Dutch Life Sciences Conference:
Accelerating change in healthcare
CORPUS Congress Centre, Leiden Bio Science Park, November 28, 2019

Personalized healthcare in oncology:
Predictive cancer diagnostics in Pathology:
todays diagnostics: ready for the precise treatment of tomorrow

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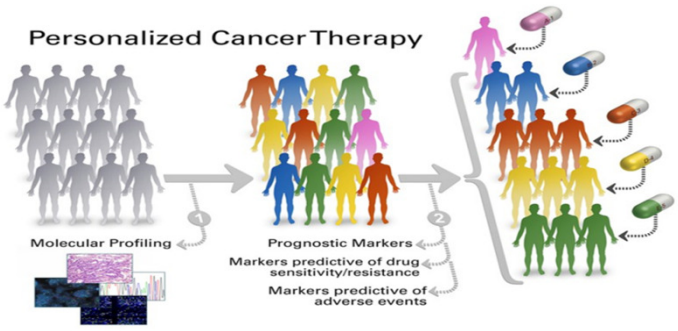
Board member Dutch Soc Pathology (NVVP)
Member Council Research and Innovation, Federation Medical Specialists (FMS)

Pathology UNIVERSITY MEDICAL CENTER GRONINGEN

Disclosures

(Potential) conflict of interest	
Potentially relevant company relationships in connection with event	**Company names**
• Research Funding	• Genentech, Merck Sharp & Dohme, Roche/Ventana, (all "non-restricted")
• Advisory board (non personal, fee to department)	• Merck Sharp & Dohme, Pfizer, Roche/Ventana, AbbVie, Bristol-Myers Squibb, .
• Lecture / course (non personal, fee to department)	• Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Glaxo Smith Kline, Biotest, Chiesi, Lilly Oncology, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Ventana

Precision Medicine – Personalized therapy
Molecular Pathology

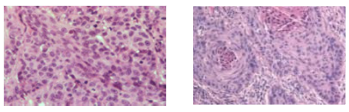


Tumor-specific molecular markers: molecular tumor profiling

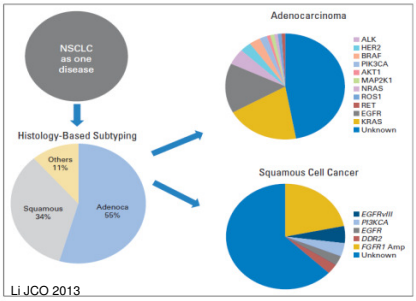
Targeted cancer therapy :
Only treat patients that benefit from the specific drug

Classification of cancer in 2019:
From classical histopathology to molecular profiling

Traditional histopathological classification



>2009: Molecular Tumor Profiling



Molecular Diagnostics in Pathology

The detection of tumor-specific genetic alterations (non-germline) in clinical practice

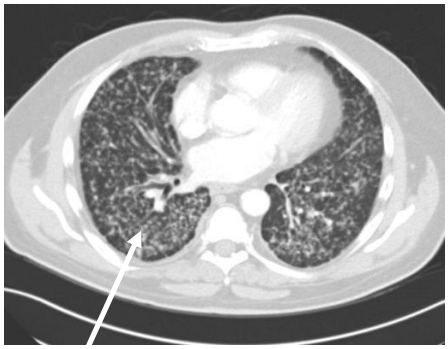
- Diagnosis: classification of tumors
- Predictive treatment-decision-making
- Disease monitoring (Minimal Residual Disease)
- Monitoring of treatment response
- Detection therapy-resistent markers

Picture from Green AMP 2014

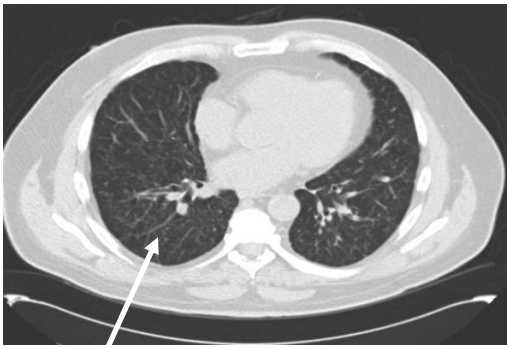
The impressive effect of specific targeted therapy in patient with lung adenocarcinoma carrying a chemoresistant EGFR mutant

PRE-treatment

6 weeks after start treatment

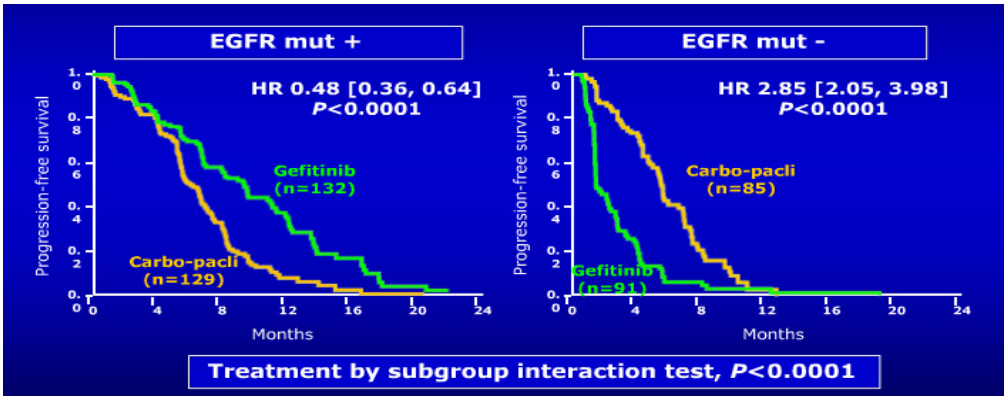


Lung with extensive tumor (white spots)



Lungs are " clean"

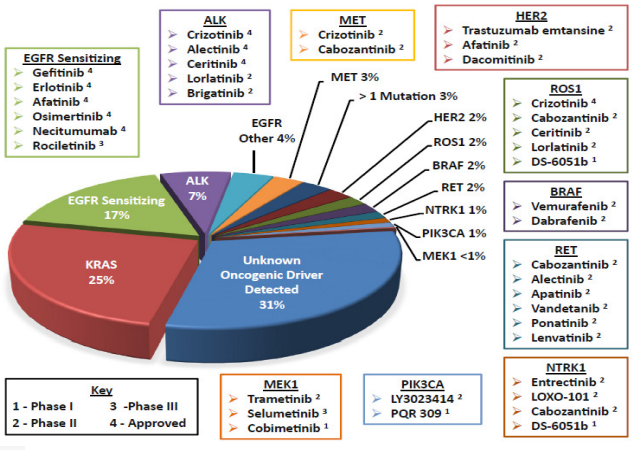
Disease-free-survival of NSCLC patients with/without EGFR-mutations treated with gefitinib or standard chemotherapy



Principle of targeted therapy:

- only treat patients that benefit from TKI
- appropriate molecular profiling is essential

Targeted therapy in advanced-stage lung cancer
Predictive mutations and associated specific drugs



NSCLC-adca in USA: Tsao J Thor Oncol 2016

Standard of care for advanced-stage Lung cancer in the Netherlands (2019):

