nNGM National Network Genomic Medicine Lung Cancer

# Precision Medicine zum Wohl des Patienten!

## Klinische Netzwerke als Behandlungsmodelle der Zukunft am Beispiel vom Lungenkrebs

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nNGM-Geschäftsstelle, Uniklinik Köln
DMEA Berlin – 11.04.2019

Network Genomic Medicine Lung Cancer

LungCancerGroup Cologne

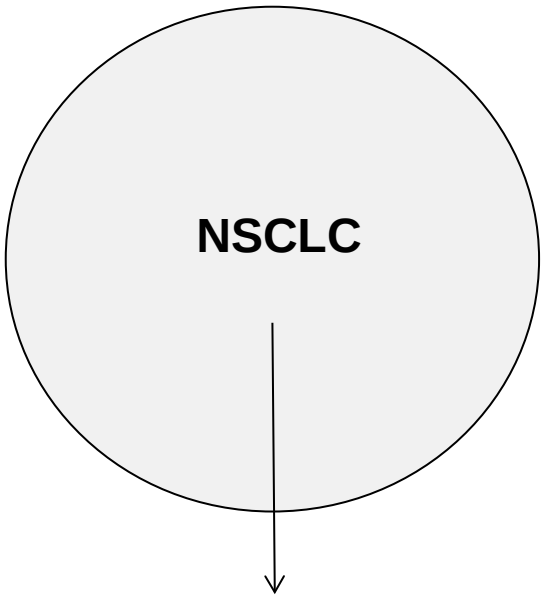
CIO Centrum für Integrierte Onkologie Köln

# Disclosures

- **None**

# Systemic cancer therapy turns into personalized therapy: example non-small cell lung cancer (NSCLC)

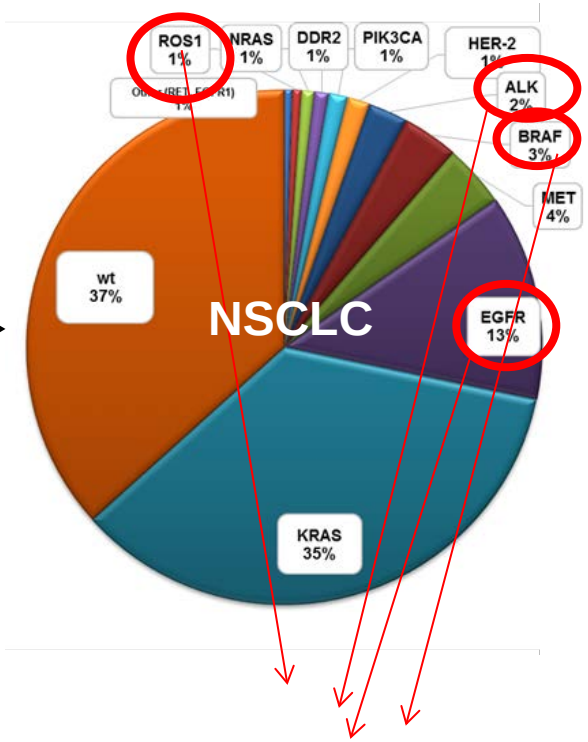
***10 years ago:***
**chemotherapy**
**in unselected patients**




**Response Rate: 20-30%**

**Med. Survival: 1 year**

***today:***
**targeted therapy (and immunotherapy)**
**in molecularly selected subgroups**




**Response Rates: 60 – 70%**

**Med. Survival 5 years and more**

**Better tolerability**

# Targetable mutations in NSCLC (Jan. 2019)

## (without resistance mutations and without markers for immunotherapy)

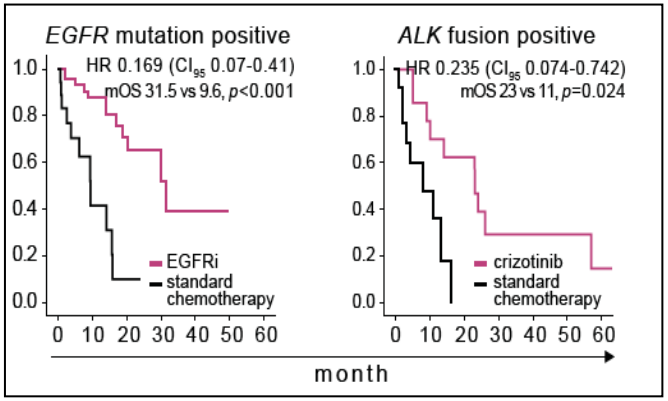
| Gene | Alteration | frequency (NSCLC) | drugs |
|---|---|---|---|
| EGFR | actvating mutation (ex 19 del., L858R) | 10 % | erlotinib, gefitinib, afatinib, osimertinib |
| ALK | fusions | 3% | crizotinib, alectinib, ceritinib,..... |
| ROS 1 | fusions | 1% | crizotinib, (cabozantinib, ponatinib....) |
| BRAFV600 | mutation | 2% | dabrafenib + trametinib |
| MET | amplification (GCN>9) | 1% | crizotinib, capmatinib, tepotinib |
| MET | exon 14 skipping | 2% | |
| MET | fusions | < 1% | |
| RET | fusions | < 1% | cabozantinib, vandetanib, alectinib, LOXO-292 |
| NRG1 | fusions | < 1% | afatinib |
| HER2 | mutation | 1-2% | (trastuzumab, pertuzumab) |
| NTRK 1-3 | fusions | < 1% (?) | larotrectinib, entrectinib |
| EGFR | exon 20 insertion | < 1% | poziotinib |
| FGFR 1-3 | fusions, mutations | 1% (each) | erdafinib, BGJ398..... |
| KRAS | mutation | 20% | LTT462 (ERKi.) + LXH254 (panRAFi.) |

standard  off-label, trial  trial only

# Personalized treatment prolongs survival substantially

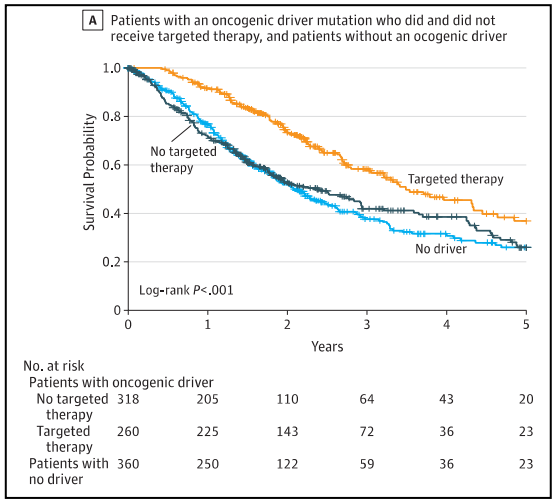
## Registry data

### Germany: Network Genomic Medicine



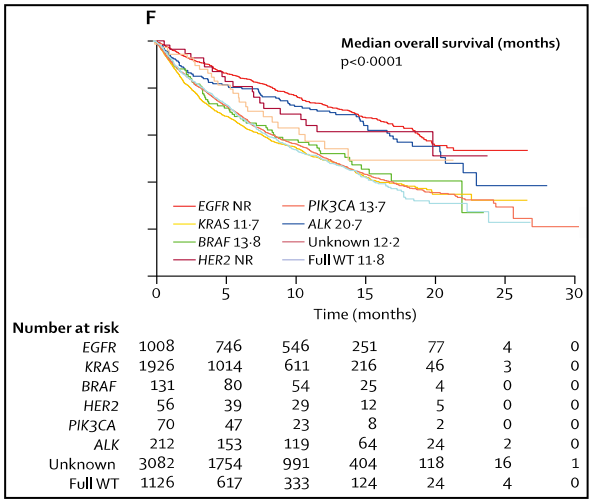

The Clinical Lung Cancer Genome Project and Network Genomic Medicine. Sci Transl Med 2013;5:209ra153

### USA: Lung Cancer Mutational Consortium




Kris et al. JAMA 2014;311:1998-2006

### France: INCA cohort




Barlesi et al. Lancet 2016;387:1415-26

# Molecular test rates are not acceptable in Germany

| Nicht-Plattenepithel-Karzinom | HJ1 2016 (n=157) | HJ2 2016 (n=249) | HJ1 2017 (n=309) | HJ2 2017 (n=492) | HJ1 2018 (n=525) | Gesamt (n=1732) |
|---|---|---|---|---|---|---|
| **Auf DrLTs getestet bei Erstlinie** | | | | | | |
| Yes | 141 (89.8%) | 232 (93.2%) | 290 (93.9%) | 464 (94.3%) | 504 (96.0%) | 1631 (94.2%) |
| **DrLTs tested at 1st-line** | | | | | | |
| EGFR | 117 (74.5%) | 197 (79.1%) | 233 (75.4%) | 372 (75.6%) | 396 (75.4%) | 1315 (75.9%) |
| ROS-1 | 84 (53.5%) | 141 (56.6%) | 190 (61.5%) | 333 (67.7%) | 338 (64.4%) | 1086 (62.7%) |
| PD-L1 | 31 (19.7%) | 70 (28.1%) | 162 (52.4%) | 349 (70.9%) | 391 (74.5%) | 1003 (57.9%) |
| ALK | 115 (73.2%) | 183 (73.5%) | 226 (73.1%) | 369 (75.0%) | 386 (73.5%) | 1279 (73.8%) |
| BRAF | 47 (29.9%) | 74 (29.7%) | 115 (37.2%) | 258 (52.4%) | 283 (53.9%) | 777 (44.9%) |

F Griesinger, AIO Herbstkongress 2018

# Possible Gain (OS in years)

- Targeted Therapies OS 5yrs (n= 6.000 pts/y)

  24.000 yrs

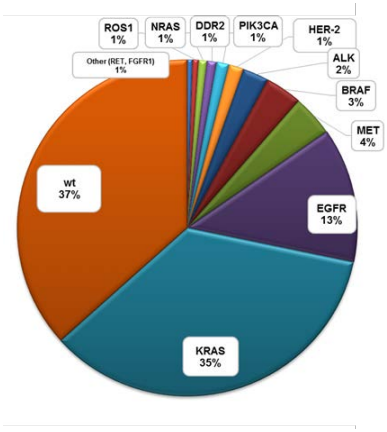
- IO-Therapies OS 2.5 yrs (n= 34.000)

  51.000 yrs

**Expected gain in life: 75.000 patient years**

# Lung cancer patients with ROS1 fusion:
# Molecular testing, off-label treatment and clinical trials save lifes

# Challenges for the implementation of personalized cancer care into clinical routine



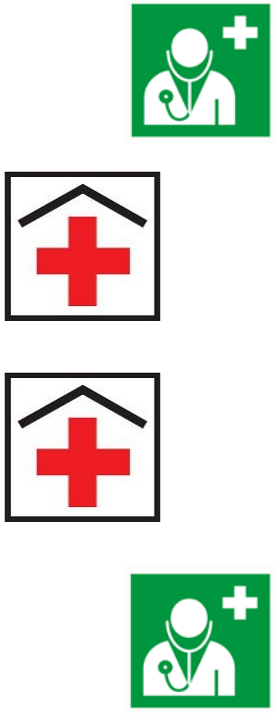



- Implementation of high-quality **molecular multiplex diagnostics**
- State-of-the-art **consultation** with regard to therapeutic consequences
- Rapid **innovation transfer** (new driver mutations) from the academic centers into broad cancer patient care
- **Evaluation** of post-approval and off-label personalized therapies
- Data-based **evidence-generation** (learning system)

