ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

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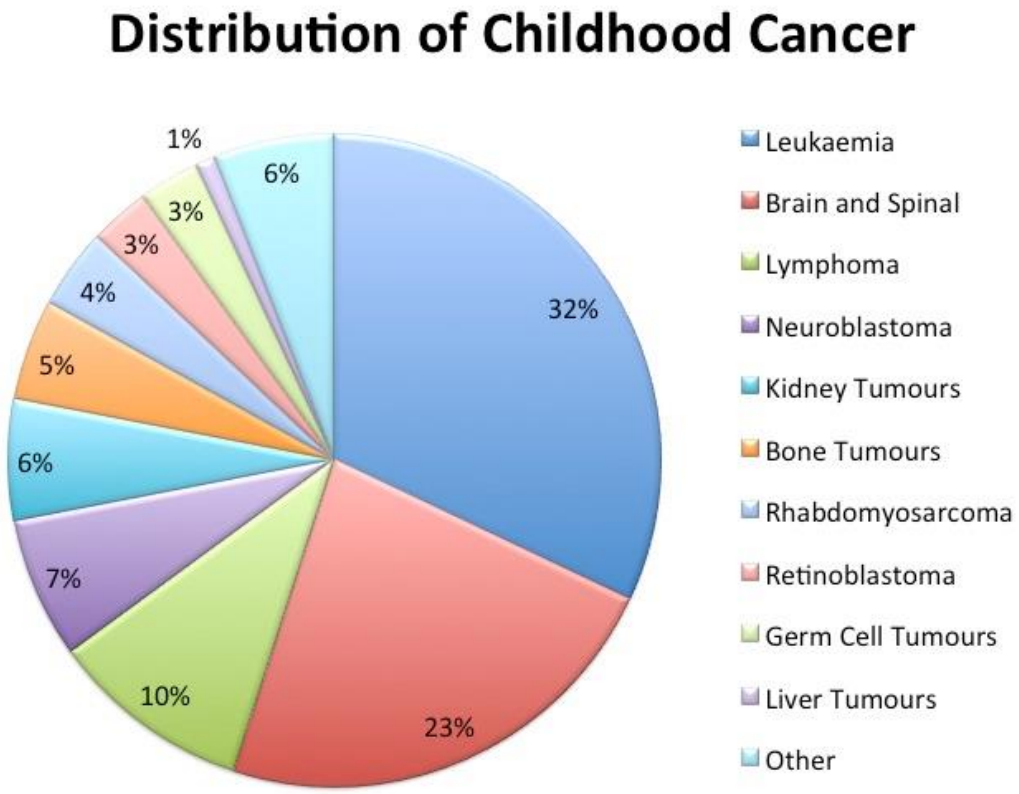
Τα Παιδιά Παθαίνουν Καρκίνο;

- 14 παιδιά ηλικίας 0- 15 ανά 100.000 παιδικού πληθυσμού και
- 20 έφηβοι ανά 100.000 πληθυσμού ηλικίας 15 έως 18 χρόνων
- 300-350 νέες περιπτώσεις / έτος

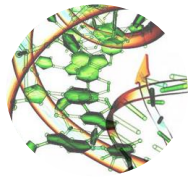


Γονιδιωματικη του Καρκινου

- Πρωτοστατεί στην εφαρμογή 'Ιατρική Ακριβείας'
- Η βιολογία του καρκίνου είναι πολύ πιο πολύπλοκη από τις αρχικές προβλέψεις

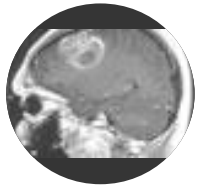
2000

Hallmarks of Cancer **δημοσίευση**



2005

Εγκαινιάζεται το πρόγραμμα Cancer Genome Atlas (TCGA)

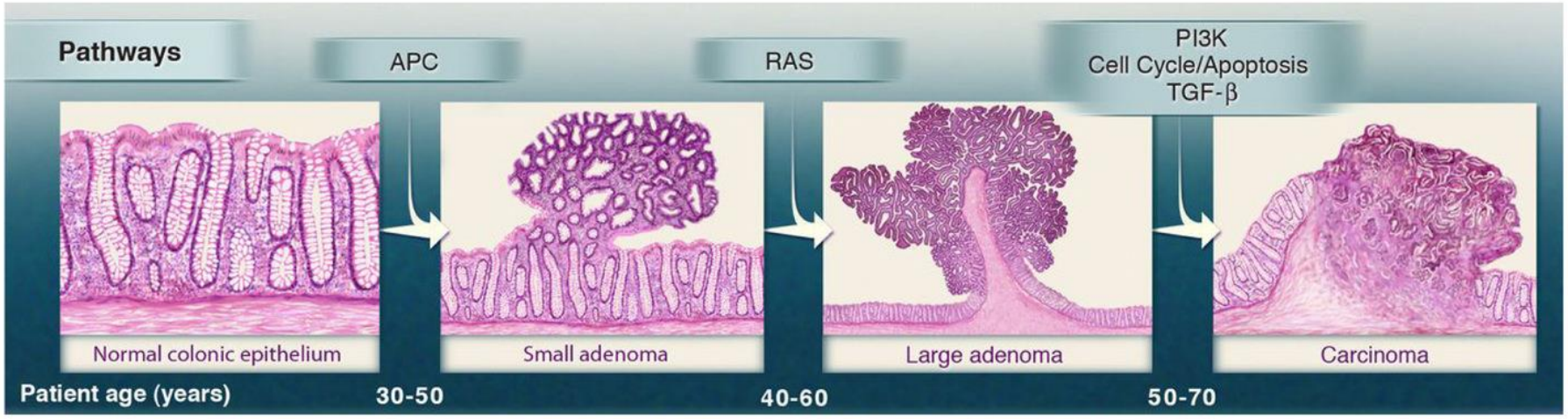


2010-2014

Γενετικοί υπότυποι γλοιβλαστώματος, καρκίνου στομάχου, κ.α. βάση αποτελεσμάτων του TCGA

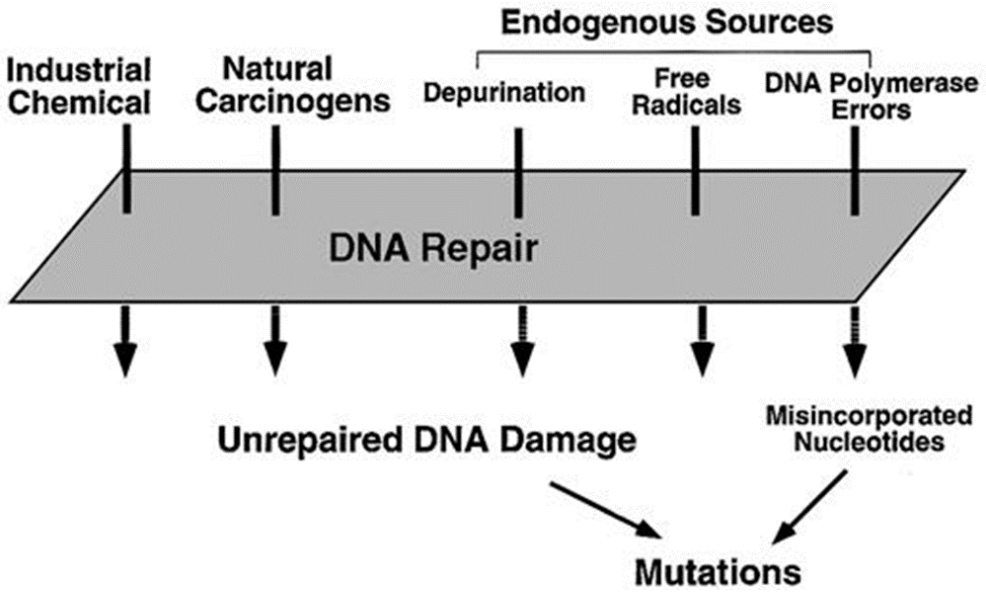
Μεταλλαξεις στην ογκολογια

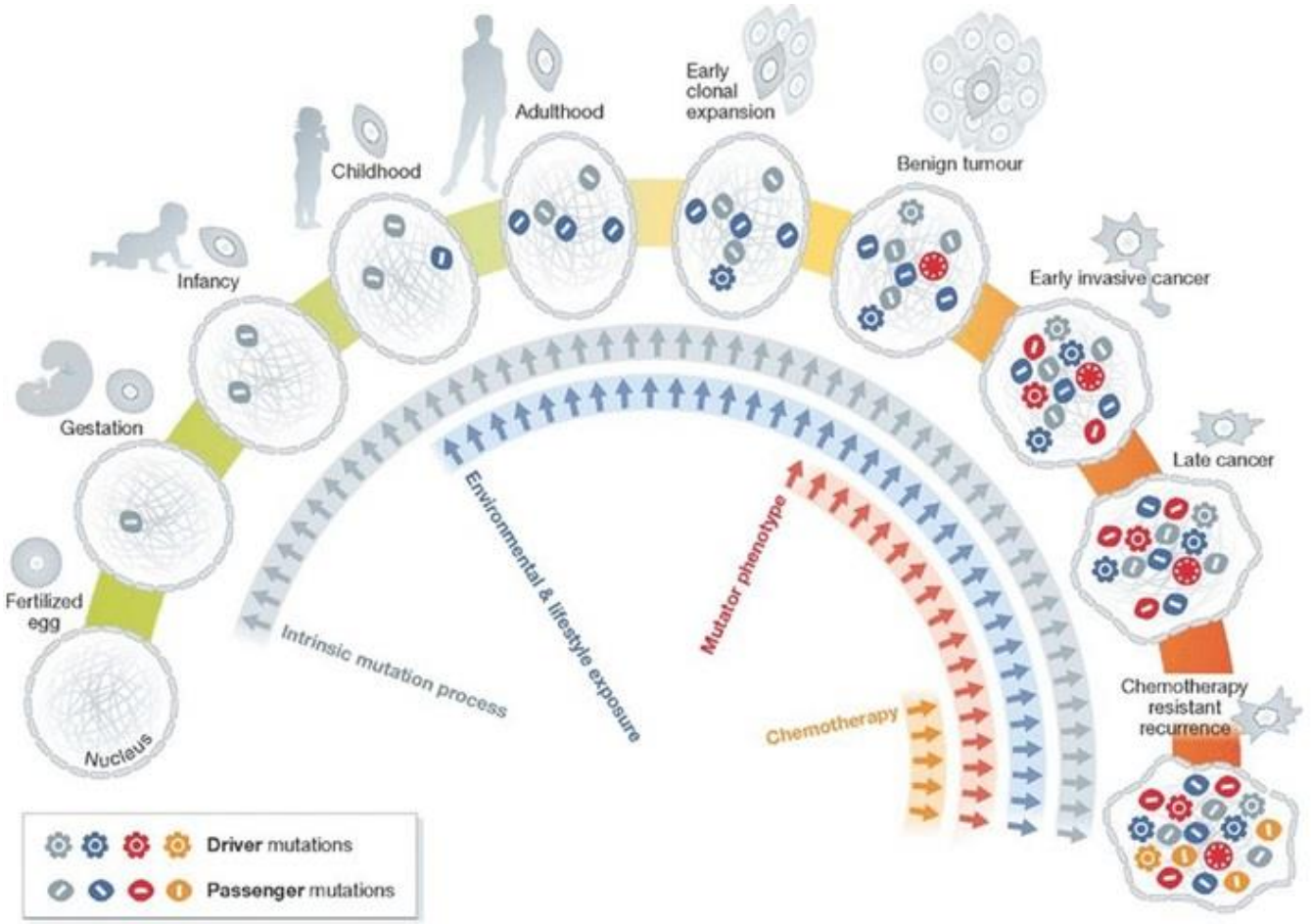
- Founder (ιδρυτικές) μεταλλάξεις → γονιδιωματική / χρωμοσωμιακή αστάθεια
- Driver (κινητήριες) μεταλλάξεις → επιλεκτικό πλεονέκτημα κυτταρικής ανάπτυξης / πολλαπλασιασμού
- Passenger (περαστικές) μεταλλάξεις → δεν προσδίνουν πλεονέκτημα ανάπτυξης



Pathogenesis of Cancer

Somatic mutations: Drivers and Passengers



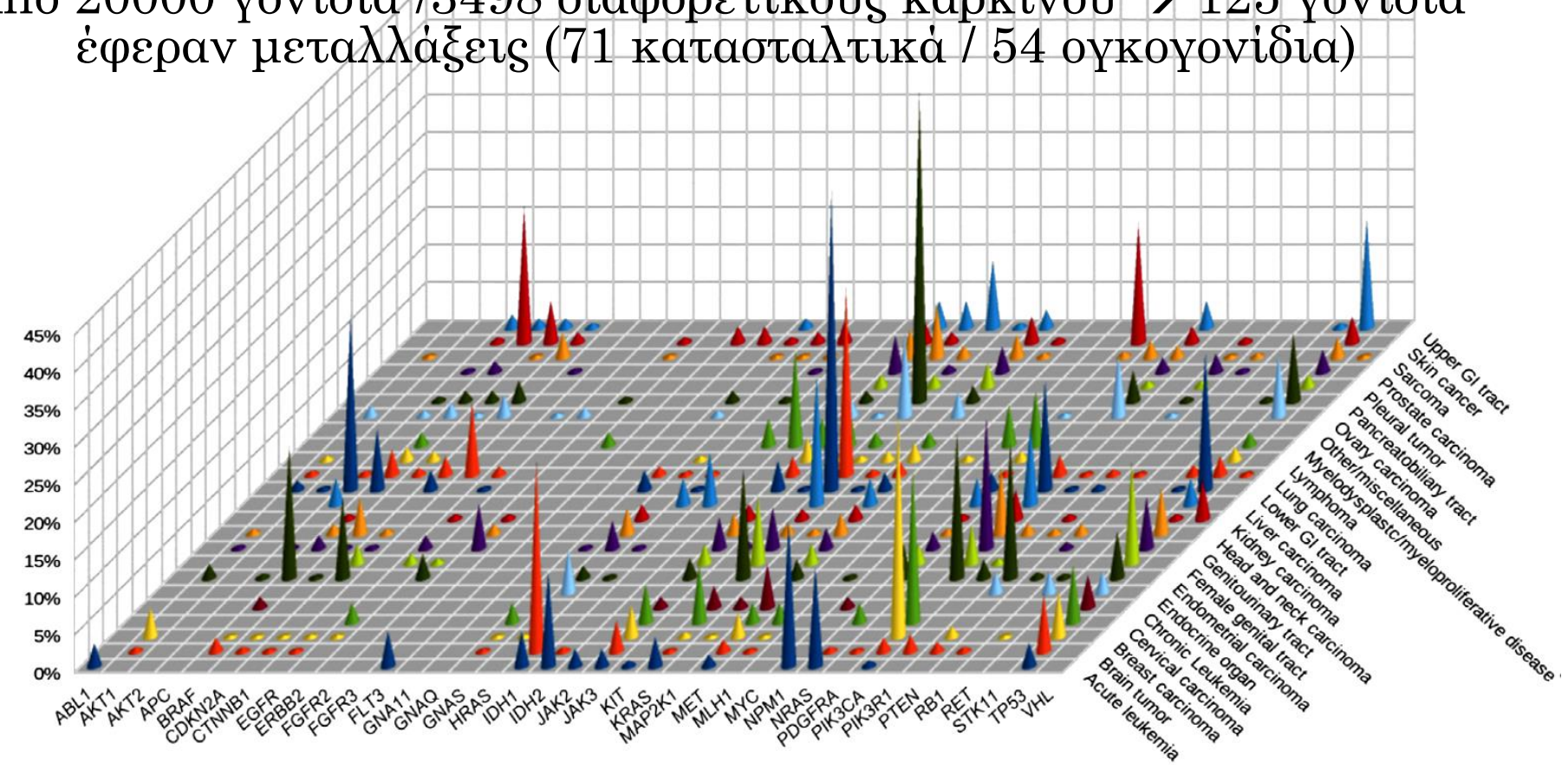


Loeb KR, **Carcinogenesis,** 2000

Stratton M, **EMBO Mol Med**, 2013

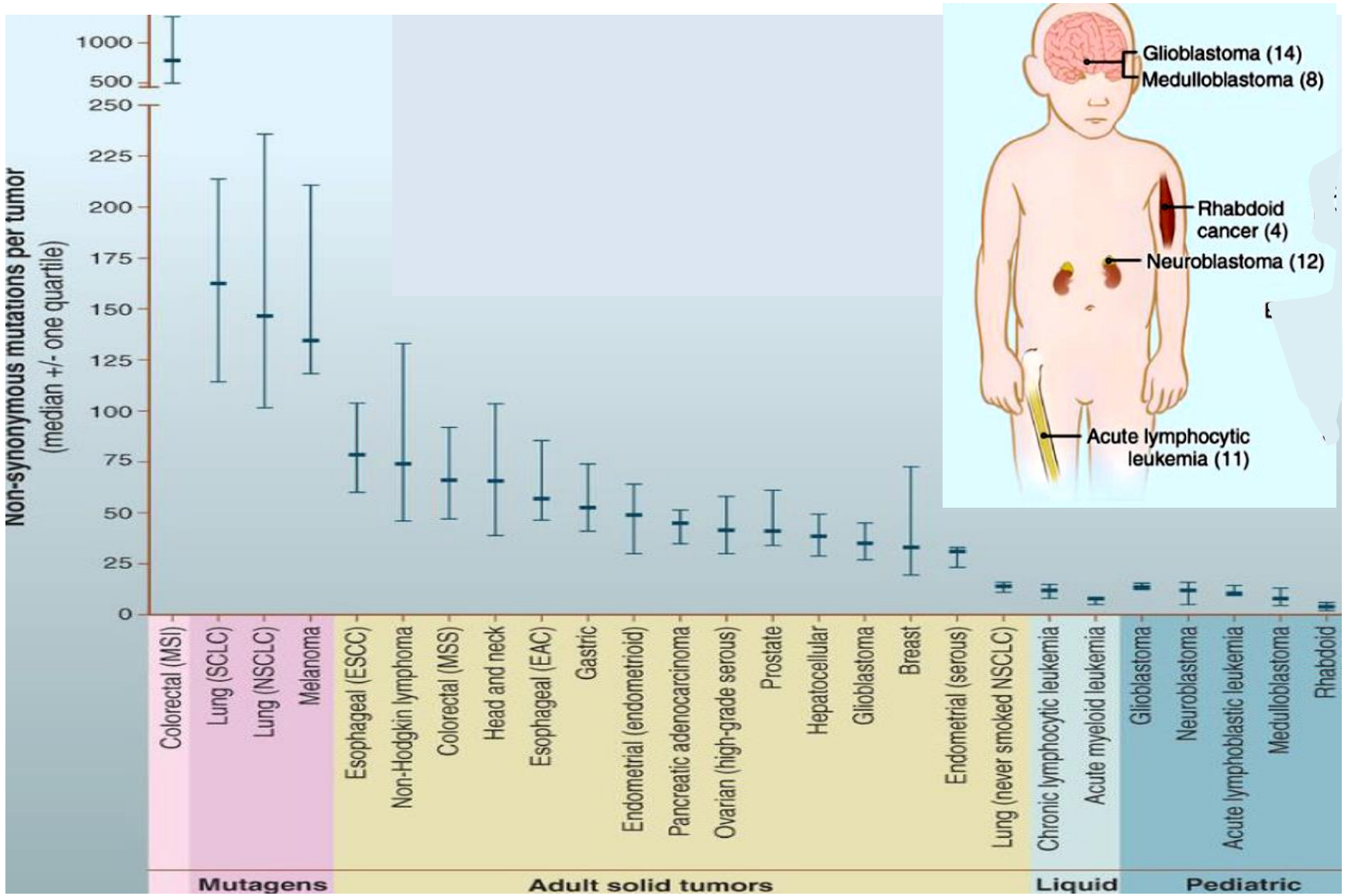
Cancer Genetics

Από 20000 γονίδια /3498 διαφορετικούς καρκίνου → 125 γονίδια έφεραν μεταλλάξεις (71 κατασταλτικά / 54 ογκογονίδια)



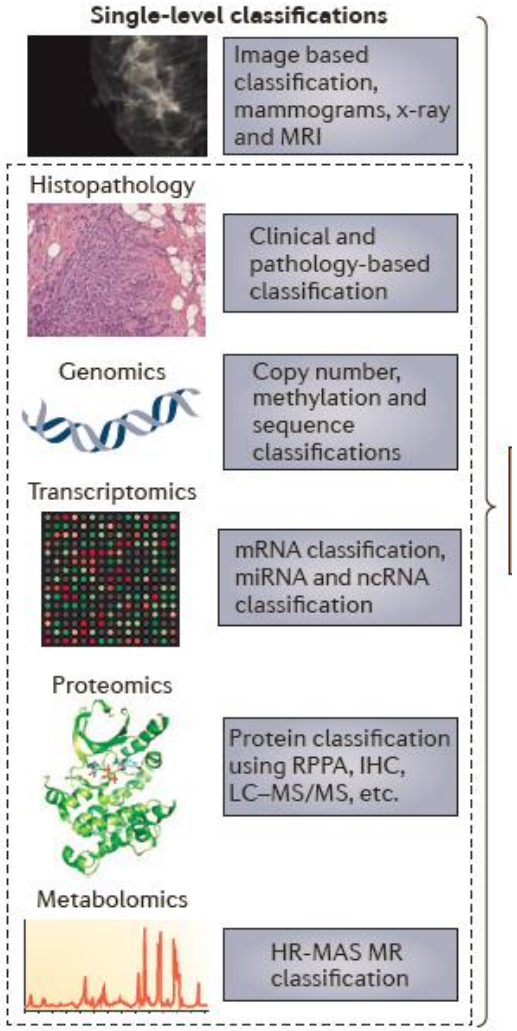
MacConaill, L, et. al., J Mol Diagn 2014, 16: 660-672

