Hasso Plattner Institut
Digital Engineering · Universität Potsdam

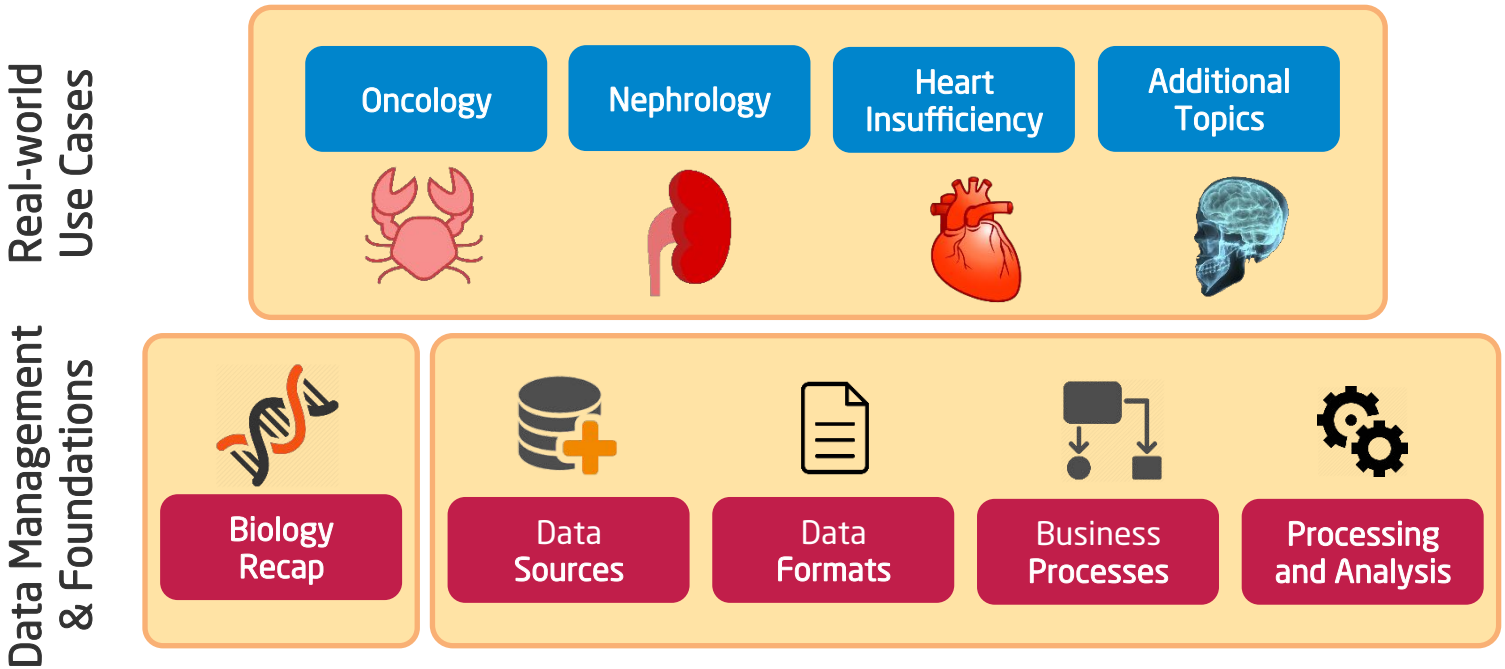
Use Case Oncology

Dr. Matthieu-P. Schapranow

Data Management for Digital Health

Summer 2017

Agenda


Real-world Use Cases
Oncology
Nephrology
Heart Insufficiency
Additional Topics
Data Management & Foundations
Biology Recap
Data Sources
Data Formats
Business Processes
Processing and Analysis

Agenda

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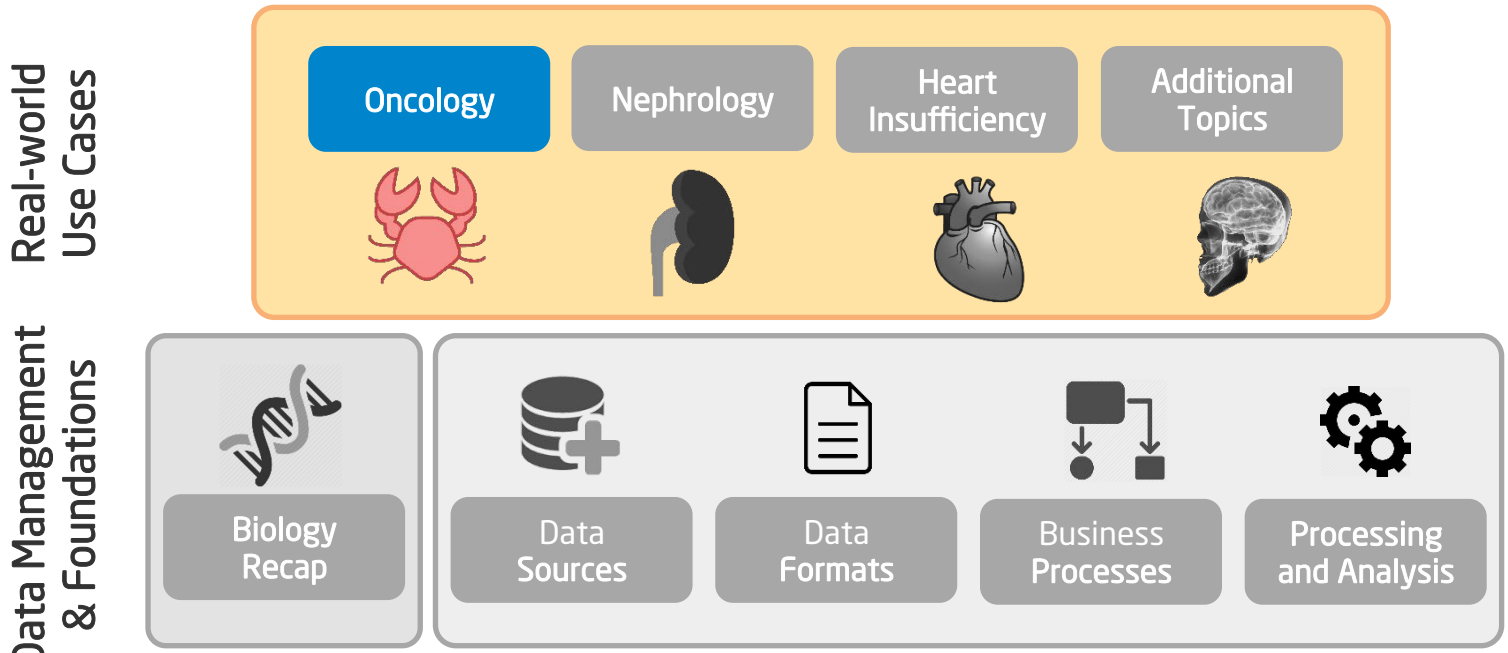

