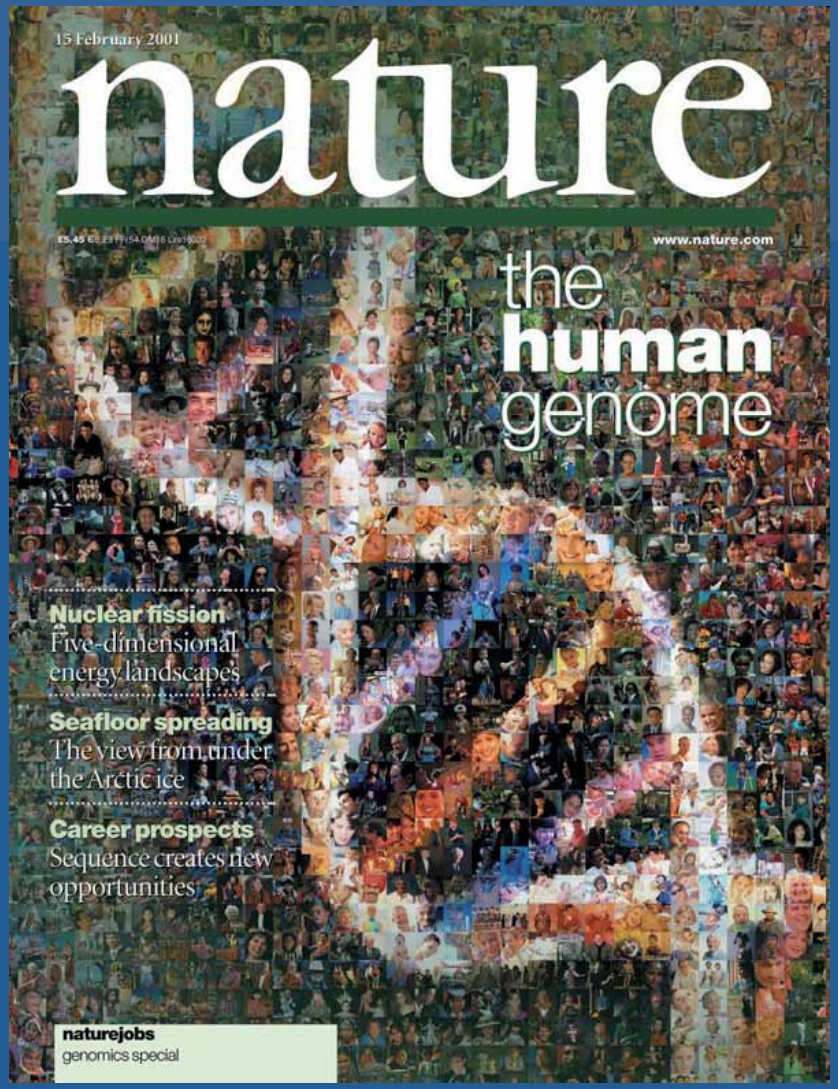
Hans Lehrach
Max Planck Institute für Molekulare Genetik, Berlin
Dahlem Zentrum für Genomforschung und medizinische Systembiologie
Alacris Theranostics Gmbh

2001: Eine ”Arbeitsversion" des menschlichen Genoms wurde im Juni 2000 fertiggestellt



Erste Analyse publiziert in 2001

2006: Technischer Fortschritt in der Sequenziertechnologie “short read” Sequenzen

Ein Lauf auf den neuen Sequenziermaschinen generiert ungefähr so viel Information wie eine Million Läufe auf den Maschinen, die wir vor etwas mehr als zehn Jahren verwendeten, um das erste menschliche Genom zu sequenzieren

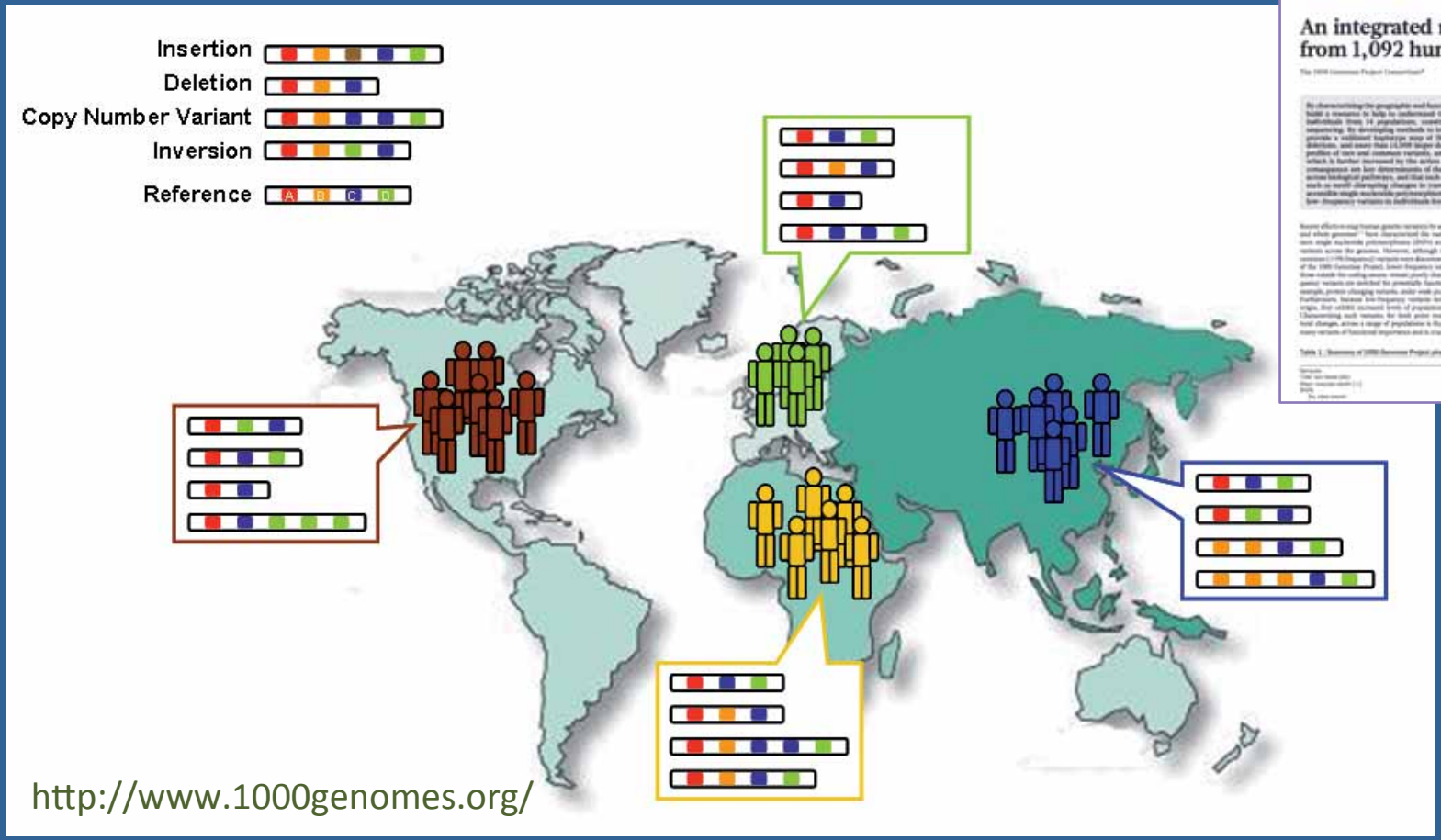
1 menschliches Genom/ 13 Jahre

1 menschliches Genom/ Tag

Internationales 1,000 Genomprojekt

Das Ziel: die genetische Variation zwischen Menschen zu vergleichen

Die DNA Sequenzen zweier Menschen sind sehr ähnlich- sie unterscheiden sich nur durch eine Base in 1000

