2023 ASCO® ANNUAL MEETING

Germline Alterations In Patients With Lung Cancer

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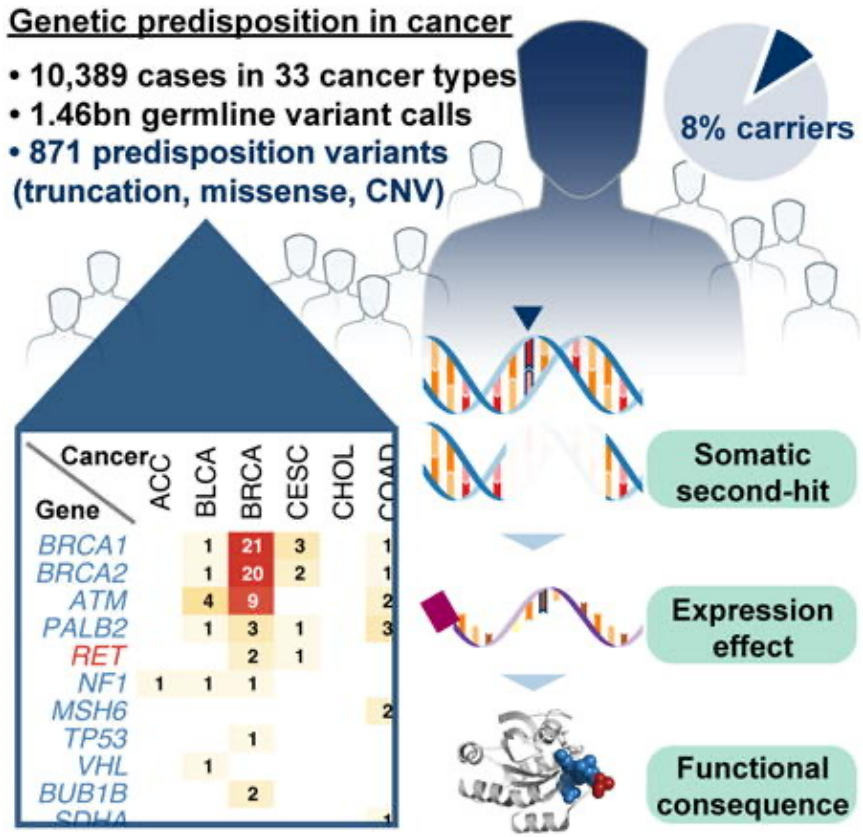
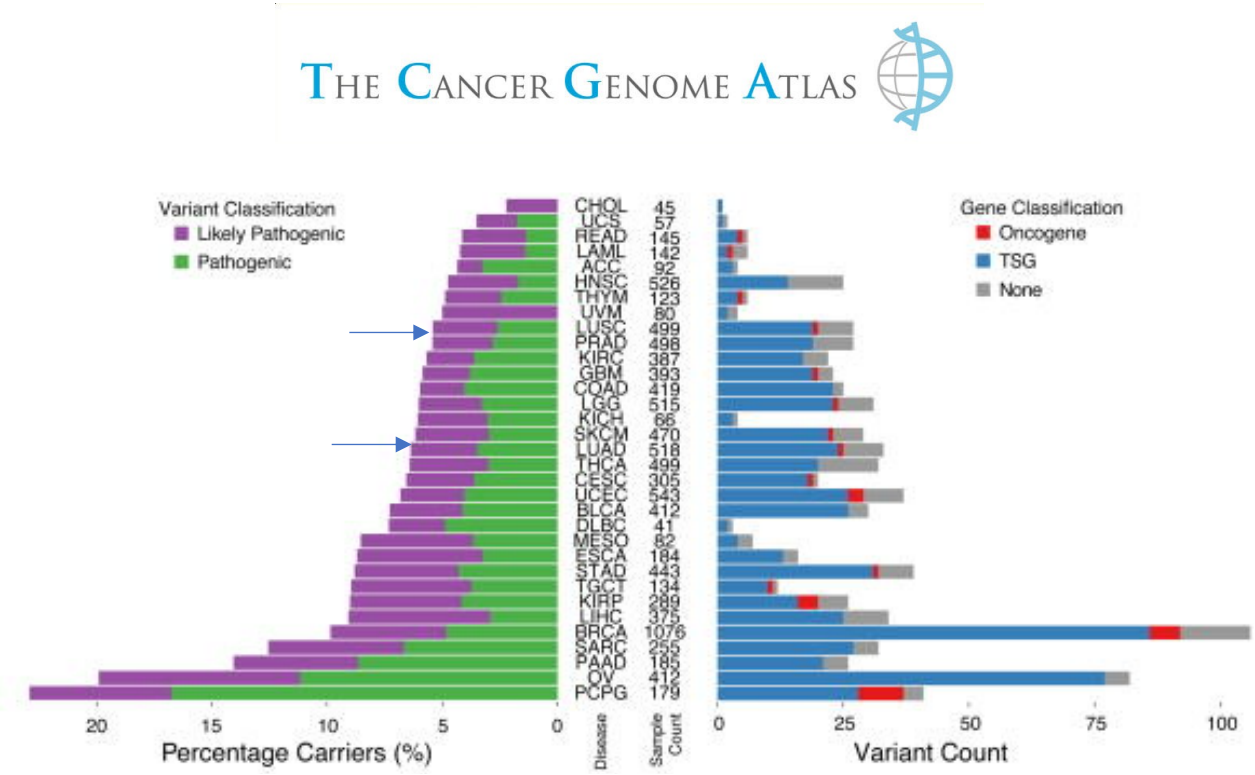
Germline alterations are prevalent at 8% across all cancers





Prevalence in lung cancer specifically?

Background

Huang K-L et al, Cell (2018)

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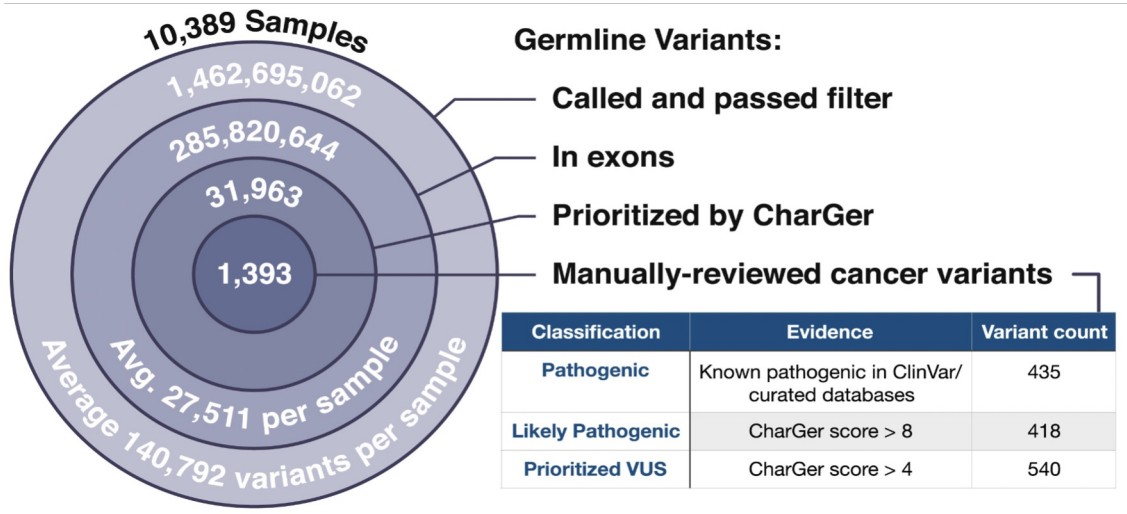
KNOWLEDGE CONQUERS CANCER

Pathogenic Germline Variants In 10,389 Adult Cancers (33 Cancer Types) TCGA

Germline variants identified, annotated and classified by CharGer pipeline (**Char**acterization of **Ger**mline variants) Scott A D et al, Bioinformatics (2019)



Classification	Evidence	Variant count
Pathogenic	Known pathogenic in ClinVar/ curated databases	435
Likely Pathogenic	CharGer score > 8	418
Prioritized VUS	CharGer score > 4	540

	Cancer	Number of samples	% Females	Age at diagnosis
LUAD	Lung Adenocarcinoma	518 (5%)	54%	63.3 +/- 10
LUSC	Lung Squamous Cell Carcinoma	499 (5%)	26%	67.3 +/- 8.6

LUAD and LUSC account for ~10% of all cancers in Cell 2018 study

Huang K-L et al, Cell (2018)