# Urgent need for building networks

*treat close to home*

*centralize diagnostics + consultation + evaluation*



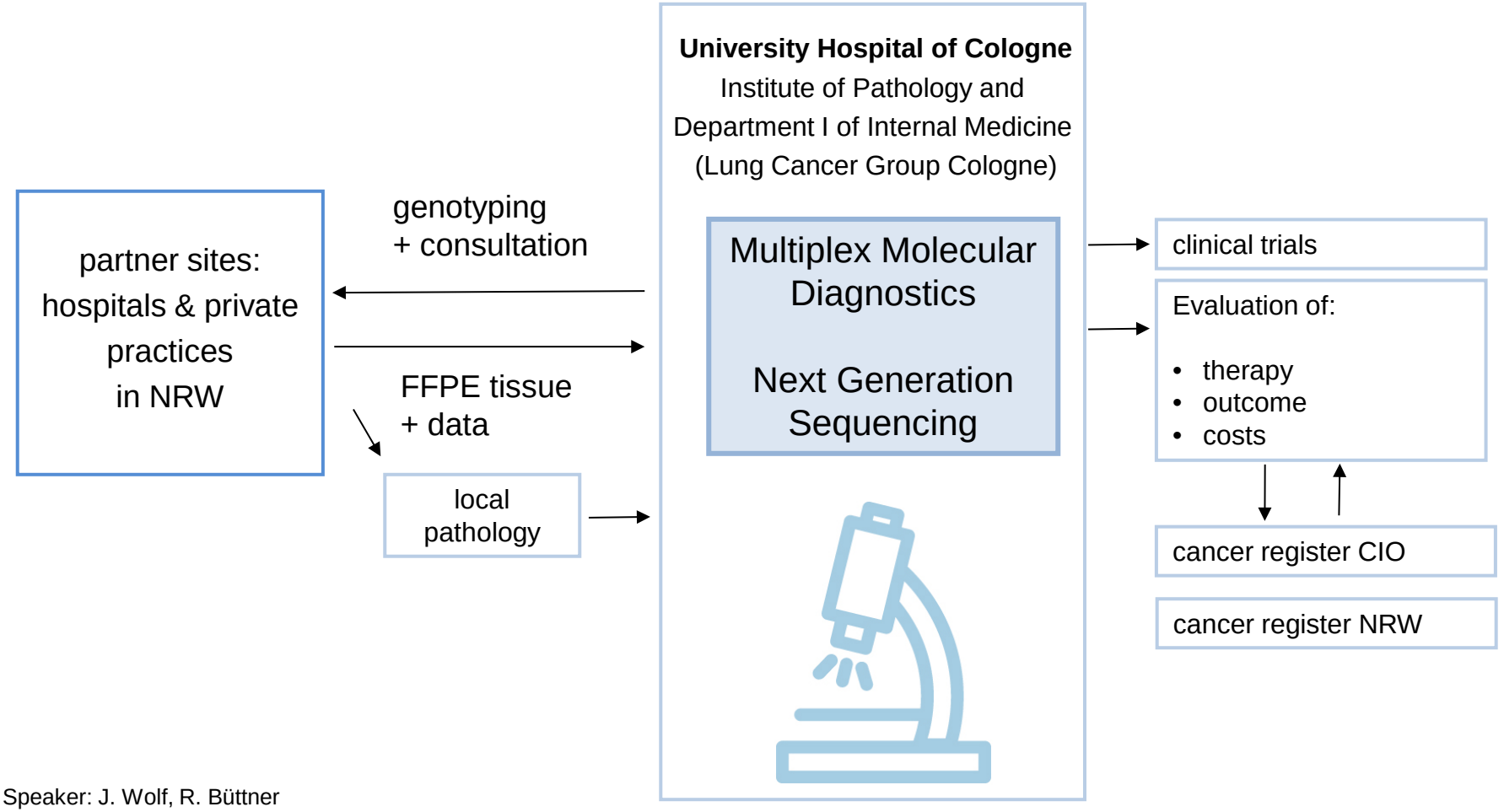

**Oncology Centers of Excellence**

- **Molecular diagnostics (NGS, WGS, RNA)**
- **Molecular Tumorboards**
- **Therapy recommendations**
- **Translational research**
- **Databases**

# Network Genomic Medicine (NGM)

Network Genomic Medicine Lung Cancer

***Founded in 2010 with funding from Ministry for Innovation and Research NRW***




Speaker: J. Wolf, R. Büttner
Scientific Coordinator: A. Kron, S. Michels

CLCGP & NGM, Sci Transl Med 2013, Scheffler et al., Oncotarget 2014, Schildhaus et al., Clin Cancer Res 2015, Scheffler et al., Oncotarget 2015, Michels et al., JTO

# Network Genomic Medicine (NGM)

Network Genomic Medicine Lung Cancer

***Founded in 2010 with funding from Ministry for Innovation and Research NRW***

**190 partner sites nationwide** (102 hospitals & 88 private practices)

genotyping + consultation

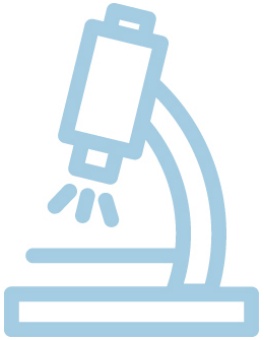
FFPE tissue + data

local pathology

**University Hospital of Cologne**
Institute of Pathology and
Department I of Internal Medicine
(Lung Cancer Group Cologne)

Multiplex Molecular Diagnostics

Next Generation Sequencing



clinical trials

Evaluation of:

- therapy
- outcome
- costs

cancer register CIO

cancer register NRW

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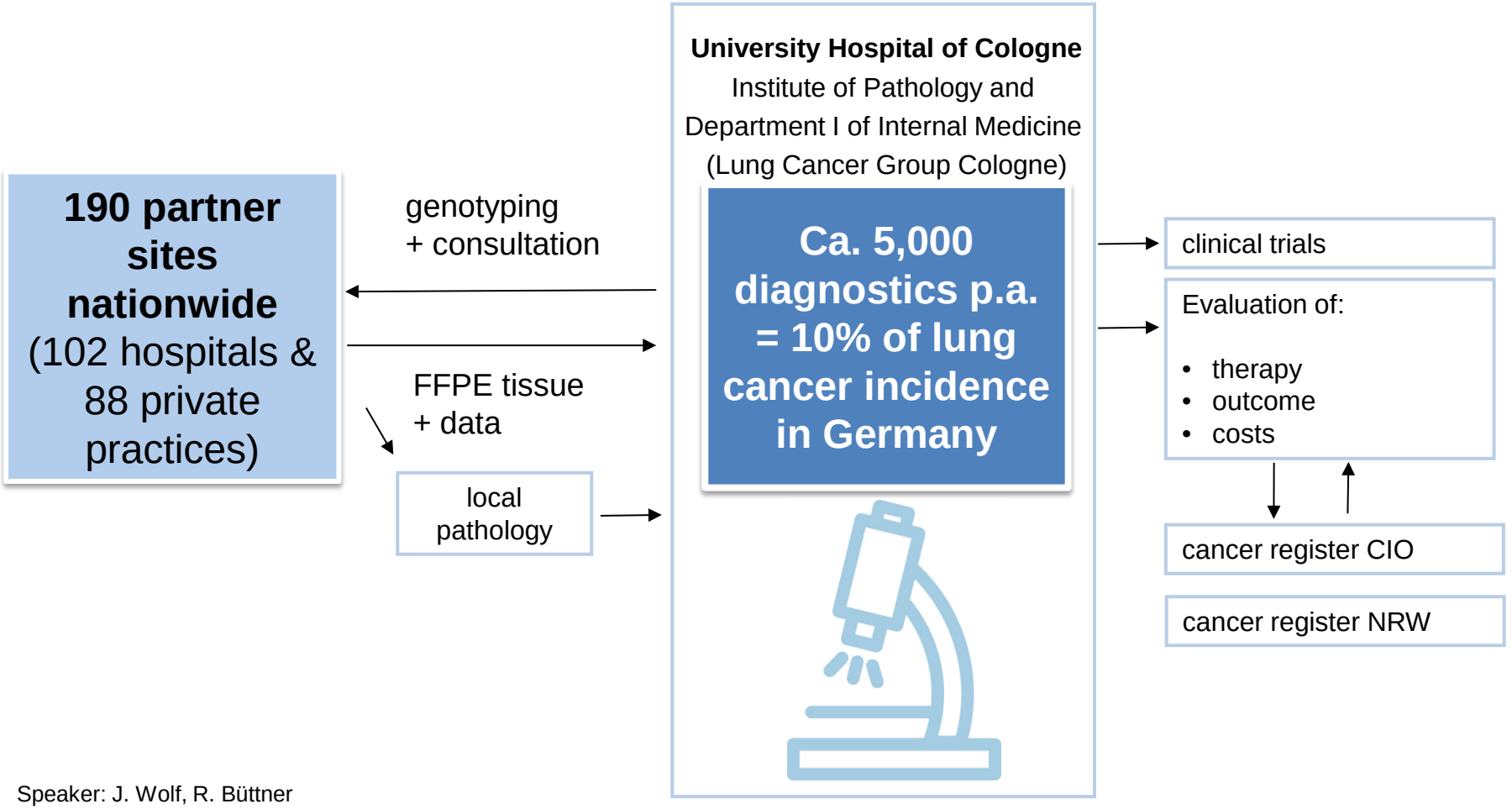


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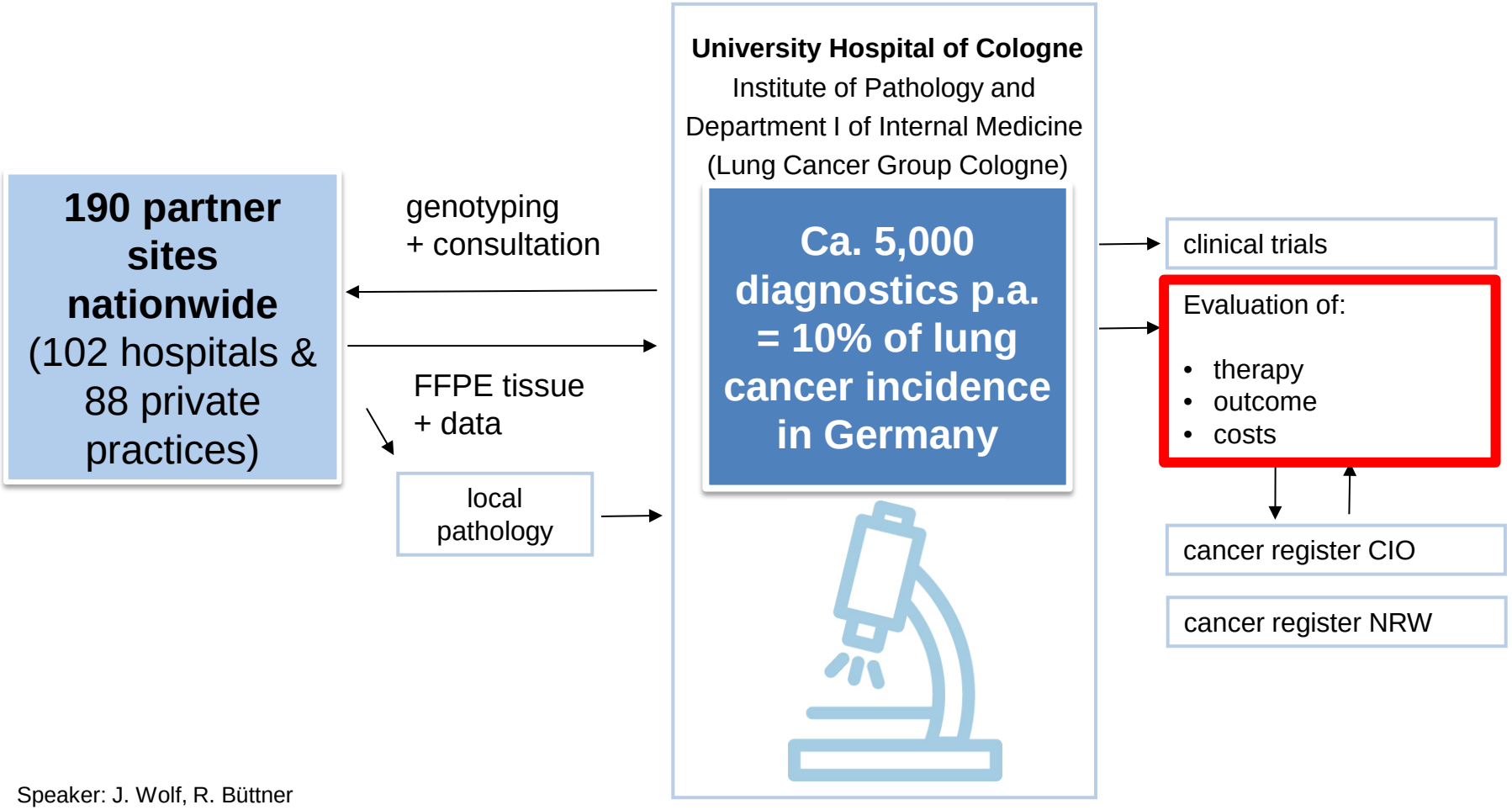