Use Case: Precision Oncology
Identification of Best Treatment Option for Cancer Patient

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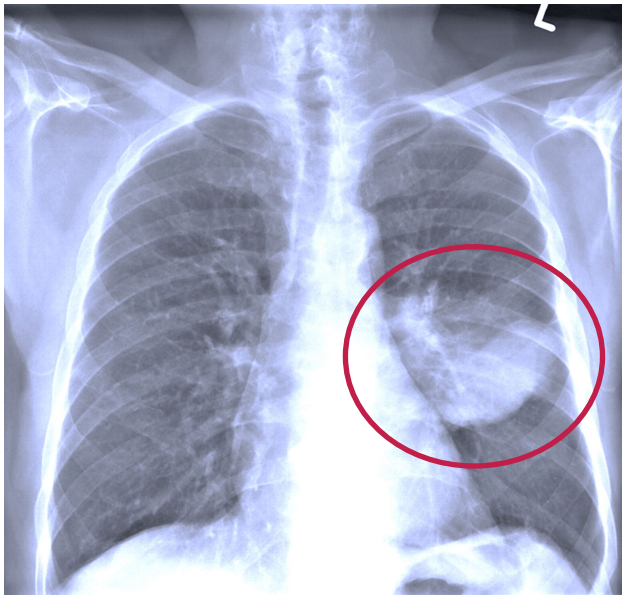
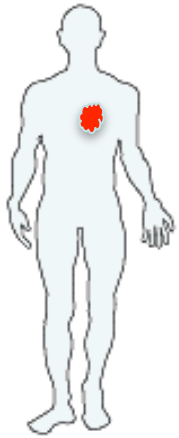
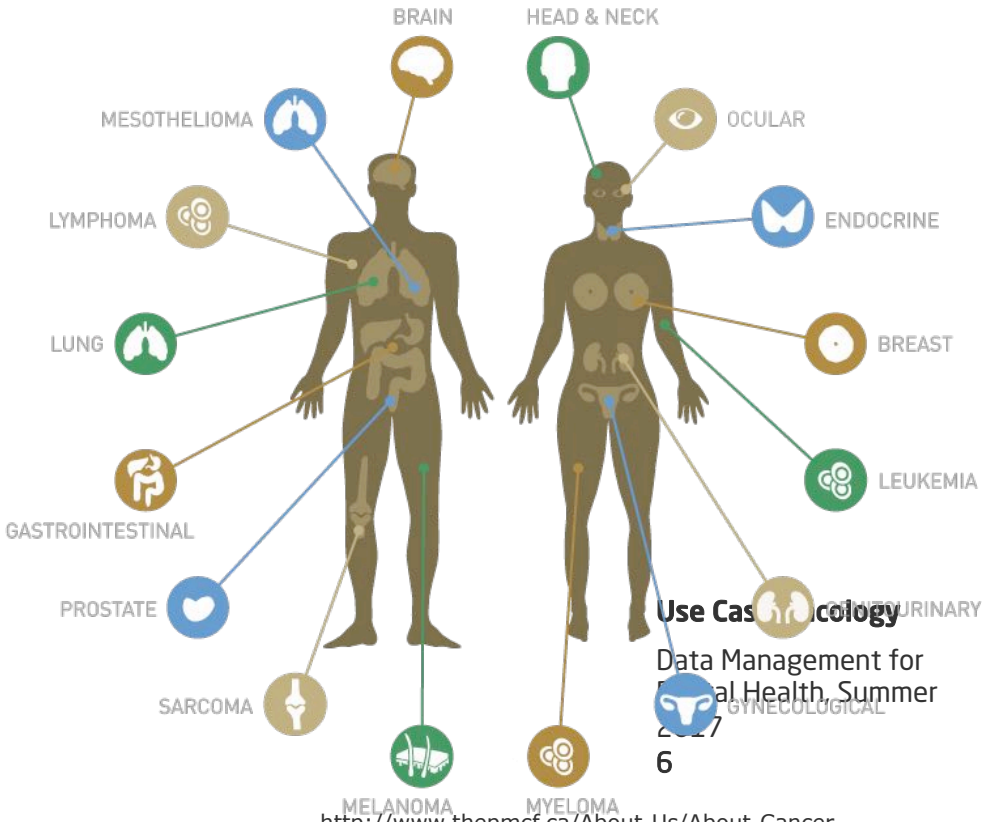
- Patient: Jane, 48 years, female, non-smoker, smoke-free environment
- Diagnosis: Non-Small Cell Lung Cancer (NSCLC), stage IV
- Markers: KRAS, EGFR, BRAF, NRAS, (ERBB2)





Types of Cancer?

