Hasso Plattner Institut
Digital Engineering · Universität Potsdam

Medical Use Case Oncology: A Global Challenge

Borchert, Dr. Schapranow

Data Management for Digital Health
Winter 2023

Agenda
Pillars of the Lecture

Hasso Plattner Institut

Medical Use Cases

Biology Recap

Oncology

Nephrology

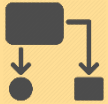
Infectious Diseases

Technology Foundation

Data Sources

Data Formats

Processing and Analysis



Software Architectures

Machine Learning

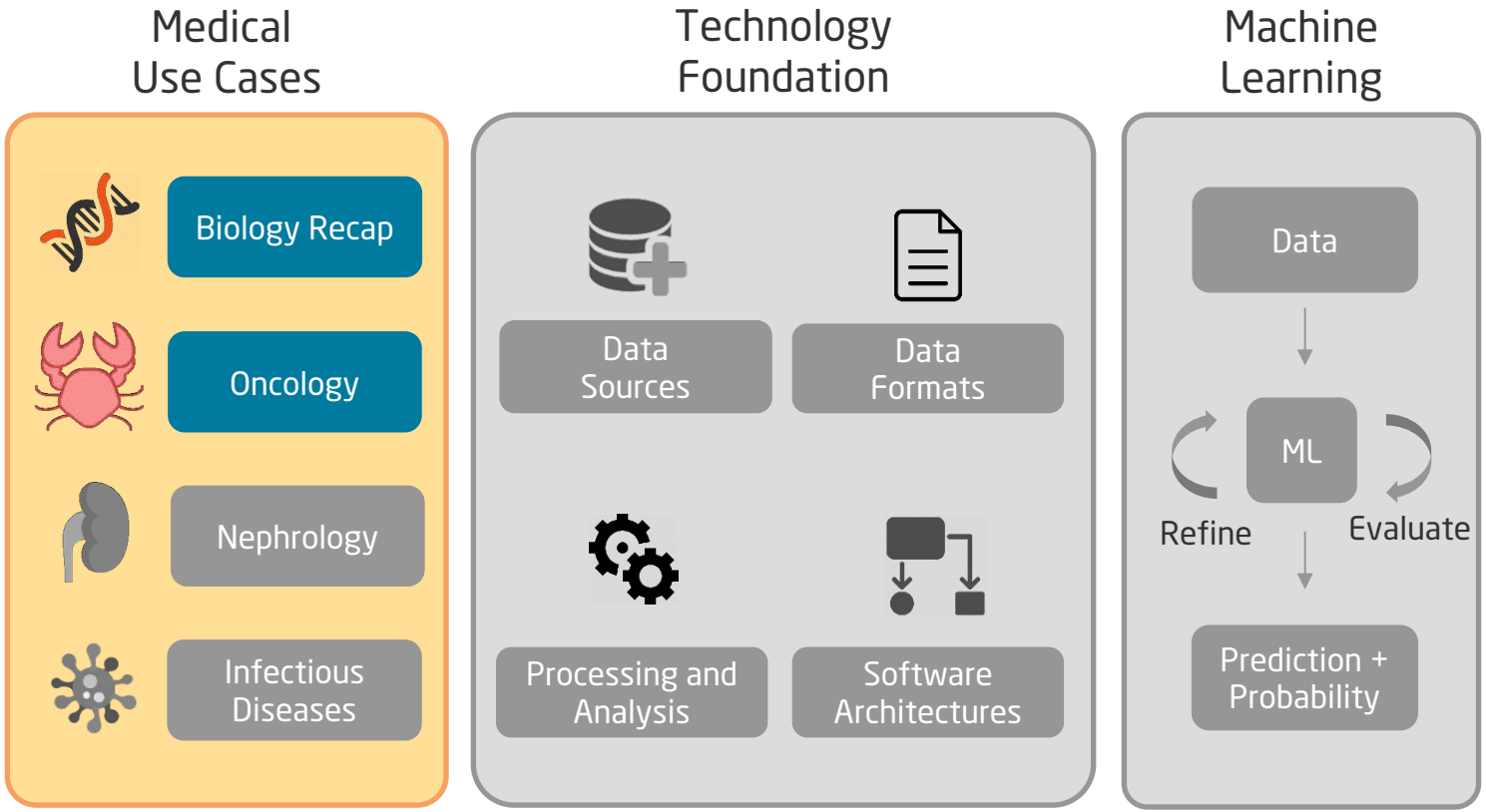
Data

Prediction + Probability

Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Agenda
Pillars of the Lecture



Agenda

- Numbers you should know
- Terms and definitions
- Disease classifications
- Cancer cells
- Treatment options
- Patient journey
- Tumor boards
- Clinical trials

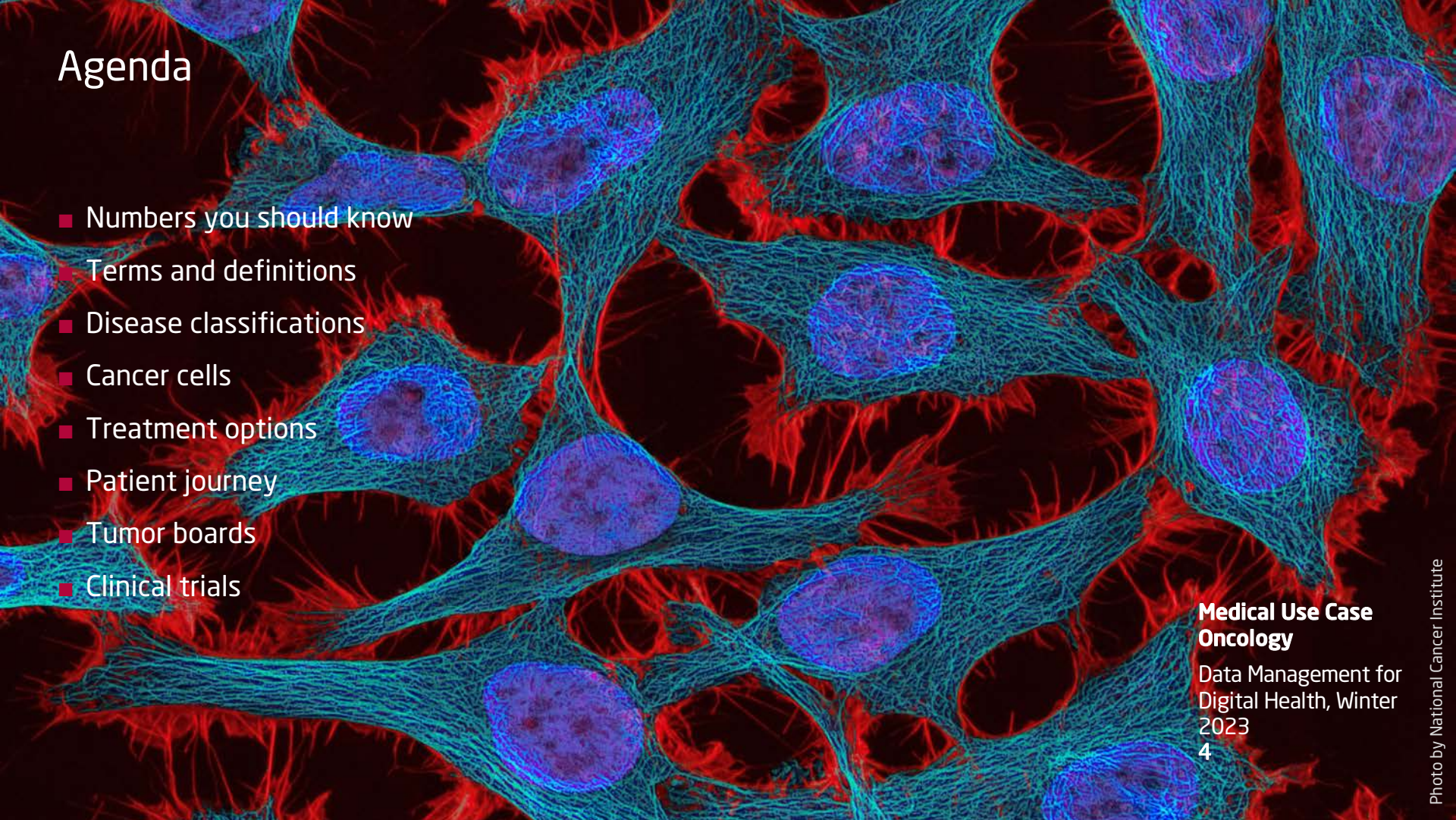
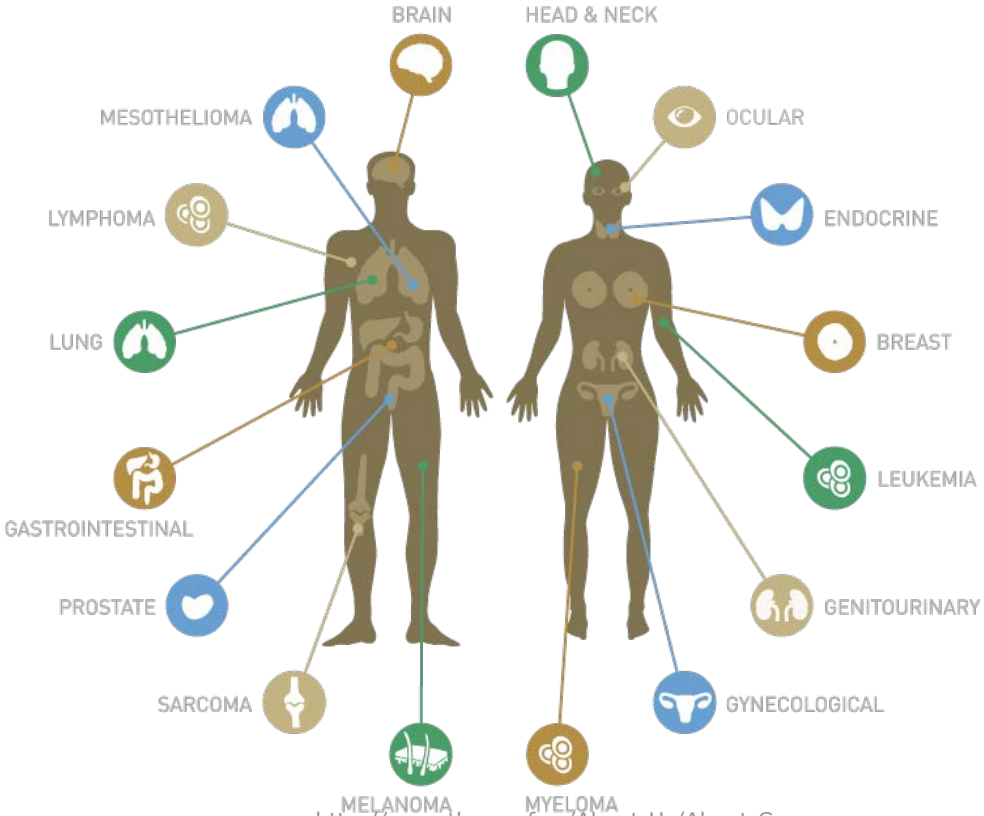


Photo by National Cancer Institute

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

Cancer Facts
<< QUIZ >>

What are the most common cancer types recently (worldwide, absolute cases)?

A. Breast

B. Lung and respiratory system

C. Colorectaral

D. Prostate

Cancer Facts
Worldwide Cancer Incidence by Type in 2020

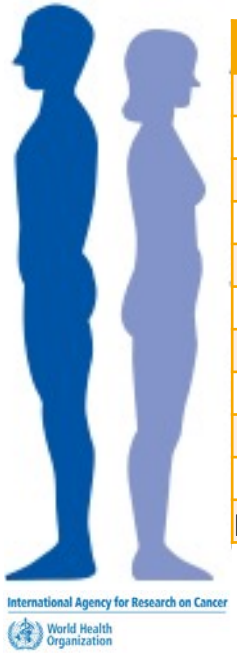
- Over 18M people received cancer diagnosis
- Top 3 cancer types contribute to 1/3 of new cases:
  - 1st + 2nd: Breast + lung cancer with 4.4M new cases
  - 3rd: Colorectal cancer with 1.9M new cases
- Top 10 cancer types contribute to 2/3 of new cases

#	ICDs	Cancer Type	Number	Ratio
	C00-97/C44	**All excl. NMSC**	**18,094,716**	**100.0%**
1	C50	Breast	2,261,419	12.5%
2	C33-34	Lung	2,206,771	12.2%
3	C18-21	Colorectum	1,931,590	10.7%
4	C61	Prostate	1,414,259	7.8%
5	C16	Stomach	1,089,103	6.0%
6	C22	Liver	905,677	5.0%
7	C53	Cervix uteri	604,127	3.3%
8	C15	Oesophagus	604,100	3.3%
9	C73	Thyroid	586,202	3.2%
10	C67	Bladder	573,278	3.2%

Adapted from https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data

Cancer Facts
Worldwide Cancer Incidence by Type and Sex in 2020

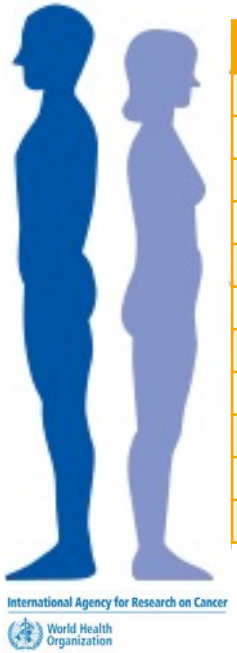
Cancer Type	Number	Ratio
All excl. NMSC	9,342,957	100.0%
Lung	1,435,943	25.8%
Prostate	1,414,259	9.9%
Colorectum	1,065,960	8.8%
Stomach	719,523	6.9%
Liver	632,320	5.1%
Bladder	440,864	4.8%
Oesophagus	418,350	4.2%
Non-Hodgkin lymphoma	304,151	3.6%
Kidney	271,249	3.1%
Leukaemia	269,503	2.7%



Cancer Type	Number	Ratio
All excl. NMSC	8,751,759	100.0%
Breast	2,261,419	25.8%
Colorectum	865,630	9.9%
Lung	770,828	8.8%
Cervix uteri	604,127	6.9%
Thyroid	448,915	5.1%
Corpus uteri	417,367	4.8%
Stomach	369,580	4.2%
Ovary	313,959	3.6%
Liver	273,357	3.1%
Non-Hodgkin lymphoma	240,201	2.7%