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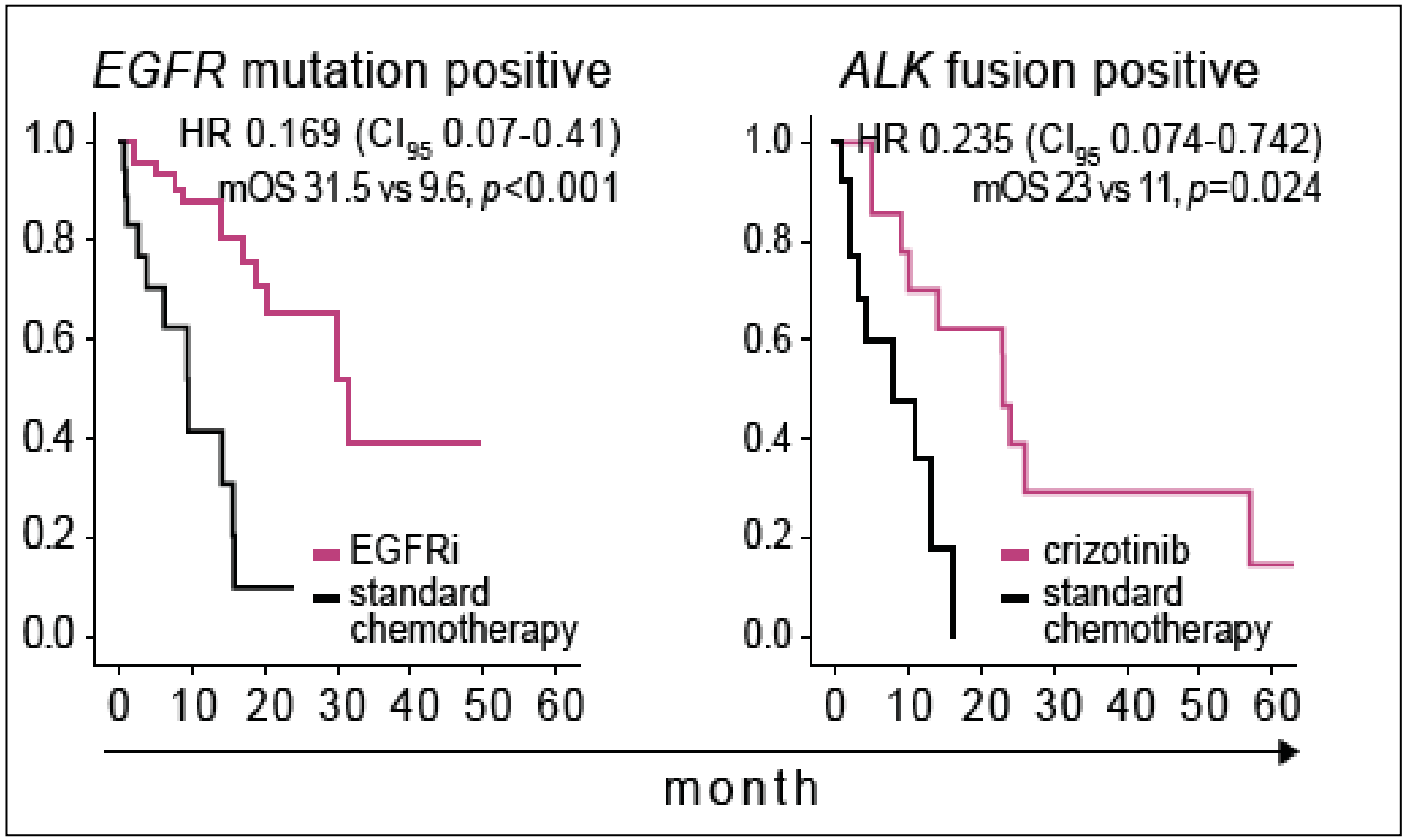
# 1st NGM Evaluation 2013:

***OS benefit with personalized therapies***

Network Genomic Medicine Lung Cancer




The Clinical Lung Cancer Genome Project and Network Genomic Medicine, Sci Transl Med 2013

# Integrated Care Contract (ICC)

Network Genomic Medicine Lung Cancer

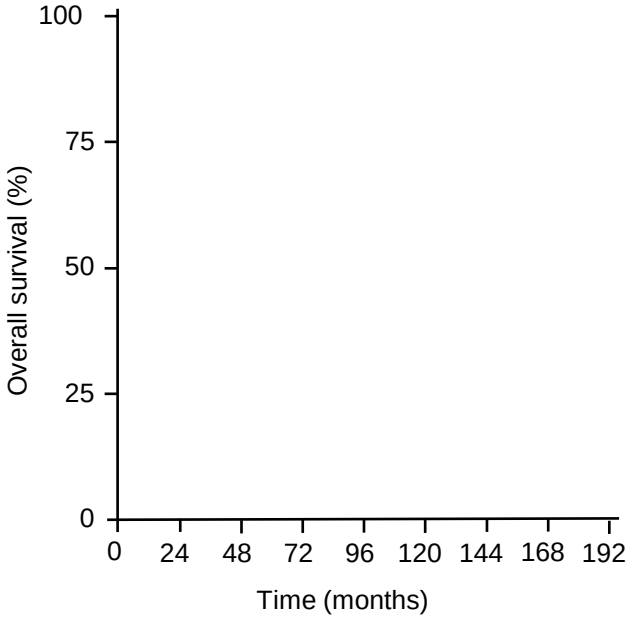

- NGS-based genotyping + consultation potentially covered by ICC for circa 50 % of all (**statutory health insured**) annually newly diagnosed inoperable lung cancer patients in Germany
- PKV Verband der Privaten Krankenversicherung first NGM contract covering the NGS-based genotyping + consultation of **private heath insured** patients was finalized in 2019

# 2nd NGM Evaluation 2018:

## *OS benefit with sequential therapies*

Network Genomic Medicine Lung Cancer

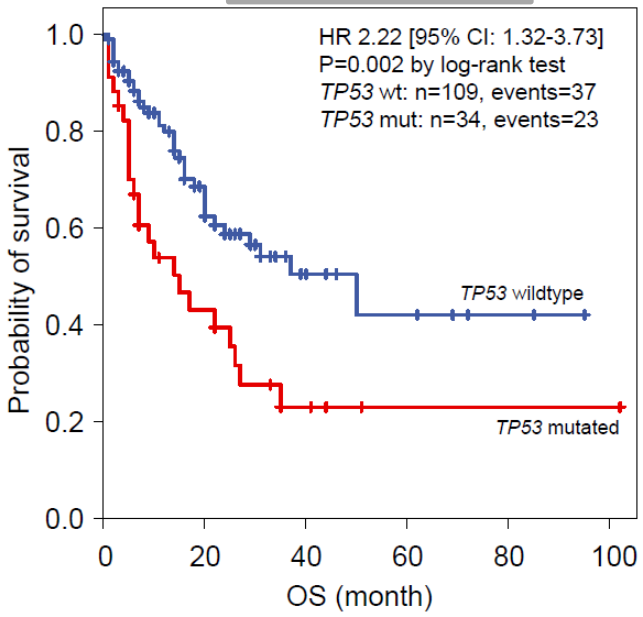
**EGFR+**




| N° at risk: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Wt | 43 | 39 | 19 | 6 | 3 | 1 | 1 | 1 | 0 |
| Ampl. | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Michels et al., JCO Precision Med 2018

**ALK+**



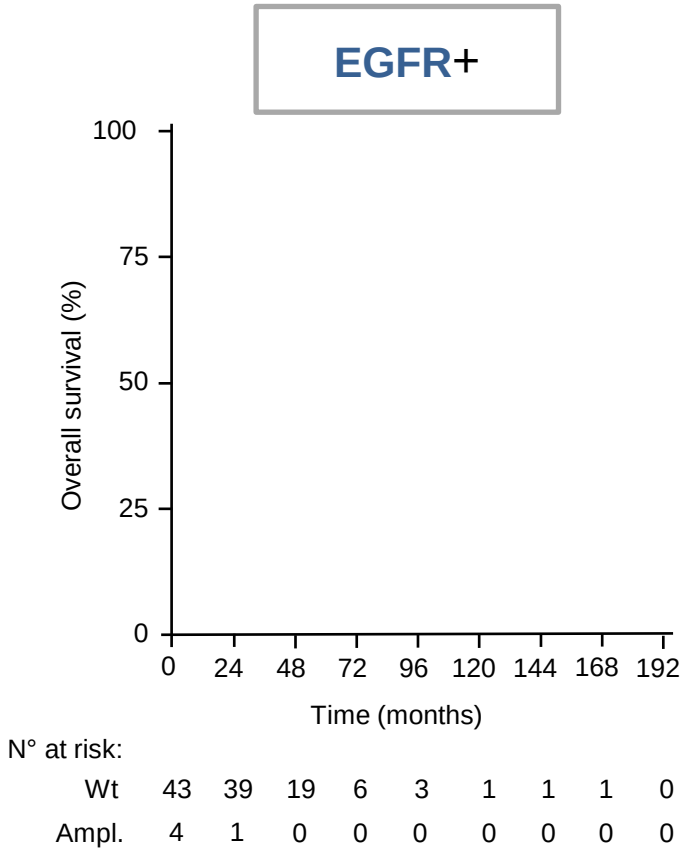

| | | | | | | |
|---|---|---|---|---|---|---|
| *TP53* wt | 109 | 44 | 11 | 5 | 2 | 0 |
| *TP53* mut | 34 | 12 | 4 | 1 | 1 | 1 |

Kron et al., Ann Oncol. 2018 Oct; 29(10): 2068–2075.