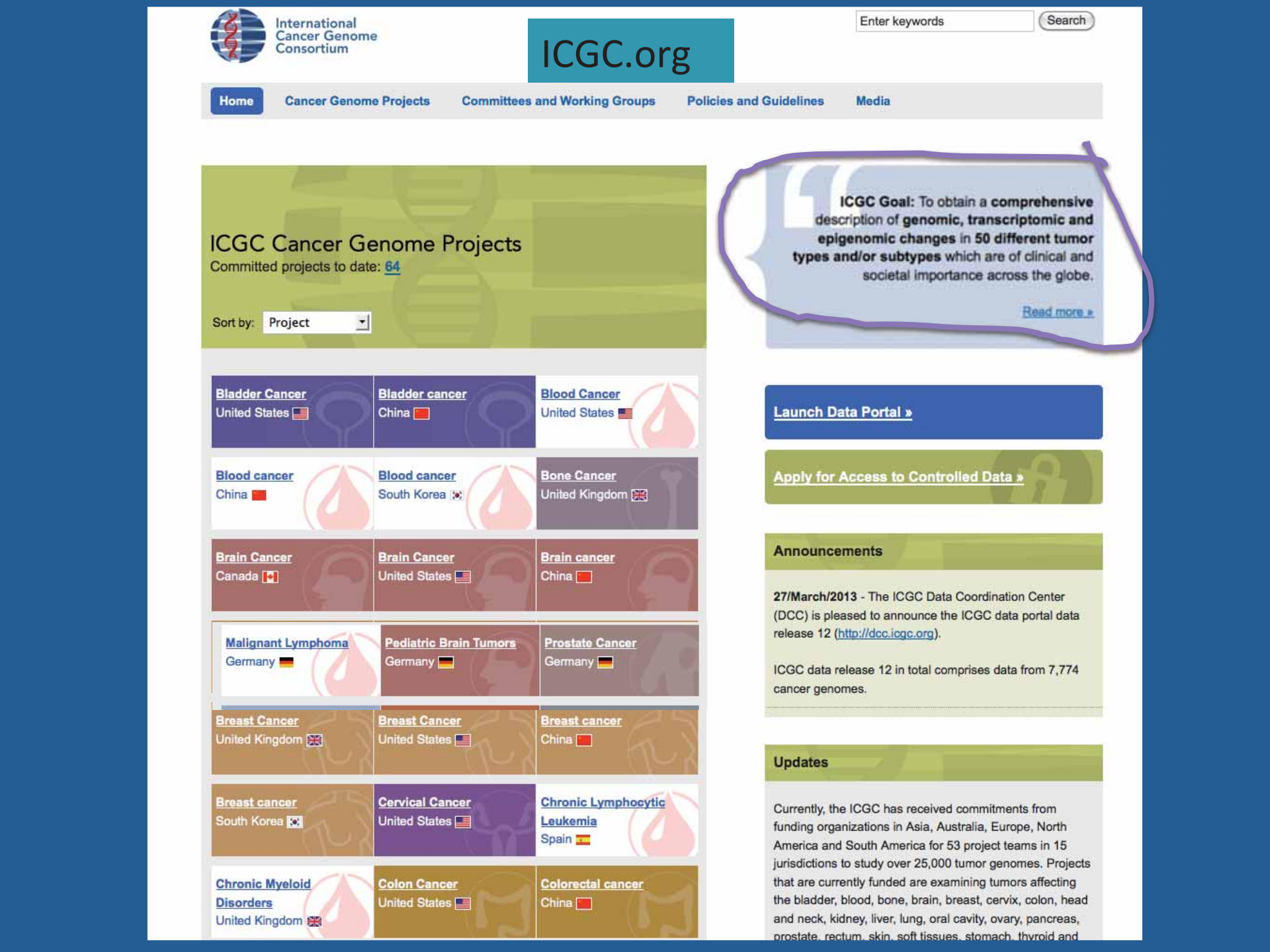


ARTICLE

An integrated map of genetic variation from 1,092 human genomes

2012

http://www.1000genomes.org/


International Cancer Genome Consortium
ICGC.org
Enter keywords
Search
Home
Cancer Genome Projects
Committees and Working Groups
Policies and Guidelines
Media
ICGC Cancer Genome Projects
Committed projects to date: 64
Sort by: Project
Bladder Cancer United States
Bladder cancer China
Blood Cancer United States
Blood cancer China
Blood cancer South Korea
Bone Cancer United Kingdom
Brain Cancer Canada
Brain Cancer United States
Brain cancer China
Malignant Lymphoma Germany
Pediatric Brain Tumors Germany
Prostate Cancer Germany
Breast Cancer United Kingdom
Breast Cancer United States
Breast cancer China
Breast cancer South Korea
Cervical Cancer United States
Chronic Lymphocytic Leukemia Spain
Chronic Myeloid Disorders United Kingdom
Colon Cancer United States
Colorectal cancer China
ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.
Read more »
Launch Data Portal »
Apply for Access to Controlled Data »
Announcements
27/March/2013 - The ICGC Data Coordination Center (DCC) is pleased to announce the ICGC data portal data release 12 (http://dcc.icgc.org).
ICGC data release 12 in total comprises data from 7,774 cancer genomes.
Updates
Currently, the ICGC has received commitments from funding organizations in Asia, Australia, Europe, North America and South America for 53 project teams in 15 jurisdictions to study over 25,000 tumor genomes. Projects that are currently funded are examining tumors affecting the bladder, blood, bone, brain, breast, cervix, colon, head and neck, kidney, liver, lung, oral cavity, ovary, pancreas, prostate, rectum, skin, soft tissues, stomach, thyroid and

Personal Genome Projekt

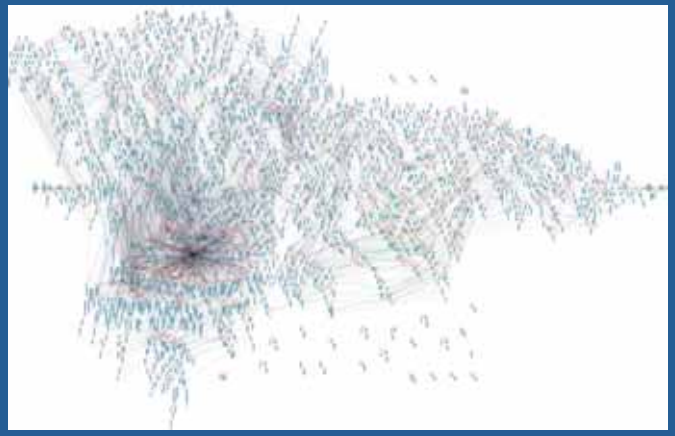
- George Church von der Harvard Medical School plant, das Genom von 100,000 Freiwilligen zu sequenzieren.
- Zusammen mit der persönlichen und medizinischen Information wird das die Kenntnisse über die genetischen Grundlagen menschlicher Krankheiten und Eigenschaftenvergrößern

http://www.personalgenomes.org/

Medizin sollte jeden Patienten individuell optimal behandeln

Surgery: individual
Millions of data points
Direct consequences

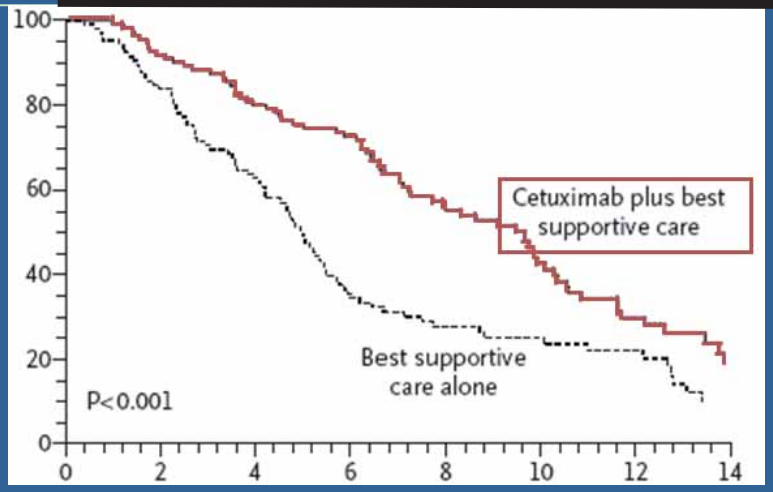
Drug therapy: at best stratified
One or few Biomarkers Prediction based on statistics



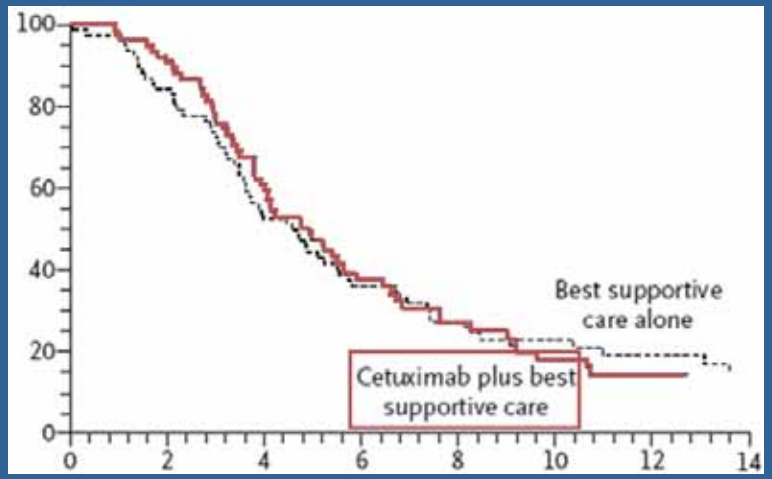
Krebs
ein kritisches Problem für die individualisierte Medizin

- Die Heilungsraten für viele Krebsformen sind nur wenig verändert
- Viele Patienten sprechen nicht auf die Therapie, die sie bekommen, an

Anti-tumor Medikamente wirken oft nur bei einem (kleinen) Teil der Patienten



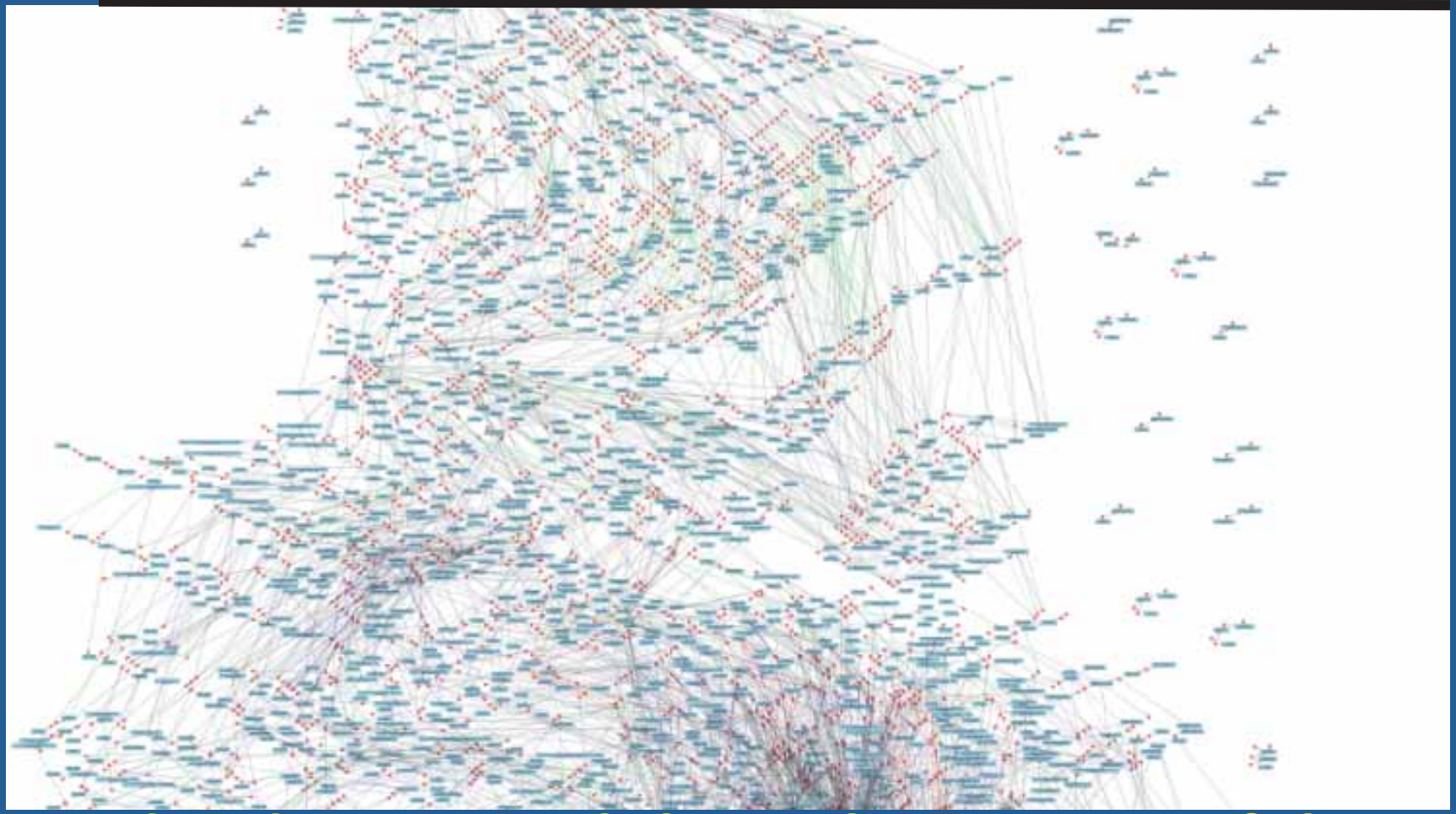
Many colon cancer patients with tumors with K-ras wild type will respond positively to treatment with EGFR receptor antagonists e.g. Cetuximab