- State-of-the-art classification takes only location of cancer into account
- Cancer is named after location of its first observation
- However, pathologic and genetic classification are adapted more and more



http://www.thepmcf.ca/About-Us/About-Cancer

Table 6. Probability (%) of Developing Invasive Cancer during Selected Age Intervals by Sex, US, 2011-2013*

		Birth to 49	50 to 59	60 to 69	70 and older	Birth to death
All sites†	Male	3.4 (1 in 30)	6.3 (1 in 16)	14.0 (1 in 7)	33.3 (1 in 3)	40.8 (1 in 2)
	Female	5.4 (1 in 18)	6.0 (1 in 17)	10.0 (1 in 10)	25.9 (1 in 4)	37.5 (1 in 3)
Breast	Female	1.9 (1 in 52)	2.3 (1 in 44)	3.5 (1 in 29)	6.8 (1 in 15)	12.4 (1 in 8)
Colon & rectum	Male	0.3 (1 in 294)	0.7 (1 in 149)	1.2 (1 in 84)	3.5 (1 in 28)	4.6 (1 in 22)
	Female	0.3 (1 in 318)	0.5 (1 in 198)	0.8 (1 in 120)	3.2 (1 in 31)	4.2 (1 in 24)
Kidney & renal pelvis	Male	0.2 (1 in 457)	0.3 (1 in 289)	0.6 (1 in 157)	1.3 (1 in 75)	2.1 (1 in 48)
	Female	0.1 (1 in 729)	0.2 (1 in 582)	0.3 (1 in 315)	0.7 (1 in 135)	1.2 (1 in 83)
Leukemia	Male	0.2 (1 in 410)	0.2 (1 in 574)	0.6 (1 in 259)	1.4 (1 in 72)	1.8 (1 in 57)
	Female	0.2 (1 in 509)	0.1 (1 in 901)	0.4 (1 in 447)	0.9 (1 in 113)	1.2 (1 in 81)
Lung & bronchus	Male	0.2 (1 in 643)	0.7 (1 in 149)	1.9 (1 in 53)	6.2 (1 in 16)	7.0 (1 in 14)
	Female	0.2 (1 in 598)	0.6 (1 in 178)	1.5 (1 in 68)	4.8 (1 in 21)	6.0 (1 in 17)
Melanoma of the skin‡	Male	0.5 (1 in 220)	0.5 (1 in 198)	0.9 (1 in 111)	2.5 (1 in 40)	3.5 (1 in 28)
	Female	0.6 (1 in 155)	0.4 (1 in 273)	0.5 (1 in 212)	1.0 (1 in 97)	2.3 (1 in 44)
Non-Hodgkin lymphoma	Male	0.3 (1 in 385)	0.3 (1 in 353)	0.4 (1 in 175)	1.8 (1 in 55)	2.4 (1 in 42)
	Female	0.2 (1 in 547)	0.2 (1 in 483)	0.2 (1 in 245)	1.3 (1 in 74)	1.9 (1 in 54)
Prostate	Male	0.3 (1 in 354)	1.9 (1 in 52)	5.4 (1 in 19)	9.1 (1 in 11)	12.9 (1 in 8)
Thyroid	Male	0.2 (1 in 533)	0.1 (1 in 799)	0.2 (1 in 620)	0.2 (1 in 429)	0.6 (1 in 163)
	Female	0.8 (1 in 127)	0.4 (1 in 275)	0.3 (1 in 292)	0.4 (1 in 258)	1.8 (1 in 57)
Uterine cervix	Female	0.3 (1 in 371)	0.1 (1 in 868)	0.1 (1 in 899)	0.2 (1 in 594)	0.6 (1 in 161)
Uterine corpus	Female	0.3 (1 in 352)	0.6 (1 in 169)	1.0 (1 in 105)	1.3 (1 in 76)	2.8 (1 in 36)

*For those who are free of cancer at the beginning of each age interval. †All sites excludes basal and squamous cell skin cancers and in situ cancers except urinary bladder. ‡Statistic is for non-hispanic whites.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.4. Statistical Research and Applications Branch, National Cancer Institute, 2016. srab.cancer.gov/devcan.

Please note: The probability of developing cancer for additional sites, as well as the probability of cancer death, can be found in Supplemental Data at cancer.org/research/cancerfactsstatistics/index.