-tumor biopsies with druggable mutations (~20%): *targeted therapy*

-tumor biopsies without druggable mutation: *eligible for immunotherapy*

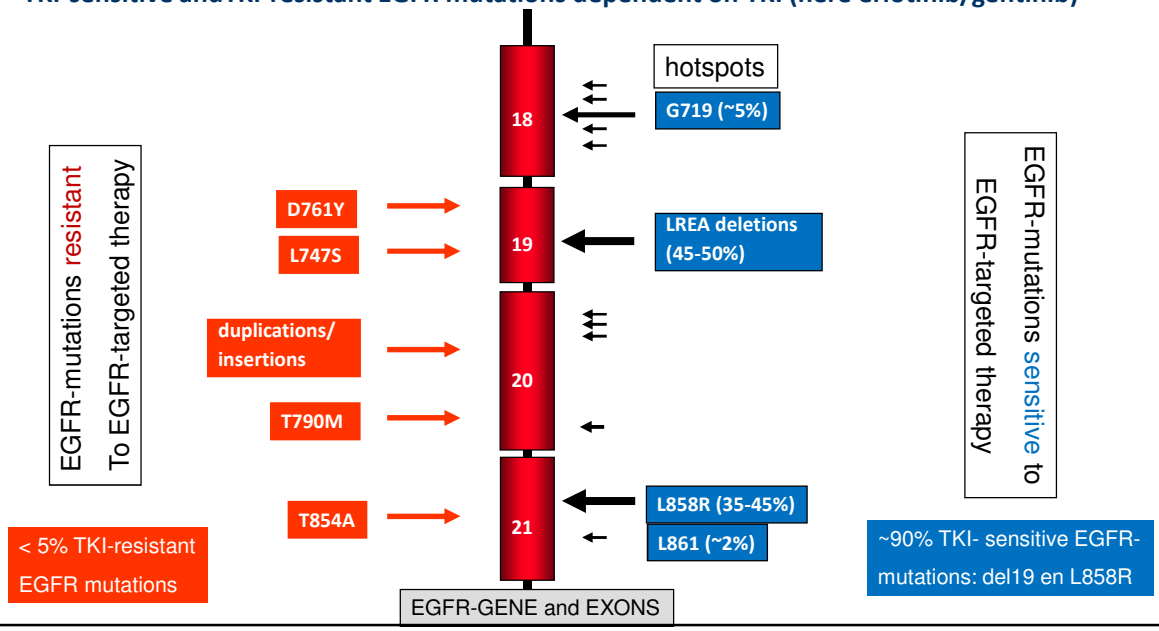
<u>Because small biopsies:</u>

Presently (NL): small gene-panels (e.g. 33 predictive biomarkers)

Selection: only those with direct consequences for treatment: registered, off-label, compassionate-use, clinical trial in NL

Detection of mutations in EGFR (>3300)

TKI-sensitive andTKI-resistant EGFR mutations dependent on TKI (here erlotinib/gefitinib)



Continously growing number of specific drugs against *different* EGFR-mutations

Table 2. Small-Molecule EGFR TKIs Clinically Available or in Development

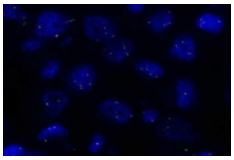
Drug Name	Generic Name	Trade Name	Manufacturer	Target	Recommended Dose	MTD	Status
Reversible							
ZD1839	Gefitinib	Iressa	AstraZeneca, Wilmington, DE	EGFR	250 mg once per day	750 mg once per day	Approved (Asia/EU)
OSI-776	Erlotinib	Tarceva	Genentech, South San Francisco, CA	EGFR	150 mg once per day	150 mg once per day	Approved
BPI-2009H	Icotinib	Conmana	BetaPharma, Branford, CT	EGFR	150 mg once every 8 hours	Not reached	Approved (China)
TAK-165	Mubritinib	NA	Takeda, Osaka, Japan	EGFR/ERBB2	NA	NA	Phase I*
XL647	NA	NA	Kadmon, New York, NY	EGFR/ERBB2†	300 mg once per day	300 mg once per day	Phase II*
ZD6474	Vandetanib	Zactima	AstraZeneca	EGFR/VEGFR2/RET	300 mg once per day	300 mg once per day	Phase III*‡
GW572016	Lapatinib	Tykerb	GlaxoSmithKline, Philadelphia, PA	EGFR/ERBB2	1,250-1,500 mg once per day	Not reached	Preclinical*§
Irreversible							
EKB-569	Pelitinib	NA	Wyeth/Pfizer, New York, NY	EGFR	50 mg once per day	75 mg once per day	Phase I*
CI-1033	Canertinib	NA	Pfizer, New York, NY	EGFR/ERBB2/ERBB4	150 mg once per day	150 mg once per day	Phase II*
HKI-272	Neratinib	NA	Puma Biotechnology, Los Angeles, CA	EGFR/ERBB2	320 mg once per day‖	320 mg once per day	Phase II*
BIBW2992	Afatinib	Tomtovok	Boehringer Ingelheim, Ingelheim, Germany	EGFR/ERBB2/ERBB4	50 mg once per day	50 mg once per day	Phase III
PF-00299804	Dacomitinib	NA	Pfizer	EGFR/ERBB2/ERBB4	45 mg once per day	45 mg once per day	Phase III
Third generation							
CO-1686	NA	NA	Clovis/Avila, Boulder, CO	EGFR T790M	NA	NA	Phase I/II
WZ4002	NA	NA	NA	EGFR T790M	NA	NA	Preclinical
Other							
AP26113	NA	NA	Ariad Pharmaceuticals, Cambridge, MA	ALK/EGFR¶	NA	NA	Phase I/II

Ohashi JCO 2013

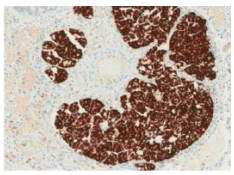
- First-line EGFR-inhibitors: erlotinib, gefitinib and afatinib
- In 2017 osimertinib registered for TKI-resistent NSCLC with EGFR-T790M mutation (Mok NEJM 2017)
- In 2019 osimertinib registered for first-line therapy in all NSCLC with any EGFR mutation (Soria NEJM 2018)

Detection and reporting of the exact EGFR-variant is essential for appropriate treatment decision making

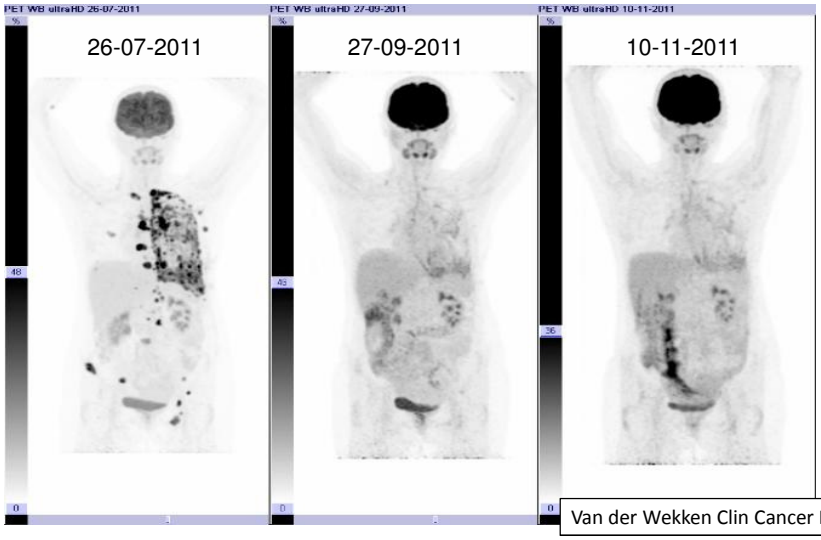
Tumor response on crizotinib in FISH ALK positive and IHC ALK positive NSCLC: complete response