Patients with tumors with K-ras mutations do not: a 30000 Euro treatment will show no effect on the tumor but will cause significant side effects on the patient

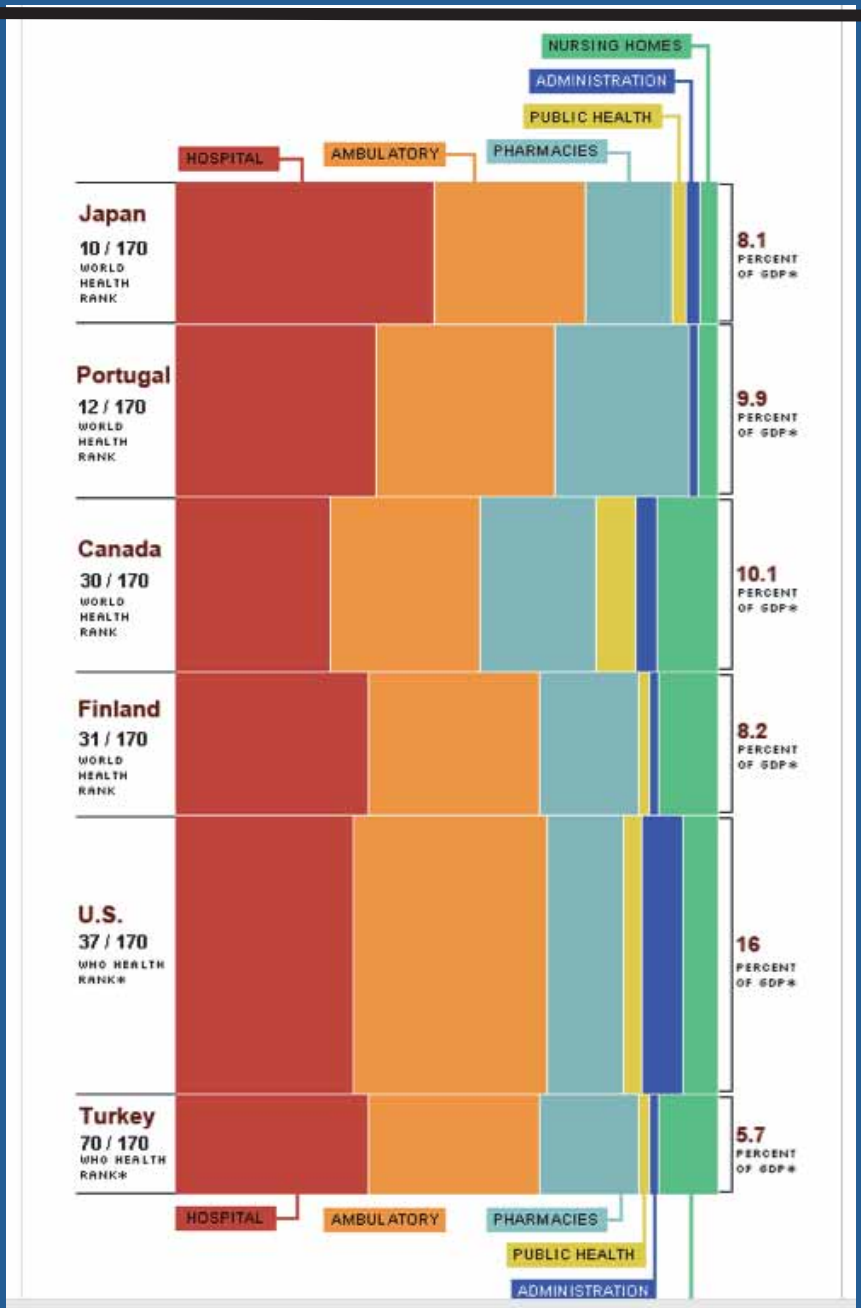
Zalcberg et al., NEJM 2008

Medizin ist komplex (selbst die Prozesse in einer einzelnen Zelle sind komplex)



Und jeder Mensch besteht aus ungefähr 100 Billionen interagierenden Zellen

teuer



ALACRiS Theranostics GmbH

www.alacris.de

… und gefährlich

Medical Errors - Third Leading Cause of Death in the US in 2000

The report apparently showed there were

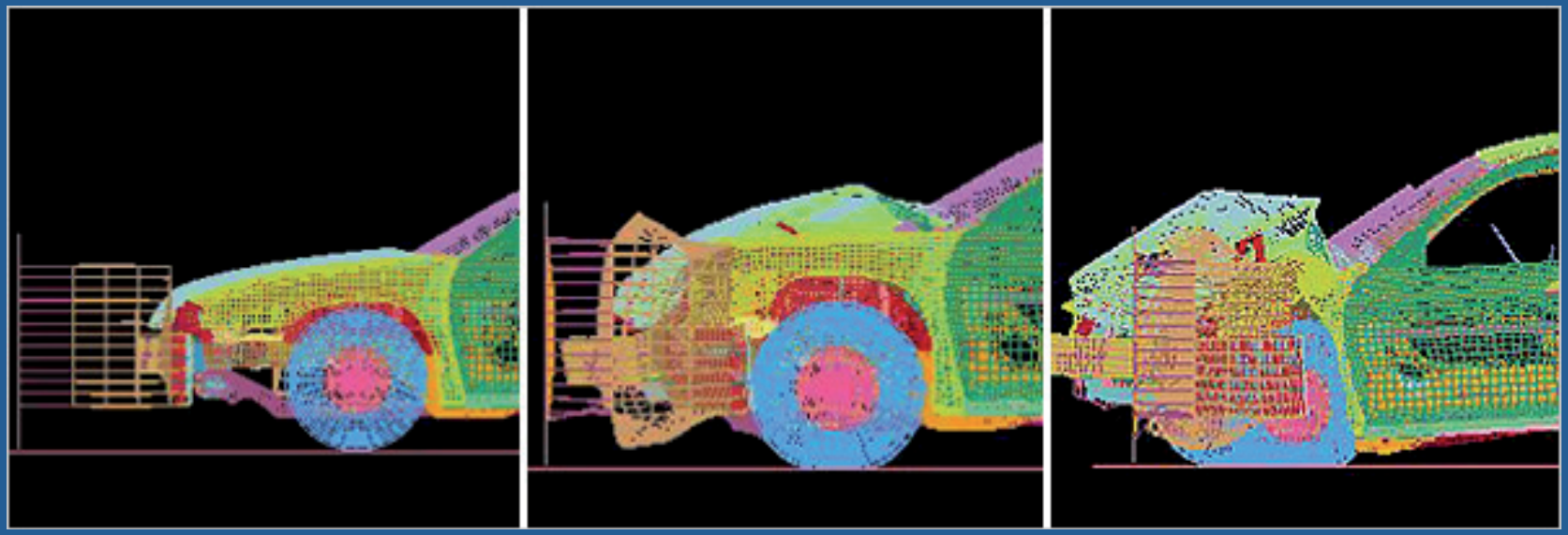
- **2,000 deaths/year from unnecessary surgery;**
- **7000 deaths/year from medication errors in hospitals;**
- **20,000 deaths/year from other errors in hospitals;**
- **80,000 deaths/year from infections in hospitals;**
- **106,000 deaths/year from non-error, adverse effects of medications.**
- **225,000 (total) deaths per year in the US**

=> drug reactions were the most common cause !

Barbara Starfield - JAMA Vol 284, No 4, July 26th 2000

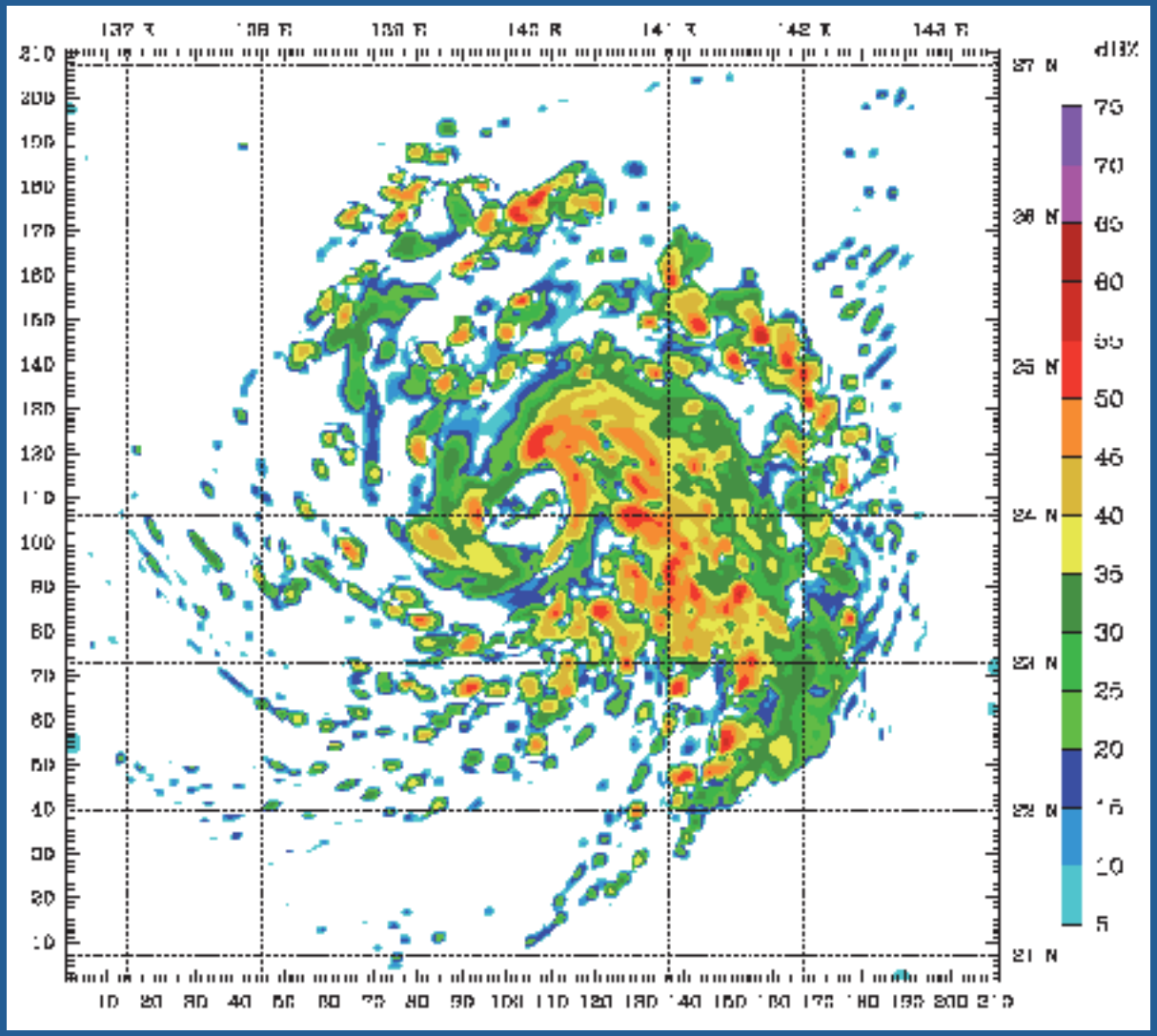
Wenn wir sonst komplexe, teure und/ oder gefährliche Probleme zu lösen haben, sammeln wir möglichst viele Daten, und modellieren das Problem (und mögliche Lösungsmöglichkeiten) im Computer, um die im Einzelfall optimale Problemlösung zu identifizieren