# 2nd NGM Evaluation 2018:

***OS benefit with sequential therapies***

Network Genomic Medicine Lung Cancer




Michels et al., JCO Precision Med 2018

**OVERALL SURVIVAL (OS)**
**P < 0.001**

*MET* wildtype **55.3 mon**

*MET* co-ampl. (high-level) **16 mon**

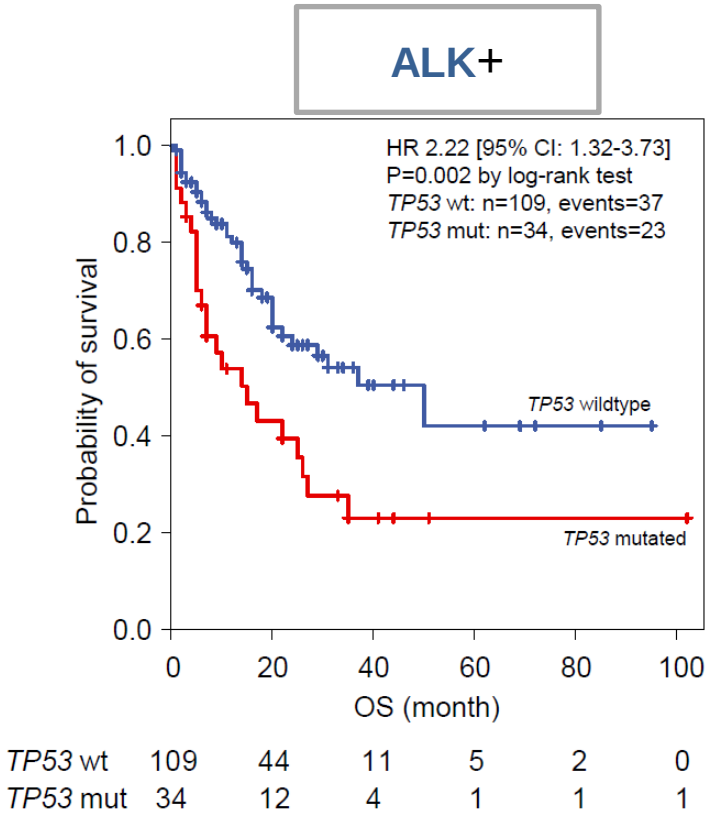
> new treatment approach ?

***MET* amplification mediates innate resistance to third-generation EGFR TKI treatment**

# 2nd NGM Evaluation 2018:

## *OS benefit with sequential therapies*

Network Genomic Medicine Lung Cancer



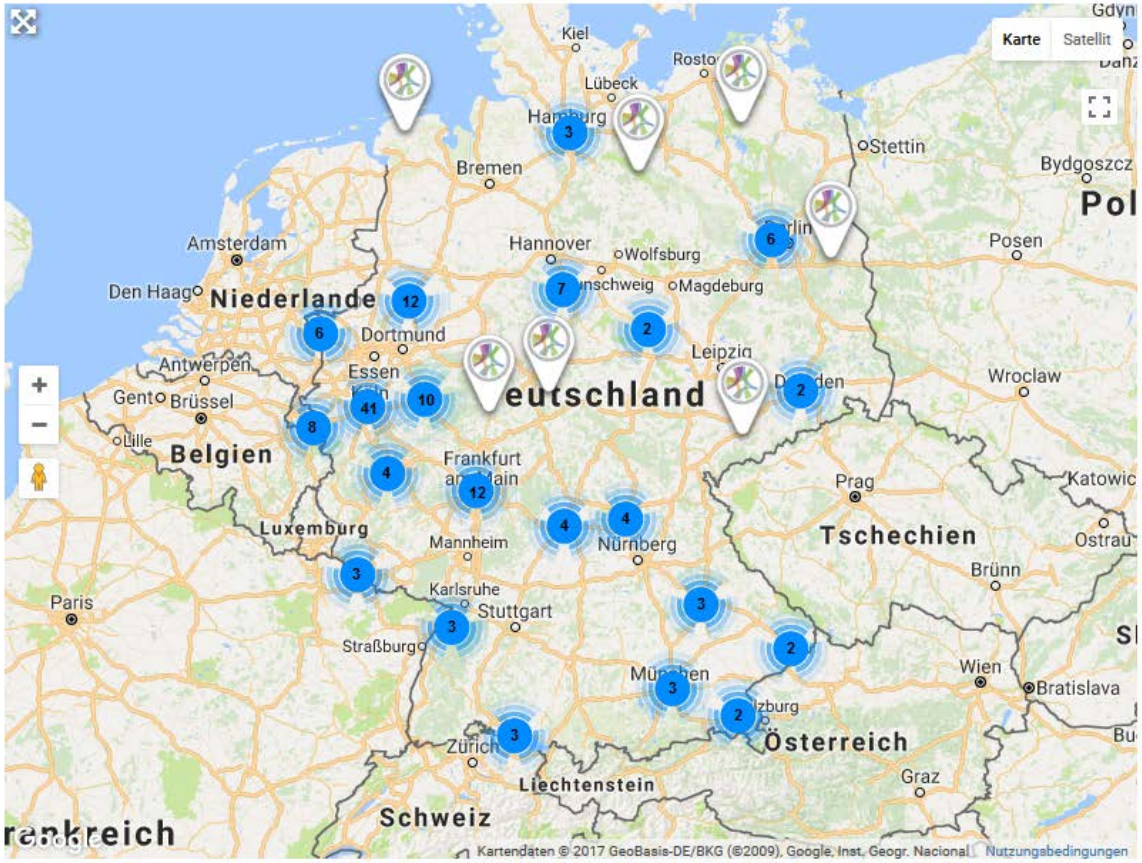

**OVERALL SURVIVAL (OS)**
**P = 0.002**

| | |
|---|---|
| *TP53* wildtype | **50 mon** |
| *TP53* co-mutation | **15 mon** |

> new treatment approach ?

Kron et al., Ann Oncol. 2018 Oct; 29(10): 2068–2075.

# Ärzte in Ihrer Nähe




## Ärzte und Kliniken finden

Bitte geben Sie den gewünschten Suchbegriff, bzw. den Ort, in dem Sie suchen möchten in dem vorgesehenen Feld ein und drücken dann auf den Button.

Alternativ können Sie über das Kompass-Symbol Ihren Standort übermitteln und nach Ärzten und Kliniken in Ihrem Umkreis suchen.

Suchen nach Namen

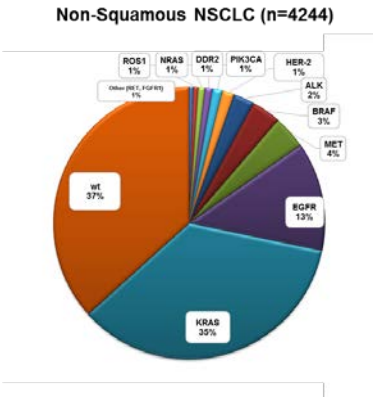
Suche nach Ort

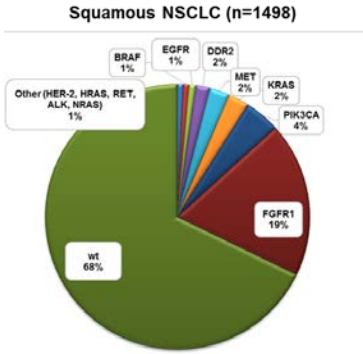
Ärzte in meiner Nähe finden

**ngm-cancer.com/aerzte-in-ihrer-naehe/**

# NGM-associated personalized clinical trial program

| | |
|---|---|
| Phase I/II platform (pharma trials) | **EGFR** (3rd gen.) mono and combos, FIM<br>**ALK** (2nd gen.), FIM<br>**MET**amp, METex.14, phase II<br>**ROS1**, phase I<br>**NTRK,**<br>**BRAF, KRAS**, FIM<br>**FGFR**amp, FIM<br>**DLL3** (SCLC), phase II<br>**RETf**us, phase II |
| Investigator-initiated trials | **EGFR+MEK** (EATON), phase I<br>**ROS 1** (EUCROSS), phase II<br>**HER2mut** (TRY), phase II<br>**FGFR**fus+mut (FIND), phase II<br>**TMB** (I-O; BIOLUMA), phase II |




> to treat all patients according to the genetic vulnerability of her/his tumor
> to allow patients early access to innovative drugs
> to allow proof-of-concept
> to develop new treatment approaches for small genetic subgroups

Shaw....Wolf....NEJM 2014; Hyman...Wolf....NEJM 2015; Rizvi....Wolf....Lancet Oncol 2015; Kim...Wolf....Lancet Oncol 2016; Nogova.....Büttner, Wolf, JCO 2017; Soria.....Wolf.... Lancet, 2017; Jänne.....Wolf....JAMA 2017.

# Nationwide extension of the NGM-model
# > national Network Genomic Medicine (nNGM)

nNGM | National Network Genomic Medicine Lung Cancer

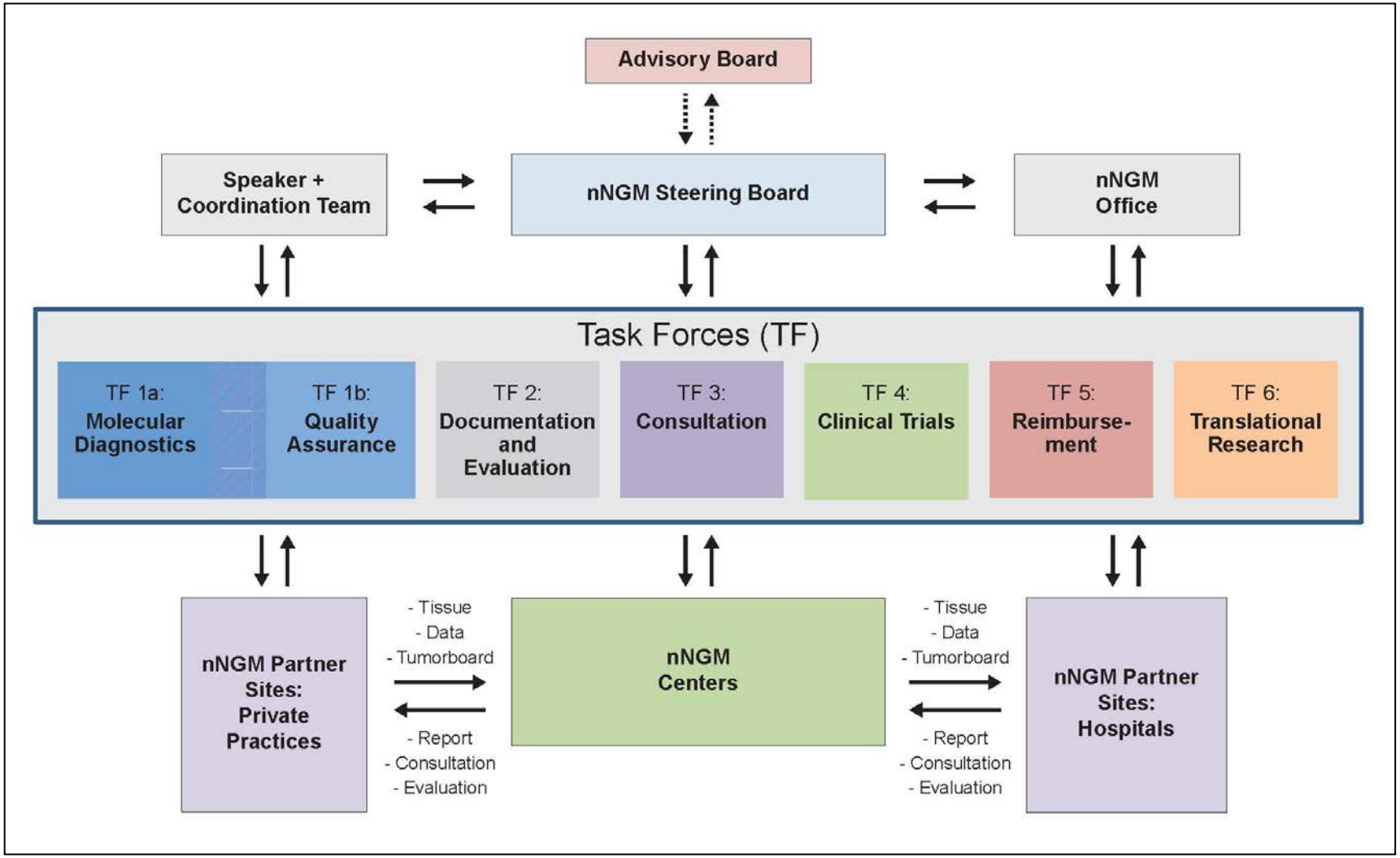
- 10 / 16 Grant application to German Cancer Aid (DKH)
- **04 / 18 Start funding of nNGM by DKH**