ΧΑΜΗΛΟ ΠΟΣΟΣΤΟ ΜΕΤΑΛΛΑΞΕΩΝ ΣΤΟΝ ΠΑΙΔΙΚΟ ΚΑΡΚΙΝΟ

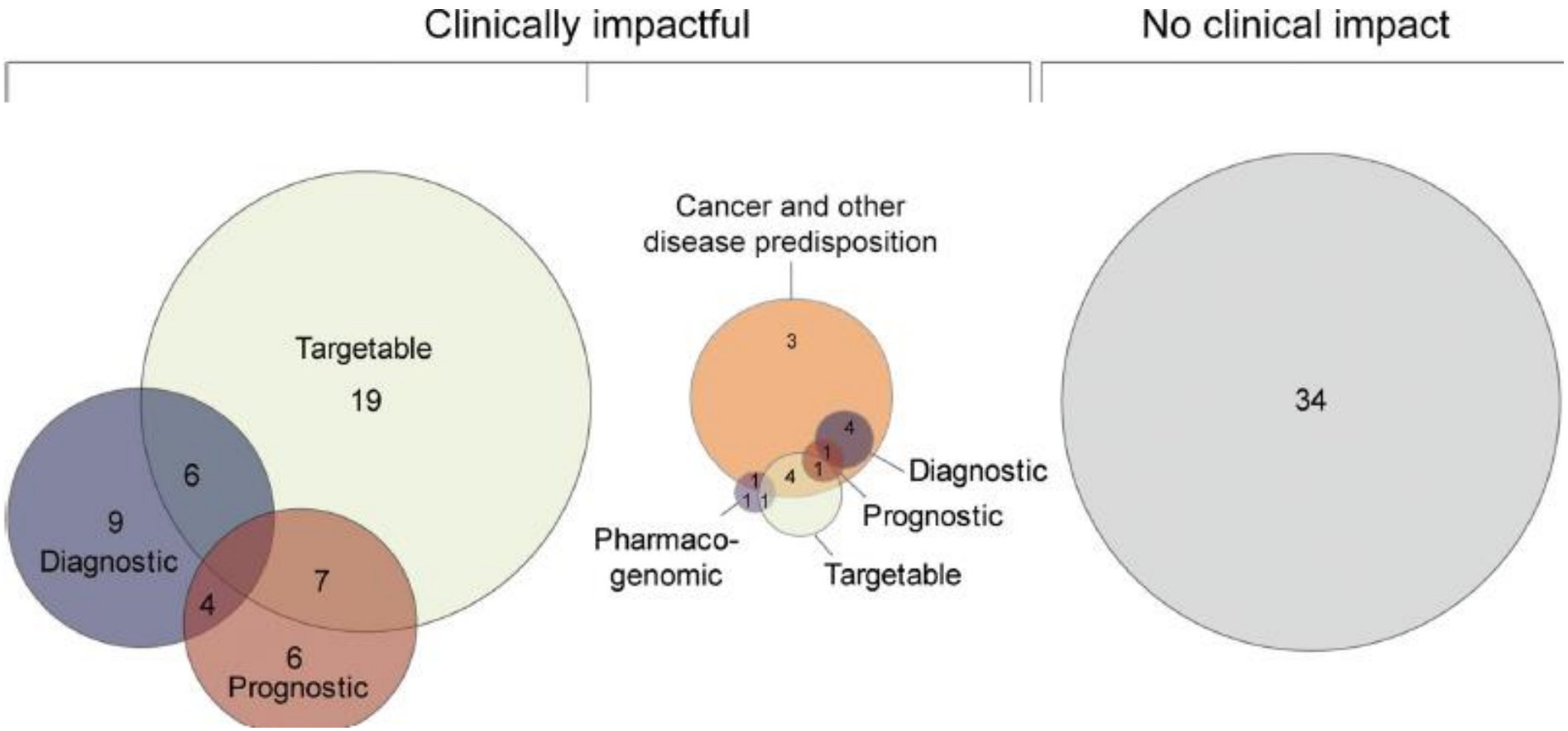


Bert Vogelstein et al: Science. 2013 ; 339(6127): 1546–1558

Τα OMICS στην ιατρική ακριβείας

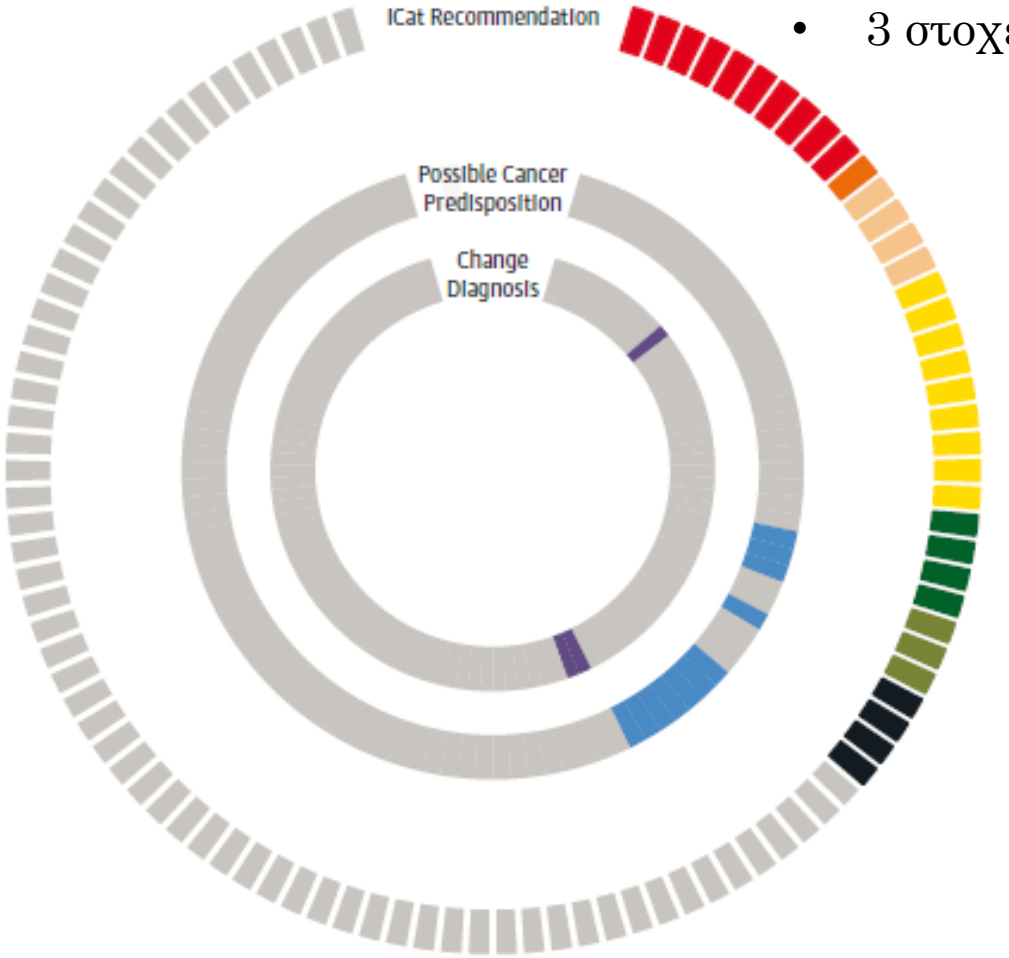


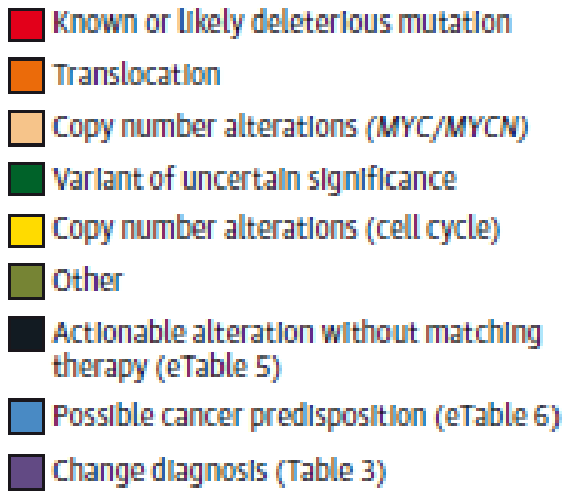
NGS στην Παιδιατρική Ογκολογία: 67/101 έδωσαν αξιοποίησιμα αποτελέσματα



Oberg et al. Genome Medicine (2016) 8:133

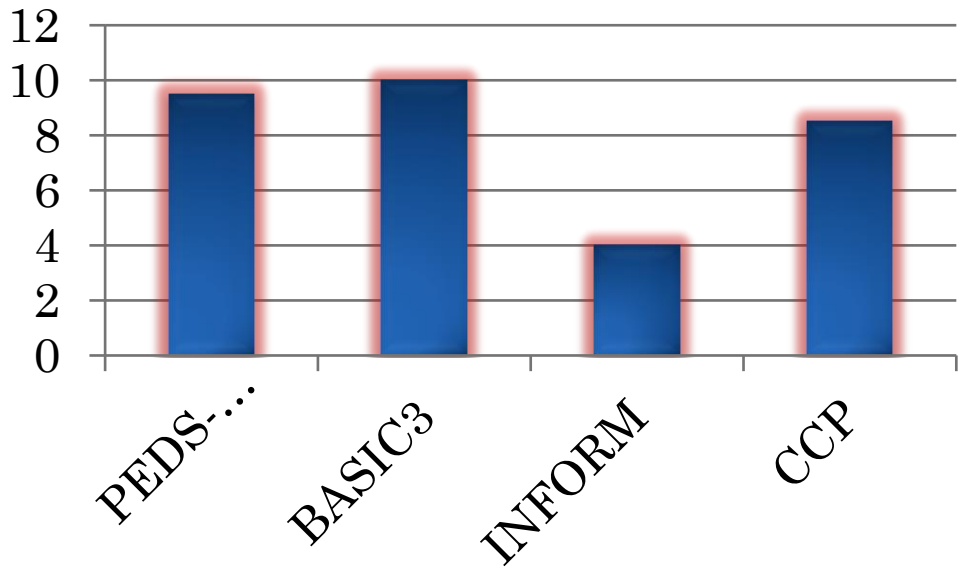
- 100 ασθενείς
- 89 τεχνικά επιτυχής γονιδιακός χαρακτηρισμός
- 31 ασθενείς δόθηκε συμβουλευτική
- 3 στοχευμένη θεραπεία

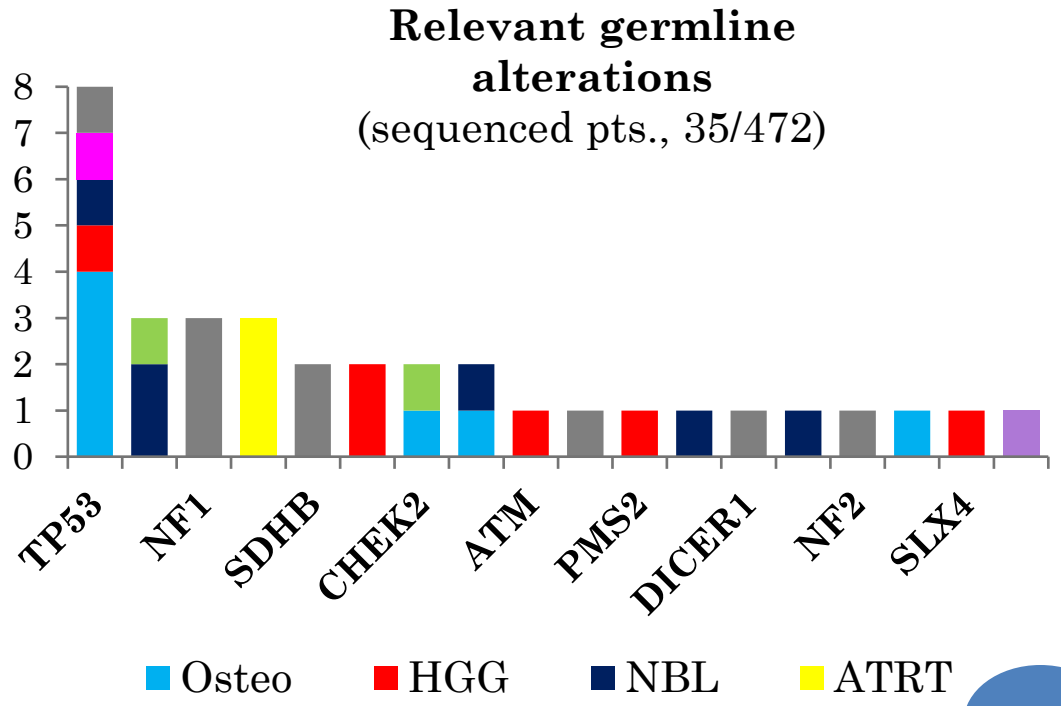




Harris M et al; JAMA Oncol. 2016;2(5):608-615.

ΥΨΗΛΟ ΠΟΣΟΣΤΟ
ΓΟΝΙΔΙΑΚΗΣ ΠΡΟΔΙΑΘΕΣΗΣ ΣΕ ΚΑΡΚΙΝΟ ΣΕ ΠΑΙΔΙΑΤΡΙΚΟΥΣ ΑΣΘΕΝΕΙΣ

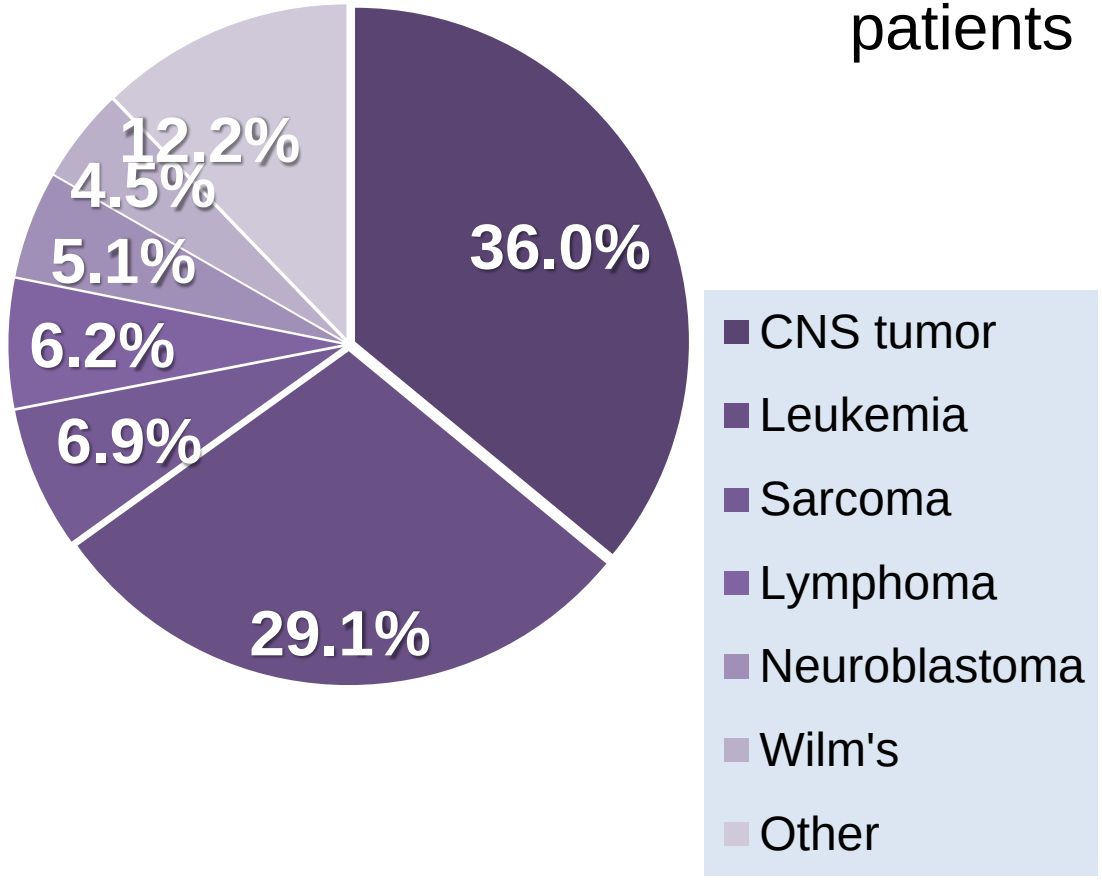




Stefan Pfister; personal communication

ΑΠΟΤΕΛΕΣΜΑΤΑ
ΜΟΝΑΔΑΣ ΑΙΜΑΤΟΛΟΓΙΑΣ ΟΓΚΟΛΟΓΙΑΣ ΕΚΠΑ– (Π.Ο.ΑΙ.Μ / ΚΕΘ)

	Patients (N)
NF1	28
TSC	5
NF2	3
Li-Fraumeni	3
Beckwith Wiedemann	2
MEN1	1
FAP	1
Rhabdoid tumor PS	2
Familial retinoblastoma	1
Fanconi anemia	2
	41 (8,7%)



ΝΟΣΗΜΑΤΩΝ ΓΕΝΕΤΙΚΗΣ ΠΡΟΔΙΑΘΕΣΗΣ ΣΕ ΚΑΡΚΙΝΟ

GENTURIS

Υπεύθυνος: Αντώνης Καττάμης

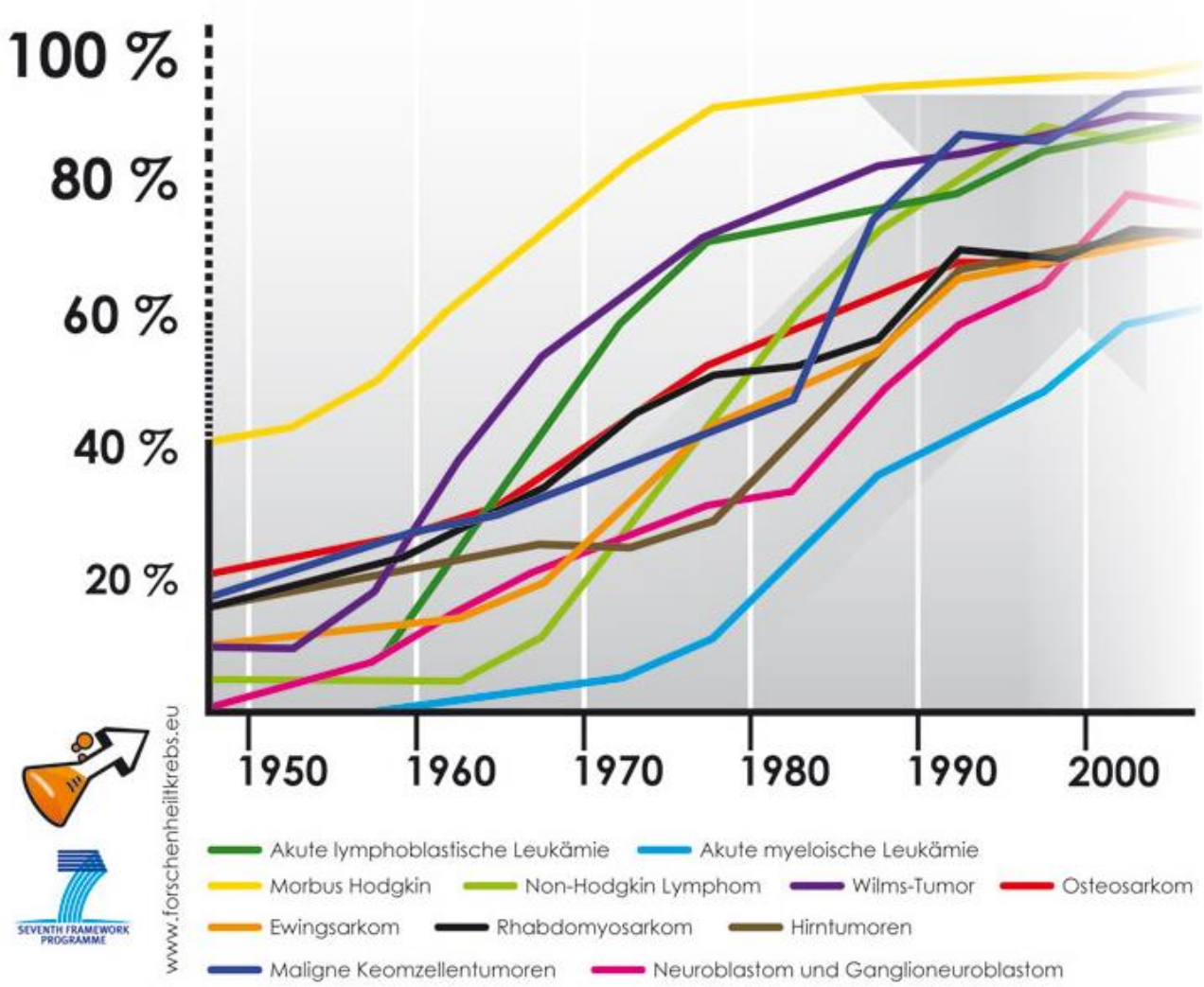
Καθηγητής Παιδιατρικής Αιματολογίας-Ογκολογίας