Wir verwenden Computermodelle, um neue Autos zu entwickeln



- automobile crash tests entirely by computer simulation.
- These days >> at least 3 to 5 million equations.
- Computer simulations to be safer than actual prototype car crash tests, because actual crash tests cannot simulate every possible situation. Robert Lange, General Motors executive director for vehicle structure and safety integration
- (from : Car crash tests and Computer Simulations, Michael Pines,
- htt://seriousaccidents.com/blog/car-technology-accident-blog/car-crash-tests-and-computer-simulation/)

Bei der Wettervorhersage



Typhoon Mawar 2005

WRF: The weather research forecasting model

Und in der Pilotenausbildung

Während wir in der Medizin noch immer ausschliesslich statistische Korrelationen verwenden, ähnlich dem Stand der Wettervorhersage vor 150 Jahren

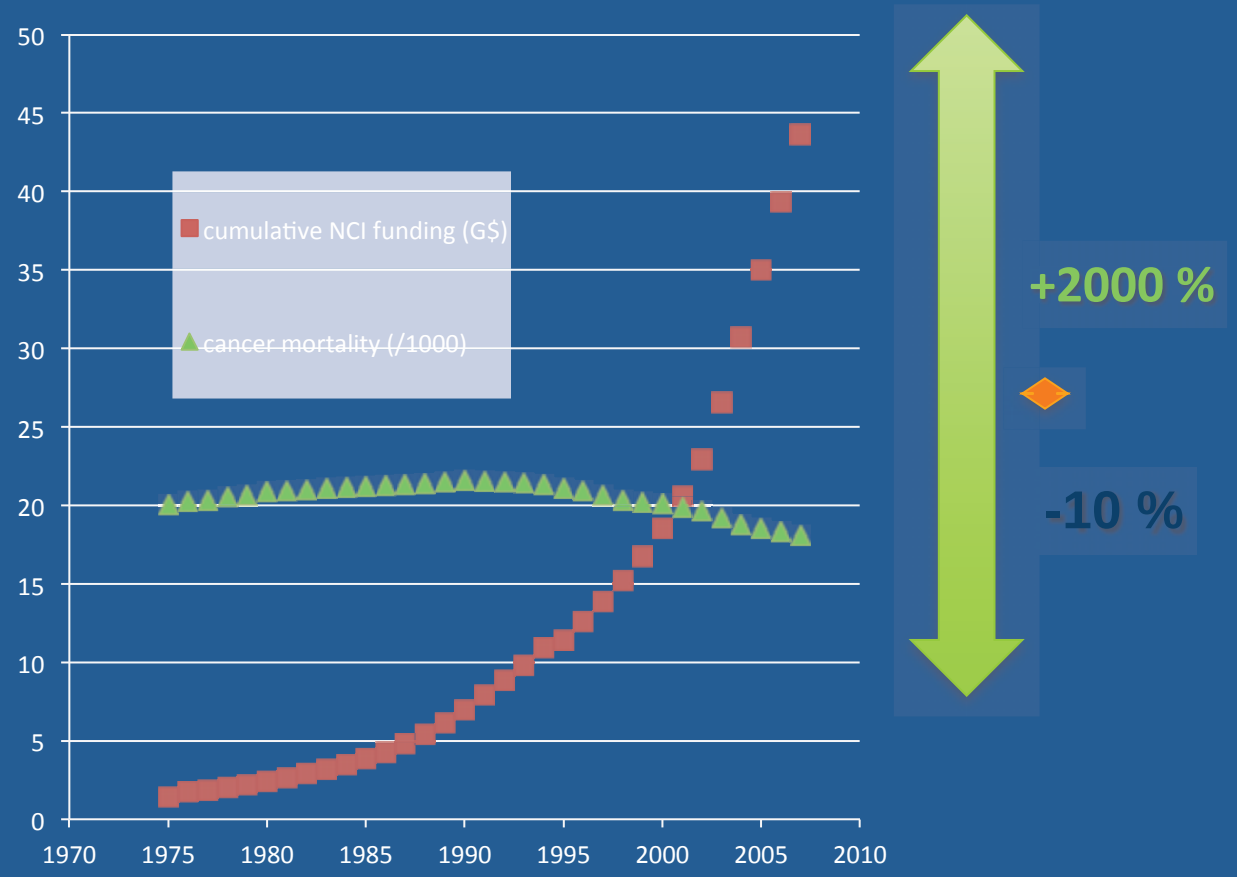
Though barometers were increasingly in circulation since 1670, it wasn't until about 1860 that a famous English sea captain, Admiral Fitzroy, former Captain of Darwin's exploration ship "the Beagle", provided a detailed weather forecasting script that he attached to his several barometer inventions. Fitzroy is credited with the beginning of the first published weather forecasting in the world and detailing the meaning behind the rise and fall of air pressure.

Als die Verfahren, die wir jetzt in der Medizin verwenden, in der ‚cutting edge' Wettervorhersage verwendet wurden, war DAS die Karte von Berlin

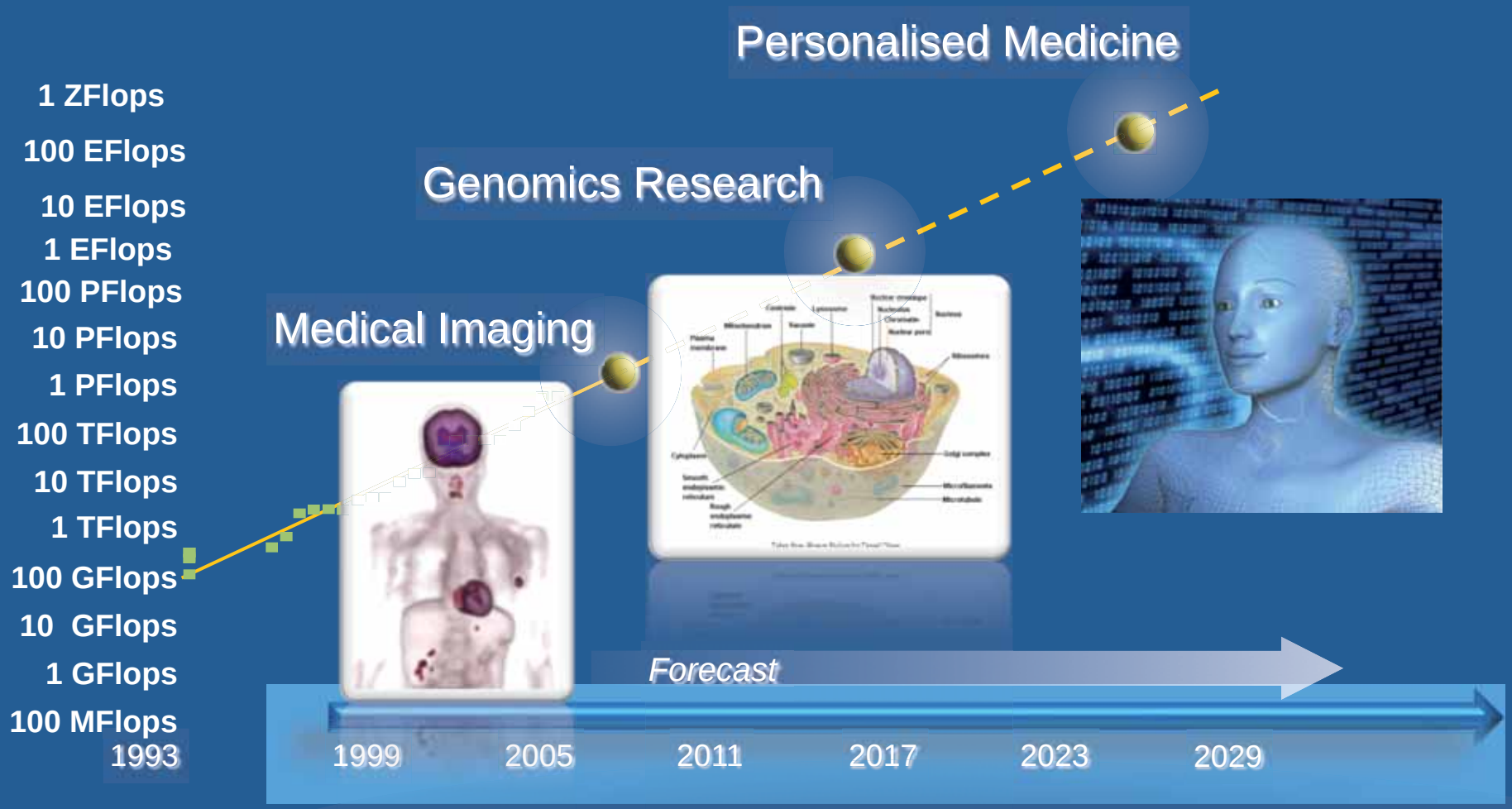
Berlin Karte Stahlstich 1860

Wir wissen viel über die grundlegenden Mechanismen der Zellen

(sollten wir auch, nach Billionenausgaben allein für die Krebsforschung in den letztebn 40 Jahren)



