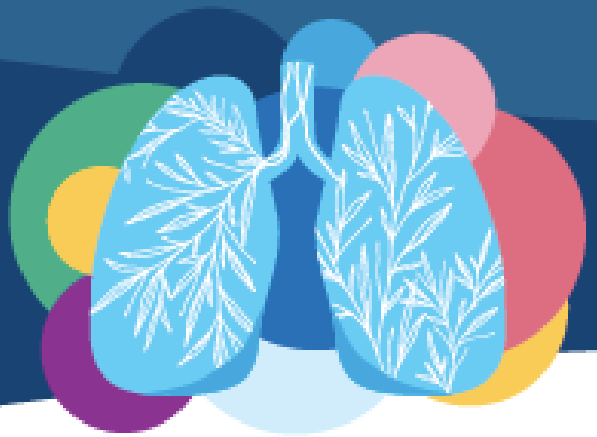


VI SIMPOSIUM
ICAPEM
16 de noviembre 2021

ASPECTOS GENÉTICOS Y PREDISPOSICIÓN

CLÍNIC BARCELONA
Hospital Universitari

Laura Mezquita
Thoracic Oncology Group; Medical Oncology Department, Hospital Clinic of Barcelona, Spain. Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS

IDIBAPS
Institut D'Investigacions Biomèdiques August Pi i Sunyer

DISCLOSURES

- **Lectures and educational activities:**
  - Bristol-Myers Squibb, AstraZeneca, Roche
- **Consulting, advisory role:**
  - Roche Diagnostics, Roche, Takeda
- **Research Grants:**
  - Bristol-Myers Squibb, Boeringher Ingelheim, Amgen, Stilla, INIVATA
- **Travel, Accommodations, Expenses:**
  - Bristol-Myers Squibb, Roche, Takeda, AstraZeneca
- **Others:**
  - International Mentorship Program funded by AstraZeneca

OUTLINE

1. **Overview of sex-related factors & lung cancer**
2. **Tumor's perspective:** sex-related impact
3. **Patient's perspective:** sex-related impact
4. **Patient – Tumor Perspective & future**
5. **Take home messages**

PATIENT - TUMOR:

Lung cancer is a complex disease

INTRINSIC FACTORS

EXPOSURE TO CARCINOGENS

- **Nicotine & cyto P450**
- **DNA adducts**
- **DNA repair systems**
- **Hormonal differences**
- **Genetic differences**

- **Smoking**
- **Radon**
- **Other factors**
- **Life-style**
- **Occupations**

Barrera-Rodríguez & Morales-Fuentes, Lung cancer 2012

My presentation today

Genomics

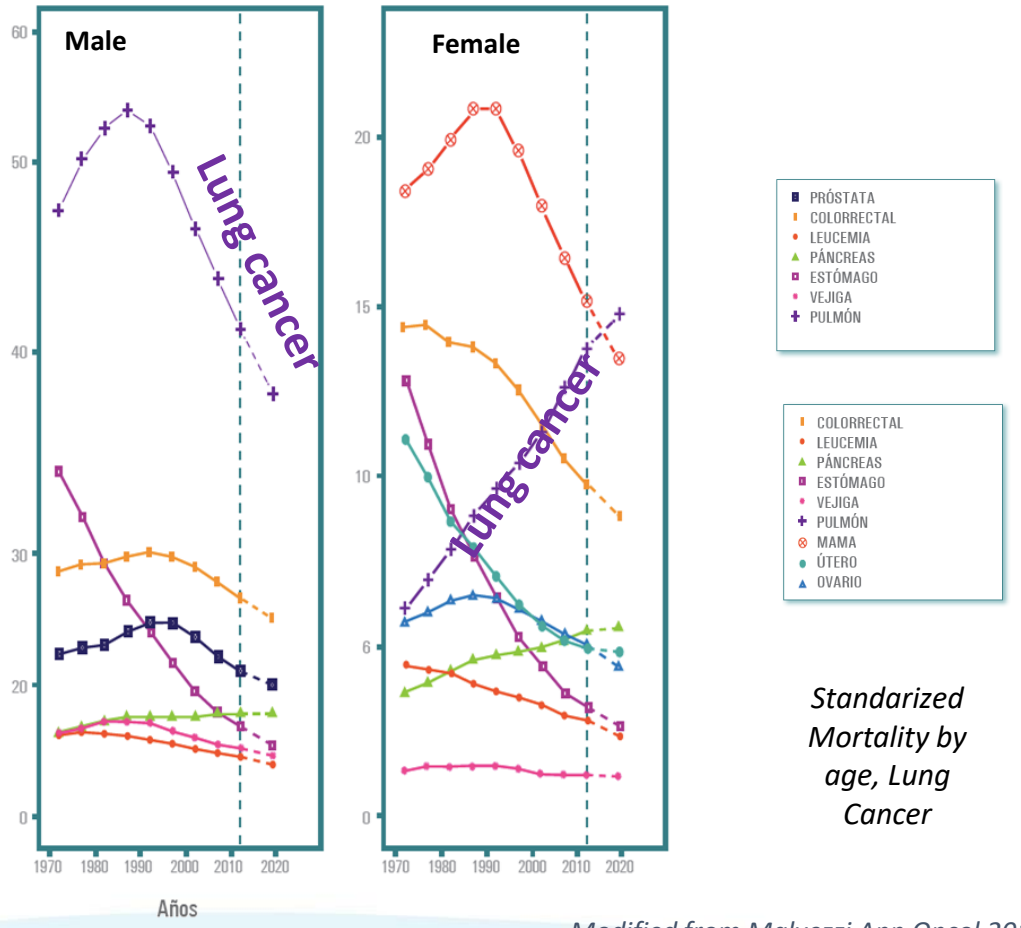
TUMOR

Genetics

PATIENT

Lung Cancer: 1st cause of cancer death

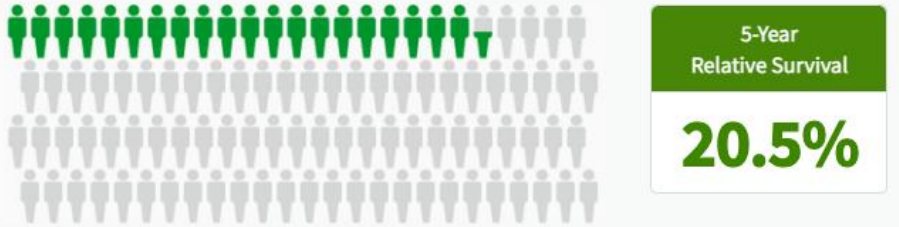
Cancer Mortality in Europe



Standarized Mortality by age, Lung Cancer

Modified from Malvezzi Ann Oncol 2015

5 years Survival rate



Based on data from SEER 18 2010–2016. Gray figures represent those who have died from lung and bronchus cancer. Green figures represent those who have survived 5 years or more.

