Die PRAEGNANT Studie – eine lebenslange, klinische und molekulare Studie

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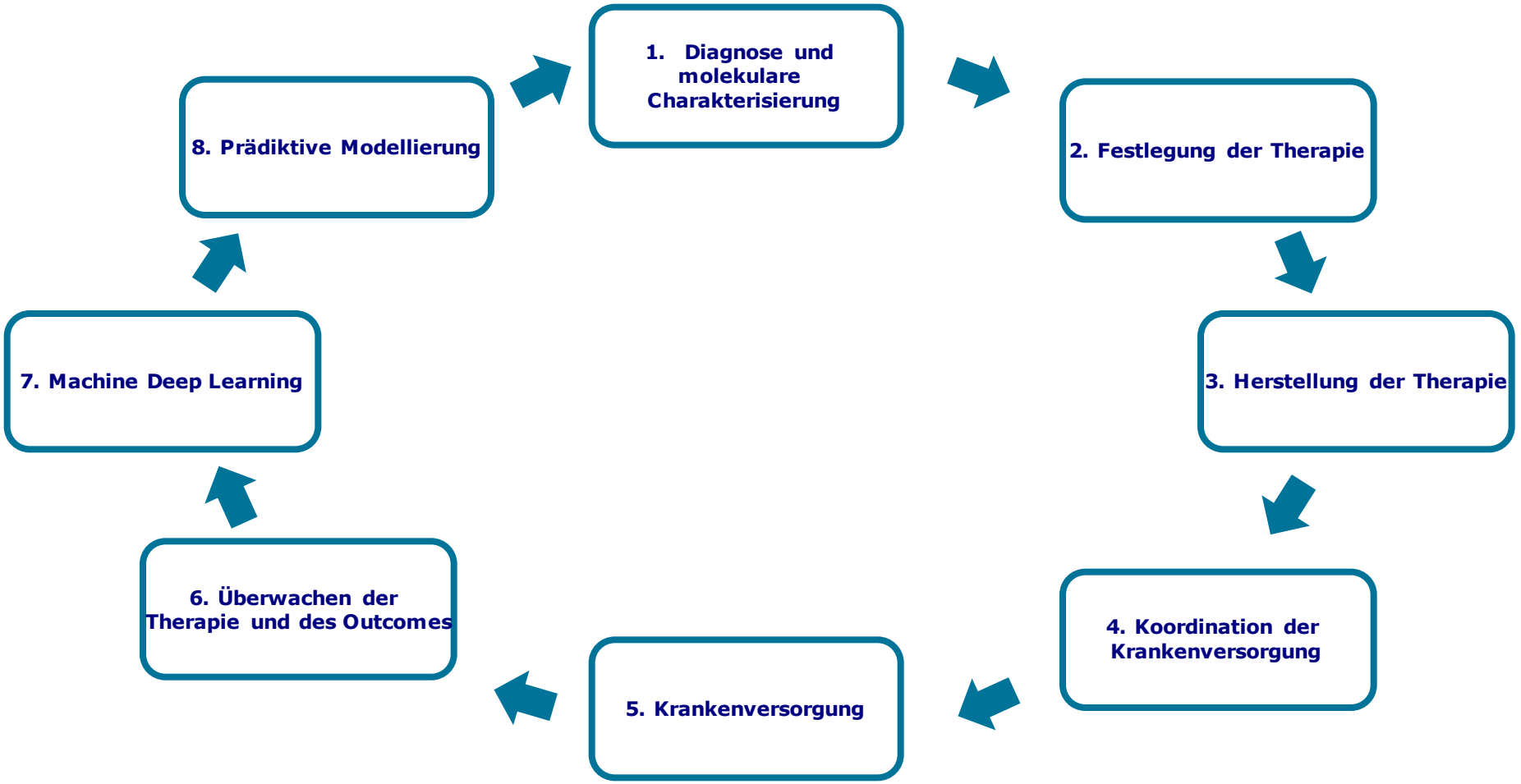
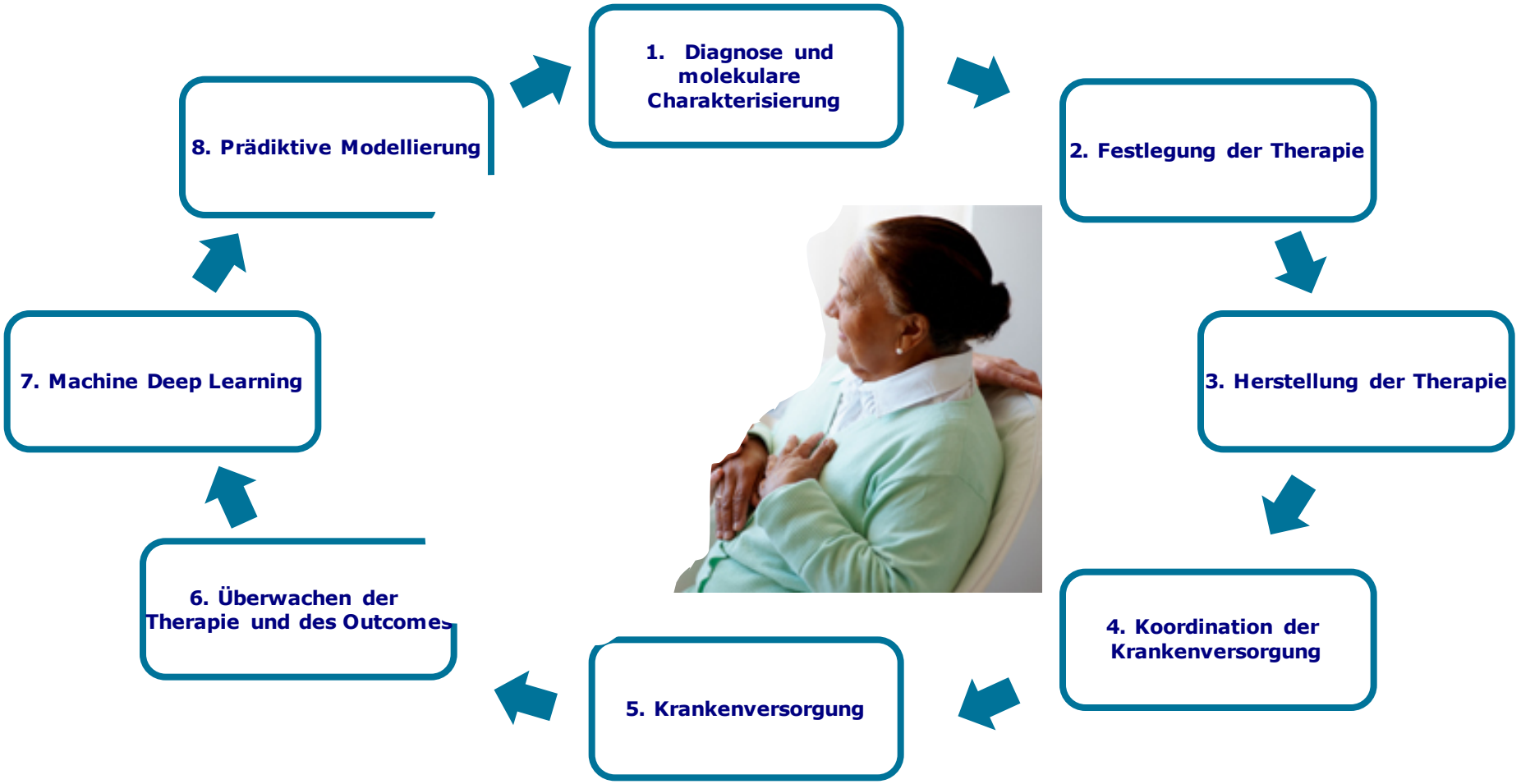
Integration von molekularen Tests in die Krankenversorgung und Forschung



Integration von molekularen Tests in die Krankenversorgung und Forschung



Integration von molekularen Tests in die Krankenversorgung und Forschung

Wie kann diese Krankenversorgung angeboten werden

- Was ist die beste Behandlung mit der niedrigsten Toxizität
- Wie kann ich Lebensqualität verbessern

Welche molekularen Tests?

Klinsiche Studien

Patientinnen Kommunikation

Medikamente Von anderen Krankheiten

Bezahlung?

Welche Nicht-molekularen Tests?