Cancer Facts
Worldwide Cancer Mortality by Type and Sex in 2020

Cancer Type	Number	Ratio
All excl. NMSC	5,491,214	100.0%
Lung	1,188,679	21.6%
Liver	577,522	10.5%
Colorectum	515,637	9.4%
Stomach	502,788	9.2%
Prostate	375,304	6.8%
Oesophagus	374,313	6.8%
Pancreas	246,840	4.5%
Leukaemia	177,818	3.2%
Bladder	158,785	2.9%
Non-Hodgkin lymphoma	147,217	2.7%



Cancer Type	Number	Ratio
All excl. NMSC	4,403,188	100.0%
Breast	684,996	15.6%
Lung	607,465	13.8%
Colorectum	419,536	9.5%
Cervix uteri	341,831	7.8%
Stomach	266,005	6.0%
Liver	252,658	5.7%
Pancreas	219,163	5.0%
Ovary	207,252	4.7%
Oesophagus	169,763	3.9%
Leukaemia	133,776	3.0%

Cancer Facts
European Union: Incidence by Sex per 100k (2012)

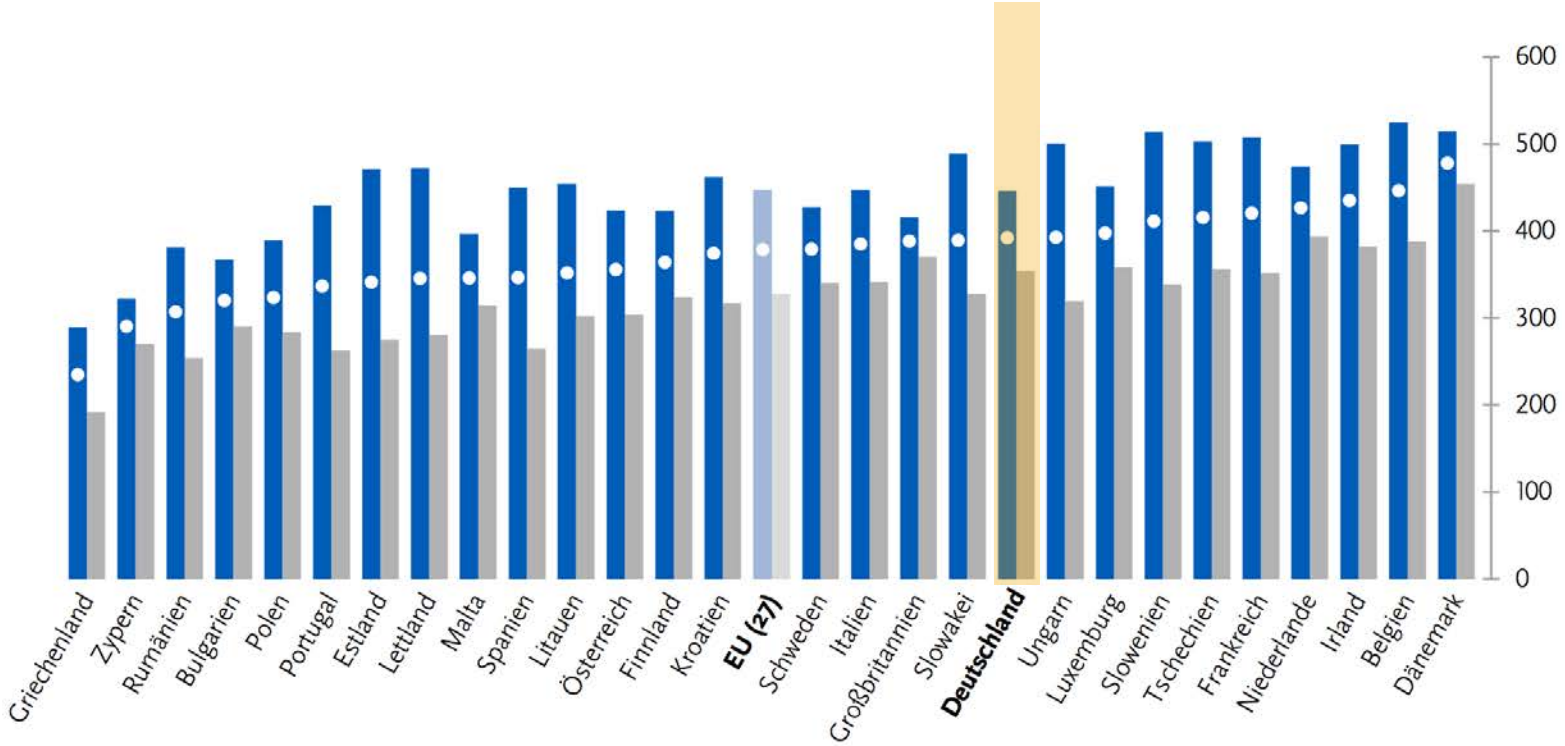
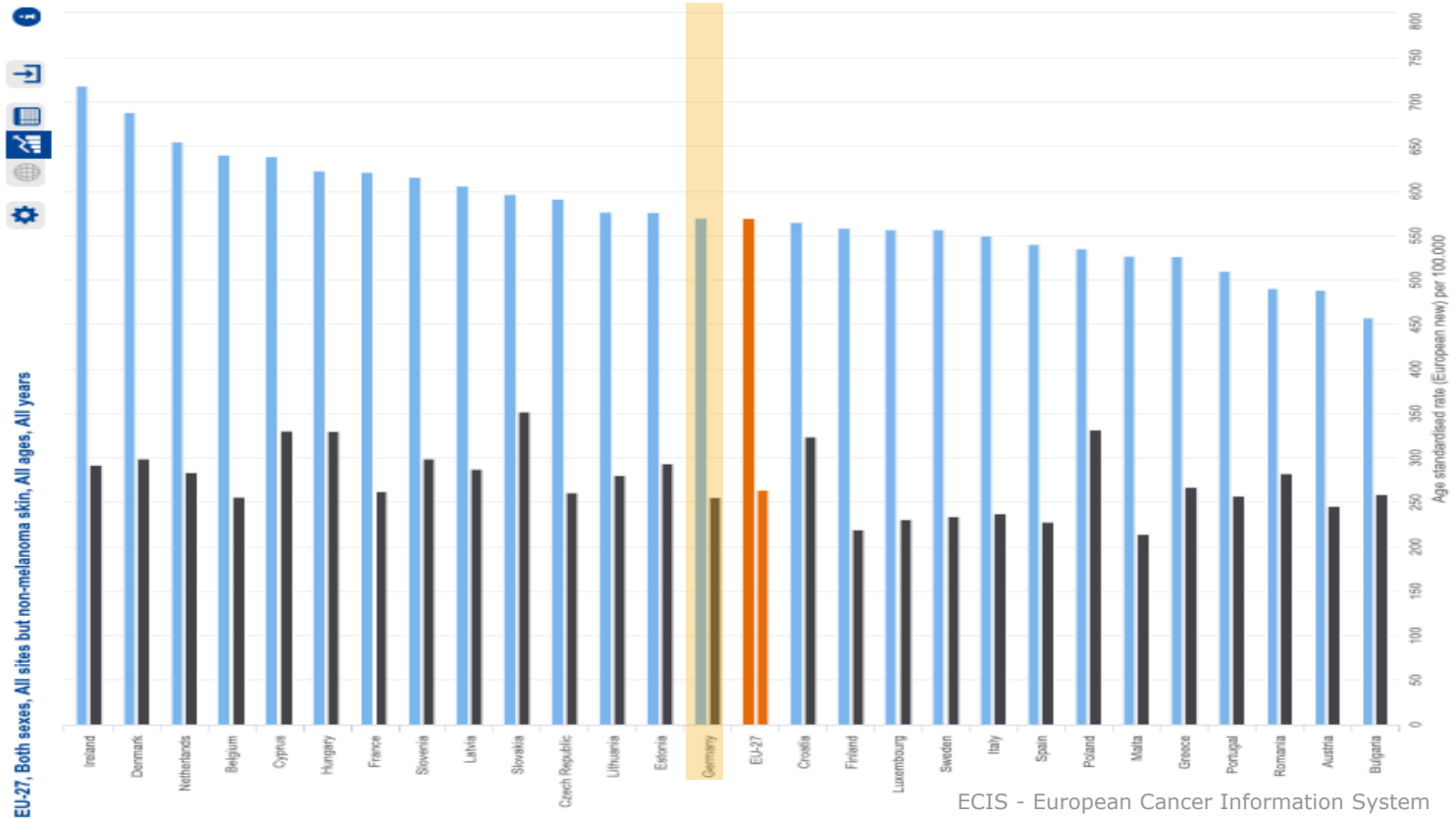


Abbildung 2.2.a4 Altersstandardisierte Neuerkrankungsraten je 100.000 Einwohner in den Mitgliedsstaaten der Europäischen Union, Krebs gesamt (ICD-10 C00–C97 ohne C44), nach Geschlecht, 2012. Quellen: European Cancer Observatory, Zentrum für Krebsregisterdaten

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

Cancer Facts
European Union: Incidence vs. Mortality per 100k (2020)

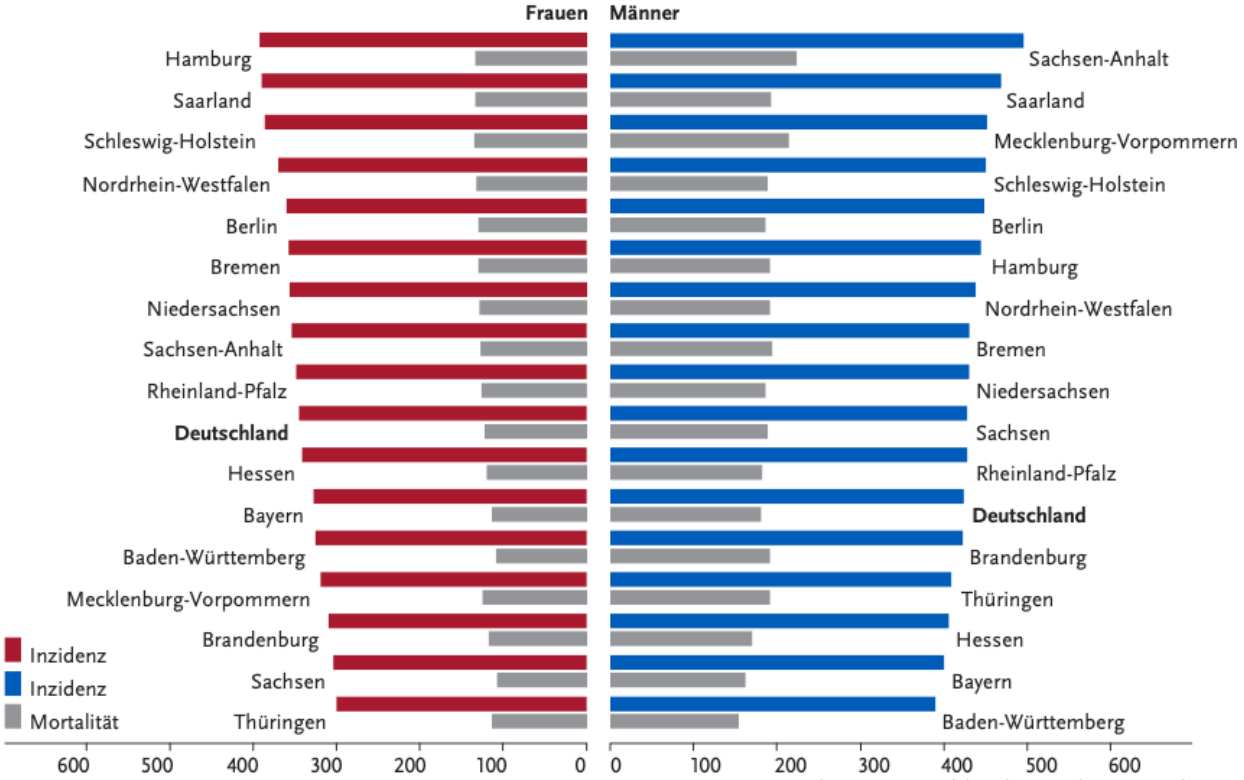


ECIS - European Cancer Information System

Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Cancer Facts: Age-standardized Incidence and Mortality per State and Sex in Germany 2017-2018



Krebs in Deutschland 2017/2018, Robert-Koch-Institut, 2021

ICD-10 C00 - C97 w/o C44, 2017-2018 per 100,000 (old European standard)

