# מה ניתן ללמוד מדוח הפתולוגיה המולקולרית לגבי תורשה

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# Disclosure

- **Grants, personal fees, non-financial support and other from:** MSD, Roche pharma, Roche diagnostics, Amgen, Novartis, Bayer, BMS, Pfizer, Takeda, Abbvie, Compugen, ADC therapeutics and AstraZeneca
- Dr. Vainer reports no direct shares holding of any of the companies mentioned above.
- **Non supports this lecture.**

# The impact of the genomic revolution

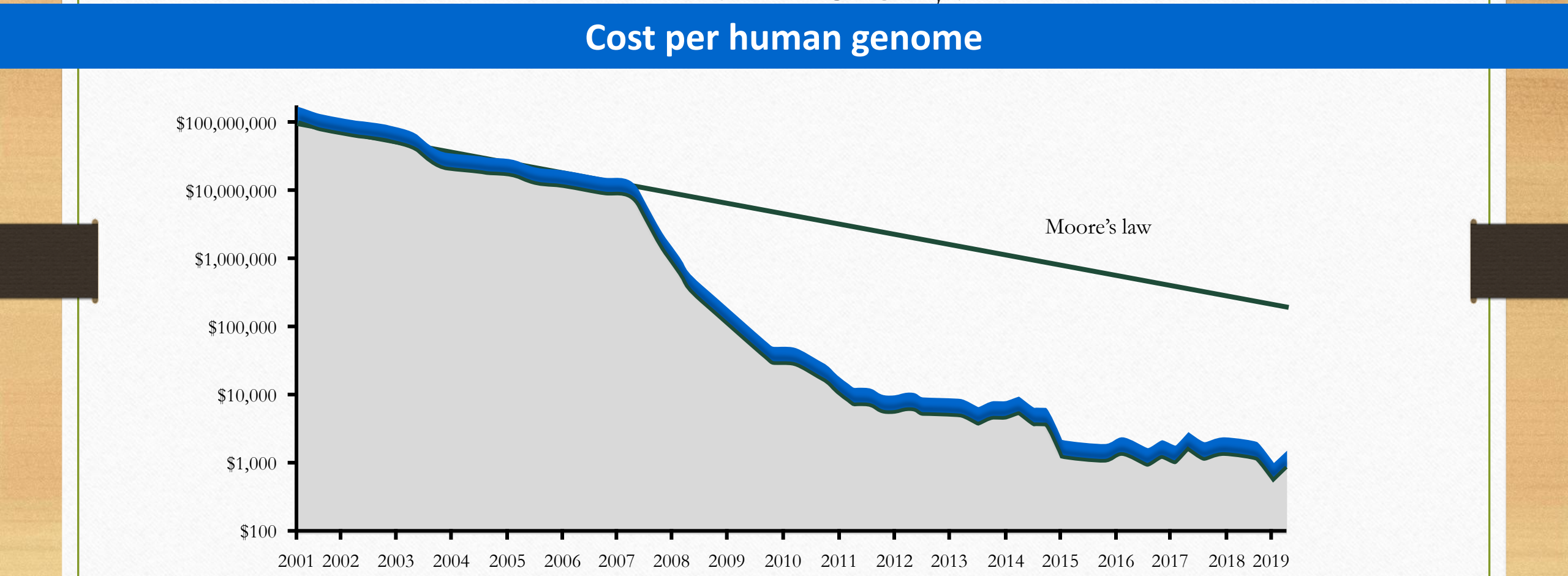
The human genome started when the sequencing cost of single nucleotide was 1 USD[1,2]

It took a decade, numerous labs, and ~3 billion USD[2]

1. Lunshof JE, *et al. Dialogues Clin Neurosci* 2010; **12**: 47–60.

2. https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

# Cost wise – no parallel revolution in human history!




Adapted from: https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

# The impact of this revolution

## In the beginning[1,2]

- The human genome cost was ~3 billion USD
- It took a decade, numerous labs, a huge amount of personnel

## In the last decade[2]

- **The human genome cost is ~500-100 USD**
- It takes **few days to sequence**
- **Few days of bioinformatics**

1. Lunshof JE, *et al. Dialogues Clin Neurosci* 2010;**12**: 47–60.

2. https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

# Because sequencing power is so cheap…

## Current Gene List[2]

Genes with full coding exonic regions included in FoundationOne®CDx for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs).