Υπεύθυνος Πανεπιστημιακής Αιματολογικής Ογκολογικής Μονάδας,

Α΄ Παιδιατρικής Κλινικής ΕΚΠΑ,

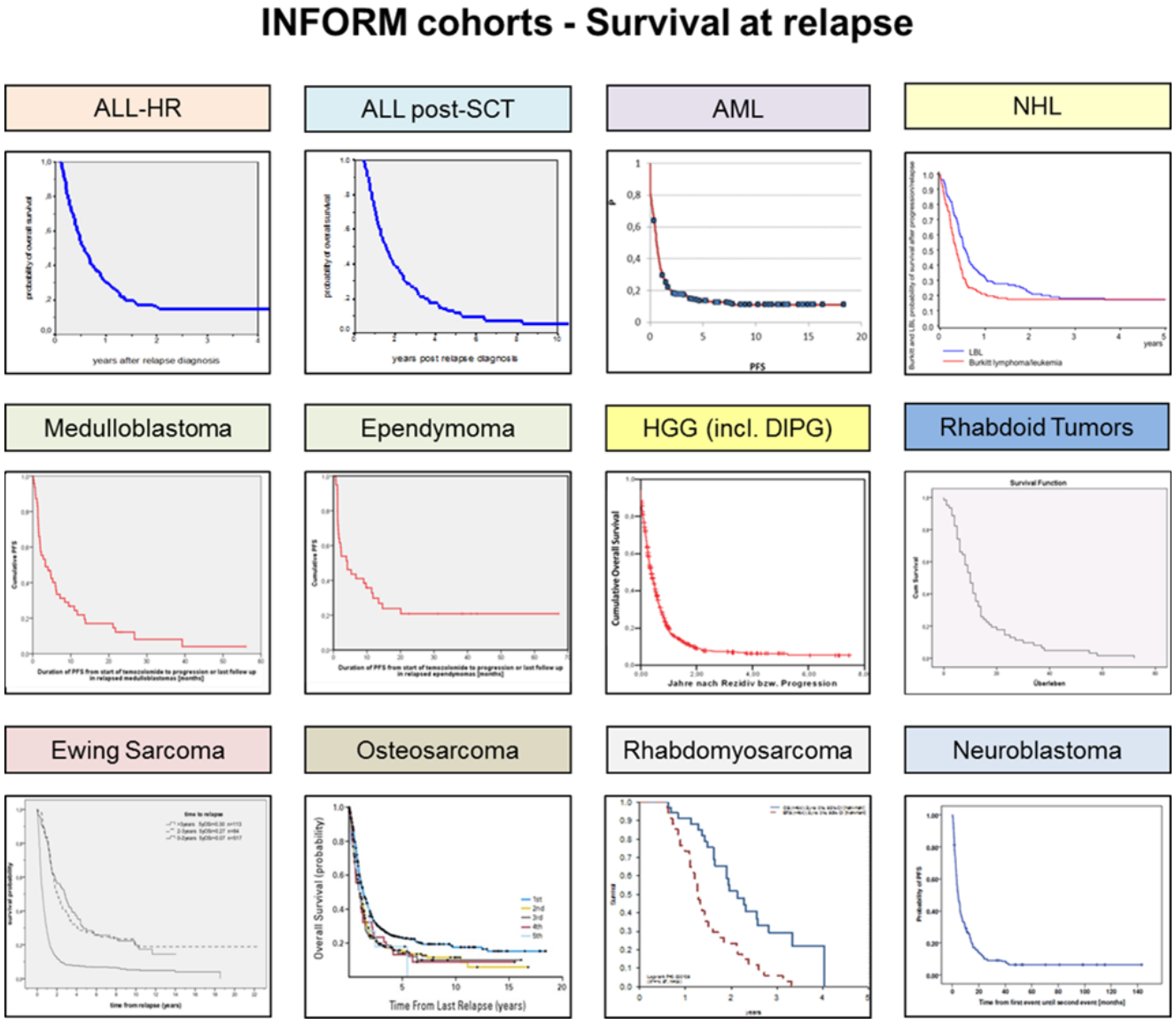
Γ.Ν. Παίδων «Η Αγία Σοφία»

Pediatric Oncology – a success story



From the German Cancer Registry

SURVIVAL AT RELAPSE…



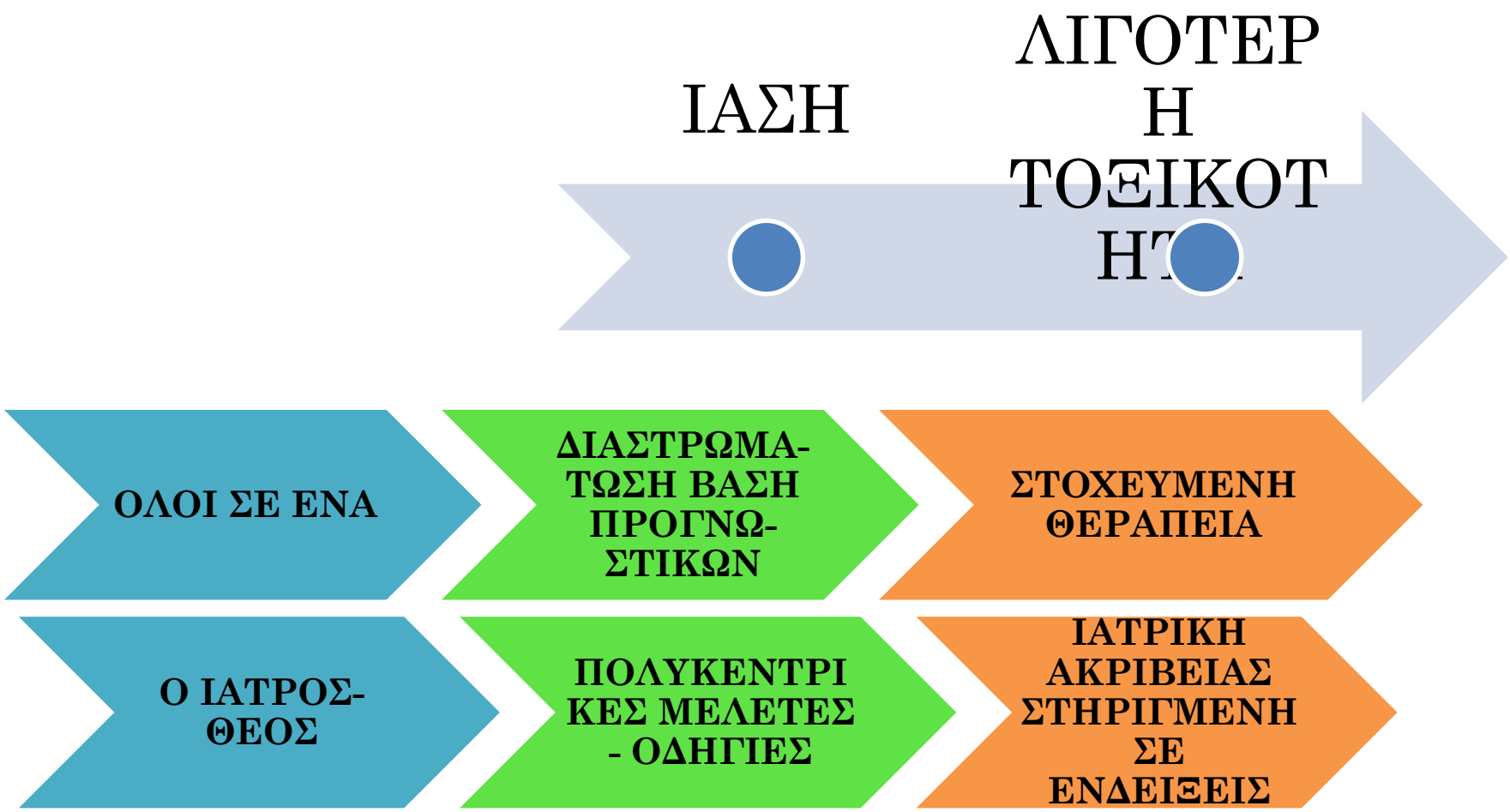
Cure rates have mostly plateaued over the last 15 years

… the „last 20%“ will probably not be cured by „more of the same“!
(still second most common cause of death after car accidents)

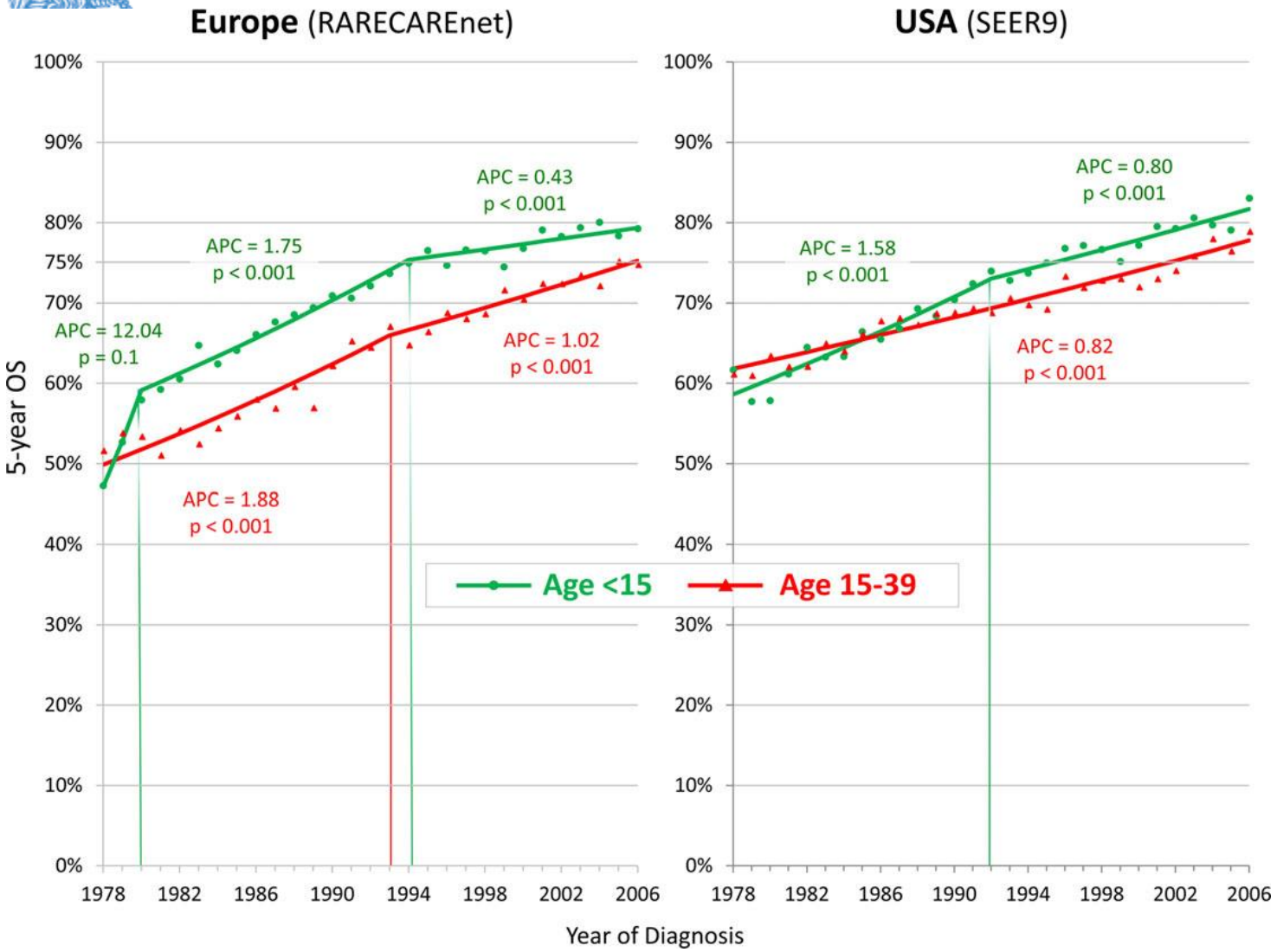
Medical need – cure at a high price!

Anthracyclines Chest Radiation	Heart failure
Radiation Alkylating agents Topoisomerase II inhibitors	Second cancers
Steroids Radiation	Osteonecrosis
Radiation	Stroke

ΔΙΑΧΡΟΝΙΚΗ ΕΞΕΛΙΞΗ ΘΕΡΑΠΕΙΩΝ



Annual 5-year OS and trends for common cancers

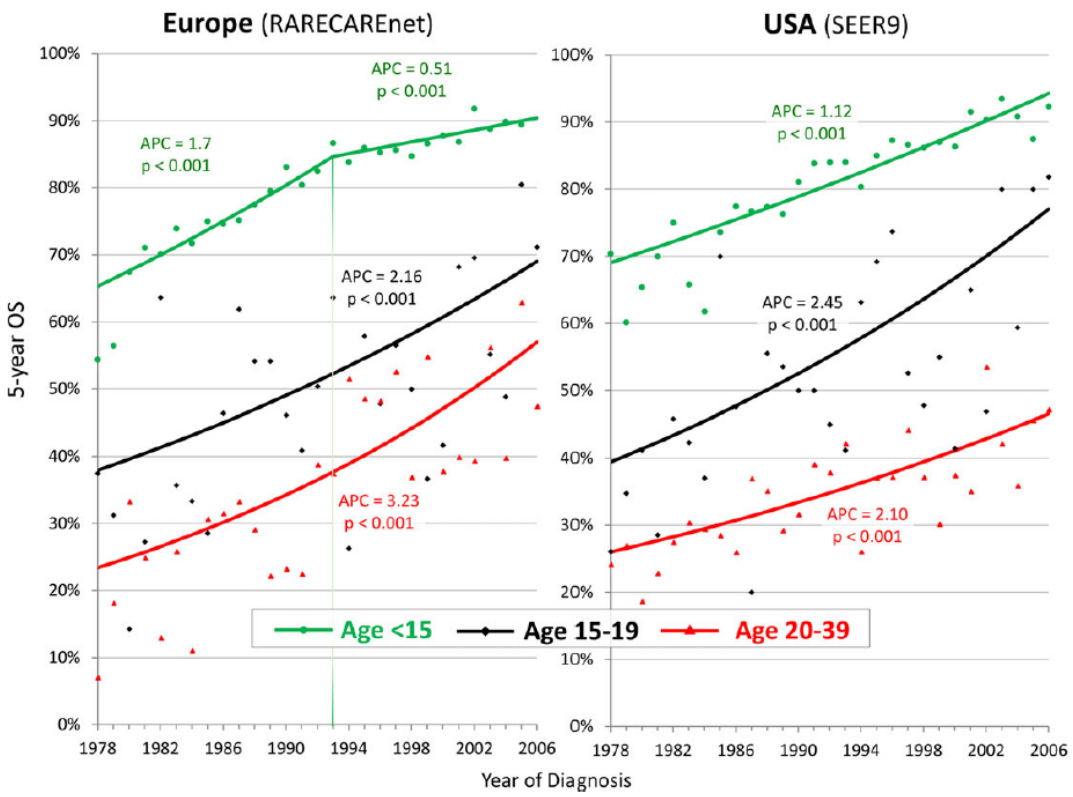


Common Cancers:
Leukemia
Lymphomas
(excl. non Burkitt NHL-males)
CNS tumors
(excl. Pilocytic Astro)
Bone Sarcomas
Soft Tissue Sarcomas

Trama A. et al; Pediatr Blood Cancer. 2019;66:e27407.

Annual 5-year OS and trends for common cancers

Leukemia



Lymphomas(excl. non Burkitt NHL-males)
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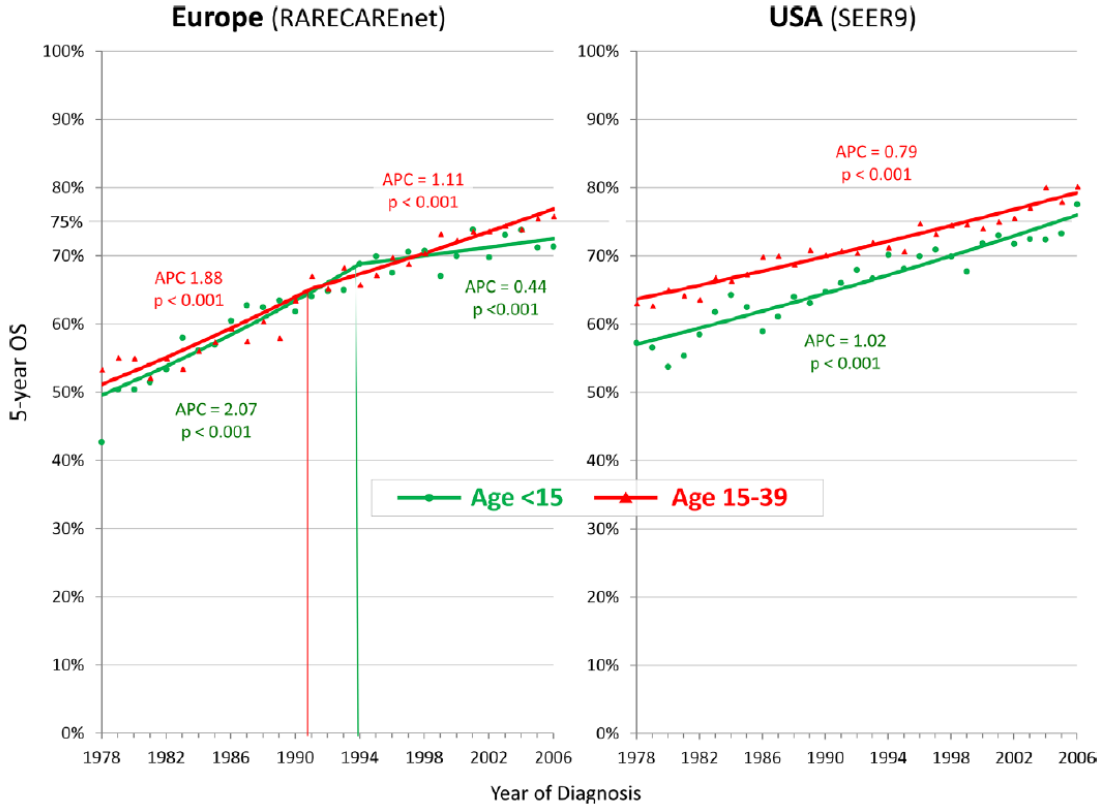
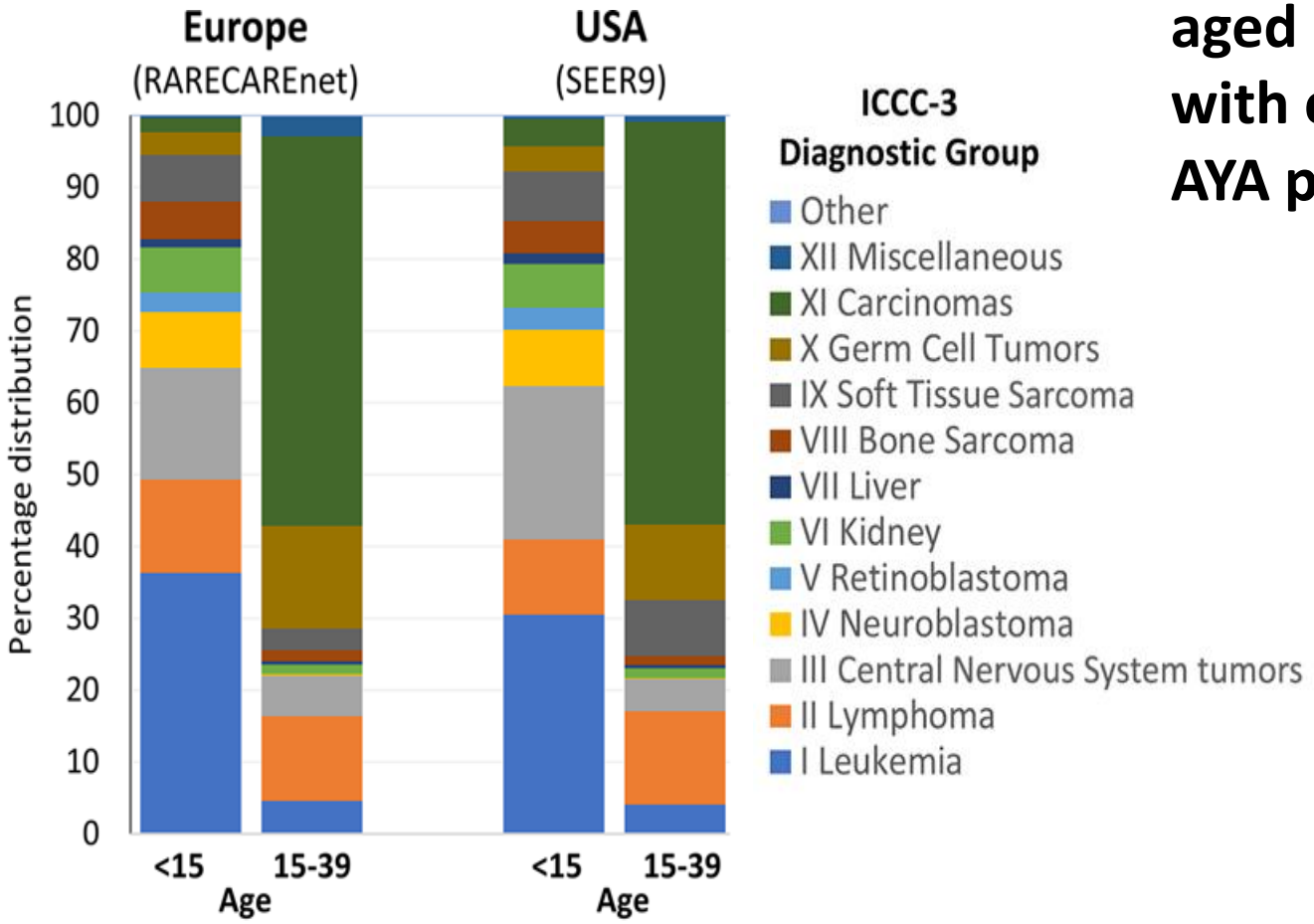


Trama A. et al; Pediatr Blood Cancer. 2019;66:e27407.