Background

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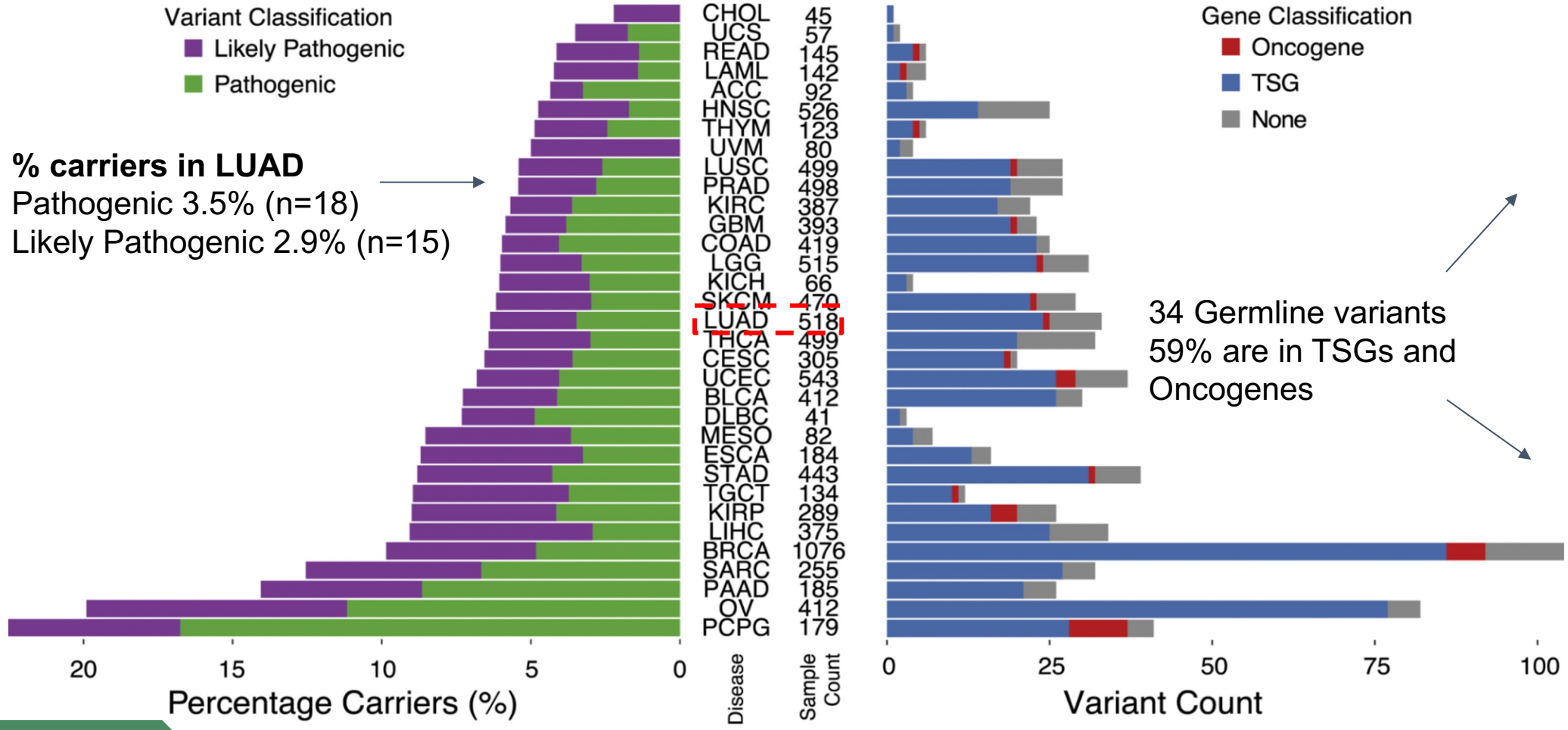
Germline Variants in TCGA
Lung Adenocarcinoma (LUAD)



Huang K-L et al, Cell (2018)

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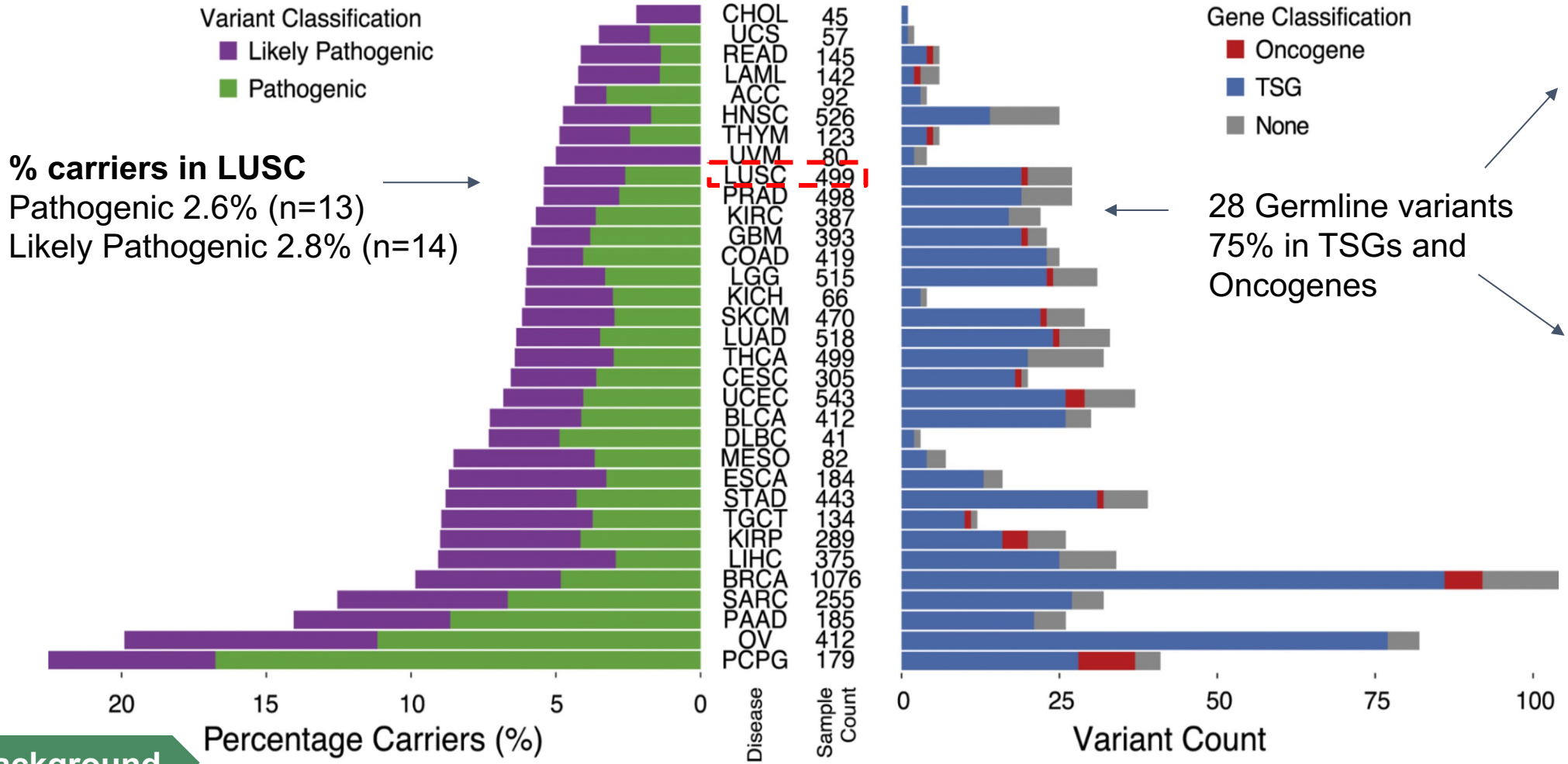
Germline Variants in TCGA
Lung Squamous Carcinoma (LUSC)



% carriers in LUSC
Pathogenic 2.6% (n=13)
Likely Pathogenic 2.8% (n=14)

28 Germline variants
75% in TSGs and
Oncogenes

ATR
BLM
BRCA1
BRCA2
BRIP1
BUB1B
CDH1
CHEK2
FANCC
PALB2
PMS2
POLD1
RET

Background

Huang K-L et al, Cell (2018)