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ABL1* | *ACVR1B* | *AKT1* | *AKT2* | *AKT3* | *ALK* | *ALOX12B* | *AMER1 (FAM123B)* | *APC* |
| *AR* | *ARAF* | *ARFRP1* | *ARID1A* | *ASXL1* | *ATM* | *ATR* | *ATRX* | *AURKA* |
| *AURKB* | *AXIN1* | *AXL* | *BAP1* | *BARD1* | *BCL2* | *BCL2L1* | *BCL2L2* | *BCL6* |
| *BCOR* | *BCORL1* | *BRAF* | *BRCA1* | *BRCA2* | *BRD4* | *BRIP1* | *BTG1* | *BTG2* |
| *BTK* | *C11ORF30 (EMSY)* | *CALR* | *CARD11* | *CASP8* | *CBFB* | *CBL* | *CCND1* | *CCND2* |
| *CCND3* | *CCNE1* | *CD22* | *CD274 (PD-L1)* | *CD70* | *CD79A* | *CD79B* | *CDC73* | *CDH1* |
| *CDK12* | *CDK4* | *CDK6* | *CDK8* | *CDKN1A* | *CDKN1B* | *CDKN2A* | *CDKN2B* | *CDKN2C* |
| *CEBPA* | *CHEK1* | *CHEK2* | *CIC* | *CREBBP* | *CRKL* | *CSF1R* | *CSF3R* | *CTCF* |
| *CTNNA1* | *CTNNB1* | *CUL3* | *CUL4A* | *CXCR4* | *CYP17A1* | *DAXX* | *DDR1* | *DDR2* |
| *DIS3* | *DNMT3A* | *DOT1L* | *EED* | *EGFR* | *EP300* | *EPHA3* | *EPHB1* | *EPHB4* |
| *ERBB2* | *ERBB3* | *ERBB4* | *ERCC4* | *ERG* | *ERRFI1* | *ESR1* | *EZH2* | *FAM46C* |
| *FANCA* | *FANCC* | *FANCG* | *FANCL* | *FAS* | *FBXW7* | *FGF10* | *FGF12* | *FGF14* |
| *FGF19* | *FGF23* | *FGF3* | *FGF4* | *FGF6* | *FGFR1* | *FGFR2* | *FGFR3* | *FGFR4* |
| *FH* | *FLCN* | *FLT1* | *FLT3* | *FOXL2* | *FUBP1* | *GABRA6* | *GATA3* | *GATA4* |
| *GATA6* | *GID4 (C17ORF39)* | *GNA11* | *GNA13* | *GNAQ* | *GNAS* | *GRM3* | *GSK3B* | *H3F3A* |
| *HDAC1* | *HGF* | *HNF1A* | *HRAS* | *HSD3B1* | *ID3* | *IDH1* | *IDH2* | *IGF1R* |
| *IKBKE* | *IKZF1* | *INPP4B* | *IRF2* | *IRF4* | *IRS2* | *JAK1* | *JAK2* | *JAK3* |
| *JUN* | *KDM5A* | *KDM5C* | *KDM6A* | *KDR* | *KEAP1* | *KEL* | *KIT* | *KLHL6* |

# Because sequencing power is so cheap…

## Current Gene List Continued[2]

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| KMT2A (MLL) | KMT2D (MLL2) | KRAS | LTK | LYN | MAF | MAP2K1 (MEK1) | MAP2K2 (MEK2) | MAP2K4 |
| MAP3K1 | MAP3K13 | MAPK1 | MCL1 | MDM2 | MDM4 | MED12 | MEF2B | MEN1 |
| MERTK | MET | MITF | MKNK1 | MLH1 | MPL | MRE11A | MSH2 | MSH3 |
| MSH6 | MST1R | MTAP | MTOR | MUTYH | MYC | MYCL (MYCL1) | MYCN | MYD88 |
| NBN | NF1 | NF2 | NFE2L2 | NFKBIA | NKX2-1 | NOTCH1 | NOTCH2 | NOTCH3 |
| NPM1 | NRAS | NT5C2 | NTRK1 | NTRK2 | NTRK3 | P2RY8 | PALB2 | PARK2 |
| PARP1 | PARP2 | PARP3 | PAX5 | PBRM1 | PDCD1 (PD-1) | PDCD1LG2 (PD-L2) | PDGFRA | PDGFRB |
| PDK1 | PIK3C2B | PIK3C2G | PIK3CA | PIK3CB | PIK3R1 | PIM1 | PMS2 | POLD1 |
| POLE | PPARG | PPP2R1A | PPP2R2A | PRDM1 | PRKAR1A | PRKCI | PTCH1 | PTEN |
| PTPN11 | PTPRO | QKI | RAC1 | RAD21 | RAD51 | RAD51B | RAD51C | RAD51D |
| RAD52 | RAD54L | RAF1 | RARA | RB1 | RBM10 | REL | RET | RICTOR |
| RNF43 | ROS1 | RPTOR | SDHA | SDHB | SDHC | SDHD | SETD2 | SF3B1 |
| SGK1 | SMAD2 | SMAD4 | SMARCA4 | SMARCB1 | SMO | SNCAIP | SOCS1 | SOX2 |
| SOX9 | SPEN | SPOP | SRC | STAG2 | STAT3 | STK11 | SUFU | SYK |
| TBX3 | TEK | TET2 | TGFBR2 | TIPARP | TNFAIP3 | TNFRSF14 | TP53 | TSC1 |
| TSC2 | TYRO3 | U2AF1 | VEGFA | VHL | WHSC1 (MMSET) | WHSC1L1 | WT1 | XPO1 |
| XRCC2 | ZNF217 | ZNF703 | | | | | | |