Initial nNGM centers = 15 DKH-funded Oncology Centers of Excellence (CCCs):

Berlin, Dresden, Düsseldorf, Erlangen, Essen, Frankfurt, Freiburg, Hamburg, Heidelberg, Köln/Bonn, Mainz, München (LMU/TU), Tübingen-Stuttgart, Ulm, Würzburg

- 11 / 18 1st positive evaluation by DKH reviewers

# Structure of nNGM: governance, task forces, regional networks



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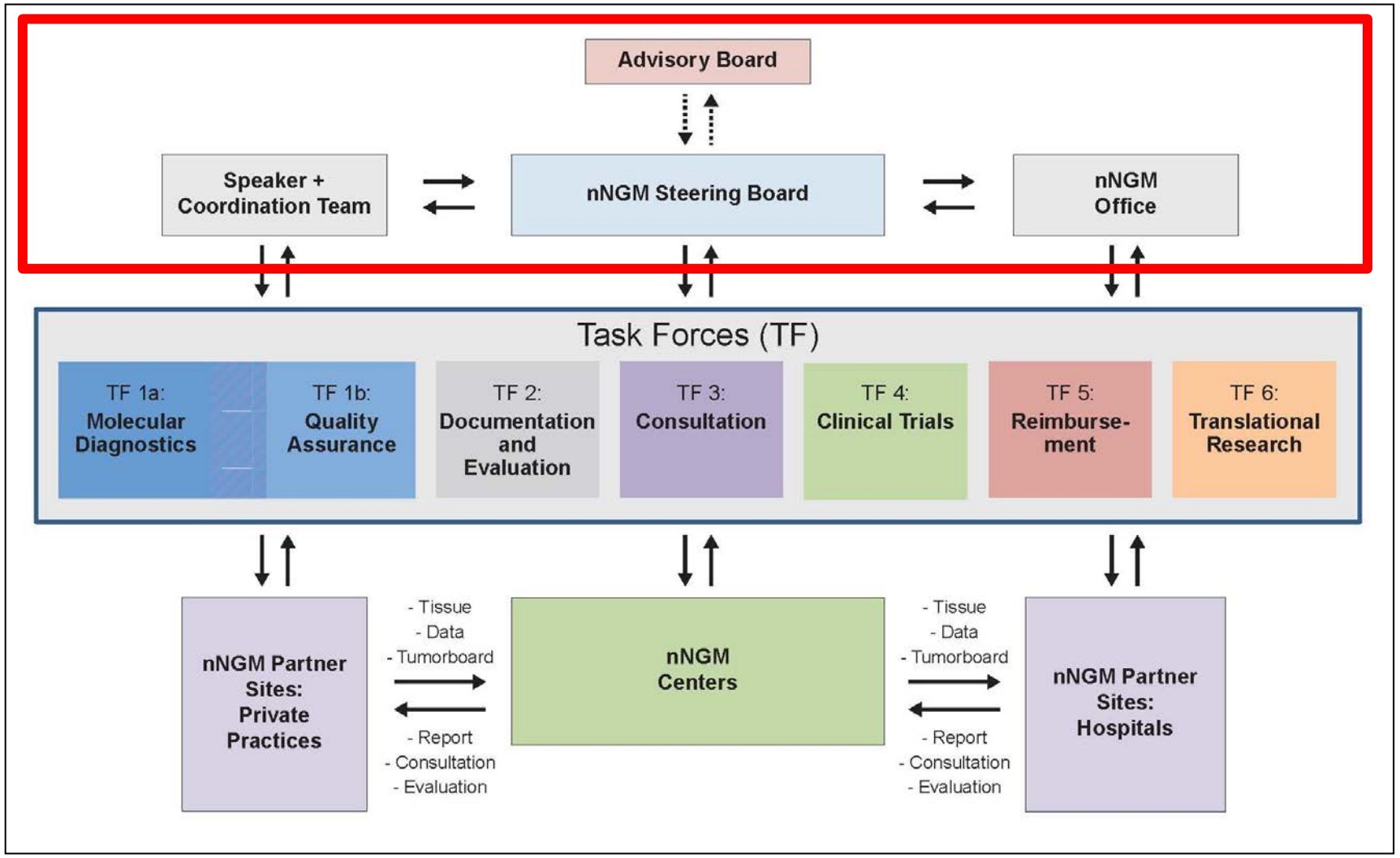

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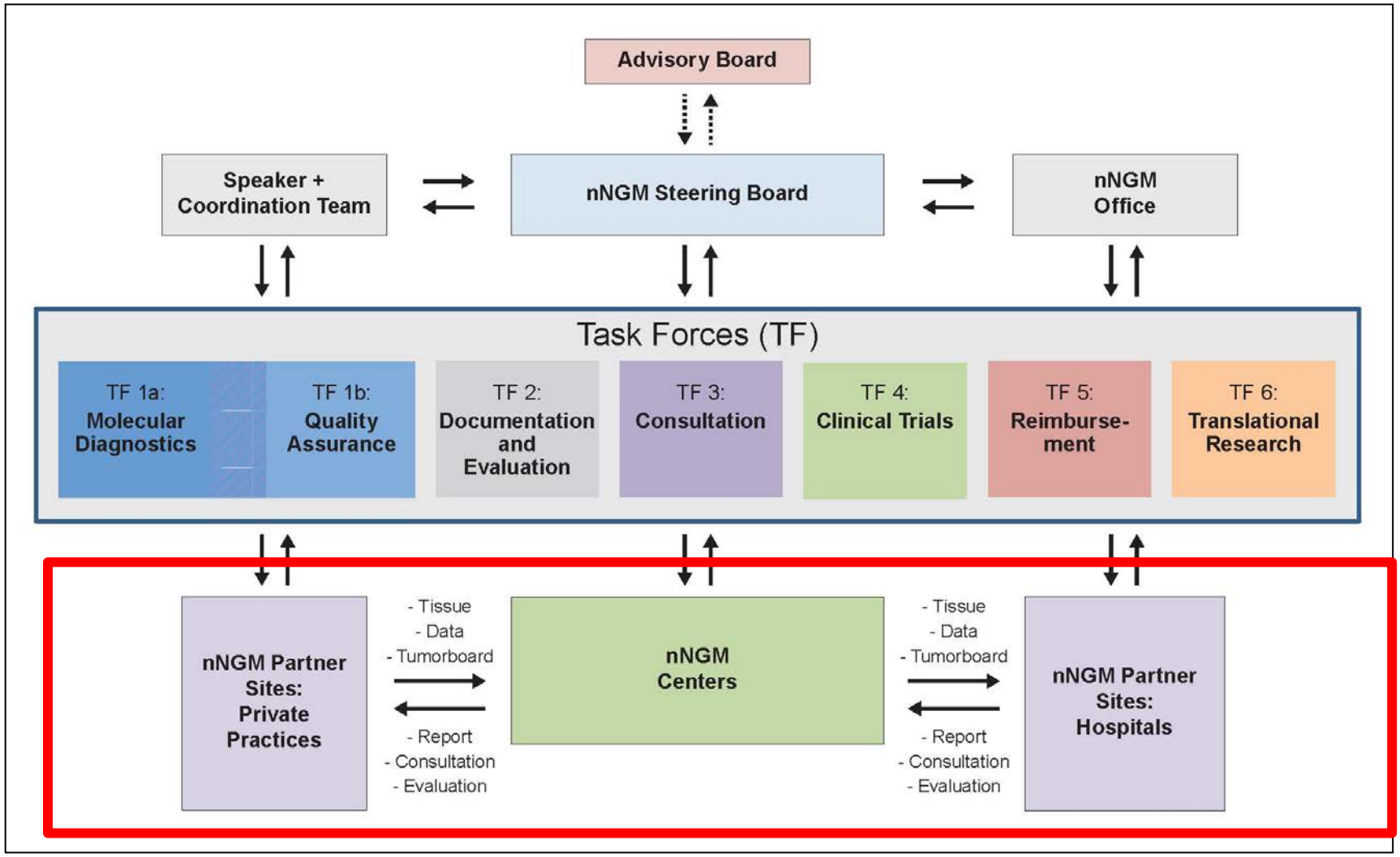

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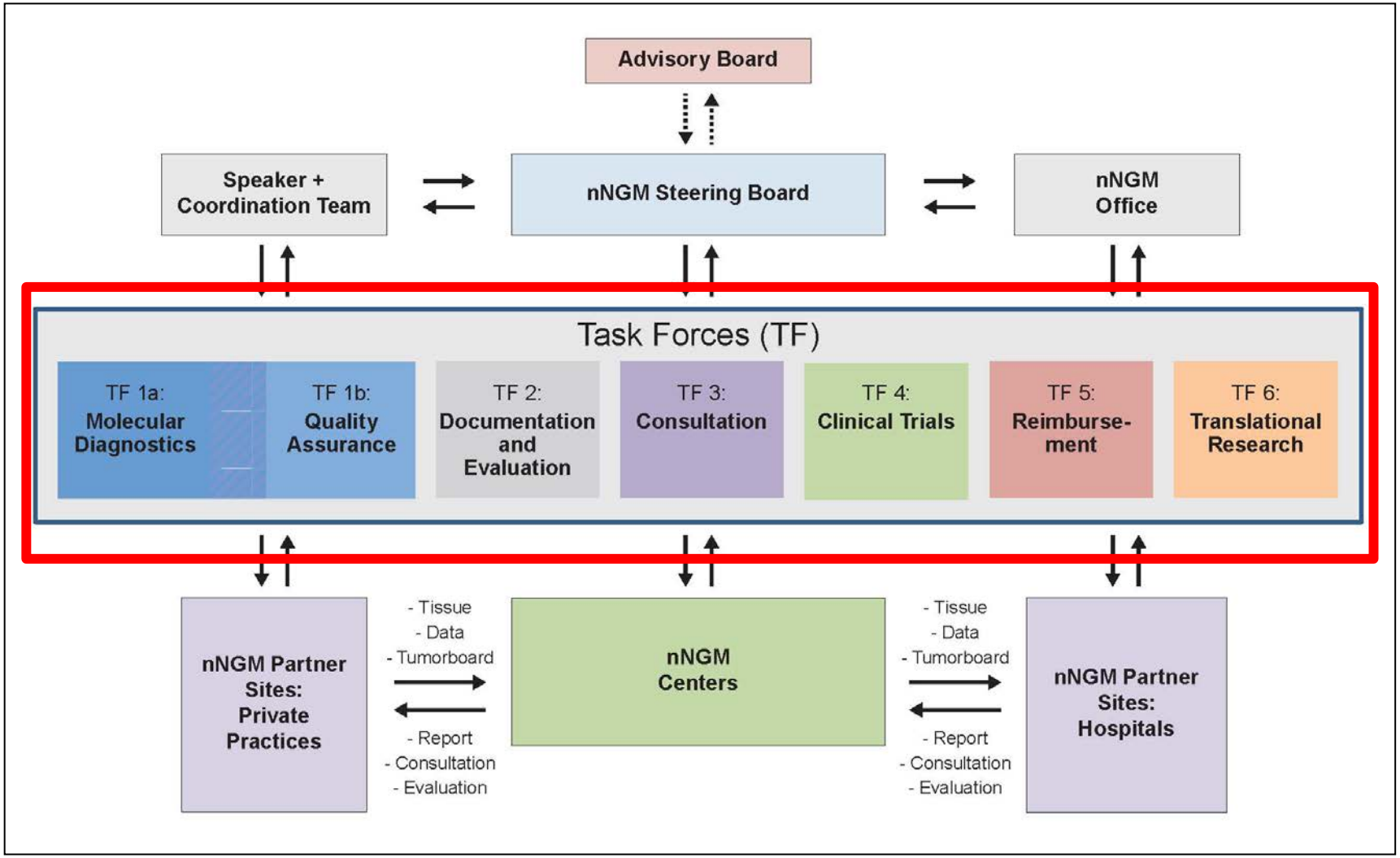