Prädiktion von Seiteneffekten

Kombinations-Therapien

Wie kann diese Krankenversorgung angeboten werden

- Was ist die igsten Toxizität
- Wie kann i

Welche molekularen Tests?

amente nderen heiten

Welche Nicht-molekula Tests?

inations- rapien

Lead: Prof. Dr. med. Diethelm Wallwiener

Co-Lead: Prof. Dr. med. Hans Tesch

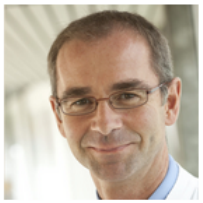
Prof. Dr. med. Peter A. Fasching

Prof. Dr. med. Sara Brucker

Prof. Dr. med. Andreas Schneeweiss

Prof. Dr. med. Peyman Hadji

Prof. Dr. med. Tanja Fehm


Prof. Dr. med. Wolfgang Janni

Dr. med. Friedrich Overkamp

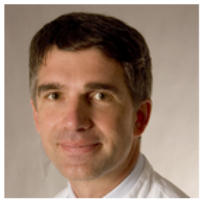
Prof. Dr. med. Diana Lüftner

Prof. Dr. med. Michael P. Lux

PD Dr. Markus Wallwiener

Dr. Johannes Ettl

PD Dr. med. Andreas Hartkopf


Prof. Dr. Volkmar Müller

Prof. Dr. Florin-Andrei Taran

Dr. Thomas Spall

Dr. Erik Belleville

Wie kann diese Krankenversorgung angeboten werden

- Was ist die igsten Toxizität
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Welche molekularen Tests?

amente nderen heiten

Welche Nicht-molekula Tests?

inations- rapien

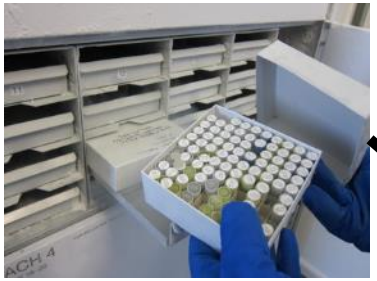
Nutzung von Daten ähnlich kinischer Studien für die Krankenversorgung

Biomaterials

Data

Patients directly enter QoL Data

Central Biobank



Central Database

Patient Data and Biomaterial Operator (PDBO)

Specialized Partners

Clinical Studies

Big Data Analysis

Molecular Diagnostics

others

Hamburg
Leer
Szczecin
Charitéplatz
Potsdam
Brunswick
Netherlands
Bottrop
Germany
Bonn
Cologne
Krankenhaus Nordwest
Prague
Luxembourg
Mannheim
Erlangen
Czech Rep
Deggendorf
Tübingen
Augsburg
Salzburg
Basel
Zürich
Austria

Warum eine Studienumgebung

- In Zeiten von Wiki und Facebook ist es
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  au
- Pa
  Stu
  Vo
  kö

1) Ich erkläre mich damit einverstanden, dass im Rahmen dieses klinischen Diagnostikprojekts erhobene Daten, insbesondere Angaben über meine Gesundheit und ggf. genetische Daten, in Papierform und auf elektronischen Datenträgern bei meinem behandelnden Arzt aufgezeichnet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden:

   d) an meinen behandelnden Arzt, sofern sich aus den Ergebnissen molekularer Tests Hinweise für eine Eignung für eine Studienteilnahme ergeben (bitte unterhalb ankreuzen, wenn Sie eine Information über die Ergebnisse molekularer Tests wünschen).

      ☐ **JA**, ich möchte über die molekularen Untersuchungsergebnisse u.a auch genetische vererbbare Veränderungen für Studienzwecke informiert werden.

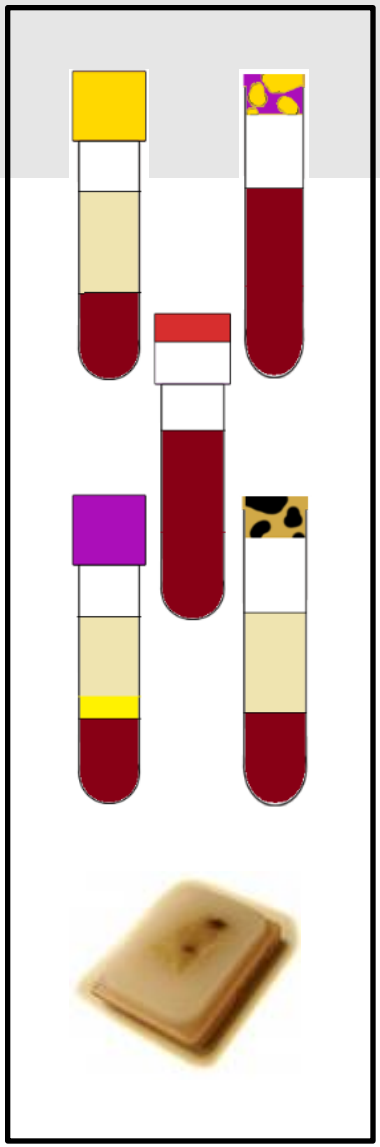
      ☐ **NEIN**, ich möchte nicht über die molekularen Untersuchungsergebnisse u.a auch genetische vererbbare Veränderungen für Studienzwecke informiert werden.

The PRAEGNANT Study Network

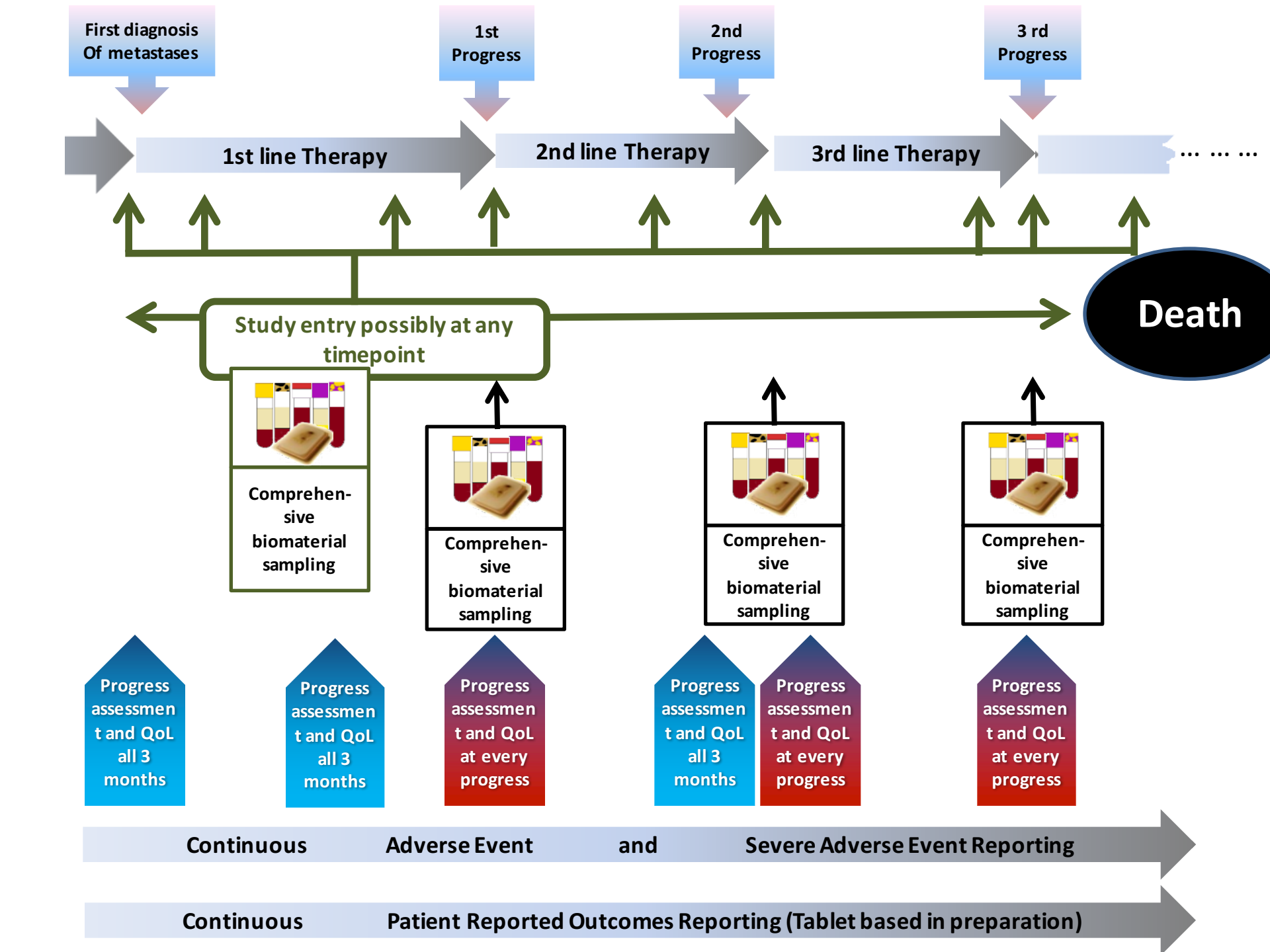
Praegnant (german) = concise (english)

pregnant (english) = schwanger (german)