Wir haben die Rechenkapazitäten

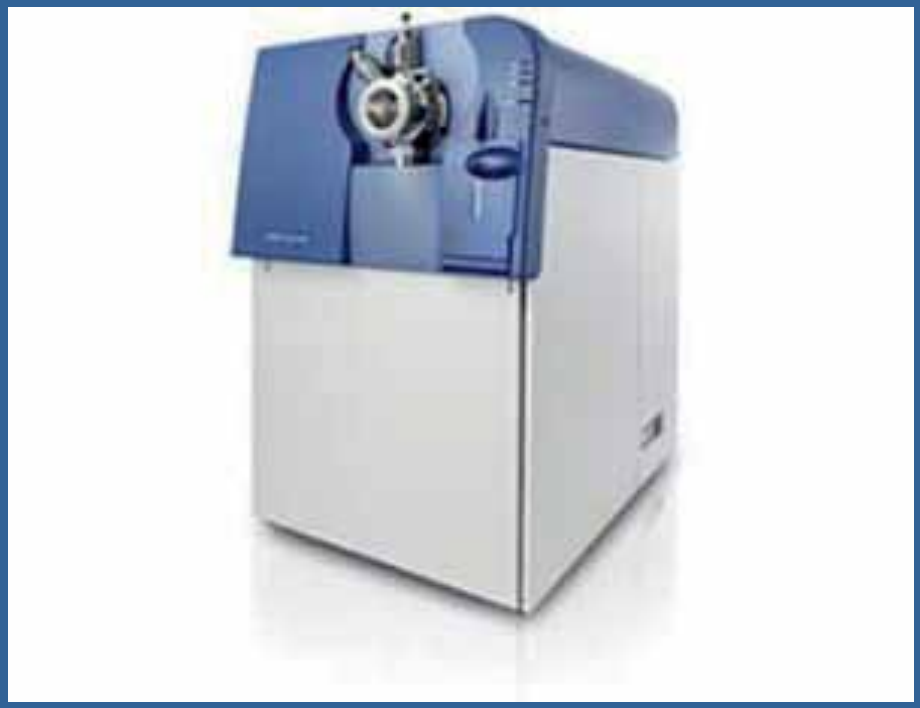


PetaFlop systems of today are the client and handheld systems 10 years later

Source: www.top500.org

Was hat gefehlt?

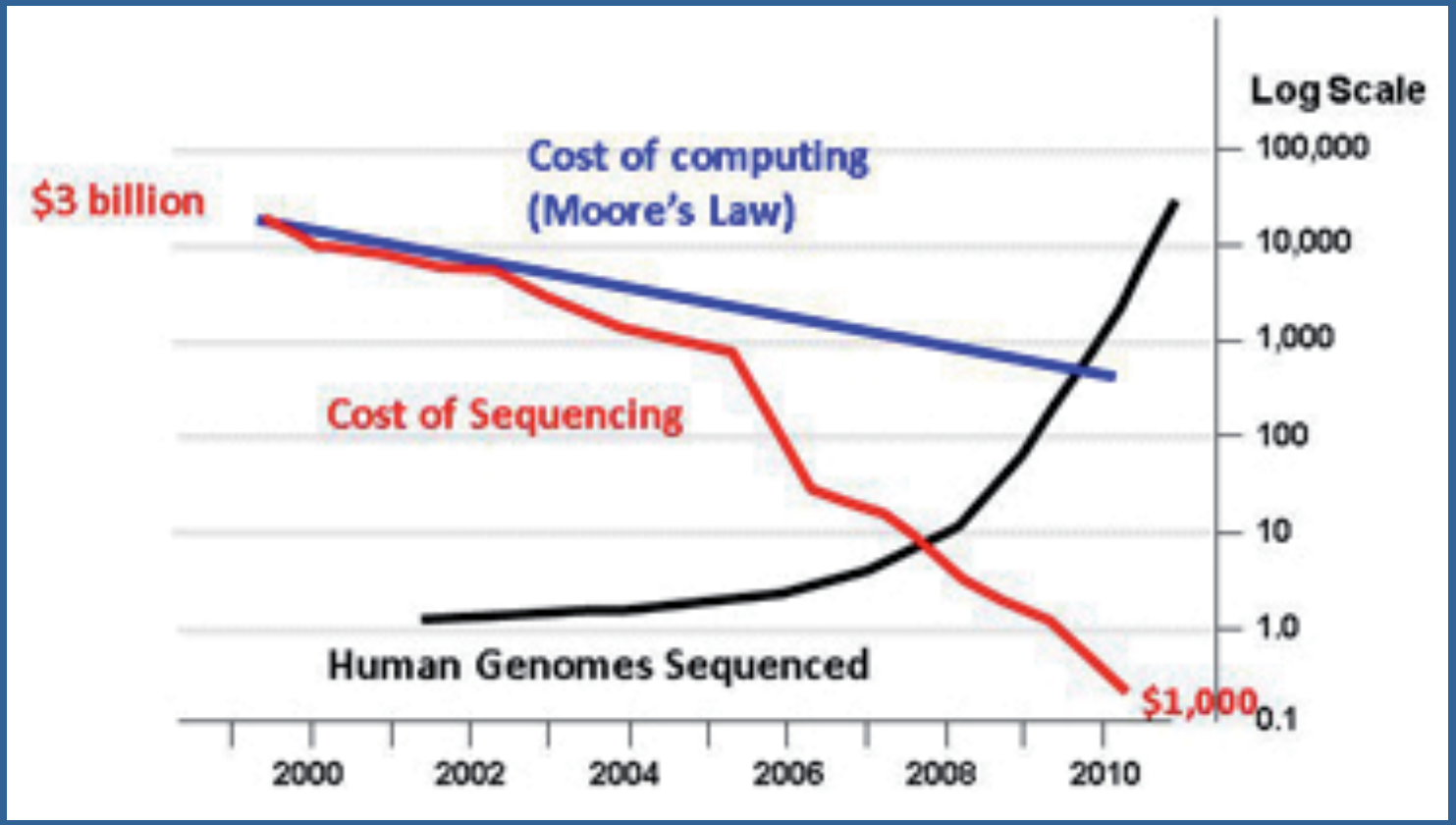
(Illumina Hiseq etc)



(Sciex 5600 etc)

(ohne Millionen von Datenpunkten würde man auch keine vernünftige Wettervorhersage durch Wettermodelle bekommen)

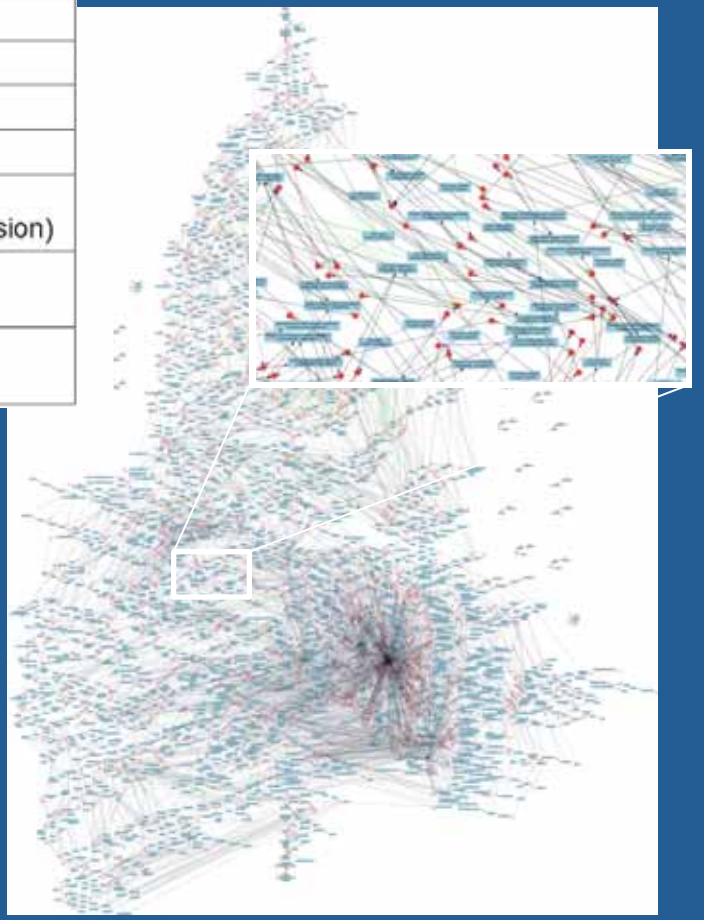
Die Sequenziertechnologie entwickelt sich weit rascher als die Rechenleistung



Das Modellierungssystem

Hanahan&Weinberg, 2011

Network components	
Reactions	4439
Kinetic parameters	4853
Components	2839
Genes	572
Mutated genes	64 (5 LoF, 58 GoF, 1 fusion)
External activators (growth factors, hormones etc.)	87
Inhibitors	56 (41 drugs)



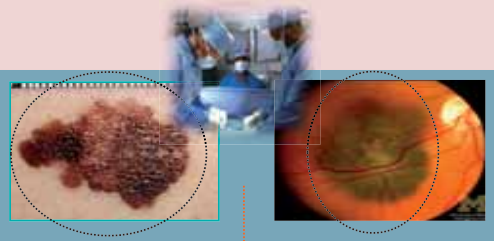
Over 40 different signaling pathways are integrated:

Cytokine signaling (e.g. CSF, IFNA, IL8), Death receptor signaling (e.g. Fas, TNFa, TRAIL), DNA repair / cell cycle, Ephrin signaling, GCPR/ Hormone signaling (e.g. Glucagon, Insulin, Testosterone), Hedgehog signaling, Notch signaling, several RTK signaling (e.g. bNGF, EGF, FGF, IGF, PDGF, VEGF), TGFb signaling (e.g. BMP, TGFb) and Wnt signaling.