# TF 1a: Molecular Diagnostics

Speakers: R. Büttner, F. Haller, S. Merkelbach-Bruse

- **Joint NGS Panel**
- **Joint SOPs for mol. diagnostics NGS, FISH....**
- **Harmonized Reports**

**> Hybrid-capture based NGS under development**

**> TMB diagnostics under development**

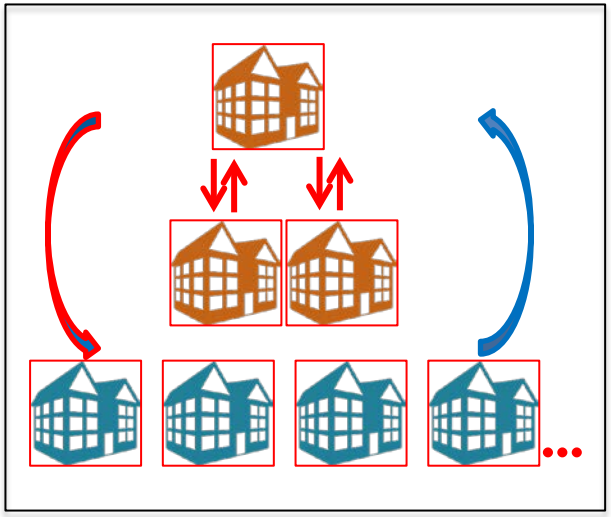
| Marker | Transkript | Exone |
|---|---|---|
| ALK | NM_004304 | 22, 23, 24, 25 |
| BRAF | NM_004333 | 11, 15 |
| CTNNB1 | NM_001904 | 3 |
| EGFR | NM_005228 | 18, 19, 20, 21 |
| ERBB2 (HER2) | NM_004448 | 8, 19, 20 |
| FGFR1 | NM_023110 | 4, 5, 6, 7, 10, 12, 13, 14, 15 |
| FGFR2 | NM_000141 | Tr-A*: 6, 7, 8, 10, 11, 13, 14, 15; Tr-B*: 8, 9, 12, 18 |
| FGFR3 | NM_000142 | 3, 6, 7, 9, 10, 12, 14, 16, 18 |
| FGFR4 | NM_213647 | 3, 6, 9, 12, 13, 15, 16 |
| IDH1 | NM_005896 | 4 |
| IDH2 | NM_002168 | 4 |
| KRAS | NM_033360 | 2, 3, 4 |
| MAP2K1 (MEK1) | NM_002755 | 2, 3 |
| MET | NM_001127500 | 14, 16, 17, 18, 19 |
| MET | NM_001127500 | Intron 13, ersten 100 bp von Intron 14 |
| NRAS | NM_002524 | 2, 3, 4 |
| PIK3CA | NM_006218 | 10, 21 |
| PTEN | NM_000314 | 1, 2, 3, 4, 5, 6, 7, 8 |
| ROS1 | NM_000245 | 34, 35, 36, 37, 38, 39, 40, 41 |
| TP53 | NM_000546 | 4, 5, 6, 7, 8 |

# TF 1b: QA Molecular Diagnostics

Speakers: P. Schirrmacher, T. Kirchner, M. Hummel

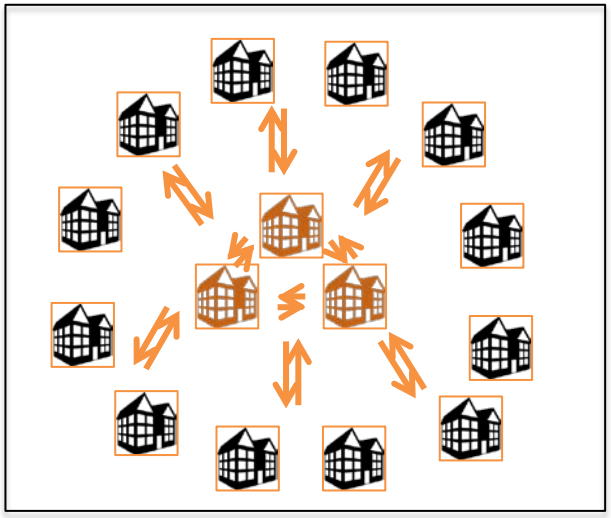
## NGS Proficiency Testing

1. Samples tested and retested by reference centers
2. Test and reporting by all centers



## NGS Performance Testing

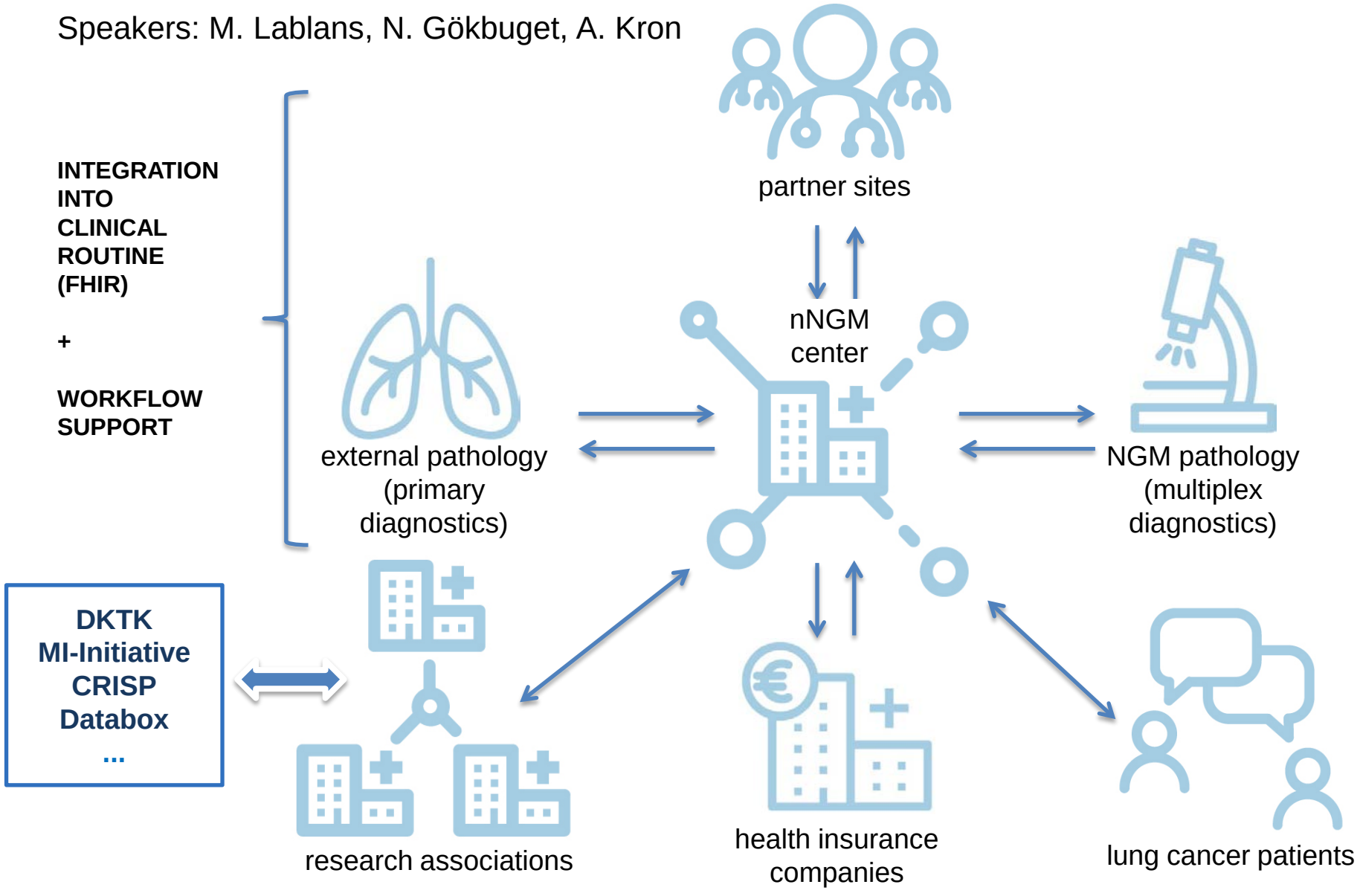
1. Random sample identification in nNGM centers
2. Retesting by reference centers



# TF 2: Dokumentation und Evaluation

nNGM National Network Genomic Medicine Lung Cancer

Speakers: M. Lablans, N. Gökbuget, A. Kron



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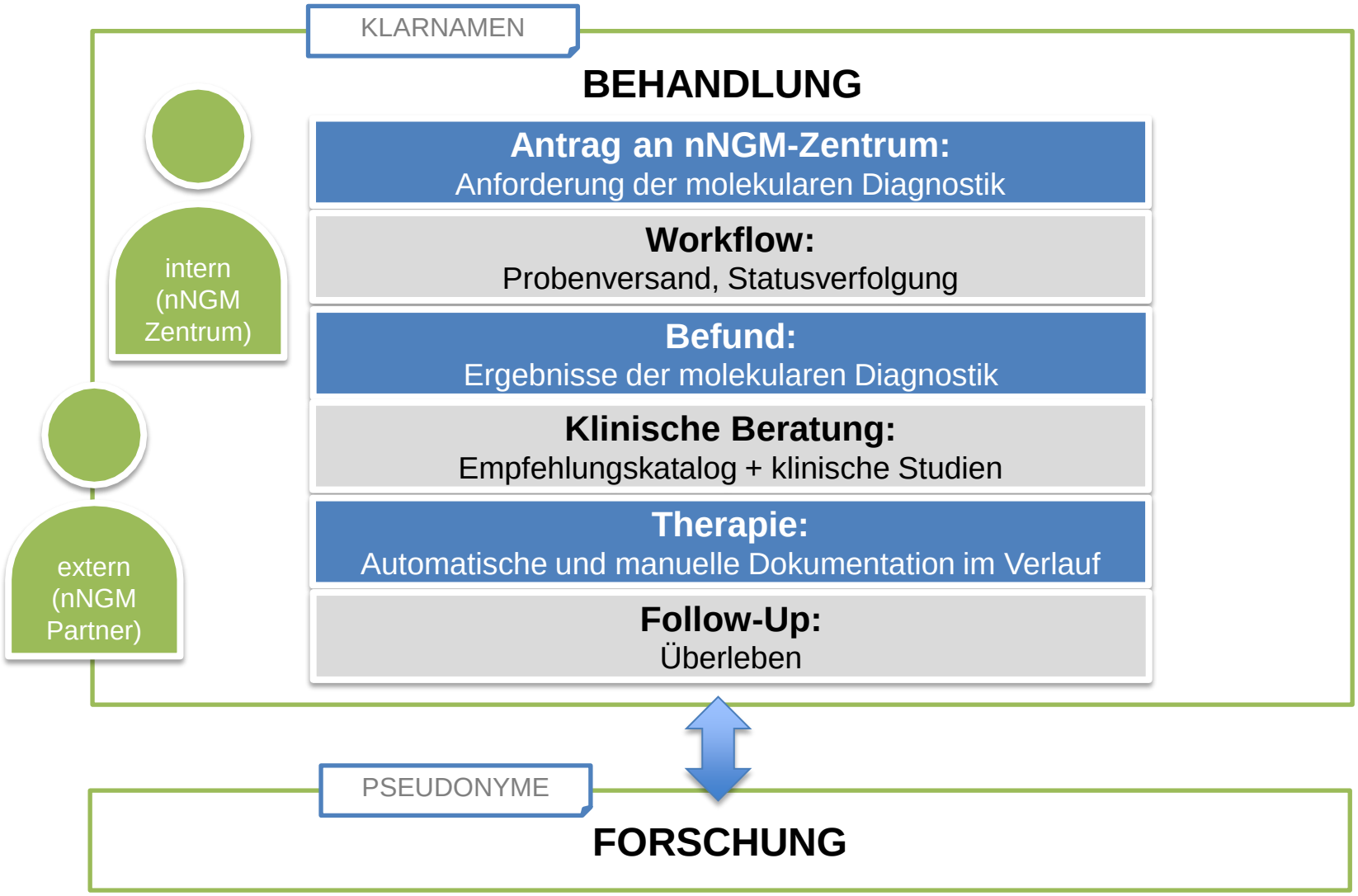