FISH-ALK-positive



IHC-ALK-positive



Van der Wekken Clin Cancer Res 2017

Choose the right ALK inhibitor

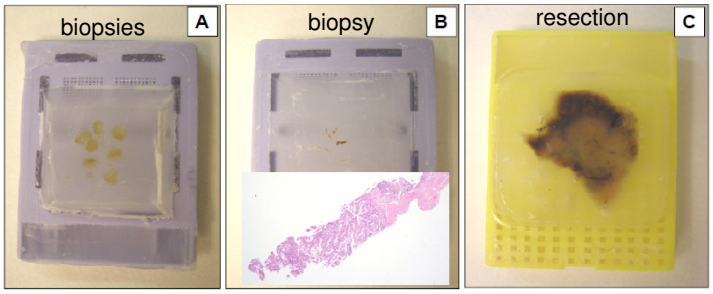
ALK Variant	TKI Activity, IC_{50} (nM) Crizotinib	Ceritinib	Alectinib	Brigatinib
Native	107	37	25	14
1151Tins	1109†	283	201	114
L1152R	844†	437†	62	11
L1152P	721	451	48	20
C1156Y	529†	195	67	45
I1171N	532†	119	724†	124
F1174C	238	109†	31	58
F1174L	253†	117	44	55
F1174V	257†	121†	46	64
V1180L	170	16	597	11
L1196M	589†	67	133	41
L1198F	17	697	84	82
G1202R	617†	354†	695†	184
D1203N	459†	159	42	79
S1206F	199†	39	34	43
S1206Y	179†	42	19	36
E1210K	240	80	59	107
G1269A	509†	29	56	9

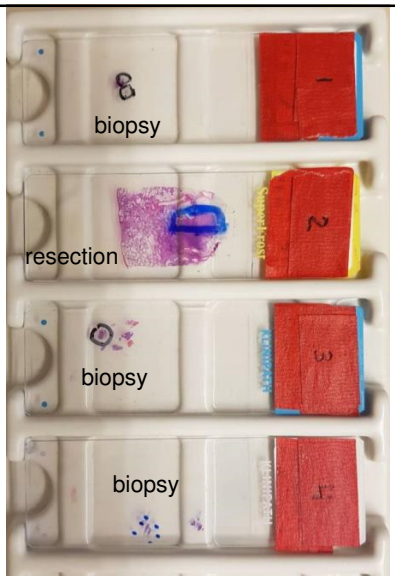
Effective Average Concentration (C_{ave}) in Patients* Exceeds IC_{50} by at Least 2-fold: Yes / No

Frequent resistence →

1. Zhang S, et al. *Cancer Res.* 2015;75(15 suppl; abstr 781)
2. Camidge D, et al. *J Clin Oncol.* 2015;33(suppl; abstr 8062)
3. Katayama R, et al. *Clin Cancer Res.* 2015;21:2227-2235
4. Friboulet L, et al. *Cancer Discov.* 2014;4:662-673.

TISSUE IS THE ISSUE





Available "tissues" in current clinical practice:

- 90% = FFPE-blocks (formaline-fixed paraffin-embedded: degraded DNA!)

  FFPE is the world-wide standard stored for >100 years

- Frozen tissues (not available in >95%)
- Liquid biopsy: circulating tumor DNA in cell-free plasma

Next generation sequencing

how to detect CNV/SNV best ?

Whole genome sequencing

High quality DNA (only frozen), high input (500 ng), 30x coverage, **most comprehensive genomic data,** high costs, long TAT, qualified expertise

Whole exome sequencing

High quality DNA (only frozen), high input (500 ng), 100x coverage, **complete coding regions,** moderate costs, long TAT, qualified expertise

Sequencing of defined target genes (gene-panel)

Low quality DNA (also FFPE), low input (10-20 ng), 500-2000x coverage, **only selected hotspots,** acceptable costs, TAT (<5d)

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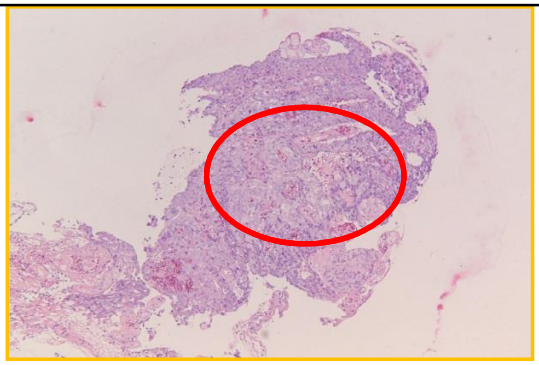


- Sufficient DNA for NGS
- >20% neoplastic cells

- Panel-Ion Torrent: 10 ng (~1600 cells)
- Panel-Miseq: 50 ng
- WES: ~500 ng
- WGS: ~500 ng

Today:
Standard lung cancer biopsies are not (yet) suitable for WES/WGS

Preferred: the use of small gene-panels (<1Mb) (1600 neoplastic cells)

Results European Quality Assessment schema (EQA-ESP):
use of NGS in 2013: 1%, 2014: 5% and 2017: 32% (no WES/WGS)

Methods to detect predictive molecular aberrations in Molecular Pathology of lung cancer at UMCG (June 2019)

NGS-mutation: EGFR, ALK, ROS, RET, KRAS, BRAF, PIK3CA, MET, HER2, DDR2, FGFR1

FISH-amplification/CNV: MET, HER2, FGFR1, EGFR1

IHC: PD-L1, HER2, ALK, ROS1

Nanostring-fusions: ALK, ROS, RET, MET exon14-skipping, BRAF, NTRK1/2/3 (NRG1)

NGS: Tumor Mutational Burden (2019: under validation)

Predictive markers targetable in other malignancies: e.g. KIT, PDGFRa

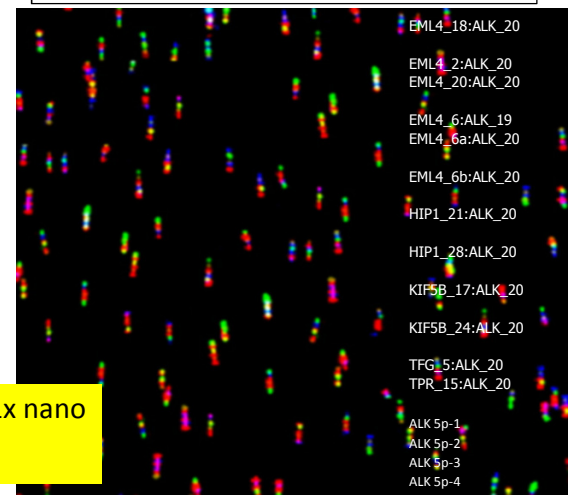
NGS only does not provide a full molecular profile (2019-2025)

Lung: Immunohistochemistry, RNA-based assays, FISH
Other cancers: MLPA, ddPCR, …

Molecular Oncological Pathology at UMCG: www.MolOncoPath.nl

nanoString – SPRINT – UMCG-lungpanel (2019)

UMCG-long panel V2.0: ALK, ROS, RET, NTRK1, NTRK2, NTRK3, NRG1 fusions and MET-skipping



lung-nano-V02: 7xFISH + 1x MET-skipping = 1x nano

- Cost reduction (considerable!)
- Tissue saving (big advantage tissue-management)

Project PATH (Predictive Analysis for THerapy) Optimizing access to personalized cancer therapy in the Netherlands; from tissue to therapy.

