initiated drug studies

First Results

- Creation of a pre final Research Governance Framework
- Accompanying the Vivantes cooperation process regarding clinical research
- Establishment of a series of strategic plans for industry cooperation's with meetings with IQVIA, Pfizer, Parexel etc.
- Continuous services for more than 200 ongoing studies
- Provision of a free eCRF service for more than 300 studies
- Established institutional cooperation's:
  - Cooperation with Institute of Pharmacology and Toxicology for preparation of annual safety reports (DSURs) as well as to obtain support for second assessments of SAEs
  - Cooperation with Institute of Biometry and Clinical Epidemiology for all biometry and clinical epidemiology aspects
  - Support of the Ethics Committee regarding advice and legal delimitation questions
- Establishment of a legal basis for provision of health-related Quality of Life in German speaking countries by the CSC

First Results

- Provision of health-related Quality of Life assessment tools & content to Academia and Industry (Switzerland, Austria, Germany)
- Strategic meetings with the BMG and *Stabstelle* VBHC to identify PRO software solutions for value-based health care in Germany
- Creation of a task force to coordinate the implementation of an umbrella consent at Charité
- Institutional collaboration meetings with the BCRT
- Creation of project fast-start-up managers
- Establishment of novel high-quality micro-RNA extraction from blood samples
- Clarification of BREXIT regulatory hurdles in clinical trials
- Signing an agreement between Charité and the State of Israel (Israel Innovation Authority)
  - 3 pilot trials
  - Full call together with other international partners (e.g. Mayo & Jefferson Clinic) in March