Significant Differences in Cancer Types Between Children and AYA

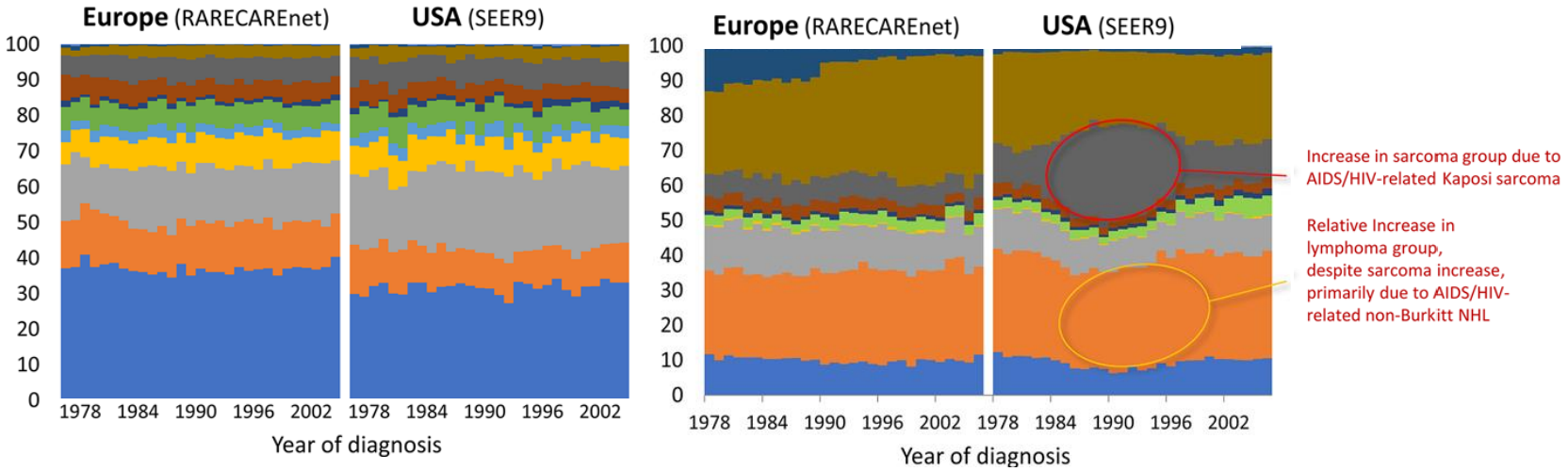


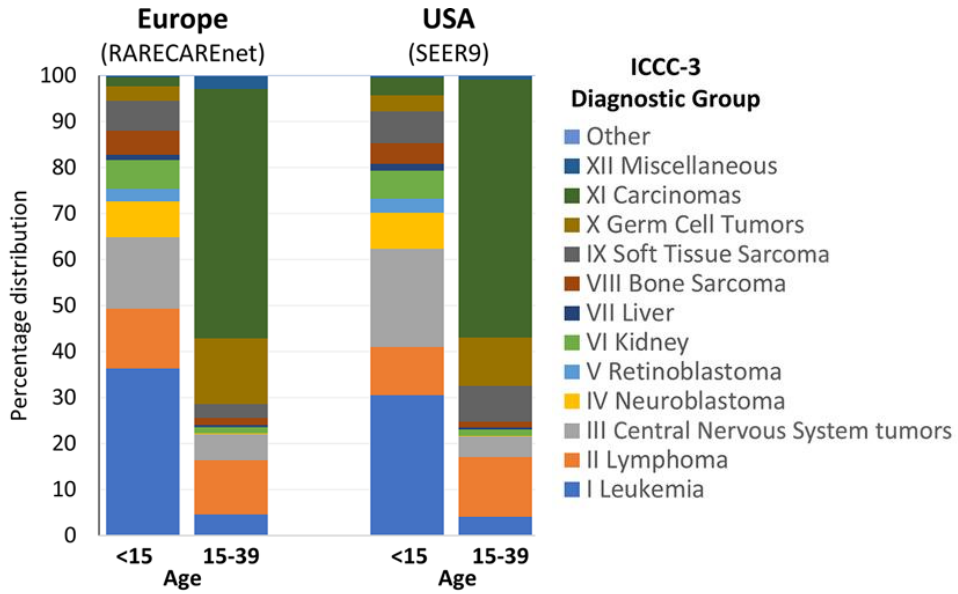
In Europe, over 66,000 adolescents and young adults (AYAs) aged 15–39 are diagnosed annually with cancer, from an estimated AYA population of just over 50 million

RARECAREnet cohort :73,613 cases (42,221 children and 31,392 AYAs)
SEER cohort: 53,274 cases (14,586 children and 38,688AYAs).

Trama A. et al; Pediatr Blood Cancer. 2019;66:e27407.

Significant Differences in Cancer Types Without Significant Changes with time





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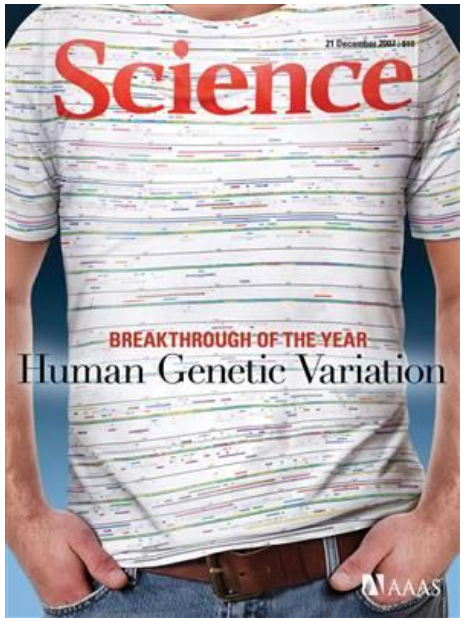
Trama A. et al; Pediatr Blood Cancer. 2019;66:e27407.

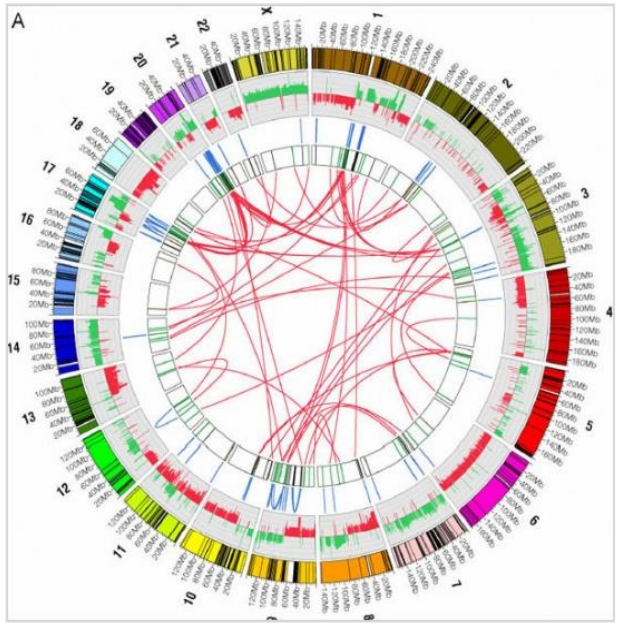
Ορισμος

- ‘Εξατομικευμένη θεραπεία’ - ‘Ιατρική Ακριβείας’

Αναδυόμενη προσέγγιση για την θεραπεία και πρόληψη ασθενειών, που λαμβάνει υπόψη ατομική μεταβλητότητα στα γονίδια, περιβάλλον, και τρόπο ζωής για κάθε άτομο



Γενετικές Παραλλαγές



Σωματικές Μεταλλάξεις

Εξατομικευμένη θεραπεία

Precision Medicine

- *Precision Medicine is an emerging approach in prevention and treatment of diseases taking into account individual variability in genes, environment, and lifestyle for each person*

- *The goal in precision cancer medicine is to improve cure rates and decrease toxicities by identifying the specific genes, proteins and pathways responsible for malignant transformation or progression of individual cancers, and utilize therapies that target these features that distinguish cancer cells from normal cells*

"Tonight I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes.

And to give us all access to the personalized information we need to keep ourselves and our families healthier."

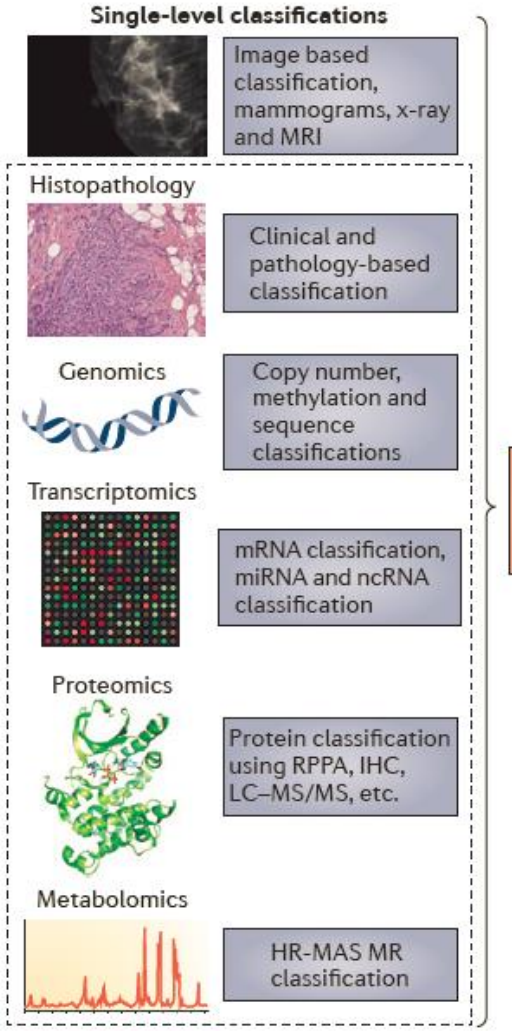
President Barack Obama
2015 State of the Union Address | January 20, 2015

European Initiatives

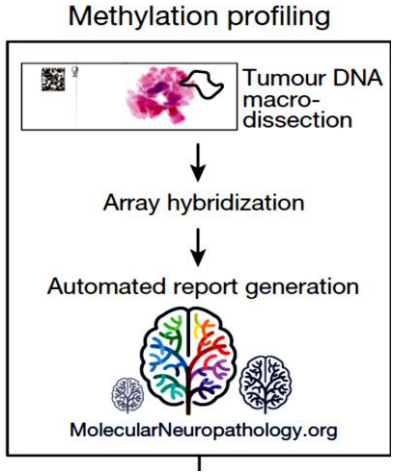
- 2011: 'Perspectives in Personalised Medicine"
- 2015: 'International Consortium for Personalised Medicine' (IC PerMed)
- 1.11.2016: IC PerMed Secreteriat
- FP7 / Horizon 2020: > 3 Billions €

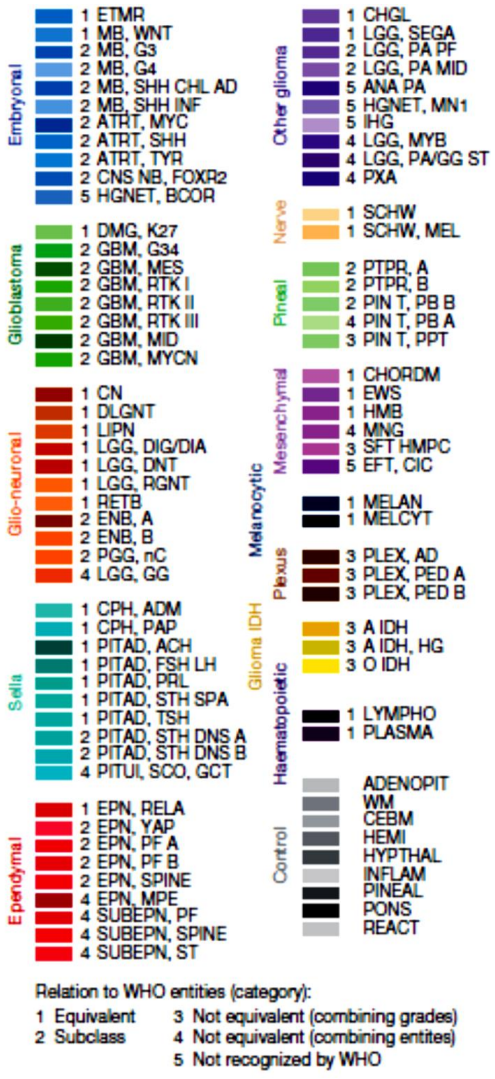
- Precision Medicine Initiative®
  215.000.000$
- NIH, FDA, and the Office of the National Coordinator for Health Information Technology.
- $70.000.000 → National Cancer Institute

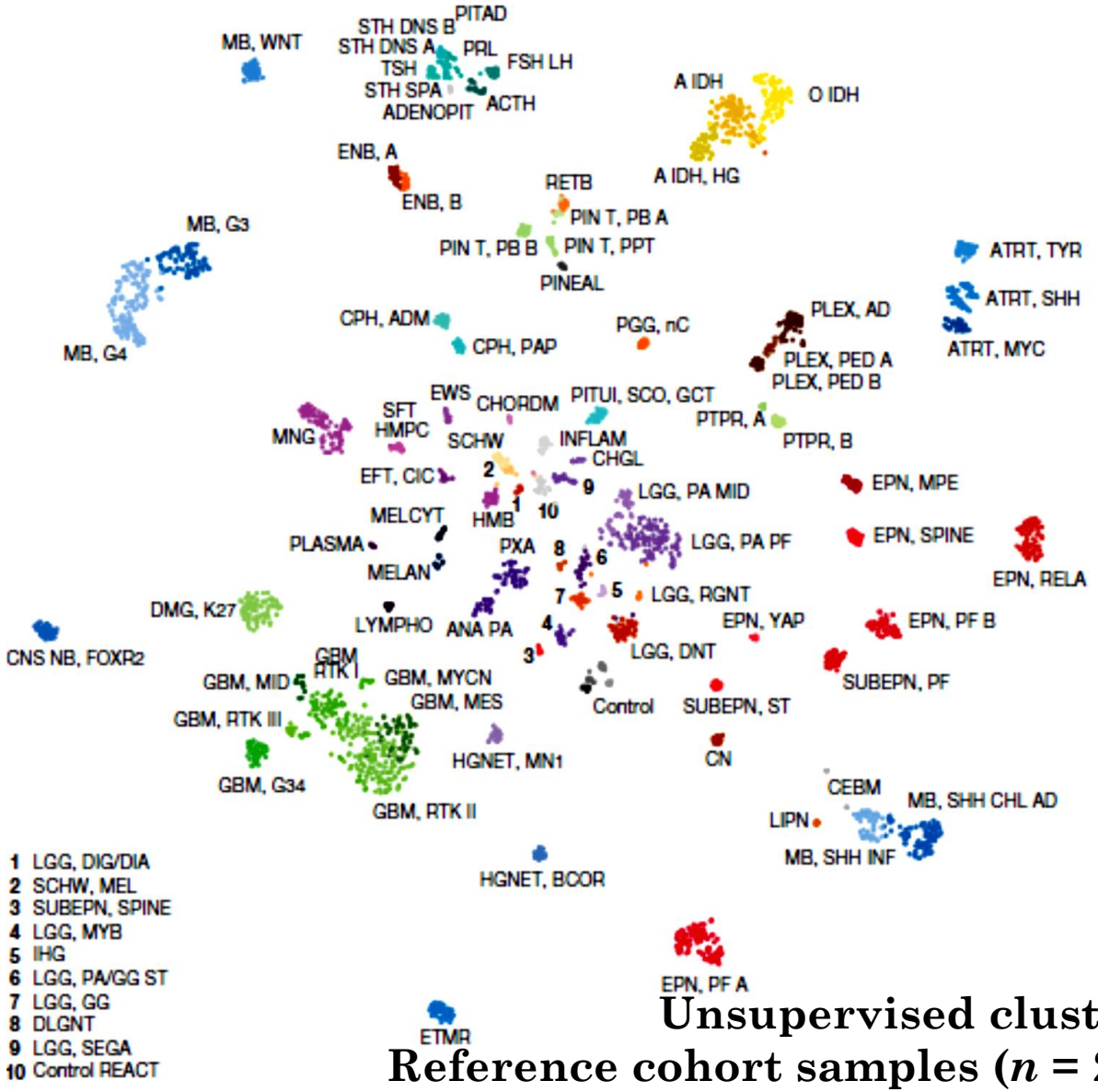
Τα OMICS στην ιατρική ακριβείας



PRECISION MEDICINE - DIAGNOSIS
DNA-Methylation based classification of brain tumors



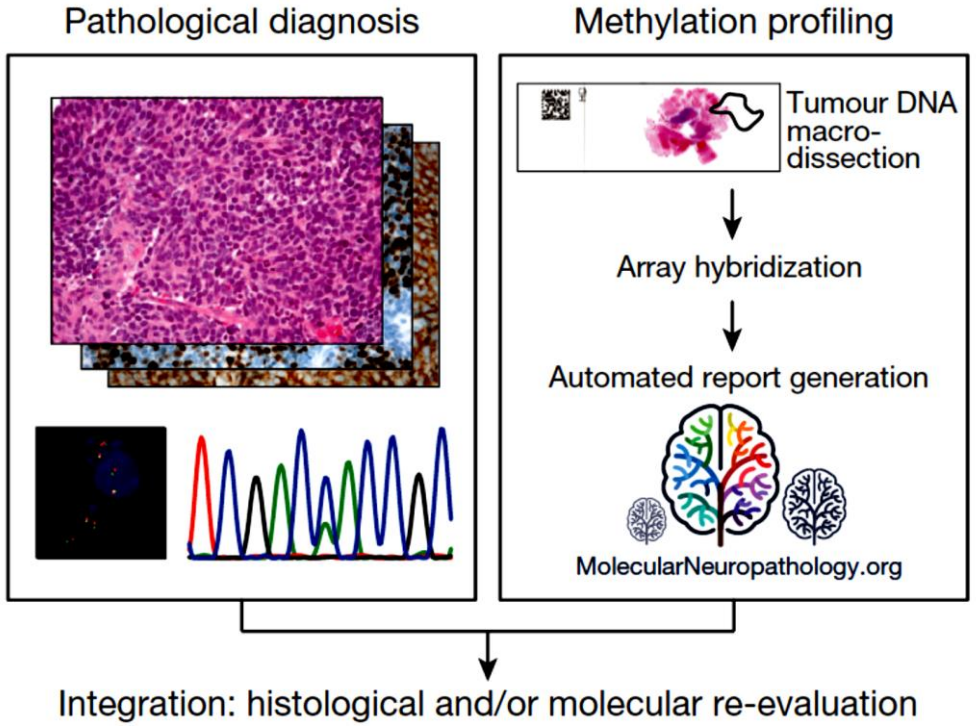


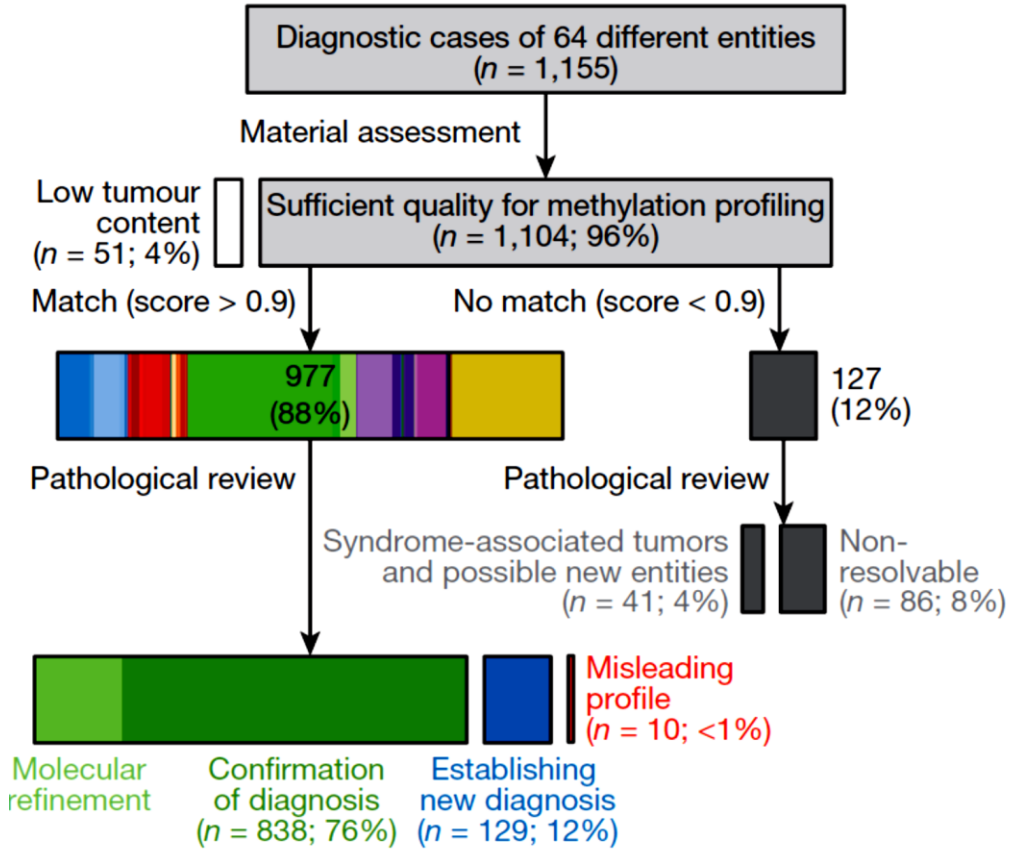


Unsupervised clustering
Reference cohort samples (n = 2,801)

Capper et al; Nature 2018

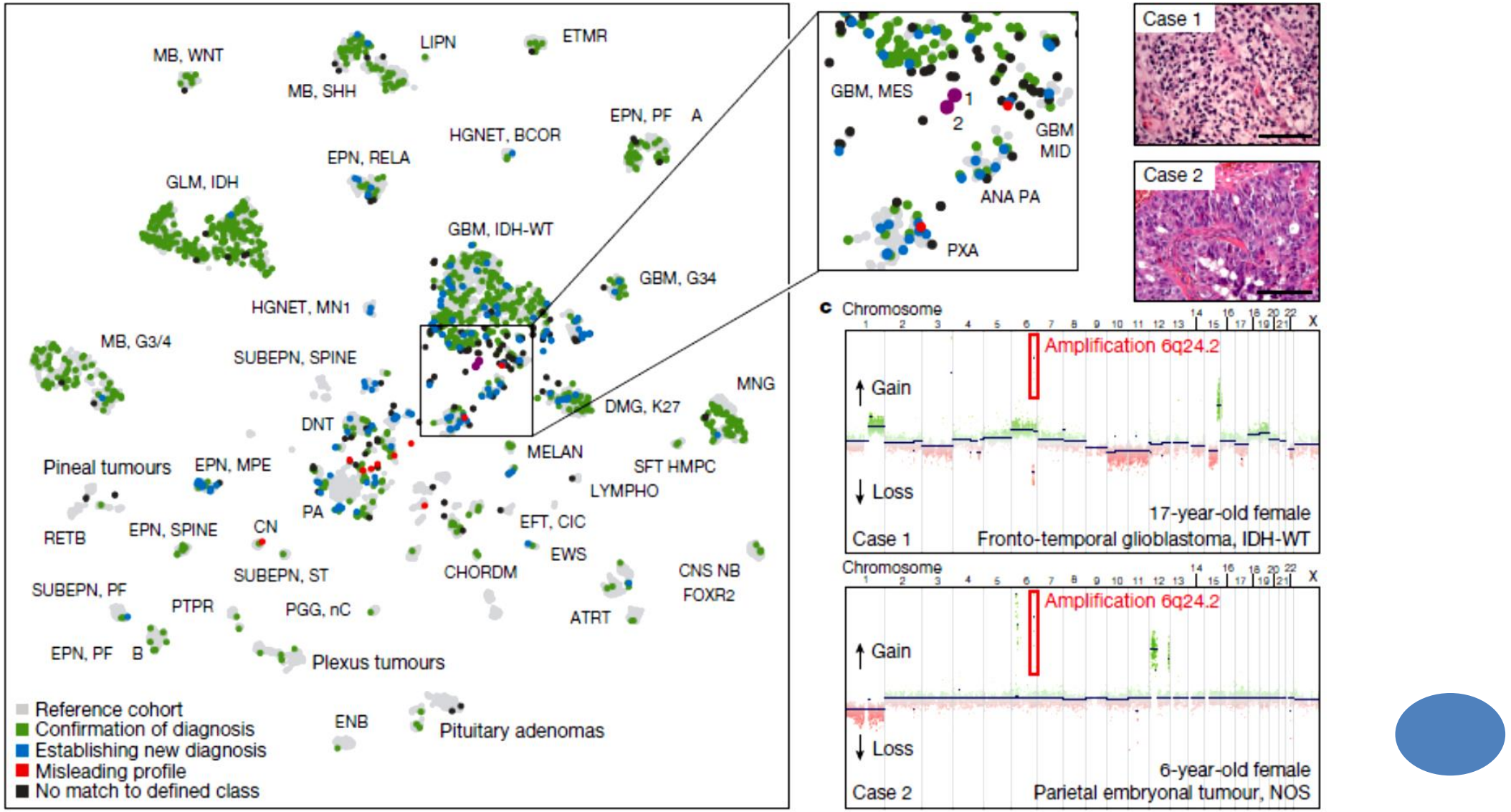
PRECISION MEDICINE - DIAGNOSIS
DNA-Methylation based classification of brain tumors





