Rolul testărilor genetice în diagnosticul pacienților simptomatici și în gestionarea opțiunilor terapeutice în Cancerul Bronhopulmonar

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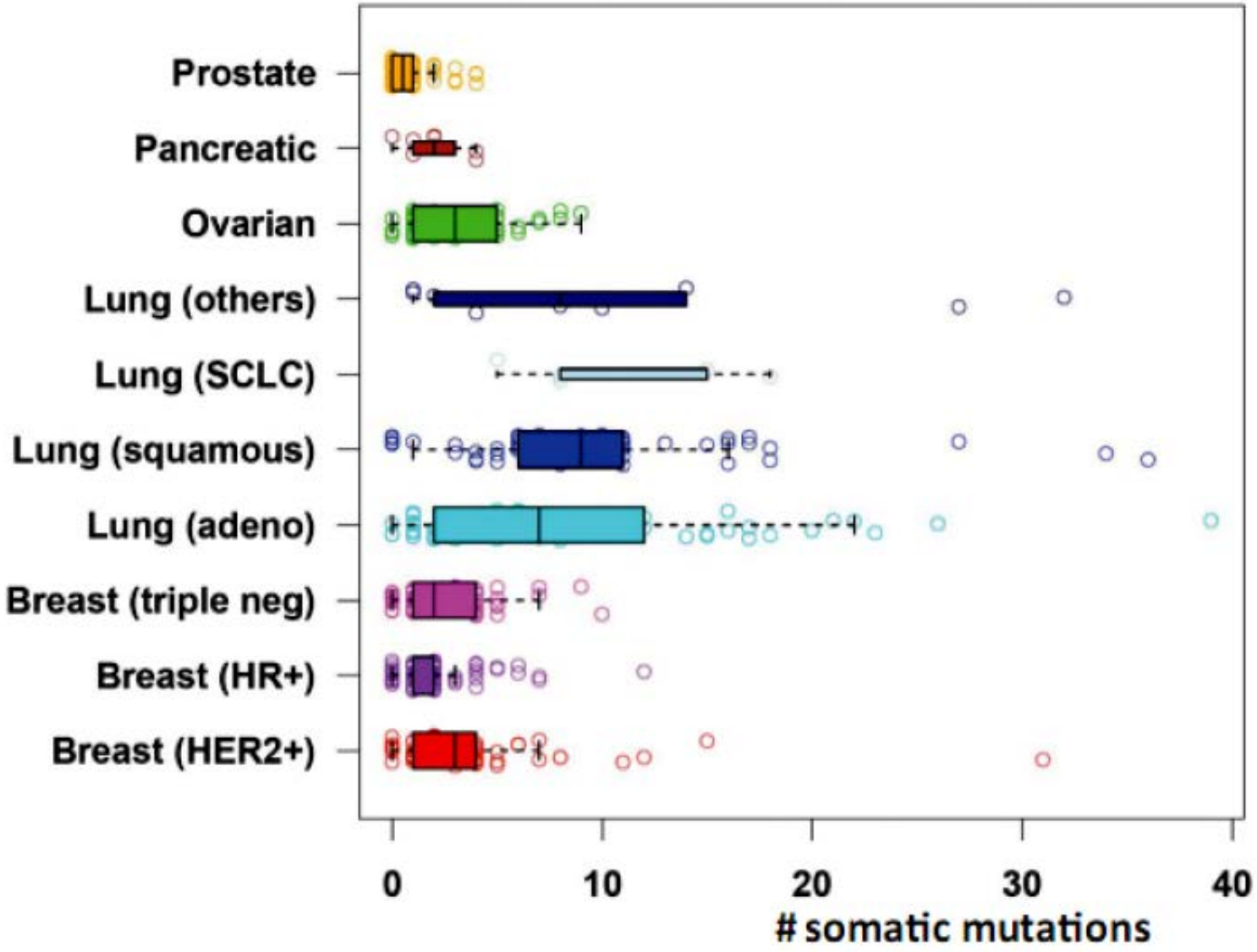
Rolul geneticii in oncogeneza