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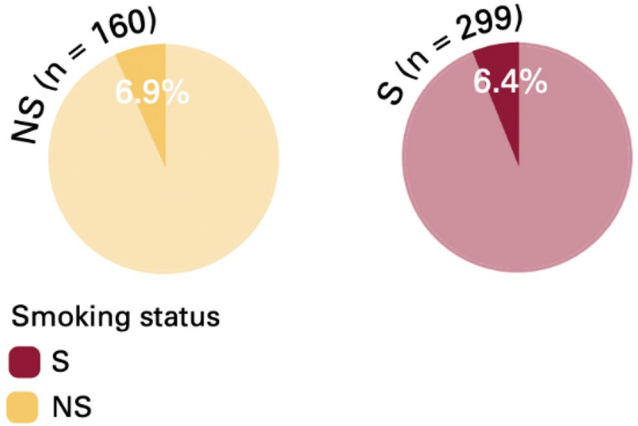
Germline Analysis From Never Smokers

CharGer classification of germline variants from 160 Never-Smokers and 299 Smokers

Classification	Variant Count		
	CPTAC	TCGA	Institutional
Pathogenic	7	14	4
Likely pathogenic	2	3	2
Prioritized VUS	5	24	5



Enriched in Smokers (Suggestive/Significant)	Enriched in Never Smokers (Suggestive/Significant)
CDKN1B	*FANCG*
FANCF	*TMEM127*
FANCI	
MUTYH	
SRY	
STAT3	

Pathogenic and likely pathogenic germline variants were observed in 6.4% of smokers and 6.9% of never-smokers

Background

Devarakonda S, Li Y, Martins F M, Journal of Clinical Oncology (2021)

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Primary Objectives Of This Study

- To explore the association between presence of pathogenic and likely pathogenic germline alterations, as defined by ACMG criteria, in lung cancer patients

- To compare the frequency of these germline alterations between smokers and never smokers, EGFR mutated vs. wild type tumors, and between different histological subtypes of lung cancer

Richards S et al, Genetics in medicine: official journal of the American College of Medical Genetics (2015)

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46 Genes (germline) Explored Within The UK Biobank And Tempus Data Analyses

APC	*ATM*	*AXIN2*	*BMPR1A*	*BRCA1*	*BRCA2*	*BRIP1*	*CDH1*
CDKN2A	*CEBPA*	*CHEK2*	*EGFR*	*EPCAM*	*ETV6*	*FH*	*FLCN*
GATA2	*MEN1*	*MLH1*	*MSH2*	*MSH3*	*MSH6*	*MUTYH*	*NBN*
NF2	*PALB2*	*PMS2*	*POLD1*	*POLE*	*PTEN*	*RAD1C*	*RAD1D*
RB1	*RET*	*RUNX1*	*SDHAF2*	*SDHB*	*SDHC*	*SDHD*	*SMAD4*
STK11	*TP53*	*TSC1*	*TSC2*	*VHL*	*WT1*		

These genes were selected based on the December 2021 xT tumor-normal match incidental germline gene list

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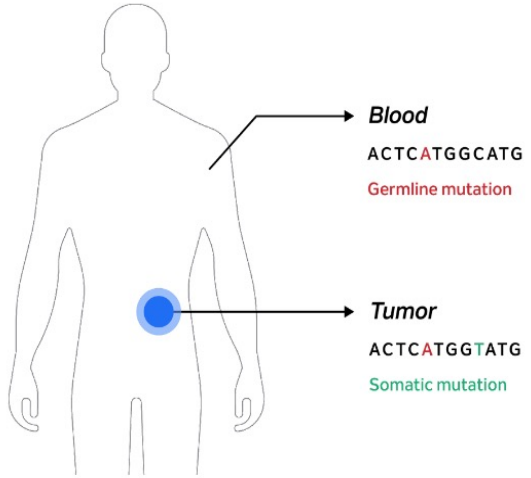
Tempus Tumor-Normal Matching And Multimodal Database

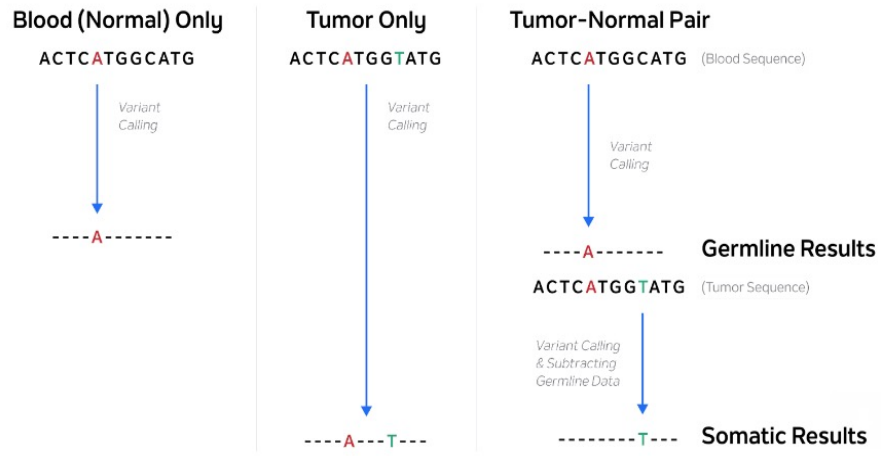
Tumor-Normal Matching

- Sequencing of tumor tissue and a normal sample parallelly
- Normal match sequencing allows for identification of incidental germline variants filtered from somatic findings



Multimodal database

- It contains over 70 petabytes of data
- It is one of the largest structured de-identified clinical and molecular databases in the world
- It includes Tempus' tumor-normal match DNA and RNA sequencing data with pathology data



Adapted from Mandelker & Ceyhan-Birsoy, 2019 (Cell Press)

Beaubier N, Bontrager M, Huether R, et al. Nat Biotechnol. 2019.
Yap TA, Ashok A, Stoll J, et al. JAMA Network Open. 2022.

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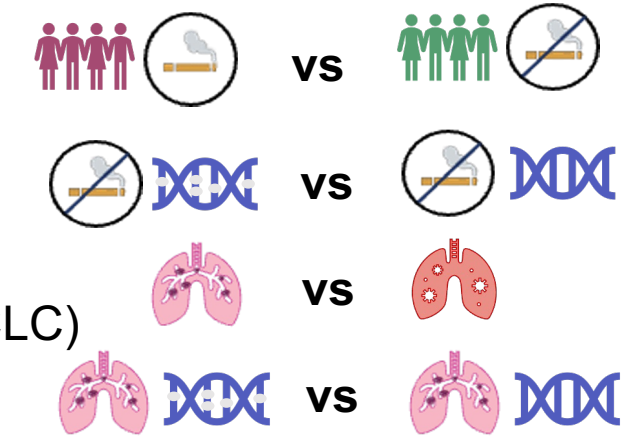
Germline Profiling Methods

Prevalence of **pathogenic/likely pathogenic (P/LP) germline alterations** as defined by ACMG criteria in **46 genes** was compared between:

- Smokers and never smokers
- Non-smoker somatic *EGFR* altered (sEGFRalt) and non-smoker somatic *EGFR* wild-type (sEGFRwt)
- Non-small cell lung histology (NSCLC) and small cell histology (SCLC)
- NSCLC sEGFRalt and NSCLC sEGFRwt