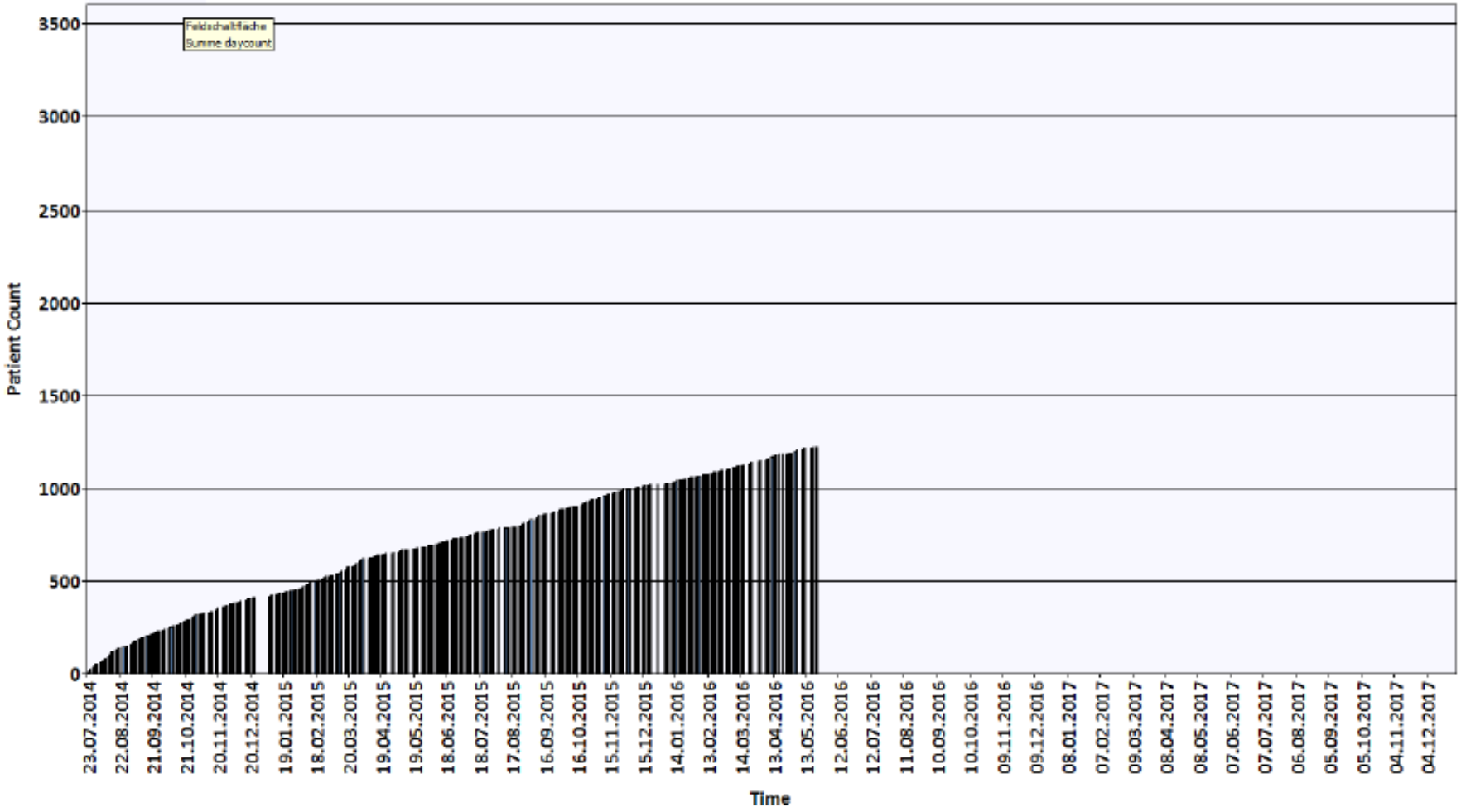
- Prospective Registry study of metastatic breast cancer patients in 60 hospitals
- N=1750, Recruitment since Aug 2015: n=1080
- Objectives: OS, PFS, QoL, Adverse Events
- Comprehensive Biomaterials at study entry and every 3 months
  - FFPE of primary tumor and metastasis
  - Serum, Plasma
  - ctDNA, CTCs
  - Leukocyte RNA (PaxGene)



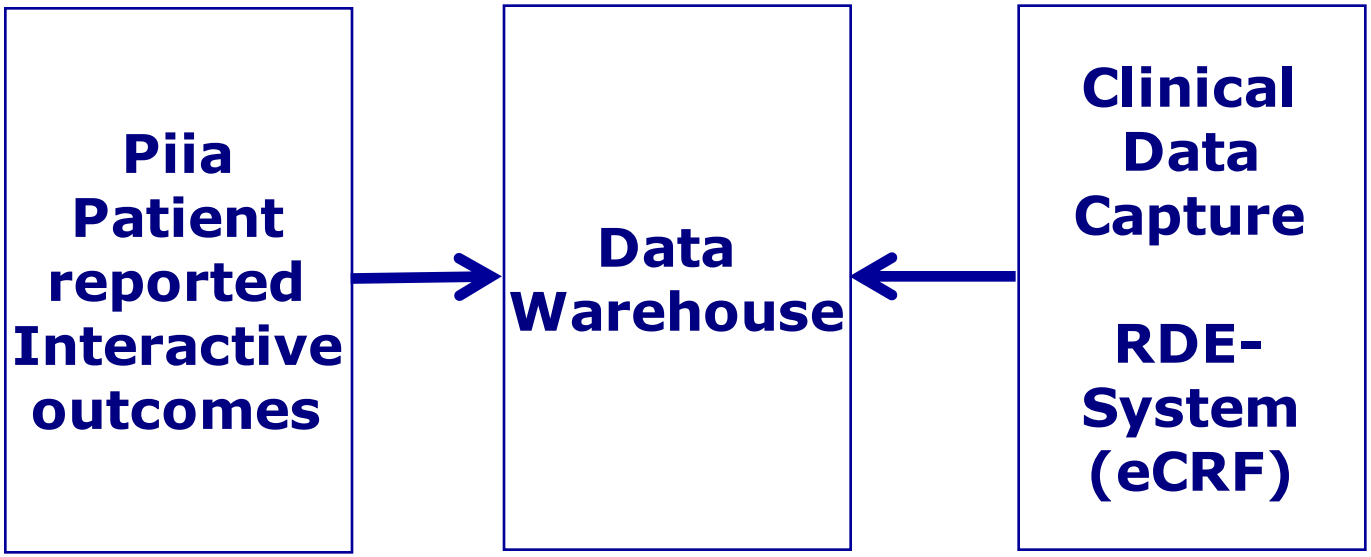
Plasma	Proteinanalysis
Serum	Proteinanalysis
Germline DNA	Chromosomal Abberationen, Mutations, Amplifications Deletions
micro-RNA	amount, patterns, regulation of gene expression
circulating Tumor DNA	Chromosomal Abberationen, Mutations, Amplifications Deletions
Leukocyte RNA	Expression of Leukocyte-RNA
CTCs	Chromosomal Abberationen, Mutations, Amplifications Deletions, RNA Expressio, Protein-Analysis, Cell culture
FFPE	DNA-Analysis, RNA-Analysis, Proteinanalysis


First diagnosis Of metastases
1st Progress
2nd Progress
3 rd Progress
1st line Therapy
2nd line Therapy
3rd line Therapy
… … …
Death
Study entry possibly at any timepoint
Comprehen-sive biomaterial sampling
Comprehen-sive biomaterial sampling
Comprehen-sive biomaterial sampling
Comprehen-sive biomaterial sampling
Progress assessmen t and QoL all 3 months
Progress assessmen t and QoL all 3 months
Progress assessmen t and QoL at every progress
Progress assessmen t and QoL all 3 months
Progress assessmen t and QoL at every progress
Progress assessmen t and QoL at every progress
Continuous Adverse Event and Severe Adverse Event Reporting
Continuous Patient Reported Outcomes Reporting (Tablet based in preparation)