It depends on the STAGE of the disease

Early stage

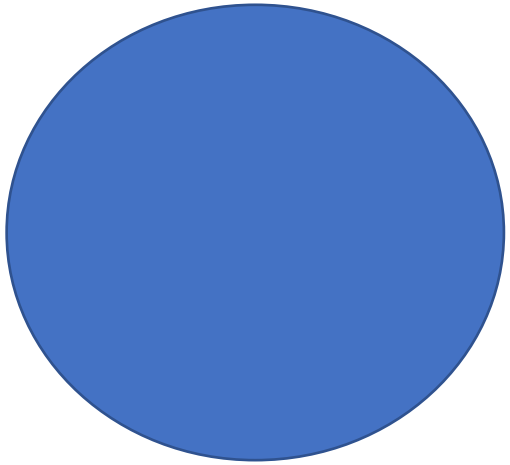
Locally advanced

Advanced stage

https://seer.cancer.gov/statfacts/html/lungb.html

TUMOR: Lung Cancer is not one disease

30 years ago



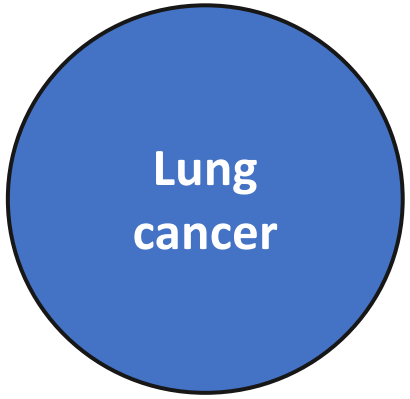
Oncologist

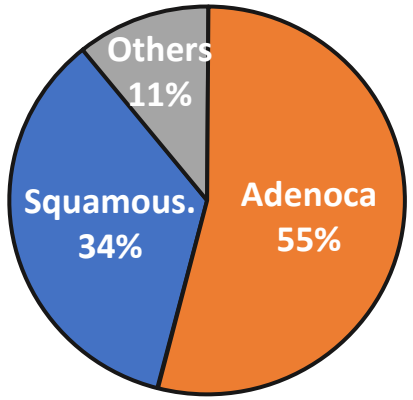
MOLECULAR PROFILE

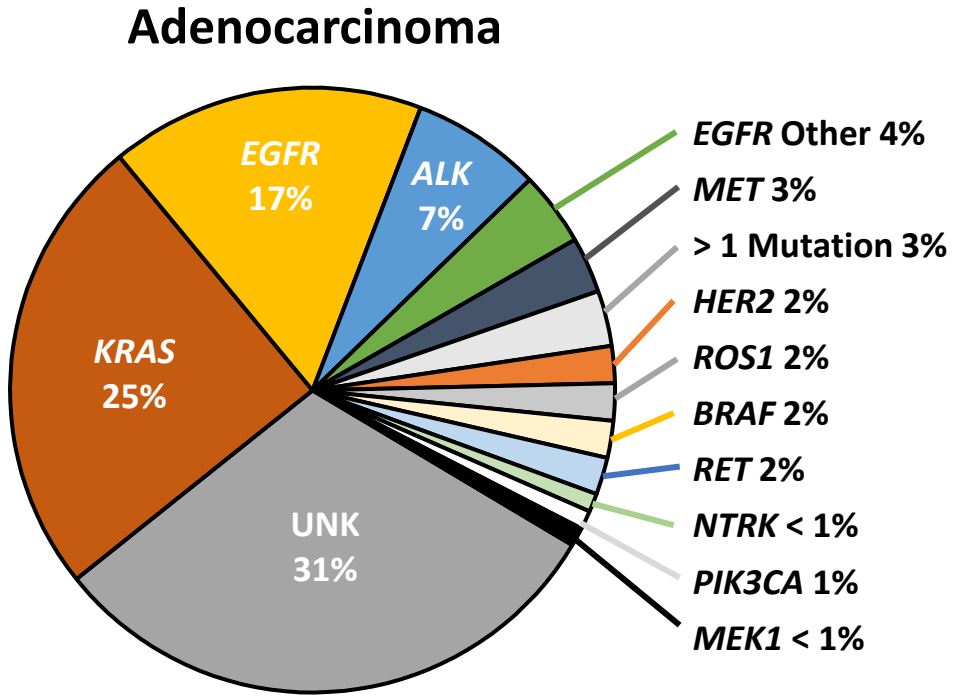
Different subpopulations

- **Clinical profile**
- **Cancer evolution**

TUMOR: Molecular subgroups







Before → HISTOLOGICAL classification → MOLECULAR classification

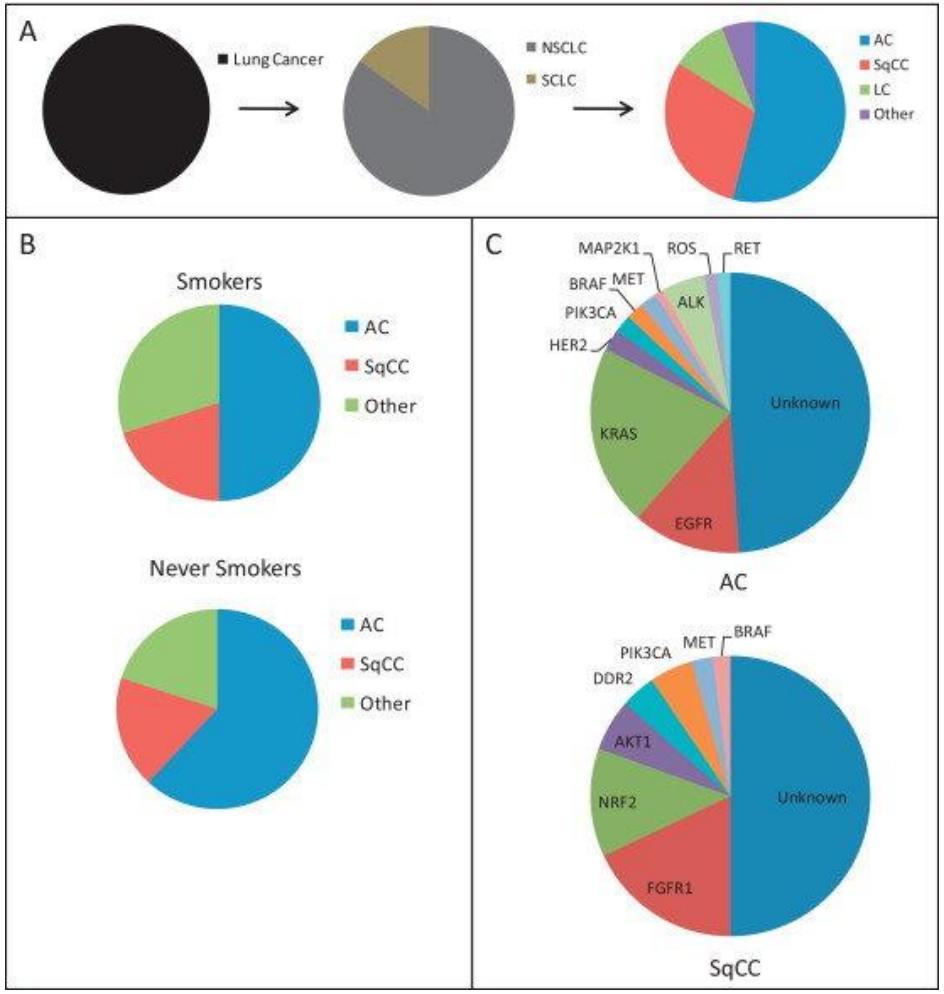
Li. JCO. 2013; Tsao. J Thorac Oncol. 2016.

TUMOR: Histology depends on smoking exposure

Smoking

Sex related factors:
- Prevalence (%)
- Influence

Female pop:
- Less smoker pop (for now!!)
- Higher impact of smoking (damage)



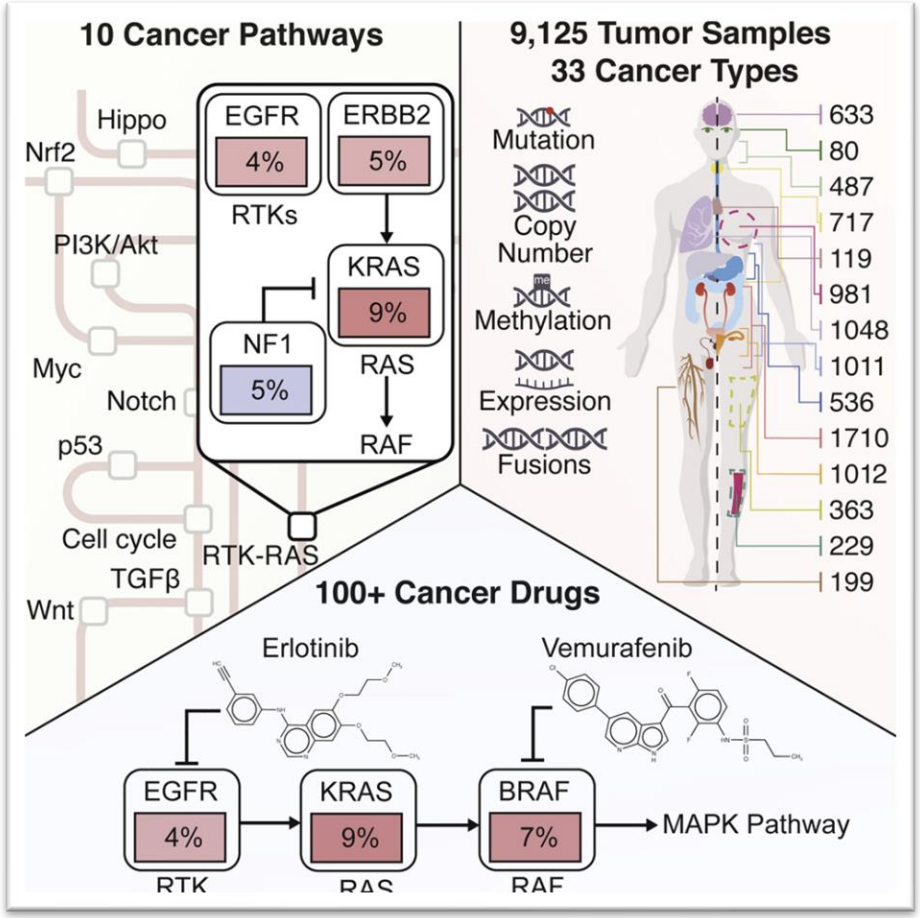
Molecular profile

Histological pattern

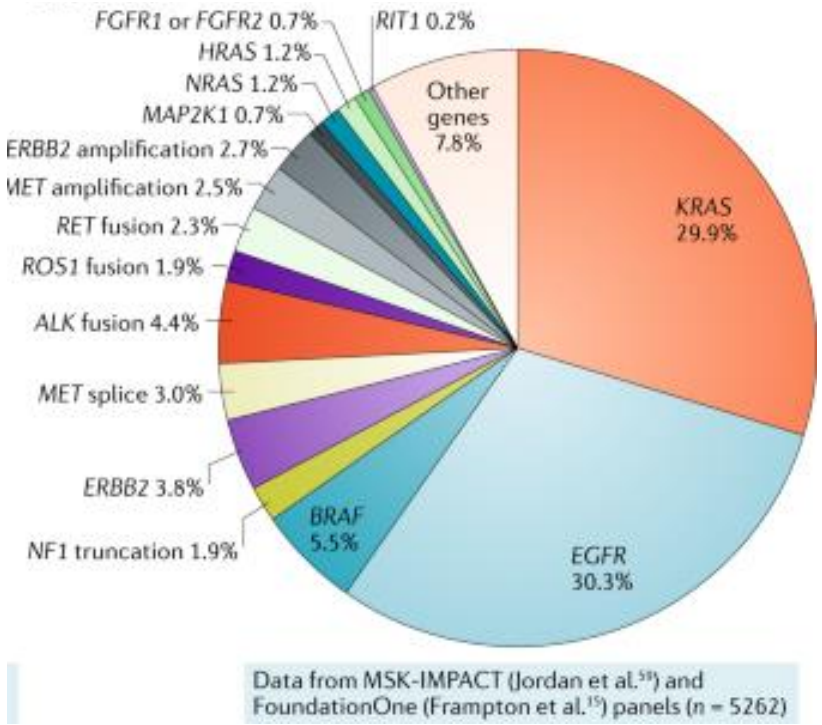
Female pop:
- Adenoca (44% vs. 34% in male)
- Less common: squamous (37%; slowly decreasing) SCLC (stable)