- National consortium of >38 pathology-labs, medical oncologists, pulmonologists, NVALT, NVMO, NVVP, PALGA
- Goal: To introduce predictive testing assay to create optimal and equal access to targeted therapies for all (lung, melanoma, GIST, CRC) cancer patients in the Netherlands
- 2016-2020: using predictive and diagnostic genes based on current guidelines, ongoing clinical trial and off-label

Nederlandse Vereniging Voor Pathologie

http://www.netwerk-path.nl

CALL ZONMW GGG: PERSONALISED MEDICINE – ONCOLOGY

Dutch consensus molecular tumor profiling

PATH-v02D DNA gene panel implemented in 4 major centers using smMIP-NGS for targeted therapy in lung, colo-rectal cancer, GIST and melanoma

Predictive gene	Aberrations	Predictive gene	Aberrations
AKT1	SNV	JAK2	SNV
AKT2	SNV	KIT	SNV + CNV
AKT3	SNV	KRAS	SNV + CNV
ALK	SNV + CNV	MAP2K1	SNV
ARAF	SNV	MDM2	CNV
BRAF	SNV + CNV	MET	SNV + CNV
DDR2	SNV	MTOR	SNV
EGFR	SNV + CNV	NRAS	SNV
ERBB2	SNV + CNV	PDGFRA	SNV + CNV
FGFR1	CNV	PIK3CA	SNV
FGFR2	CNV	POLE	SNV
FGFR3	CNV	PTEN	SNV
GNAS	SNV	RAF1	SNV
GNAQ	SNV	ROS1	SNV
GNA11	SNV	TP53	SNV + CNV
HRAS	SNV		
IDH1	SNV	MSI	
IDH2	SNV	AMELX/Y	

http://www.netwerk-path.nl

Pathology

Consortium (Dutch University Laboratories of Molecular Pathology)
Consensus on NGS mutation panel > each patient in NL receives same opportunities for therapy

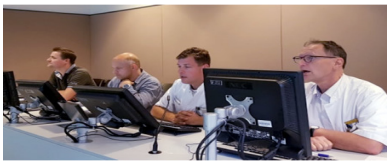
Dutch consensus molecular tumor profiling

PATH-v03 DNA gene panel in development for targeted therapy in lung, colo-rectal cancer, GIST and melanoma

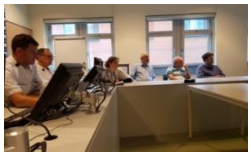
Gen	Transcript	Amino acids	Mut/del/amp	Inschatting aantal smMIPs	Melanoom	Long	Colon	GIST	Prostaat	Urotheelcelcarcinoom (blaas)	Borst	Hersenen/neuro	Lymfoom	Other	Therapie: Immuno/ targeted/other Diagnose: dd	Diagnose/ resistentie
AR	NM_000044.4	920	Mut/Amp	12											Targeted	Resistentie
APC	NM_000038	2843	Mut	41											dd	
B2M	NM_004048	119	Mut	14/4											Immuno	
CCND1	NM_053056	295	Amp	10												
CCND3	NM_001760	292	Amp	10												
CDK12	NM_016507	1490	Mut/Del	120/80												
CDK4	NM_000075	273	Amp	10												
CDK6	NM_001259	326	Amp	10												
CDKN2A (P14/P16)	NM_058195.1/NM_000077.3	132/156	Mut	20												Diagnose
CTNNB1	NM_001904.3	781	Mut												dd	Diagnose
ERCC2	NM_000400	760													Other	Diagnose
ESR1	NM_000125														Targeted	Resistentie
FGFR1	NM_001174														Targeted	Diagnose
FGFR3															Targeted	Diagnose
HIST1H3B															dd	Diagnose
														reusceltumor	dd	Diagnose
				2										chondroblastoom	dd	Diagnose
			Mut	100											Immuno	Resistentie
		1132	Mut	100											Immuno	Resistentie
	500	624	Mut	70											Other	Diagnose
	NM_003010/NM_001281435	399/410	Mut	50											Targeted	Diagnose/resistentie
MAP3K1	NM_005921	1512	Mut	180											Targeted	Diagnose/resistentie
MYC	NM_002467.5	454	CNV	10											Targeted	Diagnose
MYD88	NM_002468.4	296	Mut	8											dd	Diagnose

Updated version (end 2019): >50 predictive and diagnostic genes

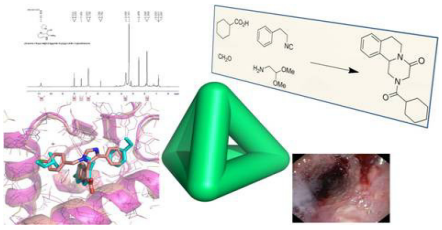
Molecular Tumor Board UMCG



This expert forum combines the expertise of clinical molecular biologists in pathology, pathologists, medical oncologists, molecular pharmacologist and pulmonologists



Pharmacochemistry: 3D modeling mutations vs drug structural variants: “best fit”

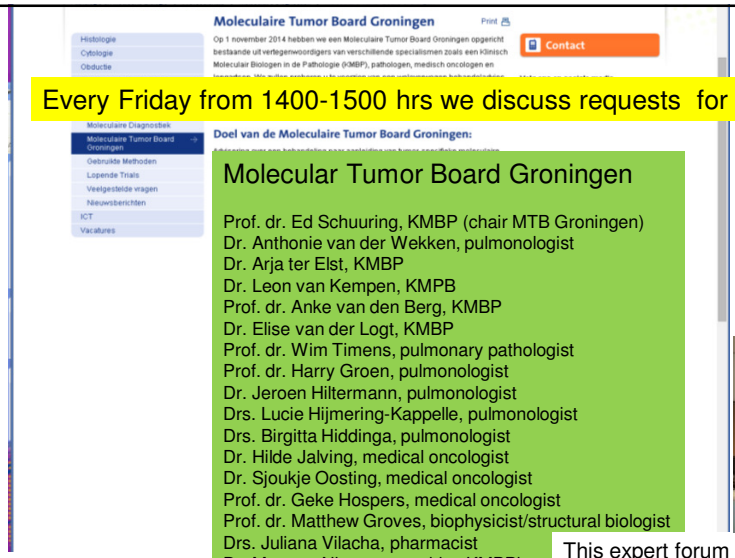


- Molecular results
- Clinical Data
- Pathology report
- Drug design

Recommendations:

- Standard therapy
- Clinical trials
- Off-label treatment

www.moloncopath.nl

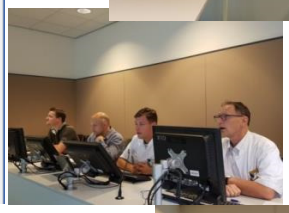


www.moloncopath.nl

Every Friday from 1400-1500 hrs we discuss requests for advice (since Nov 2014)

Molecular Tumor Board Groningen

Prof. dr. Ed Schuuring, KMBP (chair MTB Groningen)
Dr. Anthonie van der Wekken, pulmonologist
Dr. Arja ter Elst, KMBP
Dr. Leon van Kempen, KMPB
Prof. dr. Anke van den Berg, KMBP
Dr. Elise van der Logt, KMBP
Prof. dr. Wim Timens, pulmonary pathologist
Prof. dr. Harry Groen, pulmonologist
Dr. Jeroen Hiltermann, pulmonologist
Drs. Lucie Hijmering-Kappelle, pulmonologist
Drs. Birgitta Hiddinga, pulmonologist
Dr. Hilde Jalving, medical oncologist
Dr. Sjoukje Oosting, medical oncologist
Prof. dr. Geke Hospers, medical oncologist
Prof. dr. Matthew Groves, biophysicist/structural biologist
Drs. Juliana Vilacha, pharmacist
Dr. Maarten Niemantsverdriet, KMBPio
Dr. Joost Kluiver, KMBPio
Drs. Bart Koopman, MD/data-steward



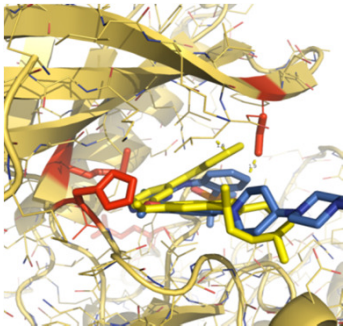
This expert forum combines the expertise of clinical molecular biologists in pathology, pathologists, medical oncologists, molecular pharmacologist and pulmonologists

Interpretation of Mutation Analysis Data

Handling of unexpected, difficult, rare mutations?