Treat20 –
Projekt zur Analyse des metastatischen Melanoms

Bundesministerium für Bildung und Forschung

Series of metastatic melanomas of various origins:
(cutaneous, acral, mucosal, uveal)



Cutaneous melanoma
- ~ 11.5 cases / 100,000

Uveal melanoma
Rare: 6 cases / million

Cancer specimens from CCCC - Berlin (Charité Comprehensive Cancer Center)

MPIMG Berlin

Next Generation Sequencing

Transcriptome & Genome Alterations

Proteome

Tumor Modeling

Cell culture

Charité-Universitätsmedizin

Validations

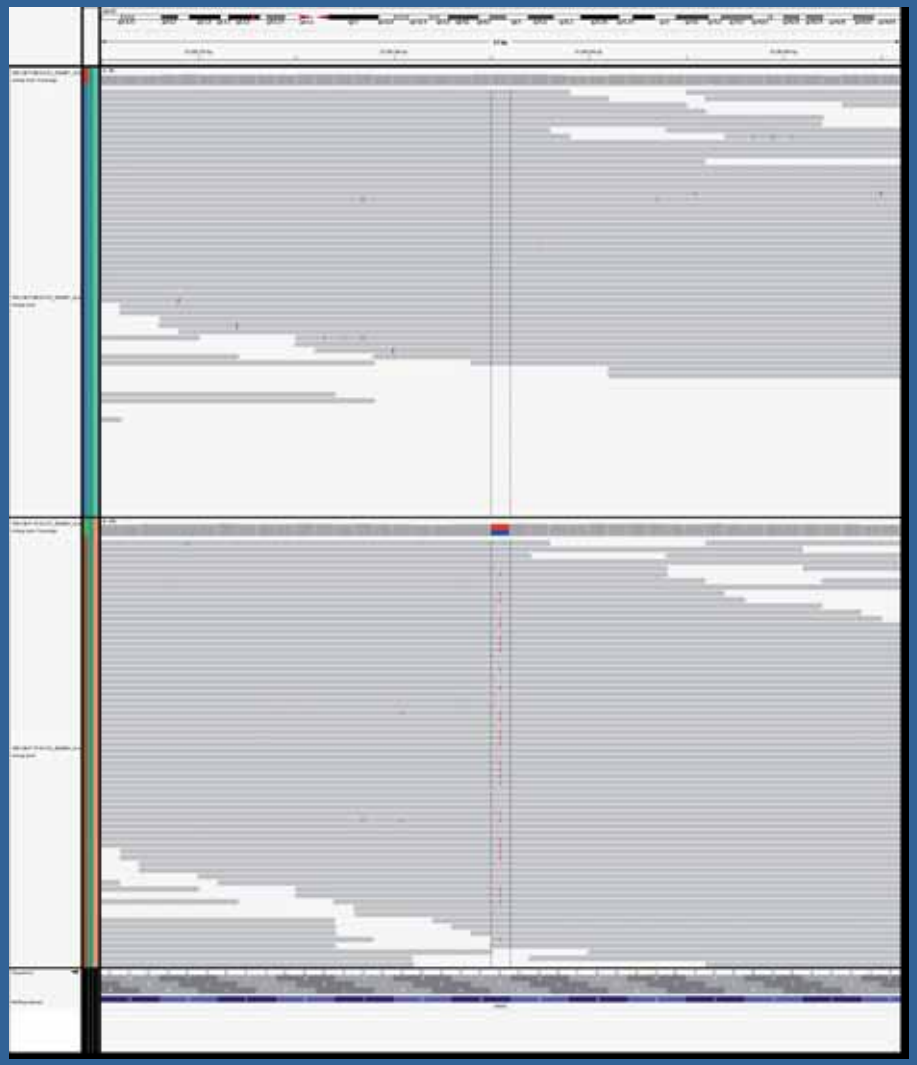
Xenografts

Experimental Pharmacology Oncology GmbH

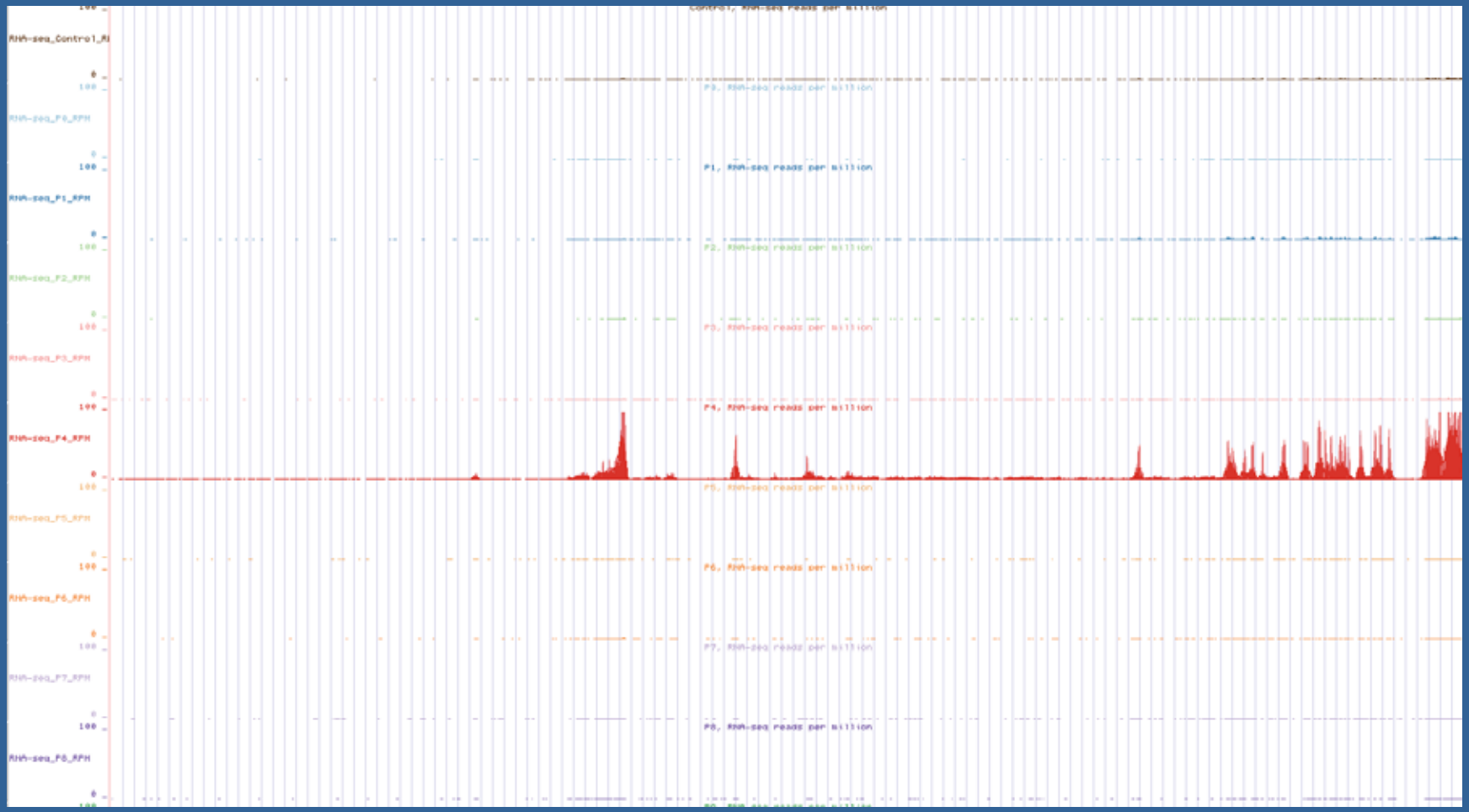
Drug optimization

Treatment

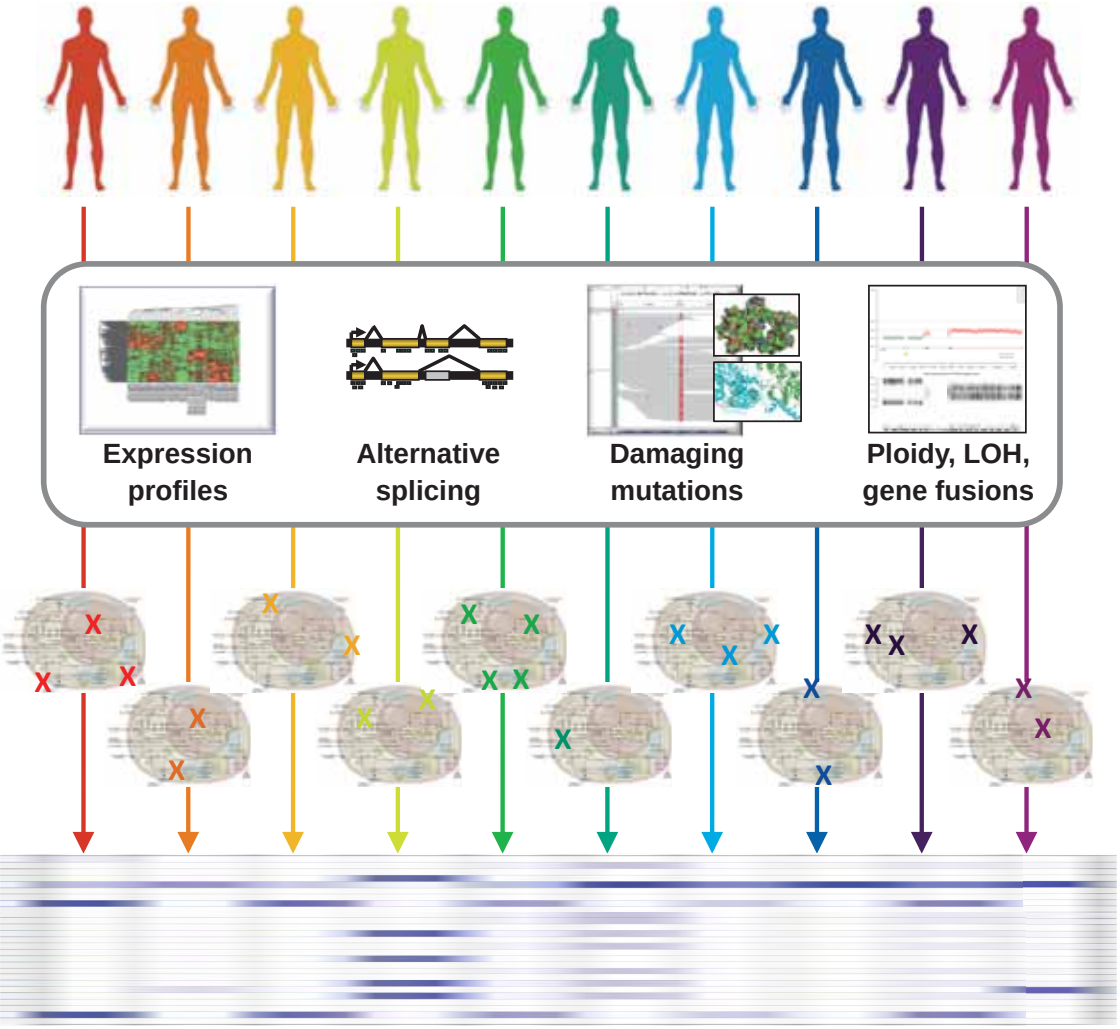
Beispiel Mutation



Abnormale Genexpression



From patient specific –omics data to patient specific drug response prediction



Patients tumors and controls

High-throughput NGS data

- 20,120 genes monitored for each patient by RNA-seq
- Mutations and gene fusions monitored for each patient by exome sequencing and WGS
- 3D protein modeling of damaging mutations