Prevalenta mutatiilor somatice in diverse tipuri de cancer



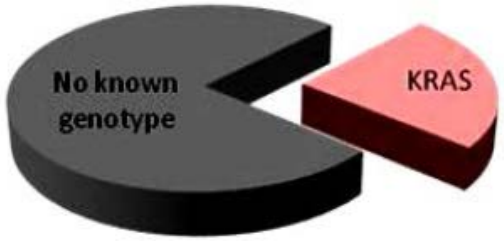
Introducere

- Cancerul bronhopulmonar - cea mai comuna cauza de deces la nivel mondial – peste 1 milion de morti anual.
- Supravietuirea la un an s-a imbunatatit, iar cea de la 5 ani a ramas relativ neschimbata in ultimii 30 de ani (de la 12 la 16%)
- Descoperirile noi din genetica cancerului pulmonar spera sa modifice aceste date.
  - S-a descoperit ca cancerul pulmonar are mutatii specifice ce stimuleaza cresterea maligna la nivelul
    - Oncogenelor – care obtin castig de functie - activate
    - Genelor supresoare de tumori - care nu mai functioneaza corespunzator. - inactivate

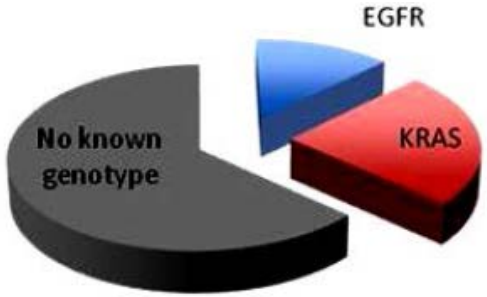
Evolutie temporala

- 1980 – 2000 in NSCLC cercetarile au fost centrate pe oncogena Kirsten rat sarcoma *(KRAS)* si proteina 53 *(p53)* genes
- In 2004, cercetarile au fost centrate pe gena epidermal growth factor receptor *(EGFR)*, un receptor membranar tirozin kinazic, care este responsabil de cresterea celulara, identificat in special la adenocarcinoame.
- In 2007, cercetarile au fost centrate pe o translocatie care asociaza fuziune genica intre echinoderm microtubule-associated protein- like 4 *(EML4)* si anaplastic lymphoma kinase *(ALK).*
- Dupa 2007 cercetarile au identificat si alte mecanisme, ceea ce a dus la urmatoarea distributie a alterarilor genice

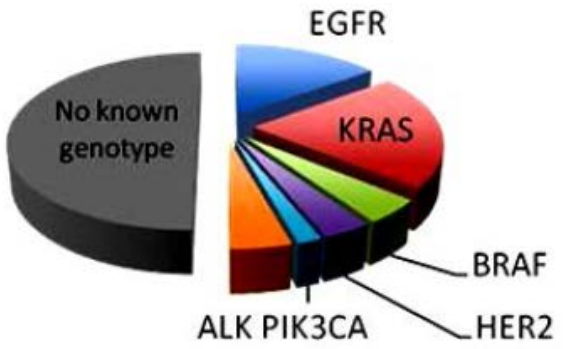
Evolutia identificarilor alterarilor genomice in adenocarcinomul bronhopulmonar