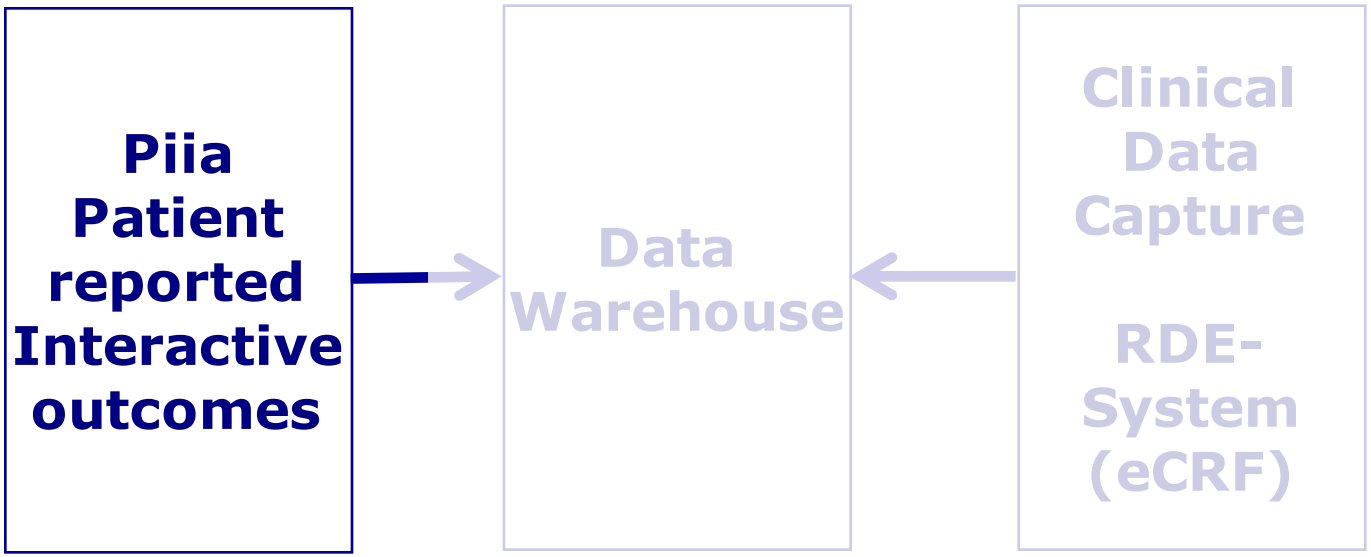
RECRUITMENT



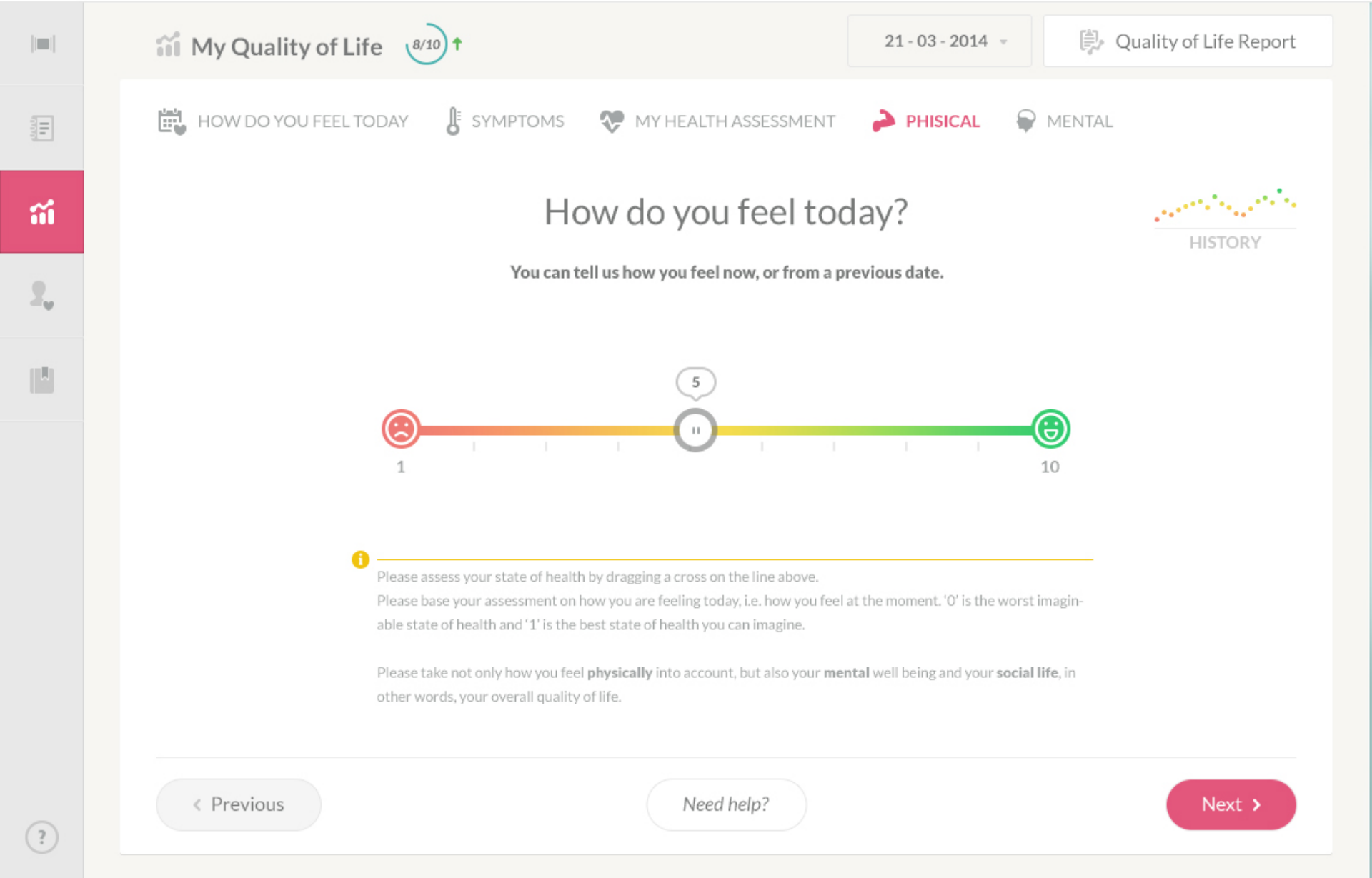
Data Management



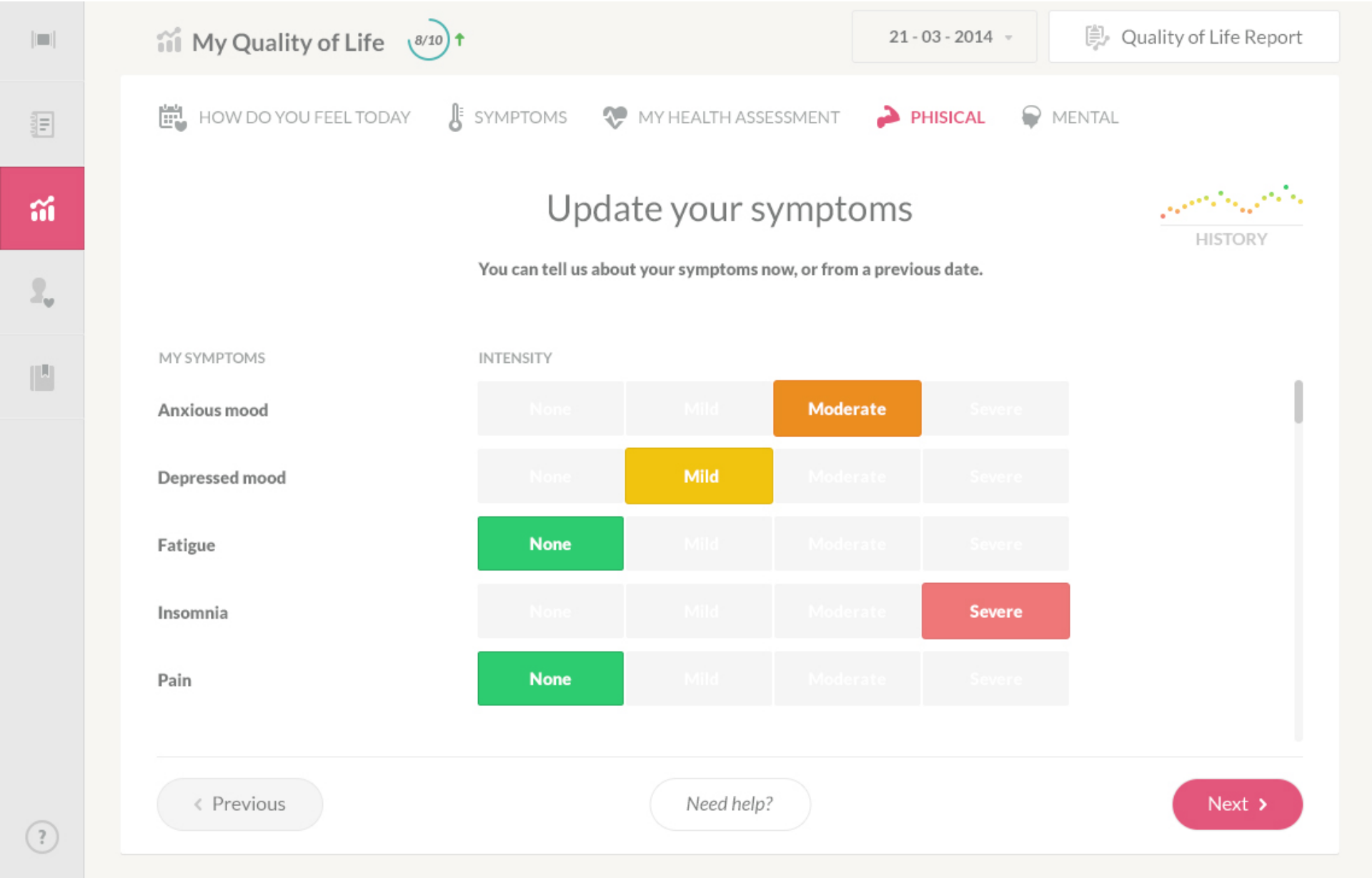
Data Management



PiiA – Self Rated Health



PiiA – Smartvisit Adverse events tracking



PiiA – Smartvisit Adverse events tracking – extended version

Launch Q2/2016

Nausea

Wie STARK war Ihre Übelkeit im schlimmsten Fall?

INTENSITY LAST WEEK

GAR NICHT | EIN WENIG | SEHR

Wie HÄUFIG hatten Sie Übelkeit?