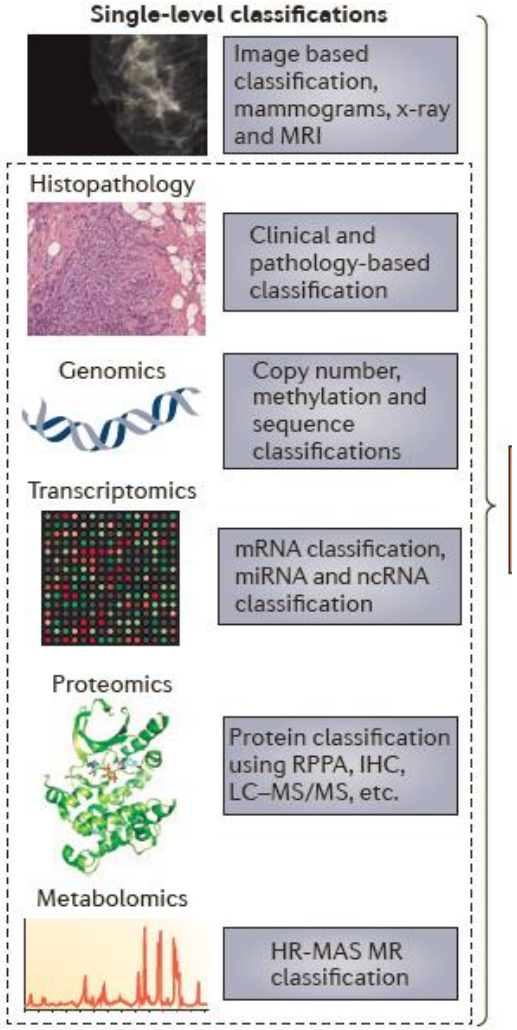
Capper et al; Nature 2018

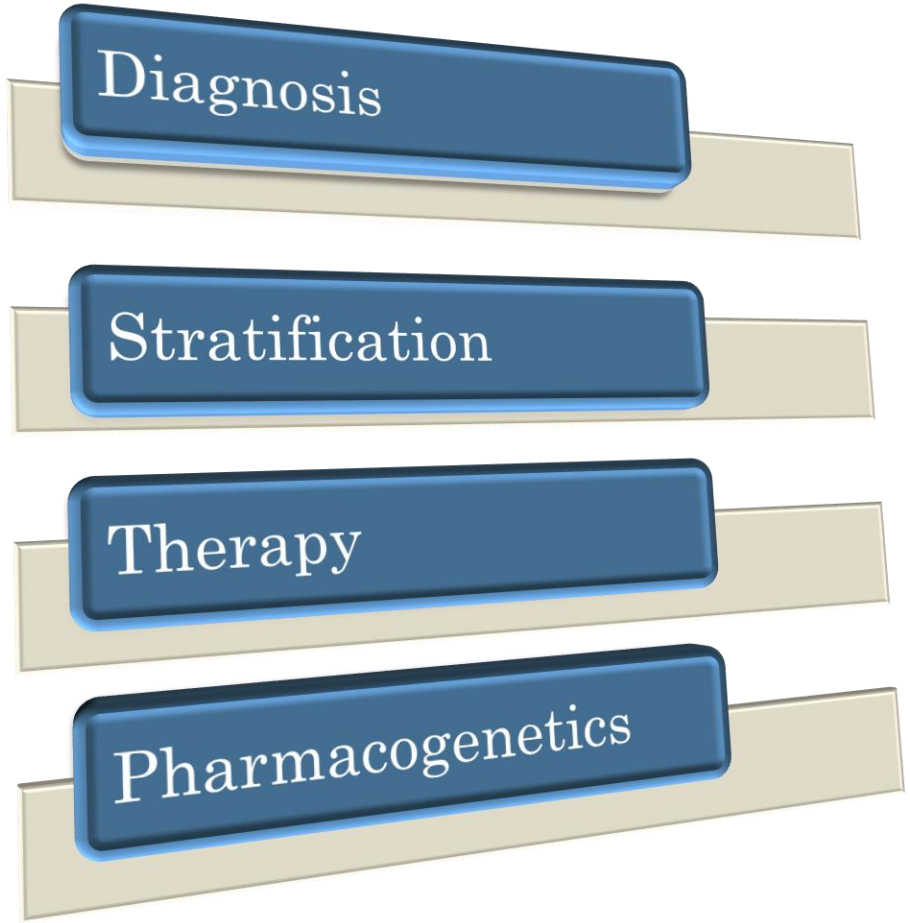
DNA-Methylation based classification of brain tumors: New entities



Capper et al; Nature 2018

The Era of Big Data - Omics





Molecular Classification in CNS tumors

CNS tumors in AYA

- 3rd most common malignancy after Breast and thyroid Ca
- iGCT: Higher frequency compared to peds

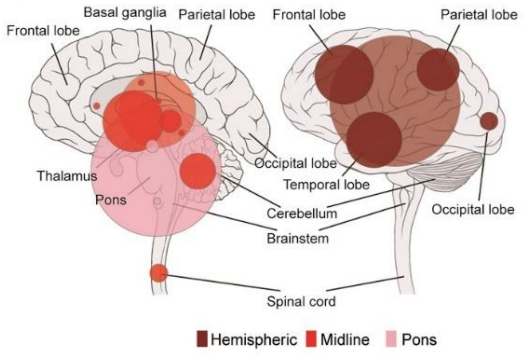
Disease	SNV	Fusions	CNA	Age
LOW-GRADE GLIOMA Pilocytic astrocytoma		KIAA1549-BRAF	7q34 duplication	
Diffuse astrocytoma (incl. IDH mutated tumors)	BRAF V600E IDH1/2, TERT	MYBL1	FGFR TKD, MYB Co-deletion 1p/19q	
HIGH-GRADE GLIOMA K27	H3.1 and H3.3 K27M, TP53, ATRX, ACVR1			
G34	H3.3 G34V/R, TP53, ATRX			
IDH	IDH1/2, TP53, ATRX			
RTK-I	TP53		EGFR amp, PDGFRA amp, chr. 10 loss	
Mesenchymal	EGFR, TP53, NF1		CDKN2A del, PDGFRA amp, EGFR amp	
PXA-like	BRAF V600E		CDKN2A del	
MEDULLOBLASTOMA Wnt	CTNNB1, TP53, SMARCA4, DDX3X		Monosomy chr. 6	
SHH	PTCH1, SUFU, TP53		GLI2 amp, NMYC amp, 10q loss, 9q loss	
Group 3	OTX2, DDX3X	PVT1-MYC	i17q, MYC amp, GFI1/GFI1B	
Group 4	KDM6A		i17q, chr. 11 loss, MYCN amp, GFI1/GFI1B	
EPENDYMOMA Posterior fossa - PFA			1q gain	
Posterior fossa - PFB				
Supratentorial		C11orf95-RELA YAP1 fusions		
Spinal	NF2		chr. 22q	
CRANIOPHARYNGIOMA Adamantinomatous	CTNNB1			
Papillary	BRAF V600E			
iGCT	KIT, KRAS, NRAS			

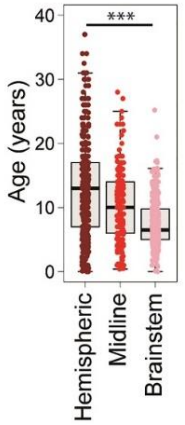
Adult (≥40) AYA (15-39) Child (<15)

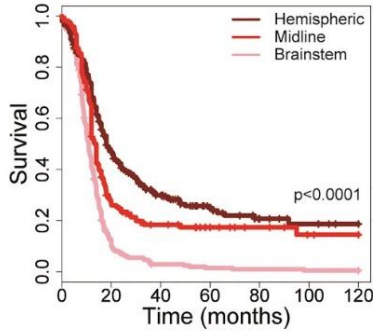
Zapototcky M et al: *Pediatr Blood Cancer*. 2018;**65**:e26861.

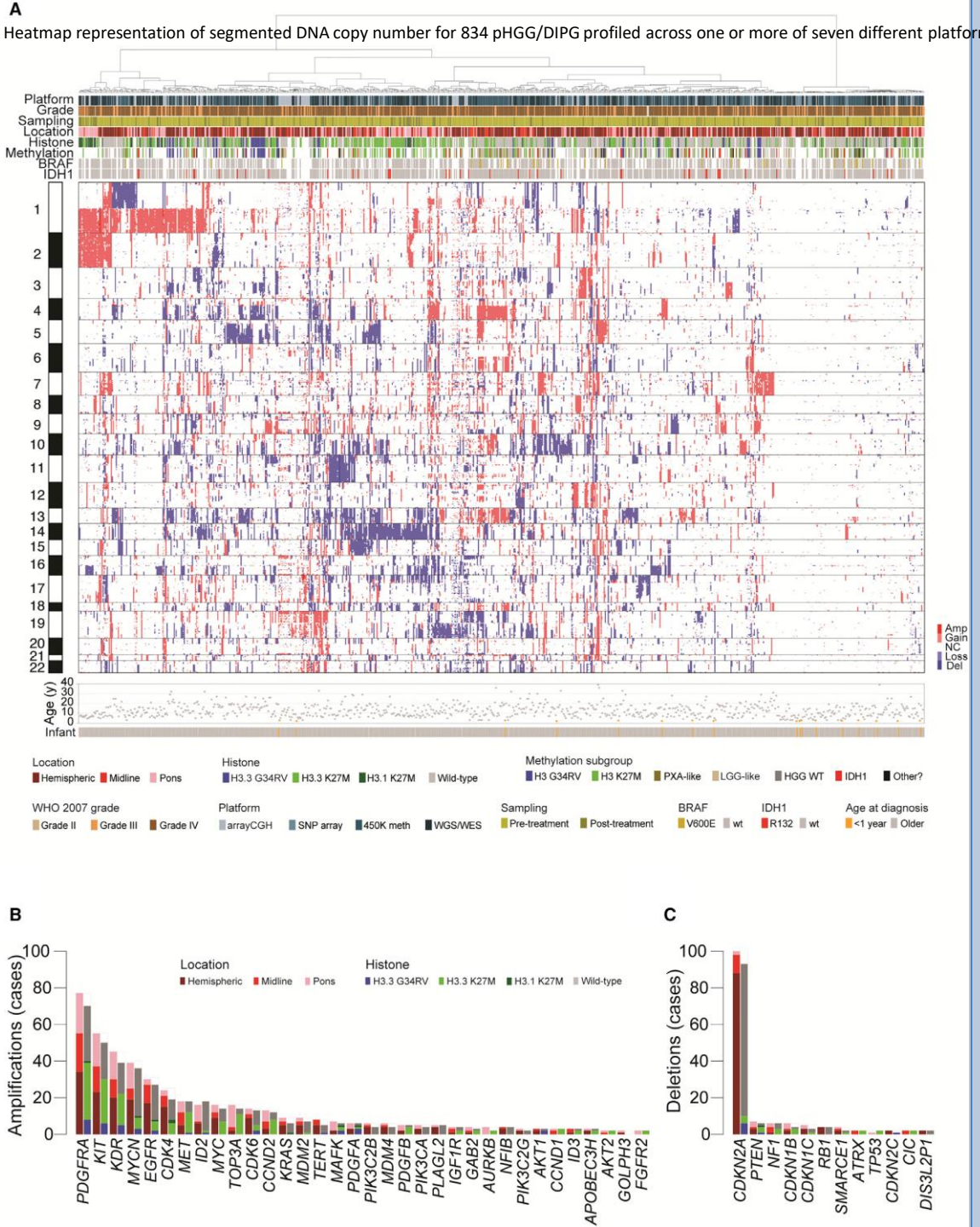
High Grade Gliomas in Pediatric and AYA patients

- Integrated molecular meta-analysis
- 1067 unique tumors (pediatrics /AYA)
- Genomic aberrations increase with age
- Prognosis dependent on tumor topography and genetic aberations







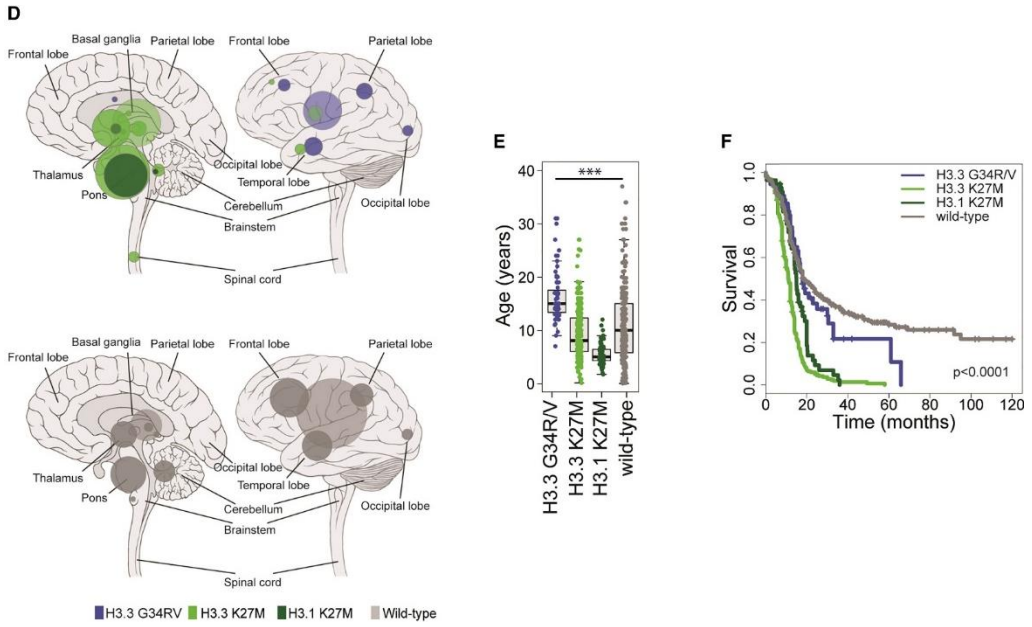


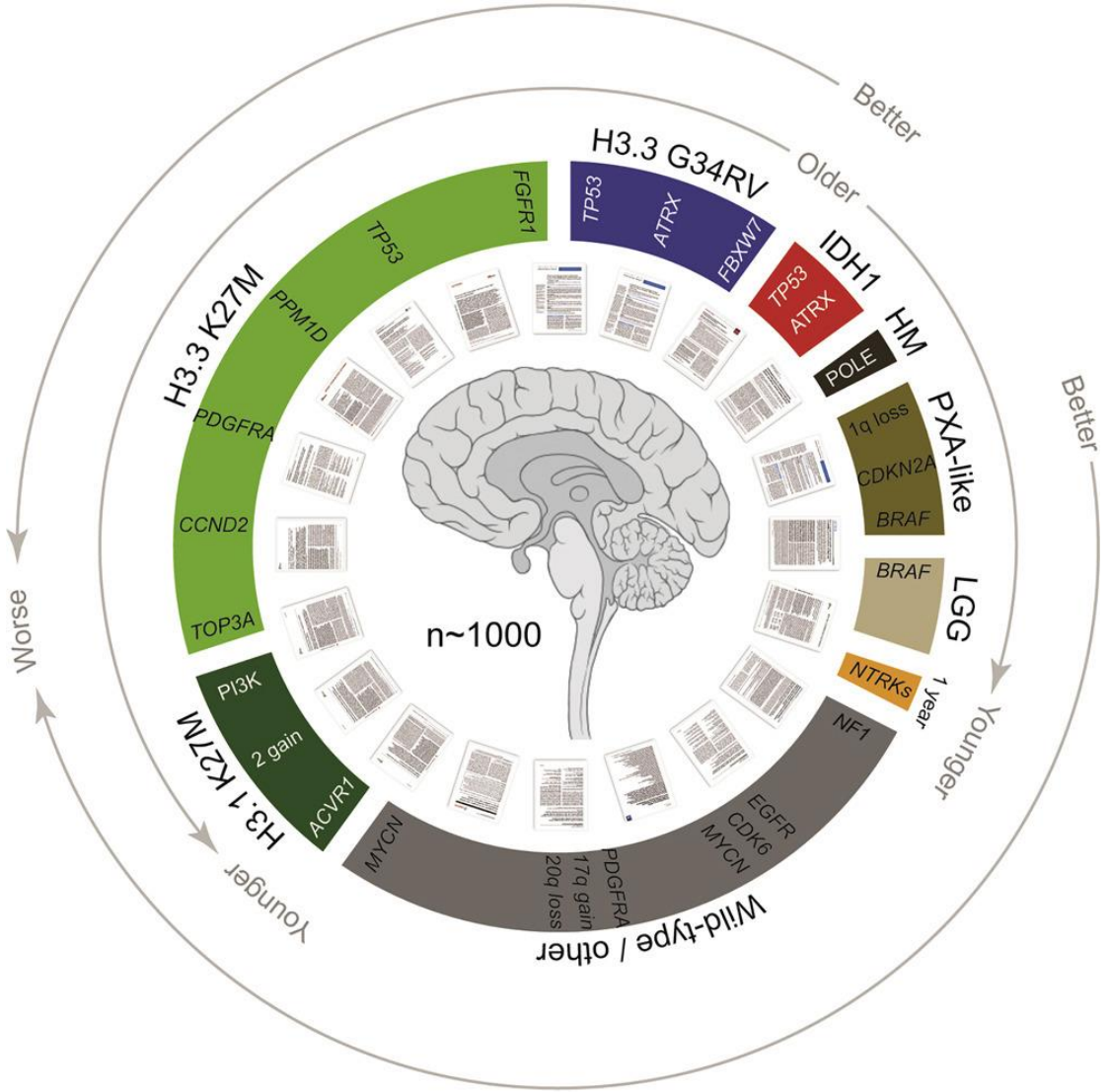
Mackay et al. Cancer Cell 2017 32, 520-537.e5DOI: (10.1016/j.ccell.2017.08.017)

HGGs arise along embryonic developmental lineages and are genomically and spatially distinct

AYA patients have Characteristic Genetic Alterations:

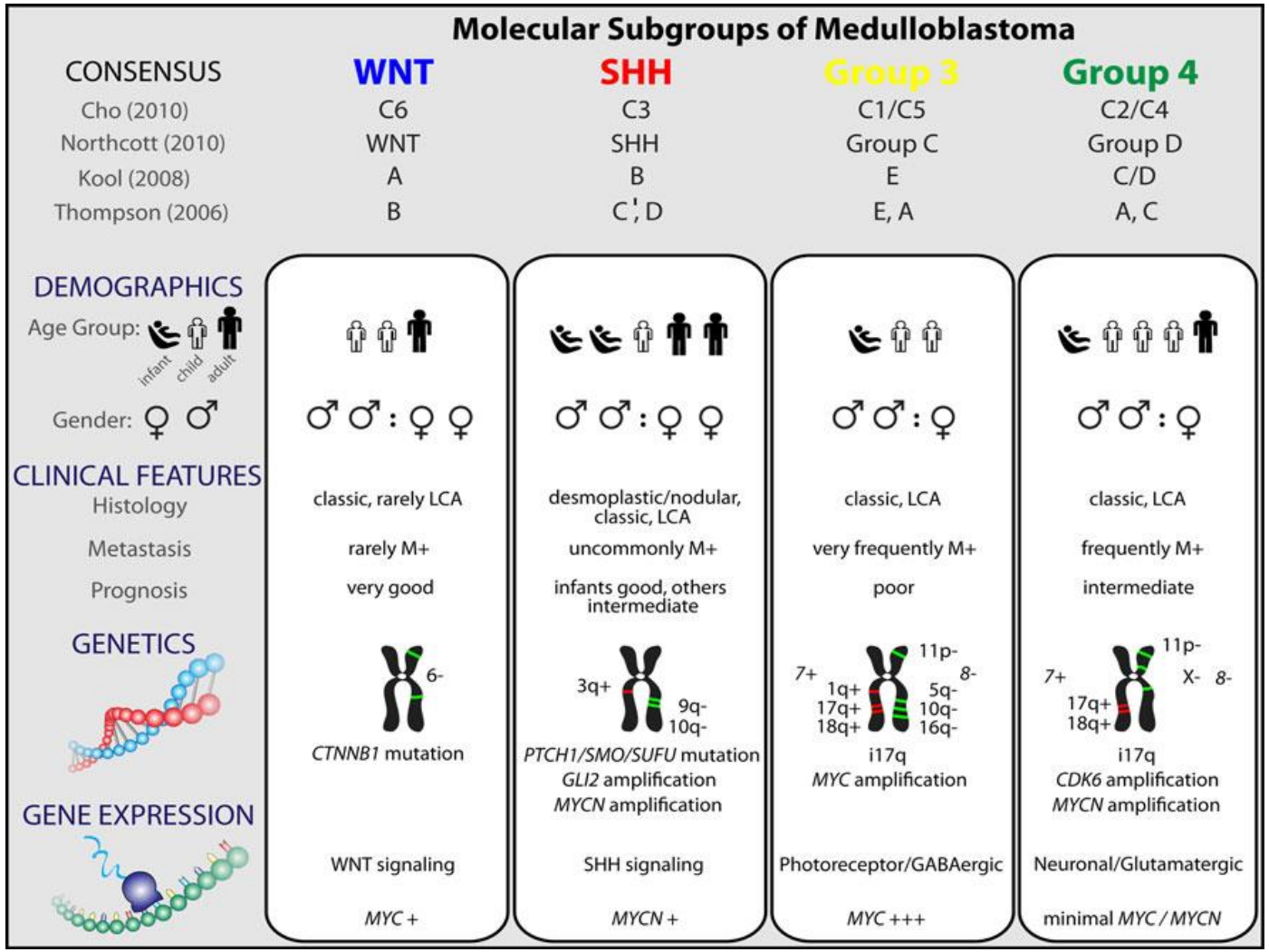
- H3.3 G34RV
- Rarely H3.3 K27M . No H3.1 K27M
- Mutated epidermal growth factor receptor (EGFR)
- *MYC* and *MYCN* amplifications not usually seen
- frequent isocitrate dehydrogenase 1 (*IDH1*) or *IDH2* mutations