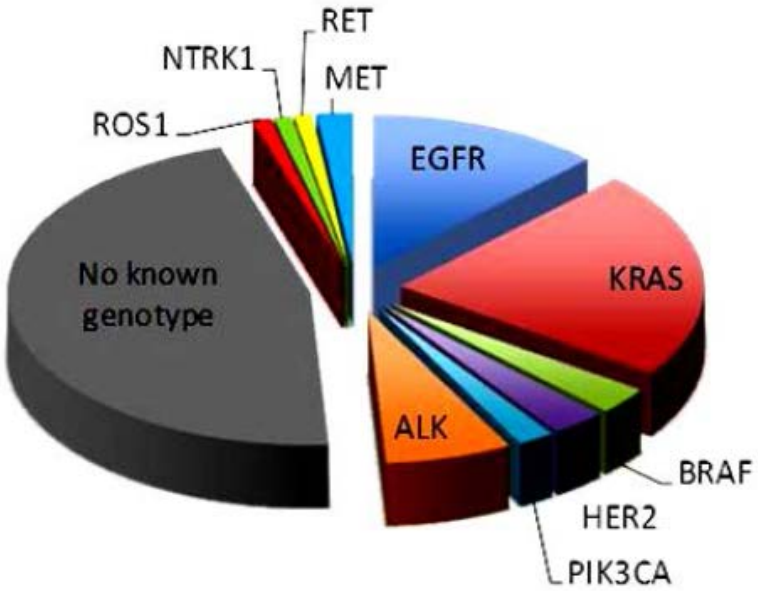
1984 - 2003



2004

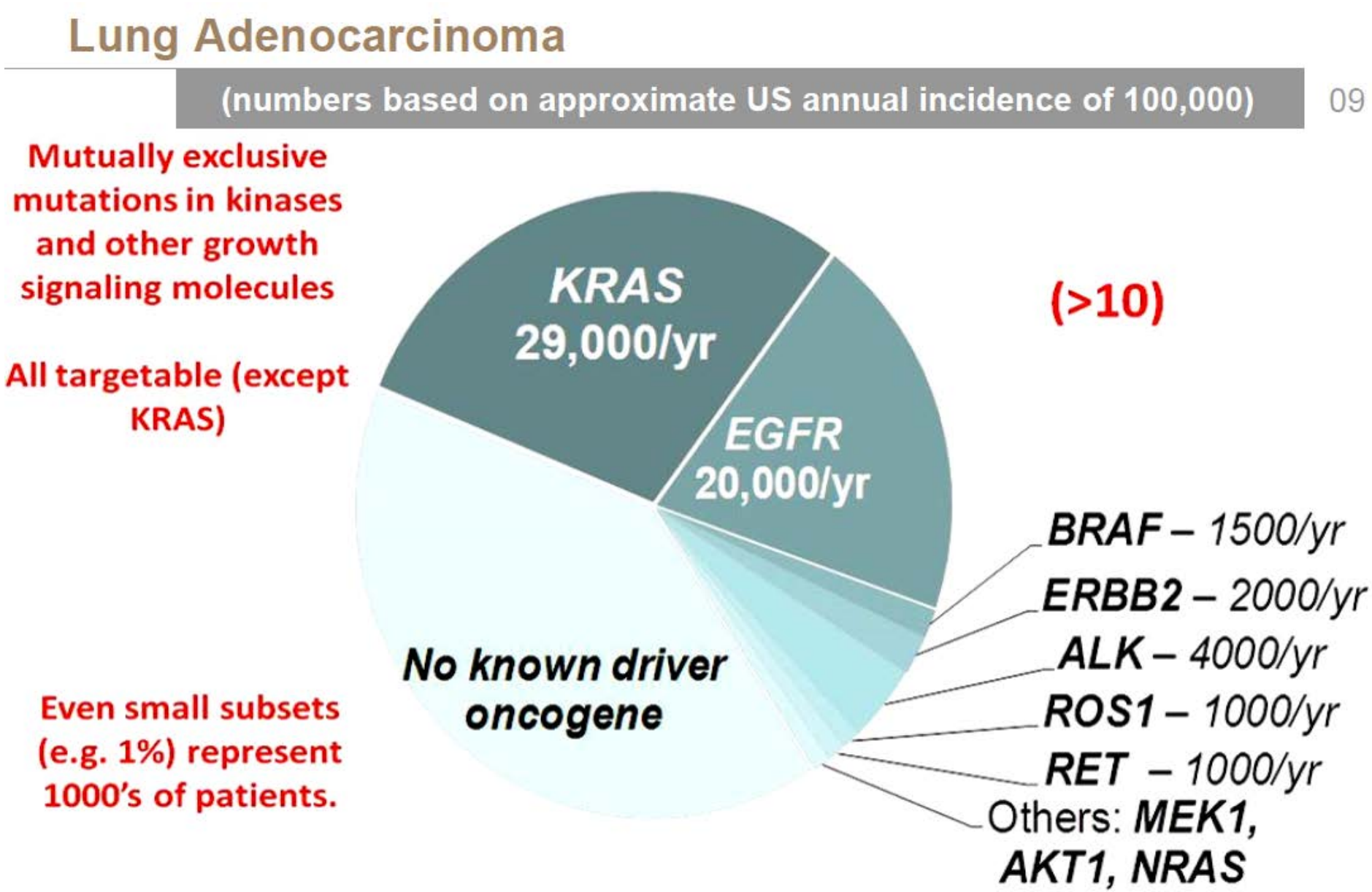


2009



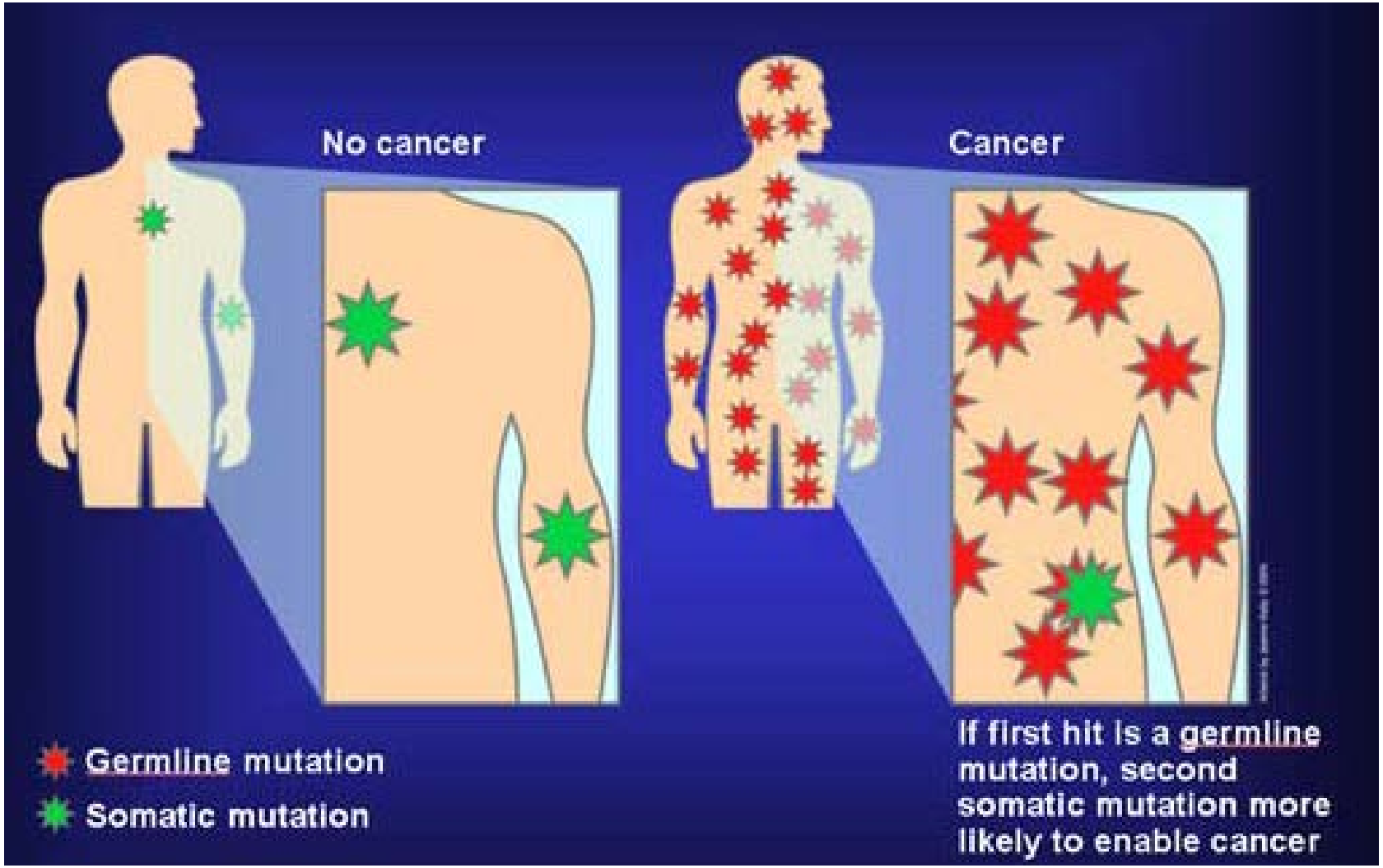
2014

Incidenta modificarilor genetice indentificate



1971, Dr. Alfred Knudson

Ipoteza „celor doua lovituri”



1. **Mutatie germinala** mostenita
Care determina risc mare de a dezvolta cancer pe parcursul vietii
   - Cancere multiple (tumori sincrone)
   - Diagnostic la varsta tanara
   - Mai multe cazuri in familie

2. Mutatie somatica dobandita
In urma expunerii la factori mutageni

Asocierea celor doua tipuri de modificari duce la aparitia cancerului

Categorii de teste genetice

Mutații Somatice

- Analizeaza genele de la nivel **tumoral** – proba parafinata
- **Analizeaza ADN-ul tumoral liber circulant** – din sangele periferic (Biopsia Lichida) – poate oferi informatii referitoare la
  - Selectia schemei terapeutice,
  - Raspunsul la tratament
- Analizeaza ADN la diagnostic – SCAN
- Analizeaza modificarile survenite in cursul terapiei - MONITOR
- „Second Hit”

Mutații Germinale

- Analizeaza genomul pacientului – evaluarea **genelor de risc mostenite** in familie – riscul de a dezvolta un cancer pe parcursul vietii
- Evalueaza riscul membrilor **familiei**
- „First hit”

Farmacogenetică

- analizeaza genele-cheie care afectează modul în care reacționează organismul pacientului la medicamente, oferind **informatii despre doza si despre medicamentul cel mai eficient** pentru acesta.
- identifica rapid tratamentele potrivite
- evita sau minimiza efectele adverse.