Patient-specific cancer models

(currently 2,982 components, steadily updated with new genes, new mutations, new gene fusions, new reactions and new drugs)

–> activated oncogenes (e.g. RTKs, MYC)

–> inactivated tumor supressors (e.g. p53, CDKN2A)

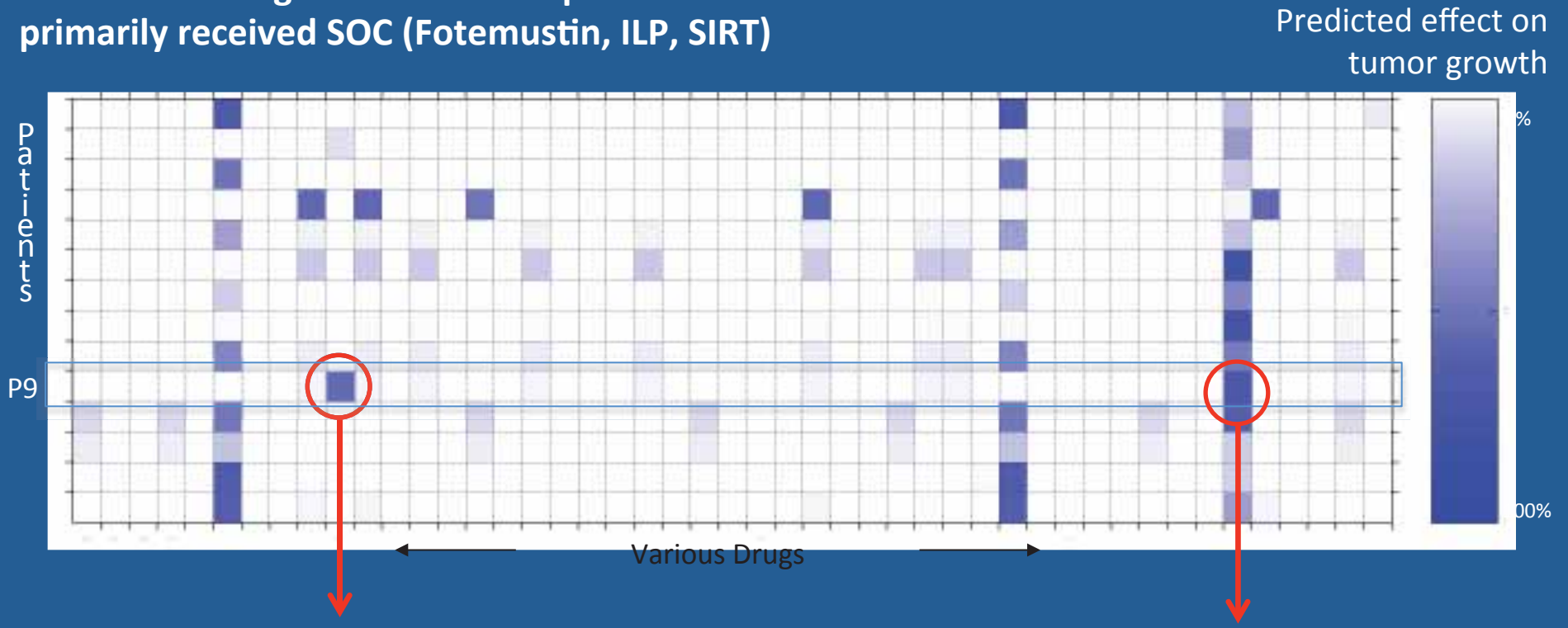
–> altered components of metabolic or signaling pathways

Patient-specific drug responses

–> treatment options

Klinische Validierung

metastatic malignant melanoma patients
primarily received SOC (Fotemustin, ILP, SIRT)

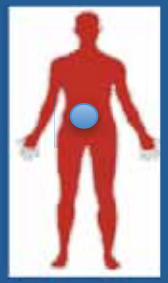


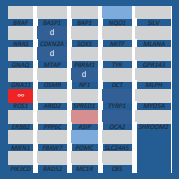
Drug used to treat rheumatoid arthritis has been used for cancer patient treatment: patient is stable since 4/2012!!!

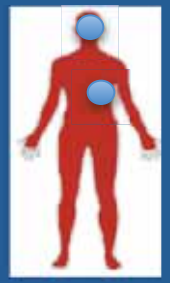
Prediction of effective but non-approved drug

Anpassung der Therapie nach einem Rückfall

Deep analysis of relapse after treatment

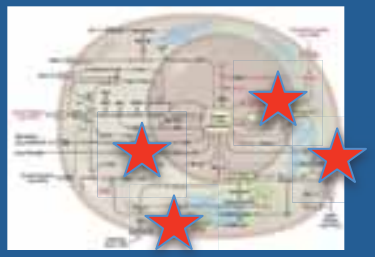






Analysis new metastasis

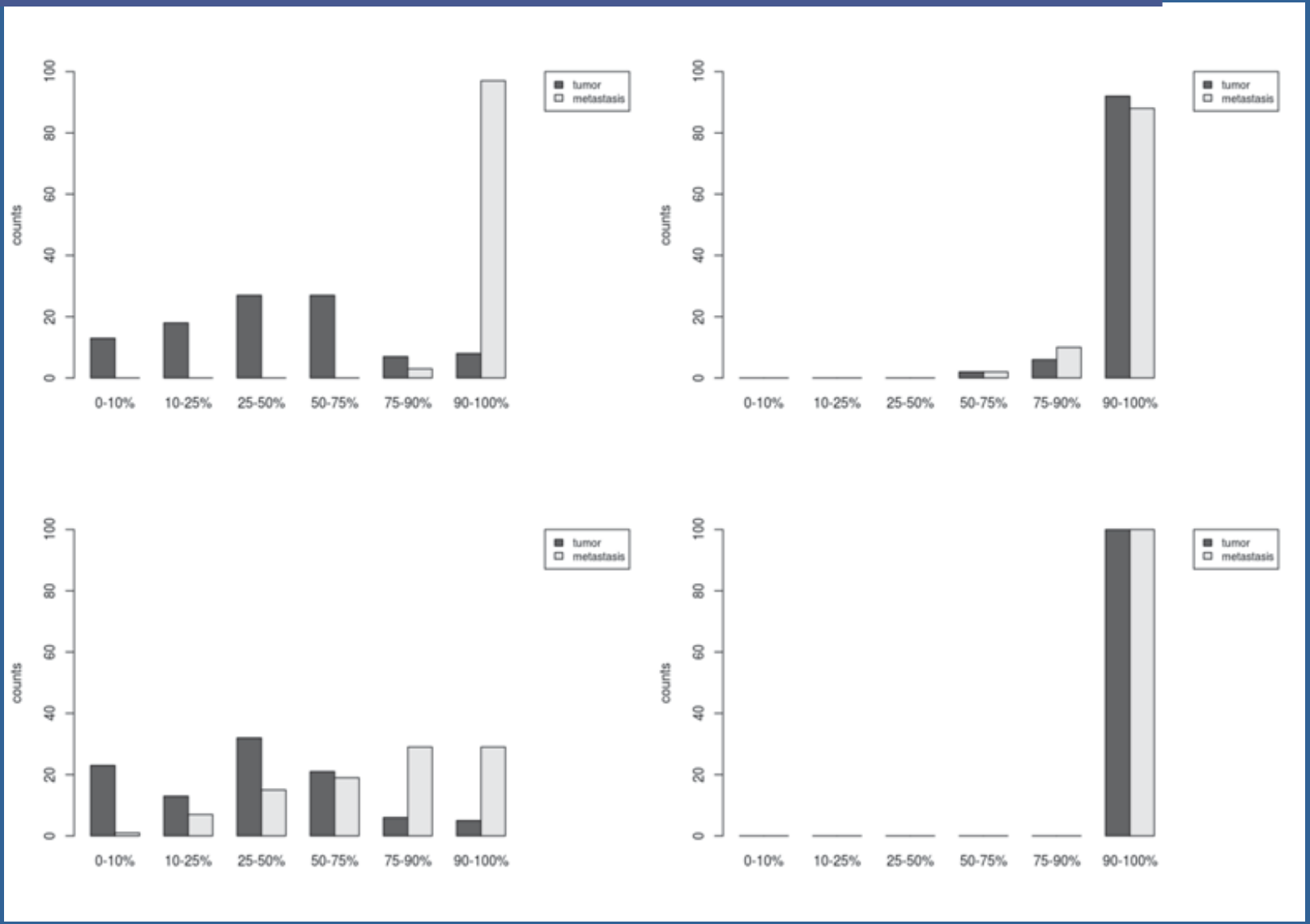
Induction of new events
Tumor evolved



POSTN metastatic

SGK3 kinase
Tumor growth

Korrekte Voraussage :
Sensitive Lebermetastase/insensitive Brustmetastase



Proof of concept project for (pre-)clinical application

primary tumor, metastasis, normal tissue from 60 patients are characterised

- RNASeq
- whole genome
- Exome
- methylome
- mouse xenograft
- CTC, cancer cell lines
- serum free DNA

Systems Biology Modelling of Colon Cancer and Biomarker Discovery

Members

Pharmaceutical Industry
AstraZeneca
Bayer Pharma
Boehringer-Ingelheim
Eli Lilly
Janssen Pharmaceutica
Merck
Pfizer
Roche