# Foundation\Avenio solid -

## 324 cancer-related genes + rearrangments

**Select Rearrangements[2,3]**

Genes with select intronic regions for the detection of gene rearrangements, one gene with a promoter region and one non-coding RNA gene.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ALK* | *BCL2* | *BCR* | *BRAF* | *BRCA1* | *BRCA2* | *CD74* | *EGFR* | *ETV4* |
| *ETV5* | *ETV6* | *EWSR1* | *EZR* | *FGFR1* | *FGFR2* | *FGFR3* | *KIT* | *KMT2A (MLL)* |
| *MSH2* | *MYB* | *MYC* | *NOTCH2* | *NTRK1* | *NTRK2* | *NUTM1* | *PDGFRA* | *RAF1* |
| *RARA* | *RET* | *ROS1* | *RSPO2* | *SDC4* | *SLC34A2* | *TERC** | *TERT* (PROMOTER ONLY)* | *TMPRSS2* |

# Today CGP is provided for:

1. NSCLC lung cancer at any stage.
2. Patients with colon and rectal cancer.
3. Patients with metastatic bladder cancer.
4. Patients with metastatic cancer of unknown primary (CUP).
5. Patients with metastatic thyroid gland cancer.
6. Metastatic stomach and bowel cancer of the sarcoma type (Gastrointestinal Stromal Tumor (GIST)).
7. Metastatic bile duct cancer (cholangiocarcinoma).
8. Metastatic prostate cancer.
9. Metastatic small intestine cancer.
10. Metastatic esophageal cancer (adenocarcinoma) and gastroesophageal junction (GEJ).
11. Metastatic adrenal gland cancer, including adrenocortical carcinoma.
12. Metastatic Triple Negative breast cancer for women with negative PD-L1 expression.
13. Rare metastatic tumors.
14. Soft tissue sarcoma in a metastatic disease or when it's not possible to operate.
15. Molecular profiling test for all solid and hematological tumors in children and adolescents (age 25).
16. Malignant brain tumors.
17. Locally advanced uterine cancer (adenocarcinoma).
18. Uterine cancer with high risk of recurrence.

# Today CGP is provided for:

## We sequence massive amount of oncological patients!

1. NSCLC lung cancer at any stage.
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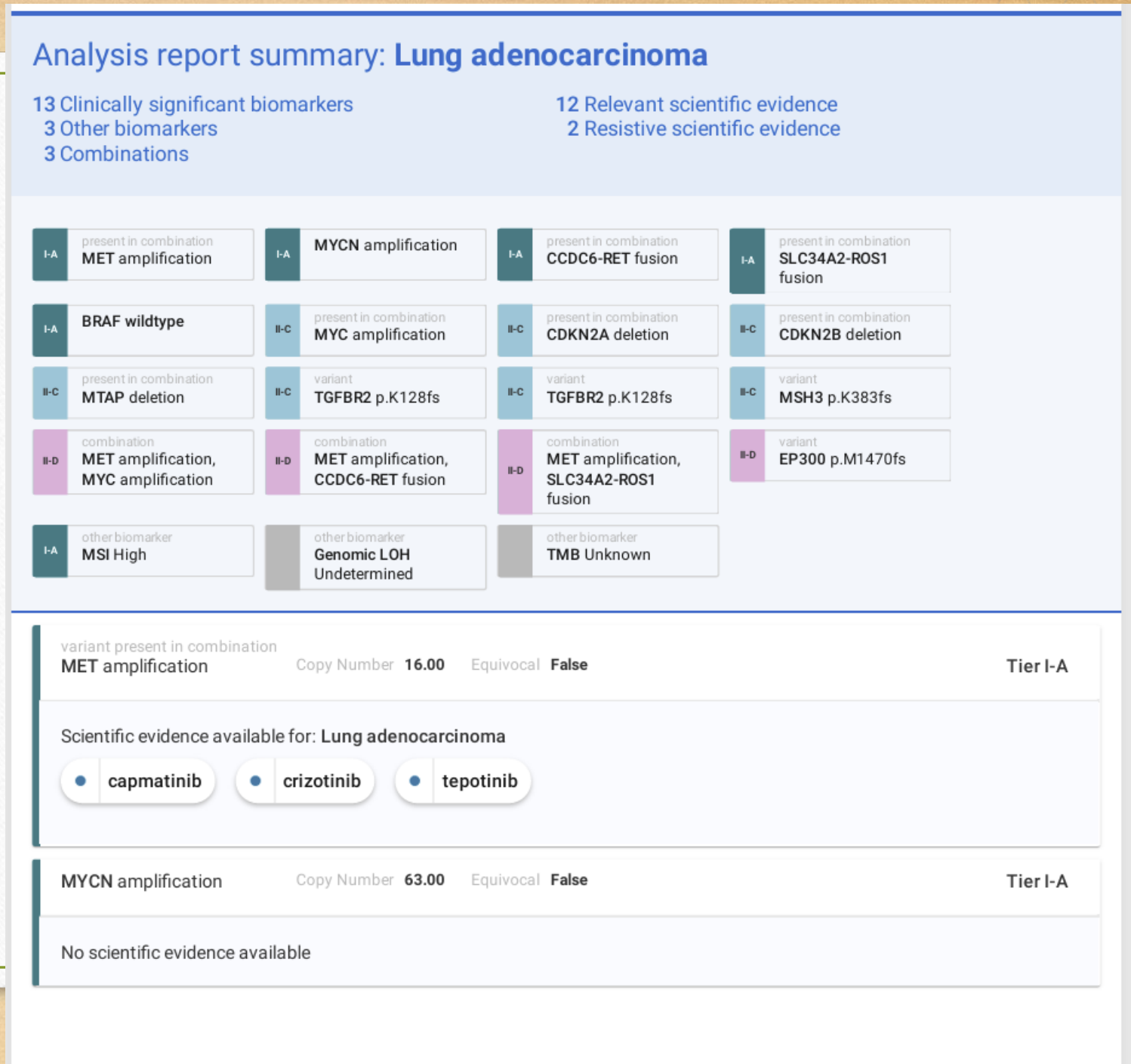
# Our Oncological oriented reporting