Pikor et al, Lung Cancer 2013; Mederos et al, ESMO Open 2020

TUMOR: Molecular classification



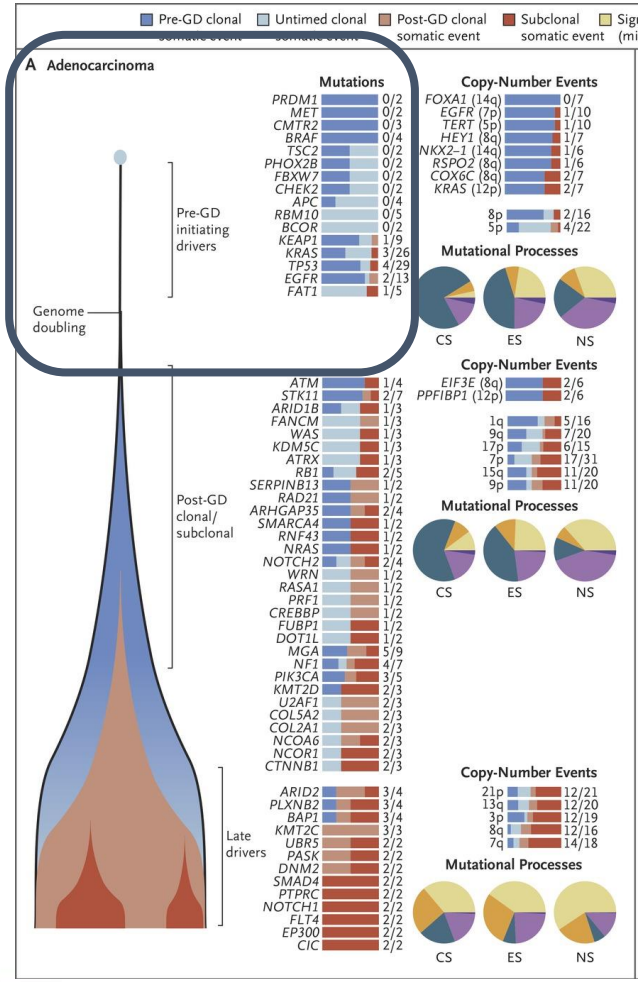
Non-small cell lung cancer



Sanchez-Vega et al., Cell 2018

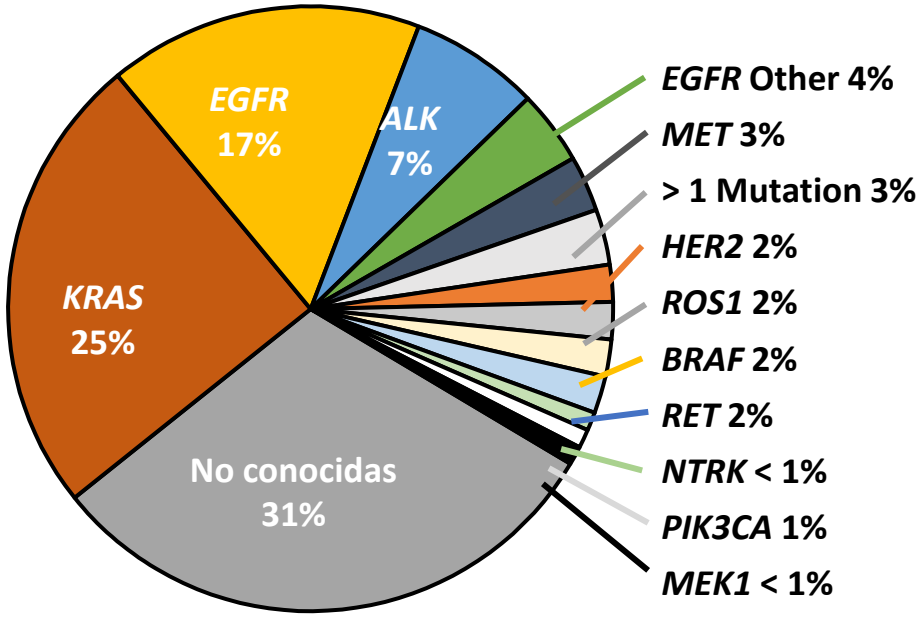
TUMOR: Molecular subgroups

Early clonal alterations



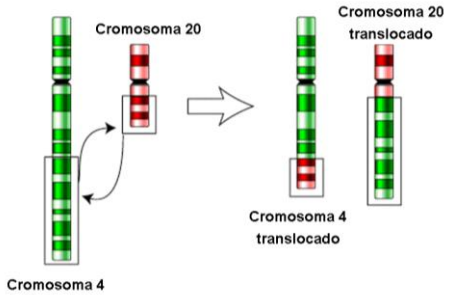
Jamal-Hanjani, M, et al, NEJM 2017

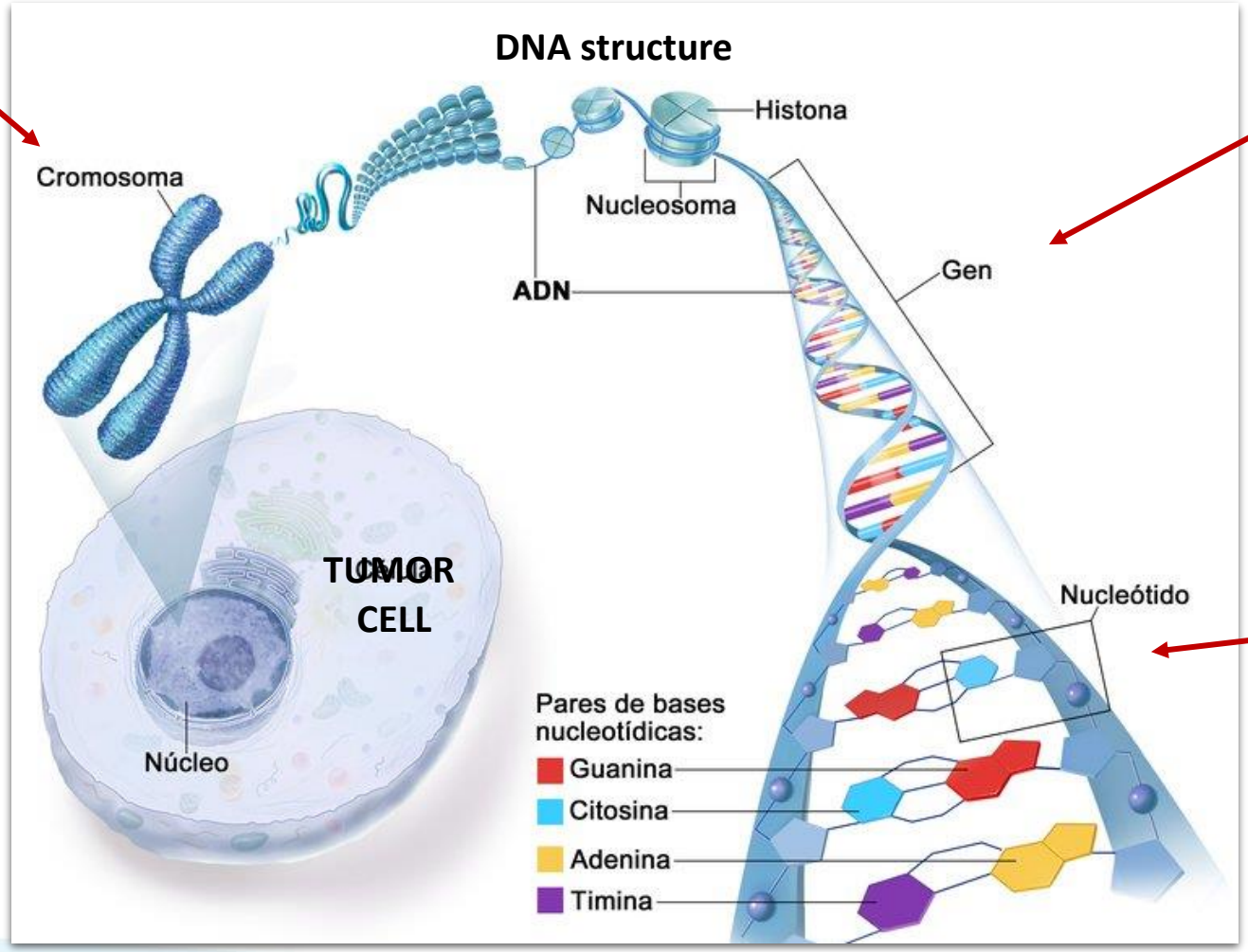
Molecular subgroups



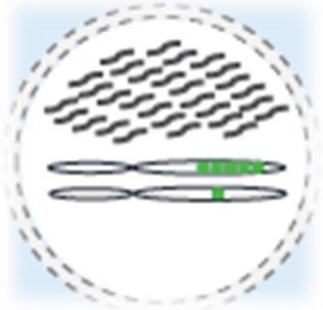
TUMOR: Oncogenic driver alterations

Rearrangement or Fusions

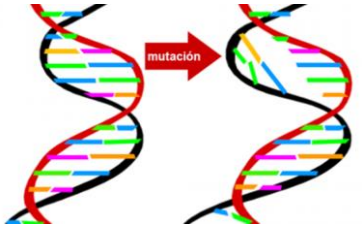




Amplificacions



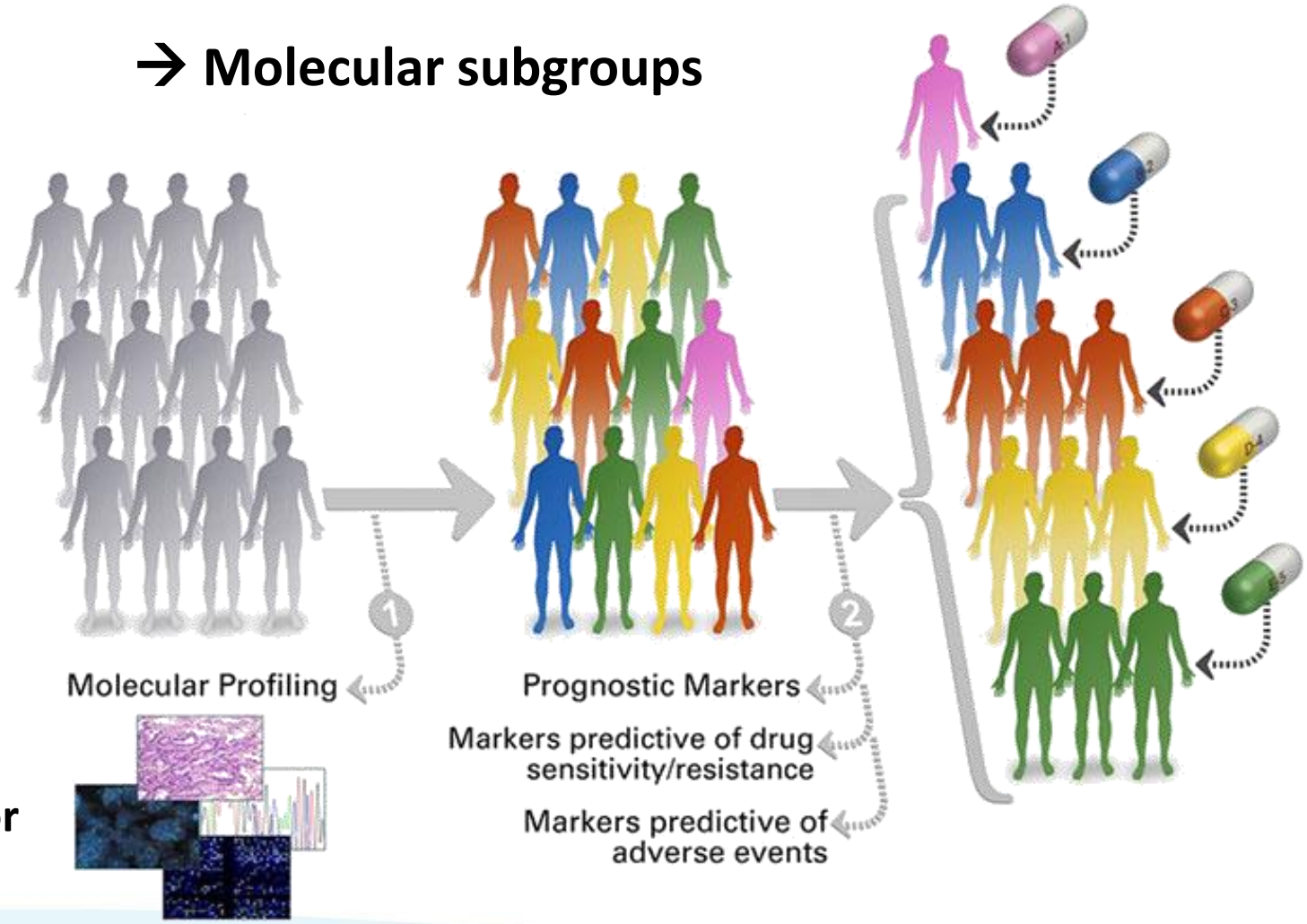
Mutations



TUMOR: Targeted therapies

→ **Molecular subgroups**

Patient

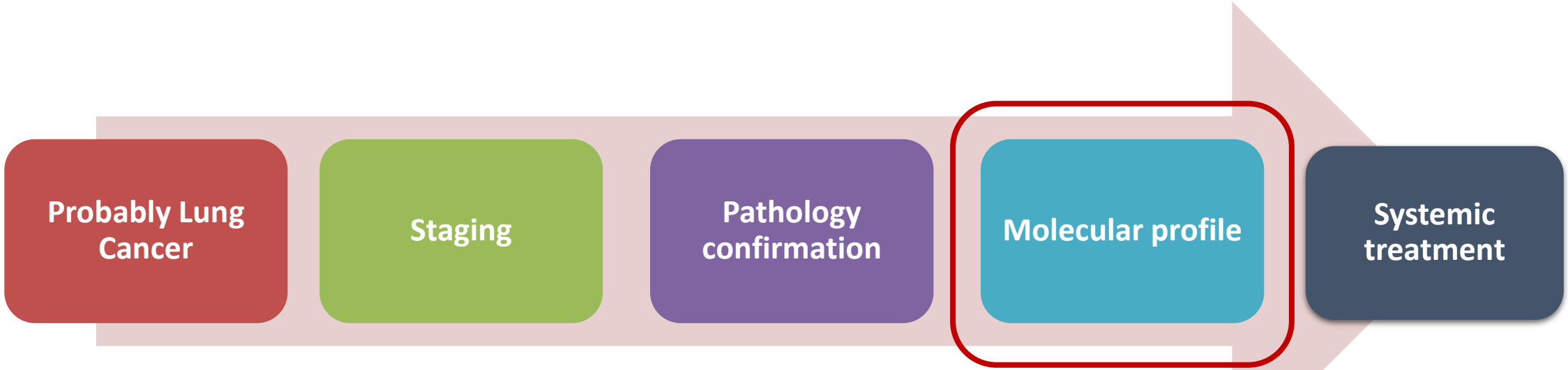


Tumor

TARGETED THERAPIES

PRECISION MEDICINE

Diagnosis Algorithm



Diagnosis

Body CT scan
PET scan
Brain MRI

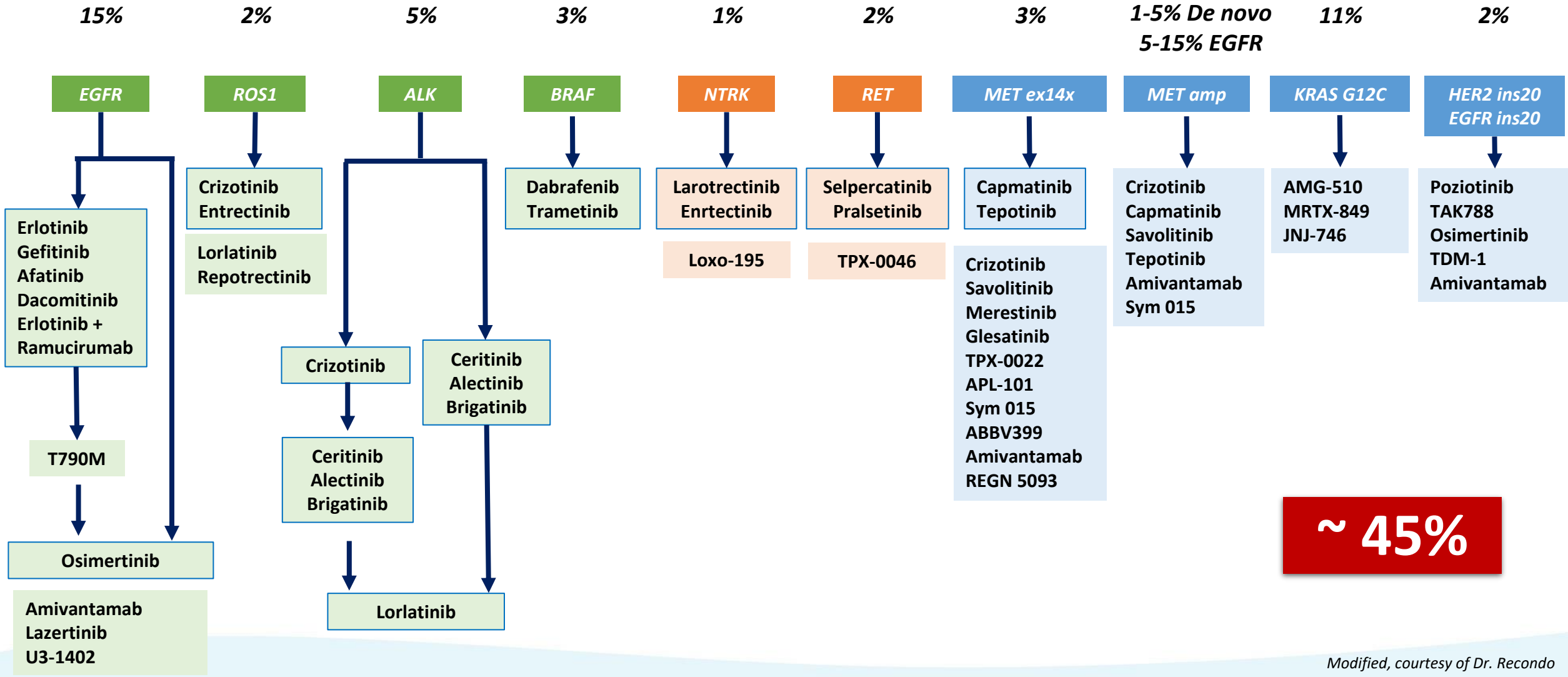
Biopsy:
Histology

Molecular techniques:
- IHC, FISH, PCR
→ **NGS**

NSCLC

- **Stage**
- **Histology**
- **Molecular alt.**

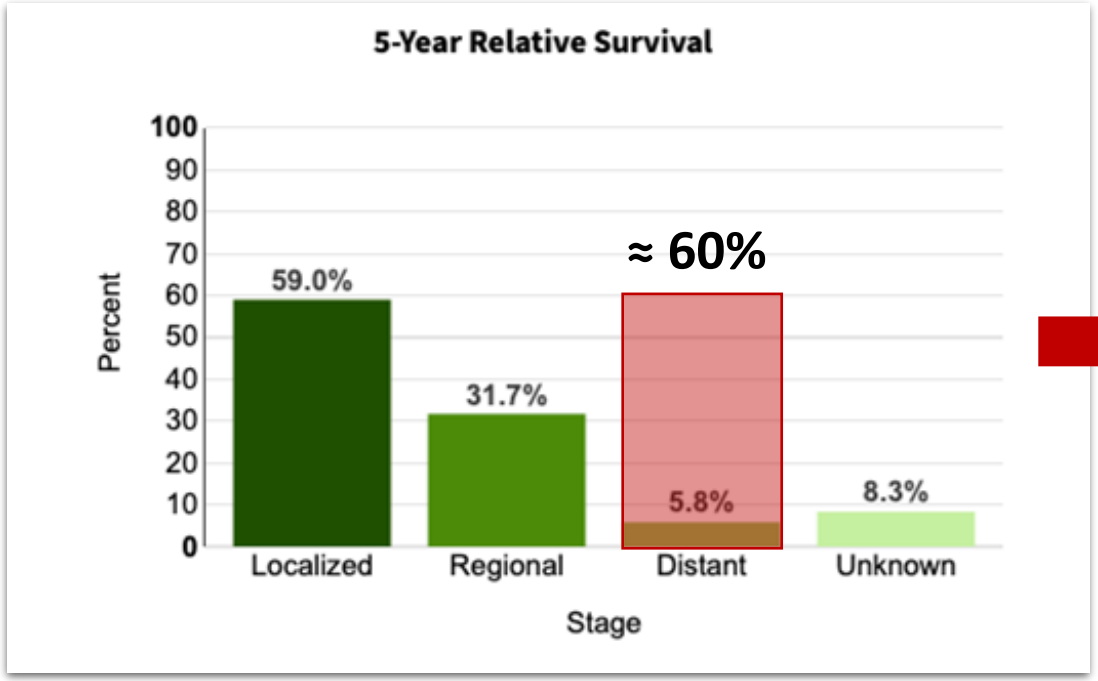
Lung cancer: Precision Medicine Therapies