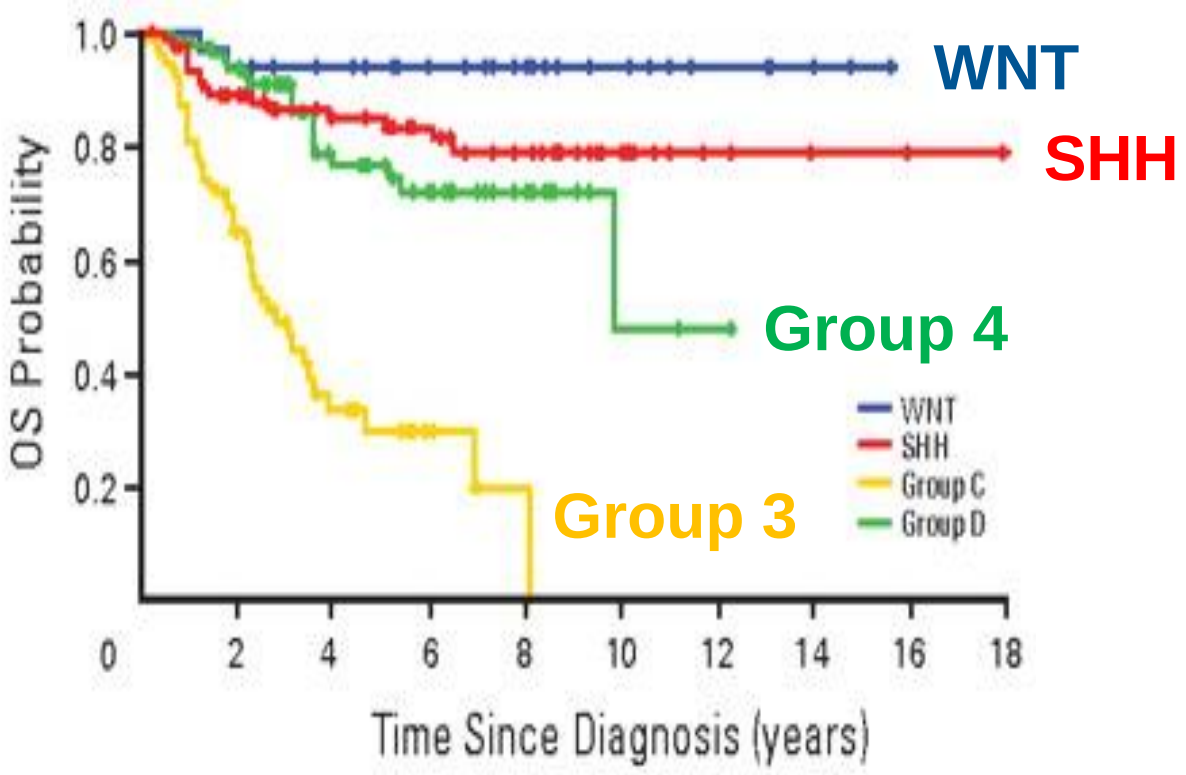
Mackay et al. Cancer Cell 2017 32, 520-537.e5DOI: (10.1016/j.ccell.2017.08.017)

EMBRYONAL TUMORS-MEDULLOBLASTOMA



M. Taylor Acta Neuropathol (2012) 123:465-472

Subgroup Influences Prognosis



Medulloblastoma in AYA

- 20% of the cases only >14 y.o.
- adult medulloblastomas are primarily of the SonicHedgehog (SHH) subgroup,
- WNT and Group 4 tumors forming a minority of cases
- SHH tumors in adults are mostly driven by mutations in *SMO* and *PTCH1*, with *GLI2* and *MYCN* amplifications rarely see and do not express *TP53*

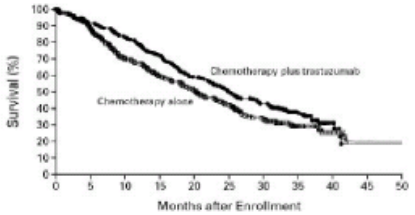
Northcott et al. J Clin Oncol 2011;29:1408

ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

- Καρκίνος χαρακτηρίζεται από το μοριακό προφιλ του κ την ιστική προέλευση
- Εκπληκτικά αποτελέσματα στοχευμένης θεραπείας έναντι κινητήριων μεταλλάξεων

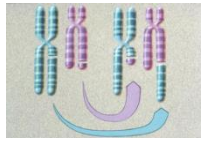
1997

1º Στοχευμένη rituximab



1998

Trastuzumab εναντι HER2+ Ca μαστού



2001

Imatinib

FDA

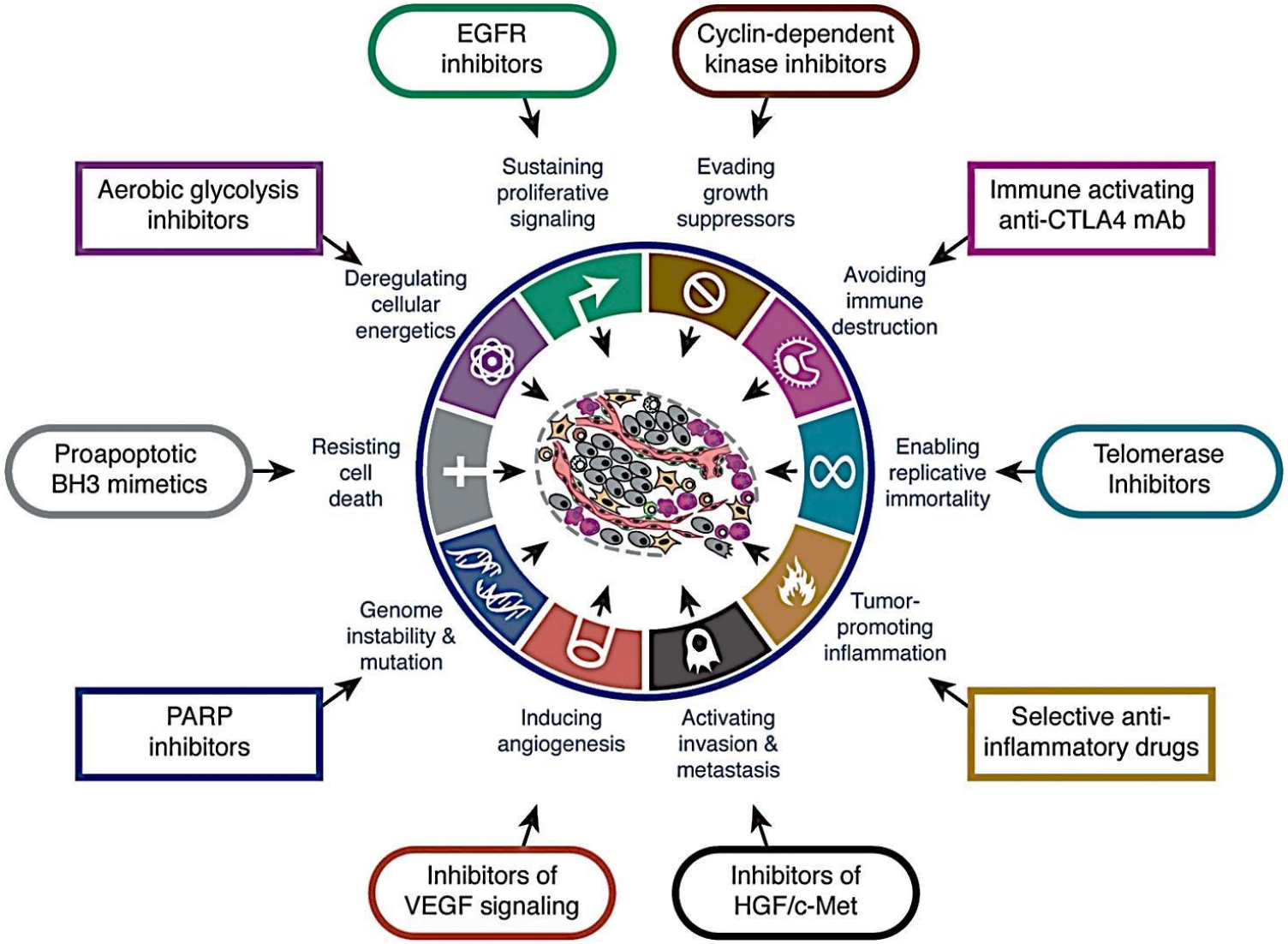
1997-2016

100+ FDA-approved Στοχευμένη θεραπείας

CancerProgress.Net

Image Sources: Slamon D, et al. Engl J Med 2001; 344:783-792; NCI; FDA

PRECISION MEDICINE: TARGETED THERAPY



Hanahah D & Weinberg RA. *Cell* 2011 144, 646-674

Precision Medicine: Targeted Therapy

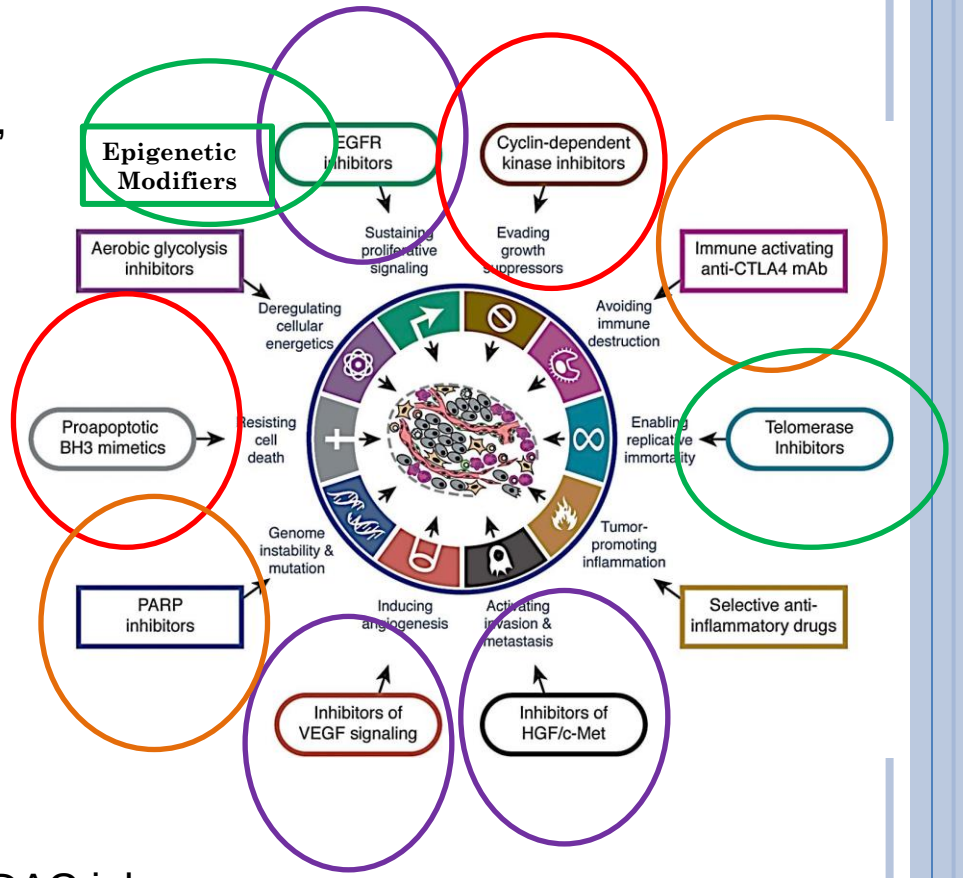
Most actionable events:

- **Growth factor signalling pathways**
  - Receptors of Tyr Kinases- related (ALK, FGFR, NTRK, PDGFR, EGFR, VEGFR, KIT, MET)
  - RAS–MEK-MAPK signalling pathways
  - JAK-STAT
  - PI3K–AKT–mTOR signalling pathways
    - While PI3K inhibitors show toxicity
    - mTOR inhibitors with proven cytostatic efficacy

- **Cell Cycle Regulation**
  - D type cyclins, CDK4 and CDK6
  - Suppressor gene (CDKN2A) CDKinh p14 and p16
  - Apoptic signaling pathways (inhibiton of MDM2, BCL2)

- **Developmental Signalling Pathways**
  - SHH signaling
  - other transcriptional networks: indirectly by epigenetic modifiers, like HDAC inh (like in MYC, MYCN, PAX3,PAX7–FOXO1 expression)

- **Cancer phenotypic vulnerabilities**
  - high mutational burden (immune checkpoint inhibitors)
  - 'BRCAness' signature (PARP inhibitors)



Hanahah D & Weinberg RA. *Cell* 2011 144, 646-674

Registry Patient ΥΦΧΩ

Overexpression of HDAC5

HDAC5 belongs to the group of histone deacetylases which are involved in various cellular processes. There is not much known about the precise role of HDACs in aRMS, but HDACi were shown to inhibit RMS tumor growth in vivo (PMID:26162688).

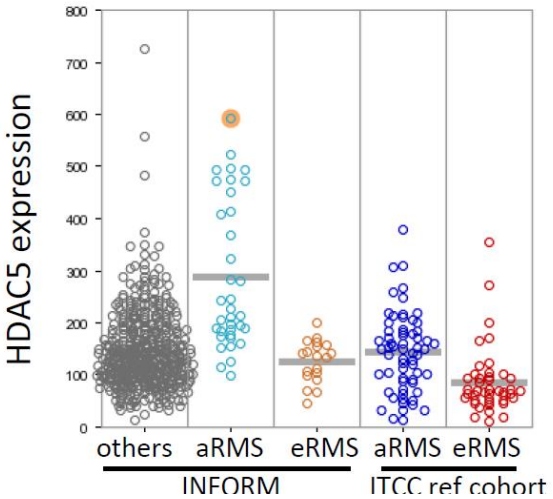
→ consider **HDACi**

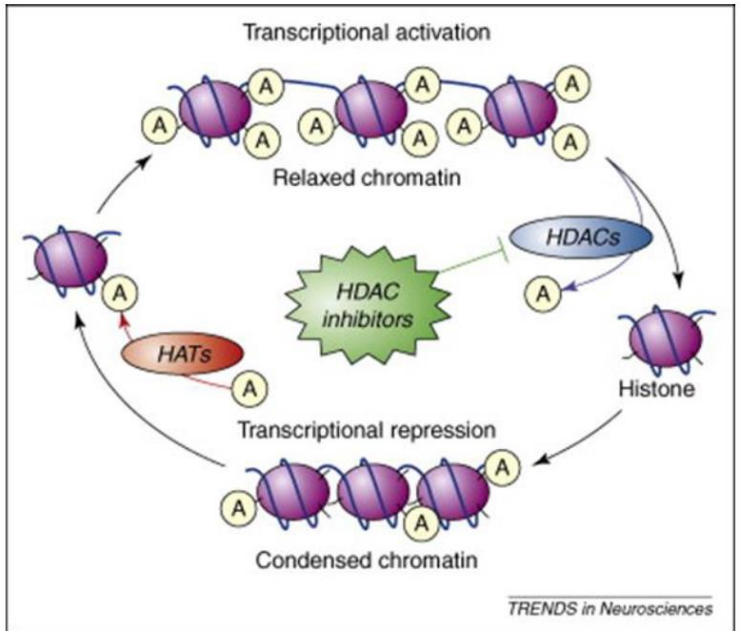
potential matching drugs: approved: **Vorinostat, Panobinostat, Belinostat, Valproic acid**

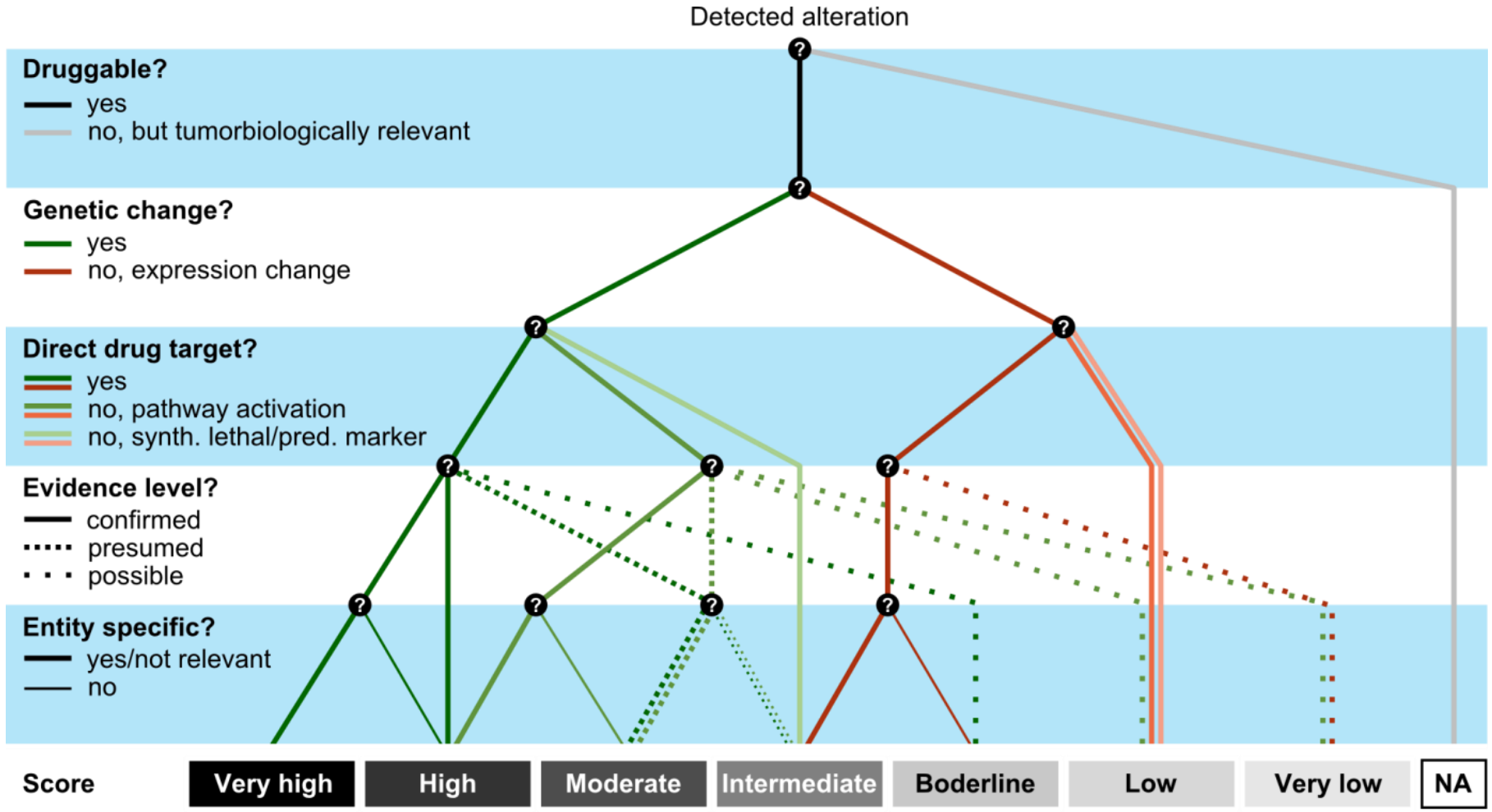
in development: **CUDC-907, Pracinostat, AR-42, Givinostat (ITF2357)**

open clinical trials: no suitable pediatric trials available

Priority	Alteration type	Entity	Target Type	Action of drug
5. borderline	Expression	Other	Overexpressed driver	Direct





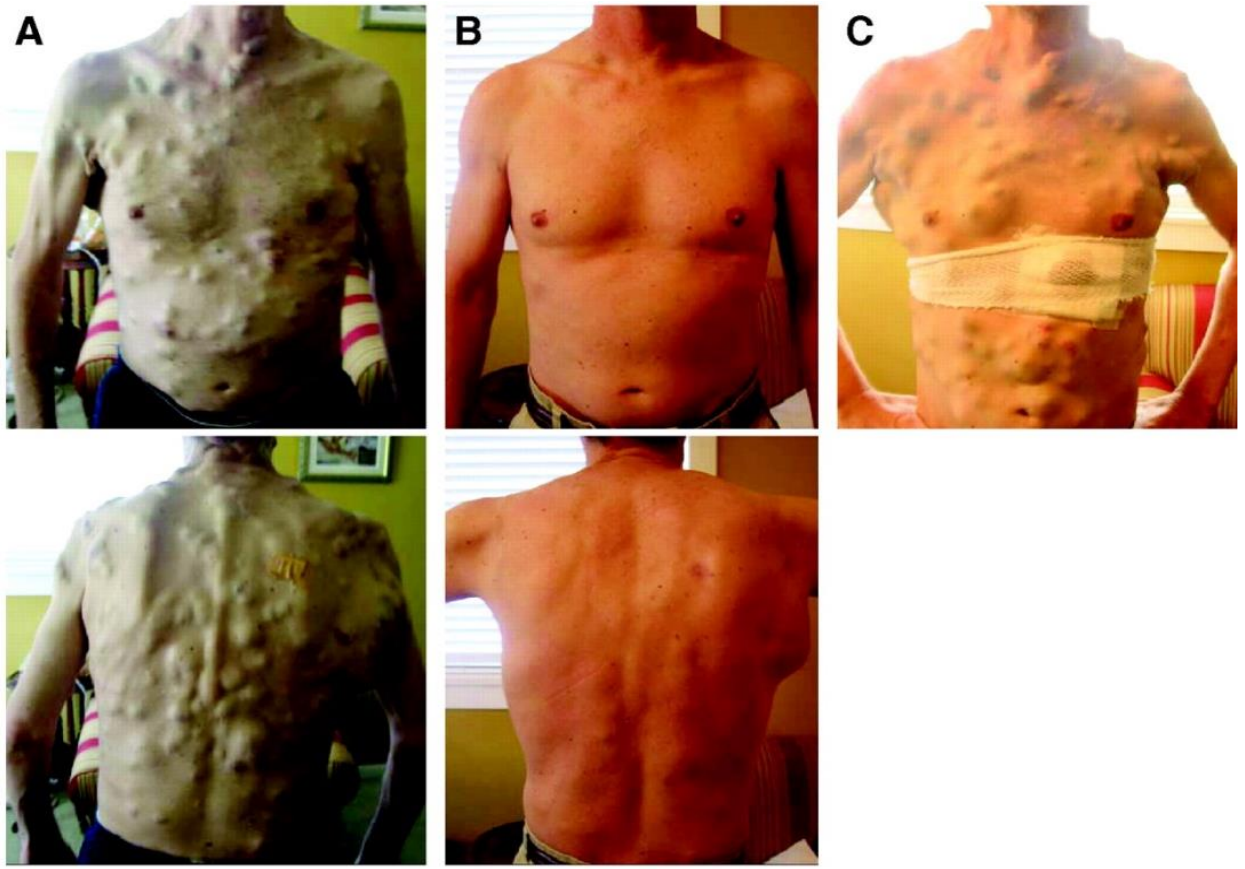


Adapted from Worst BC et al. *EJC* 2016,
Kindly provided by Stefan Pfister

ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

Στοχευμένη θεραπεία αποτυγχάνει λόγω πολυπλοκότητας της νεοπλαστικής εξεργασίας

.