NSCLC patient

2012: EGFR: c.2155G>A; p.(G719S)



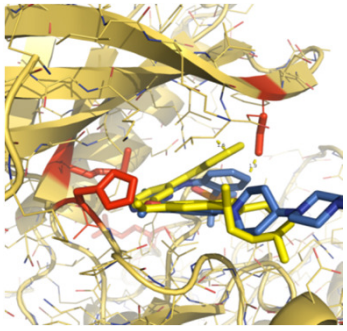
+ Erlotinib

3D-modeling (UMCG-Moleculaire Tumor Board): treatment-decision-making

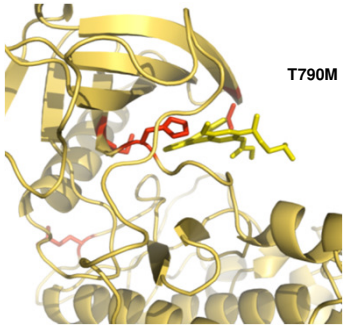
UMCG-MTB:Innovation in treatment-decision-making for rare mutations by 3D-modeling

NSCLC patient

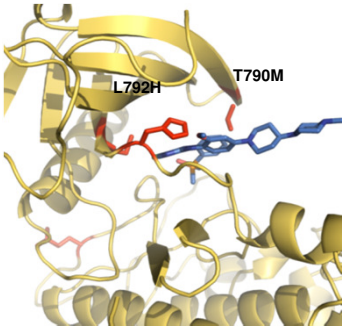
2012: EGFR: c.2155G>A; p.(G719S)
2016: EGFR: c.2582T>A; p.(L861Q) and EGFR c.2369C>T; p.(T790M)
2017: EGFR c.2375T>A; p.(L792H)



+ Erlotinib



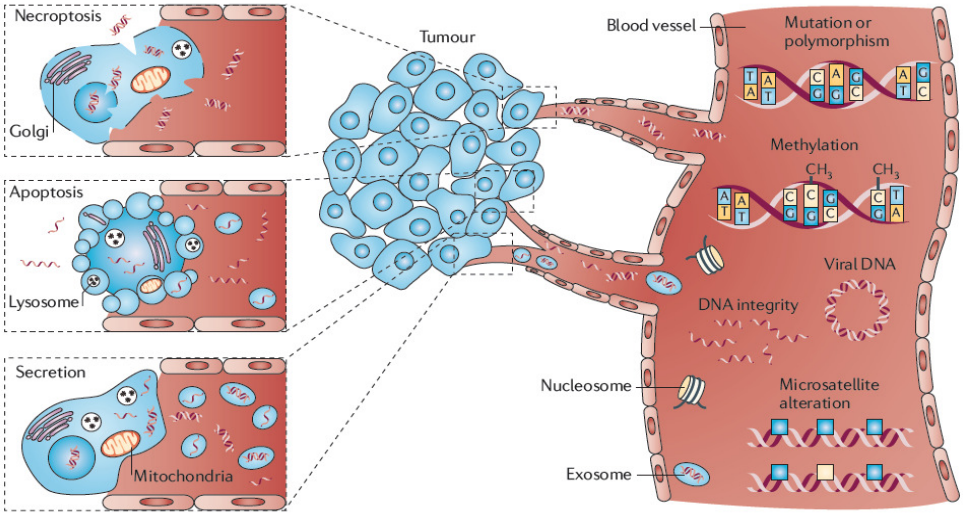
+Osimertinib



+Brigatinib

Liquid biopsies represent a molecular pattern of cancer

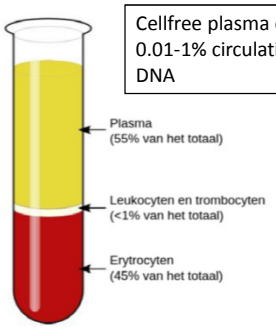
Tumor DNA shed in bloodplasma



Schwarzenbach Nat Rev Cancer 2011

Advantages of liquid biopsies (ctDNA) over tissue biopsies for diagnostic molecular testing

- Insufficient tumor tissue
- Insufficient neoplastic cells in biopsy
- Insufficient or poor quality of DNA
- Obtaining (re-) biopsy not possible (localisation)
- (Re-) biopsy inconvenient or to incriminating
- Rebiopsy not allowed
- Heterogeneity (total "overview" of multiple locations)
- Minor invasive predictive testing

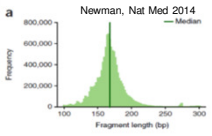


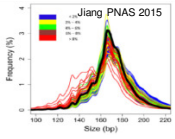
Dutch onco-guideline (2015) and EMA:
predictive testing on liquid biopsy in case no biopsy

Remark: Molecular testing on tissue biopsy is standard of care

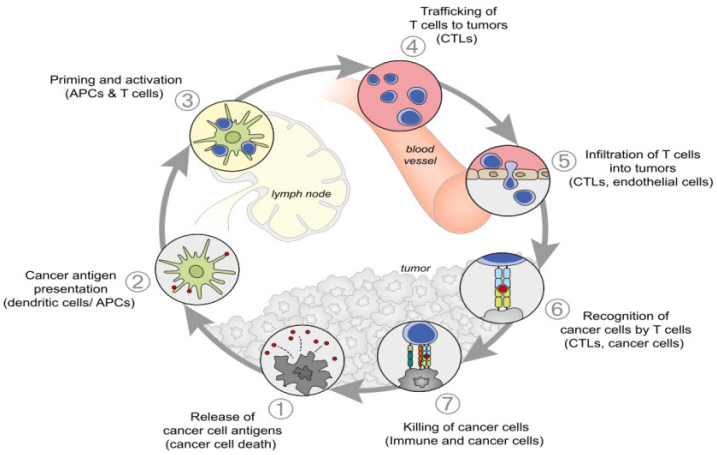
Drawbacks of liquid biopsies over tissue biopsies for diagnostic molecular testing

- Very low levels of circulating tumor DNA
- ctDNA is small fraction of total cell free DNA
- Nucleosome-protected DNA is small and the same for cfDNA/ctDNA
- Variable cfDNA levels (age, exercise, infections, pre-analytical processing)
- DNA extraction methods do not discriminate ctDNA from cfDNA
- High false-negative rates (associated with stage of disease)
- Shedding, degradation and clearance unknown
- Heterogeneity (no info on separate multiple locations)

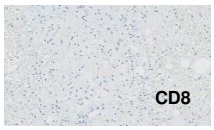




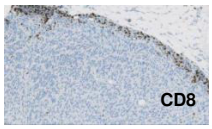
Immunotherapy: The Cancer-Immunity Cycle is Central to Immune Surveillance and Defence



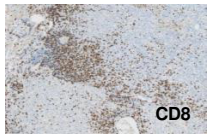
Chen DS, Mellman I. Immunity. 2013



Immunologic ignorance



Excluded infiltrate



T cells present but..

…unable to act

Mechanisms by which Cancers Evade Immune Destruction

Potential biomarkers to predict response to immunotherapy

- **PD-L1/PD-1 IHC of tumors**
- Hypermutation analysis of tumors (neo-antigens, TMB)
- Mutations associated with resistance (e.g. STK11)
- Microsatellite instability
- Copy-number-alterations
- Imaging with PD-L1 tracers
- Serum profiling (e.g. interleukins)
- Immunogram (immune cell profile)
- Immune cell infiltration
- Expression profiling microbiome
- Monitoring circulating tumor DNA (Tumor Volume)

Today no optimal predictive markers for response to immunotherapy

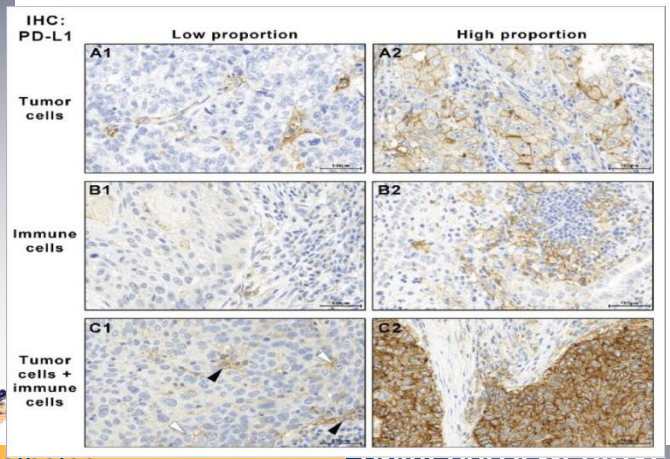
ONCOIMMUNOLOGY
2016, VOL. 5, NO. 5, e1131379 (9 pages)
http://dx.doi.org/10.1080/2162402X.2015.1131379