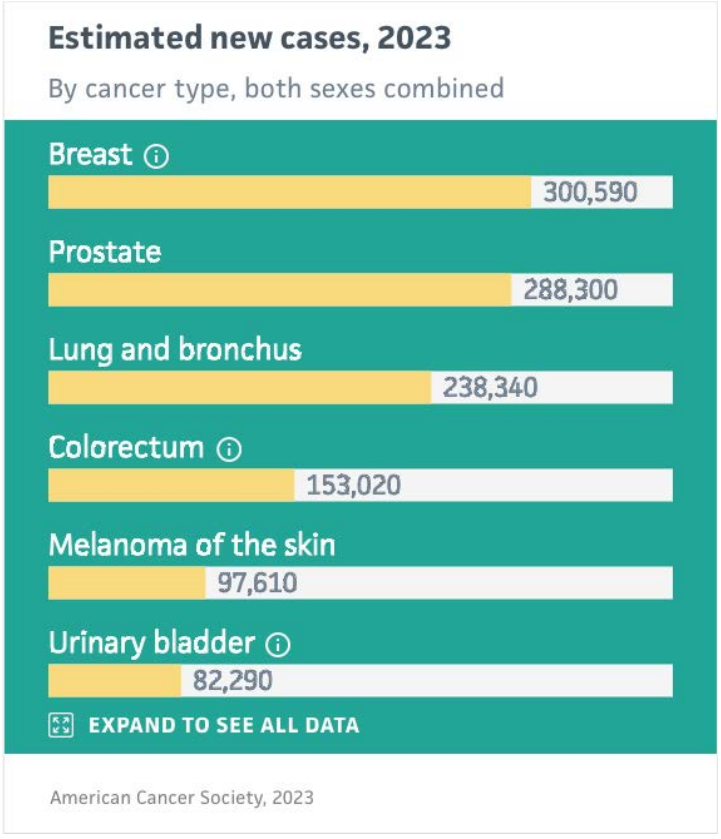
Medical Use Case Oncology

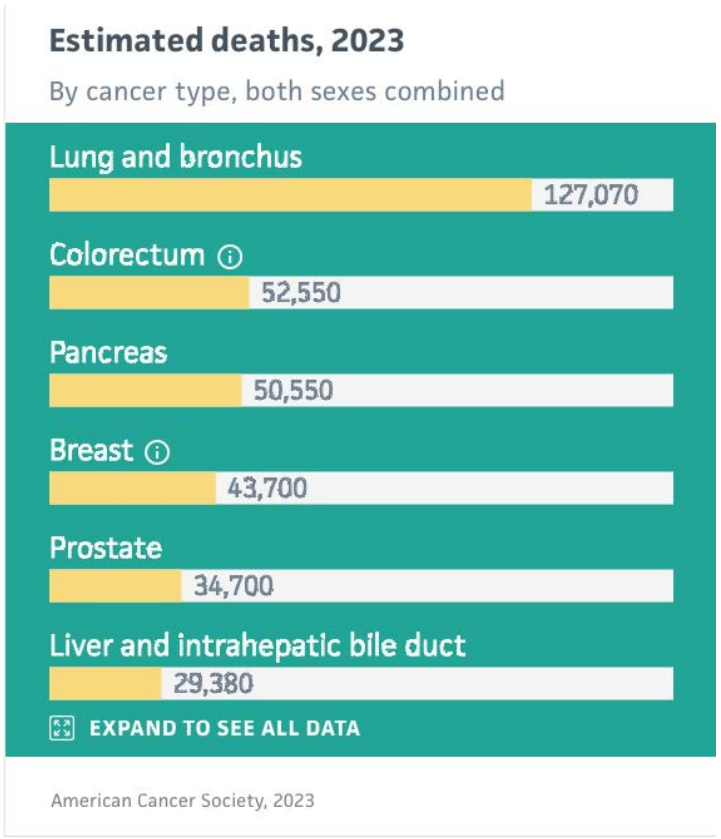
Data Management for Digital Health, Winter 2023

Cancer Facts
United States of America (2023)

https://cancerstatisticscenter.cancer.org/

Cancer Facts
USA Estimated New vs. Deaths (2023)





https://cancerstatisticscenter.cancer.org/

Table 6. Probability (%) of Developing Invasive Cancer During Selected Age Intervals by Sex, US, 2017-2019*

Site	Sex	0 to 49	50 to 59	60 to 69	70 and older	Birth to death
All sites†	Male	3.5 (1 in 29)	6.2 (1 in 16)	13.8 (1 in 7)	34.0 (1 in 3)	40.9 (1 in 2)
	Female	5.8 (1 in 17)	6.4 (1 in 16)	10.4 (1 in 10)	27.2 (1 in 4)	39.1 (1 in 3)
Breast	Female	2.1 (1 in 48)	2.4 (1 in 41)	3.5 (1 in 28)	7.0 (1 in 14)	12.9 (1 in 8)
Colon & rectum	Male	0.4 (1 in 241)	0.7 (1 in 138)	1.1 (1 in 90)	3.1 (1 in 33)	4.3 (1 in 23)
	Female	0.4 (1 in 267)	0.5 (1 in 191)	0.8 (1 in 130)	2.8 (1 in 36)	3.9 (1 in 26)
Kidney & renal pelvis	Male	0.3 (1 in 389)	0.4 (1 in 250)	0.7 (1 in 144)	1.4 (1 in 69)	2.3 (1 in 44)
	Female	0.2 (1 in 609)	0.2 (1 in 504)	0.3 (1 in 292)	0.8 (1 in 124)	1.3 (1 in 75)
Leukemia	Male	0.3 (1 in 380)	0.2 (1 in 538)	0.4 (1 in 263)	1.4 (1 in 69)	1.8 (1 in 55)
	Female	0.2 (1 in 495)	0.1 (1 in 820)	0.2 (1 in 425)	0.9 (1 in 111)	1.3 (1 in 78)
Lung & bronchus	Male	0.1 (1 in 848)	0.6 (1 in 178)	1.7 (1 in 59)	5.6 (1 in 18)	6.2 (1 in 16)
	Female	0.1 (1 in 746)	0.5 (1 in 183)	1.4 (1 in 72)	4.7 (1 in 21)	5.8 (1 in 17)
Melanoma of the skin‡	Male	0.4 (1 in 246)	0.5 (1 in 205)	0.9 (1 in 114)	2.6 (1 in 38)	3.5 (1 in 28)
	Female	0.6 (1 in 162)	0.4 (1 in 247)	0.5 (1 in 191)	1.1 (1 in 88)	2.4 (1 in 41)
Non-Hodgkin lymphoma	Male	0.3 (1 in 400)	0.3 (1 in 354)	0.6 (1 in 181)	1.8 (1 in 55)	2.3 (1 in 43)
	Female	0.2 (1 in 535)	0.2 (1 in 473)	0.4 (1 in 250)	1.3 (1 in 74)	1.9 (1 in 53)
Prostate	Male	0.2 (1 in 457)	1.8 (1 in 55)	5.2 (1 in 19)	9.2 (1 in 11)	12.6 (1 in 8)
Thyroid	Male	0.2 (1 in 487)	0.1 (1 in 767)	0.2 (1 in 599)	0.2 (1 in 416)	0.6 (1 in 155)
	Female	0.8 (1 in 125)	0.3 (1 in 290)	0.3 (1 in 318)	0.4 (1 in 276)	1.7 (1 in 59)
Uterine cervix	Female	0.3 (1 in 340)	0.1 (1 in 803)	0.1 (1 in 934)	0.2 (1 in 593)	0.7 (1 in 153)
Uterine corpus	Female	0.3 (1 in 305)	0.6 (1 in 161)	1.0 (1 in 97)	1.5 (1 in 68)	3.1 (1 in 33)

*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 6.8.0. Statistical Research and Applications Branch, National Cancer Institute, 2022. surveillance.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.

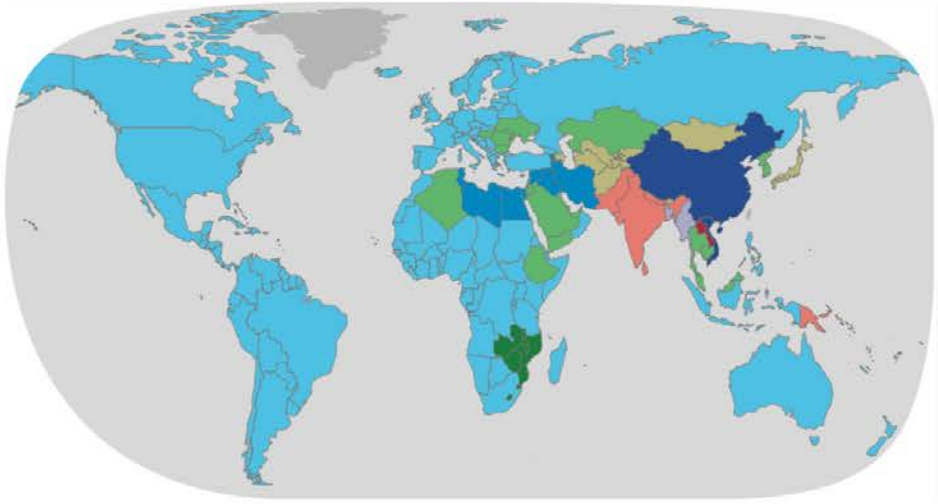
Hasso Plattner Institut

Medical Use Case Oncology

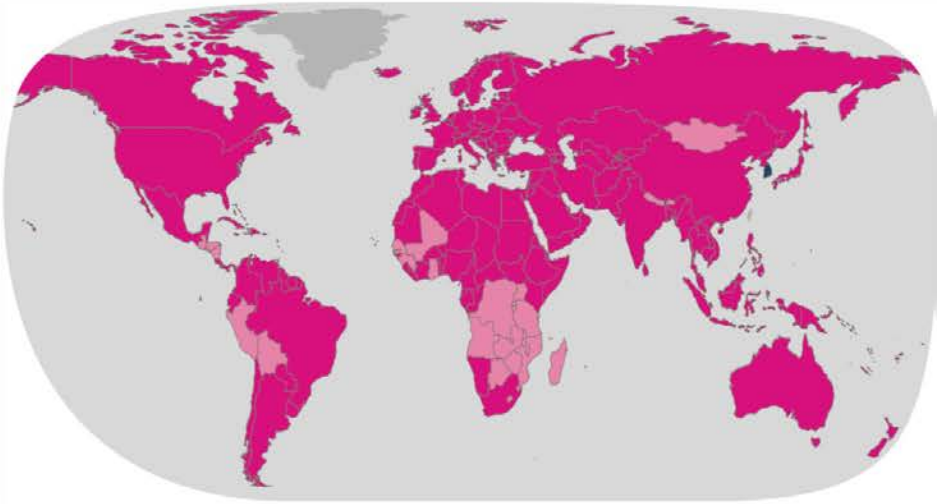
Data Management for Digital Health, Winter 2023

Prevalence 2012 // Most prevalent cancer by country

Males



Females



1. **Prostate** - **124 countries** worlwide
2. **Bowel** - **23 countries** in Africa, Asia and Eastern Europe
3. **Stomach** - **9 countries** in Asia
4. **Lip, Oral Cavity** - **7 countries** in South-Central Asia and Melanesia
5. **Bladder** - **7 countries** in Northern Africa, Asia
6. **Kaposi Sarcoma** - Lesotho, Malawi, Mozambique, Swaziland, Zimbabwe, Zambia
7. **Liver** - Gambia, Laos
8. **Lung** - China, Vietnam
9. **Pharynx** - Bangladesh, Myanmar

1. **Breast** - **151 countries** worldwide
2. **Cervix** - **30 countries** in Africa, the Americas and Asia
3. **Thyroid** - South Korea

WHO World Cancer Factsheet, 2014

Questions?

Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Photo by Mika Baumeister

Evidence-based Medicine

- Evidence-based medicine (EBM) is "[...] the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."

(Sackett et al.: Evidence based medicine: What it is and what it isn't, 1996)

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

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

Cancer Classification
<< QUIZ >>

What do you think are important cancer classifiers?

A. Location

B. Size

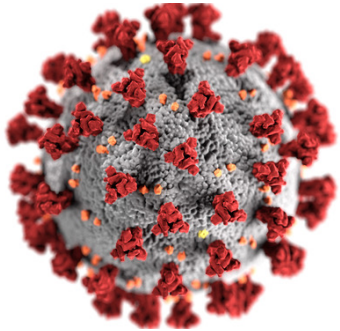
C. Progression

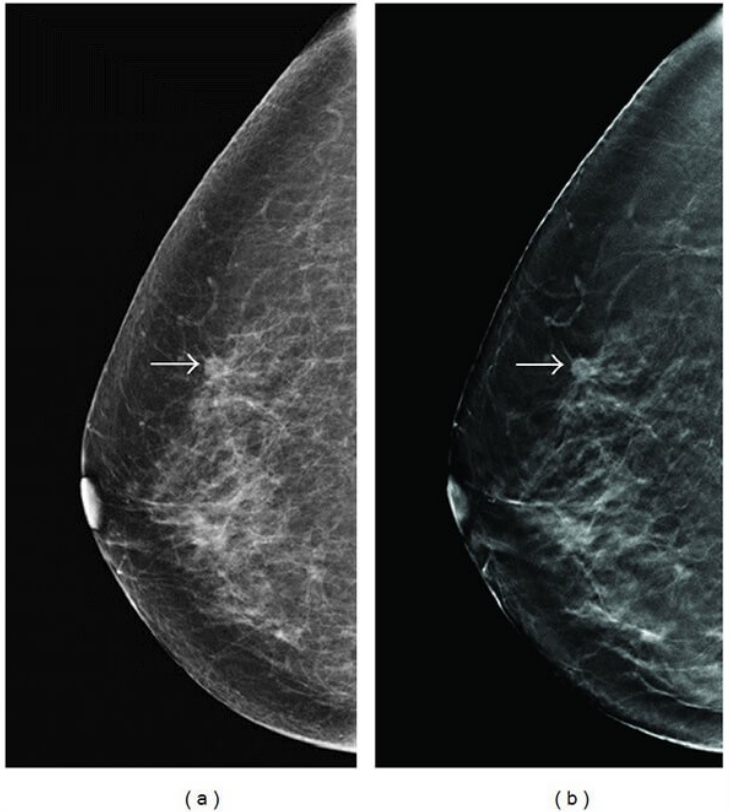
D. All of them

Cancer Disease Management Strategies

- Prevention, e.g. identification of risk factors to avoid them
- Early detection, e.g. regular screening
- Treatment, e.g. personalized cancer treatment
- Palliative care, i.e. mainly to reduce pain

- Bear in mind: Patients receiving cancer treatment are at high risk for infectious diseases, e.g. Coronavirus.