# Today…



## Analysis report summary: **Lung adenocarcinoma**

13 Clinically significant biomarkers
3 Other biomarkers
3 Combinations

12 Relevant scientific evidence
2 Resistive scientific evidence

| | | | |
|---|---|---|---|
| I-A present in combination **MET** amplification | I-A **MYCN** amplification | I-A present in combination **CCDC6-RET** fusion | I-A present in combination **SLC34A2-ROS1** fusion |
| I-A **BRAF** wildtype | II-C present in combination **MYC** amplification | II-C present in combination **CDKN2A** deletion | II-C present in combination **CDKN2B** deletion |
| II-C present in combination **MTAP** deletion | II-C variant **TGFBR2** p.K128fs | II-C variant **TGFBR2** p.K128fs | II-C variant **MSH3** p.K383fs |
| II-D combination **MET** amplification, **MYC** amplification | II-D combination **MET** amplification, **CCDC6-RET** fusion | II-D combination **MET** amplification, **SLC34A2-ROS1** fusion | II-D variant **EP300** p.M1470fs |
| I-A other biomarker **MSI** High | other biomarker **Genomic LOH** Undetermined | other biomarker **TMB** Unknown | |

variant present in combination
**MET** amplification — Copy Number **16.00** — Equivocal **False** — **Tier I-A**

Scientific evidence available for: **Lung adenocarcinoma**

- **capmatinib**
- **crizotinib**
- **tepotinib**

**MYCN** amplification — Copy Number **63.00** — Equivocal **False** — **Tier I-A**

No scientific evidence available

# Today…

DRAFT

variant present in combination
**CCDC6-RET** fusion — # Reads **56** AF **212%** Inframeness **Unknown** — **Tier I-A**

Scientific evidence available for: **Lung adenocarcinoma**

- cabozantinib
- pralsetinib
- selpercatinib

variant present in combination
**SLC34A2-ROS1** fusion — # Reads **56** AF **412%** Inframeness **True** — **Tier I-A**

Scientific evidence available for: **Lung adenocarcinoma**

- ceritinib
- crizotinib
- entrectinib
- lorlatinib
- repotrectinib

**BRAF wildtype** — **Tier I-A**

Scientific evidence available for: **Lung adenocarcinoma**

- dabrafenib (resistance)
- encorafenib (resistance)

variant present in combination
**MYC** amplification — Copy Number **53.00** Equivocal **False** — **Tier II-C**

No scientific evidence available

variant present in combination
**CDKN2A** deletion — Copy Number **0.00** Equivocal **False** — **Tier II-C**

No scientific evidence available

variant present in combination
**CDKN2B** deletion — Copy Number **0.00** Equivocal **False** — **Tier II-C**

No scientific evidence available

# Today…

## Addendum

DRAFT

### MET amplification

Tier I-A

**Scientific evidence**

| Scientific evidence | Approvals & recommendations from |
|---|---|
| **capmatinib** | NCCN for this cancer |
| **crizotinib** | NCCN for this cancer |
| **tepotinib** | NCCN for this cancer |
| Note: Refer to the full guidelines of NCCN recommendations and NCCN Categories of Evidence and Consensus. | |

**Gene summary**
Oncogenic alterations in MET, such as rearrangements, mutations, or amplification, have been found in multiple cancers, including lung, kidney and head and neck cancers (PMID: 17311534). These mutations cause ligand-independent activation of MET (PMID: 24959087). Some germline MET mutations are associated with hereditary papillary renal carcinoma (PMID: 28603720). Multiple targeted therapies with activity against MET are under investigation or are approved or recommended for MET-altered cancers (PMID: 35266116).