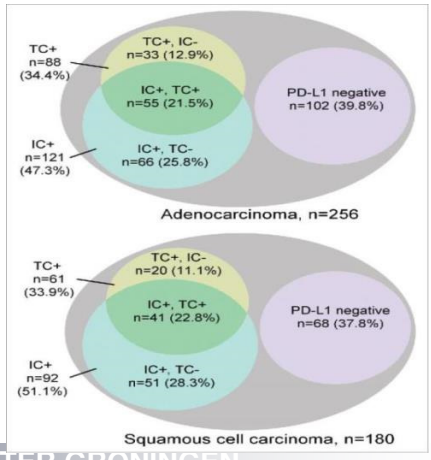
Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

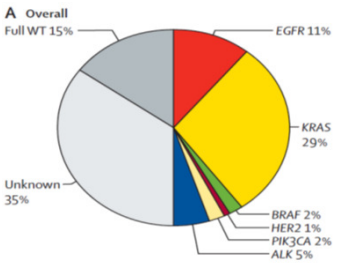
PD-L1 expression in non-small cell lung cancer: Correlations with genetic alterations

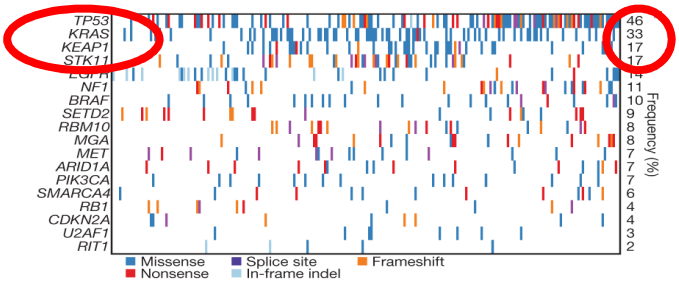
Andreas H. Scheel[a,*], Sascha Ansén[b,c,*], Anne M. Schultheis[a], Matthias Scheffler[b,c], Rieke N. Fischer[b,c], Sebastian Michels[b,c], Martin Hellmich[d], Julie George[e], Thomas Zander[b,c], Michael Brockmann[f], Erich Stoelben[g], Harry Groen[h], Wim Timens[i], Sven Perner[j], Michael von Bergwelt-Baildon[b,c], Reinhard Büttner[a], and Jürgen Wolf[b,c]





Tumor-specific mutants (non-KRAS) as potential biomarkers to detect response to immunotherapy in advanced-stage NSCLC





French SEQ-data of ~20.000 samples:
- In ~80% adca/scc: no targeted therapy

Barlesi Lancet Oncol 2016

TP53, KRAS, KEAP1 and STK11:
- In >90% adca/scc

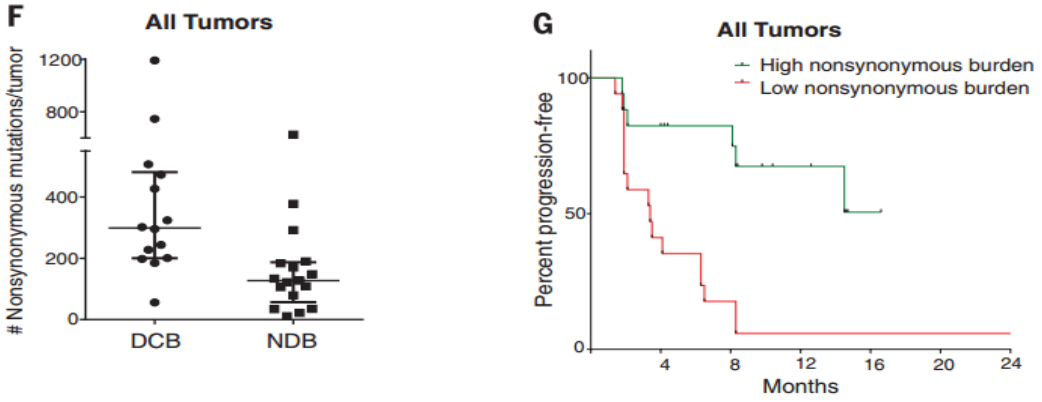
CGARN Nature 2014

Tumor Mutational Burden TMB

CANCER IMMUNOLOGY

Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer

Rizvi et al, Science 2015



Tumor Mutational Burden TMB

- Requires a lot of DNA: most biopsies not enough
- Claim “checkmate 227” in PD-L1- stage IV: TMB >10mut/Mb excellent predictor: **HR 0.77** (95% CI: 0.56 to 1.06 (Hellmann et al NEJM 2018**)**
- Oktober 19 2018: Press release BMS
- TMB < 10 mut/Mb: **HR 0.78** (95% CI: 0.61 to 1.00)
- **Nihilation of TMB predictive value!!**

Bristol-Myers Squibb

Press Release

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Bristol-Myers Squibb Provides Update on the Ongoing Regulatory Review of Opdivo Plus Low-Dose Yervoy in First-Line Lung Cancer Patients with Tumor Mutational Burden ≥10 mut/Mb

New analysis submitted to U.S. Food and Drug Administration (FDA) constitutes a major amendment to the Company's supplemental Biologics License Application (sBLA)

CATEGORY: CORPORATE/FINANCIAL NEWS

FRIDAY, OCTOBER 19, 2018 4:16 PM EDT

Targeted Oncology

The Community Resource in Targeted
Driving Knowledge. Empowering Change. Optimizi

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BMS Withdraws Nivolumab/Ipilimumab Application in TMB-High NSCLC

Gina Columbus
Published Online:9:29 PM, Fri January 25, 2019

T-cell analysis?

LETTERS
https://doi.org/10.1038/s41591-018-0045-3
nature medicine
Corrected: Publisher Correction

Global characterization of T cells in non-small-cell lung cancer by single-cell sequencing

Xinyi Guo[1,6], Yuanyuan Zhang[1,6], Liangtao Zheng[2,6], Chunhong Zheng[1,6], Jintao Song[3,6], Qiming Zhang[1], Boxi Kang[1], Zhouzerui Liu[1], Liang Jin[3], Rui Xing[4], Ranran Gao[1], Lei Zhang[2], Minghui Dong[1], Xueda Hu[1], Xianwen Ren[1], Dennis Kirchhoff[5], Helge Gottfried Roider[5], Tiansheng Yan[3]* and Zemin Zhang[1,2]*

ARTICLES
https://doi.org/10.1038/s41591-018-0136-1
nature medicine

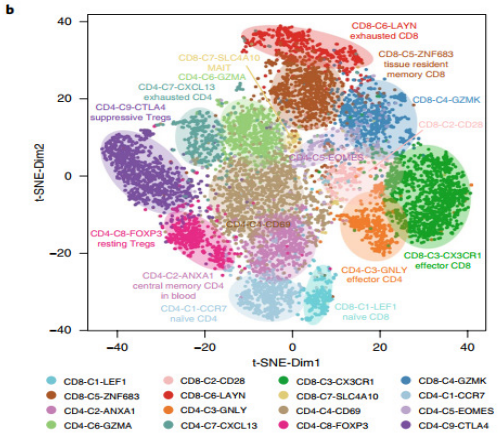
Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response

Peng Jiang[1,2,10], Shengqing Gu[3,10], Deng Pan[4,5,10], Jingxin Fu[6], Avinash Sahu[1,2], Xihao Hu[1,2], Ziyi Li[6], Nicole Traugh[3], Xia Bu[3], Bo Li[1,2,9], Jun Liu[7], Gordon J. Freeman[3], Myles A. Brown[3,8], Kai W. Wucherpfennig[4,5,11]* and X. Shirley Liu[1,2,6,8,11]*