Mutații Germinale

- Oncogene - proto-oncogene **activate**
- Proto-oncogenele sunt gene ce intervin in proliferarea si diferentierea celulara. Mutatii la nivelul acestor gene determina supraexprimarea oncoproteinelor si stimularea necontrolata a diviziunii celulare.
- Gene supresoare de tumori inhiba procesele de diviziune celulara, care au loc intr-o maniera necontrolata
  - **Caretaker –** asigura stabilitatea ADN-ului si repararea lui, iar mutatiile acestor gene permite acumularea de mutatii
  - **Gatekeeper –** regleaza cresterea celulara, inhiba progresia celulara si inducerea apoptozei.
  - **Landscaper –** gene reglatoare care relationeaza cu factorii de mediu, care induc proliferare necontrolata

Gene de risc pentru Cancerul Pulmonar
Variante genice de risc ce pot fi dobandite

- Testarea ADN – ului germinal – panele Multi-Cancer

  Secventiere ADN si evaluare CNV

- Gene de risc
  - BRCA2, CDKN2A, EGFR, FAM111B, TP53, CHEK2, ATM, TRK1, EXT2, BRIP1, PALB2, *HER2*, *RET*, *BRCA1*, *PARK2*, *YAP1*, *TERT* , *CDKN2A*, *MET*, *NBN.*

Mutații Somatice

- **Detectia mutatiilor** in exonii 18, 19, 20, 21 in gena EGFR in cancerul pulmonar (**tesut inclus in parafina)**
- **Biopsia lichida** poate detecta pacientii cu risc crescut de a avea mutatii somatice – cancer
- **Biopsia lichida** poate identifica pacientii care sunt eligibili pentru terapii tintite sau care sunt rezistenti la anumite terapii
- Gene cancer pulmonar ALK, BRAF, EGFR, ERBB2, KRAS, MAP2K1, MET, NRAS, PIK3CA, ROS1, TP53

Farmacogenetică

- **Gene implicate in farmacodinamica** - indica efectul pe care îl are un medicament asupra organismului. Ajută la informarea cu privire la selectarea medicamentelor care sunt sigure (care nu dau efecte secundare sau care dau efecte secundare foarte scăzute) și care sunt eficiente în ameliorarea simptomelor. Analiza acestor gene ofera informatii si despre terapii sau suplimente .

- **Gene implicate in farmacocinetica** - indică efectul pe care corpul îl are asupra medicamentului, ele determinând: distribuţia, metabolizarea si durata de eliminare a medicamentului din organism. Aceste gene informează despre doza optima.

