ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

Καθ. Αντώνης Καττάμης

Α’ Πανεπιστημιακή Παιδιατρική Κλινική

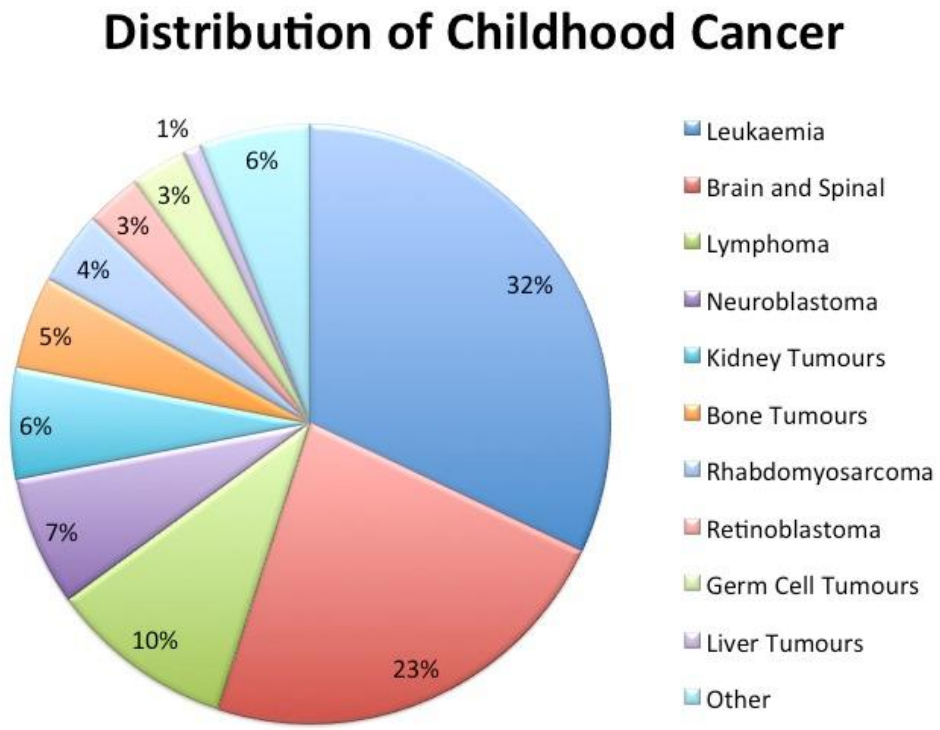
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

European Reference Network Center for Genetic Tumor Risk Syndromes

European Reference Network Center for Paediatric Cancer

Καρκίνος
της Παιδικής (0-14 ετών) – Εφηβικής Ηλικίας (15-19 ετών)

- Σπάνιοι καρκίνοι (<6/100,000/έτος)
- 1% του συνόλου των περιστατικών καρκίνου
- 2η αιτία θανάτου στα παιδιά μετά τα ατυχήματα
- Ευρώπη : 14.000 νέα περιστατικά καρκίνου στις ηλικίες 0-19 ετών το 2022.
- Αναμενόμενοι θάνατοι 2.000 /έτος.
- Ελλάδα περίπου 350 περιστατικά/έτος



