DATA INTEGRATION IN PRECISION MEDICINE: EXAMPLE MOLECULAR TUMORBOARD

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e:Med Workshop on Biomedical Data Management

Tübingen, 11.04.2018
MIRACUM (Medical Informatics in Research and Care in University Medicine) is . . .

Biggest consortium within the BMBF Medical Informatics Initiative (MI-I)

- 8 University Hospitals and Medical Faculties (Erlangen, Frankfurt, Freiburg, Gießen, Magdeburg, Mainz, Mannheim, Marburg)
- 2 Universities of applied science
- 1 Industry partner (Averbis GmbH)
- . . . over 5 federal states
- Associated with 4 German Health Research Centers (DZL, DZHK, DZI, DKTK)
MIRACUM . . .

Biggest consortium within the BMBF MI-I

- 8 University Hospitals and Medical Faculties
- . . . comprises ~¼ of all German University Hospital
- . . . provides access to care and research data of >10 million patients
- . . . has a large area

Map was generated based on in-patient data loaded into the eight MIRACUM DIC
MIRACOLIX Ökosystem

Medical Informatics Reusable eCo-system of Open source Linkable and Interoperable software tools – X

• pragmatically
• modular
• reusable
• open source
• interoperable
• federated
MIRACOLIX Ökosystem

Toolbox

• pragmatically
• modular
• reusable
• open source
• interoperable
• federated

| TALEND ETL | i2b2 | li2b2 | RELMA | ...
|------------|------|-------|-------|------
| Mainzel-liste | Molgenis | OMOP | gICS | oAuth
| tranSMART | ... | ... | XNAT | FHIR
| iRODS / CKAN | IHE | cBioportal | ARX | ...

MIRACOLIX Ökosystem

Toolbox

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• federated
MIRACUM Data Integration Center

MI-I Kerndatensatz (Basismodule):
- person
- demography
- case data
- diagnoses
- procedures
Federated data usage based on MIRACOLIX 0.9
„Bring the analysis to the data“
Federated data usage based on MIRACOLIX 0.9
„Bring the analysis to the data“
3 Use Cases:

**Use Case 1:** Alerting in Care – IT Support for Patient Recruitment
(TP Leitung: U. Prokosch, C. Schade-Brittinger, H. Serve)

**Use Case 2:** From Data to Knowledge – Clinico-molecular Predictive Knowledge Tool
(TP Leitung: H. Binder, U. Prokosch, H. Renz, T. Acker)

**Use Case 3:** From Knowledge to Action – Support for Molecular Tumor Boards
(TP Leitung: M. Börries, M. Boeker, U. Prokosch)
Molekulares Tumorboard (MTB): „Example“ Freiburg

- 31 physicians and scientists
- Interdisciplinary platform for individual patient care
- Since March 2015 / 135 patients per year
- Biweekly
- Inclusion Criteria:
  - Routine diagnostics completed
  - Presentation on the organ boards
Molecular Tumorboard

Molecular diagnostic:
- all diagnostic methods/techniques available in pathology (z.B. IHC, ISH, Mikrodissektion, Panel/NGS)
- WES/RNA-Seq/Methylome with bioinformatic analysis

Overview:
- Treatment recommendations in 46% of patients
- mostly off-label therapy recommendations (antibodies or tyrosine-kinase inhibitors)
- Treatment Response: 29%, Stable Disease: 24%
- additionally: generation of new scientific projects, new studies, promotion of education
Case Report I: Patient diagnosed with melanoma in the MTB

- Patient: progressive stage IV of melanoma
- Presentation in MTB => extended molecular diagnostics and WES

- 62 somatic mutations (24 LoH)
- BRAF V600E negative
- BRAF D594G Mutation: Inactivation of BRAF kinase (paradoxical activation)
Results: Molecular Diagnostic and WES

Several Copy Cumber Variations (CNVs), gains in RAS activators

\[ \text{CNVs} \rightarrow \text{NRas}^* \rightarrow \text{D594G} \rightarrow \text{Sorafenib} \rightarrow \text{Trametinib} \rightarrow \text{ERK} \rightarrow \text{Tumorwachstum} \]

**Increased pERK Level (IHC)**

\[ \text{MelA} \rightarrow \text{pERK} \]

**Silke Lassmann**

**In vitro Validation**

- \[ \text{HA (B-Raf)D594G} \]
- \[ \text{pMEK} \]
- \[ \text{tMEK} \]
- \[ \text{pERK} \]
- \[ \text{tERK} \]
- \[ \text{Gapdh} \]

**Tilman Brummer**

**Individual Therapy Recommendation**

- \[ \text{Sorafenib + Trametinib} \]

\[ \text{kidney} \rightarrow \text{colon} \]