Research Governance Framework 1/2

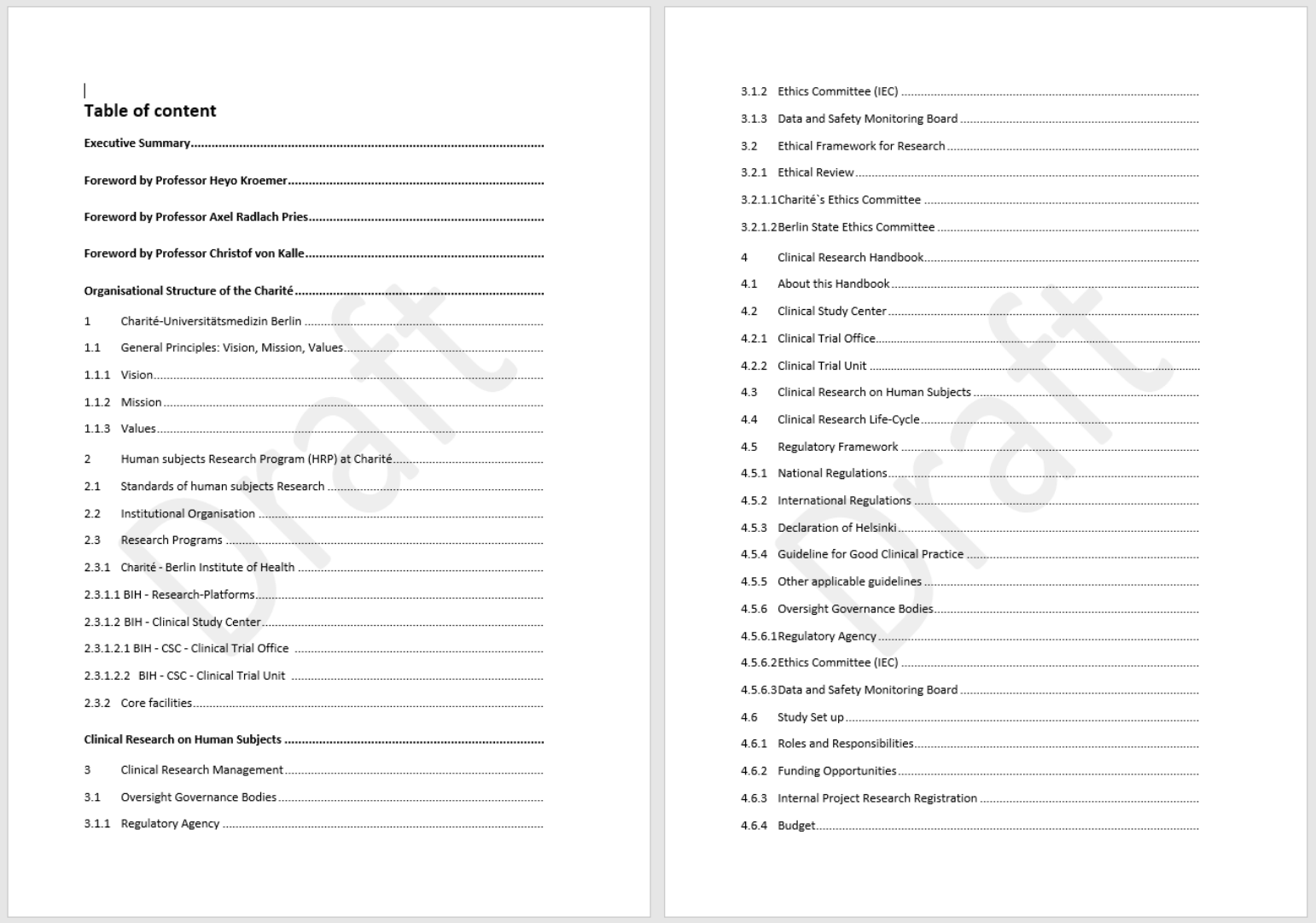


Table of content

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC

Translation Delivered...

...through understanding each individual patient‘s disease at the molecular level

1. ...in obstetrics/gynecology
   through high-throughput sequencing for non-invasive prenatal testing

2. ...in gene transfer and gene editing
   through pharmacokinetics and -dynamics of gene transfer and editing (integration site analysis, vector safety, clonal dynamics, VCN, on- and off-site gene editing, bioinformatics)

3. ...in cancer
   through molecular profiling based on whole-exome/genome and RNA sequencing in a multi-institutional clinical setting
   through centralized high-end molecular multiplex (NGS-based) diagnostics, regional networks, precision oncology and personalized therapies

Translation Delivered...

4. ...as a center
   through interdisciplinarity, identity and visibility, scientific and clinical excellence

5. ...in the digital age
   through smart analysis concepts and patient empowerment

6. ...as a society
   through targeting a Vision Zero

7. ...@ BIH/Charité
   through hard smart exciting work!

People

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Prof. Dr. Stefan Fröhling, Dr. Peter Horak, Dr. Simon Kreutzfeldt, Dr. Titus Brinker

dkfz.

Dr. Priya Chudasama, Dr. Raffaele Fronza

geneWERK

Dr. Manfred Schmidt, Dr. Annette Deichmann

Clinical Translational Research

vdek Die Ersatzkassen

Dr. Martın Kluxen

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN PARTNERSTANDORT DRESDEN UNIVERSITÄTS KREBSCENTRUM UCC

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Carl Gustav Carus Dresden
Medizinische Fakultät Carl Gustav Carus, TU Dresden
Helmholtz-Zentrum Dresden-Rossendorf

Prof. Dr. Hanno Glimm, Dr. Christoph Heining, Dr. Daniela Richter

USZ Universitäts Spital Zürich

Prof. Dr. Thorsten Zenz, Dr. Maja Zenz

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health Charité & MDC


Neuartige Therapien
für personalisierte
Behandlungen
Thank You

Translating Data into Health:

Clinical Translational Research in the Digital Age

Prof. Dr. med. Christof von Kalle
BIH Chair Clinical-Translational Research

Charité – University Medicine Berlin and
Berlin Institute of Health (BIH)

Charitéplatz 1, 10117 Berlin
+49 (0)30 450 525 053
christof.kalle@charite.de

www.charite.de
www.bihealth.org

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

BIH Berlin Institute of Health
Charité & MDC

Turning Research into Health