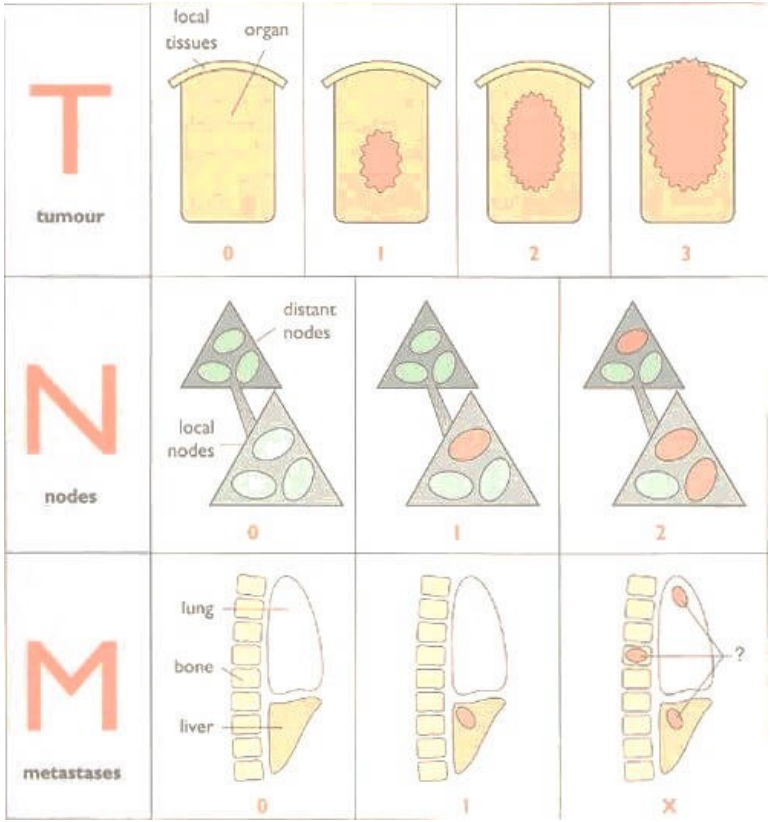


Breast nodules detected during screening by standard (a) 2D digital mammogram and (b) tomosynthesis

https://www.cancer.gov/news-events/cancer-currents-blog/2017/tmist-breast-cancer-screening

Cancer Classification

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

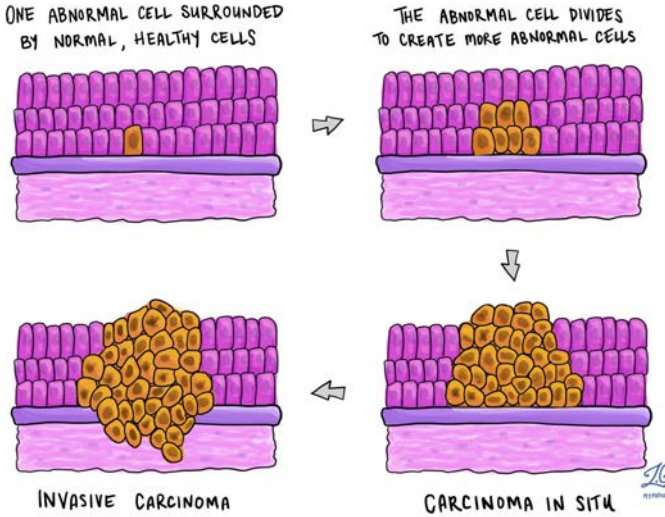


http://epomedicine.com/medical-students/tnm-classification-cancer-staging-simplified/

Tumor Stage Grouping

- Staging takes the progress of the disease into account

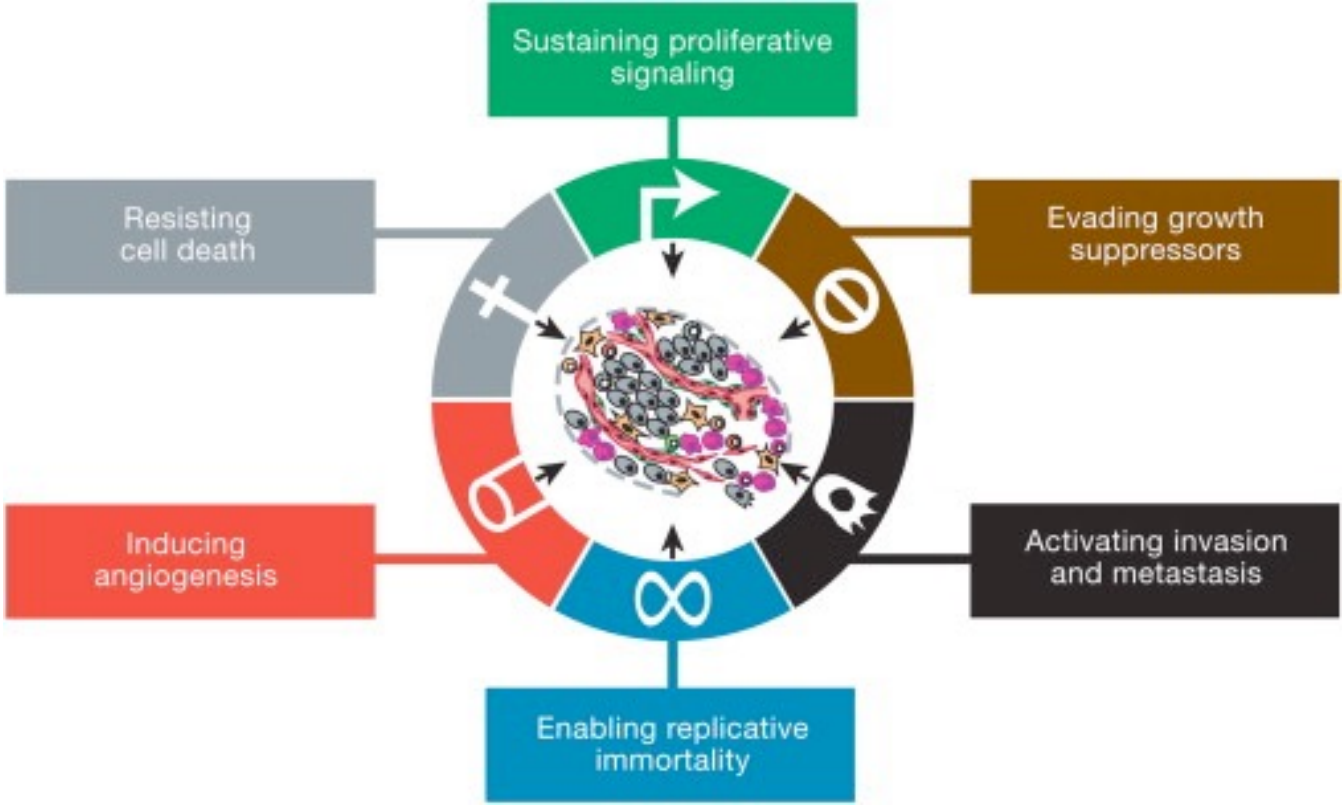
Stage	Description	Metastases
0	Carcinoma In Situ (CIS)	No
I	Localized	No
II	Locally advanced, but early stage	No
III	Locally advanced, late stage	No
IV	Tumor metastases are detected	Yes



https://www.mypathologyreport.ca/de/pathology-dictionary/carcinoma-in-situ/

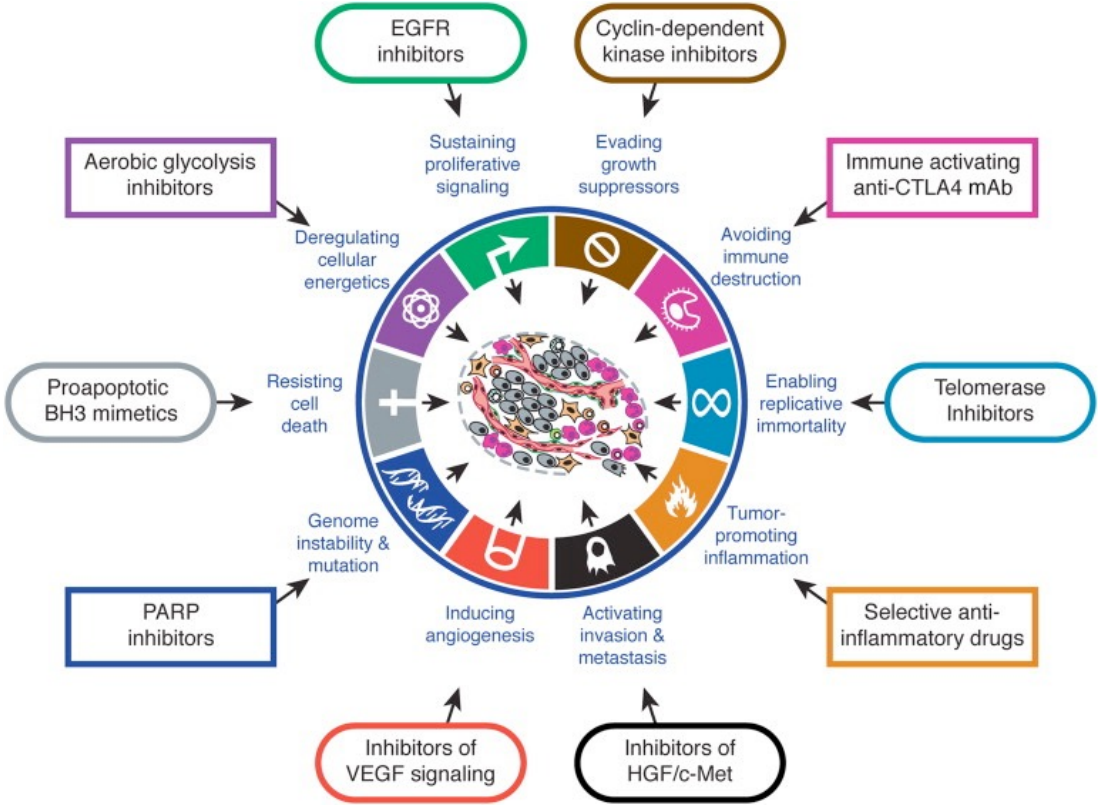
- Example: NSCLC, stage IV: Primary lung tumor spread remote metastases

Hallmarks of Cancer Cells (2000)



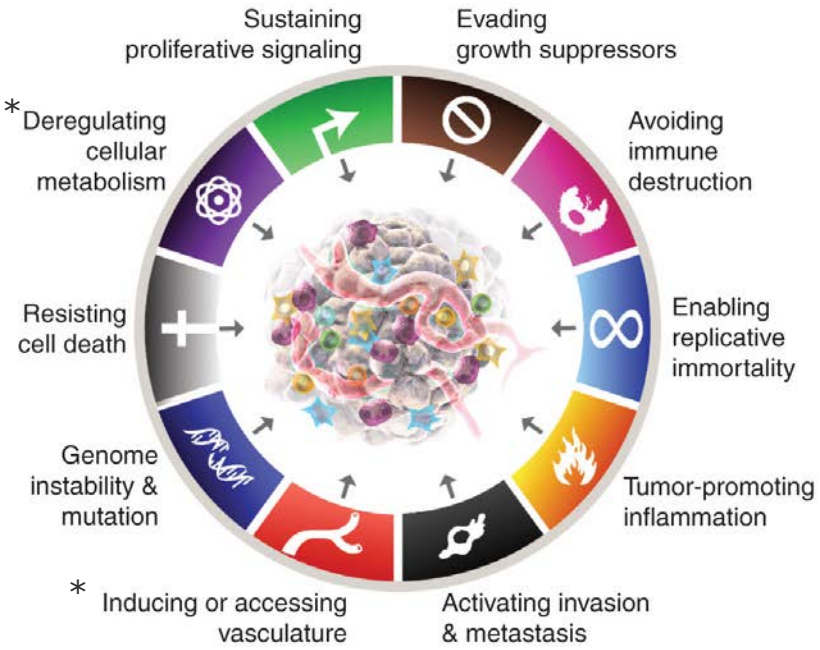
Hanahan D, Weinberg RA (January 2000). "The Hallmarks of Cancer". Cell. 100 (1): 57–70.

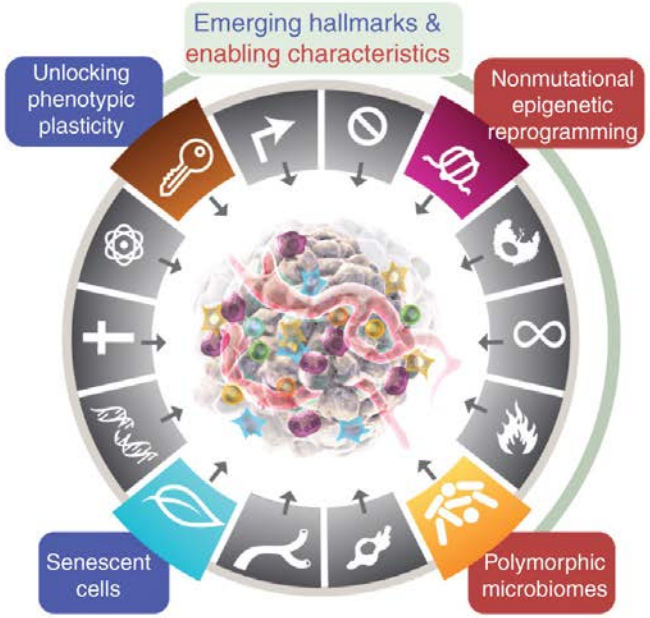
Hallmarks of Cancer Cells (2011) and Therapeutic Targets for Cancer Cells



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

Hallmarks of Cancer Cells
left: 2011 (reviewed *), right: 2022





Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Hanahan D (Jan 2022). "Hallmarks of Cancer: New Dimensions". Cancer Discovery. 12 (1): 31–46.

Oncogenes
https://www.oncokb.org/cancer-genes

- **Proto-Oncogenes** := Encode proteins responsible for growth, division, and differentiation of cells.
- **Oncogenes** := Damaged versions of proto-oncogenes, which might results in accelerated or uncontrolled cell functions.

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.

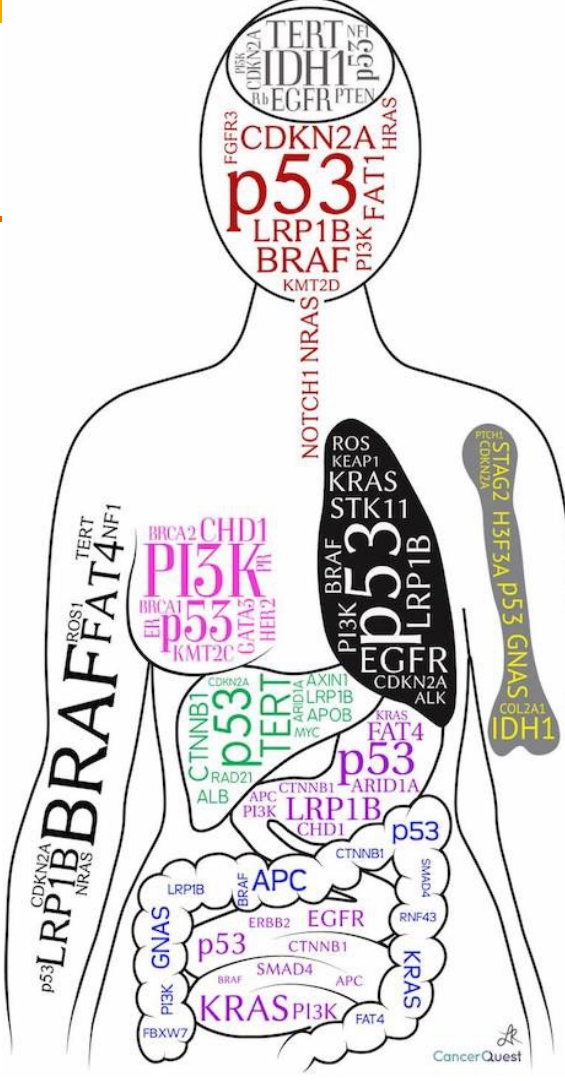
Angiogenesis: AKT1, CTNNB1, EGF, ERBB2, NF1, PML, RUNX1, TGFB1.