Modified, courtesy of Dr. Recondo

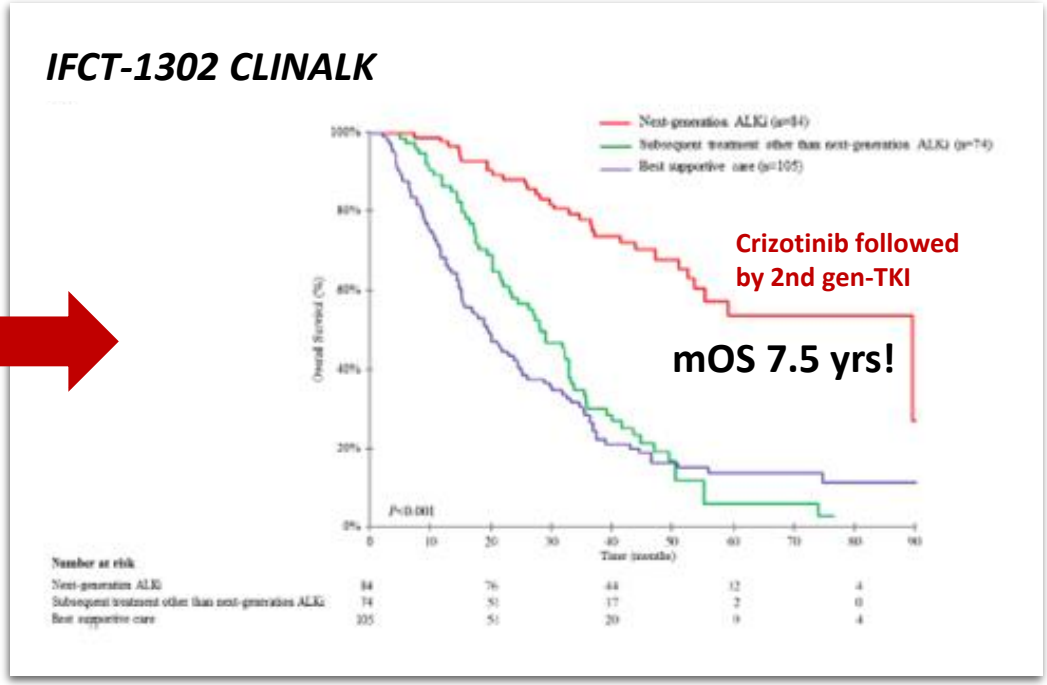
Why is this relevant?

Classical Lung cancer stats



SEER 18 2010-2016, All Races,
Both sexes by SEER Summary Stage 2000

ALK population, treated with ALK-TKIs

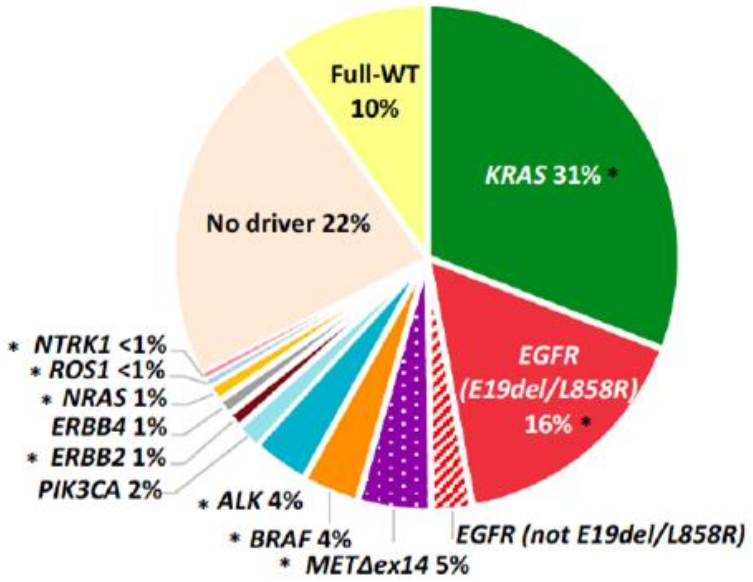


Duruisseaux M et al, Oncotarget 2017

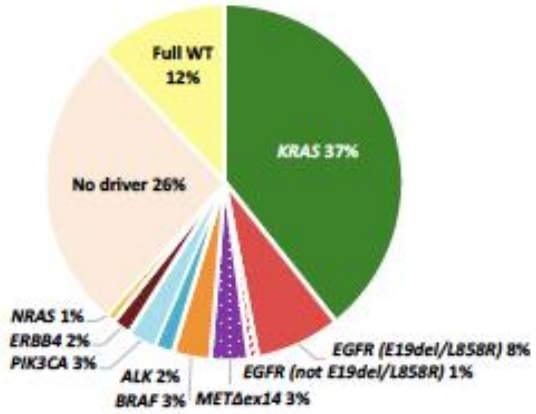
TUMOR: Driver alterations in NSCLC

Hospital Clinic, NSCLC

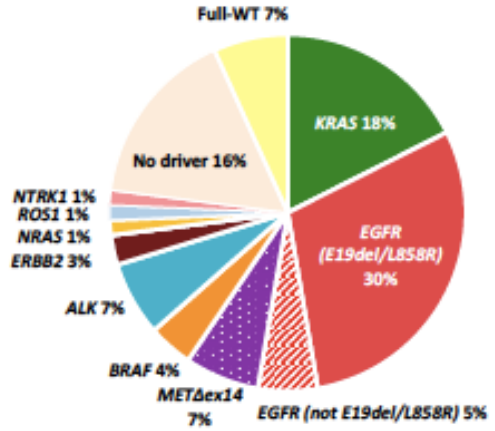
Overall pop



MALE



FEMALE

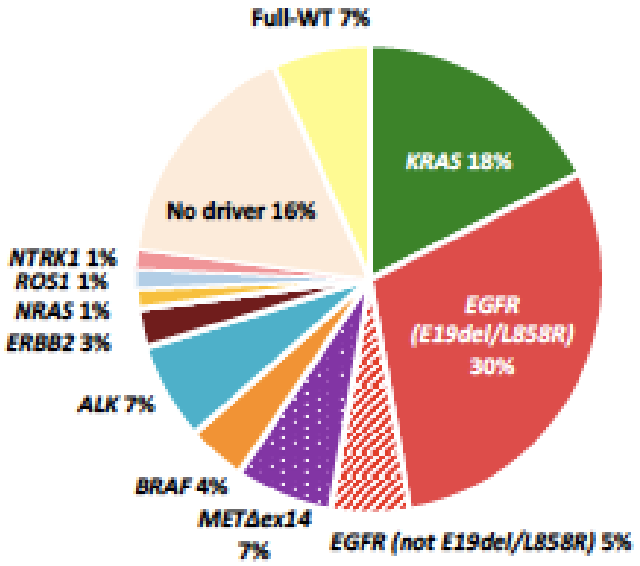


Differences on % of driver oncogenic alterations

Marin E et al, Cancers 2020

TUMOR: Driver alterations in NSCLC

Female pop



Marin E et al, Cancers 2020

- **<u>Overall</u> female pop:**

Differences on *HER* oncogene family:

- ↑ *EGFR mut*
- ↑ *HER2 mut*
- ↑ East Asian patients

↑ *BRAFV600E* in non-smoker female patients

No differences in fusions

- **In <u>smoker</u> female pop:**

↑ *TP53 mut*

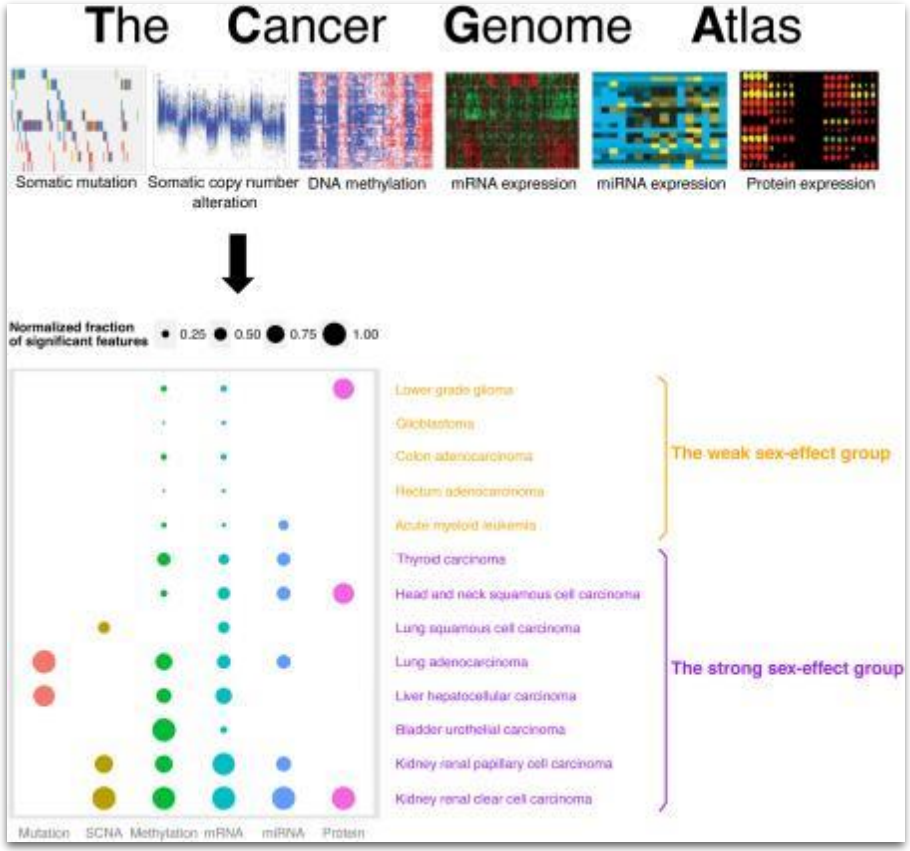
- Frequency of G:C→T:A transversion is lower
- G:C→A:T transversion ↑ in female nonsmokers vs. female smokers