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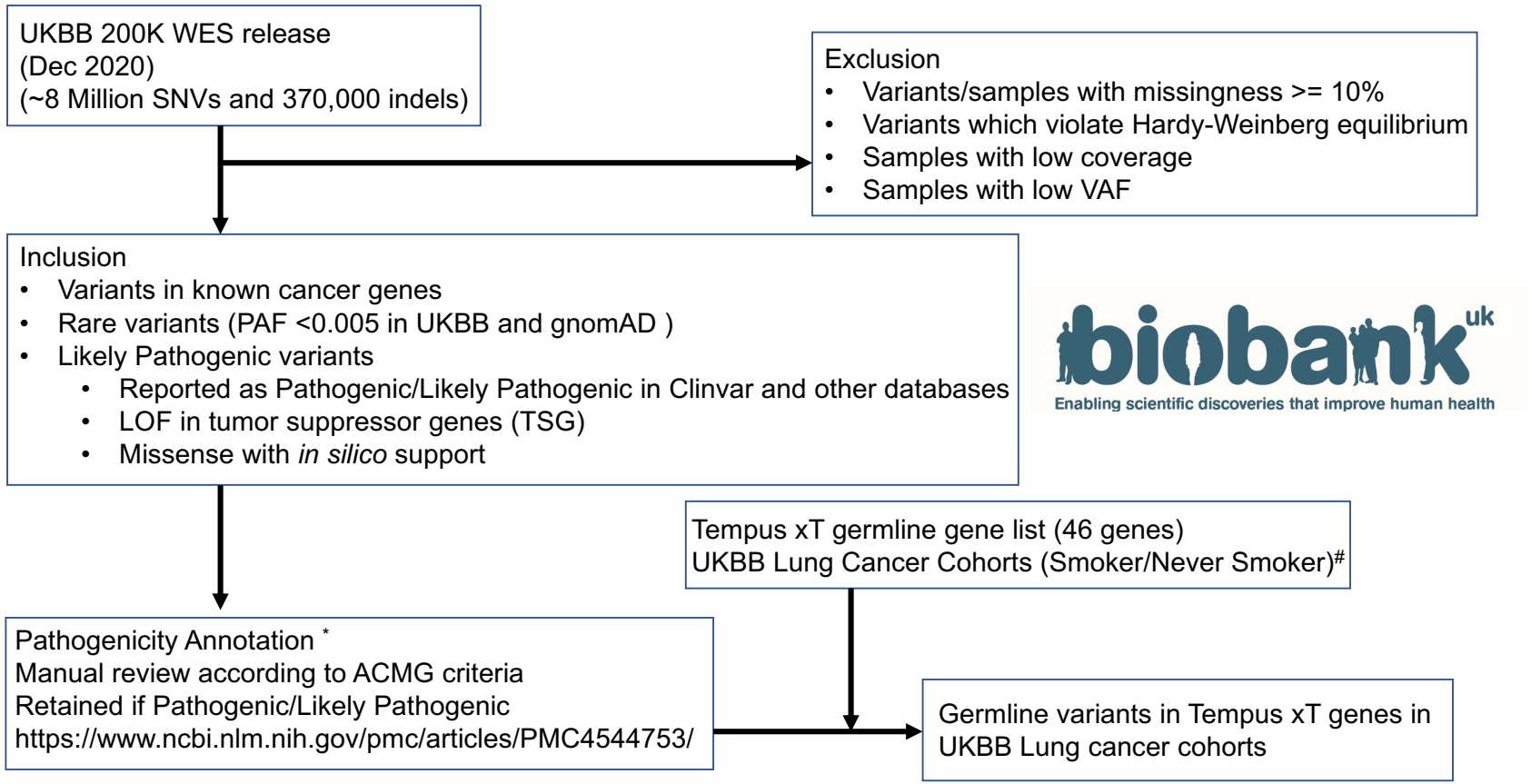
Germline Variants in 46 genes
UKBB Lung Cancer Samples



*Liu J and Bolton K, Wash U in St Louis
Zong X and Cao Y, WashU in St Louis

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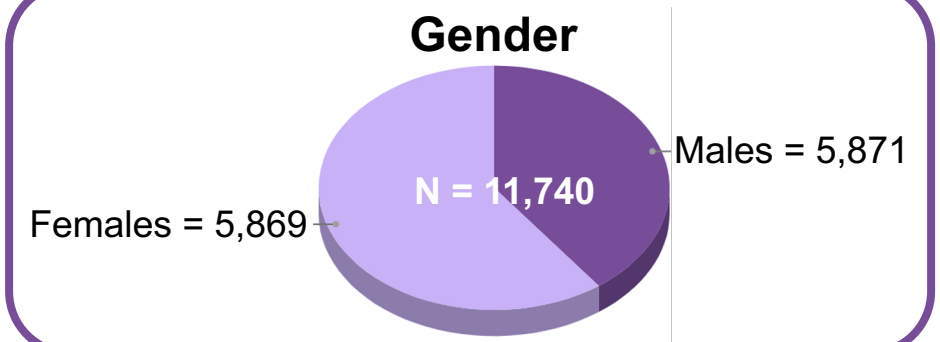
Demographic Characteristics
Tempus Cohort