FREQUENCY LAST WEEK

Nie | Selten | Gelegentlich | **Haufig** | Fast immer

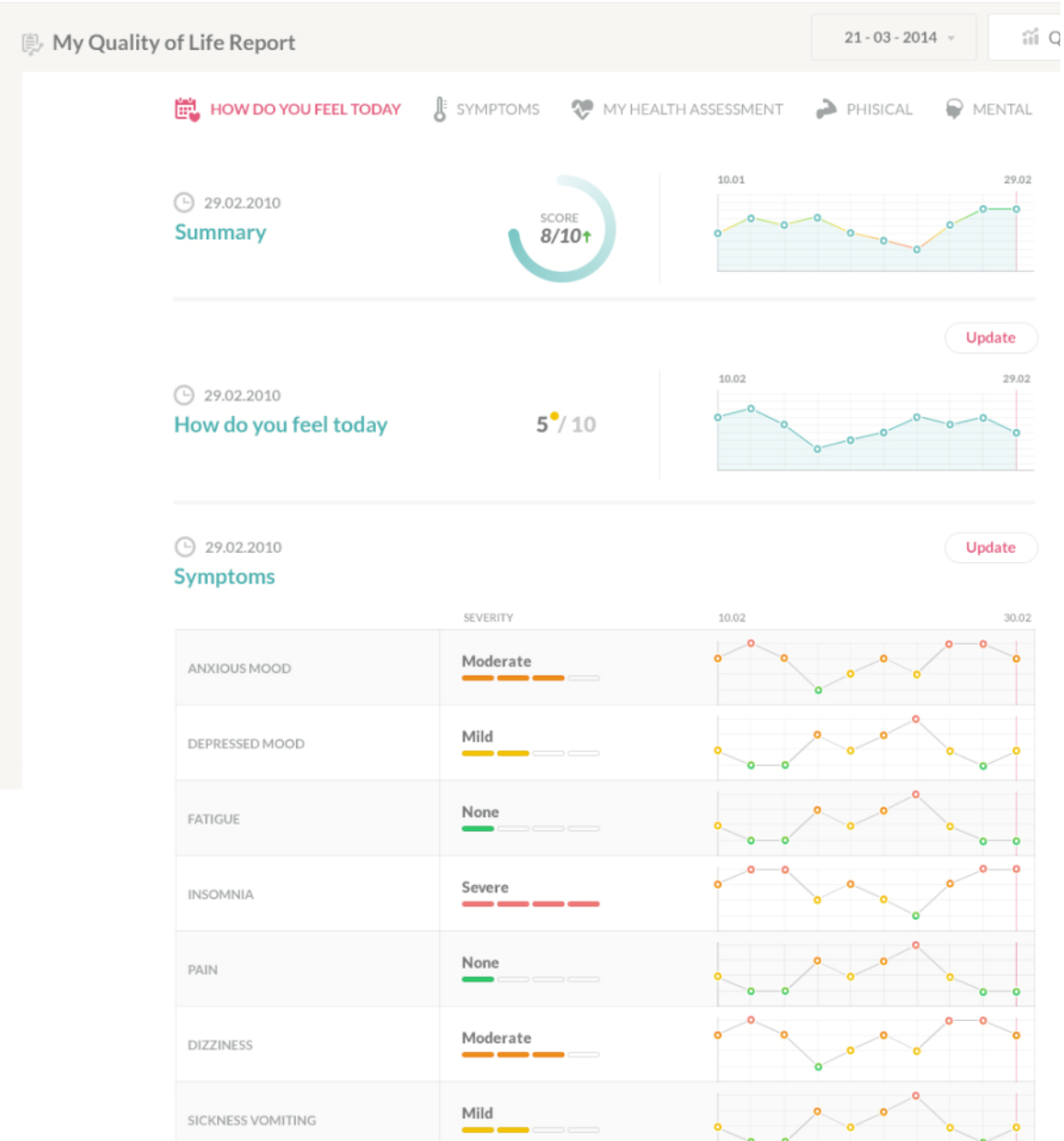
Wie SEHR haben Schmerzen Sie in Ihren alltäglichen Aktivitäten GESTÖRT?

BOTHERED LAST WEEK

GAR NICHT | EIN WENIG | SEHR

‹ Previous | *Need help?* | Next ›

PiiA InSights – Patient / Doctor point of care report



Launch
Q2/2016

Versatile cloud based QOL tracking platform

Assessment toolbox

Patient-reported outcomes (PRO)
Quality of life (**EORTC QLC 30, EQ-5D, FACT-B**)

PROMIS
Patient Reported Outcomes Measurement Information System

PRO CTCAE
Adverse events tracking

Psychological
(Distress-Thermometers, PHQ-9)

Physical Activity
IPAQ

Nutrition
(Food Frequency Assessment)

Compliance
Assessment of factors influencing treatment adherence

Assessment Wizard

1. Set-up tools

2. SmartVisits

3. Collect PRO data

4. Analyze

Benefits

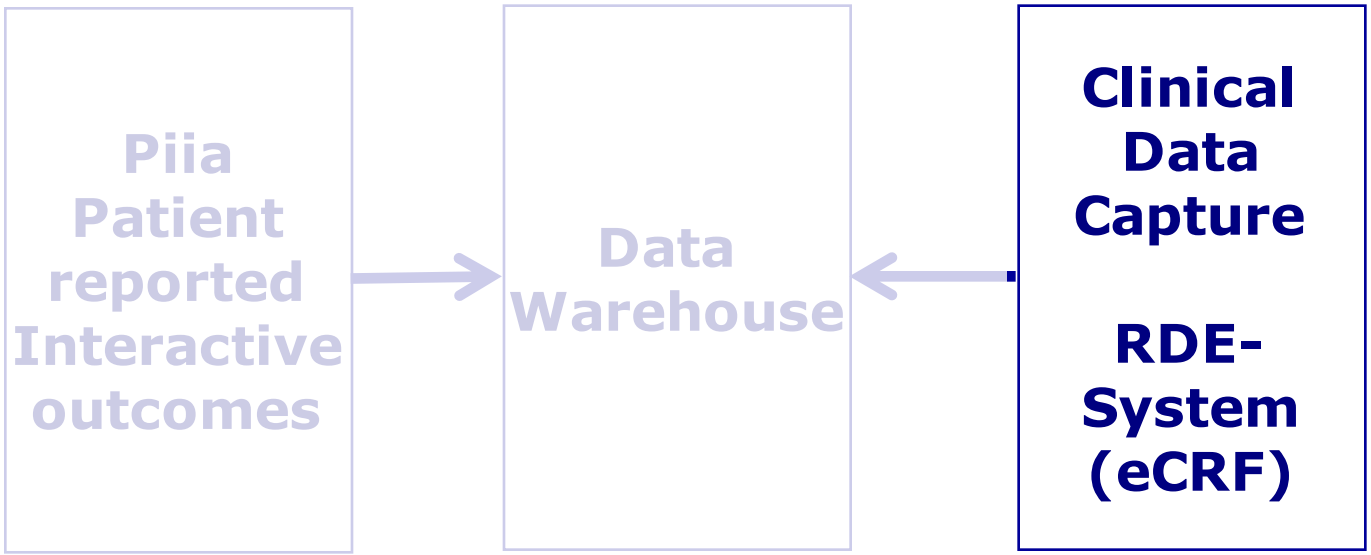
Information
In-depth guidance and edutainment

Screening
Detection of patients at risk for AEs

Monitoring
QoL, Lifestyle and Adverse events

Take Action
Individualized tipps and alerts

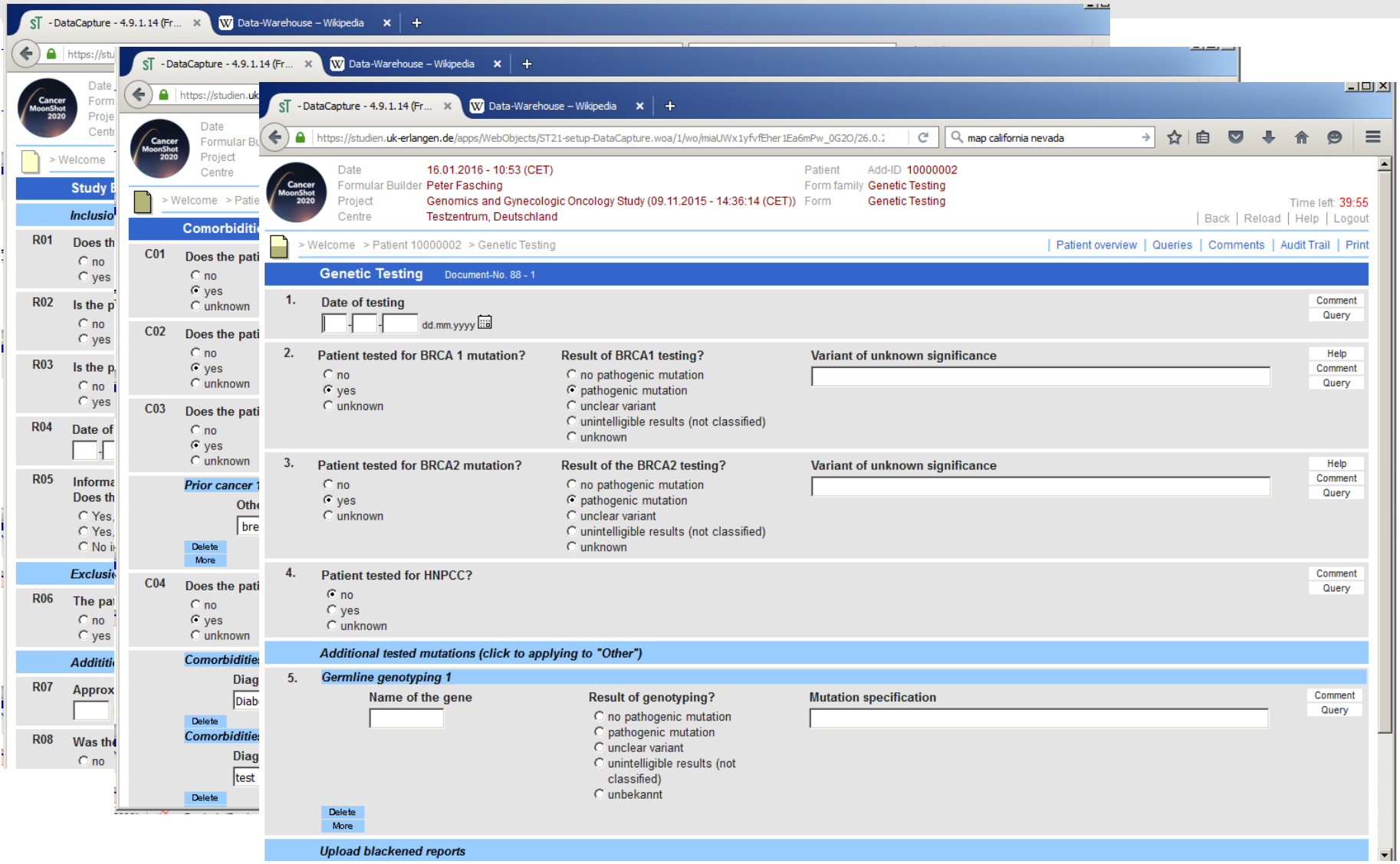
Data Management



eCRF

- Umfangreiche Datensammlung
- Ko-Morbiditäten
- Behandlung von Ko-Morbiditäten
- Epidemiologische Daten
- Alle Krebstherapien
- Aktuelle Adverse Events
- State of the Art eCRF (aber viel mehr Daten)