**Variant group summary**
There are recommended therapies for certain patients with non-small cell lung cancer (NSCLC) harboring high-level MET amplification (outlined in evidence table). Sensitivity to these drugs is supported by phase II trials (PMID: 31584608)(PMID: 32877583)(J Clin Oncol 39: 2021 (abstr 9021)).

In a phase II study, 26 of 84 patients with NSCLC harboring high-level MET amplification (at least 10 copies) responded to capmatinib, which was fewer than the prespecified threshold for clinical relevance (PMID: 32877583). In a phase I trial, capmatinib treatment resulted in partial response in 47% (7/15) of non-small cell lung carcinoma patients with six or more copies of the MET gene (PMID: 32240796). Treatment of MET-amplified NSCLC patients with investigational MET inhibitors resulted in no objective response (0/3) and stable disease in 33% (1/3) of patients in a phase II trial (PMID: 30366938), partial response in four of 22 patients in a phase I trial (PMID: 29145039), and overall response rate of 30.6% (11/36) in patients with amplifications and/or MET exon 14 skipping mutations (AACR annual meeting 2020, abstr. CT127). In a phase II trial, MET-targeting antibody-drug conjugate telisotuzumab vedotin treatment demonstrated safety in patients with non-squamous NSCLC harboring high MET expression and wild-type EGFR, and led to an objective response rate of 36.5% (19/52) (J Clin Oncol 40, 2022 (suppl 16; abstr 9016)). In additional studies in MET-positive NSCLC, this drug resulted in objective responses of 23% (9/40) (PMID: 34426443) and 9% (2/15) (PMID: 33221175). In a phase II trial, this drug in combination with erlotinib resulted in an objective response rate of 34.5% of EGFR-mutant (n=29) and 28.6% of EGFR non-mutant (n=7) MET overexpressed/amplified NSCLC patients (J Clin Oncol 37, 2019 (suppl; abstr 3011).

In a phase II clinical trial, onartuzumab in combination with erlotinib demonstrated efficacy in patients with MET-positive NSCLC (PMID: 24101053). However, a subsequent phase III clinical trial was unable to confirm this efficacy (PMID: 25806331). A phase I trial with the bivalent MET antibody emibetuzumab in combination with erlotinib showed preliminary efficacy (PMID: 27803065). In a phase I/II study, three of four evaluable patients with MET-positive NSCLC responded to the combination of capmatinib and erlotinib, including a patient harboring a MET amplification who had a complete response (JCO Precision Oncology no. 5 (2021) 177-190). In a phase Ib trial (NCT02099058), combined treatment with telisotuzumab vedotin and erlotinib resulted in a DCR of 100% (6/6) in patients with NSCLC harboring MET amplification (PMID: 36288547).

In a clinical case study, two patients with NSCLC harboring EGFR T790M progressed after osimertinib treatment, and were found to have lost EGFR T790M and acquired a MET amplification (PMID: 30268451).

**Gene biological summary**
MET is a receptor tyrosine kinase, which activates MAPK, PI3K/AKT, SRC, and STAT, signaling pathways in response to the HGF ligand, promoting numerous cellular functions, like survival and proliferation (PMID: 22128289). The most important domains in MET are the kinase domain (residues 1078-1345), the semaphorin domain (residues 27-515), the IPT repeats (residues 563-863), and the juxtamembrane domain (residues 956-1093) (PMID: 21904579) (UniProt).

**Variant group functional summary**
MET amplification indicates an increased number of copies of the MET gene. MET gene amplification has been reported to result in constitutive MET kinase activation and to be oncogenic (PMID: 25055117).