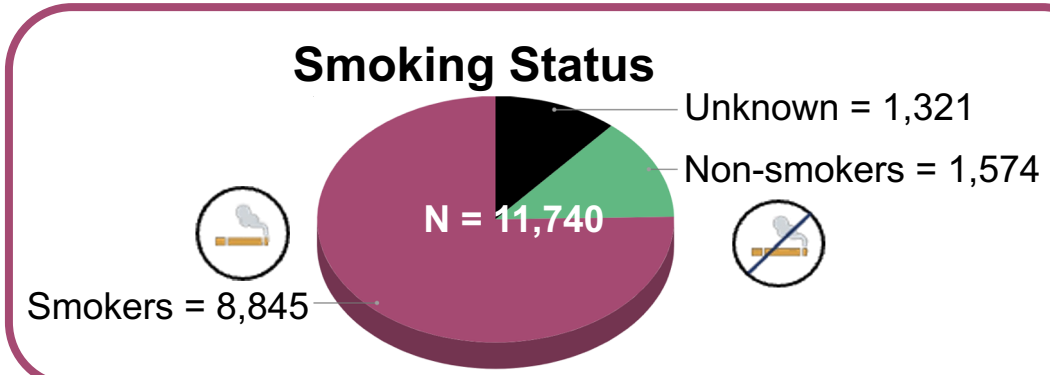
Gender



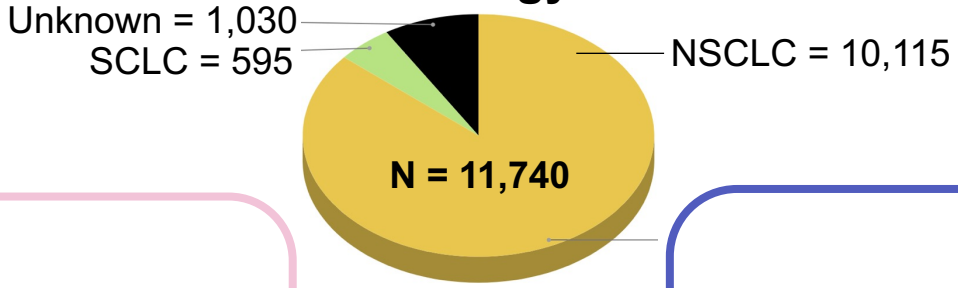
Median Age

68 years

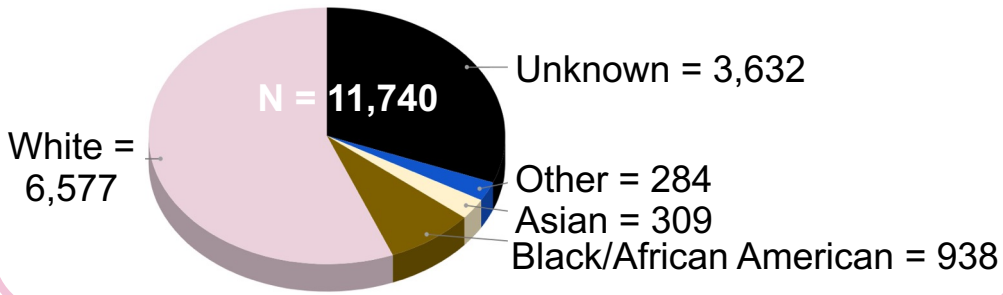
Smoking Status



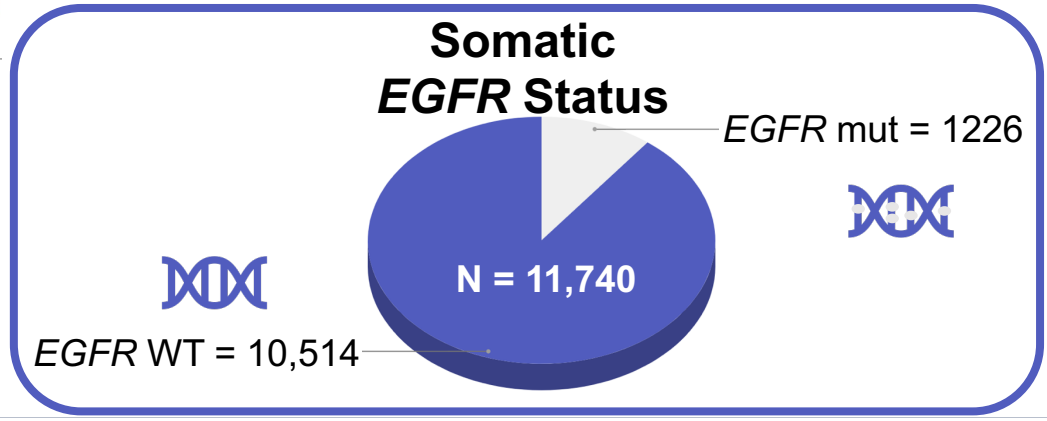
Histology



Race



Somatic *EGFR* Status



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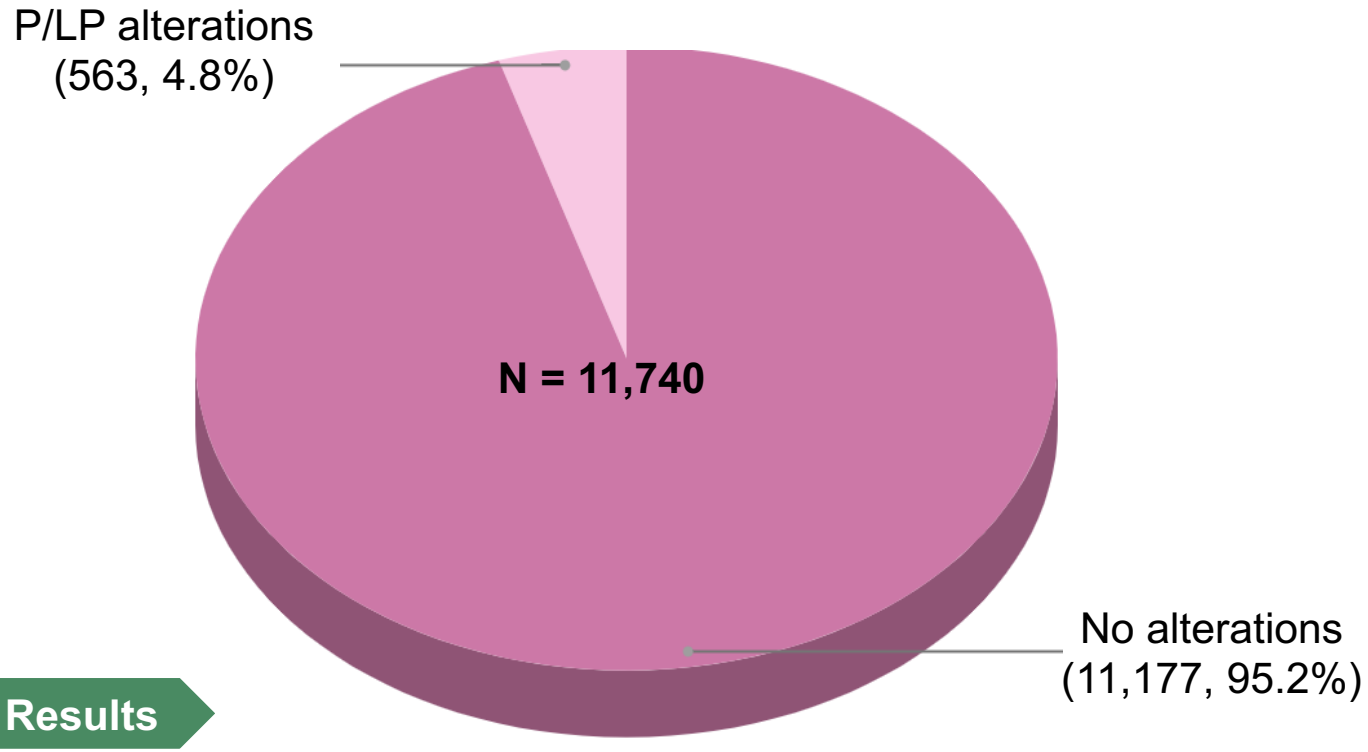
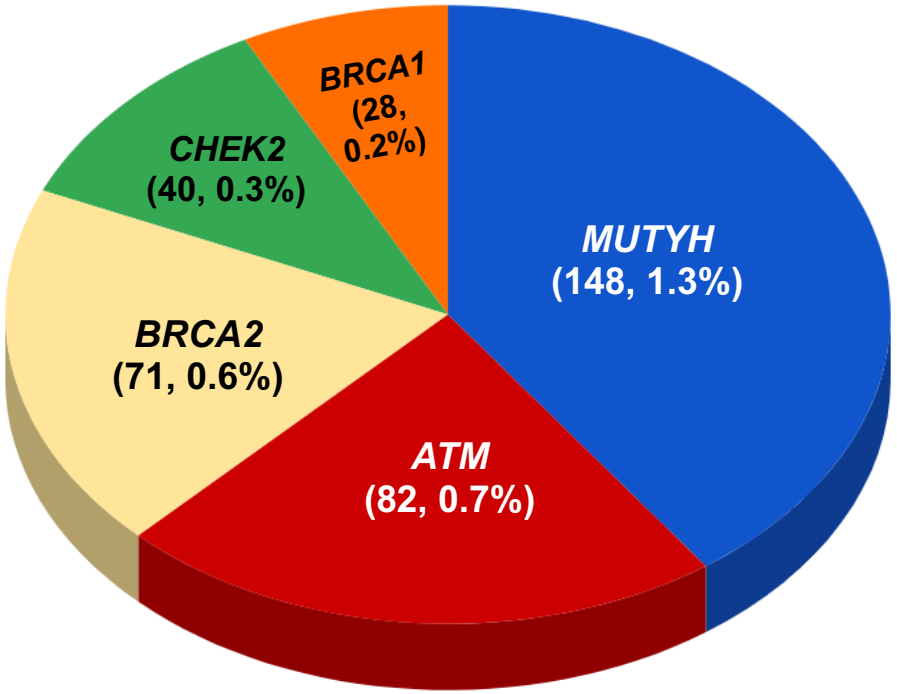
Germline Alterations in Patients with Lung Cancer Tempus Cohort

Patients with Pathogenic/Likely Pathogenic (P/LP) incidental germline findings



Five most prevalent P/LP incidental germline genes of the total population



Results

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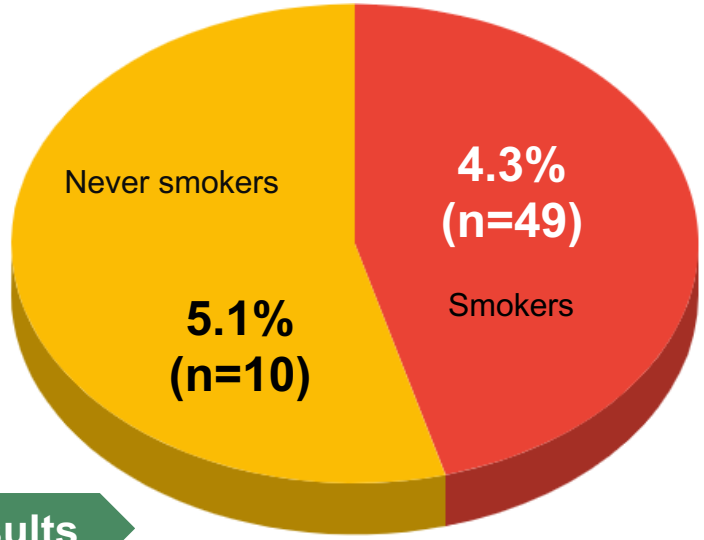
Frequently Altered Genes In Smokers And Never Smokers With Lung Cancer (UKBB)

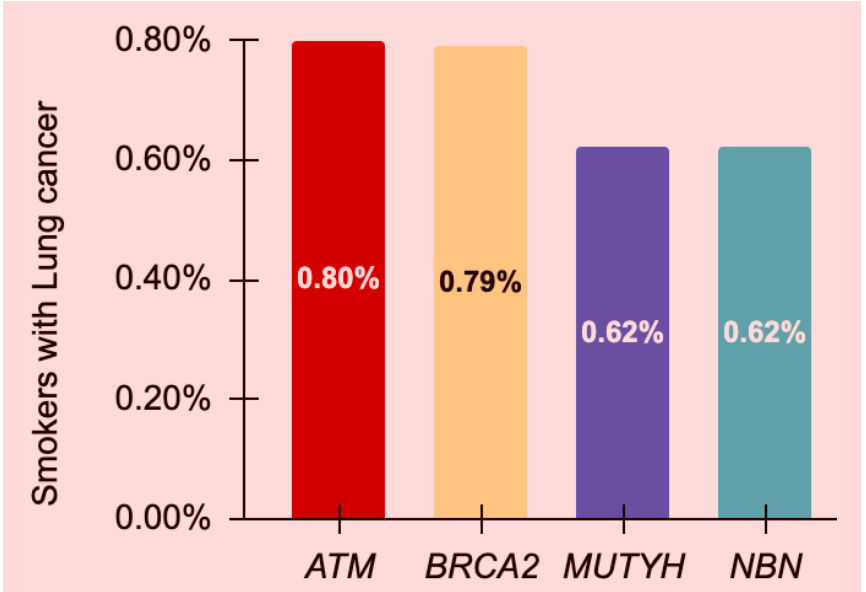
Never smokers with lung cancer (N=198)

