Molecular Pathology Practice in Germany

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Who performs molecular pathology?

- Pathologists
  - University and larger non-academic hospitals
  - Private practice pathologists, including pathologists’ networks
- Clinical geneticists
- Laboratory medicine and hematologists
- Commercial providers
  - In collaboration with pathologists
Practice patterns

**Pathologists**
- Predominantly smaller, disease-focussed assays
  - Small units
  - Correlation with morphology

**Geneticists**
- Frequently larger panels
- parallel germ line testing
- Some larger units

**Commercial providers**
- Black box, frequent one-size fits all tests
- Generation of proprietary databases
- Direct marketing
What methods are used?

Pathology

Smaller units: limited number of tests for standard indications, frequently commercial assays/platforms (Idylla), simpler assays like allele-specific PCR, pyrosequencing etc.

Larger units, most university hospitals: rapid change to panel-based NGS
If a pathologist (MD), how is she/he trained? Is there a special degree / diploma?

- Board certification for pathology includes molecular pathology
  - Special qualification MP was abolished
- No special training required
  - Training in molecular pathology may be provided by collaboration with practicing institution
- Level of knowledge in MP very variable
- Great variety of training opportunities, including hands-on courses
Who is allowed to perform molecular pathology?

- Any board-certified pathologist may perform molecular studies
- No accreditation required, but increasingly done by most major labs
  - According to norm DIN EN ISO/IEC 17020
- Free choice of technique (since 2016)
- Broad range of external quality control trials offered by QUiP
  - EGFR
  - ALK
  - Liquid biopsy T790M
  - And many more
What is current (old) standard?

- **Diagnostic Markers**
  - Hematopathology
    - Clonality
    - FISH for translocations
  - Common markers in acute leukemias
  - Common mutations in MN
  - Sarcoma
    - FISH/RT-PCR for common translocations

- **Predictive/prognostic markers**
  - MSI, RAS, BRAF in colorectal cancer
  - EGFR, ALK, ROS, PD-L1 in NSCLC
  - BRAF in melanoma
  - BRCA1/2 in ovarian cancer
  - KIT/PDGFRA in GIST
  - HER2 FISH for breast and gastric cancer
Rapid rise of NGS-based panel testing

- NGS-based testing allowed for BRCA1/2 in ovarian cancer in 7/2016
- 2017: small (<20 kb) and large panel (>20 kb) mutational testing
  - Not bound to specific indication!
  - Large panel requires individual permission from insurance company
- 2018: liquid biopsy for T790M in metastatic lung cancer
- Standard indications changed to panel Dx, frequent use in patients with metastatic tumors and lack of established therapies
First NGS ring trial within DKTK (Hirsch B et al, Virchows Arch 2018)
NGS ring trial - results

High coverage (av. 2000x)
High sensitivity (1% tumor cells)
Great homogeneity within platform

But: Heterogeneity in VAF, dependent on panel used

Detection of the predefined mutations by amplicon NGS

Results with the DNA provided to the NGS sites
Is molecular pathology reimbursed?

• Fairly complex system of reimbursement
• Inpatient care, general insurance
  • Molecular diagnostics included in DRGs, but no increase in DRGs
• Outpatient care
  • Until 2016 NGS was not allowed as technique
  • Molecular diagnostics reimbursed according to guidelines
  • Molecular diagnostics now outside of general budget – expansion of reimbursement
<table>
<thead>
<tr>
<th>RAS*</th>
<th>EBM</th>
<th>GOÄ (GOÄ-Faktor je nach Rechnungsempfänger)</th>
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<tr>
<th>Code</th>
<th>Beschreibung</th>
<th>Kategorie</th>
<th>Preise</th>
<th>Multiplikator</th>
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<tbody>
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<td>19450</td>
<td><strong>In-situ-Hybridisierung</strong> (Charakterisierung struktureller chromosomaler Aberrationen), je Zielsequenz</td>
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<td>ab 21 x: 24.914</td>
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<td>19454</td>
<td><strong>Mutationssuche</strong> in mehr als 20 kb kodierender Sequenz (<em>große Mutationssuche</em>), 1 x in 4 Quartalen</td>
<td>Jahr</td>
<td>IOW</td>
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<td>19456</td>
<td><strong>BRCA1 / 2 zur Indikationsstellung Therapie</strong>, 1 x in 4 Quartalen</td>
<td>Jahr</td>
<td>IOW</td>
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<td>19460</td>
<td><strong>Liquid Biopsy T790M</strong>, höchstens 4 x in 4 Quartalen</td>
<td>Qu/Jahr</td>
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<td>7.868 = 2 x</td>
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</tbody>
</table>

**Wenn notwendig, bei zusätzlicher Stufendiagnostik:**
- **ALK** 2 x 19452****
- **ROS1** 2 x 19452
- **RET** 2 x 19411

**Stufendiagnostik ALK, ROS1, RET:**
Je 1 x 4872 A
How to deal with explosion of molecular testing?

Harmonization
Cross-sectoral reimbursement
Concentration
Goals of nNGM Lung cancer

- 3-year funding by German Cancer Aid
- Harmonized, advanced molecular testing available to all NSCLC patients
- Quality control of molecular diagnostics
- Collection of rare mutations
- Access to molecularly targeted clinical trials
- Central documentation
- Consultation
- Cross-sectoral reimbursement
- Translational research
Current diagnostic workup NSCLC within nNGM

NGS 19 Gene panel V1.0
- ALK
- BRAF
- CTNNB1
- EGFR
- ERBB2
- IDH1
- IDH2
- FGFR1
- FGFR2
- FGFR3
- FGFR4
- KRAS
- MAP2K1
- MET
- NRAS
- PIK3CA
- PTEN
- TP53
- ROS1

IHC
- PD-L1

IHC/FISH
- ALK
- ROS1

FISH
- RET
- MET

Optional:
- NTRK1 FISH

Panel V2 in preparation, change from IHC/FISH workup to NGS-based fusion detection

Problems:
- 500 cases/year as required by insurances difficult to reach for some centers
- competition between nNGM centers and affiliates and other pathologists
- Centralized database and central informed consent vs. local rules
Bridge the gap between cancer research and patient care
Promote advanced diagnostics and innovative clinical trials
Improve networking between cancer centers
Generate large databases with epidemiological, clinical and biological („multi-omics“) data
Molecularly Aided Stratification for Tumor Eradication Research - MASTER

Molecular diversity and genetic taxonomy of cancer

Individual, “private” patterns of molecular lesions

Actionability of molecular lesions

- Young adults with advanced-stage cancer
- Patients with rare tumors
- Fast-track exome and RNA sequencing
- >60 external partners, including all DKTK sites

Start: 06/2013

NCT/DKTK MASTER Registry Trial

Since 10/2016: Genome sequencing (60x)

- Feasibility
- Diagnostic information
- Therapeutic opportunities

Moleculartly stratified clinical trials

Courtesy of A. Stenzinger
Centers for personalized medicine

- Currently being established at the 4 university hospitals in Baden-Württemberg
- Goal: offer advanced molecular diagnostics and other services for targeted therapy
- Harmonized approach and central database
- Aims at preventing uncontrolled molecular testing, therefore supported by insurances
- Cancer as first use case, but will be rolled out to other diseases
Merci Beaucoup!