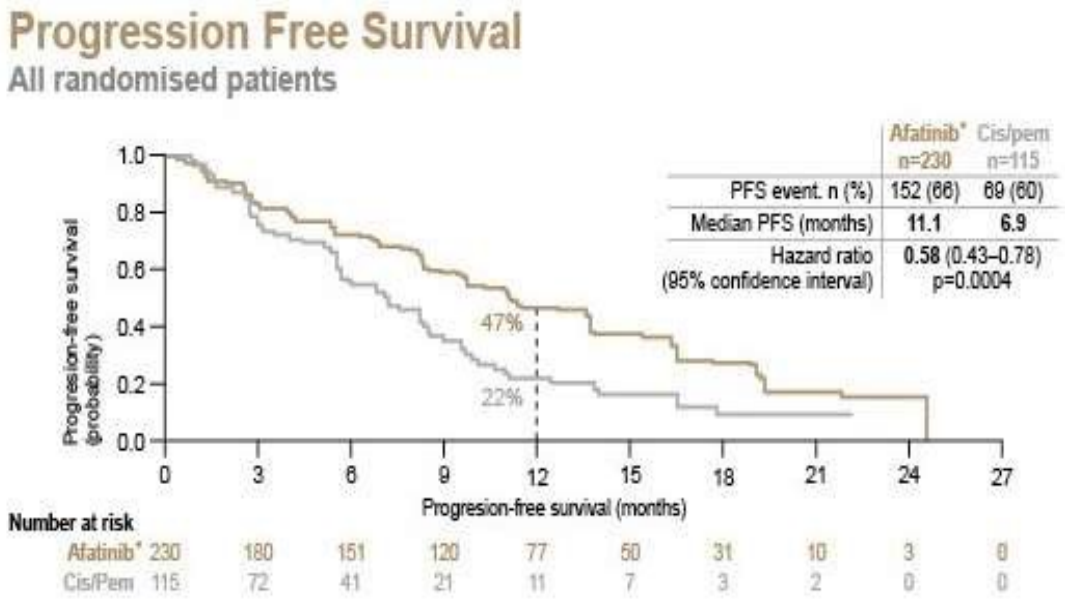
Terapie tintita - EGFR

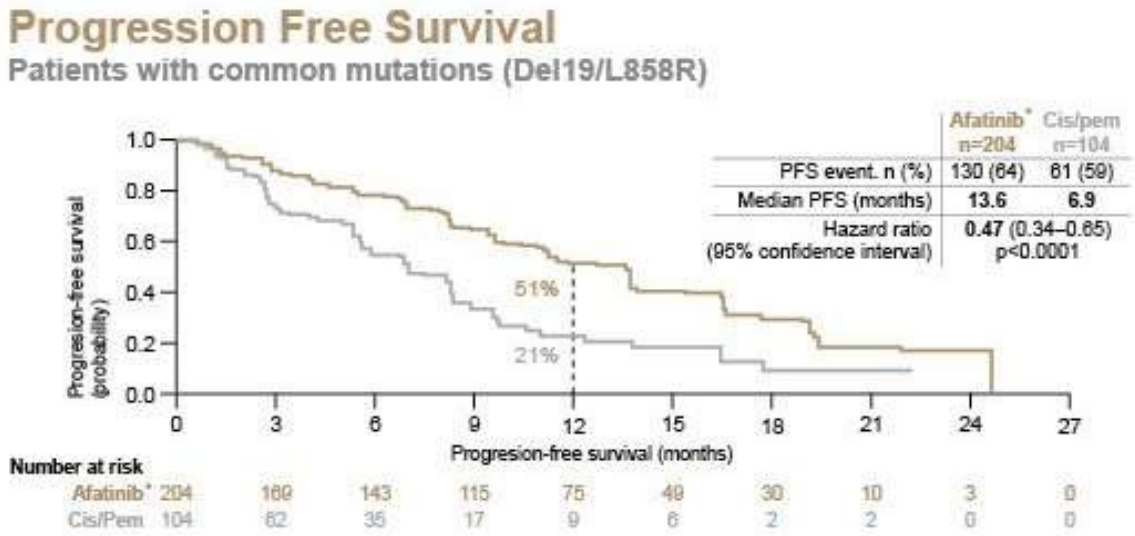
- Mutațiile genei EGFR sunt mult mai frecvent întâlnite la femeile nefumătoare de origine est-asiatică cu histologie cu adenocarcinom.
- Incidența mutațiilor EGFR la asiatici este de 25% până la 35%,
- Incidența pacienților din America de Nord și Europa de Vest este de aproximativ 15%.
- **Erlotinib, Geftinib, Crizotinib sunt inhibitori ai TK.**
  - Un număr mare de studii retrospective au demonstrat că rata de răspuns a pacienților cu mutație EGFR pozitivă la TKI EGFR depășește 60%.
- **Anticorpi monoclonali direcționați împotriva EGFR.**
  - Cetuximab, matuzumab, necitumumab și panitumumab

Rezistenta la terapia cu TKI

- Practic toți pacienții care inițial răspund la terapia EGFR TKI vor dezvolta rezistență și vor suferi o recidivă clinică.
- Aproximativ 50% din cazurile de rezistență dobândită TKI sunt atribuite unei mutații secundare a genei EGFR, mutația punctului treonină la metionină la aminoacidul 790 (**T790M**) în exonul 20.
- **Afatinib** este medicamentul de electie.

Lux Lung 3 Trial





Studiul LUX-Lung 3 a investigat eficacitatea și siguranța afatinibului în comparație cu pemetrexed / cisplatin la pacienții cu adenocarcinom pulmonar în stadiul IIIB / IV cu mutație EGFR.

Tratamentul cu afatinib a dus la o SFP semnificativ prelungită comparativ cu pemetrexed / cisplatin (mediană 11,1 vs. 6,9 luni).

Blocarea secvențială este o altă abordare pentru tratarea rezistenței TKI.