### MYCN amplification

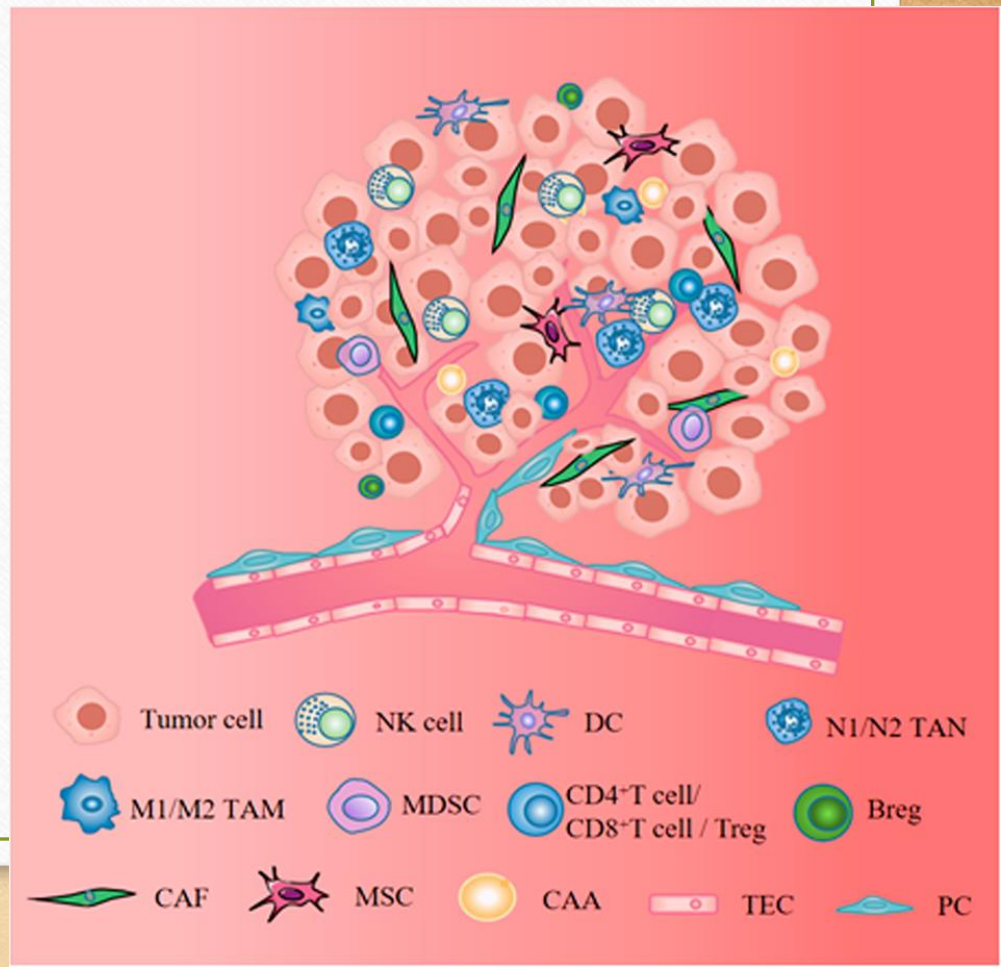
Tier I-A

**Gene summary**
Alterations in MYCN are found in cancers, including pediatric tumors, prostate cancer, lung cancer, skin cancer, and leukemia. Somatic alterations in MYCN are also associated with Wilms tumor (PMID: 28825729). Amplifications in MYCN promote cell proliferation and survival and drive tumor initiation and progression. Missense mutations in the FBXW7 binding region result in impaired binding to FBXW7 and increased MYCN protein stability

# But we sequence a tumor mass

**A chimera of:**

- Malignant cells
- Non-malignant stroma
- (And lymphocytes)



# CGP: A Dual-Purpose Tool

- Comprehensive Genomic Profiling (CGP) = 300+ genes.
- Designed for therapy selection, but acts as a 'de facto' screen for hereditary syndromes.

~10-15% of patients harbor a pathogenic germline variant.

# Defining the Intersection

- Somatic: Acquired mutations, tumor-specific, **therapeutic** targets.
- Germline: Constitutional, every cell - hereditary risk.

- The Overlap: Many genes are relevant to both.
  - BRCA1/2 – PARP inhibitors
  - MMR genes - IO

# Variant Allele Fraction (VAF)

- VAF represents the % of sequencing reads carrying the mutation.
- Germline suspicion: VAF near 50% (heterozygous) or 100% (homozygous/LOH).
- Low VAF (<20%) usually suggests a somatic origin.

# Our rule of thumb: 40% VAF

- VAF represents the % of sequencing reads carrying the mutation.
- Germline suspicion: VAF near 50% (heterozygous) or 100% (homozygous/LOH).
- Low VAF (<20%) usually suggests a somatic origin.

# We have two tier system

- Highest: Molecular oncogenetics MOH, 13/2020 – 52 mutations of table 5

# We have two lists\tiers

| | | | | |
|---|---|---|---|---|
| Jewish | p.Gln324ValfsX8 | c.970_971delCA | MSH2 | 31 |
| Jewish | IVS7-1G->A | c.1277-1 G>C | MSH2 | 32 |
| Jewish | p.Arg389X | c.1165C>T | MSH2 | 33 |
| Jewish | p.Ala1320Glufs | c.3959_3962delCAAG | MSH6 | 34 |
| Jewish | p.Leu330ValfsX12 | c.3984_3987dupGTCA | MSH6 | 35 |
| Jewish | p.Gly396Asp | c.1187G>A | MUTYH | 36 |
| Jewish | p.Tyr179Cys | c.536A>G | MUTYH | 37 |
| Jewish | p.Glu480del | c.1437_1439delGGA | MUTYH | 38 |
| Jewish | p.Asn657LysfsX6 | c.1970dupA | PMS2 | 39 |
| Jewish | p.Leu731Ter | c.2192T>G | PMS2 | 40 |
| מיעוטים | | | | |
| Arab | G<IVS17+3A | c.5074+3A>G | BRCA1 | 41 |
| Arab | p.Trp1815* | A<c.5444G | BRCA1 | 42 |
| Arab | p.Val409* | c.1224delA | BRCA1 | 43 |
| Arab | p.Asn257fs | c.771_775delTCAAA | BRCA2 | 44 |
| Arab | p.Gln1429Serfs*9 | c.4284dupT | BRCA2 | 45 |
| Arab | p.Glu2229* | c.6685G>T | BRCA2 | 46 |
| Arab | Stop770 ( exon 11) | c.2482delGACT | BRCA2 | 47 |
| Druze, Christian Arabs | p.Gly167Arg | c.499G>A | CHEK2 | 48 |
| Druze | p.Asp236Thrfs | c.705delA | MSH2 | 49 |
| Beduine | p.Arg870Serfs* | c.3603_3606delAGTC | MSH6 | 50 |
| Arab | p.Ser229fs | c.686_687delCT | PMS2 | 51 |
| Jerusalem Arab | p.Arg181Cys | c.541C>T | TP53 | 52 |