Screenshots



Data Structure was designed witht the main aim of competitive scientific analyses

- Überlebensanalyse
- Prädiktion des Therapieansprechens
- Prädiktion der Lebensqualität
- Mindset: Try a „full take“

Utilization Registry Data to improve healthcare

Improve healthcare / Standard of Care

Design of clinical Trials

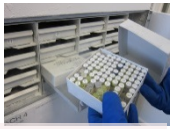
Selection of patients for Clincial trials

Beispiel 1

Workflow eines next generation Tests

Register Patient and transfer Data and Biomaterials to Data and Biomaterial Center

Biomaterials


Central Biobank

Central Data Server

Patient Reported Outcomes

Whole Genome Sequencing and Proteomics

Big Data Mining for Treatment and study options

Whole Genome Sequencing

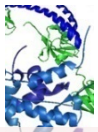
Bioinformatics Clinical Genome Analysis

Patient Data Analysis

Big Data Analysis

Return Report to participating site

Genomic Results


Proteomics

ALTERATIONS IDENTIFIED IN:
3 TREATABLE genes,
1 KNOWN ONCOGENE, and
3 KNOWN TUMOR SUPPRESSORS
Summary and detail Reports

Active Clinical Trials

Target	Drug
DEPTOR Amplification (13.6x), RPTOR Amplification (14.1x), RPTOR Amplification (26.2x), RPTOR Amplification (13.9x)	MLN0128
IGF1R Amplification (52.8x), IGF1R Amplification (52.5x)	Ganitumab

Treatment and Study Suggestions

Integration of whole genomics and data analysis in tumor board at study site

Tumor BOard

Results Dissemination

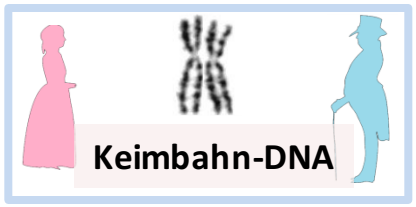
Patient Integration

Determine Individual Treatment

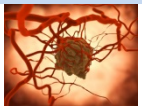
Standard Treatment	Compassionate Care	Phase III Study	up to 10 Phase II Studies

Wissenschaftlicher Fortschritt

Ein Test, eine Interpretation.

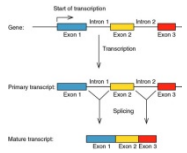


Keimbahn-DNA



Tumor-DNA

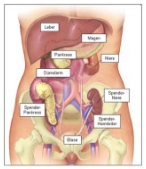
Von der DNA



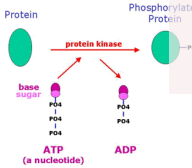
Splicing

Organ

Tumor-RNA

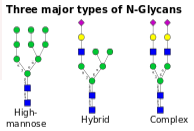


zur RNA



Phosphory-lisierung

Glykosy-lierung



Protein

zum Protein

Detektion

Therapieprädiktion

Prognose

Biologische Funktion

zur Funktion.

Kontinuierliches update der Interpretation durch “Supercomputer” (maschnielles Lernen)

Akademia
- Kliniken/Medizin
- Informatik/Bioinformatik
- Künstliche Intelligenz
- Rechenzentren

Health Care Systems
- Blue Cross Shield
- Anthem
- Providence
- UCLA
- ….

Big Pharma
- Google
- Microsoft
- SAP
- SIEMENS
- NantWorks

Regierung

Testresultat in verständlicher Form (GPS Cancer)

Zusammenfassung

NANTOMICS GENOME PROTEOME SEQ (GPS) CANCER REPORT

General Information

ID 0148452628 SEX

PATHOLOGY Breast DATE ANALY

Genome Proteome Seq (GPS) Findings

TARGET	DRUG	STATUS	ADDITIONA
RPTOR Amplification (26.2x)	1. **MLN0128**	Investigational	Activity agair
RPTOR Amplification (14.1x)			+ Drug 1 listed
RPTOR Amplification (13.9x)			+ Drug 1 listed
IGF1R Amplification (52.8x)	2. **Ganitumab**	Investigational	Activity agair
IGF1R Amplification (52.5x)			+ Drug 2 listed
DEPTOR Amplification (13.6x)			+ Drug 1 listed

Additional Findings

ACMG-RECOMMENDED INCIDENTAL FINDINGS Germline variants in BRCA2

MICROSATELLITE INSTABILITY Tumor genome does not ex

CYTOGENETIC ANALYSIS Sample purity is estimated t

COMPLEX PHENOMENA *Kataegis, Extreme gains in* detected.

MUTATION SIGNATURES The mutational signature as active.

SAMPLE	WHOLE GENOME	EXO
Tumor	757x, Aug 25, 2015	Nor
Matched-Normal	36.7x, May 26, 2015	Nor
Provenance	99.5% match	

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Studienvorschläge

NANTOMICS GPS CANCER REPORT ID 0148452628

FDA Approved Against This Target

No FDA-approved targets were identified in this tumor sample.

FDA Approved But Not Against This Target

No relevant targets were identified in this sample.

Active Clinical Trials

A total of 2 clinical trials are actively recruiting participants for drugs predicted to have potential respo detected. In addition to testing a relevant drug, the clinical trials listed below must also match at least on If too few trials match the tissue search term used here, consider adding additional tissue-specific search 15 clinical trials satisfying these criteria are listed in the table below. Click on the NCT ID link to find out m the clinicaltrials.gov website.

Drugs under investigation in active clinical trials likely relevant to patie

TARGET
DEPTOR Amplification (13.6x), RPTOR Amplification (14.1x), RPTOR Amplification (26.2x), RPTOR Amplification (13.
IGF1R Amplification (52.8x), IGF1R Amplification (52.5x)

Potentially Resistant Therapies

No resistance biomarkers were identified in this tumor sample.

Mutationsliste

NANTOMICS GPS CANCER REPORT ID 0148452628

Mutation Analysis

A total of 493,117 somatic variants were identified in this patient sample and supporting data as described in the Methods. The tumor sample's mutation ra this sample's mutation rate to the mutation rate of 13 cancer types sequenc according to pathogenicity category and variant class can be found in the app

The table below lists lists up to 25 of the top ranked variants according to p determining the variant's CATEGORY in addition to any known clinical associat estimate of 57% and a ploidy estimate of 2.4n.

Top mutations ranked by pa

CATEGORY	GENE	CLASS	VARIANT	ALT. / TOTAL	DI
Pathogenic	GATA3	Frame Shift	p.G444Gfs*63	24 / 88	Cl
Pathogenic	NEB	Nonsense	p.K4523*	11 / 51	H
Pathogenic	NCOR1	Nonsense	p.E304*	6 / 18	Pa
Pathogenic	LEPR	Frame Shift	p.S1076Sfs*3	4 / 21	H
Likely Path.	MFGE8	Missense	p.E197Q	31 / 404	Cl
Likely Path.	MFGE8	Missense	p.R206I	29 / 422	Cl
Likely Path.	ZNF117	Missense	p.E189G	5 / 56	Su
Unkn. Sig.	MYLK2	Frame Shift	p.P69Ffs*112	17 / 44	Cl
Unkn. Sig.	PLEKHG6	Nonsense	p.Q780*	17 / 63	Cl
Unkn. Sig.	SLITRK2	Missense	p.G539W	14 / 54	Cl
Unkn. Sig.	TRIP12	Missense	p.R18G	11 / 83	Su
Unkn. Sig.	KCNJ3	Missense	p.E449V	9 / 59	Su
Unkn. Sig.	ZNF91	Missense	p.G110E	5 / 55	Su
Unkn. Sig.	RUNX1T1	Frame Shift	p.L62Lfs*35	4 / 32	Su
Unkn. Sig.	CDC27	Missense	p.L275V	4 / 30	Su
Unkn. Sig.	DHX9	Missense	p.I992S	4 / 49	Su
Likely Benign	KIAA1755	Missense	p.D954Y	17 / 75	Cl
Likely Benign	MDN1	Missense	p.V4613L	11 / 77	Su
Likely Benign	MDN1	Missense	p.S584C	6 / 85	Su
Likely Benign	UBXN4	Missense	p.D43Y	6 / 41	Su
Benign	TEX2	Missense	p.G694S	319 / 459	Cl
Benign	GOLGA6L4	Missense	p.Q228H	67 / 216	Cl
Benign	ALPK1	Missense	p.R38H	25 / 97	Cl
Benign	WASH3P	Missense	p.R59Q	23 / 30	Cl
Benign	SPTB	Missense	p.R521H	20 / 65	Cl

ACMG-Recommended Incidental Findings

Based on an analysis of patient's germline data, we identified 1 variant of poten

Summary of ACMG-recommended incidental

ASSOC. CONDITION	GENE	CLASS	VARIANT
Hereditary breast and ovarian cancer	BRCA2	Nonsense	p.K3326*

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Andere molkulare Tests

NANTOMICS GPS CANCER REPORT ID 0148452628

Alterations in significantly mutated genes

We identified 45 significantly mutated genes with non-silent and/or deviations in copy number in the tumor sample. The tables below present up to 10 alterations in the highest-ranked oncogenes and tumor suppressors.