Terapie tintita - KRAS

- 20 - 40% din pt cu NSCLC are mutație RAS.
- 90% sunt mai frecvent la fumători - adenocarcinom
- Asociaza prognostic mai prost.
- Abordările terapeutice actuale care vizează RAS se încadrează în trei mari categorii:
  - inhibarea sintezei proteinelor RAS,
  - alterarea localizării membranei RAS - Salirasib
  - inhibarea moleculelor efectoare în aval de RAS mutant - Sorafenib

Farmacogenetica – in dezvoltare
Dovezi stiintifice

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ORIGINAL ARTICLE

Pharmacogenetics of advanced lung cancer: Predictive value of functional genetic polymorphism *AGXT* Pro11Leu in clinical outcome?

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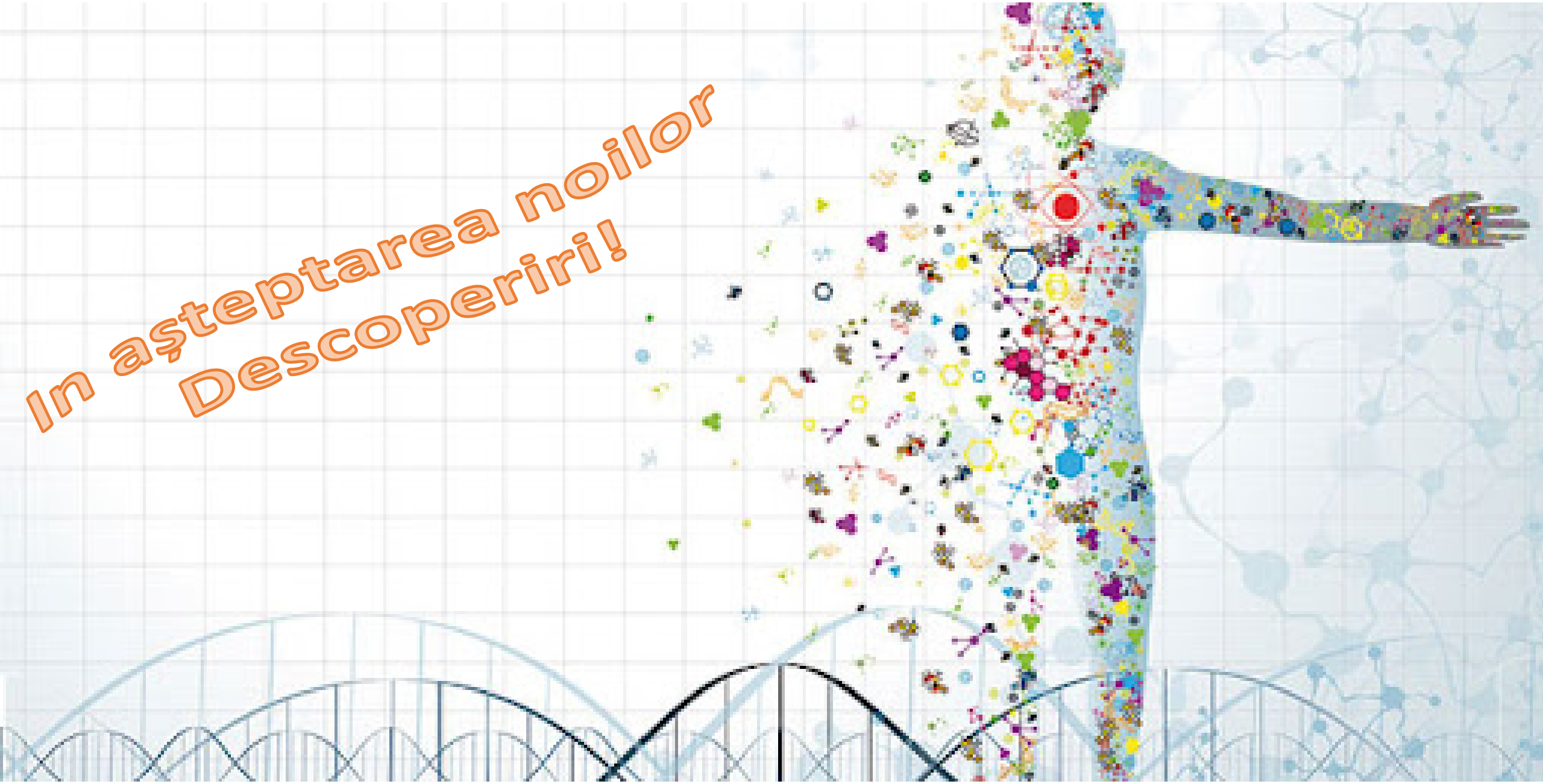
KEYWORDS
Non-small cell lung cancer;
Single nucleotide polymorphism;
Pharmacogenetics;
Cohort study