5. רשימת המוטציות הכלולות ב"פאנל המוטציות" ראה בטבלה שלהלן:

טבלת פאנל מוטציות

| Ethnicity | Mutation (Protein) | Mutation (DNA) | Gene | |
|---|---|---|---|---|
| יהודים ( + (Caucasian | | | | |
| Jewish | p.Ile1307Lys | c.3920T>A | APC | 1 |
| Jewish | | Exon 3-12 deletion | BMPR1A | |
| Jewish | p.Tyr978Ter | c.2934T>G | BRCA1 | 2 |
| Jewish | p.Cys61Gly | c.181T>G | BRCA1 | 3 |
| Jewish | p.Glu75Valfs | c.224_227delAAAG | BRCA1 | 4 |
| Jewish | p.Ala1708Glu | c.5123C>A | BRCA1 | 5 |
| Jewish | p.Gln1756Profs | c.5382insC/c.5266dupC | BRCA1 | 6 |
| Jewish | p.Glu23Valfs | c.68_69delAG (185delG) | BRCA1 | 7 |
| Jewish | p.Cys328Terfs | c.981_982delAT | BRCA1 | 8 |
| Jewish | p.Asn1355_Gln1356?fs | c.4065_4068delTCAA | BRCA1 | 9 |
| Non-Jewish | p.Glu1346fs | c.4153delA | BRCA1 | 10 |
| Jewish | p.Pro733fs | c.2311_2317delTTGGTAC | BRCA1 | 11 |
| Jewish/ Non Jeiwsh - Caucasian | p.Pro1812Ala | c.5434 C>G | BRCA1 | 12 |
| Jewish | p.Arg1203* | c.3607C>T | BRCA1 | 13 |
| Jewish | p.Val2527* | c.7579delG | BRCA2 | 14 |
| Jewish | p.Ser1982Argfs | c.5946delT/c.6174delT | BRCA2 | 15 |
| Jewish | IVS2 +1G>A | c.67+1G>A | BRCA2 | 16 |
| Jewish | p.Arg2336His | c.7007G>C | BRCA2 | 17 |
| Jewish | p.Glu2846Glyfs | c.8537_8538delAG/c.8765delAG | BRCA2 | 18 |
| Jewish | p.Thr1251Asnfs | c.3751insA | BRCA2 | 19 |
| Jewish/ Non Jeiwsh - Caucasian | p.Val1283Lysfs | c.3847_3848del / 4075delGT | BRCA2 | 20 |
| Jewish | p.Glu1646Glnfs | c.4936_4939delGAAA | BRCA2 | 21 |
| Jewish | p.Val1610Glyfs | c.4829_4830delTG/ 5057delTG | BRCA2 | 22 |
| Jewish | p.Ala938fs | c.2808_2811delACAA/3036delACAA | BRCA2 | 23 |
| Jewish | p.Ile605?fs | c.1813_1814insA | BRCA2 | 24 |
| Non-Jewish + Jewish | p.Thr367Metfs | c.1100delC | CHEK2 | 25 |
| Jewish | p.Ser428Phe | c.1283C>T | CHEK2 | 26 |
| Jewish | p.Gly167Arg | c.499G>A | CHEK2 | 27 |
| Jewish | p.Lys471AspfsX19 | c.1411_1414delAAGA | MLH1 | 28 |
| Jewish | p.Asp591Ter | c.1771-1772delGA | MLH1 | 29 |
| Jewish | p.Ala636Pro | c.1906G>C | MSH2 | 30 |

# We modified the list to fit our genomic data

- Our bioinformatitian, Michal Inbar, generated a script to scan each and every case.
- Automatically…

# We have two tiers

- Highest: Molecular oncogenetics MOH, 13/2020 – 52 mutations of table 5
- General referral lists:
  - ACMG
  - Our genetics dep.
  - ESMO high & low
  - NCCN

# Genomic ‘signatures' as Clues

- MSI-High: Strong indicator for Lynch Syndrome follow-up.
- HRD (Homologous Recombination Deficiency): Suggests BRCA-ness.
- TMB (Tumor Mutational Burden):
  - Extreme TMB suggests Polymerase (POLE/POLD1) germline defects.
  - High TMB suggests MMRD defects.