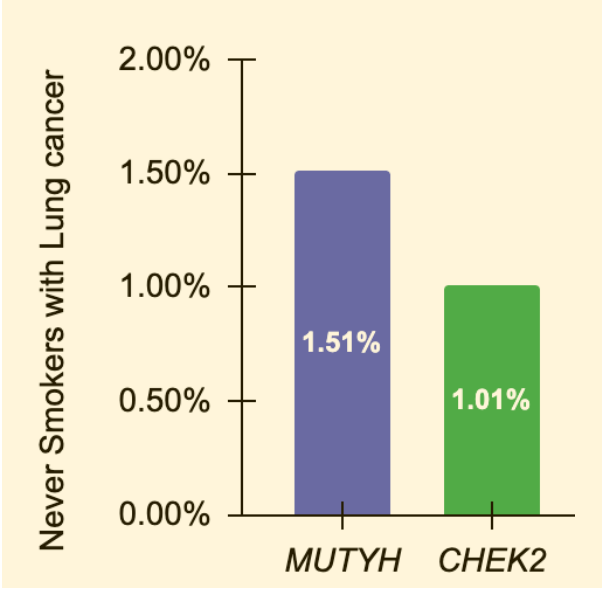
Smokers with lung cancer (N=1132)

% with P/LP germline alterations in the 46 gene panel



Most commonly mutated genes





Results

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Germline Alterations in Patients with Lung Cancer Smokers vs Non-smokers

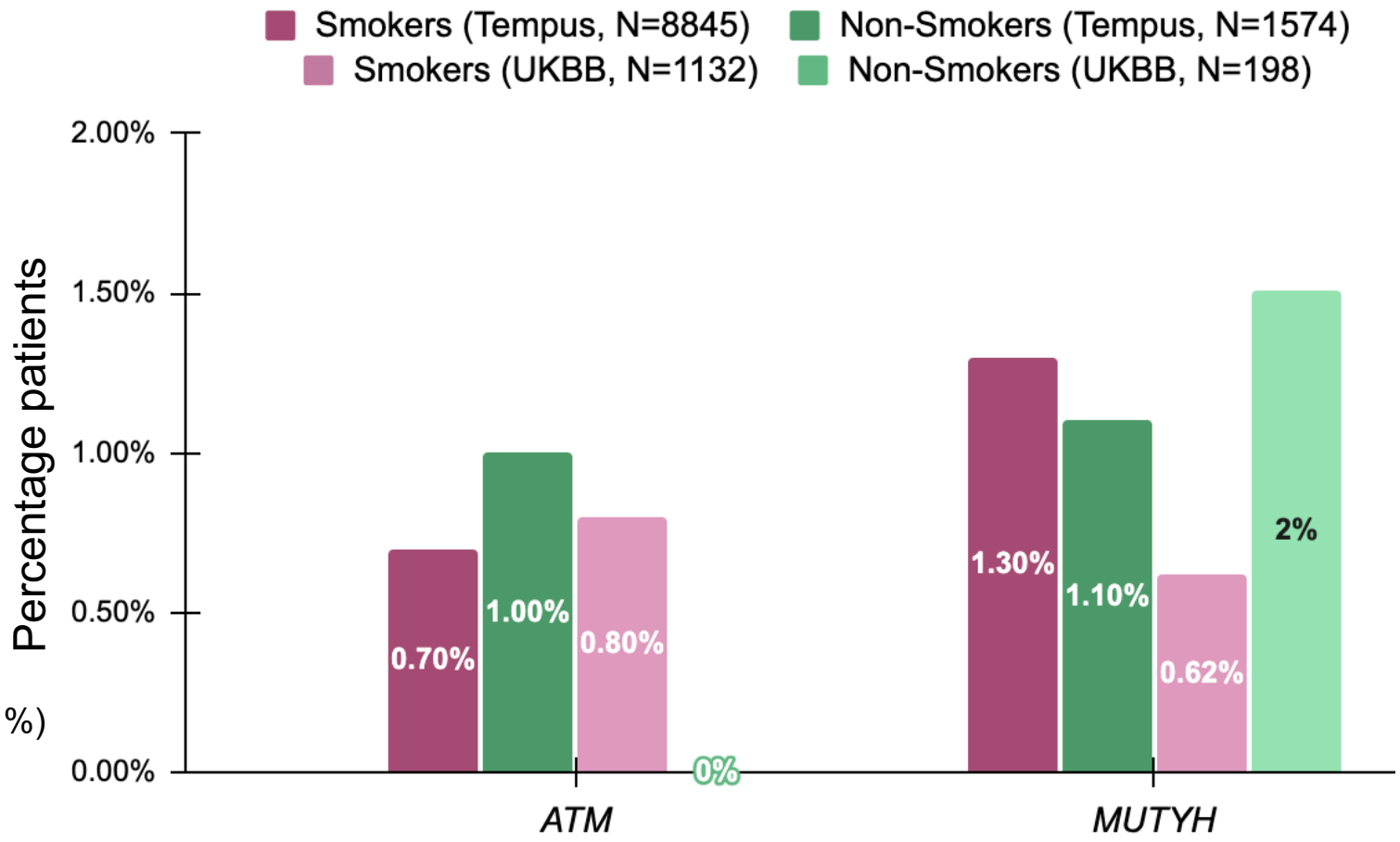
Tempus

Smokers vs Never smokers

UK BioBank (UKBB)

Smokers vs Never smokers

Note - *EGFR* discovered in smokers (<.1%) vs nonsmokers (0.4%) in Tempus data



Results

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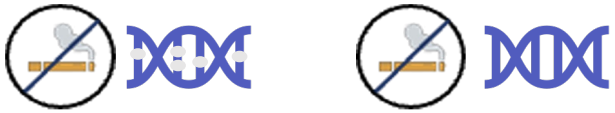
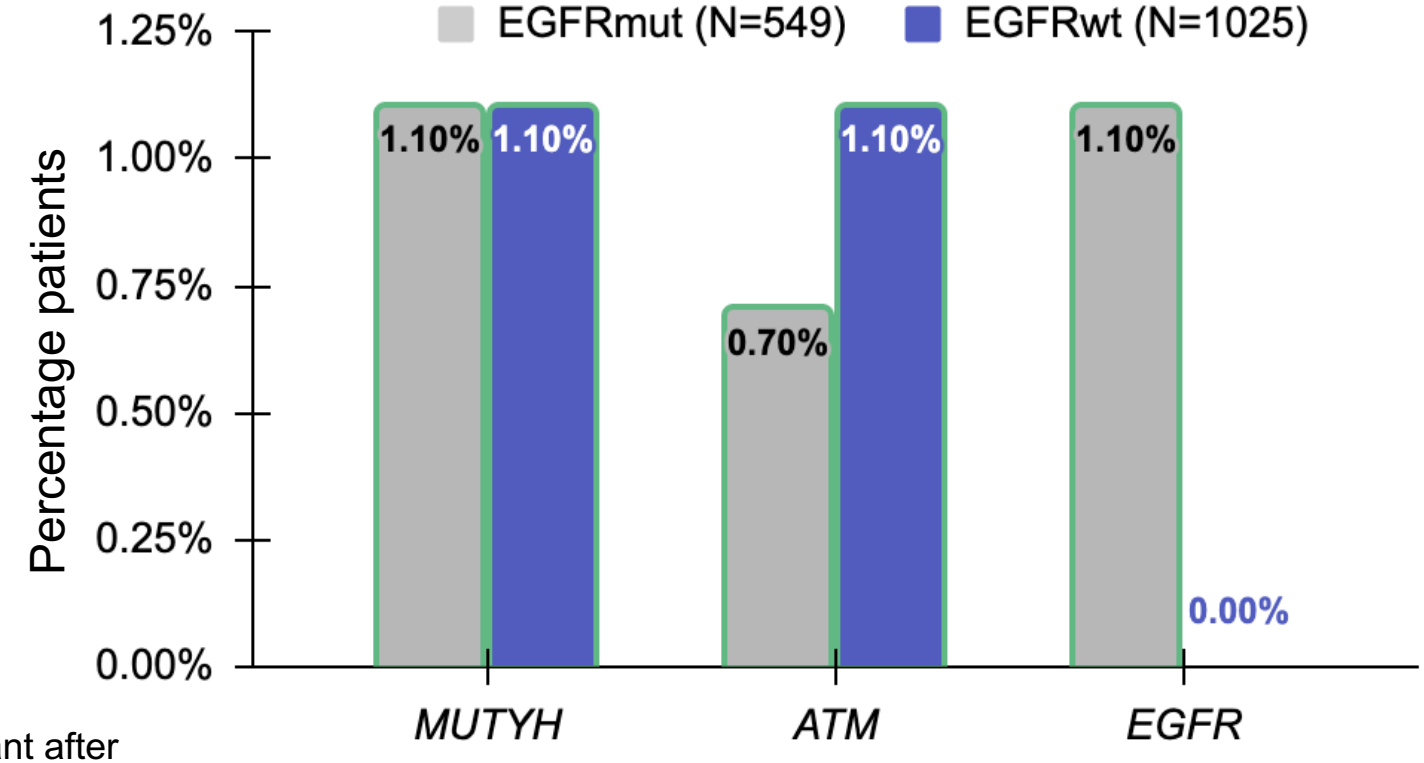
Germline Alterations in Never Smokers with Lung Cancer