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Cancer Facts USA

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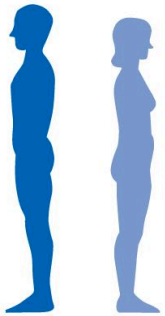
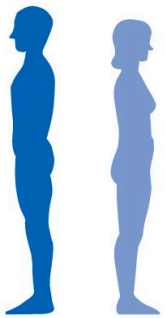
Estimated New Cases

Male			Female		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All sites	**836,150**	**100%**	**All sites**	**852,630**	**100%**



Estimated Deaths

Male			Female		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All sites	**318,420**	**100%**	**All sites**	**282,500**	**100%**



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Cancer Facts EU

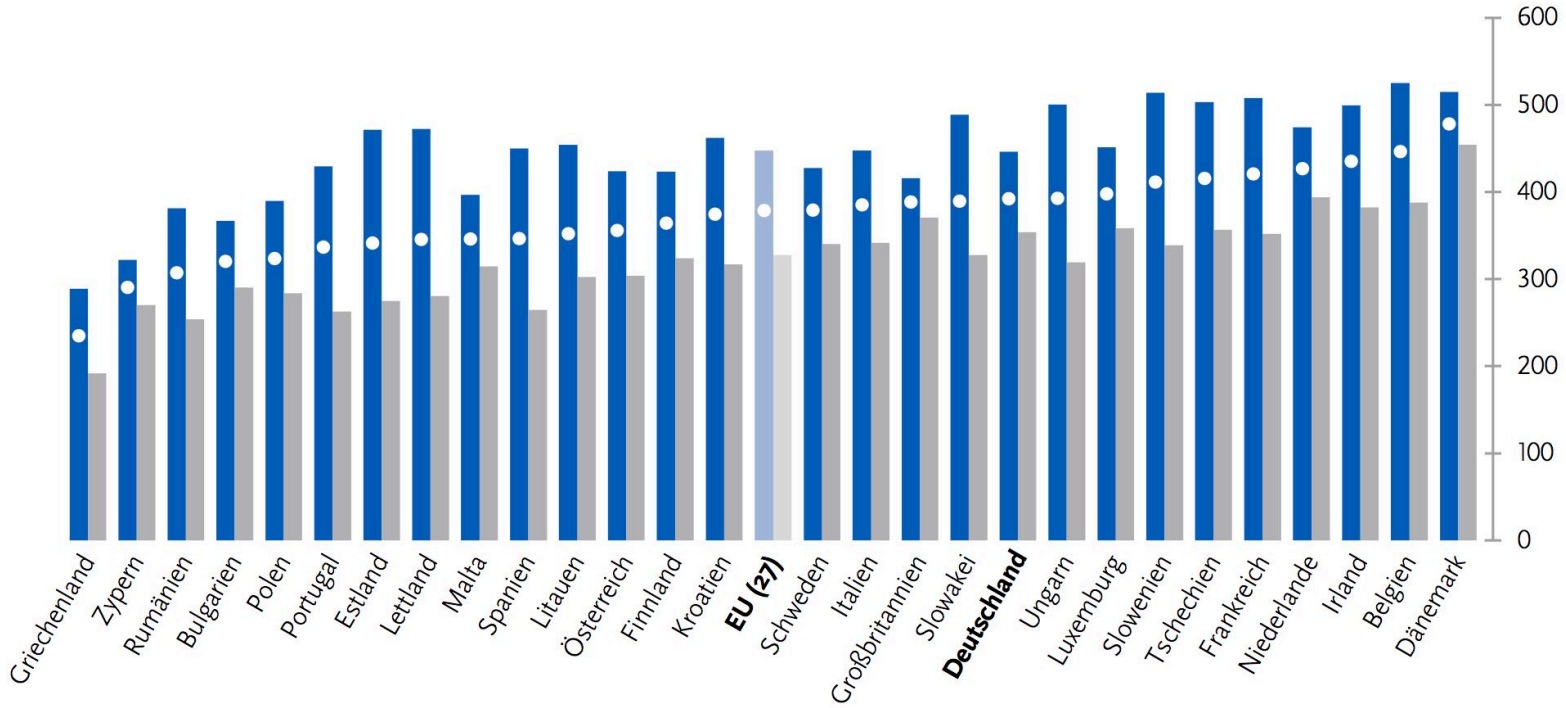


Abbildung 2.2.a4 Altersstandardisierte Neuerkrankungsraten je 100.000 Einwohner in den Mitgliedsstaaten der Europäischen Union, Krebs gesamt (ICD-10 C00–C97 ohne C44), nach Geschlecht, 2012. Quellen: European Cancer Observatory, Zentrum für Krebsregisterdaten

Bericht zum Krebsgeschehen in Deutschland 2016, Robert-Koch-Institut, 2016

Cancer Treatment Alternatives
Chemotherapy

http://www.barwonhealthfundraising.org.au/event/ProjectLove

Cancer Treatment Alternatives (cont'd)