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

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

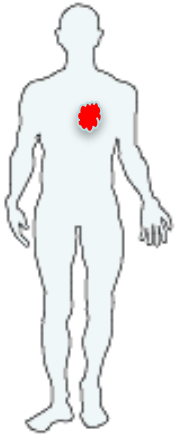
Cell Cycle: ATM, BRCA1, BRCA2, CCND1, CDK4, CDKN1A, CDKN2A, CDKN2B, CDKN3, E2F1, HGF, MEN1, STK11, TP53.

Oncogenes & Tumor Suppressor Genes PCR Array, Qiagen, 2012



Patient Journey: Lung Cancer in 2024
Screening, Diagnosis, Treatment, and Prevention

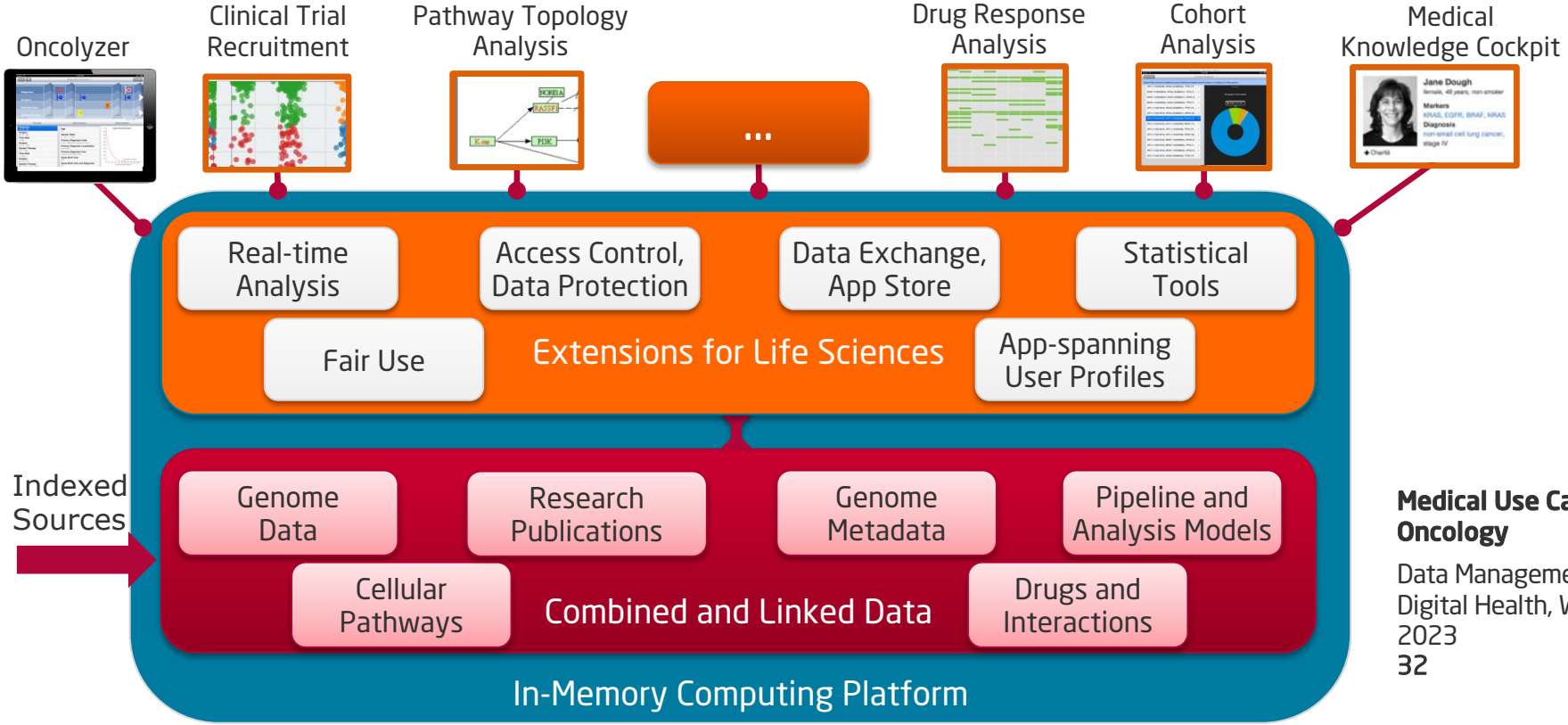
- Case vignette: 65-year old, male, former smoker, COPD patient
- How does his patient journey looks like?



Medical Use Case Oncology

Our Approach: AnalyzeGenomes.com
In-Memory Computing Platform for Big Medical Data

Hasso Plattner Institut



Medical Use Case Oncology

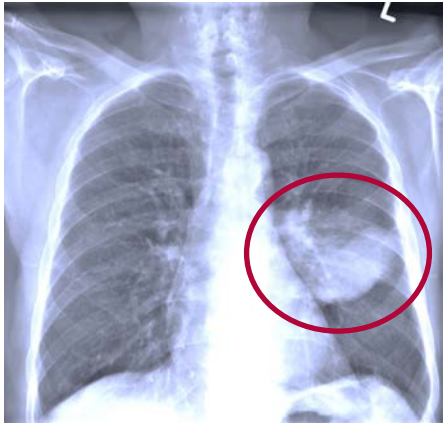
Patient Journey: Lung Cancer in 2024
Screening

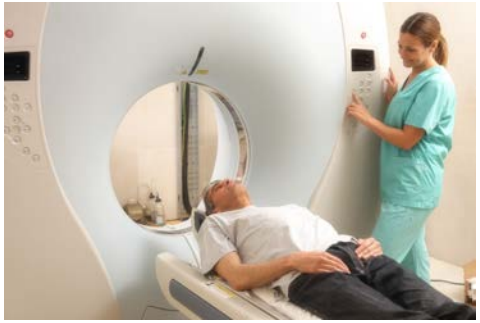
Personal risk score

- Personal risk score based on patient anamnesis, e.g. COPD or former smoker, regularly calculated by algorithms
- → Regular check-ups supported through direct notifications, e.g. annual respiratory screening recommended

Patient Journey: Lung Cancer in 2024
Diagnosis

- Lung function test + low-dose CT scan of the lung
- AI system supports radiologists in detecting lung tissue changes
- Minimal invasive CTC test reveals cells carrying relevant genetic changes, e.g. EGFR+ and ERBB2+
- → Biopsy from lung validated hypothesis





Marker

EGFR

ERBB2

Medical Use Case Oncology

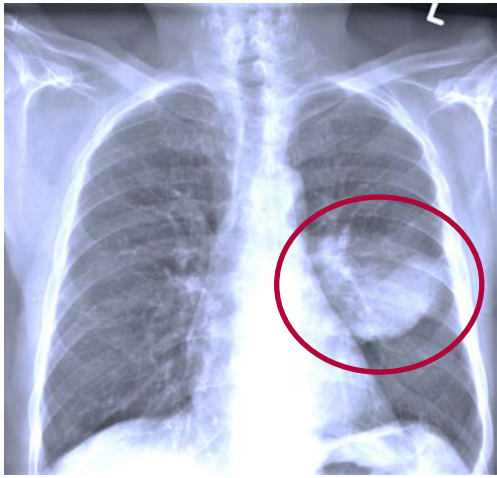
Data Management for Digital Health, Winter 2023

https://www.plattform-lernende-systeme.de/anwendungsszenario-2.html

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

Hasso Plattner Institut

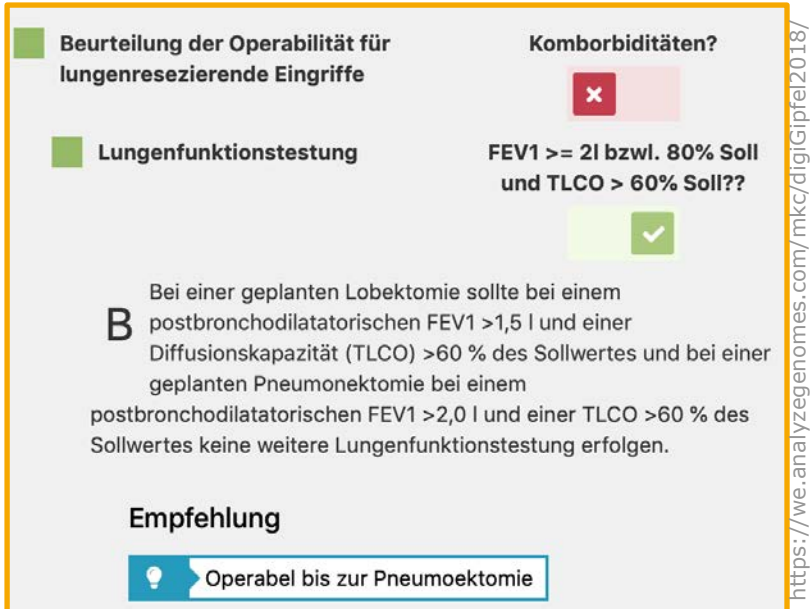
- Diagnosis: Non-Small Cell Lung Cancer (NSCLC), stage IV
- Markers: EGFR, ERBB2



1. Send tumor sample to laboratory for DNA extraction
2. Sequencing of tumor DNA is possible in <24hrs
3. Analysis involves 1+ TB of raw genome data per sample and takes days
4. Process raw genome data, e.g. alignment, variant calling, and annotate
5. Identify relevant variants using international medical knowledge
6. Decision making requires global medical knowledge, e.g. similar cases

Patient Journey: Lung Cancer in 2024
Treatment

- AI-based therapy support based on, e.g.
  - Clinical guidelines
  - Historic patient cases
  - Latest international medical knowledge and publications
- → Fully compliant with latest clinical guidelines surgery can be performed



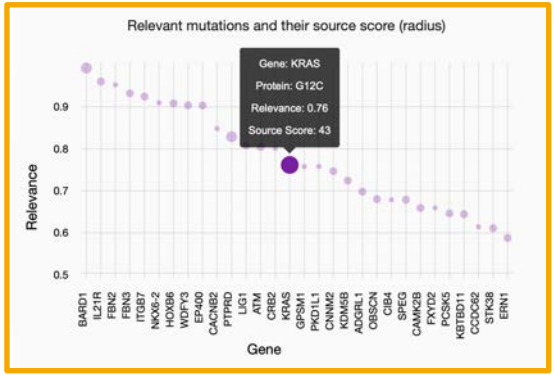
https://we.analyzegenomes.com/mkc/digiGipfel2018/

Use Case: Molecular Tumor Boards

- Multidisciplinary exchange format for oncologists
- Incorporates genetic dispositions
- Focus on data management, e.g. data retrieval, variant annotations, case presentations, documentation, and follow-up

Search for mutation

Gene	Protein	Type	Relevance	Sources
KRAS	G12V	Missense Mutation	0.76	PubMed ASCO CIVIC Historic 1
SETBP1	L1278M	Missense Mutation	0.73	PubMed ASCO
LRRK1	W1108L	Missense Mutation	0.72	PubMed



Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Patient Journey: Lung Cancer in 2024
Treatment

- Comparison of outcome of similar patients
- Quantitative real-time analysis of therapy efficiency
- Assessment of alternative therapy options
- Break-through: bringing clinical trials to participants

- → Adjuvant therapy based on specific combination of chemotherapy is selected

⊗ Dabrafenib, Trametinib, and Navitoclax in Treating Patients With BRAF Mutant Melanoma or Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

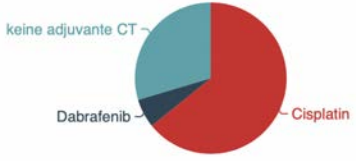
▲ 14 ▼ This partially randomized phase I/II trial studies the side effects and best dose of dabrafenib, trametinib, and navitoclax and to see how well they work in treating patients with v-raf murine sarcoma viral oncogene homolog B (BRAF) mutant melanoma or solid tumors that have spread to other parts of the body or cannot be removed by surgery. Dabrafenib, trametinib, and navitoclax may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

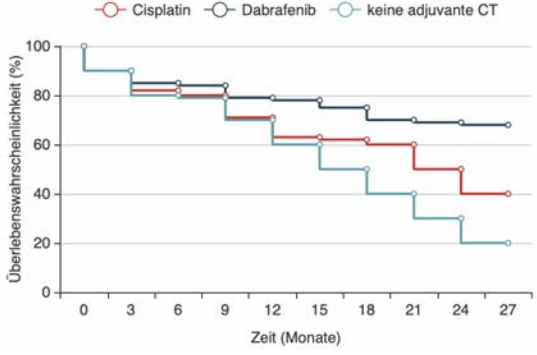
⊕ U3-1402 in Metastatic or Unresectable EGFR-mutant Non-Small Cell Lung Cancer

⊕ S1613, Trastuzumab and Pertuzumab or Cetuximab and Irinotecan Hydrochloride in Treating Patients With Locally Advanced or Metastatic HER2/Neu Amplified Colorectal Cancer That Cannot Be Removed by Surgery