EGFR Mutant vs *EGFR* Wild type Lung Adenocarcinoma

Tempus Never smokers (N=1574)
***EGFR* mutated vs *EGFR* WT**





Results

Note - Germline EGFR was significant after FDR adjustment ($q < 0.037$) in this population

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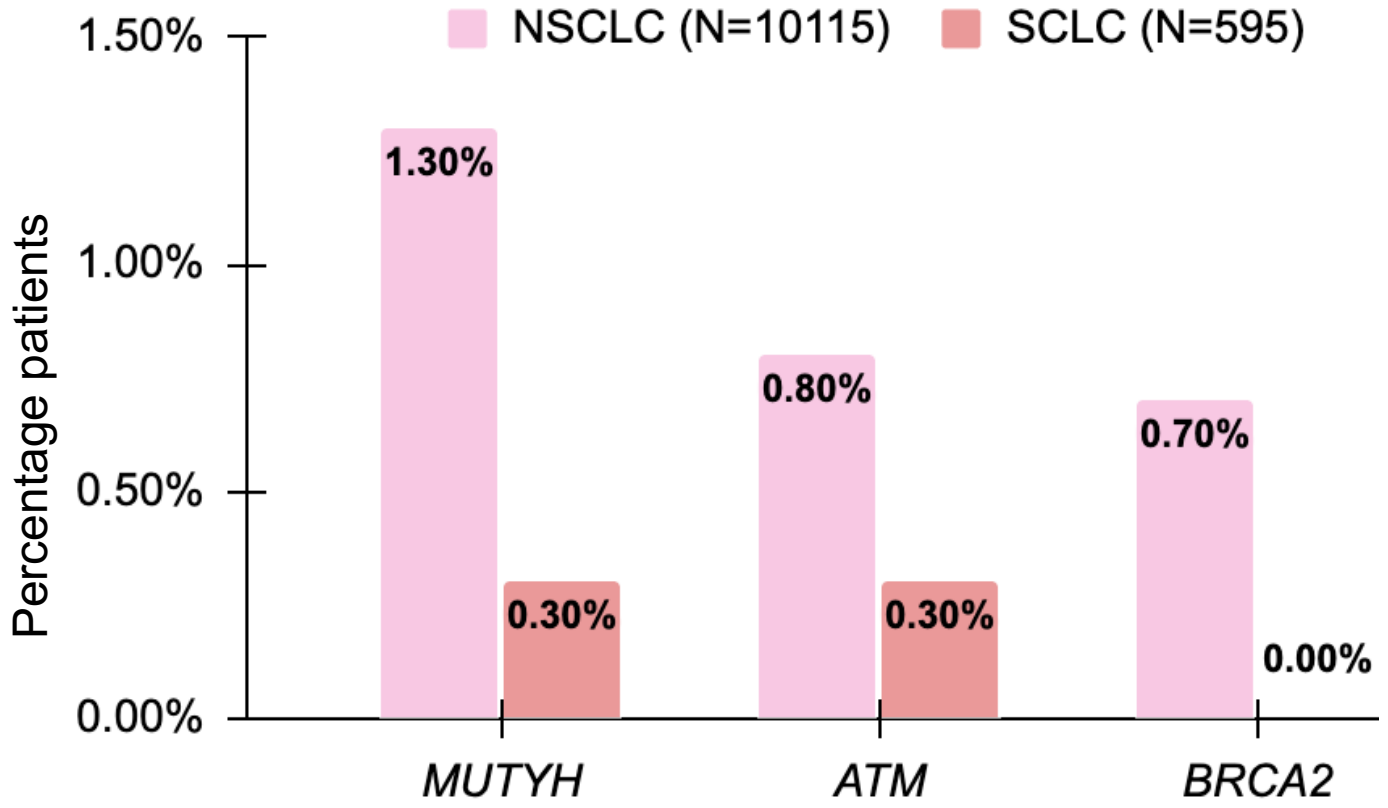
Germline Alterations in Patients with Lung Cancer

NSCLC vs SCLC

Tempus
Non-Small Cell Lung Cancer (NSCLC)

vs

Small Cell Lung Cancer (SCLC)



Results

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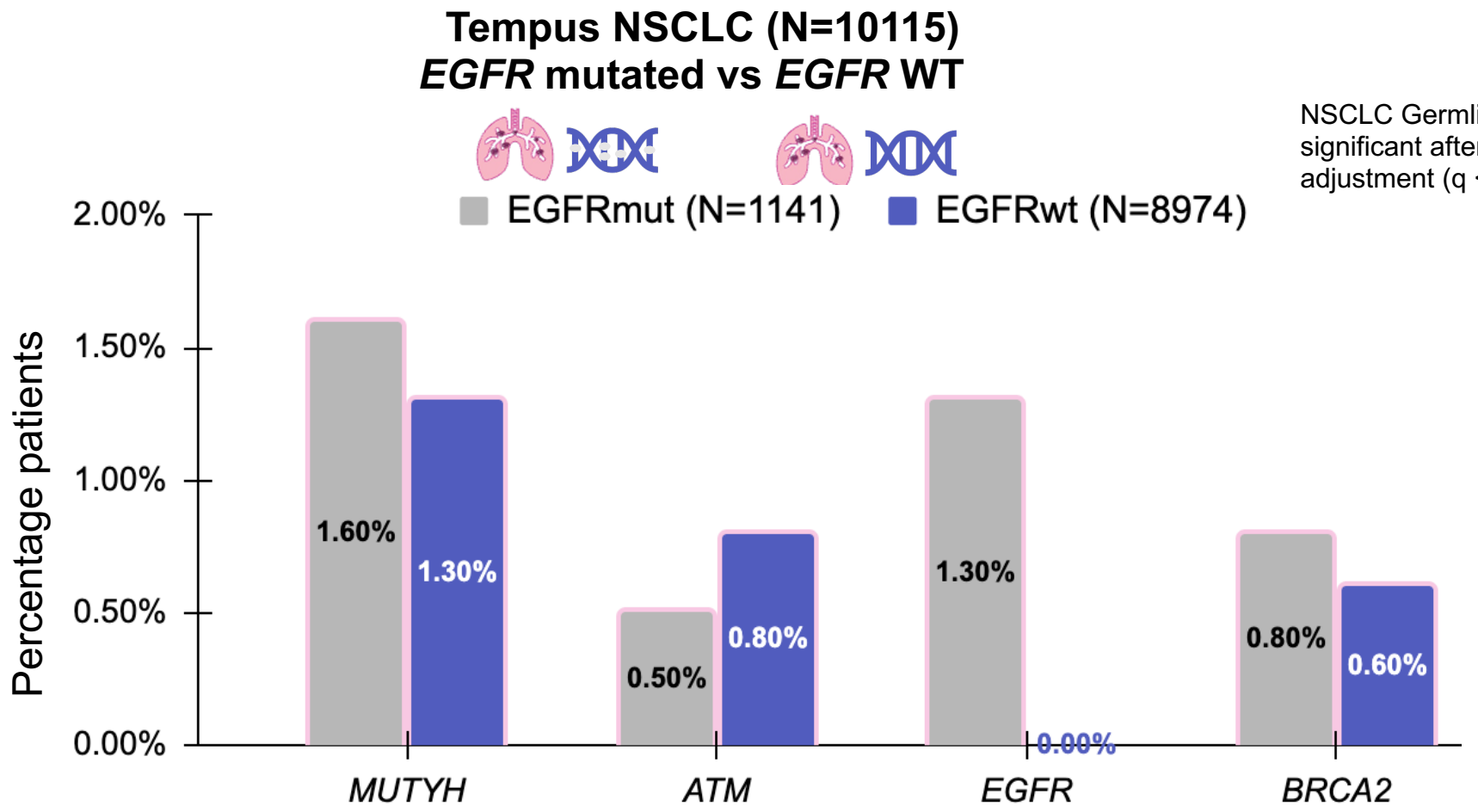
Commonly Altered Germline Genes in Patients with EGFR mutant Lung Cancer