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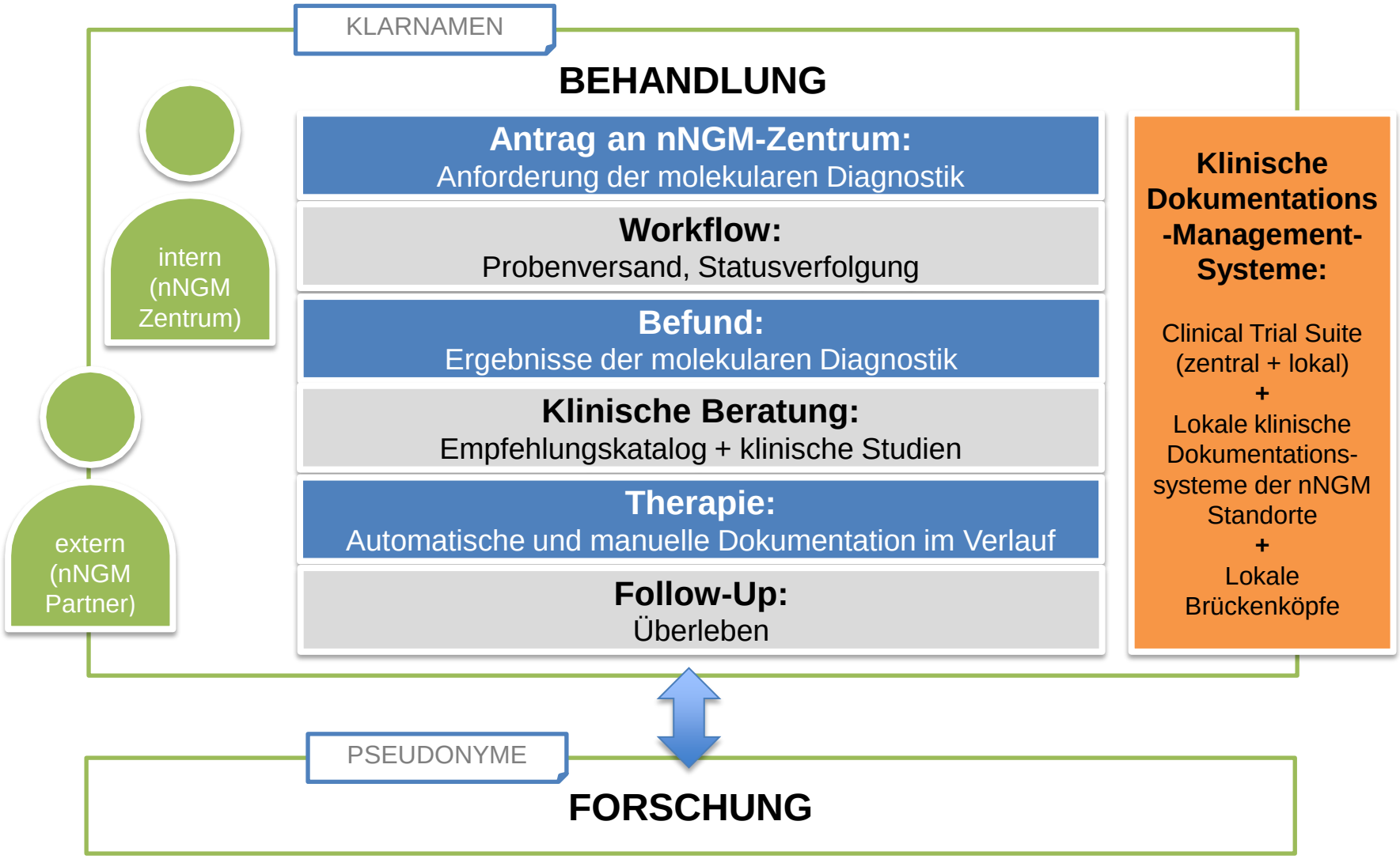
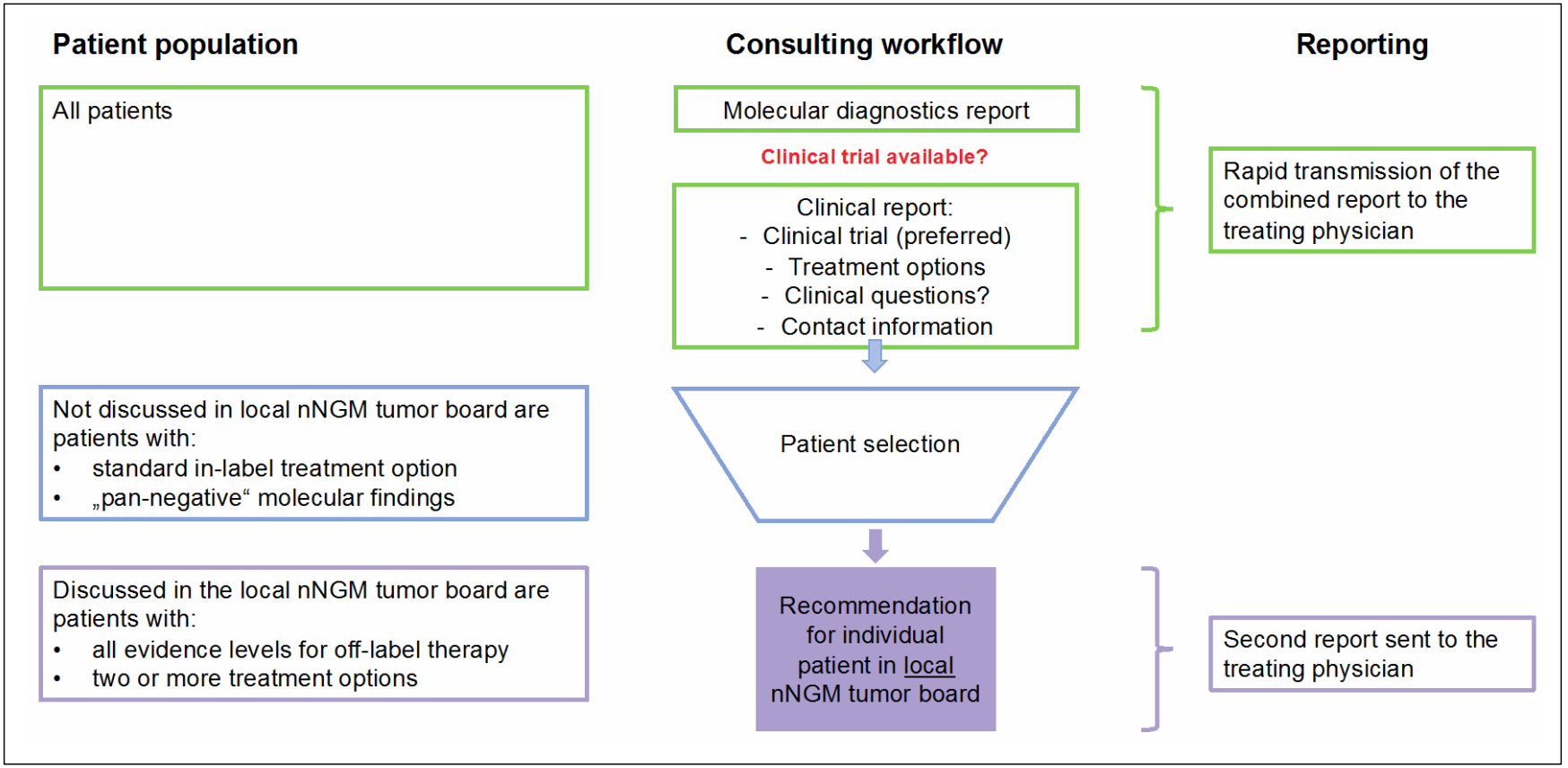


# TF 3: Consultation > harmonized workflow

Speakers: C. Brandts, E. Schröck, N. v. Bubnoff

in collaboration with A. Heyll, MDK Kompetenzzentrum Onkologie



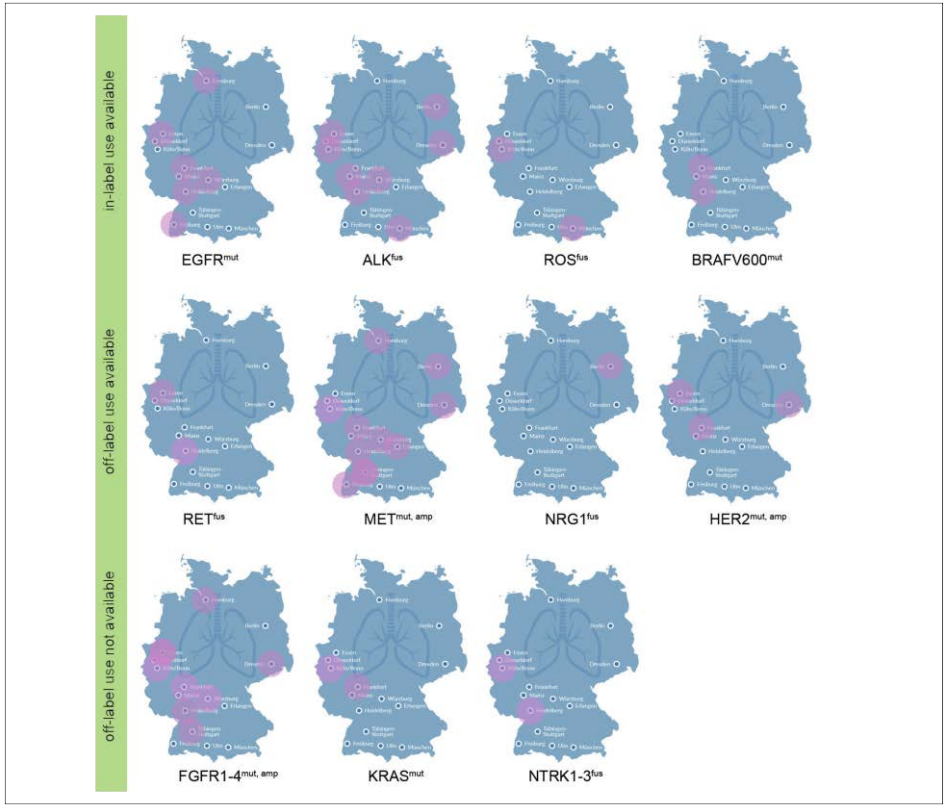
# TF 4: Clinical Trials

Speakers: J. Wolf, M. Sebastian, M. Thomas

- **Status quo assessment of trial activity in nNGM centers**
  **> harmonization**