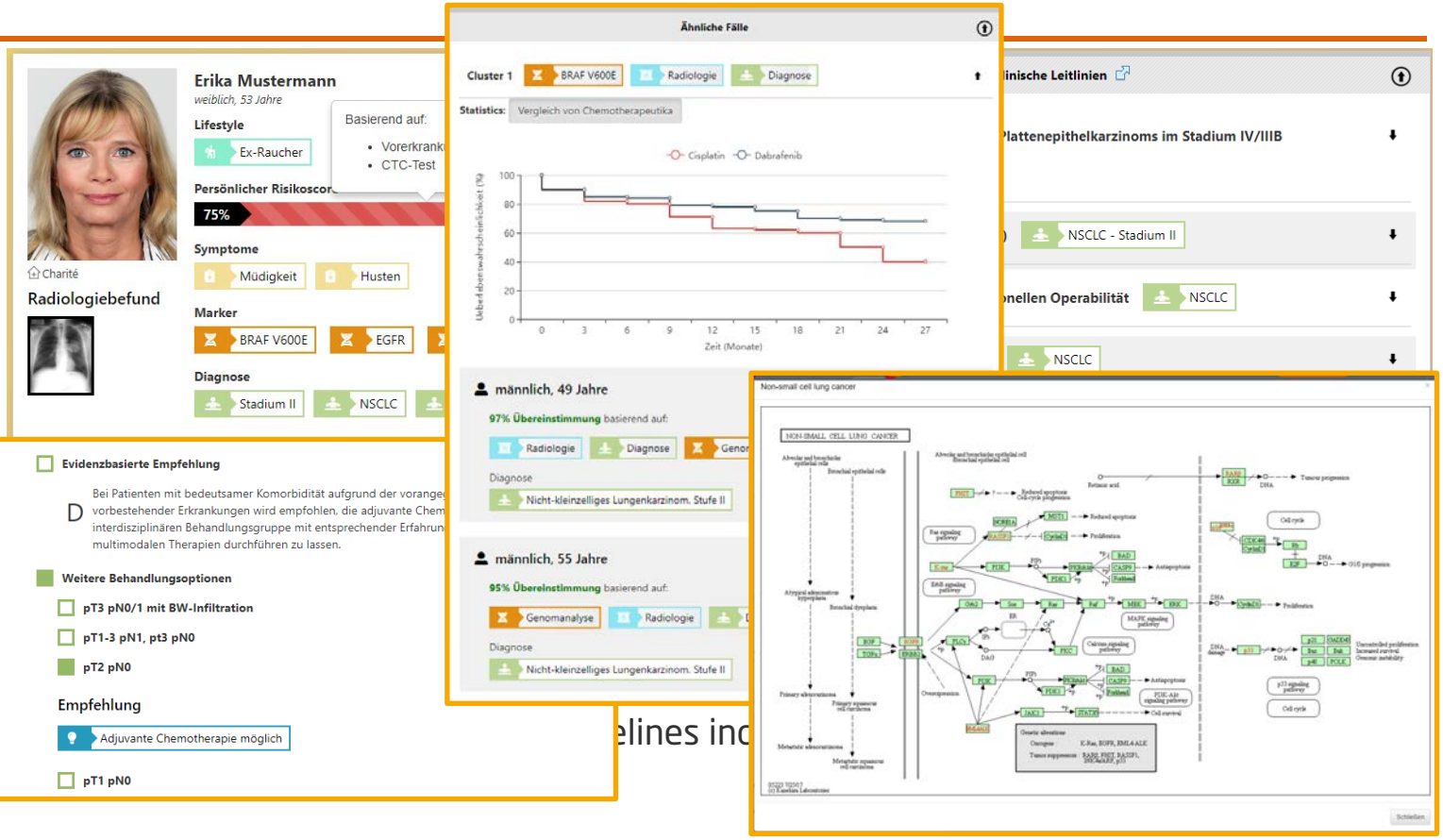
Lernende Systeme
DIE PLATTFORM FÜR KÜNSTLICHE INTELLIGENZ

Statistiken: Vergleich von Chemotherapeutika





Use Case: Medical Process and Knowledge Support



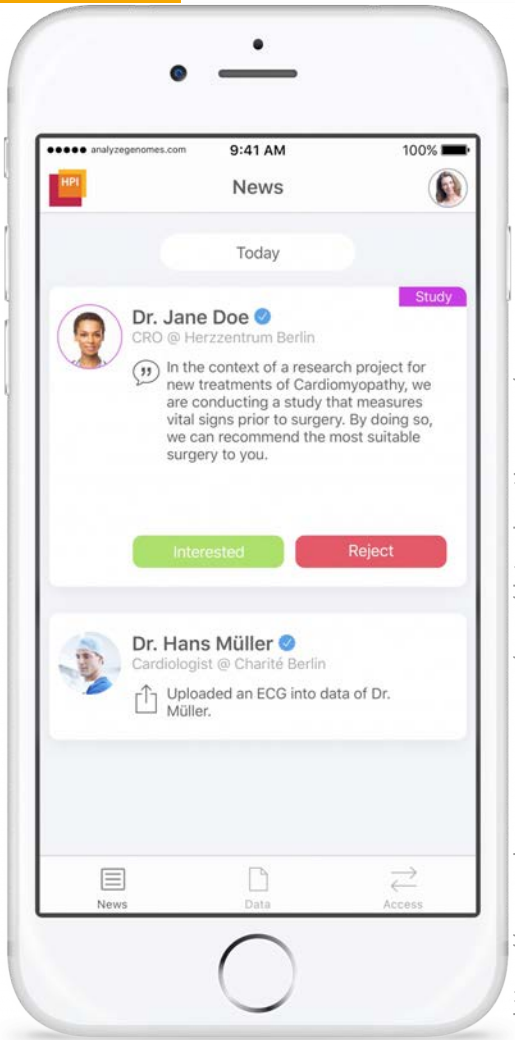
Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Patient Journey: Lung Cancer in 2024
Prevention

- Federal Institute of Digital Health Data envisioned:
  - Maintains population data for a healthier society
  - Provides access to subject-matter experts
  - Supports development of innovative DH solutions

- Data Donation Pass as citizen-facing tool:
  - Enable sovereign use of healthcare data
  - Control access to personal healthcare data
  - Donate de-identified data for research projects

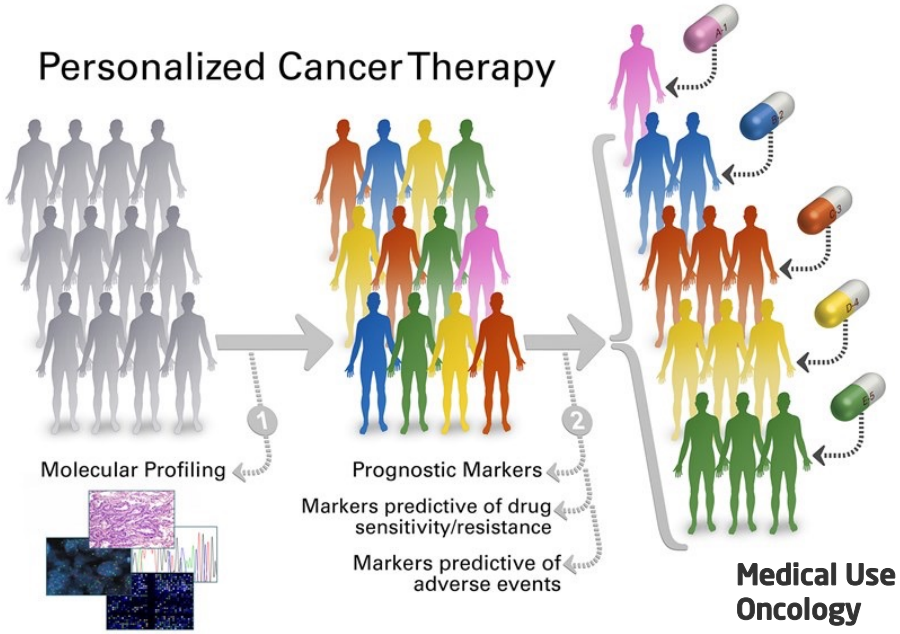


https://we.analyzegenomes.com/apps/data-donation-pass/


BACK TO THE FUTURE
MONTH DAY YEAR AM PM HOUR MIN
NOV 05 1955 06 00
DESTINATION TIME
MONTH DAY YEAR AM PM HOUR MIN
NOV 09 2023 02 05
PRESENT TIME
MONTH DAY YEAR AM PM HOUR MIN
OCT 26 1985 01 20
LAST TIME DEPARTED
http://www.int33h.com/test/tc/

Cancer Treatment Options
Personal Cancer Therapy

- No one-size-fits-all approach!
- "Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies."
- "This approach is founded upon the idea that tumor biomarkers are associated with patient prognosis and tumor response to therapy."
- 1. Stratification of patients into cohorts based on their individual biomarkers
- 2. Selection of personalized therapy alternatives per patient cohort



Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

About Biomarkers

- "Tumor biomarkers can be
  - DNA,
  - RNA,
  - protein and metabolomic profiles that predict therapy response."

- "...most recent approach is the sequencing of tumor DNA, which can reveal genomic alterations that have implications for cancer treatment."

https://pct.mdanderson.org

Cancer Treatment Options

- What kinds of treatment options for cancer have you heard of?

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

Cancer Treatment Options

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. program the immune system to detect individual 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

Level of Evidence

- **Level of Evidence (LoE)** describes the quality of existing evidence (trials, cohort studies, case-control studies, expert opinion) that address a specific clinical question
- Quality of evidence is assessed in terms of number of trials, sample size, methodology, bias, heterogeneity

LoE	Reasoning
I	Evidence from at least one large RCT of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores, 2020

Grade of Recommendation

- **Grade of Recommendation (GoR)** incorporates:
  - Quality of evidence (as in LoE)
  - Clinical significance/magnitude of benefit or harm given by a (novel) therapy

GoR	Reasoning
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores, 2020

Evidence-based Assessment of Clinical Cancer Therapies

- The higher the GoR and LoE, the more evidence about a success of the desired treatment is available

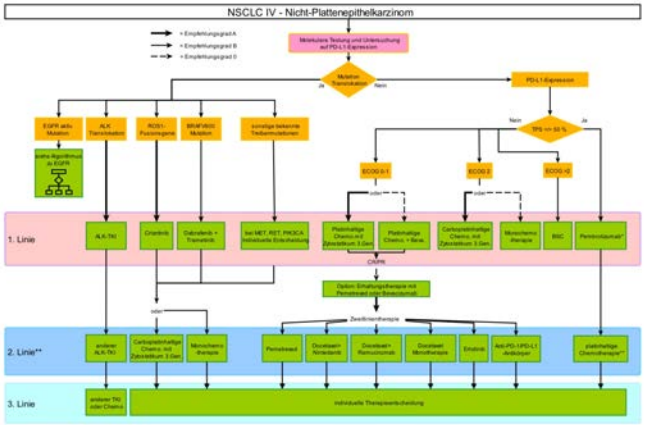
GoR	LoE	Type of Study
A	1a	Systematic review of (homogeneous) randomized controlled trials
A	1b	Individual randomized controlled trials (with narrow confidence intervals)
B	2a	Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects
B	2b	Individual cohort study / low-quality randomized control studies
B	3a	Systematic review of (homogeneous) case-control studies
B	3b	Individual case-control studies
C	4	Case series, low-quality cohort or case-control studies
D	5	Expert opinions based on non-systematic reviews of results or mechanistic studies

https://guides.library.stonybrook.edu/evidence-based-medicine/levels_of_evidence

Hasso Plattner Institut

Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms

Version 2.2 – Juli 2023
AWMF-Registernummer: 020-007OL



8.6.9 Systemtherapie bei Patienten mit BRAF-V600-Mutation

8.126	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **B**	NSCLC IV- Patienten mit nachgewiesener BRAF-V600-Mutation sollte eine Kombination aus Dabrafenib und Trametinib angeboten werden. Nicht-V600 Mutations+ NSCLC Patienten sollten in einem Thorax-Onkologischen Tumorboard besprochen werden.	
Level of Evidence **2b**	[1171], [1172], [1173]	
	Starker Konsens	

Hintergrund

Bei ungefähr 2 bis 4 % der NSCLC-Patienten liegt eine Mutation der BRAF-Kinase vor. In wiederum 1 bis 2 % dieser Patienten lässt sich eine BRAF-V600-Mutation nachweisen. Damit geht eine Aktivierung des entsprechenden Signalweges daher, welches wiederum Voraussetzung ist, dass eine antitumoröse Behandlung mit einem BRAF- und einem MEK-Inhibitor erfolgsversprechend ist.

Clinical Guidelines
American Society of Cancer Oncology

- Published via ascopubs.org
- Updated regularly
- Mostly narrative, designed for humans
- Machine-readable format missing

(ASCO Expert Panel's Statements in ***bold italics***.)

Acute Radiation Skin Reaction

- Aloe vera and hyaluronic acid cream should not be recommended for improving acute radiation skin reaction. (Grade D)

Anxiety and Stress Reduction

- Meditation is recommended for reducing anxiety. (Grade A)
- Music therapy is recommended for reducing anxiety. (Grade B)
- Stress management is recommended for reducing anxiety during treatment, but longer group programs are likely better than self-administered home programs or shorter programs. (Grade B)
- Yoga is recommended for reducing anxiety. (Grade B)
- Acupuncture, massage, and relaxation can be considered for reducing anxiety. (Grade C)

http://ascopubs.org/doi/10.1200/JCO.2018.79.2721

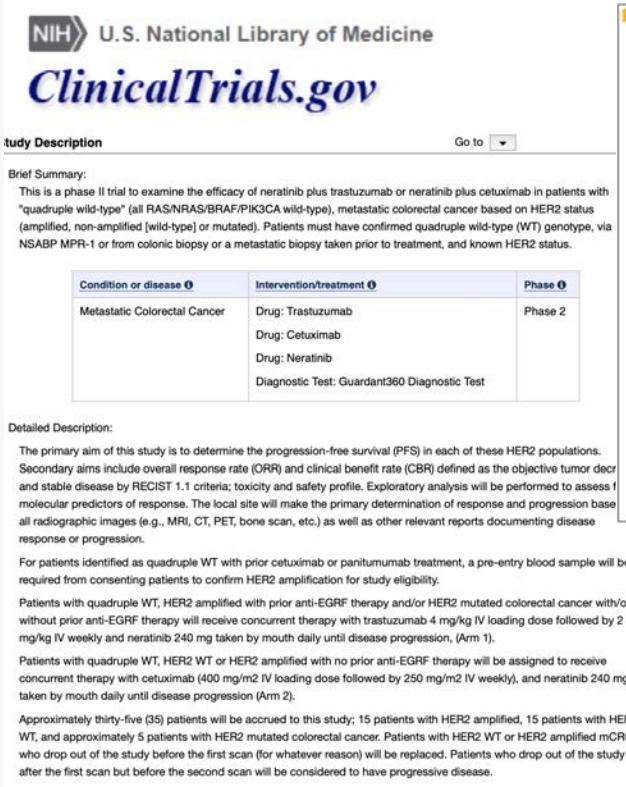
Drug Development Cycle

https://www.saama.com/blog/setting-new-standards-optimizing-clinical-development-processes-saama-launches-life-science-analytics-cloud/

Clinical Trials
International Effort towards Innovative Pharmaceuticals

Terms and Synonyms Searched:

Terms Synonyms	Search Results*	Entire Database**
cancer	64,874 studies	64,874 studies
Neoplasm	56,802 studies	56,802 studies
Tumor	14,549 studies	14,549 studies
Malignancy	2,813 studies	2,813 studies
Oncology	1,000 studies	1,000 studies
Neoplasia	560 studies	560 studies
neoplastic syndrome	541 studies	541 studies
Neoplastic Disease	18 studies	18 studies



NIH U.S. National Library of Medicine

ClinicalTrials.gov

tudy Description Go to

Brief Summary:

This is a phase II trial to examine the efficacy of neratinib plus trastuzumab or neratinib plus cetuximab in patients with "quadruple wild-type" (all RAS/NRAS/BRAF/PIK3CA wild-type), metastatic colorectal cancer based on HER2 status (amplified, non-amplified [wild-type] or mutated). Patients must have confirmed quadruple wild-type (WT) genotype, via NSABP MPR-1 or from colonic biopsy or a metastatic biopsy taken prior to treatment, and known HER2 status.