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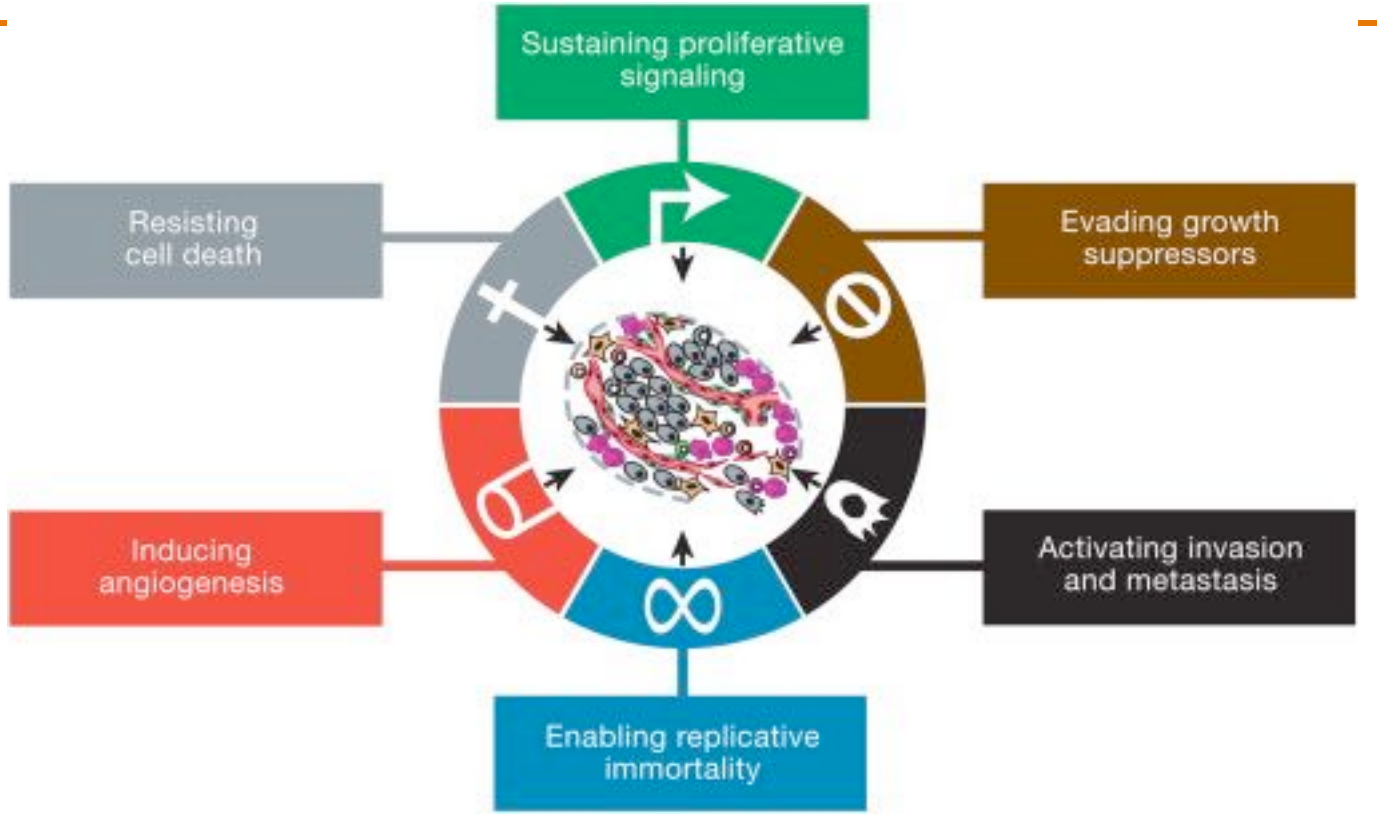
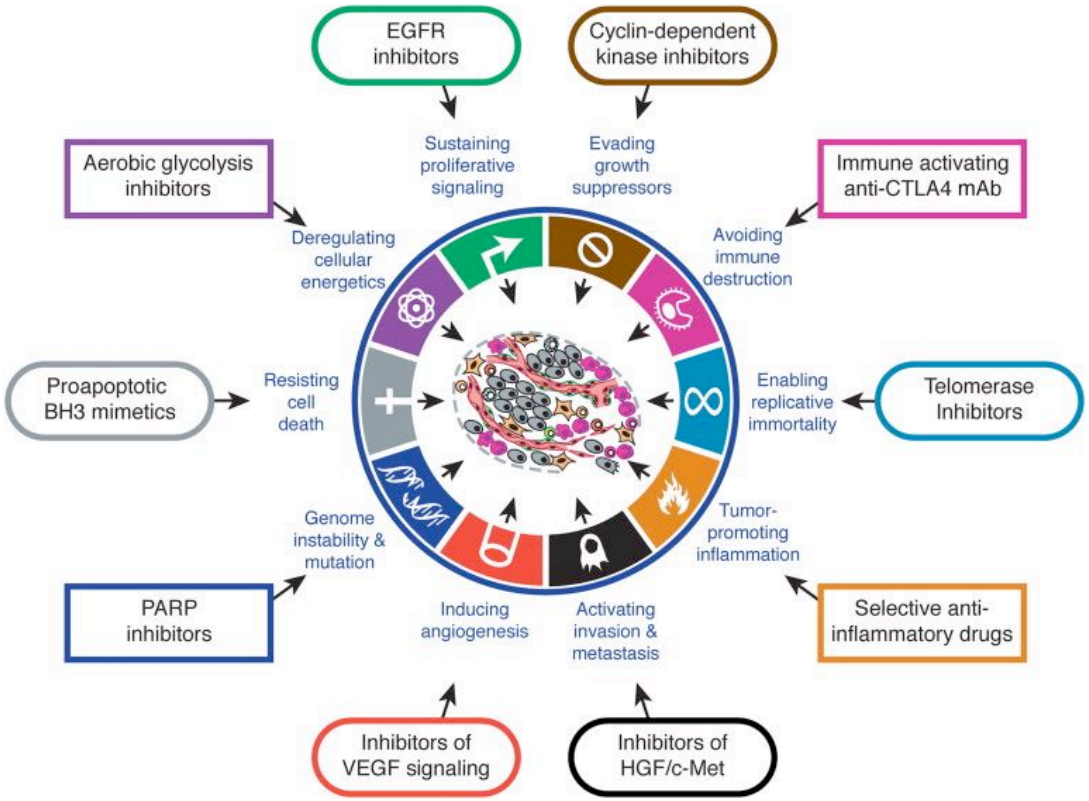
- Clinical guidelines define best "average treatment" option, e.g.:
  - Chemotherapy, i.e. typically multiple combined drugs to affect cancer cells
  - Radiation, i.e. use high-dose precisely applied types of radiation to burn cancer and neighborhood tissue
  - Immunotherapy, i.e. enable human immune system to identify cancer cells
  - Targeted therapy, i.e. address pathway targets within cancer cells only
  - Hormone therapy, i.e. remove or replace hormones, which certain cancer types use to grow, e.g. breast and prostate cancer
  - Stem cell transplant, i.e. reactivate the bodies production of blood cells after chemo- or radio therapy
  - Surgery, i.e. if possible remove cancer and neighborhood tissue completely