Academia & Clinics
MPI Molecular Genetics
Uppsala University
Universite Paris-Sud
Charite Berlin
Medical Univers. of Graz
Technical Univers. Dresden
Vall d'Hebron Inst. Oncology, Barcelona

SME´s

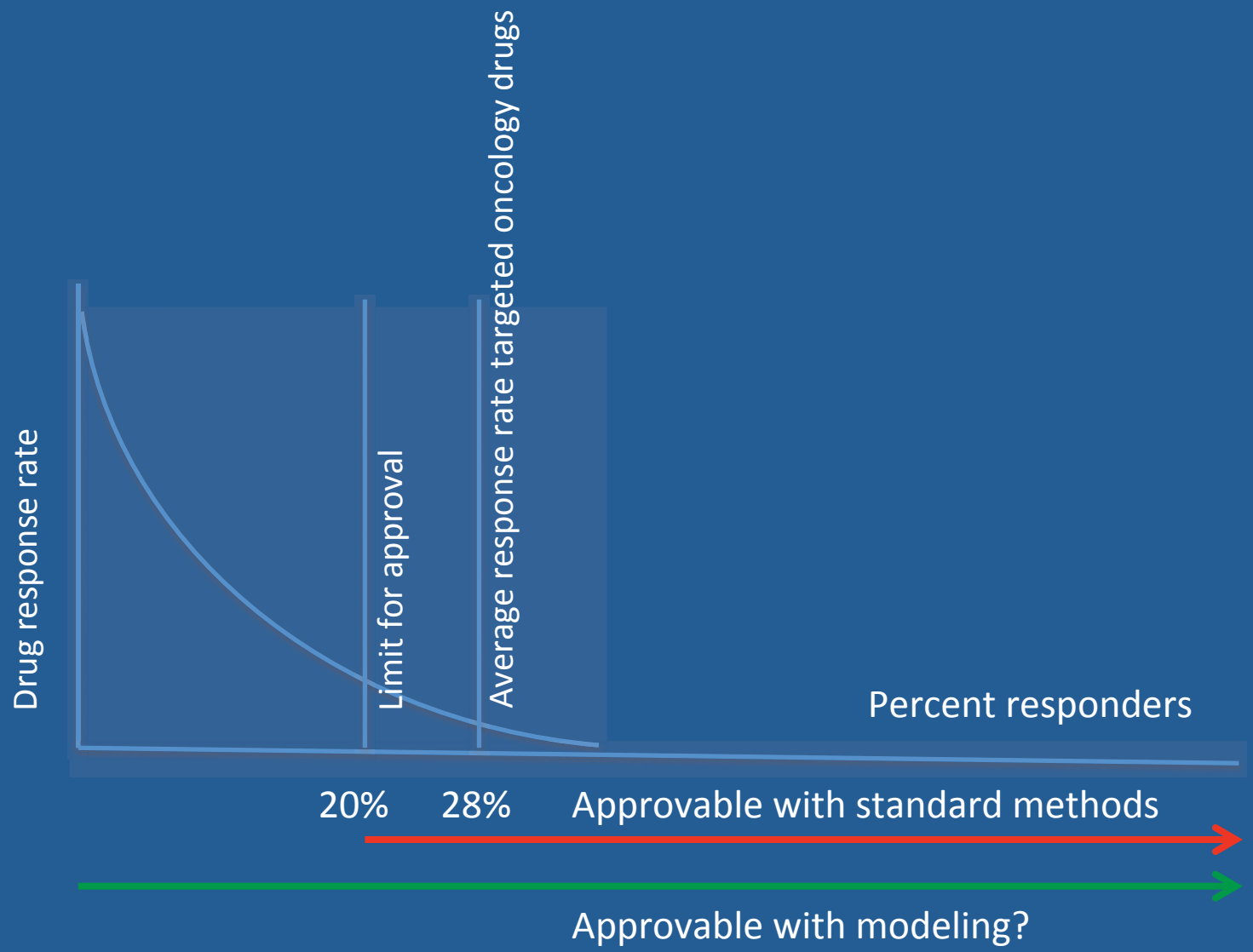
Alacris Theranostics GmbH
Experim. Pharmakologie & Onkologie Berlin
International Prevention Research Institute
GABO:mi

Research Spending per New Drug

Company	Number of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca	5	$11,791	$58,955
GlaxoSmithKline	10	$8,171	$81,708
Sanofi	8	$7,909	$63,274
Roche Holding AG	11	$7,804	$85,841
Pfizer Inc.	14	$7,727	$108,178
Johnson & Johnson	15	$5,886	$88,285
Eli Lilly & Co.	11	$4,577	$50,347
Abbott Laboratories	8	$4,496	$35,970
Merck & Co Inc	16	$4,210	$67,360
Bristol-Myers Squibb Co.	11	$4,152	$45,675
Novartis AG	21	$3,983	$83,646
Amgen Inc.	9	$3,692	$33,229

10? Facher Anstieg der Medikamente in der Onkologie

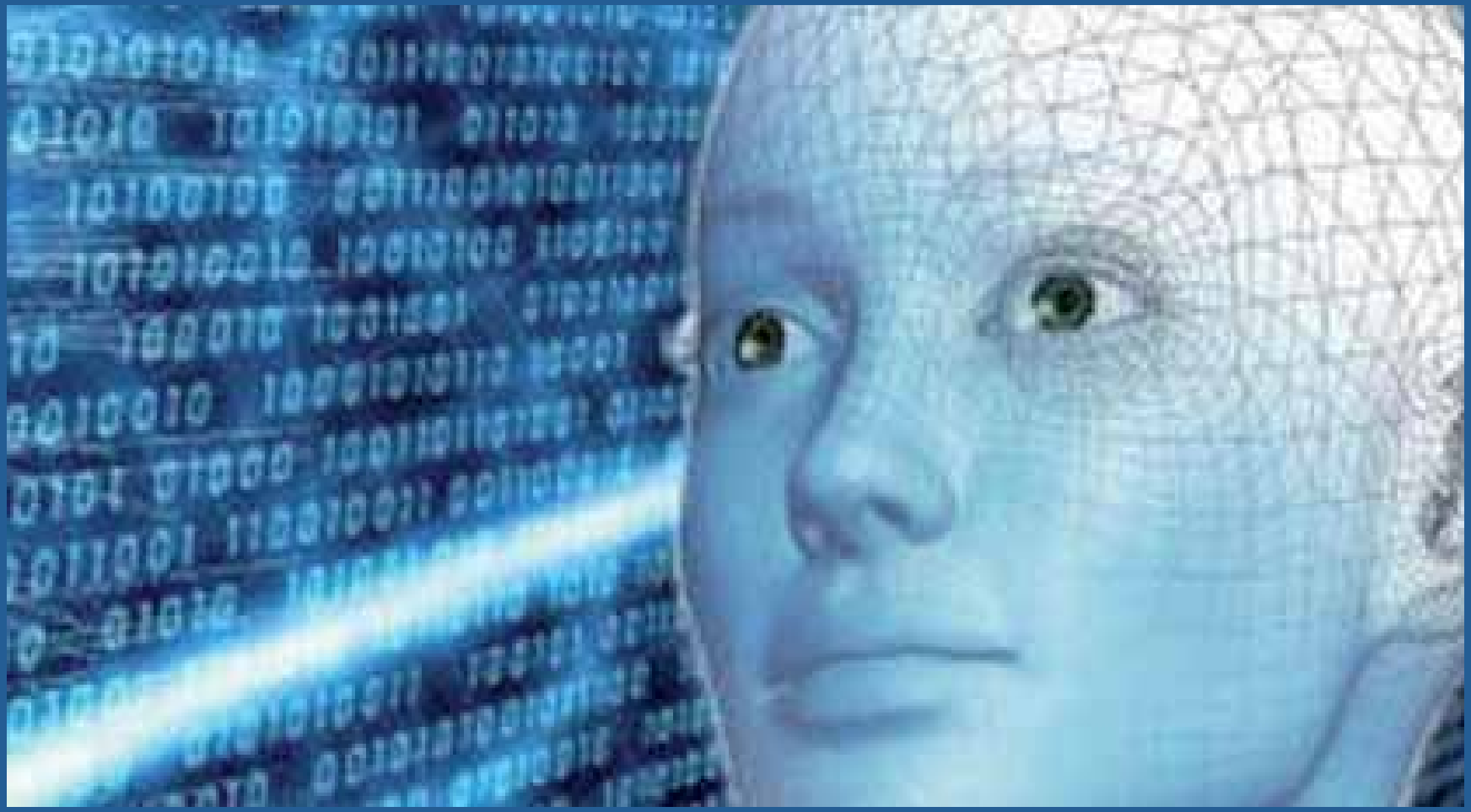
- Response rate



Ziele einer Virtualisierung der Medikamentenentwicklung

- Ten fold increase in drugs to market/reduction in risk per drug
- Ten to hundred fold decrease in the size of clinical trials (10x fold responders, 10x statistical power?)
- Ten to hundred fold decrease in costs per drug with similar market potential (molecular definition instead of disease area)
- 2/3 decrease in development times (car industry): doubling of patent protected sales period?

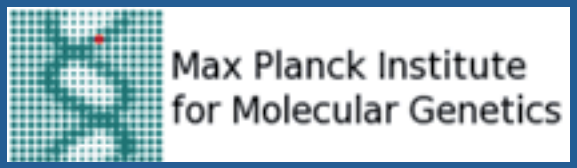
Der virtuelle Patient



„Computermodelle des individuellen Patienten helfen dem Arzt, die optimale Therapie für jeden einzelnen Patienten zu identifizieren
und ermöglichen der pharmazeutische Industrie, weit mehr neue Medikamente in einem Bruchteil der Zeit und zu einem Bruchteil der Kosten zu entwickeln

- **Revolutionen können genau so leicht in Dahlem wie in Silicon Valley beginnen**
- **(aber es scheint VIEL leichter, sie in Silicon Valley, Shanghai etc finanziert zu bekommen)**

Acknowledgements-



Dr. Marie-Laure Yaspo
Dr. Christoph Wierling

www.molgen.mpg.de

Dr. Bodo Lange
D. Alexander Kühn

www.alacris.de

Prof. Dr. Peter Schlag
Prof. Dr. Ulrich Keilholz
Prof Dr. Reinhold Schäfer

www.charite.de

www.itfom.eu