Condition or disease	Intervention/treatment	Phase
Metastatic Colorectal Cancer	Drug: Trastuzumab Drug: Cetuximab Drug: Neratinib Diagnostic Test: Guardant360 Diagnostic Test	Phase 2

Detailed Description:

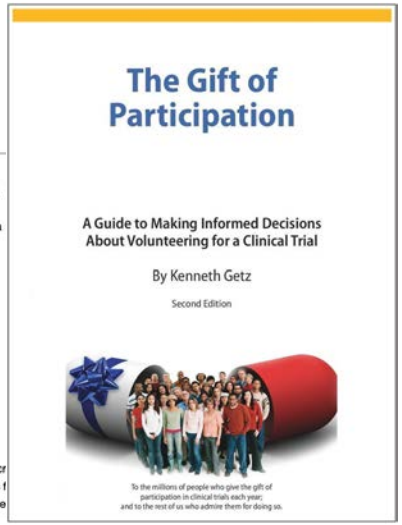
The primary aim of this study is to determine the progression-free survival (PFS) in each of these HER2 populations. Secondary aims include overall response rate (ORR) and clinical benefit rate (CBR) defined as the objective tumor decr and stable disease by RECIST 1.1 criteria; toxicity and safety profile. Exploratory analysis will be performed to assess f molecular predictors of response. The local site will make the primary determination of response and progression base all radiographic images (e.g., MRI, CT, PET, bone scan, etc.) as well as other relevant reports documenting disease response or progression.

For patients identified as quadruple WT with prior cetuximab or panitumumab treatment, a pre-entry blood sample will be required from consenting patients to confirm HER2 amplification for study eligibility.

Patients with quadruple WT, HER2 amplified with prior anti-EGRF therapy and/or HER2 mutated colorectal cancer with/or without prior anti-EGRF therapy will receive concurrent therapy with trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly and neratinib 240 mg taken by mouth daily until disease progression, (Arm 1).

Patients with quadruple WT, HER2 WT or HER2 amplified with no prior anti-EGRF therapy will be assigned to receive concurrent therapy with cetuximab (400 mg/m2 IV loading dose followed by 250 mg/m2 IV weekly), and neratinib 240 mg taken by mouth daily until disease progression (Arm 2).

Approximately thirty-five (35) patients will be accrued to this study; 15 patients with HER2 amplified, 15 patients with HER2 WT, and approximately 5 patients with HER2 mutated colorectal cancer. Patients with HER2 WT or HER2 amplified mCRC who drop out of the study before the first scan (for whatever reason) will be replaced. Patients who drop out of the study after the first scan but before the second scan will be considered to have progressive disease.



Medical Use Case Oncology

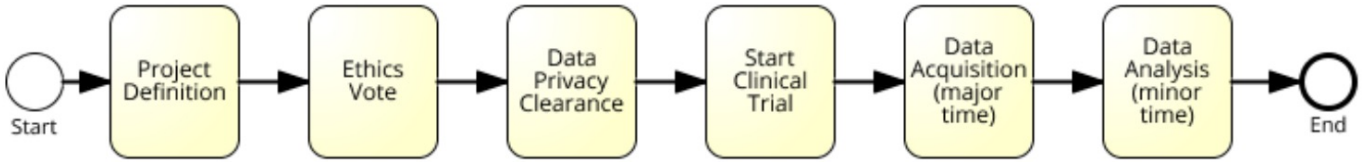
Data Management for Digital Health, Winter 2023

Clinical Trials
Good Clinical Practice (GCP)

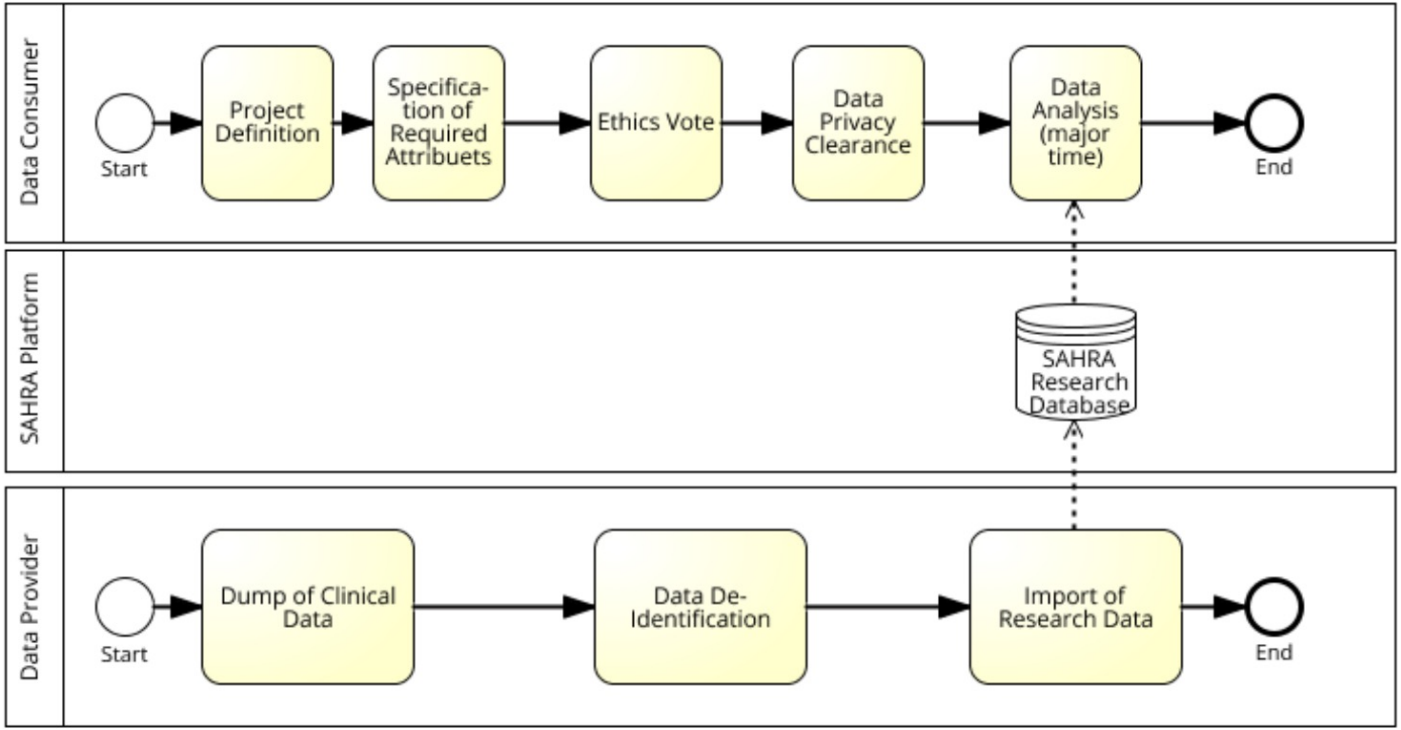
- Ethical compliance
- Risk identification and assessment
- Safety of trial subject first
- Sufficient information about investigated product
- Research protocol
- Review by Institutional Review Board (IRB) / Independent Ethics Committee (IEC)
- Qualification of investigator and staff
- Informed Consent 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



Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Molecular Tumor Board
State of the Art

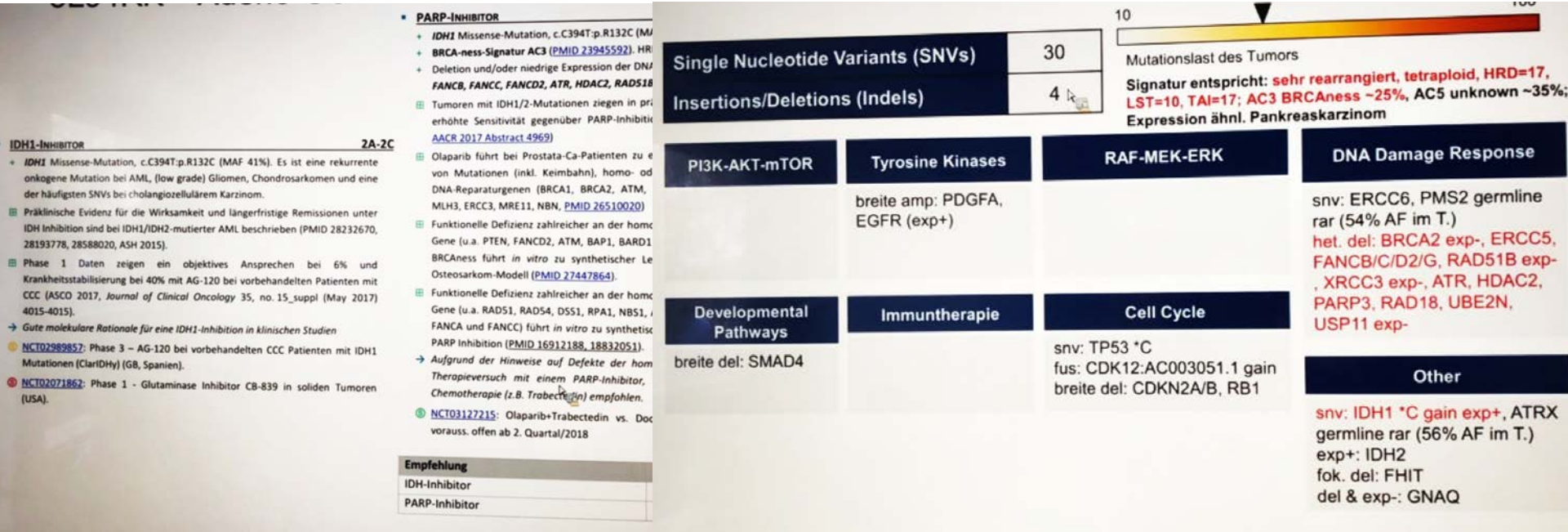
https://www.nct-heidelberg.de/en/fo -patients/treatment/tumor-board.html

Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Molecular Tumor Board
State of the Art

- Involves a lot of manual research
- Analysis results are prepared and presented during MTB session