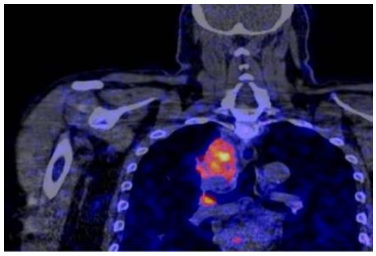
ARTICLES
https://doi.org/10.1038/s41591-018-0057-z
nature medicine

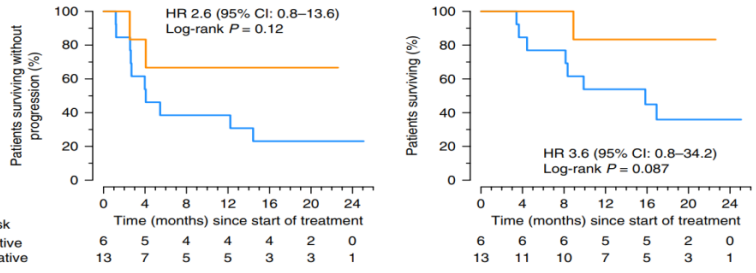
A transcriptionally and functionally distinct PD-1$^+$ CD8$^+$ T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade

Daniela S. Thommen[1,2]*, Viktor H. Koelzer[3,4,13], Petra Herzig[1,13], Andreas Roller[5,13], Marcel Trefny[1], Sarah Dimeloe[6], Anna Kiialainen[5], Jonathan Hanhart[3], Catherine Schill[7], Christoph Hess[6], Spasenija Savic Prince[8], Mark Wiese[9], Didier Lardinois[9], Ping-Chih Ho[10], Christian Klein[11], Vaios Karanikas[11], Kirsten D. Mertz[3], Ton N. Schumacher[2,14] and Alfred Zippelius[1,12,14]*



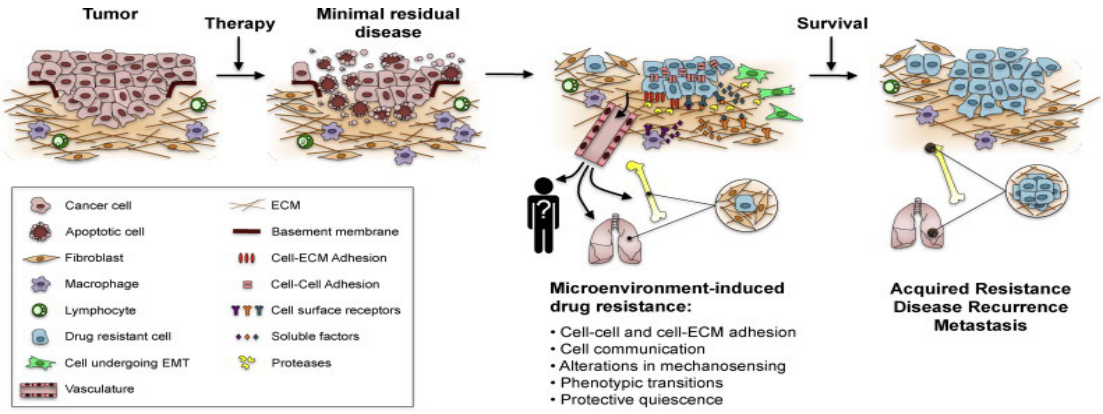
Imaging with labeled drug:



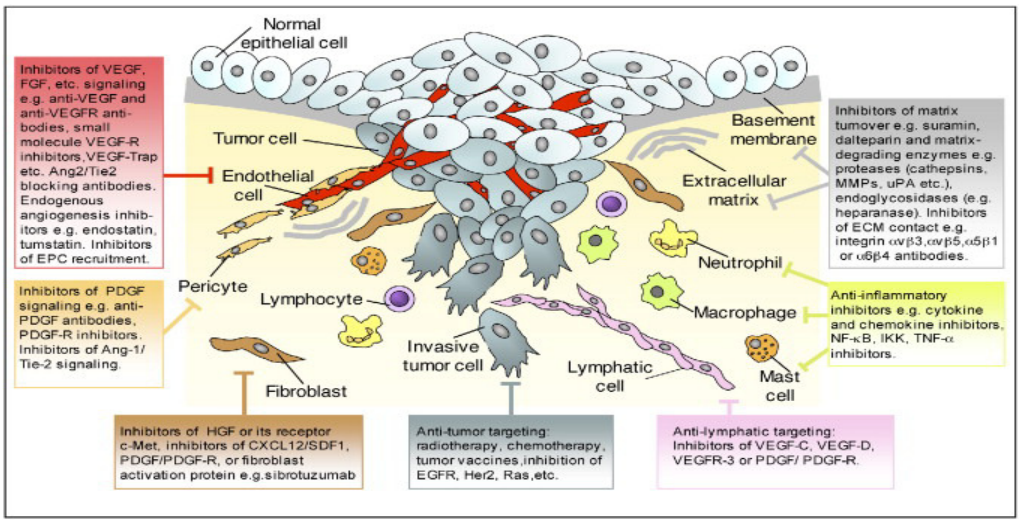


Bensch et al
Nature Med 2018

Tissue micro-environment: role in therapy-resistance

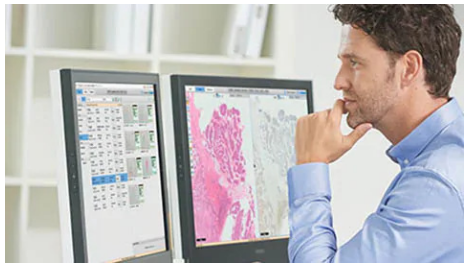


Correia & Bissel, Drug Resistance Updates 2012, 15: 39 - 49



Joyce, Cancer Cell 2005, 7(6): 513 - 520

Digital Pathology and image analysis

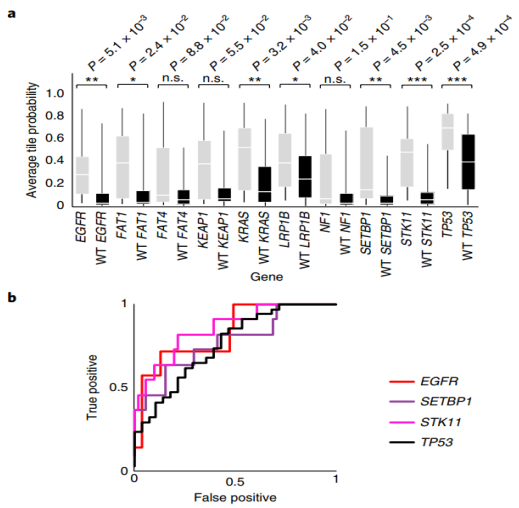


AI / Deep learning:

- Tumor detection
- Tumorcell percentage
- Metastasis detection lymph nodes

Images:www.Philips.nl

Mutation prediction from NSCLC histopath images using deep learning



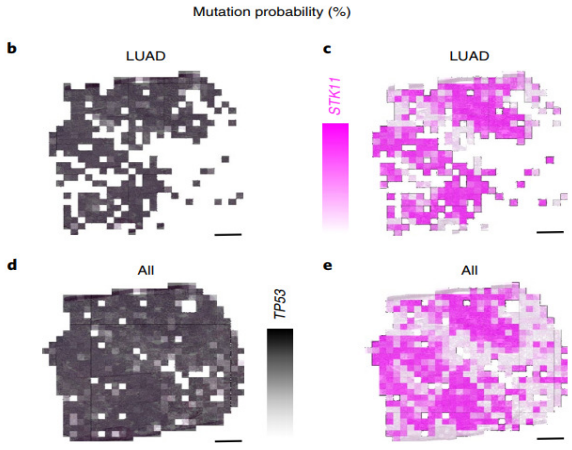
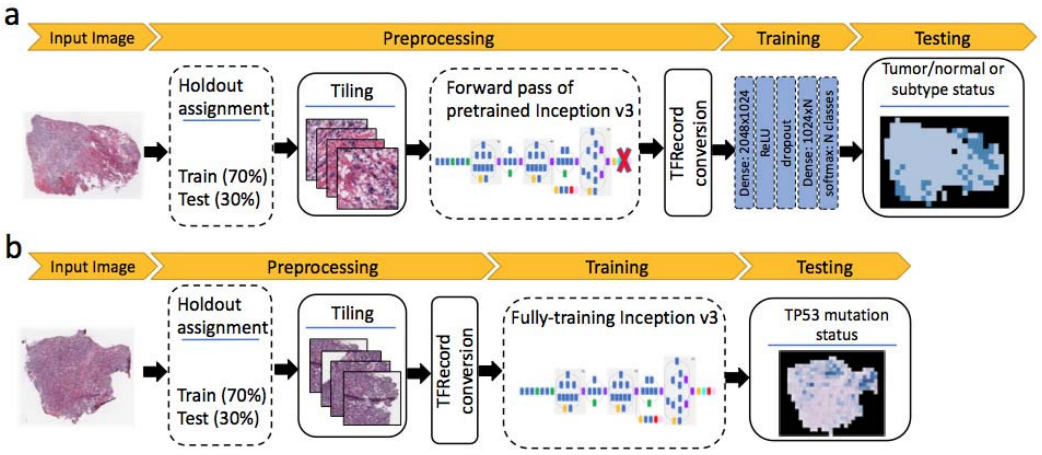


Fig. 4 | Spatial heterogeneity of predicted mutations. a, Probability

Coudray et al. Nature Med 2018

Pan-cancer classifications of tumor histological images using deep learning



Noorbakhsh et al. BioRivX 2019

The role of Molecular Pathology in Precision Medicine: Challenges (and opportunities)

- Predictive testing is essential to <u>select</u> patients that benefit from targeted therapy
- Molecular Pathology is <u>expanding rapidly</u> and is highly dynamic (new druggable mutations, new drugs) : continuous panel adaptation
- <u>Interpretation</u> of rare/uncommon variants is complex: (regional MTB's are essential)
- <u>Tissue</u> is the Issue (low amount of tissues, variable tumor content, FFPD/degraded DNA)
- Costs (<u>no re-imbursement</u> for implementation, testing new assays, testing /drugs for MTB-approved therapies)
- Assays other than NGS (IHC, FISH, nanoString, ctDNA)

Outlook:

- 3D modeling of mutation variants and drugs as a component of MTBs
- A role for AI in pathology imaging for support of molecular pathology, (incl. mutationdetection?)
- Need for advanced steps in further diagnostics in immunotherapy (PD-L1 has not yet lost its role…): T-cells? MHC? ….?
- The value of TMB is unclear
- Imaging with labeled drugs or target cells may give additional diagnostic info / monitoring
- Diagnostics and (adjuvant) treatment aimed at tumor-micro-environment may give new perspectives

Molecular Pathology UMCG-team

MD-technicians:
- Ingrid de Boer-Huitema
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- Erik Nijboer
- Tom Artz
- Paskal van Norel
- Rianne Pelgrim
- Inge Platteel
- Martin Schipper
- Jantine Sietzema
- Klaas Kooistra

KMBP:
- Elise van der Logt
- Arja ter Elst
- Anke van den Berg
- Ed Schuuring (head of lab)
- Leon van Kempen
- Maarten Niemantsverdriet (KMBPio 2016-2020)
- Joost Kluiver (KMBPio 2018-2021)

Pathologists:
- Wim Timens
- Arjan Diepstra

Molecular Tumor Board Groningen
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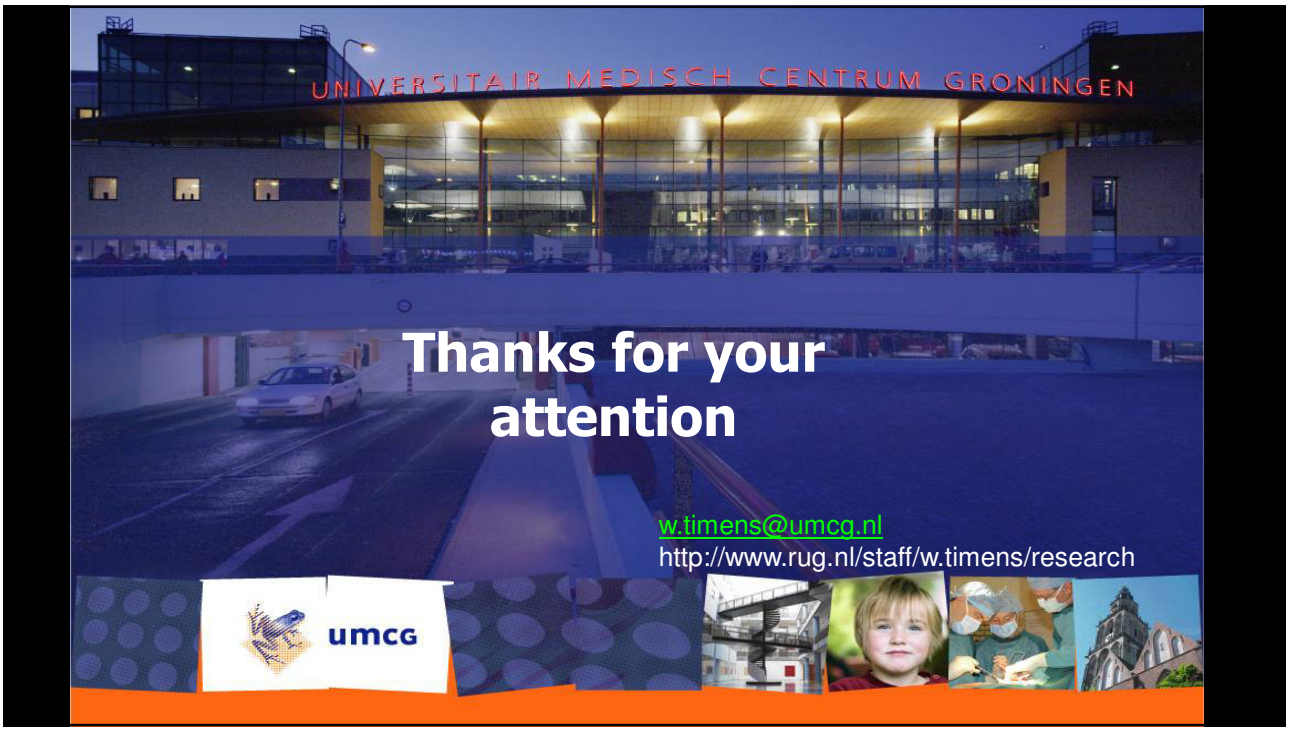
Anke van den Berg, KMBP
Wim Timens, lungpathologist
Harry Groen, pulmonologist
Jeroen Hiltermann, pulmonologist
Anthonie van der Wekken, pulmonologist
Lucy Hijmering-Kappelle, pulmonologist
Birgitta Hiddinga, pulmonologist
Geke Hospers, medical oncologist
Hilde Jalving, medical oncologist
Sjoukje Oosting, medical oncologist
Matthew Groves, drug-design (Pharmacy)
Juliana Vilachá Madeira R Santos, drug-design (Pharmacy)
Maarten Niemantsverdriet, KMBPio
Joost Kluiver, KMBPio

Saskia Offermans, pathologist Isala
Jos Stigt, pulmonologist Isala

ESP-EQA-lung-team: Els Dequeker, Cleo Keppens, Veronique Tack, Kelly Dufraing, Jan von der Thusen, Ed Schuuring

Info: www.moloncopath.nl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