SEPTEMBER
CHILDHOOD CANCER
AWARENESS MONTH

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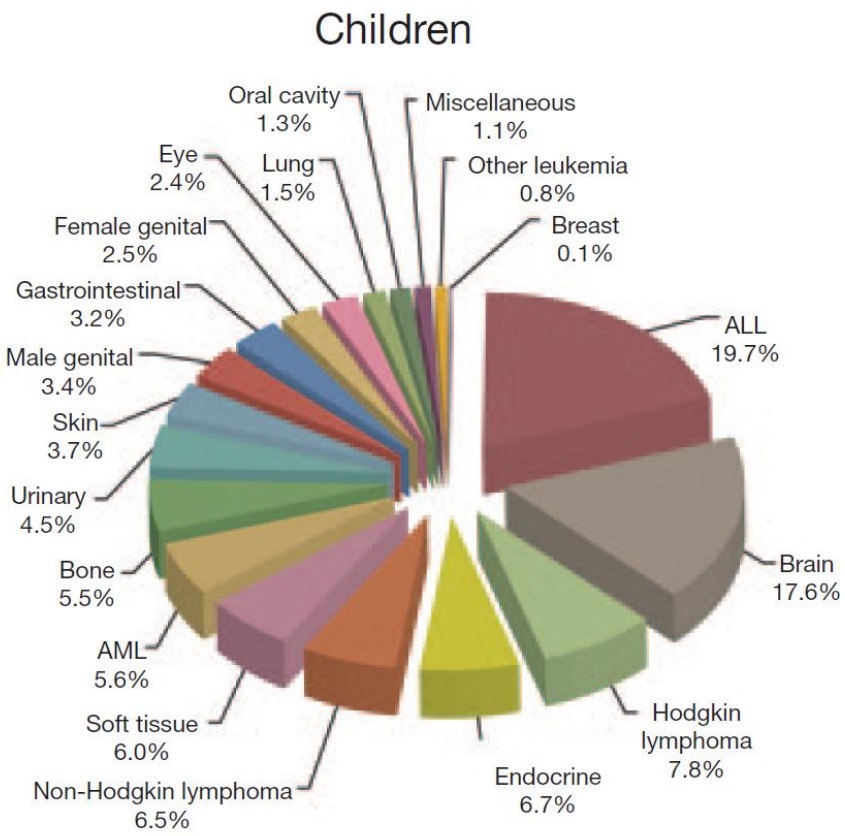
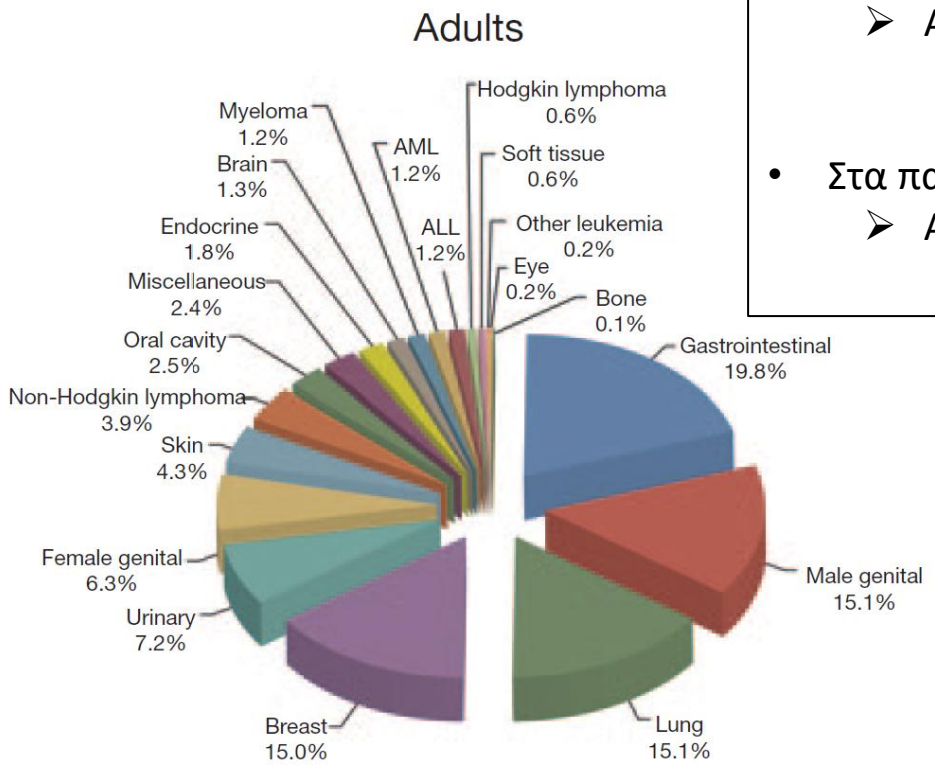
Where they are treated