↑ *KRAS mut*

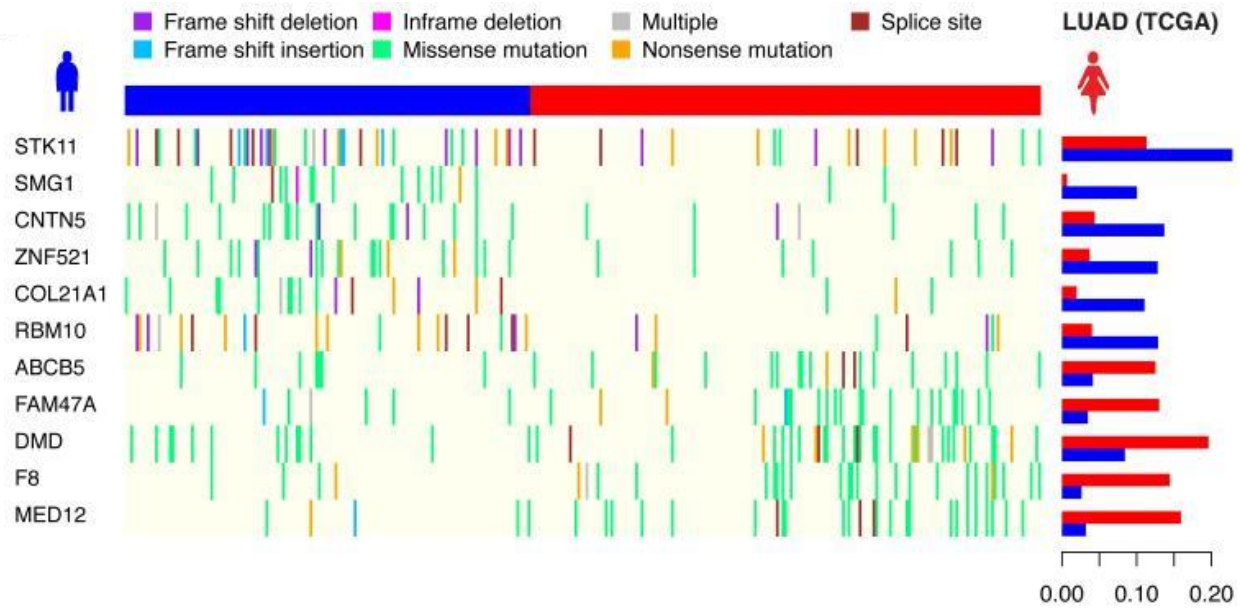
Mederos, et al, ESMO Open 2020

TUMOR: Molecular differences in cancer by sex

13 major TCGA cancer types



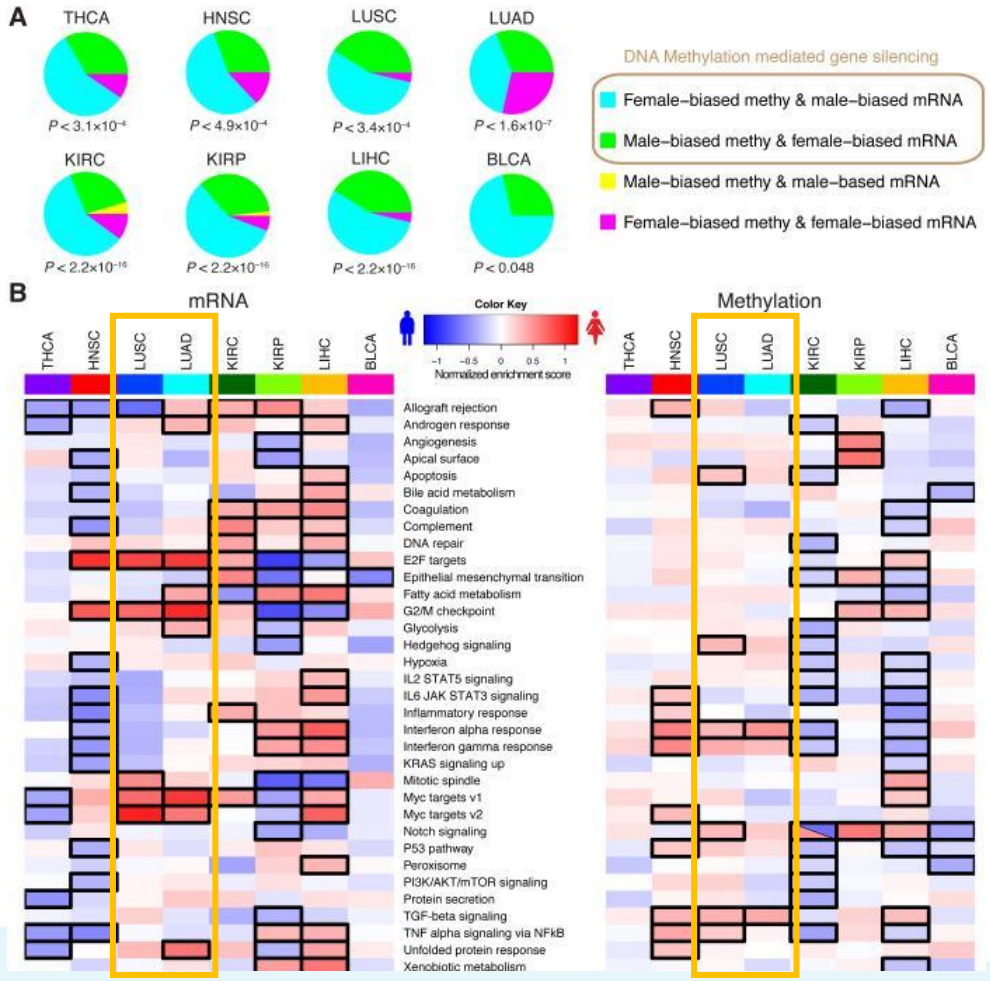
Lung Adenocarcinoma



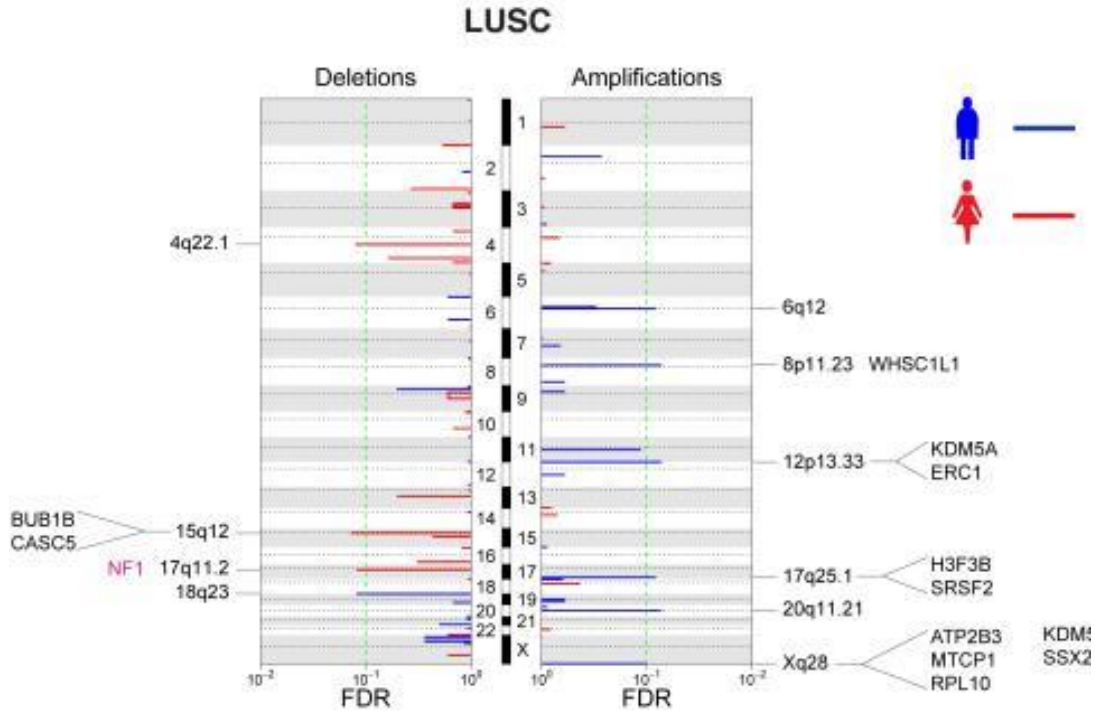
Yuan Y et al, Cancer Cell 2017

TUMOR: Molecular differences in cancer by sex

RNA expression & Metilation



Amplification/Deletion patterns



Yuan Y et al, Cancer Cell 2017

PATIENT: Lung cancer Risk factors, IARC (WHO)

Carcinogens, Group 1, WHO

- Smoking
- Radon gas
- Asbestos
- Second-hand smoking
- Genetics
- Radiation
- Occupational
- Arsenic (H_20), diesel...