Alterations to top ranked oncogenes

RANK	GENE	VARIANT	CNV
43	GNAS		Loss
138	BCLAF1	p.N629S	Normal
198	CDC73		Moderate Amp.

Alterations to top ranked tumor suppressors

RANK	GENE	VARIANT	CNV
13	GATA3	p.G444Gfs*63	Normal
40	EP300		Loss
64	NCOR1	p.E304*	Normal
65	USP28		Loss
101	KMT2A		Loss
159	RAD21		Amplification

Microsatellite Instability

Out of the 2,553 microsatellites analyzed in the tumor with sufficient coverage, 30 were deemed unstable. The percentage of unstable loci (relative to matched-normal, if available) was calculated to be 1.2%, characteristic of a microsatellite stable (MSS) genome. The summary of the analysis can be found in the table below.

Summary of microsatellite analysis on patient's samples.

SAMPLE	# LOCI	% UNSTABLE
Tumor	2,553	1.18
Normal	148	0.00

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Realität von Heute – Erfahrung mit 60 Patientinnen (SABCS 2015)

P6-04-14

Integrating Whole Genome Sequencing Data With RNAseq, Pathway Analysis, and Quantitative Proteomics to Determine Prognosis After Standard Adjuvant Treatment With Trastuzumab and Chemotherapy in Primary Breast Cancer Patients

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Background

- Despite improvements in the treatment of HER2-positive breast cancer, a high proportion of patients develop resistance to HER2-targeted agents.
- A number of mechanisms of resistance have been proposed, including:
  - Mutations in *PIK3CA*
  - Lack of antibody-dependent cellular cytotoxicity
  - Low levels of HER2 expression
- Disease recurrence in a subpopulation of HER2-positive patients suggests that approaches are needed to accurately assess HER2 status and/or identify potential resistance markers to identify all patients who may benefit from anti-HER2 therapies.
- Here we report a comprehensive panomics approach that integrates whole genome sequencing (WGS), RNA sequencing (RNAseq) and quantitative proteomics to determine associations between tumor molecular profiles and prognosis among patients with HER2-positive breast cancer.

Patients and Methods

Patients

- Patients were enrolled in the SUCCESS A,[1] SUCCESS B,[2] and PRAEGNANT[3] studies.
- SUCCESS A and SUCCESS B include high-risk breast cancer patients after primary surgery. All HER2-positive patients received a standard chemotherapy, including 3 cycles of FEC followed by 3 cycles of docetaxel or docetaxel plus gemcitabine. Trastuzumab was given to all patients for a total of 12 months.
- PRAEGNANT is a registry of metastatic breast cancer patients. All patients selected for this study received a standard adjuvant chemotherapy, including anthracyclines and taxanes. Trastuzumab was given to all patients for a total of 12 months.
- Patients selected for analysis were divided into Cases and Controls:
  - Cases (nonresponders): all patients who recurred or developed a metastasis within 5 years after diagnosis.
  - Controls (responders): all patients with no recurrence or metastasis within 5 years after diagnosis.

Genomic Analysis

- Matched tumor-normal samples (FFPE tumors and whole blood) underwent WGS; provenance testing was done to ensure specimen purity.
- WGS data were processed using Contraster.[4]

Transcriptomic Analysis

- RNAseq of matched tumor-normal samples was performed to confirm the presence of gene mutations and was used to identify mutational and transcript abundance.

Proteomic Analysis

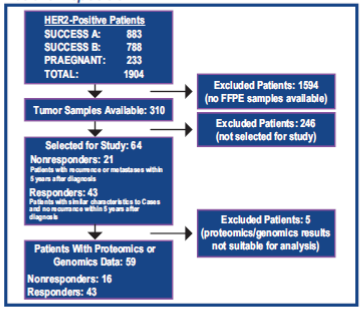
- Proteomics analysis was performed using a quantitative, multiplexed, selected reaction monitoring-mass spectrometry (SRM-MS) assay comprising a panel of 52 proteins.
- Tumor areas from FFPE tissue sections were laser microdissected, solubilized, and enzymatically digested.
- Absolute quantitation of proteins was accomplished through the simultaneous detection of endogenous targets and identical, synthetic, labeled heavy peptides; protein levels were normalized to total protein extracted from each sample.

References

1. Widschwendter P, Friedl TW, Schwenkhar L, et al. *Breast Cancer Res.* 2015; 17:129.
2. Andergassen U, Neugebauer J, Janni W, et al. *Breast.* 2011; 20:S186-S66.
3. Fasching PA, Brucker SY, Reiter TN, et al. Geburtshilfe Frauenheilkd. 2015; 75:41-50.
4. Sanborn JZ, Salama SR, Grifford M, et al. *Cancer Res.* 2013; 73:6036-6045.

Results

Patient Disposition



Patient Characteristics

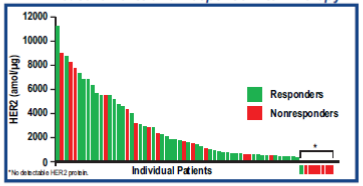
Characteristic	Category	Nonresponders (n=21)	Responders (n=43)
Age, mean (SD)		55.4 (±10.2)	56.9 (± 11.6)
pT, n (%)	1	10 (47.6)	14 (32.6)
	≥ 2	11 (52.4)	29 (67.4)
pN stage, n (%)	Negative	10 (47.6)	20 (46.5)
	Positive	11 (52.4)	23 (53.5)
Grade, n (%)	1	0 (0)	2 (4.7)
	2	10 (47.6)	22 (51.2)
	3	11 (52.4)	19 (44.2)
Hormone receptor status, n (%)	Negative	5 (23.8)	26 (60.5)
	Positive	16 (76.2)	17 (39.5)

Proteins Associated With Response Status

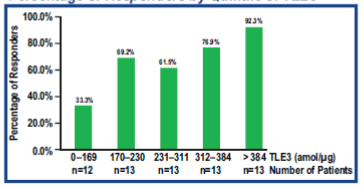
Protein	P-Value	Protein	P-Value	Protein	P-Value
TLE3	0.0027	ERCC1	0.1718	Axl	0.5089
XRCC1	0.0261	HER2	0.2406	P16	0.5622
RRM1	0.0480	TOPO1	0.2709	hENT1	0.5721
MGMT	0.0490	RFC	0.3096	AR	0.6187
Fralpha	0.0749	GART	0.3132	SYP	0.6517
MRP1	0.0749	Ki-67	0.3265	KRAS	0.7738
Ecad	0.0821	TOP2A	0.3895	PTEN	0.9175
ER	0.1331	KRT7	0.4027	SPARC	0.9365
EGFR	0.1524	Vimentin	0.4527	TUBB3	0.9655
PR	0.1524	IDO1	0.4706	DHFR	0.9770
KRT5	0.1717	HGF	0.4853	HER3	0.9906

P-value by Mann-Whitney test.

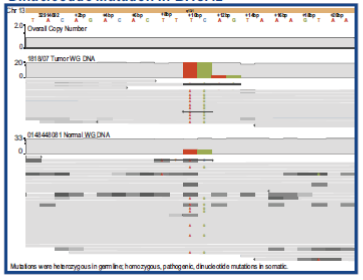
HER2 Measurements and Response After Therapy



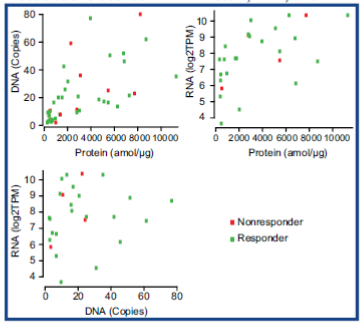
Percentage of Responders by Quintile of TLE3



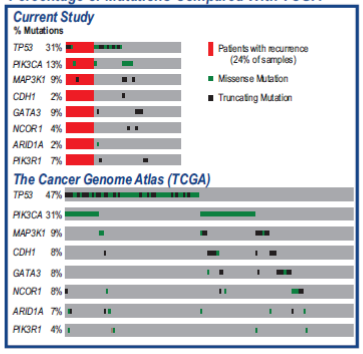
Patient With Pathogenic, Nonsynonymous, Dinucleotide Mutation in BRCA2



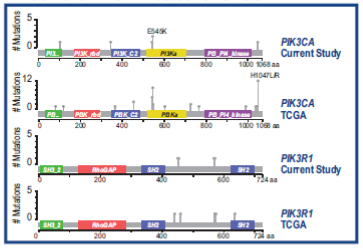
Associations between HER2 Protein, DNA, and RNA



Percentage of Mutations Compared With TCGA



PIK3CA and PIK3R1 Mutations vs TCGA



Conclusions

- In this small, exploratory study of patients treated with chemotherapy and trastuzumab, there appeared to be enrichment for higher response when higher levels of TLE3 protein were detected (92.3% top quintile vs 33.3% bottom quintile).
- Compared with HER2-positive breast cancer patients in TCGA, the rates of *TP53* and *PIK3CA* mutations are different (Fisher's exact test, *TP53* P=0.0794; *PIK3CA* P=0.0279), potentially due to enrichment of patients with metastatic disease.
- A customized genome browser identified a LOH-mediated selection of a pathogenic dinucleotide *BRCA2* variant as a potential driver of disease due to the loss of a section of chromosome 13 encoding for a wild-type *BRCA2* copy.
- RNAseq performed on these archival tissues was successful in > 40% of cases (26/64), but did not produce sufficient numbers for meaningful statistical analysis.
- In this cohort of patients, HER2 expression status was not significantly associated with prediction of recurrence; however, patients with low levels (bottom quintile) of detectable HER2 protein had a notably worse response rate (41.7%) than those with higher HER2 expression (73.1%).
- The treatment regimen, comprising taxanes, anthracyclines, 5-FU, and cyclophosphamide may explain the number of responders with little or no detectable *HER2* amplification or HER2 protein.
- Some patients with high HER2 did not respond to trastuzumab-containing regimens probably due to the complexity of resistance pathways for individual cancer patients.
- Performing comprehensive omics analyses will enable a better understanding of the molecular mechanisms driving recurrence in the real-world setting where patients receive complex treatment regimens.