# A case

- 41y.o. woman
- Never smoker
- Came with lung mass and suspected brain metastasis

רופא שולח : פרופ' רוטנברג יקיר

גורם שולח : שרותי בריאות כללית דרום

תאריך לקיחה : לא צויין

תאריך תשובה : 29/12/2025

**הדגימות שהתקבלו**

ריאה ל- פרופיל מולקולרי מקיף

**נתונים קליניים**

בקשה ל- פרופיל מולקולרי מקיף

**ממצא מיקרוסקופי**

## AVENIO Tumor Tissue CGP Test Results

Diagnosis used for analysis: Lung adenocarcinoma (DOID:3910).
Based on: ADENOCARCINOMA (81403), LUNG, NOS (C34.9)

Quality Assurance: Pass

### Biomarker Findings

Microsatellite Instability (MSI): MS-STABLE

Tumor Mutational Burden (TMB): 3.62 Muts/Mb

## Genomic Findings

EGFR NM_005228 c.2236_2250del p.E746_A750del nonframeshift allele-freq: 55%

CHEK2 NM_007194 c.1283C>T p.S428F missense allele-freq: 50% *

ATM NM_000051 c.5919-1del splice allele-freq: 24%

TP53 NM_000546 c.742C>T p.R248W missense allele-freq: 82% **

PRKCI Amplification Copy Number: 8 (Equivocal)

TERC Amplification Copy Number: 8 (Equivocal)

AKT2 Amplification Copy Number: 7 (Equivocal)

Note: The clinical significance of variants with allele frequencies below 5% is uncertain. Contextual interpretation is recommended.

* Founder Variants in Israeli population (Ministry of Health)

| | | | |
|---|---|---|---|
| CHEK2 | p.S428F | c.1283C>T | 50% |

Potential germline implications; consider oncogenetic counseling.

** Putative Germline Variants in Genes Associated with Cancer Predisposition

| | | | |
|---|---|---|---|
| TP53 | c.742C>T | p.R248W | 82% |

Potential germline implications; consider oncogenetic counseling.

## Variants of Unknown Significance

| | | | | |
|---|---|---|---|---|
| SETD2 | NM_014159 | c.2798G>T | p.G933V | 86% |
| SOX2 | NM_003106 | c.859G>A | p.A287T | 58% |
| FGFR3 | NM_000142 | c.1573G>C | p.E525Q | 40% |
| AR | NM_000044 | c.571A>G | p.M191V | 30% |
| NPM1 | NM_002520 | c.709A>T | p.T237S | 18% |
| PBRM1 | NM_018313 | c.2807G>A | p.G936D | 10% |

## Assay Description

This test was performed using the AVENIO Tumor Tissue CGP Kit version 2.0.0, analysed on the FoundationOne Analysis Platform version 1.2. The AVENIO Tumor Tissue CGP Kit is for Research Use Only (RUO). For detailed information about the assay and the list of assayed genes, please visit the AVENIO Tumor Tissue CGP site.

Terms Used in the Report:
* Broad: Large genomic alterations affecting over 20 MB or 50% of a chromosomal arm.
* Subclonal: Alteration detected in less than 10% of the assayed tumor DNA.
* Equivocal: Borderline evidence suggesting, but not confirming, copy number amplification.

**אבחנה פתולוגית**

See Pathology Microscopic.

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# Path CGP is not a genetic test

- Our results are complex and only suggestive due to many pitfalls

# Pitfall: Clonal Hematopoiesis (CHIP)

- Age-related mutations in WBCs (DNMT3A, TET2, ASXL1).
- These show up in tumor tissue (infiltrating blood).
- They look like germline/tumor mutations.

- In a recent case we identified a JAK2 mutation in a lung cancer.
- In  patient with myelofibrosis – with the same JAK2 mutation.

# Pitfall: Loss of Heterozygosity (LOH)

- Somatic loss of the wild-type allele can push a somatic mutation to 80-90% VAF.
- This 'mimics' a homozygous germline variant.
- Requires careful correlation with Copy Number data.

# The Molecular Tumor Board – 13 year at HMC

- Bridging the gap: Pathologist + Oncologist + Genetic Counselor.
- Reviewing 'Tumor-Only' reports for potential germline signals.
- Establishing local reflex testing protocols.

# Take-Home Messages

1. We spend much time on this germline topic (especially the VUS)
2. Every somatic report is a potential genetic screen.
3. VAF of 40% is our rule of thumb.
4. Screening for germline variants in oncology patients –

- Free, fast, robust.
- But cannot replace germline testing.

# Thank you

Any questions?