REALITY = misperception

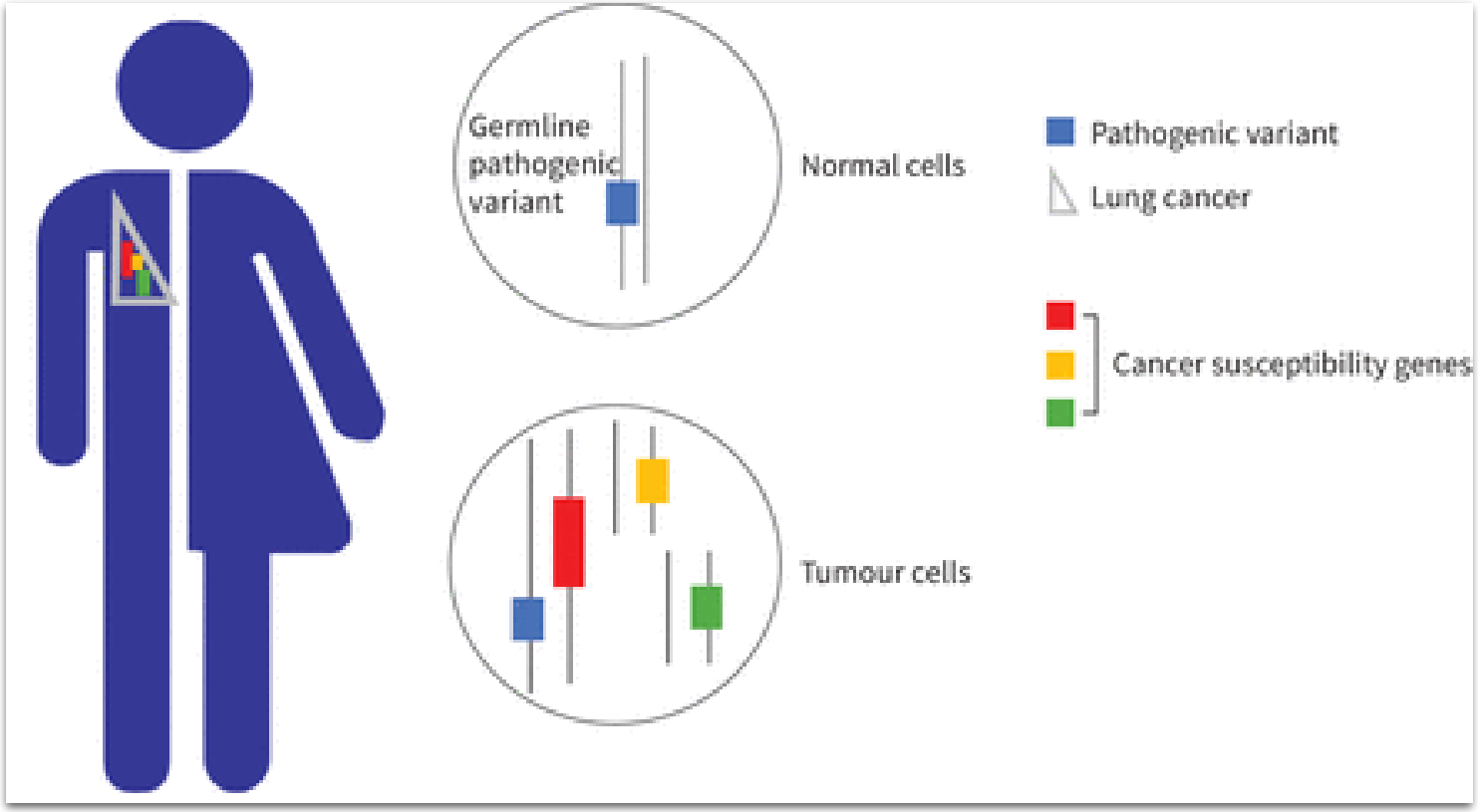
TOBACCO Stigma minimizes the others

- Smoking
- Radon gas
- Asbestos
- Second-hand smoking
- Genetics
- Radiation
- Occupational
- Arsenic (H_20), diesel...

PATIENT: Cancer-predisposing genes

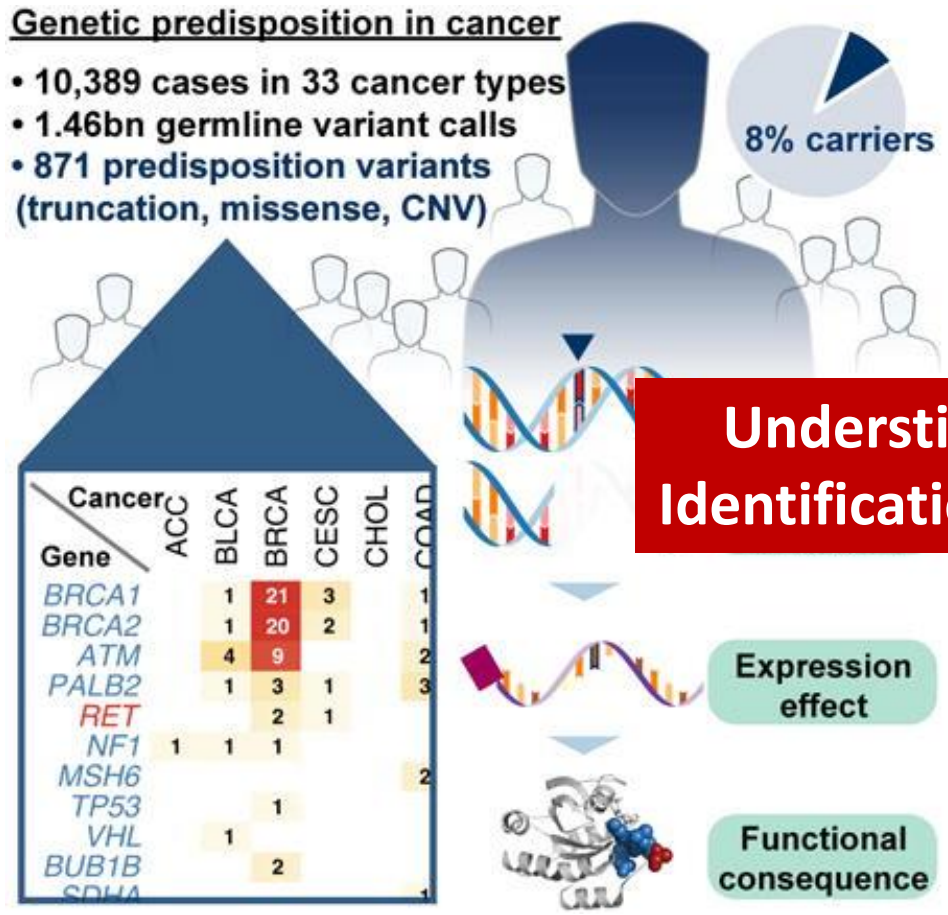
*"What is not **detected** is not reported, what is not **reported** does not exist & what does not **exist** is not prevented"*

PATIENT: Lung Cancer-predisposing genes



Benusiglio PR et al, European Respiratory Review 2021

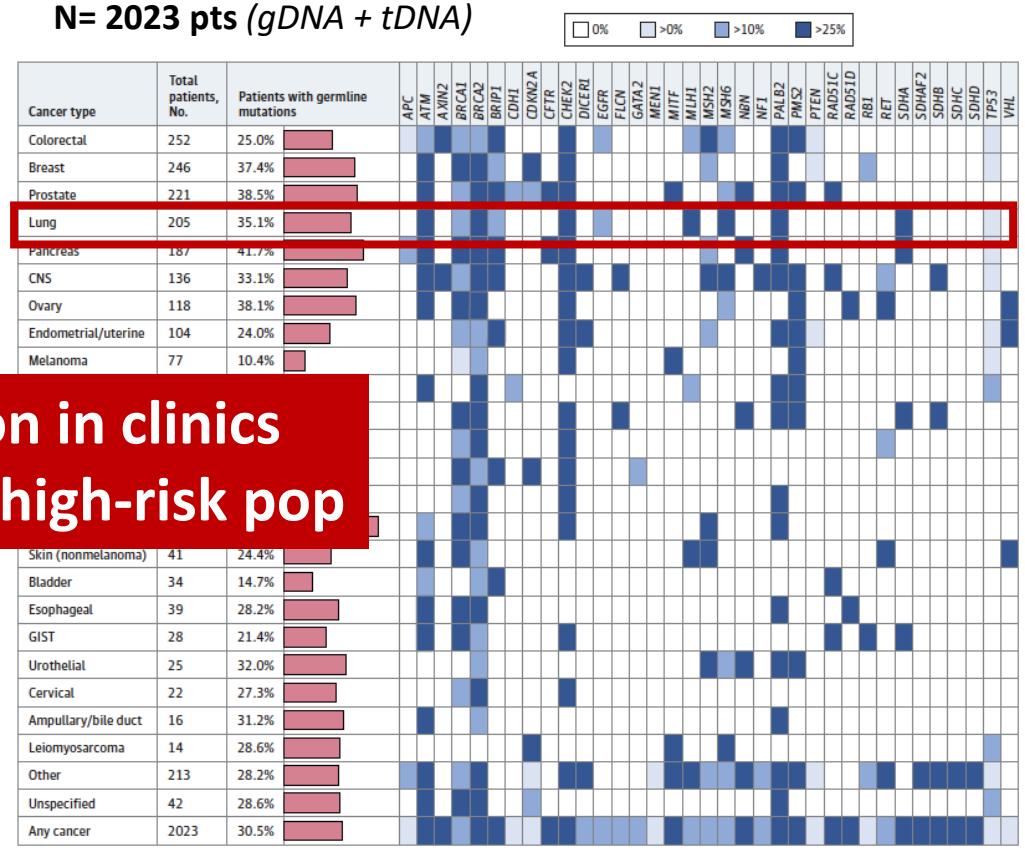
PATIENT: Genetics in Solid Tumors



Huang et al, Cell 2018

Understimation in clinics
Identification of high-risk pop

N= 2023 pts *(gDNA + tDNA)*



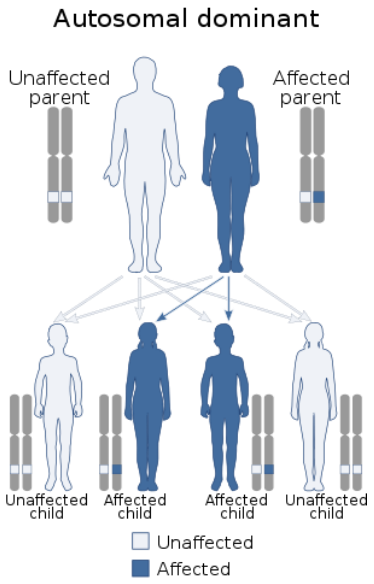
→ **20% PGV-carriers pts did not meet criteria for germline testing**

Lincoln et al, JAMA Open Network 2020

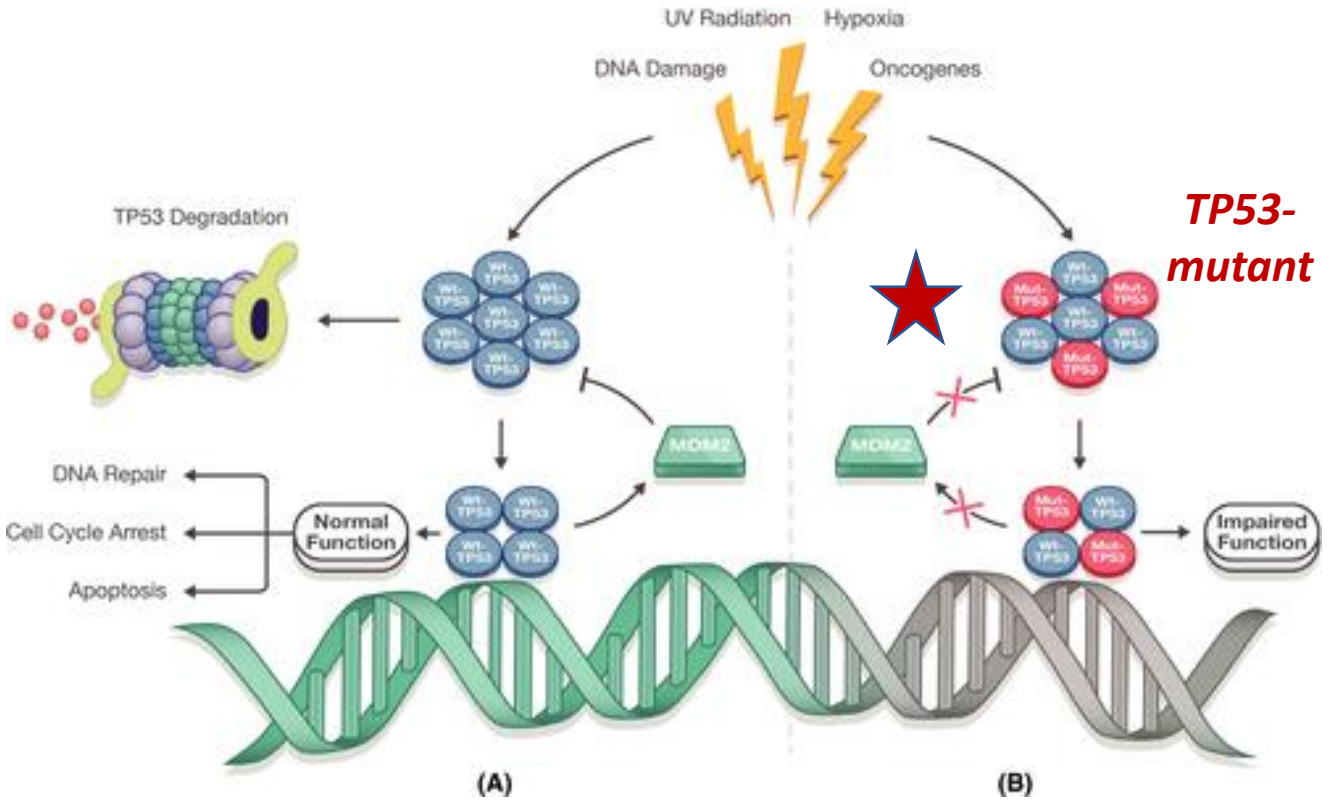
PATIENT: Genetics (predisposition) in Lung cancer