Hallmarks of Cancer Cells



Hanahan D, Weinberg RA (January 2000). "The Hallmarks of Cancer". Cell. 100 (1): 57–70.

Therapeutic Targets for Cancer Cells



Hanahan D, Weinberg RA (March 2011). "The Hallmarks of Cancer: The Next Generation". Cell. 144 (5): 646–74.

Oncogenes

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Oncogenes: BAX, BCL2L1, CASP8, CDK4, ELK1, ETS1, HGF, JAK2, JUNB, JUND, KIT, KITLG, MCL1, MET, MOS, MYB, NFKBIA, NRAS, PIK3CA, PML, PRKCA, RAF1, RARA, REL, ROS1, RUNX1, SRC, STAT3, ZHX2.

Tumor Suppressor Genes: ATM, BRCA1, BRCA2, CDH1, CDKN2B, CDKN3, E2F1, FHIT, FOXD3, HIC1, IGF2R, MEN1, MGMT, MLH1, NF1, NF2, RASSF1, RUNX3, S100A4, SERPINB5, SMAD4, STK11, TP73, TSC1, VHL, WT1, WWOX, XRCC1.

Both Oncogenic & Tumor Suppressor Properties: BCR, EGF, ERBB2, ESR1, FOS, HRAS, JUN, KRAS, MDM2, MYC, MYCN, NFKB1, PIK3C2A, RB1, RET, SH3PXD2A, TGFB1, TNF, TP53.

Transcription Factors: ABL1, BRCA1, BRCA2, CDKN2A, CTNNB1, E2F1, ELK1, ESR1, ETS1, FOS, FOXD3, HIC1, JUN, JUNB, JUND, MDM2, MEN1, MYB, MYC, MYCN, NF1, NFKB1, PML, RARA, RB1, REL, RUNX1, RUNX3, SMAD4, STAT3, TGFB1, TNF, TP53, TP73, TSC1, VHL, WT1, ZHX2.

Epithelial-to-Mesenchymal Transition: BRCA2, CDKN2B, CTNNB1, ERBB2, HGF, JAK2, KIT, MCL1, NF1, RUNX3, S100A4, SMAD4, TGFB1, VHL.

Angiogenesis: AKT1, CTNNB1, EGF, ERBB2, NF1, PML, RUNX1, TGFB1.

Apoptosis: BAX, BCL2, BCL2L1, BRCA1, CASP8, E2F1, MCL1, MGMT, TNF, VHL.

Cell Adhesion: APC, CDH1, CDKN2A, CTNNB1, KITLG, NF1, NF2, TGFB1.

Cell Cycle: ATM, BRCA1, BRCA2, CCND1, CDK4, CDKN1A, CDKN2A, CDKN2B, CDKN3, E2F1, HGF, MEN1, STK11, TP53.

Oncogenes & Tumor Suppressor Genes PCR Array, Qiagen, 2012

Stratified Medicine

- "Stratified medicine is based on the identification of subgroups of patients that differ in their mechanisms of disease, their susceptibility to a particular disease, or in their response to a medicine."
- "Personalized medicine takes this approach a step further by using targeted medicines and also taking information such as the patient's genotype and lifestyle into account when deciding on the best treatment."

(European Patients' Academy, 2015)

President Obama speaks on the Precision Medicine Initiative, Jan 30, 2015

Personalized Medicine

- Personalized medicine "[...] is the concept that selection of a treatment should be tailored according to the individual patient's specific characteristics [...] versus a decision based on 'standards of care' derived by averaging responses across large cohorts of individuals in clinical trials"

  (K. Jain: "Textbook of Personalized Medicine", 2009)

President Obama speaks on the Precision Medicine Initiative, Jan 30, 2015

Precision Medicine

- Precision Medicine is "[…] an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

(U.S. National Institute of Health, 2015)

President Obama speaks on the Precision Medicine Initiative, Jan 30, 2015

The Setting
Actors in Oncology

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- **Patients**

  - Individual anamnesis, family history, and background
  - Require fast access to individualized therapy

- **Clinicians**

  - Identify root and extent of disease using laboratory tests
  - Evaluate therapy alternatives, adapt existing therapy

- **Researchers**

  - Conduct laboratory work, e.g. analyze patient samples
  - Create new research findings and come-up with treatment alternatives

Motivation
Informed Decision Making

- Can we enable doctors to:
  - Select best treatment options for their patients,
  - Analyze latest diagnostic data about patient's status, and
  - Exchange knowledge with patients to improve quality of living.