NSCLC Germline EGFR was significant after FDR adjustment (q < 0.001)

Results

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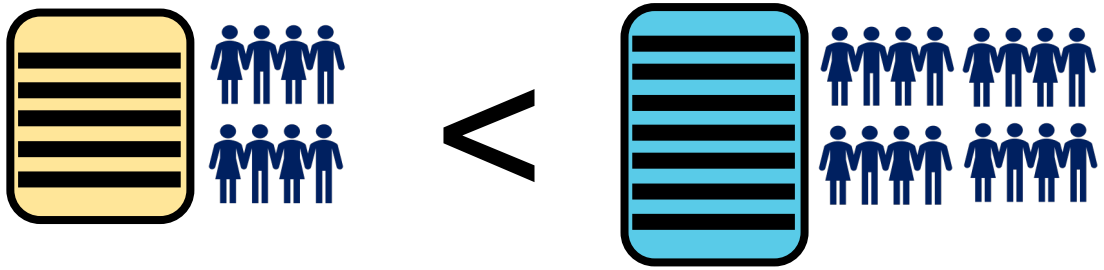
Limitations To Be Addressed In Future

- This analysis included 46 genes of common hereditary genes, larger panels may enable the capture of more patients

46 hereditary gene panel in this study

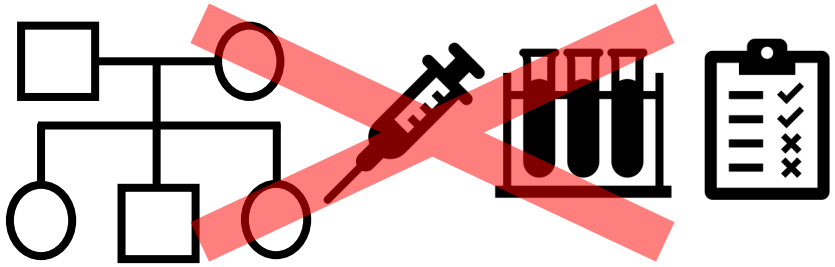


Larger panel capturing more patients

- This analysis lacked zygosity assessment of MUTYH

- This analysis lacked information on family history and follow up confirmatory testing and genetic counseling results

Family history & Testing



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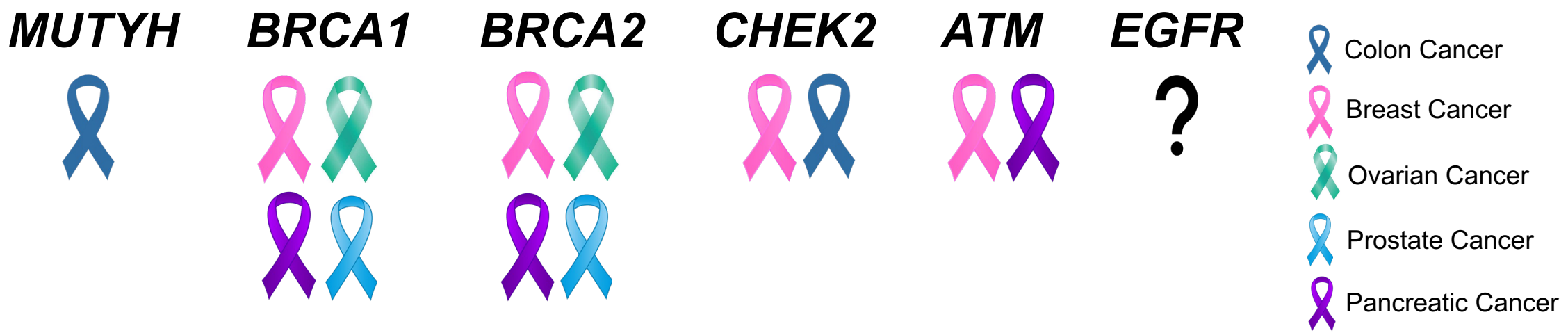
There Are No Current Guidelines For Those With Lung Cancer Or Germline *EGFR* Alterations

- Identification of germline findings in lung cancer patients can transcend other cancer types and have clinical implications for both the patient and family
- Germline EGFR alterations do not have screening guidelines but should be further studied to determine treatment implications, overall survival, and family impact



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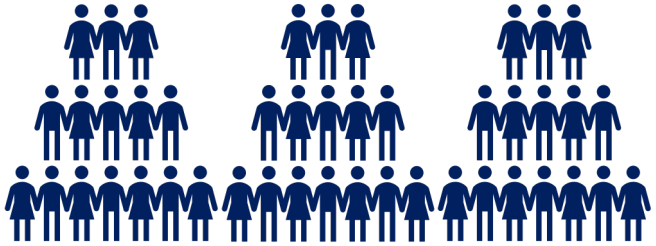
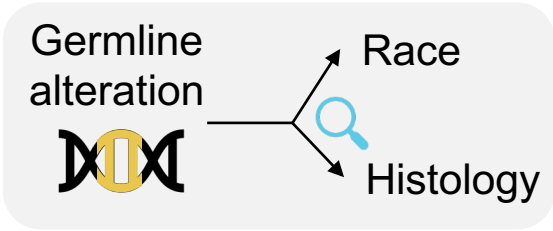
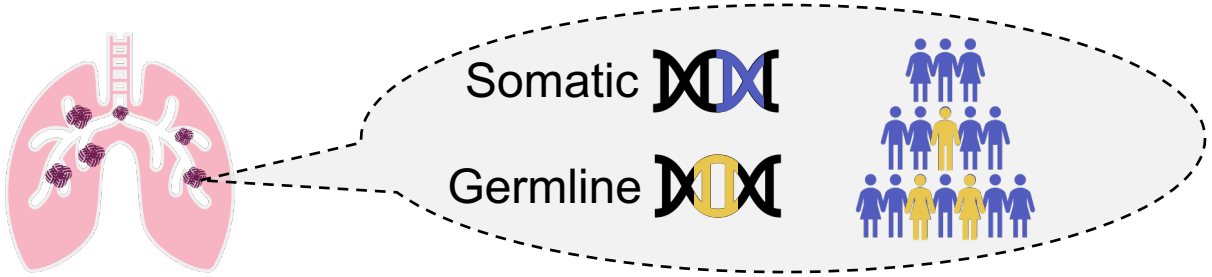
Key Takeaways

1. The largest analysis of germline alterations in cancer-predisposing genes across **histologies** of lung cancer

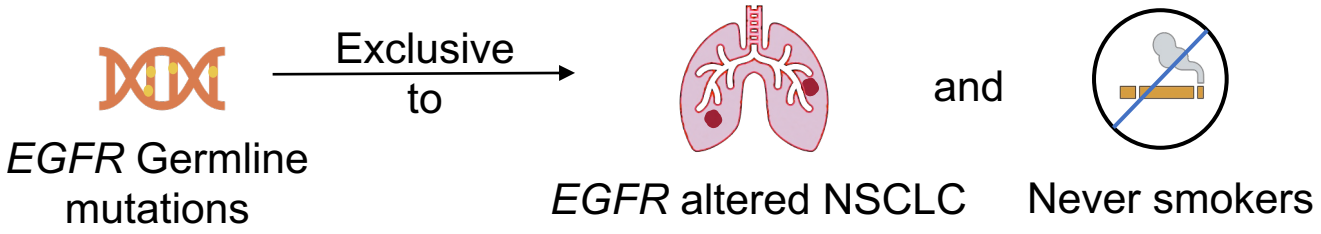




2. Germline alterations in cancer-predisposing genes occur in 5% of patients with lung cancer



3. *EGFR* germline mutations are exclusive to somatic *EGFR* altered NSCLC, and never smoker populations



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