LiFraumeni syndrome

Cancer predisposing condition



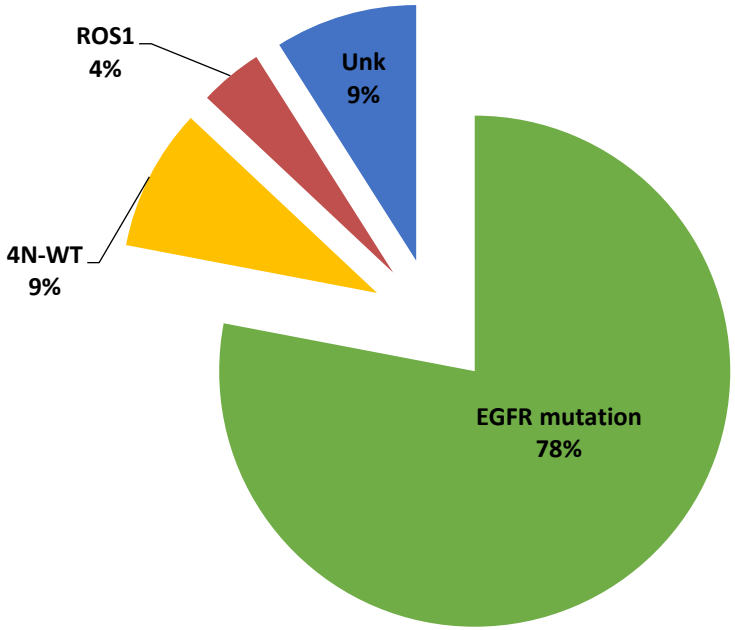
Diff. cancer types

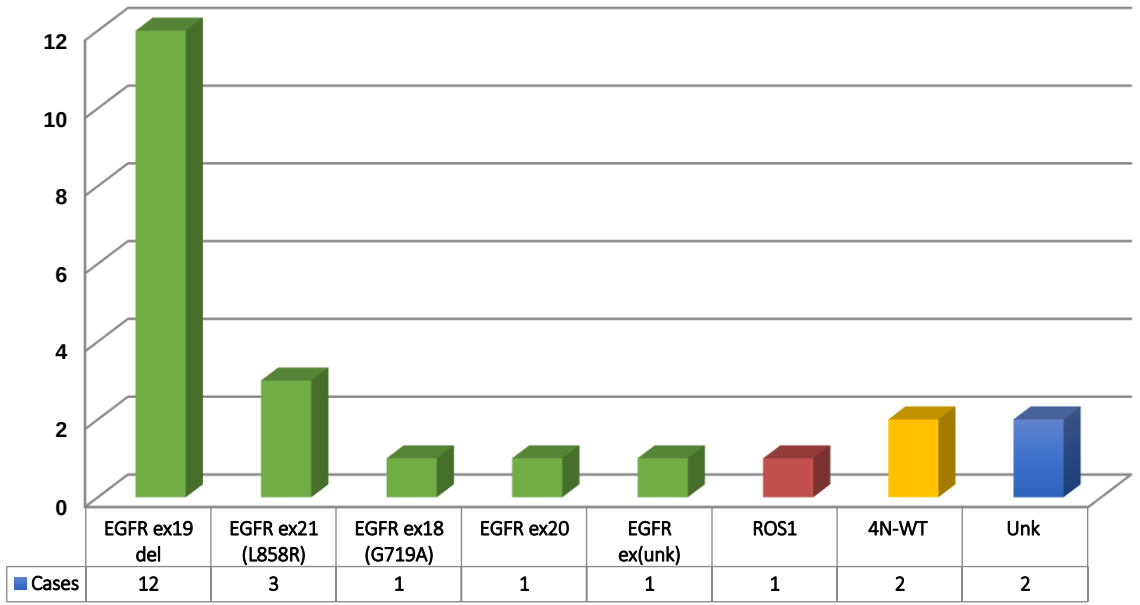


Valdez et al, B J Haemat, 2017; Bahar et al, Anticancer Research 2015

PATIENT: LiFraumeni-Lung cancer

90% LFS lung cancer pts (19/21) with somatic oncogenic driver alt.



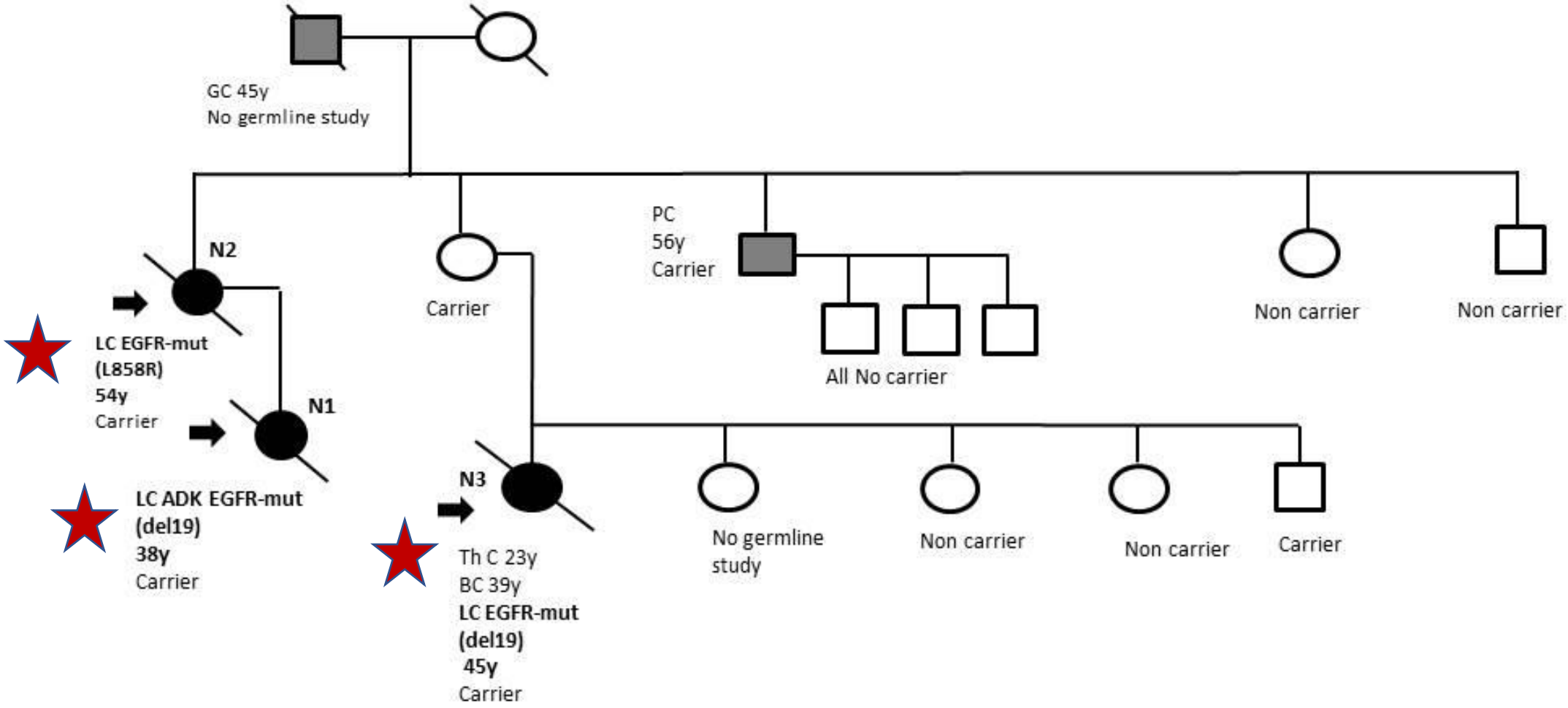


4N: four negative (*EGFR* and *BRAF* wildtype, *ALK* and *ROS1* not rearranged)

64% of cases were female

Mezquita, Jove et al, et al, J Thorac Oncol 2020

Li-Fraumeni Lung Cancer family

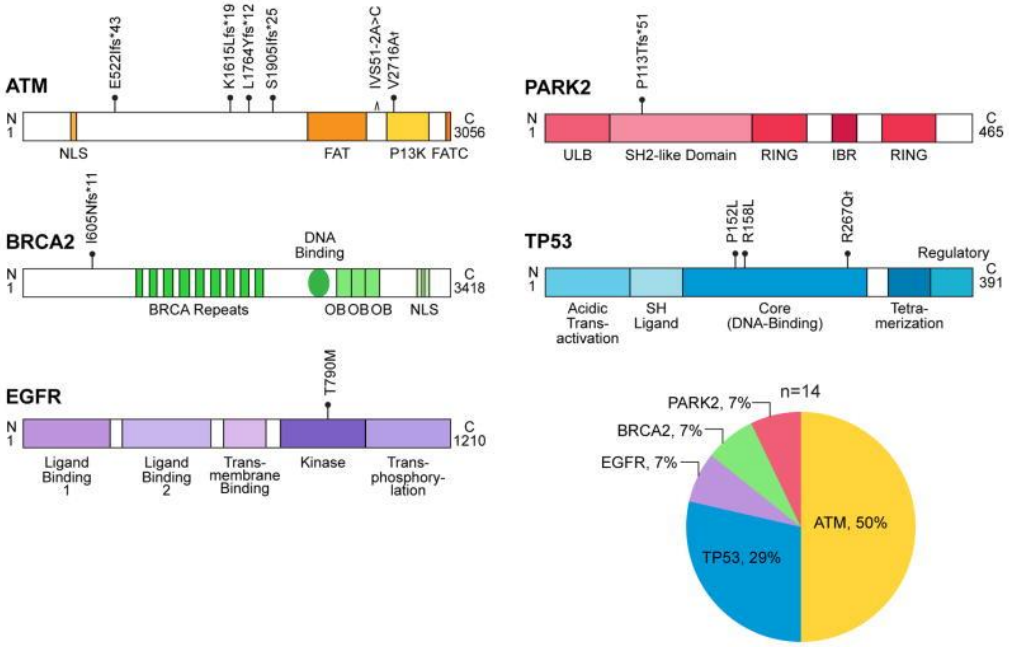


TP53mut. p.R158H variant

Mezquita, Jove et al, et al, J Thorac Oncol 2020

PATIENT: Other germline mutations in lung cancer

- **N=555 patients with lung adenocarcinoma**
- **2.5% of cases with PGV** (n=14 PGVs, 5 genes)
- Most common: ***ATM (50%), TP53, BRCA2, EGFR, PARK2***



EM et al J Thor Oncol 2017

Cancer-Predisposing Genes in NSCLC

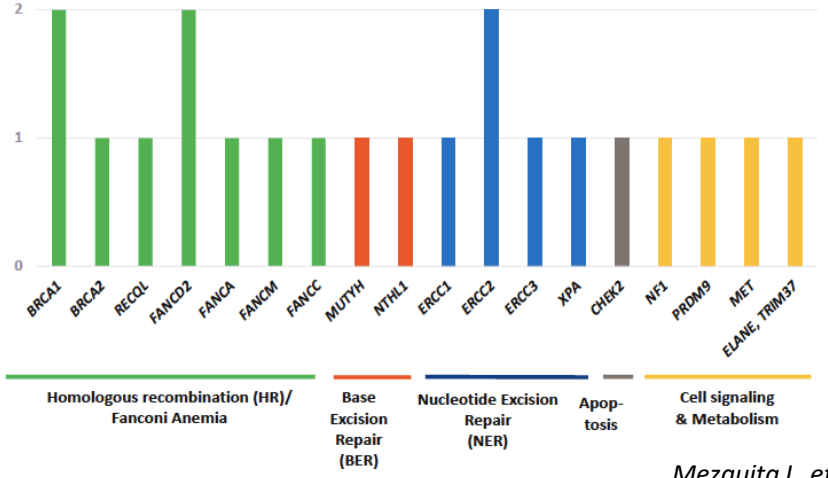
Prevalence of PGVs in lung cancer

Figure 1. Prevalence of PGV in our study population

- **PGV in cancer-predisposing genes were found in 22 patients (15%);** 4 patients had additional somatic mutations (2) or LOHs (2) in the same genes

N= 134 pts with NSCLC

77% DNA repair pathways



Mezquita L, et al AACR 2021

PATIENT: Genetics (predisposition) in Lung cancer

- In the 22 PGV-carriers, **68% had a somatic oncogene-driven alteration** (15/22)