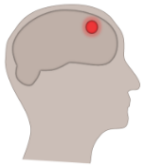


Source: Wagle, N et al. Dissecting Therapeutic Resistance to RAF Inhibition in Melanoma by Tumor Genomic Profiling. JCO August 1, 2011 vol. 29 no. 22 3085-3096

Limitations of Molecular Targeted Therapies in Pediatric and AYA patients

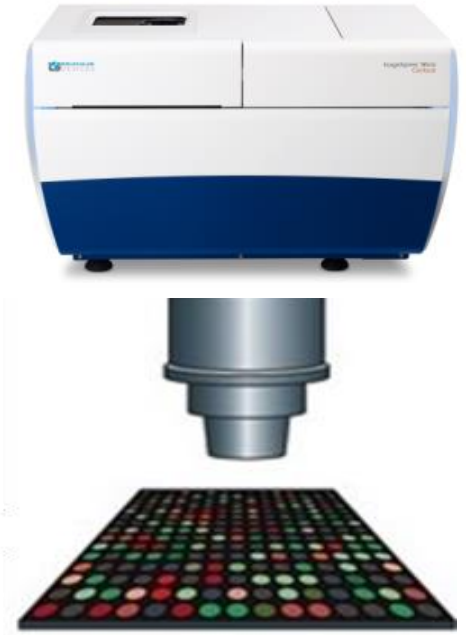
- Most Data on targeted therapies derives from:
  - Case reports/ Small series / Pilot studies
  - Evaluated in relapse / resistant diseases
- Reasons for failure
  - Intra-tumoral / between metastasis heterogeneity
  - Cross-talk between more than 1 signaling pathways
  - Development of resistance (new mutations in the gene or in genes affecting the pathway downstream)
- Many Cancer in AYA patients remain rare
- Number of potential therapies increases dramatically: very difficult to plan for large trials

Επόμενο Στάδιο : in-vitro drug screening

(Epi-)Genomic profiling ⟵  ⟶ Co-clinical Drug Screening

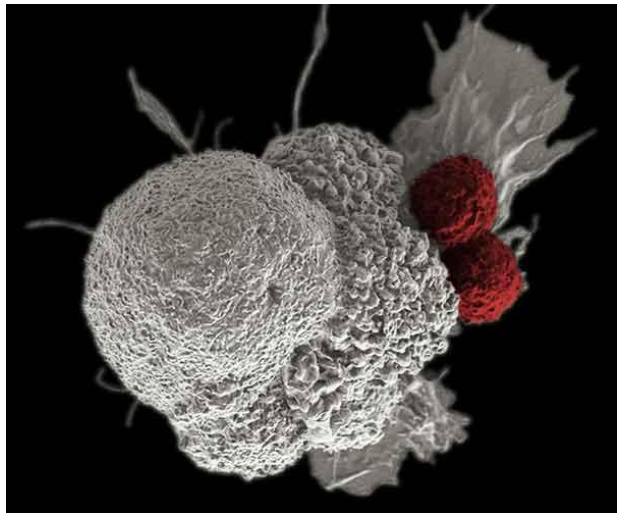
short-term tumor cell culture *in vitro* drug treatment

image-based high-content drug profiling



Ανοσοθεραπεια

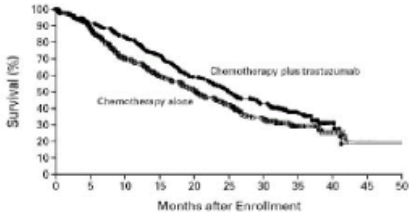
- ‘Απλά’ MoAbs
- MoAbs συνδεδεμένα με τοξίνη
- MoAbs που διεγείρουν ανοσολογική απάντηση



ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

1997

1° Στοχευμένη rituximab



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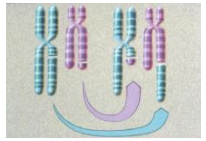
Trastuzumab εναντι HER2+ Ca μαστού



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CancerProgress.Net

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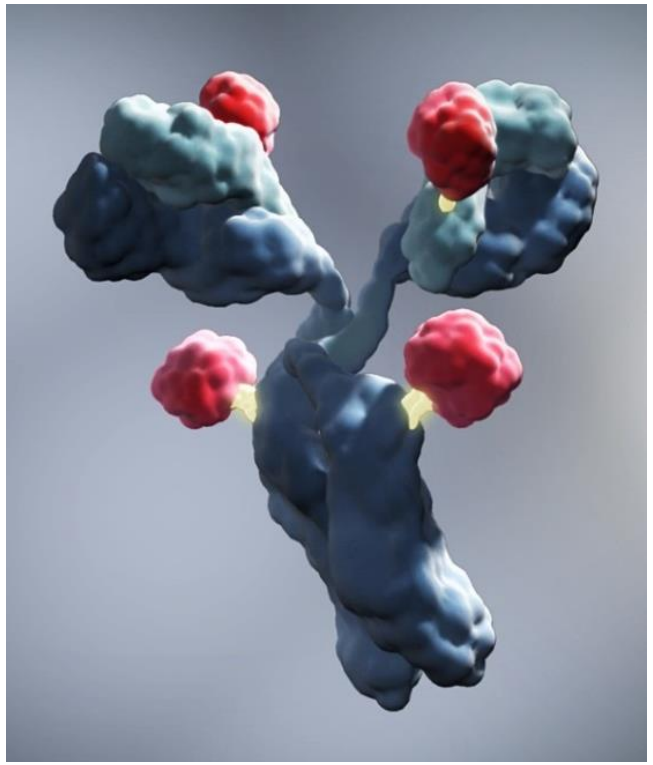
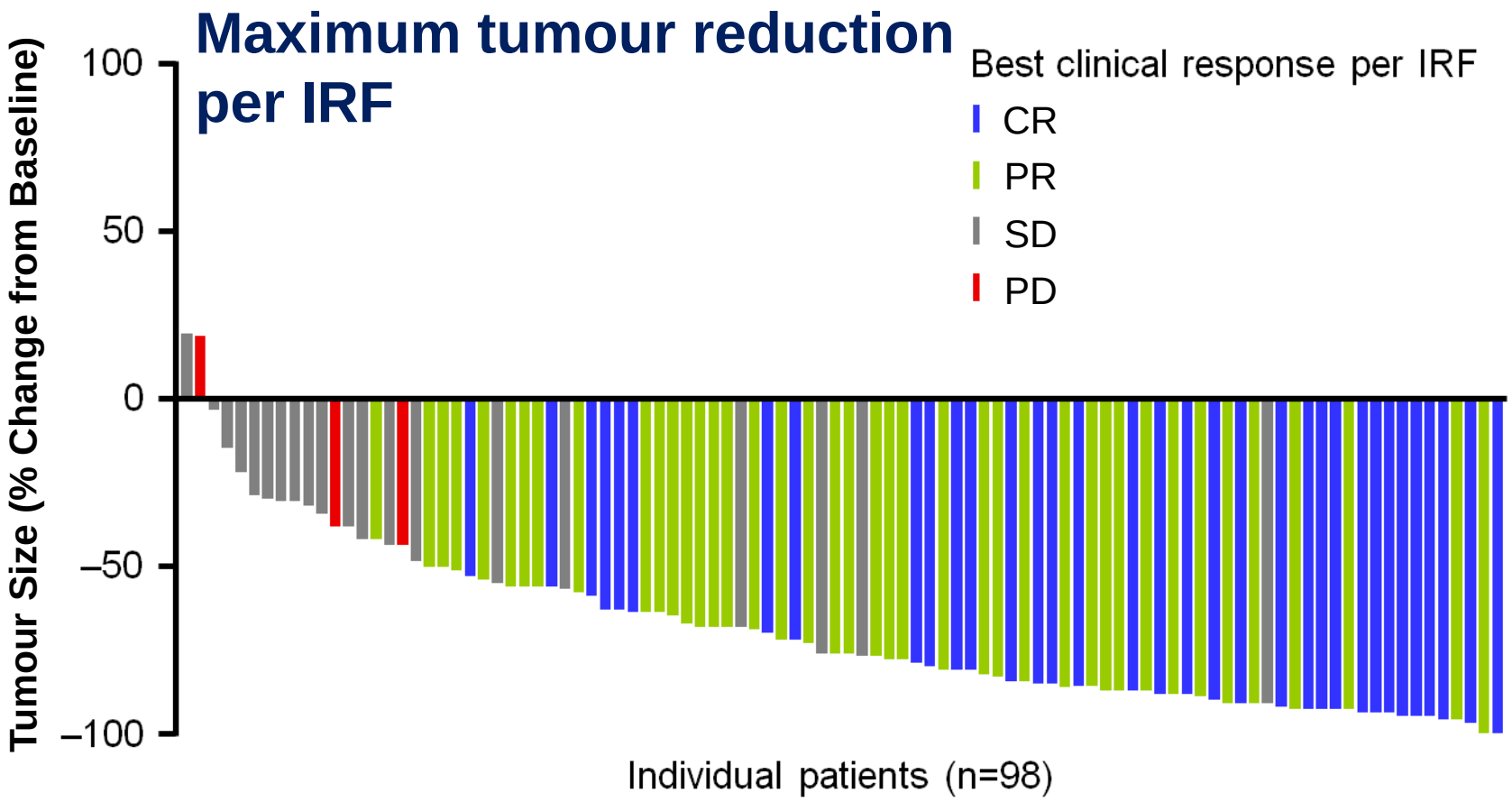
BRENTUXIMAB VEDOTIN



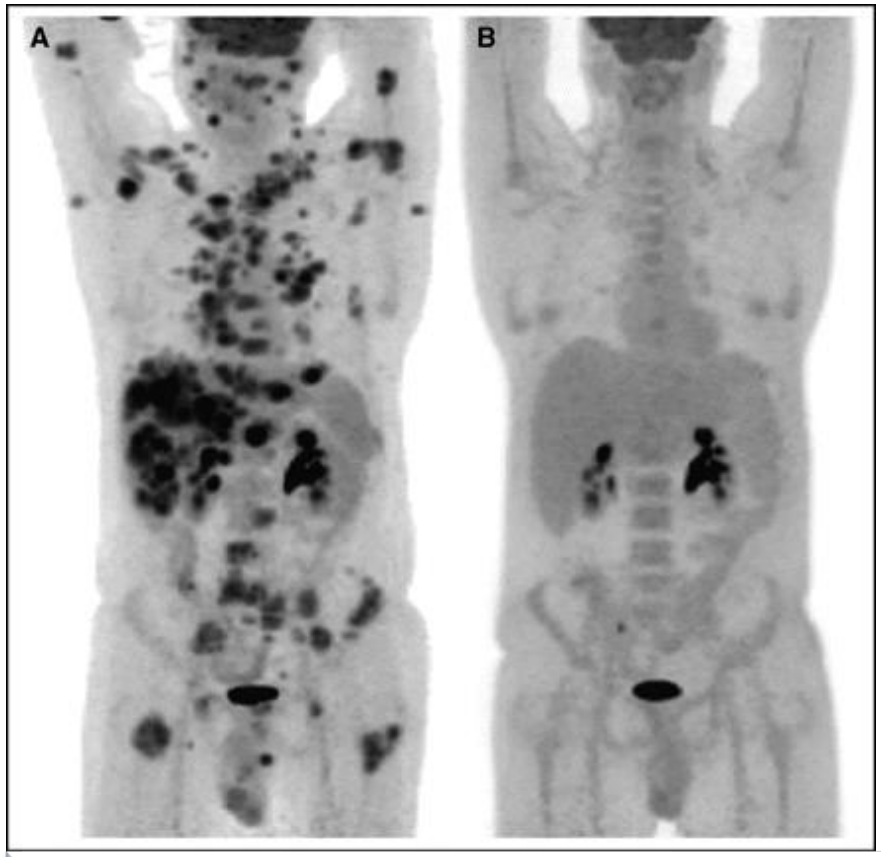
Σύζευγμα αντισώματος-φαρμάκου (ADC):

- Υποτροπη/ανθεκτικο HL κ ως 1η γραμμή σε υψηλού κινδύνου
- Αναπλαστικό Λέμφωμα (2η γραμμή)
- Παιδιατρική ένδειξη υπο μελέτη

SG035-0003: Phase 2 pivotal study of brentuximab vedotin in patients with rel/ref HL post ASCT



Younes A, et al. J Clin Oncol 2012;30: 2183-2189.



Πλήρης ύφεση μετά από 4 κύκλους θεραπείας με Brentuximab vedotin

Pro B, et al. J Clin Oncol 2012; 30:2190-2196.

BLINATUMOMAB

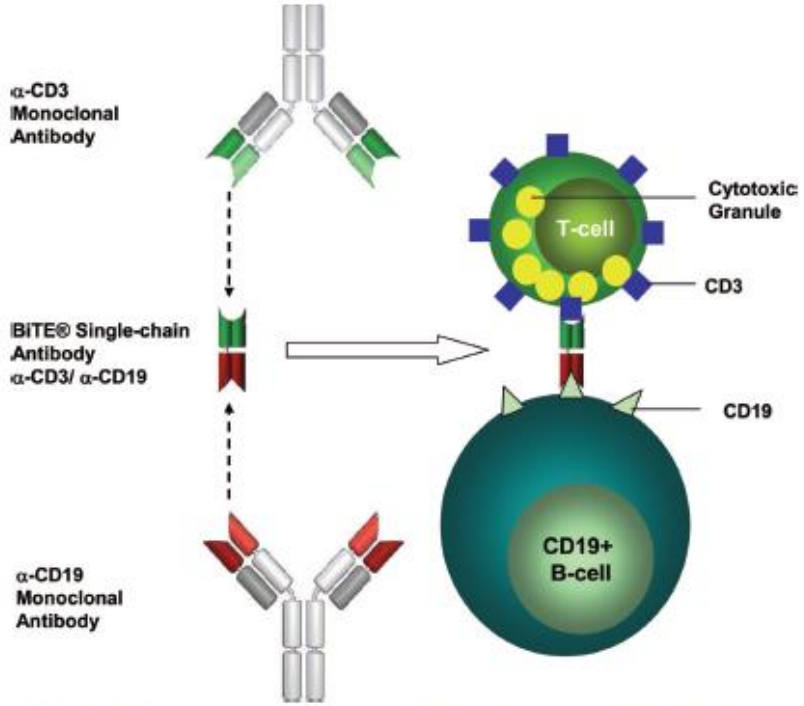


Figure 1. Single-chain antibody blinatumomab redirects CD3+ T cells to kill CD19+ B cells.

- Bi-specific T-cell engaging (BiTE) antibody that links CD3+ T-cells to CD19+ cells, enabling killing of the CD19+ cells by the patient's own cytotoxic T-cells

  Given by continuous 28-day infusion

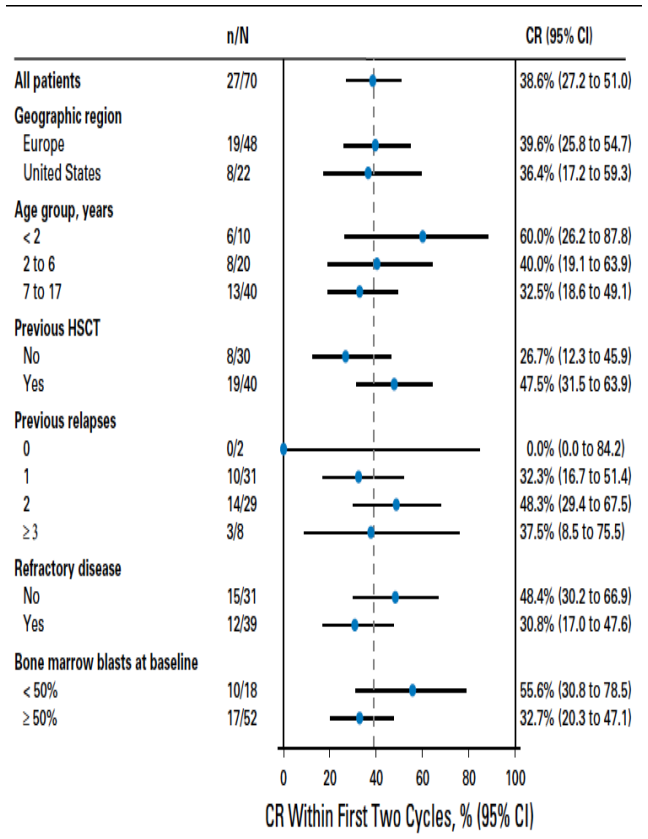
  Side effect profile very different from cytotoxic chemotherapy
  - Causes lymphopenia but no significant anemia, thrombocytopenia or neutropenia
  - Very low incidence of serious infections
  - Unique CNS toxicities including hallucinations and seizures

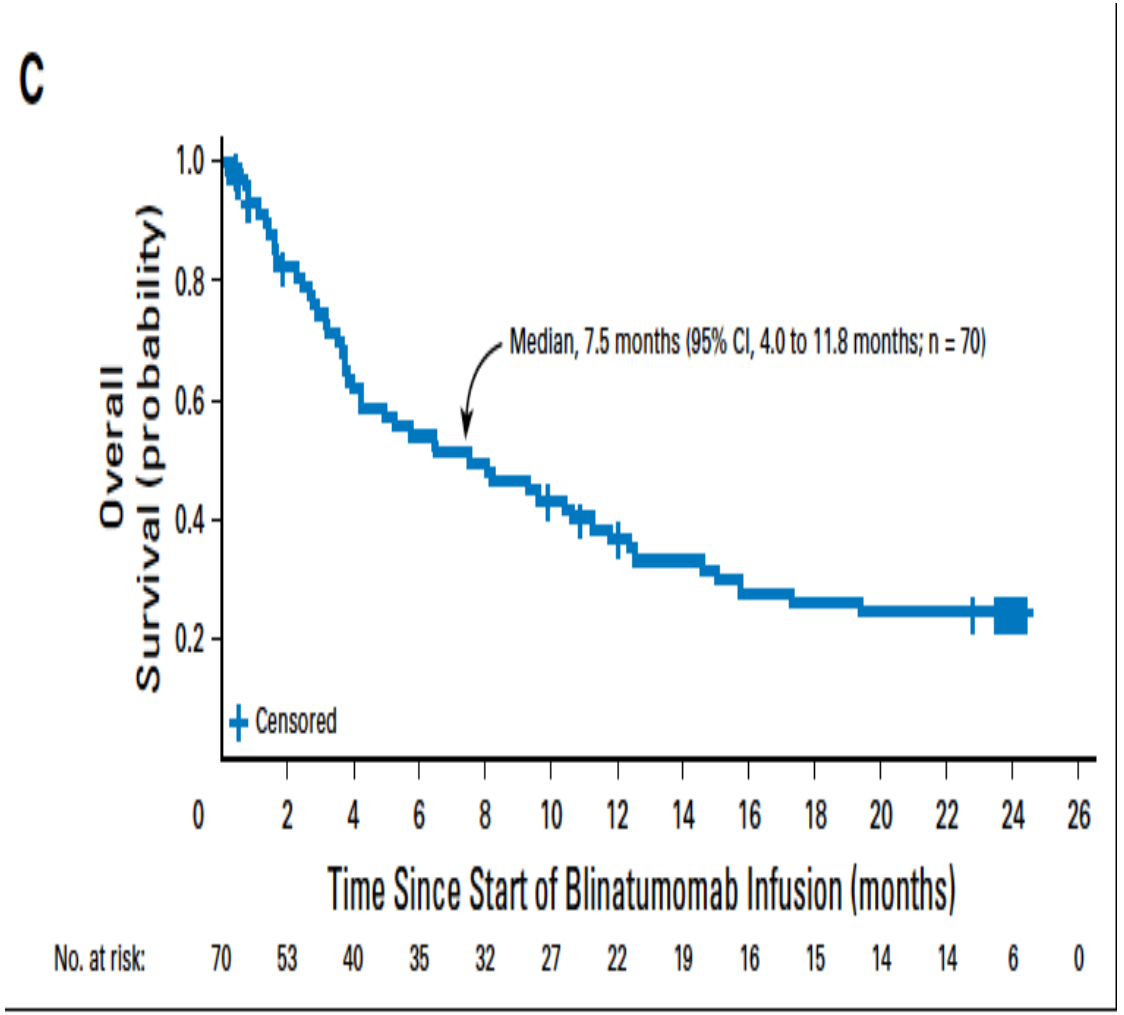
VOLUME 34 · NUMBER 36 · DECEMBER 20, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

Arend von Stackelberg, Franco Locatelli, Gerhard Zugmaier, Rupert Handgretinger, Tanya M. Trippett, Carmelo Rizzari, Peter Bader, Maureen M. O'Brien, Benoît Brethon, Deepa Bhojwani, Paul Gerhardt Schlegel, Arndt Borkhardt, Susan R. Rheingold, Todd Michael Cooper, Christian M. Zwaan, Phillip Barnette, Chiara Messina, Gérard Michel, Steven G. DuBois, Kuolung Hu, Min Zhu, James A. Whitlock, and Lia Gore