Abstract
Introduction: *AGXT* gene codes for the enzyme alanine glyoxylate aminotransferase, which is involved in hepatic peroxisomal metabolism of platinum-based chemotherapeutic agents. The association of genetic variant *AGXT* rs34116584 on the clinical outcome and response to chemotherapy of patients with non-small cell lung cancer (NSCLC) remains to be established. Our aim was to evaluate the association of functional *AGXT* gene polymorphism in NSCLC progression, considering as primary and secondary endpoint, progression free survival (PFS) and overall survival (OS), respectively.
Methods: Genotyping of the*AGXT* rs34116584 genetic polymorphism was performed by mass spectrometry on 168 DNA samples from patients with NSCLC (stages IIIA-IVB). Univariate survival analysis included the study of Kaplan-Meier curves with the Log-Rank test, while Cox regression was used as a multivariate analysis.
Results: Multivariate analysis showed shorter PFS for T carriers [HR = 2.0, 95% CI, 1.4–3.0, p < 0.0001] and shorter OS [HR = 1.8, 95% CI, 1.1–3.0, p = 0.017] globally, as well as in a subgroup of patients (n = 144) treated with first line platinum-based chemotherapy [HR = 2.0, 95% CI, 1.3–3.1, p = 0.001] and [HR = 1.8, 95% CI, 1.1–3.1, p = 0.026], respectively.
Conclusion: This polymorphism seems to have an impact on NSCLC progression, opening new perspectives for its inclusion as a pharmacogenetic predictor of response to platinum-based chemotherapy.

Table I. *Portrayal of the most important polymorphisms identified, their functional effect, the anticancer drugs involved and expected event(s).*

Gene polymorphism	Functional effect	Anticancer drugs involved	Observed event
MRP2 C2366T (16)	T allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
MRP2 C4348A (16)	A allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
MRP2 C-24T (17)	T allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
MRP2 C3972T (17)	T allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response and increased toxicity
MRP2 G1249A (17)	A allele is associated with decreased transporter activity	Cisplatin	Polymorphism associated with better treatment response
GSTP1 A313G (20)	G allele is associated with decreased enzyme activity	Cisplatin	Polymorphism associated with better survival and increased toxicity
GSTP1 A342G (19)	G allele is associated with decreased enzyme activity	Cisplatin	Polymorphism associated with better survival and increased toxicity
GSTM1 gene deletion (23)	Loss of function	Cisplatin	Polymorphism associated with better response to platinum drugs
GSTT1 gene deletion (24)	Loss of function	Cisplatin	Polymorphism associated with shorter survival
XRCC1 G28152A (31-37)	A allele is associated with decreased DNA repair activity	Cisplatin	Polymorphism associated with lower OS and response rate
ERCC1 C8092A (41-44)	A allele is associated with decreased DNA repair activity	Cisplatin	Polymorphism associated with better survival and increased toxicity
ERCC1 C19007T (45-46)	C allele is associated with decreased DNA repair activity	Cisplatin	Polymorphism associated with better survival
MTHFR C677T (48-52,70-74)	T allele is associated with decreased enzyme activity	Cisplatin, pemetrexed	Polymorphism associated with better response to platinum; Homozygous mutant shows increased PFS
MTHFR A1298C (49, 70)	C allele is associated with decreased enzyme activity	Cisplatin, pemetrexed	Homozygous mutant has shorter PFS
MDR1 C3435T (56-57,77)	T allele is associated with decreased transporter activity	Gemcitabine, vinorelbine	Polymorphism associated with worse response to gemcitabine; Lower risk of progression in patients treated with Vinorelbine
MDR1 G2677T (80)	T allele is associated with decreased transporter activity	Gemcitabine, vinorelbine	Polymorphism associated with increased toxicities and better OS and PFS in patients treated with Gemcitabine; Better response to Vinorelbine
CYP3A4*1B (89)	Polymorphism associated with decreased enzyme activity	Paclitaxel, vinorelbine	Polymorphism associated with response
CYP3A5*3 (88, 73)	Polymorphism associated with decreased enzyme activity	Paclitaxel, vinorelbine	Polymorphism associated with response
TTSER 28 bp VNTR (2R/3R) (68)	3R allele is associated with increased TS expression (increased enzyme activity)	Pemetrexed	Survival observed was significantly longer in patients with high expression genotype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