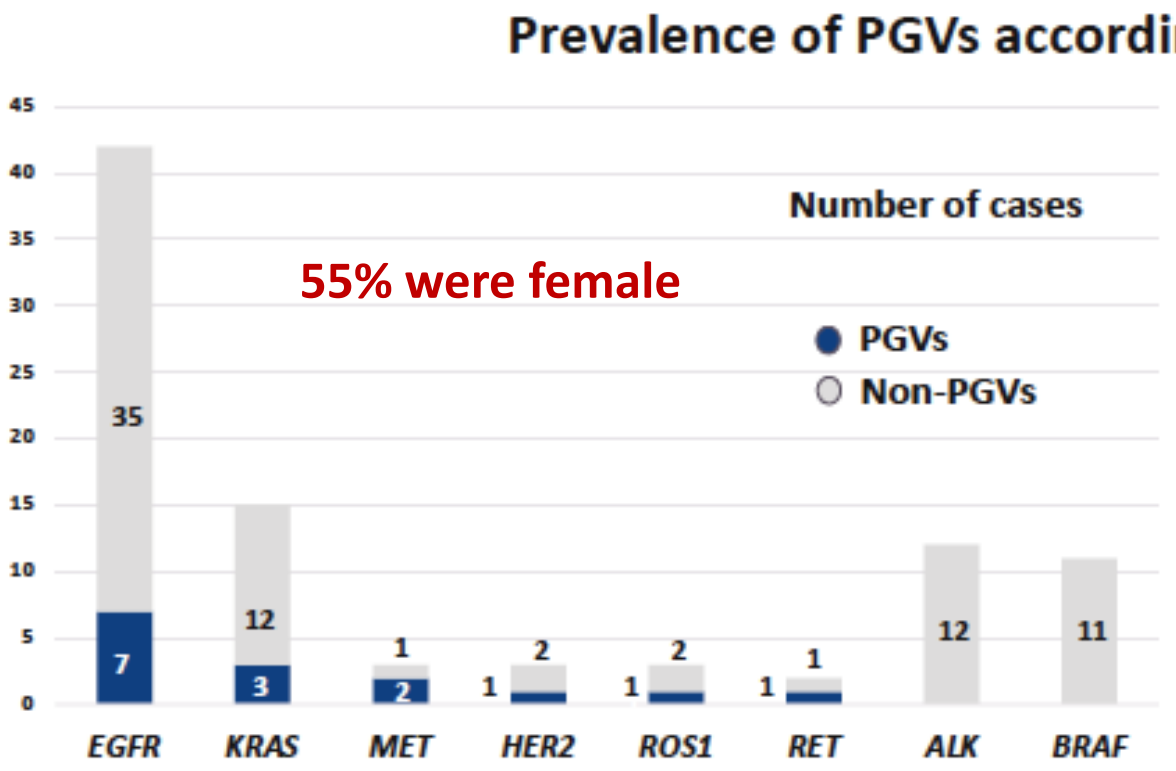


Figure 4. Frequency (N) of PGVs in each molecular group

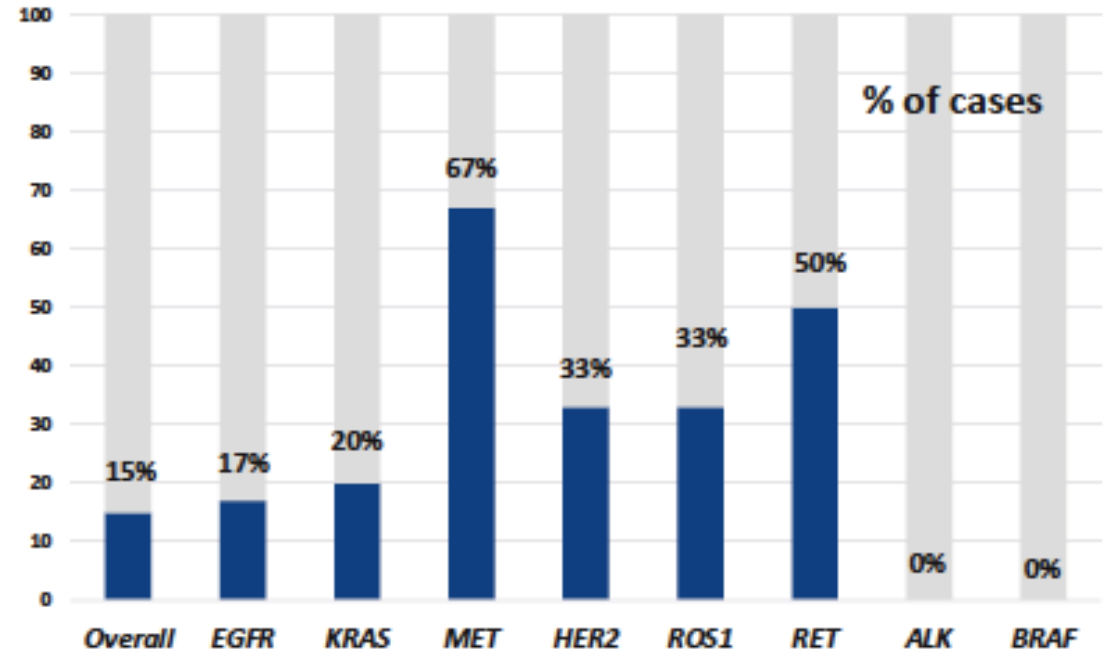


Figure 5. Frequency (%) of PGVs in each molecular group

Mezquita L, et al, AACR 2021

PATIENT: Family History in Lung cancer

Family History of Cancer and Lung Cancer: information from the Thoracic Tumors Registry (TTR study)

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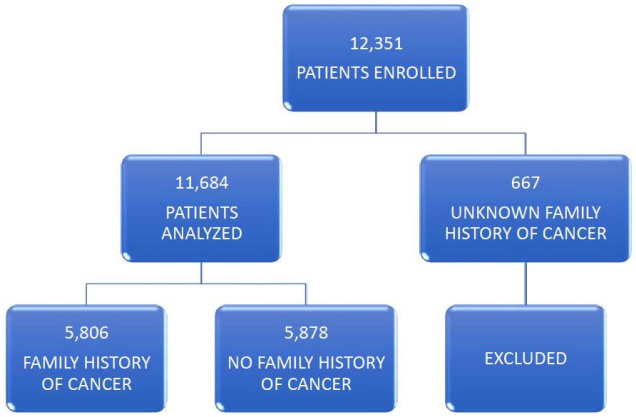
RESULTS



CONCLUSIONS

- Patients with a family history of cancer were diagnosed at a younger age
- Patients with a family history of cancer were more often women
- Significant differences were found:
  - Regarding tobacco habit
  - In the percentage of patients diagnosed with limited-stage small-cell lung cancer (LS-SCLC)
  - In overall survival

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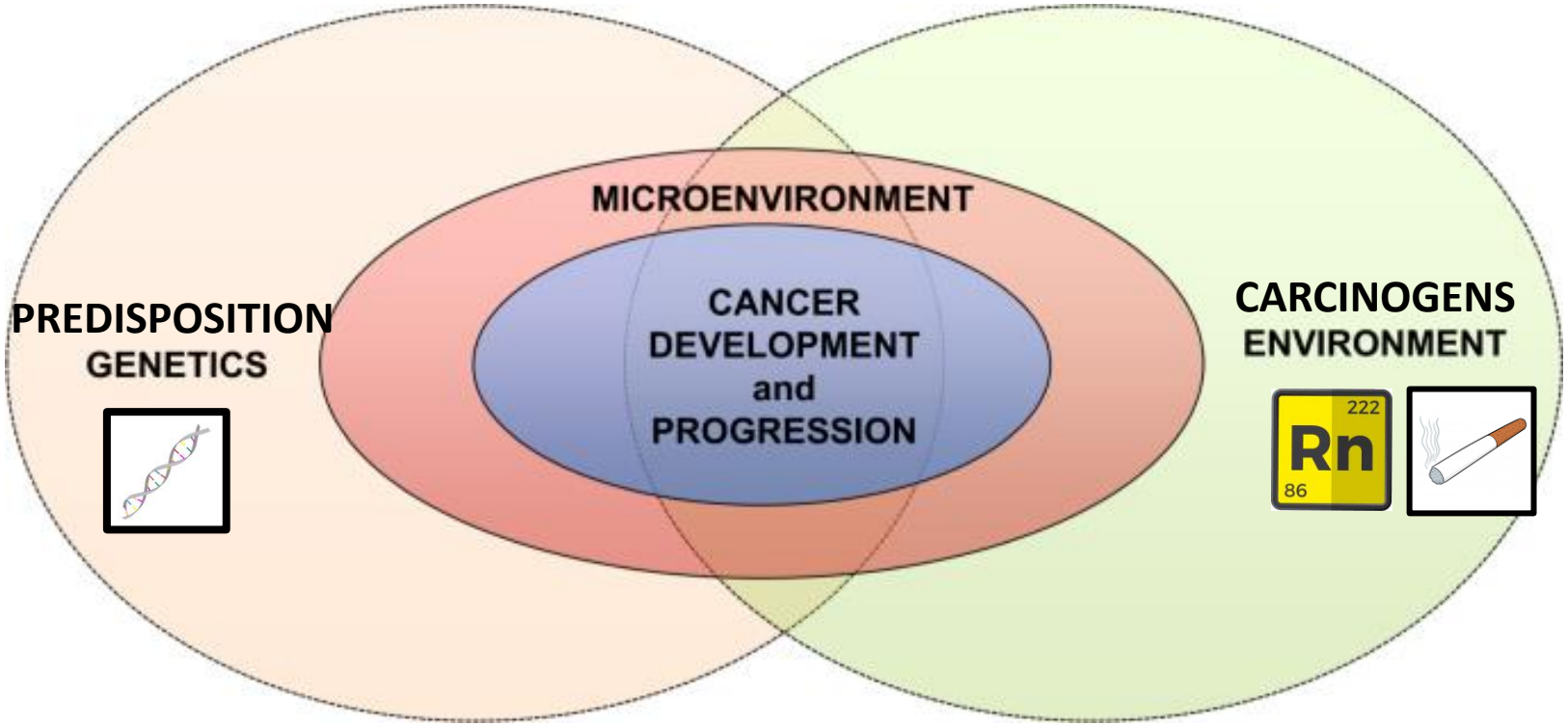
Calvo V et al, WCLC 2021

PATIENT - TUMOR: Genetics & other factors



Lung cancer development in one patient

Modificado de Carbone, et al; Cell Death & Differentiation 2018

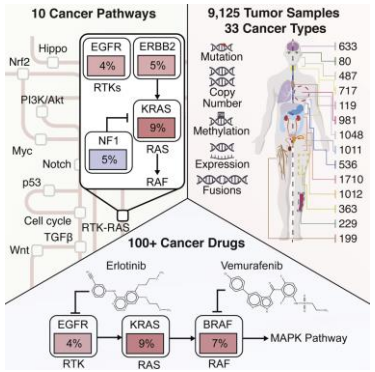
PATIENT - TUMOR: Genetics & Genomics in NSCLC

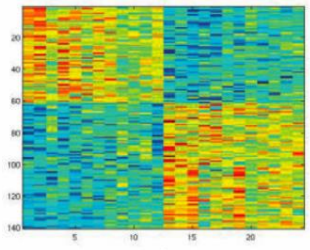
- ✔ Strengthen **MOLECULAR KNOWLEDGE**
- ✔ **INTEGRATE the DATA** (sex-related)
- ✔ **PRECISION MEDICINE Program**

Inherity study (ICAPEM)

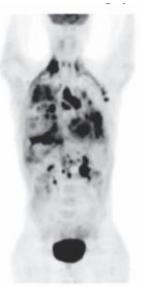
INTEGRATED RESEARCH

TUMOR data





PATIENTS data



TAKE-HOME MESSAGES

✔ **LUNG CANCER is a complex disease:**

- Patient & carcinogen(s) interaction
- Sex-related differences

✔ **TUMOR genomics:** different molecular profile by sex

✔ **PATIENT genetics:** different predisposition by sex

✔ **INTEGRATED data for future research** (sex-related factors)

Thanks!

CLÍNIC BARCELONA Hospital Universitari

Translational genomics and targeted therapies in solid tumors

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