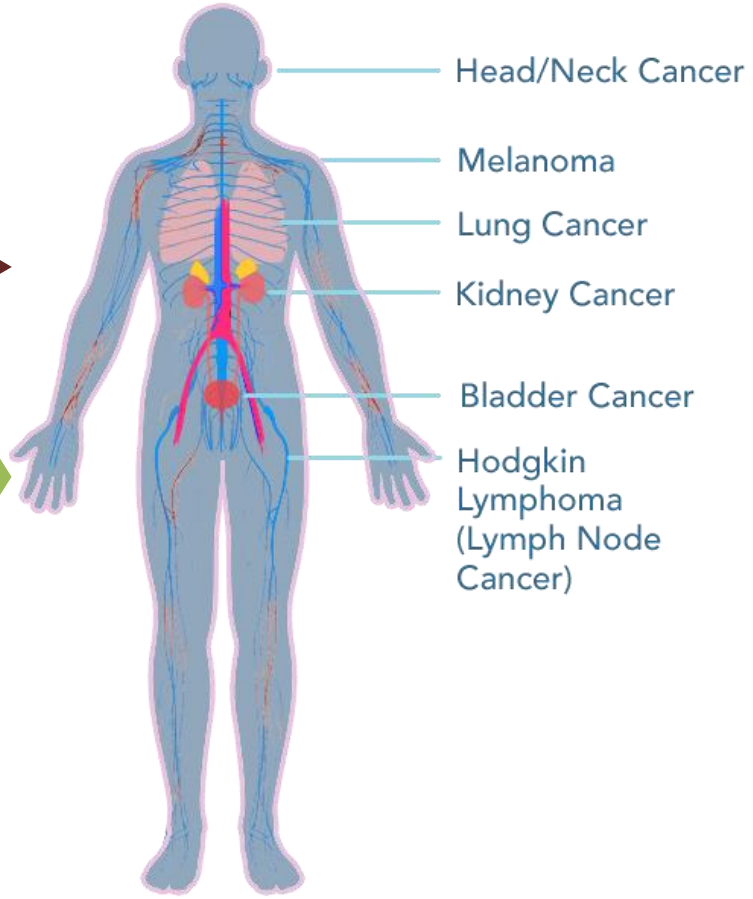
Η ΑΝΟΙΞΗ ΤΗΣ ΑΝΟΣΟΘΕΡΑΠΕΙΑΣ

2016 ASCO
Advance of the Year

2011
Ipilimumab introduced for melanoma

2014
Pembrolizumab, nivolumab approved for melanoma

2015-2016
PD-1/L-1 drugs benefit even more of cancers



Check Point Inhibitors

T-cell exhaustion

- Programmed death-1 (PD-1)
- Cytotoxic T-lymphocyte associated protein 4 (CTLA4)
- Cell lymphocyte activation gene-3 (LAG-3)

Cancer Cells

- PD-ligand 1

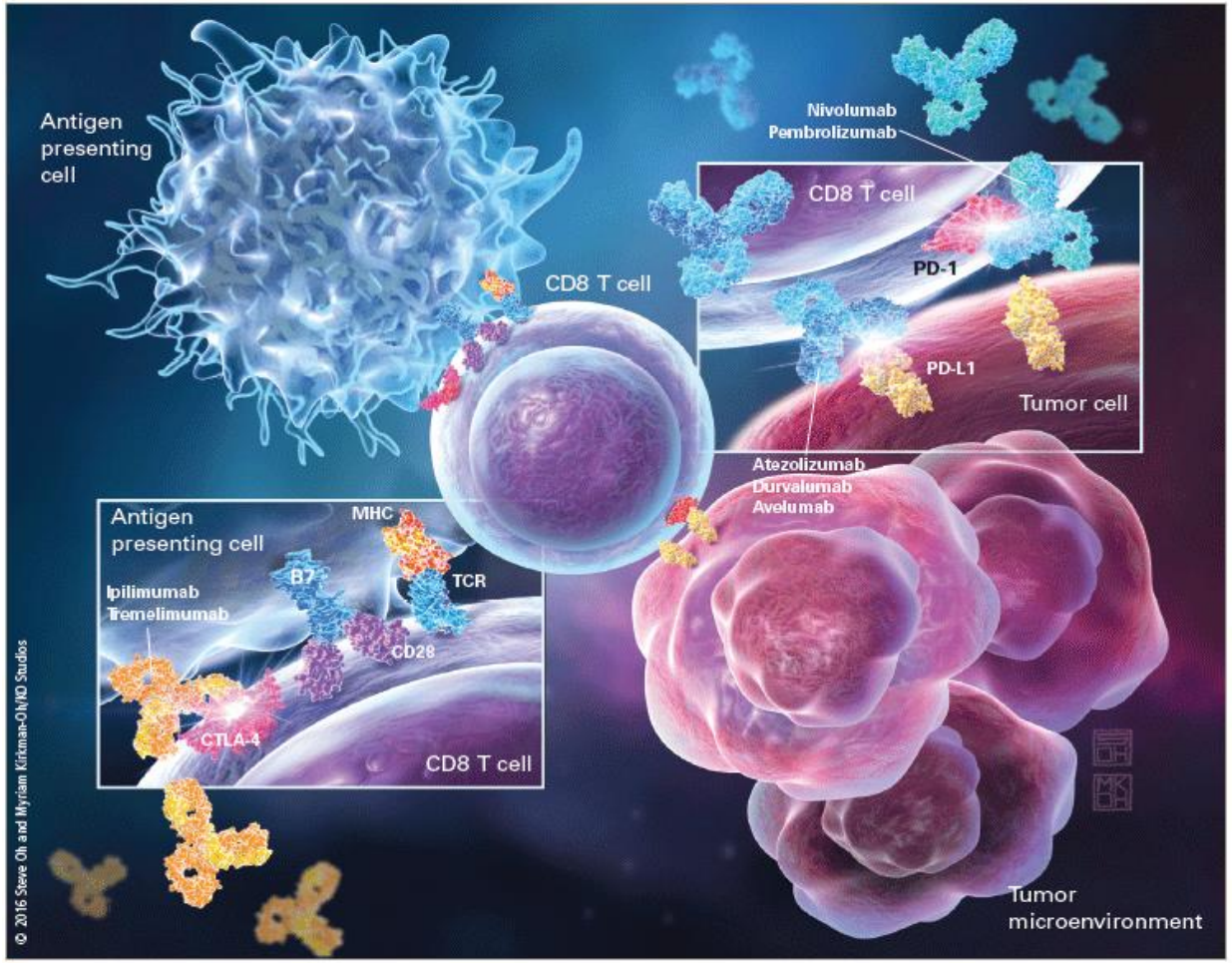
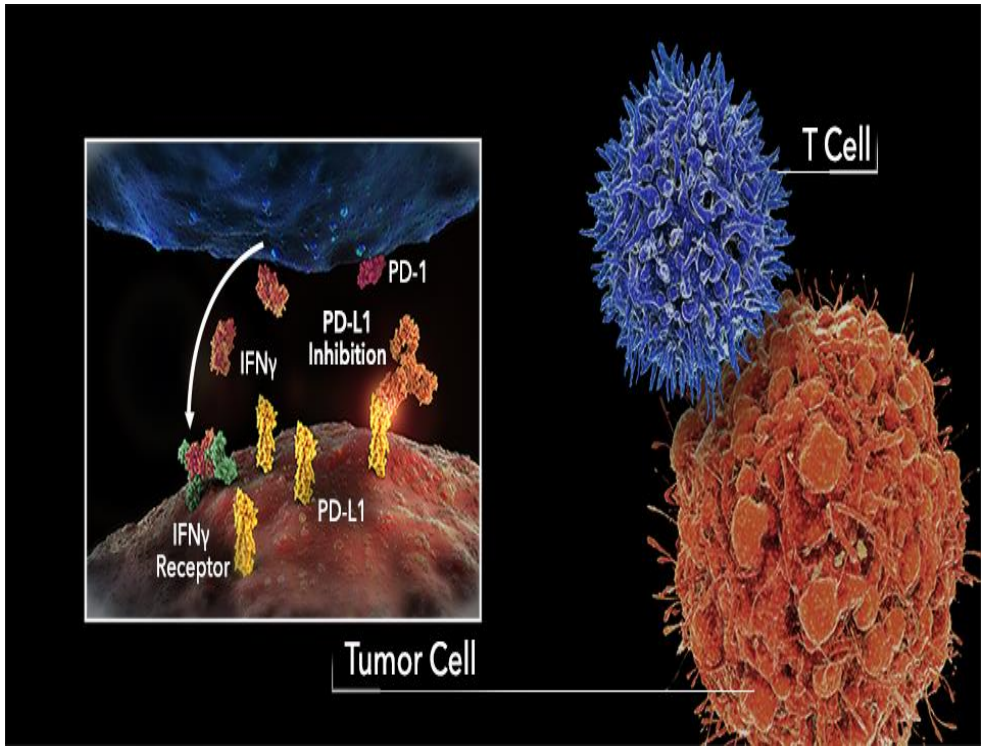


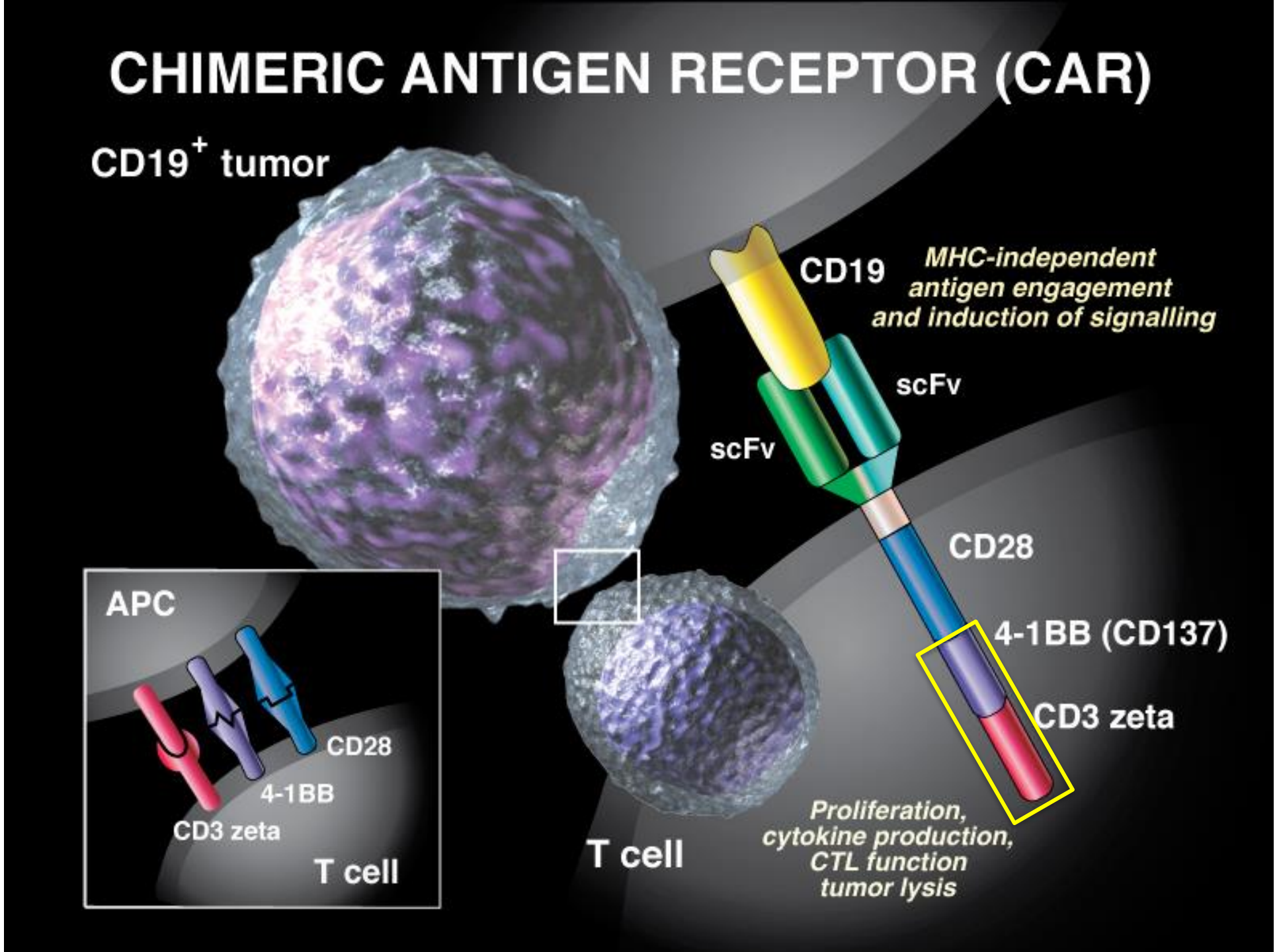
Figure. Immune Checkpoint Inhibition Mechanisms of Action Relevant to Lung Cancer Immunotherapy—T cells

Check Points Inhibitors

Anti- PD- 1

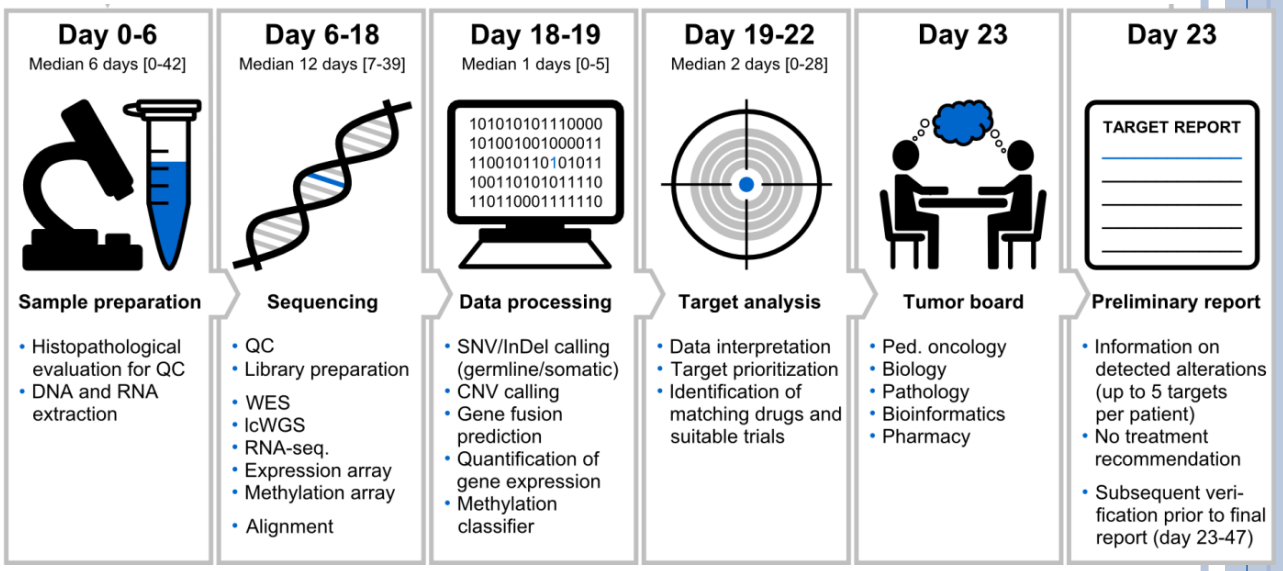
- Nivolumab (Bristol-Myers Squibb) IgG4 anti-PD-1
- Pembrolizumab (Merck & Co.) IgG4 anti-PD-1
- Atezolizumab (Genentech) IgG1 anti-PD-L1 monoclonal metastatic NSCLC
- Atezolizumab studied in diffuse large B-cell lymphoma and follicular lymphoma.
- Durvalumab (AstraZeneca) bladder / lymphoid / myeloid
- Avelumab (Merck KGaA & Pfizer), CA-170 (Curis, Inc.) hematological malignancies




CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent
antigen engagement
and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation,
cytokine production,
CTL function
tumor lysis

Ιατρικη Ακριβειας

- Πολλές πλαρφόρμες μοριακής ανάλυσης (INFORM, MASTER, MAPPYACTS, SPECTA)
  - Τράπεζες Big Data Banks
  - Πολυσυστηματική προσεγγιση

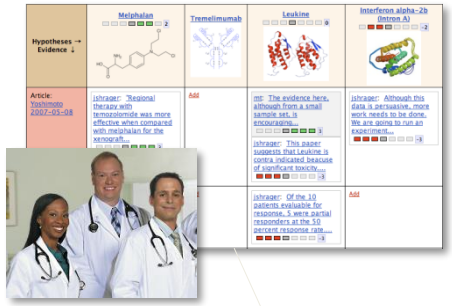


Graph adapted from Worst BC et al. *EJC* 2016

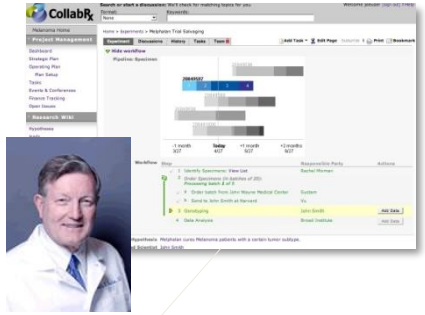
Η εποχή των Μαζικών Δεδομένων

Επιστήμονες

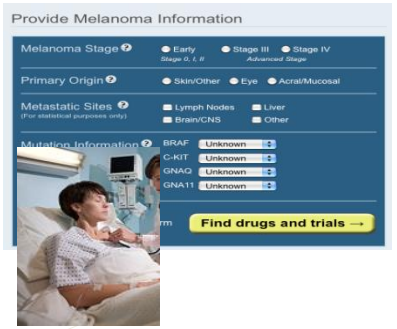
Κλινικοί Ερευνητές



Ιατροί

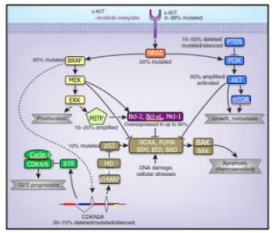


Ασθενείς

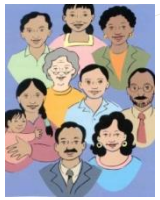


Data

Rapid Learning System

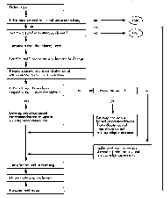


Μοριακά Μοντέλα Ασθενειών



Μελέτες

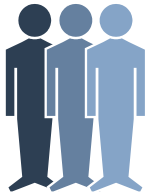
Θεραπείες



Κατευθυντήριες Οδηγίες

Βιβλιογραφικά Δεδομένα

Tests



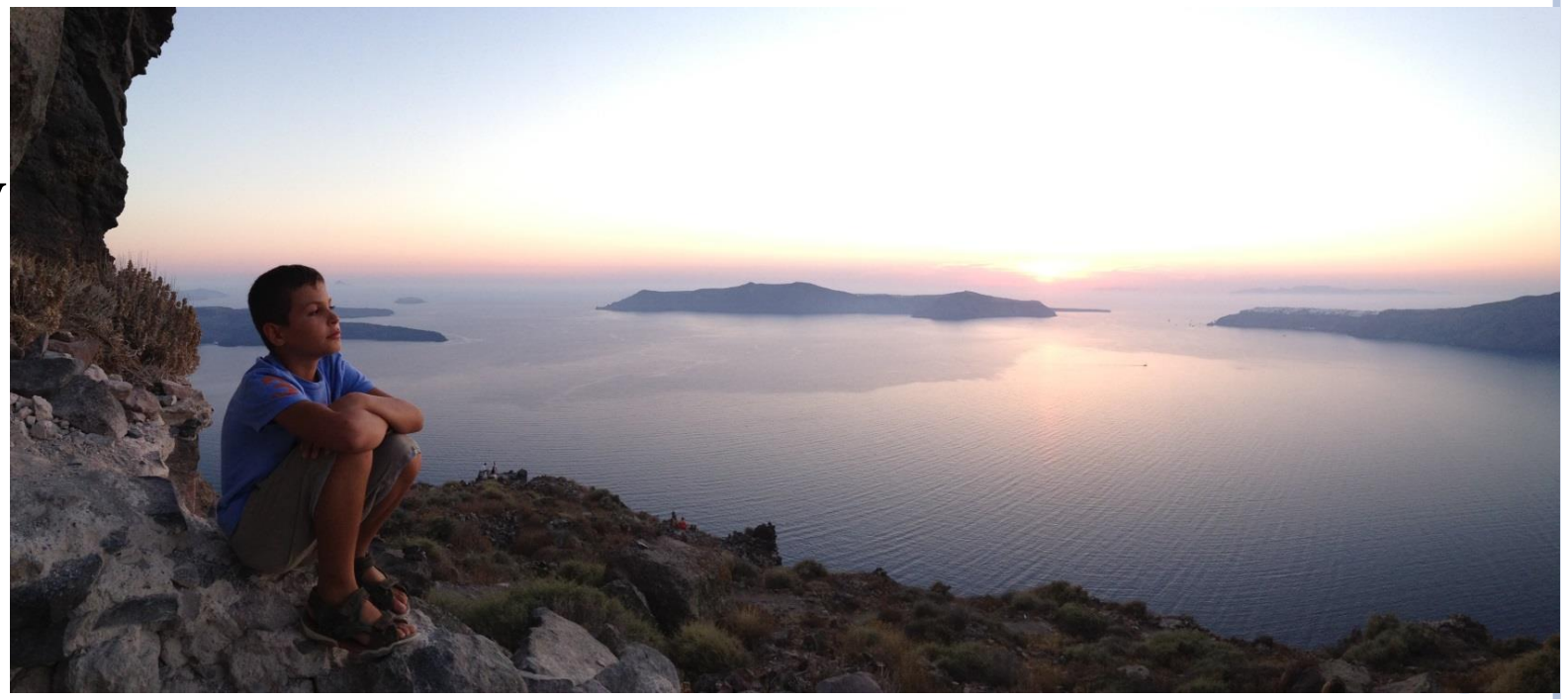
Περιπτώσεις

EPILOGUE…

Precision Medicine –Targeted Therapies: The Future

- More Accurate Diagnosis
- More complex but more precise therapy-oriented stratifications
- More targeted therapies more efficacious, less toxic, less costly and included as First line

DEFINITELY BRIGHTER



Sunset from Skaros at Santorini Island