**Woche 3**

**Woche 11**

- \[ \text{Nikolas v. Bubnoff} \]
Case Report II: Patient diagnosed with Glioblastoma multiforme in the MTB

- Patient: stage IV of GBM
- Presentation in MTB => extended molecular diagnostics and WES
  - Mutation load: 43 somatic SNVs, 2 LoH, 34 CNVs
  - 3 mutations in TSG (3x) und oncogene (1x)

Tumor suppressor genes:
- **TP53** (V80M, V173M, V41M), **VAF 27.89%**, TARGET: Wee1 Inhibitors, Condel: D, COSM98966, COSM3388205, COSM98965, COSM121041, COSM98964, COSM2744864, COSM11084 (insgesamt 45x davon 1x central_nervous_system)
- **PTEN** (A126T), mutation in phosphatase-Domain (biochemically not analyzed), **VAF 11.11%**, TARGET: PI3K/AKT/MTOR Inhibitors, Condel: D, COSM5051 (3x endometrium, 3x central_nervous_system)
WES Results

Oncogene:

- **EGFR (G598V):** Mutation in extracellular region, known driver mutation (also for GBM), but rarer than the typically in-frame vIII Deletionen (worse prognosis), **VAF 23.87%,** Condel: D, COSM21690, COSM1187304 (1x lung), 33x central_nervous_system)
**Vivanco et al (2012):**

- EGFR mutations: in EC region=> insufficient inhibition of class I inhibitors (erlotinib and gefitinib).
- *In vitro*: very effective inhibition by lapatinib (tyrosine kinase inhibitor Type 2) => corresponding doses could not reached in GBM patients (delivery problem)
- Nevertheless there are some lapatinib trials, also in combination with Temodal.
- Since 2012, several new EGFR inhibitors such as neratinib, also class IV, which covalently bind to EGFR, e.g. afatinib, are under trial in GBM patients.
Somatic mutations in important signaling pathways

**PIK3-AKT-mTOR:** TP53, PTEN

**RAF-MEK-ERK:** TP53, EGFR,

**DNA Damage Response:** TP53

**Cell Cycle:** TP53

**Tyrosine Kinases:** EGFR
### Results WES

**CNVs in Tumorsuppressoren**

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<td>KMT2C</td>
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<tr>
<td>13</td>
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<td>BRCA2,RB1</td>
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**CNVs in Onkogenen**

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<td></td>
<td></td>
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<td>AKT1</td>
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</tbody>
</table>

- **loss vom q-Arm von Chromosom 10 (bekannt)**
- **EGFR Amplifikation (bekannt)**
- **gain von Chromosom 7 (bekannt)**
- **AKT1 Amplifikation**
Result/Summary WES

Summary:
- total mutation: 43, 3 TSG und 1 oncogen
- Driver mutation: TP53 und EGFR
- Typical CNVs
- Transcriptome: increased Expression AKT1, EGFR, FGFR, GNAS, Increased signaling pathways: PI3K/AKT, VEGFR1/2 and MAPK

Therapy Recommendation:
- further treatment after guideline therapy (Temodal)
- in case of recurrence: application of tyrosine kinase inhibitors of e.g. type 2 with possible combination of Temodal or possible inhibition of PI3K with EGFR mutation and signal path increase of PI3K/AKT
Implementation of the MTB in MIRACUM

What is available?

1. Pipeline for Whole Exome Sequencing => Transferable/applicable at all partner sites

<table>
<thead>
<tr>
<th>DNA</th>
<th>Raw Seq Data QC, Trimming</th>
<th>QC, Global Alignment</th>
<th>Re-Alignment QC</th>
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</thead>
<tbody>
<tr>
<td>Variant-Calling</td>
<td>Annotation: somatische Varianten</td>
<td>Structured Report</td>
<td></td>
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</tbody>
</table>

⇒ Tools/Software: Open Source
⇒ R-Script and Galaxy (Docker)
Implementation of the MTB in MIRACUM

Goals?

2. Extension of annotations:
   - Integration of further databases
     - Mycancergenome.gov
     - InterVar
     - OnkoKB
   - Integration von cBioPortal
   - Integration of clinical studies (e.g. ClinicalTrials.gov)
   - Targeted therapy
   - Copy Number Variations

3. Visualization of the results

4. Transfer: from the structured report to a presentation form

5. Linking with clinical data
cBioPortal for Cancer Genomics

The portal is developed and maintained by the Computational Biology (cBio) Center at Memorial Sloan-Kettering Cancer Center

Provides:
- Visualization
- Analysis
- download of large-scale cancer genomics data sets
Date: 10.04.2018:
Therapy recommendation: Ivosidenib (small molecule inhibitor of IDH1)
Basis for decision: mutation in IDH1 ......

comment: the drug has not yet approved for this tumor entity
Use Case 3 at the different partner sites
Acknowledgement

**MIRACUM Team**
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