- **Central Clinical Trial Registry in collaboration with DKTK**
  **> [www.nngm.de](http://www.nngm.de) (CCP-Office / TF 2)**

- **1st nNGM trial launched in Q1 2019: FGFR-inhibition in squamous cell lung cancer (phase II IIT FIND)**



# TF 5: Reimbursement

nNGM National Network Genomic Medicine Lung Cancer

Speakers: J. Wolf, A. Kron


AOK Die Gesundheitskasse. | BUNDESVERBAND

- First nNGM contract covering the NGS-based genotyping (tissue and T790M liquid biospy) + consultation of **statutory health insured** patients

***AOK BAYERN***
***AOK BREMEN***
***AOK HESSEN***
***AOK RHEINLAND/HAMBURG***
***AOK NIEDERSACHSEN***
***AOK NORDWEST***

# TF 6: Translational Research

nNGM National Network Genomic Medicine Lung Cancer

Speakers: M. Schulter, R. Thomas, W. Weichert

- Pilot projekt 1: **Changes in the mutational landscape during therapy**
  NGS-based rebiopsy analyses to detect and in future overcome the resistance mechanisms

- Pilot project 2: **Comparison of sequencing pipelines (WES, Panel) between Köln, Heidelberg, München**

- **Linking of nNGM to large research consortia in lung cancer:** consortial research coordination structure, which will oversee and harmonize research requests directed at the consortium

# www.nngm.de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Kontakt
Datenschutz
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nNGM
Nationales Netzwerk Genomische Medizin Lungenkrebs
Über das nNGM
Zentren
Task Forces
Studien
Patienten
gefördert durch Deutsche Krebshilfe
Das nNGM zentralisiert erstmals die molekulare Diagnostik für Lungenkrebs deutschlandweit
DIE ZENTREN
Die Deutsche Krebshilfe fördert 15 universitäre Krebszentren
Über ein bundesweites Netzwerk sollen in Deutschland künftig alle Patienten mit fortgeschrittenem Lungenkrebs Zugang zu molekularer Diagnostik und innovativen Therapien erhalten.
Dafür schließen sich 15 universitären Krebszentren im „nationalen Netzwerk Genomische Medizin (nNGM) Lungenkrebs" zusammen – darunter alle 13 onkologischen Spitzenzentren, die aktuell von der Deutschen Krebshilfe gefördert werden.
nNGM ist eine Weiterentwicklung des Kölner Netzwerks Genomische Medizin ( zur Website), das sich seit 2010 erfolgreich für die Implementierung personalisierter Therapien in der Routineversorgung von Patienten mit Lungenkrebs einsetzt. Ziel des bundesweiten Netzwerks ist, den schwer kranken Patienten Zugang zu modernster molekularer Diagnostik und neuesten Therapien, auch im Rahmen klinischer Studien, zu ermöglichen.
Die Deutsche Krebshilfe unterstützt dieses Verbundprojekt seit dem 1. April 2018.
BERLIN
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ERLANGEN
ESSEN
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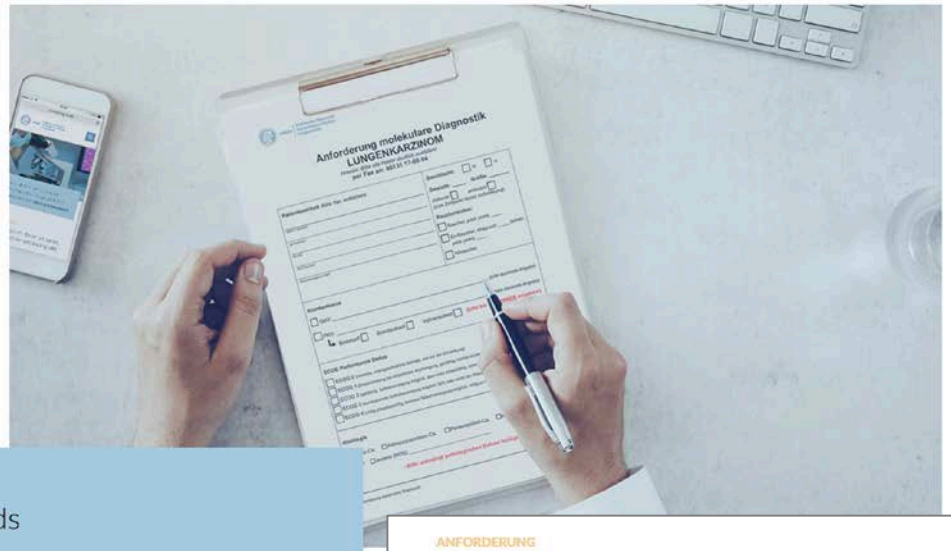
MAINZ
MÜNCHEN
TÜBINGEN-STUTTGART
ULM
WÜRZBURG
DIE ZIELE DES
nNGM Verbunds
Aufbau einer gemeinsamen Dokumentations- und

nNGM | Nationales Netzwerk Genomische Medizin Lungenkrebs

Über das nNGM | Zentren | Task Forces | Studien | Patienten

gefördert durch Deutsche Krebshilfe




Downloads

nNGM | National Network Genomic Medicine Lung Cancer

ANFORDERUNG

## Für Zuweiser: Anforderungscheine molekulare Diagnostik Lungenkarzinom

| | | |
|---|---|---|
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| ESSEN PDF | FRANKFURT PDF | KÖLN Zur Website |
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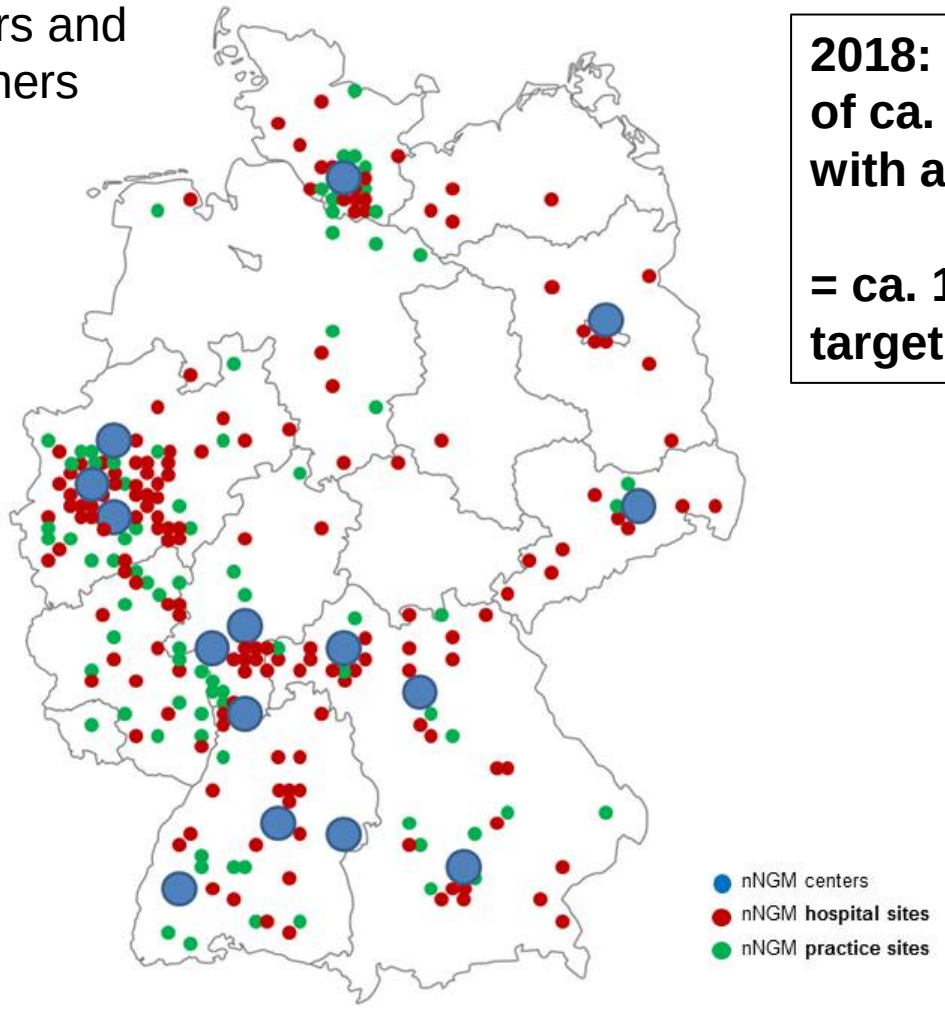
Download:
Test requests for
all nNGM centers

# Current status of nNGM

nNGM National Network Genomic Medicine Lung Cancer

nNGM-centers and network partners

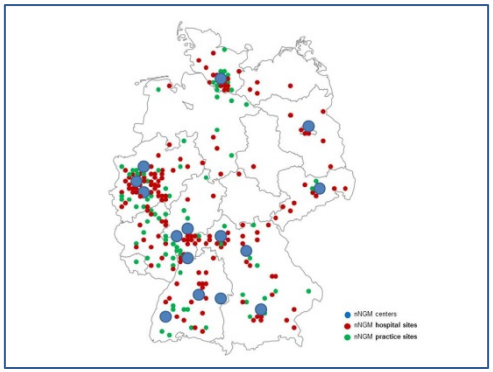



**2018: molecular diagnostics of ca. 10.000 pts. with advanced NSCLC**

**= ca. 1/3 of the target population**

**> Personalized cancer medicine becomes reality**

# Our vision for all patients with (lung) cancer




Partner Hospital
- Primary Diagnostics
- Treatment

FFPE-tissue, blood
Clinical Data + Follow-Up

Diagnostic Report
Recommendation

nNGM Center
NGS-Diagnostics
nNGM Tumorboard
Consultation
Database
Clinical Trial
Research

nNGM Center
H
P

2nd opinion
Clinical Trial

Diagnostic Report
Recommendation

FFPE-tissue, blood
Clinical Data + Follow-UP

Partner Practice
- Primary Diagnostics
- Treatment

P
nNGM Center
H

# Zusammenfassung

nNGM | National Network Genomic Medicine Lung Cancer

- ***NGM = etabliertes Modell, das mit DKH-Förderung auf aktuell 15 Zentren ausgeweitet wurde***
- ***nNGM ist offen für Beitritte weiterer Netzwerkzenten und vieler regionaler Netzwerkpartner***
- ***Kostenerstattungsregelungen mit den Krankenkassen als wesentlicher Meilenstein wurde erreicht***
- ***Zentrale klinische Datenbank in Köln + Kooperationen mit anderen Verbünden wie DKTK und MI-Initiativen***
- ***nNGM modelhaft für die Zukunft anderer onkologischer Entitäten***

# Thank you !

nNGM | National Network Genomic Medicine Lung Cancer

- nNGM-centers
- Task Force - speakers
- Center manager
- nNGM-office
- Patients

- **all regional network partners**

LungCancerGroup Cologne

DKTK Deutsches Konsortium für Translationale Krebsforschung

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

- **all patients and their families**

THE ROSIDERS BRIDGING ROS1+ PATIENTS TO RESEARCH

- **Deutsche Krebshilfe**
- **Ministerium für Kultur und Wiss. NRW**
- **BMBF**

Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.

Ministerium für Kultur und Wissenschaft des Landes Nordrhein-Westfalen

Bundesministerium für Bildung und Forschung

AOK Die Gesundheitskasse. BUNDESVERBAND

vdek Die Ersatzkassen

PKV Verband der Privaten Krankenversicherung

**... and further health insurances**

# SAVE THE DATE: 2nd Cologne Conference on Lung Cancer

NETWORK GENOMIC MEDICINE 2019

## 2nd Cologne Conference on Lung Cancer

26 – 27 JUNE 2019 | GERMANY

**www.cologne-clc.com**