Vision
Interdisciplinary Tumor Board

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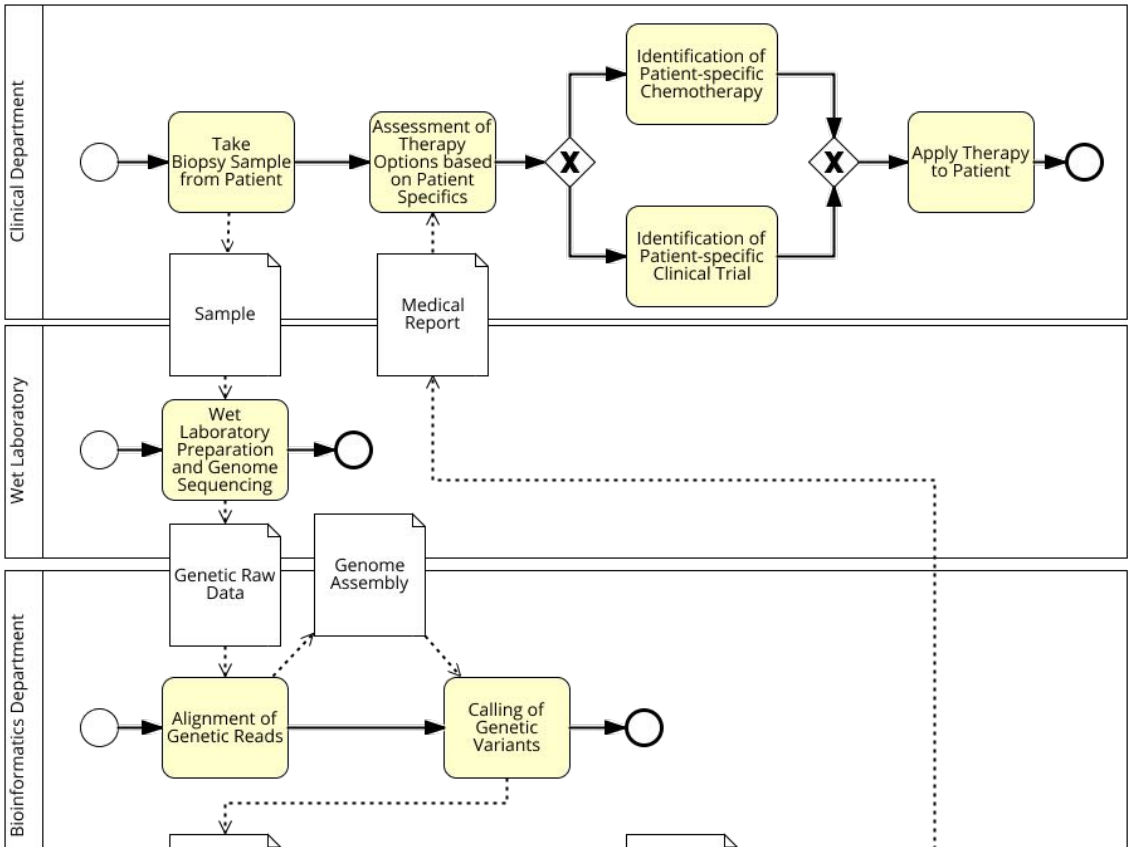
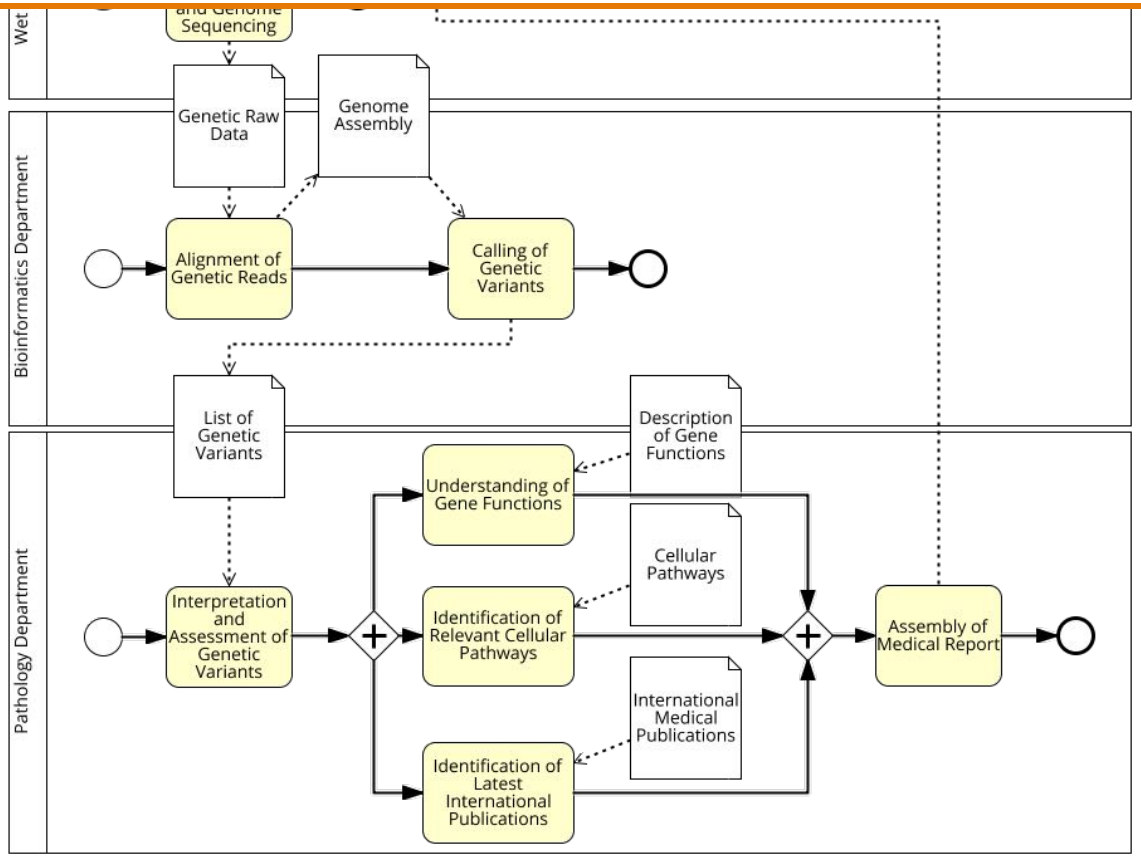
Tumor Board
State of the Art