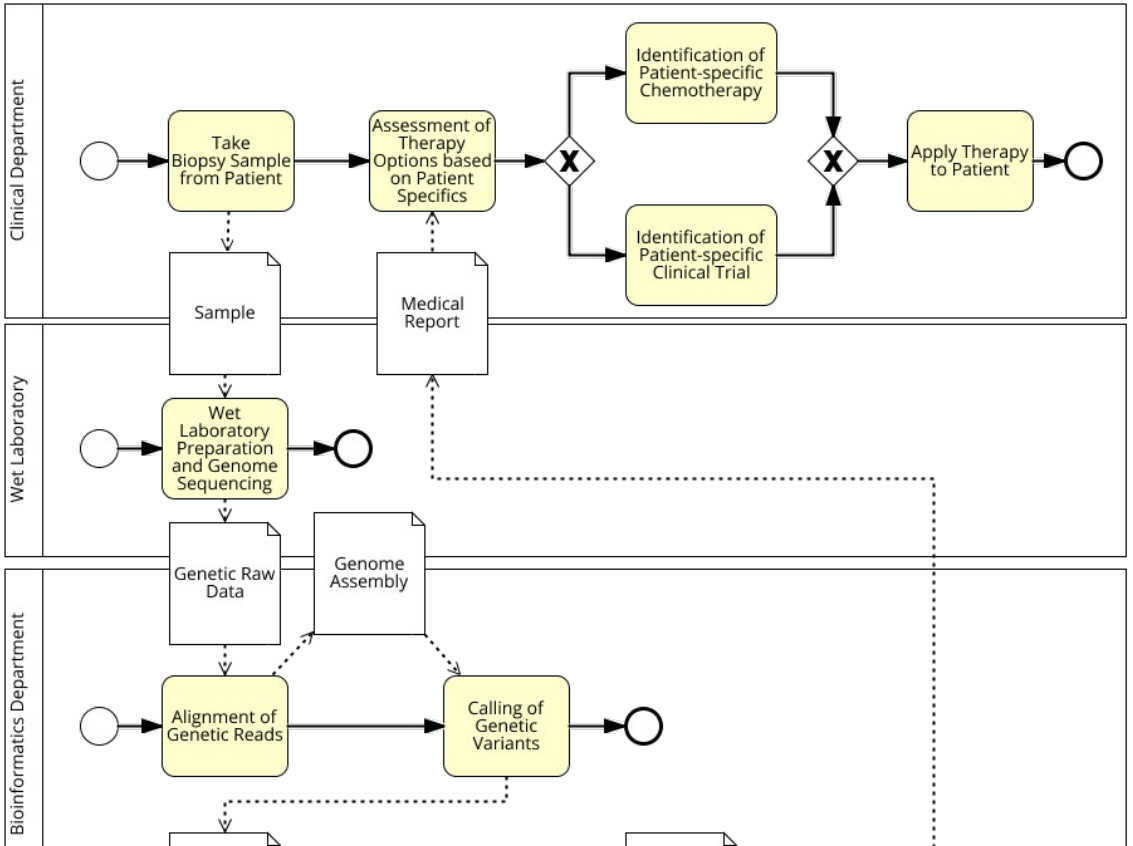
Vision of Interdisciplinary Tumor Board

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

Medical Use Case Oncology

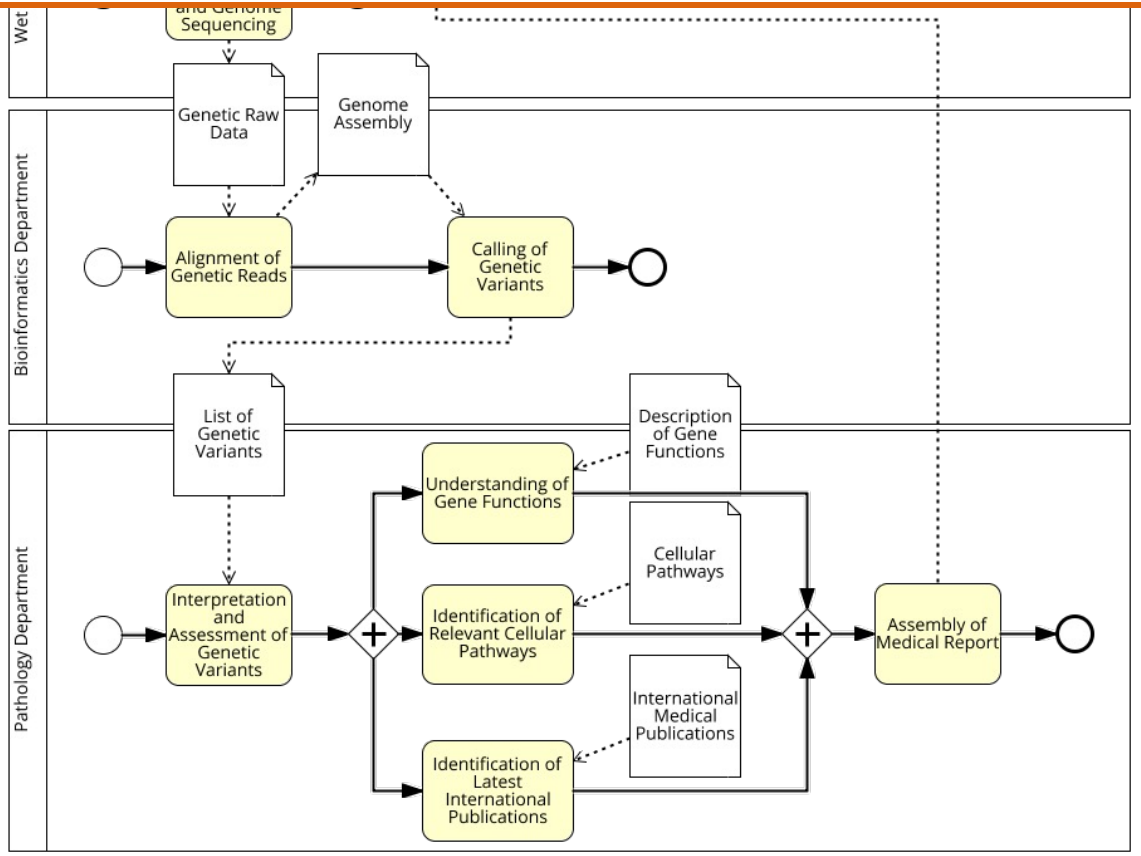
Simplified Clinical Oncology Process (1/2)



Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Simplified Clinical Oncology Process (2/2)

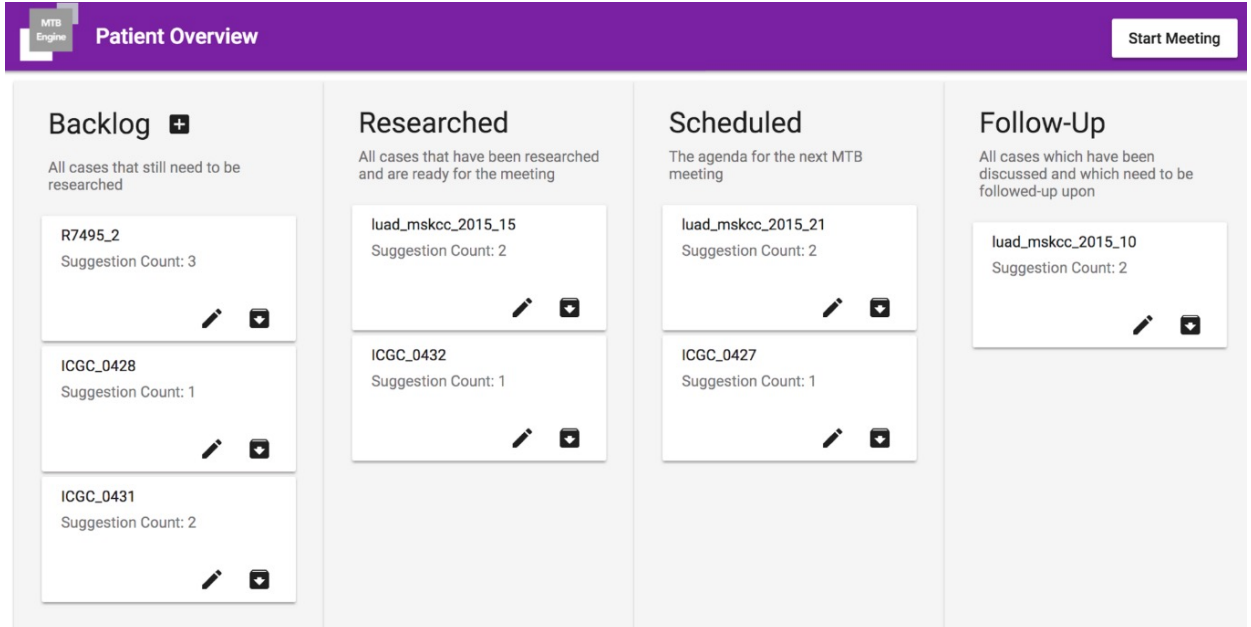


Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Molecular Tumor Board
Structured Clinical Process and Software Support

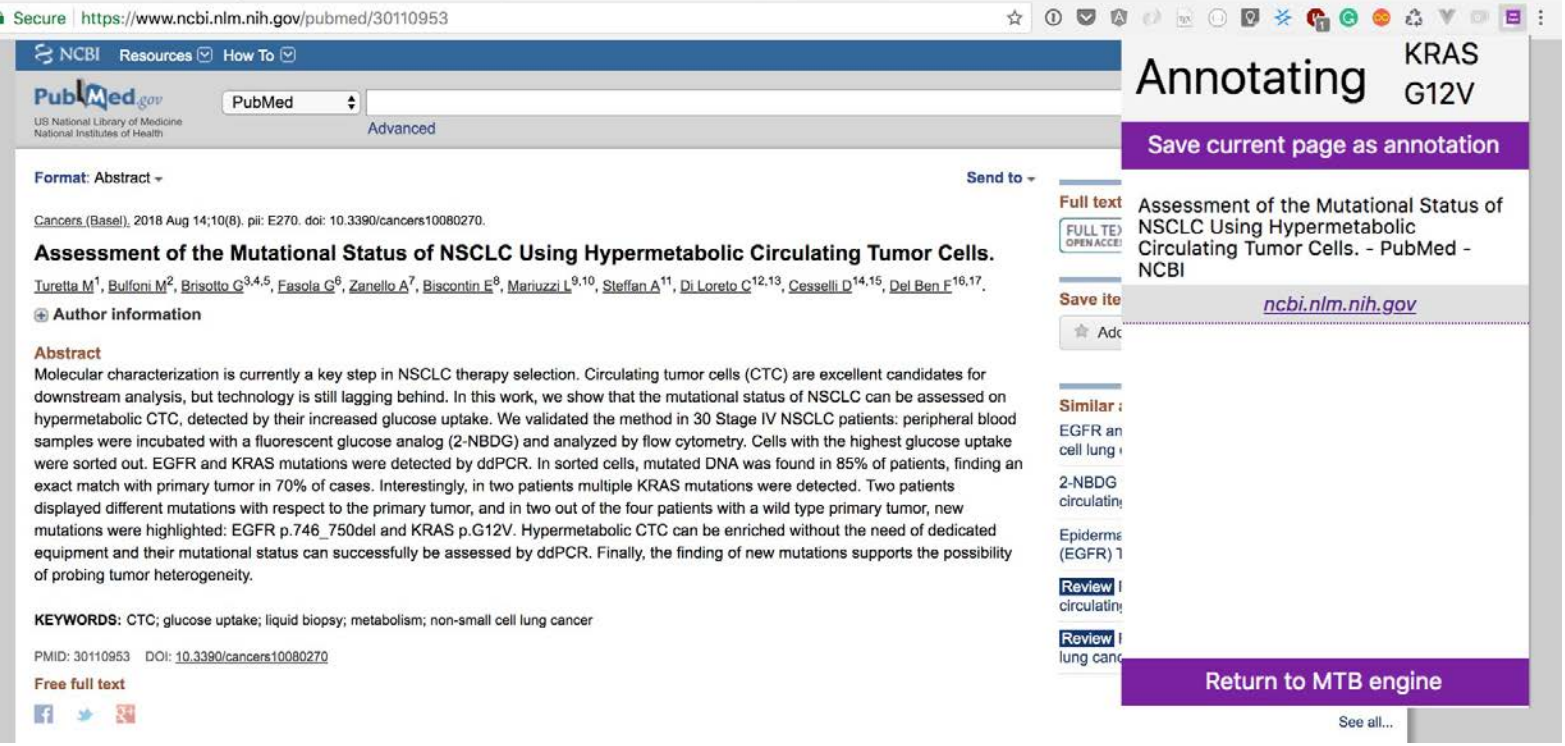
- Scrum methodology applied to Molecular Tumor Board (MTB)
- Supports preparation, actual meeting, and follow-up of the MTB
- Enables experts to work together on MTB cases



Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Molecular Tumor Board
Identification of Annotations



Medical Use Case Oncology

Data Management for Digital Health, Winter 2023

Molecular Tumor Board
Assess Therapeutic Alternatives incorporating Historic Cases

Hasso Plattner Institut

MTB Engine

LUAD_MSKCC_2015_29 53 years, White/Caucasian

Disease Information

Cancer Type: **Non-Small Cell Lung Cancer (Lung Adenocarcinoma)**
Survival since initial diagnosis: **59.3 months**
Diagnosis Age: **48**

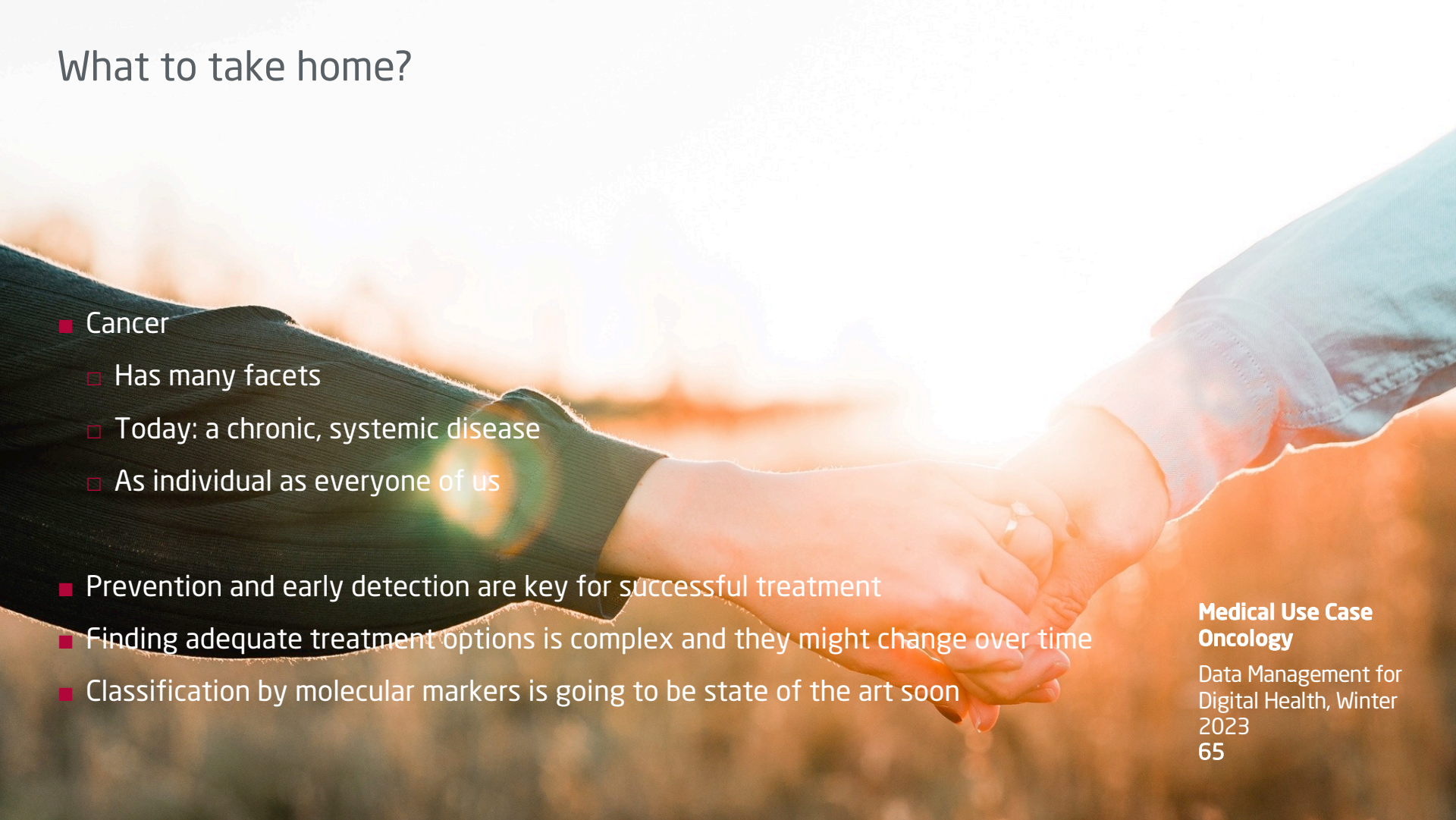
Therapeutic Suggestions | Mutations

Therapeutic Suggestions

Gene	Protein	Type	Drug	Evidence Level	Reasoning
KRAS	G12V	Missense Mutation	dual PI3 kinase/mTOR inhibitor GDC-0980	1a	

Organic cation/carnitine transporter OCTN2 (SLC22A5) -207C>G (rs2631367) polymorphism is not associated with male infertility. ncbi.nlm.nih.gov

What to take home?



- Cancer
  - Has many facets
  - Today: a chronic, systemic disease
  - As individual as everyone of us
- Prevention and early detection are key for successful treatment
- Finding adequate treatment options is complex and they might change over time
- Classification by molecular markers is going to be state of the art soon