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Beispiel 2

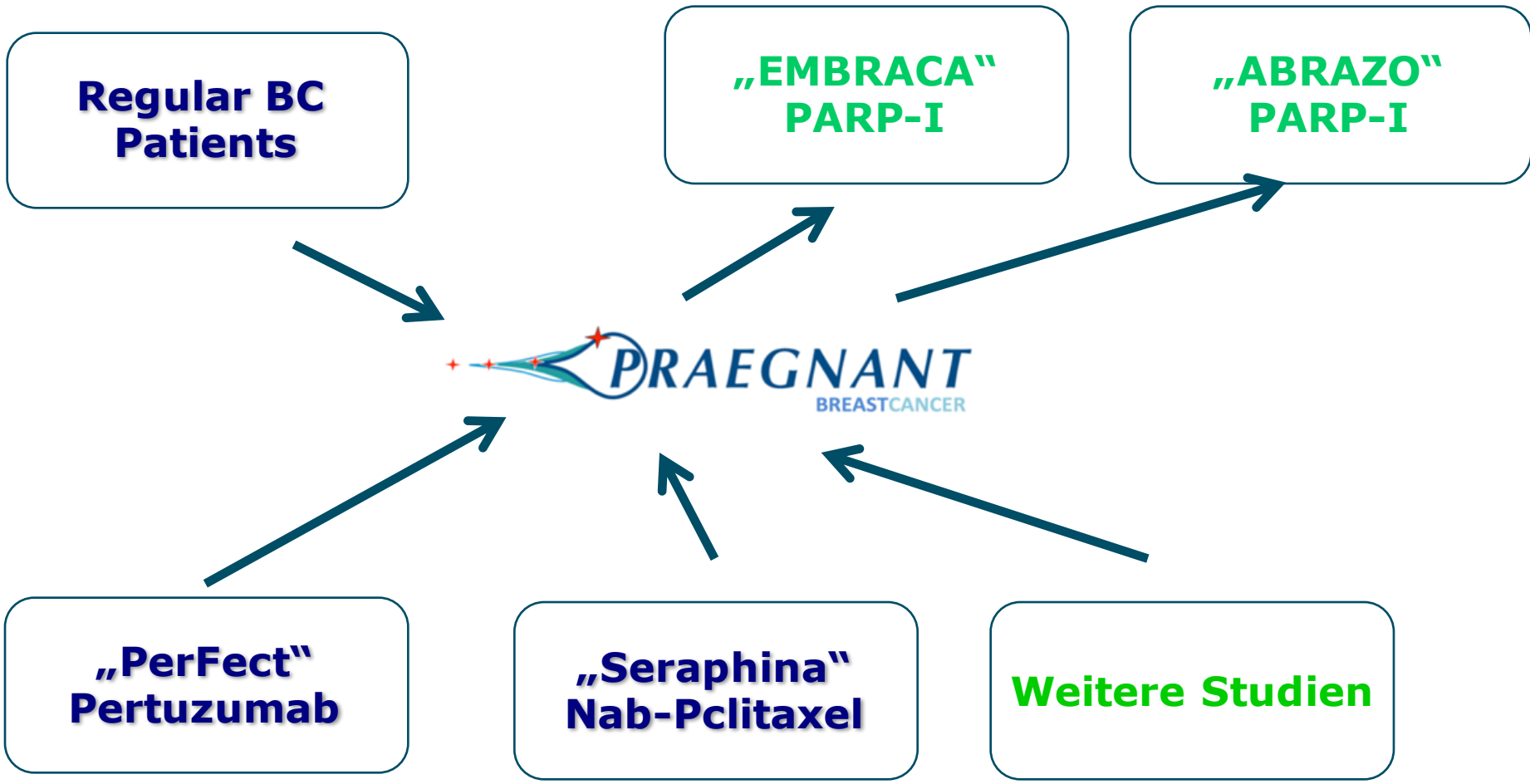
Example Patient selection for PARP Inhibitor Trial

- Inclusion Criteria:
  - No more than 2 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease
  - Prior treatment with a taxane and/or anthracycline in the adjuvant or metastatic setting
  - ECOG performance status ≤ 1
- Exclusion Criteria:
  - Prior platinum treatment for metastatic disease. Subjects who have received platinum in the adjuvant or neoadjuvant setting are eligible
  - CNS metastasis
  - Prior malignancy except for prior BRCA-associated cancer
  - Known to be HIV positive, active hepatitis C virus, or active hepatitis B virus

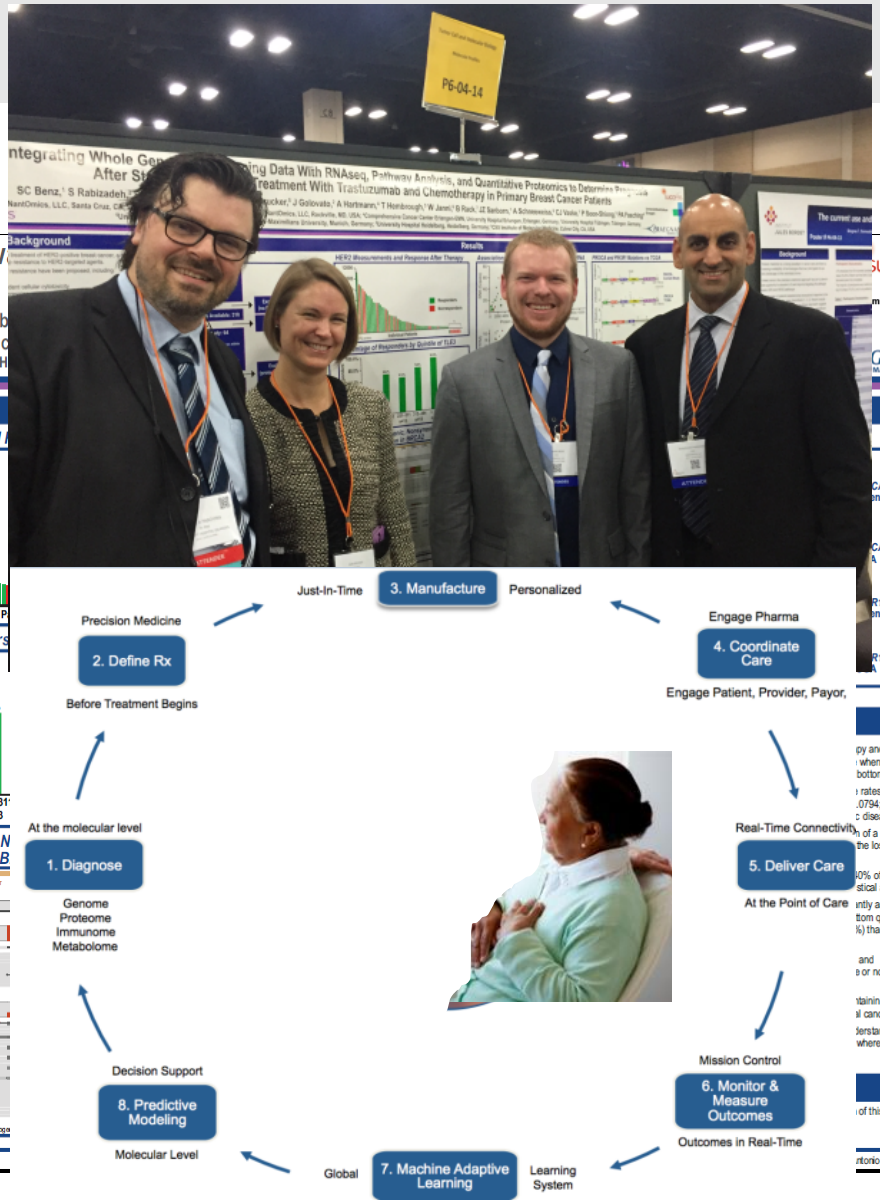
Comparison Computer Algorithm vs. Human Gold Standard

- Assessement of 320 patients health records by two independent trained investigators of this PARP Study -> 120 patients eligible
- Assessment of these patients by computer algorithm (simple SQL statements) -> 129 patients eligible
- **Sensitivity >90%**
- **Specificity >90%**

PRAEGANT Distribution (Basket in and basket out)



German Registry Programs

Organ	Name
Breast	PRAEGNANT
Ovarian, Endometrial, Vulvar, Cervix	G20 (Genomics and Gynecologic Oncology
Bladder	Planned
Renal	Planned

GPS Cancer Pro(?)