https://www.nct-heidelberg.de/en/for-patients/treatment/tumor-board.html

Simplified Clinical Oncology Process (1/2)



Simplified Clinical Oncology Process (2/2)



From Raw Genome Data to Clinical Decision Support (cont'd)

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- Identification of individual genetic dispositions
- Interpretation and assessment of genetic dispositions
- Therapy assessment
- Clinical trials

From Raw Genome Data to Clinical Decision Support

- **DNA Sequencing:** Transformation of analogues DNA into digital format
- **Alignment:** Reconstruction of complete genome with snippets
- **Variant Calling:** Identification of genetic variants
- **Data Annotation:** Linking genetic variants with research findings

Cancer Classification

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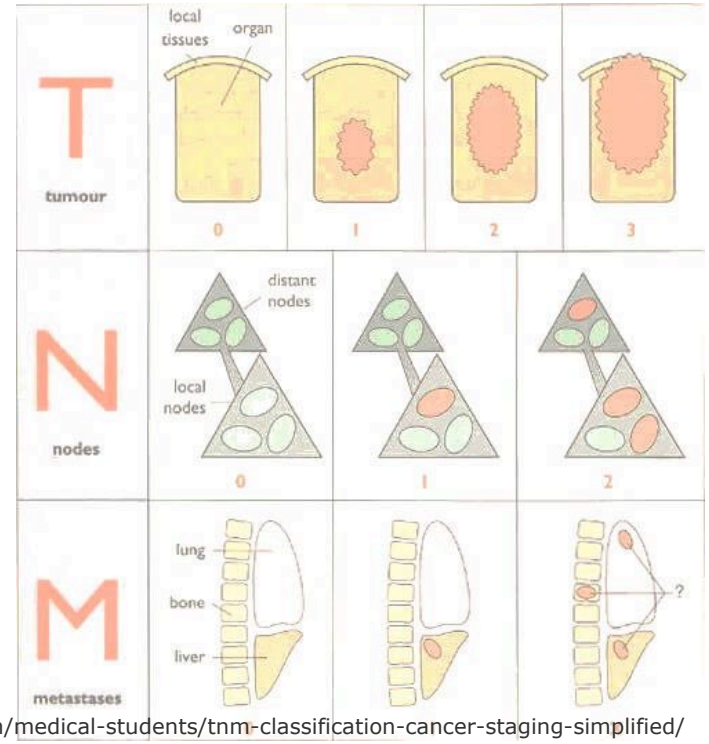
- General TNM classification describes clinical and pathologic observations of tumors
  - c := Clinical observation
  - p := Pathological observation
  - T := Size and extent of the primary tumor
  - N := Number of affected nearby lymph nodes
  - M := Number of metastases

- For example, cT1aN0M0 for NSCLC:
  - Tumor <= 2 cm
  - No regional lymph nodes affected
  - No distant metastases



http://epomedicine.com/medical-students/tnm-classification-cancer-staging-simplified/

Tumor Stage Grouping

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- Staging take more the progress of the disease into account
- Stage 0: Carcinoma in situ (CIS)
- Stage I: Localized
- Stage II: Locally advanced, but early stage
- Stage III: Locally advanced, late stage
- Stage IV: Tumor metastases are detected

- For example, stage IV for NSCLC:
  - Primary lung tumor spread remote metastases

Clinical Trials
Good Clinical Practice (GCP)

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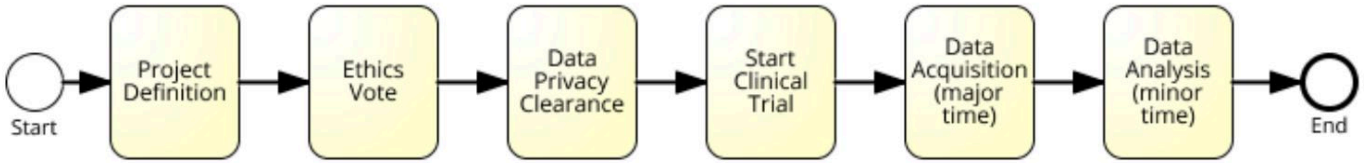
- Ethical compliance
- Risk identification and assessment
- Safety of trial subject first
- Sufficient information about investigated product
- Research protocol
- Review by Institutional Review Board (IRB) / Independent Ethics Committee (IEC)
- Qualification of investigator and staff
- Informed Consent Form (ICF)
- Proper recording, handling, and storing of trial information
- Privacy of personal data
- Good Manufacturing Practices (GMP)
- Quality Assurance (QA) measures

Guideline for Good Clinical Practice E6 (R2), ICH, 2015

Clinical Trials Workflow Prospectively



Clinical Trials Workflow Retrospectively