- Around 300 new patients / year
- Legal Framework: <16 years old
- 7 Units
- 1 Bone Marrow Transplant Unit
- 2-3 Affiliated Clinics

Διαφέρει ο καρκίνος ανάλογα με την ηλικιακή ομάδα?- Τύπος καρκίνου

Συχνότητα τύπων καρκίνου σε παιδιά και ενήλικες – SEER data, 2012





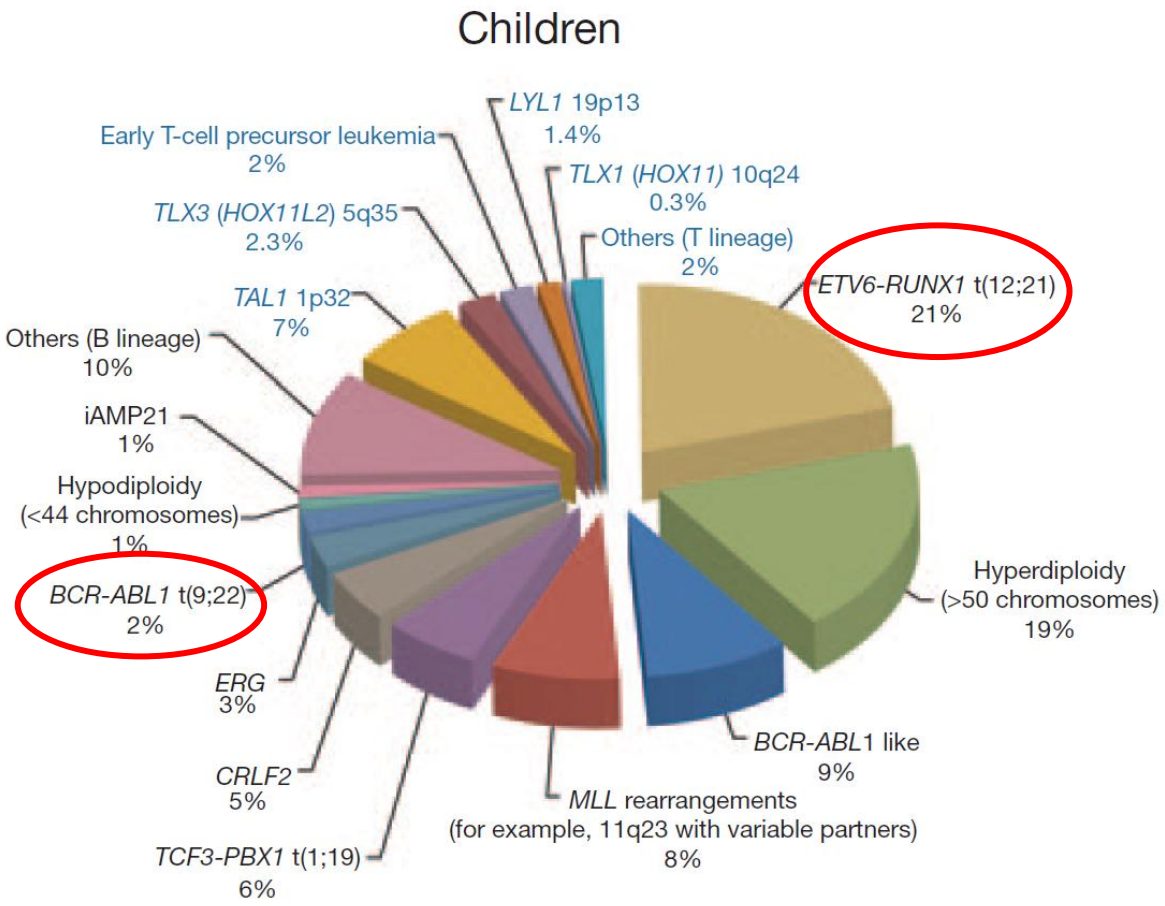
4 πιο συχνοί τύποι καρκίνου

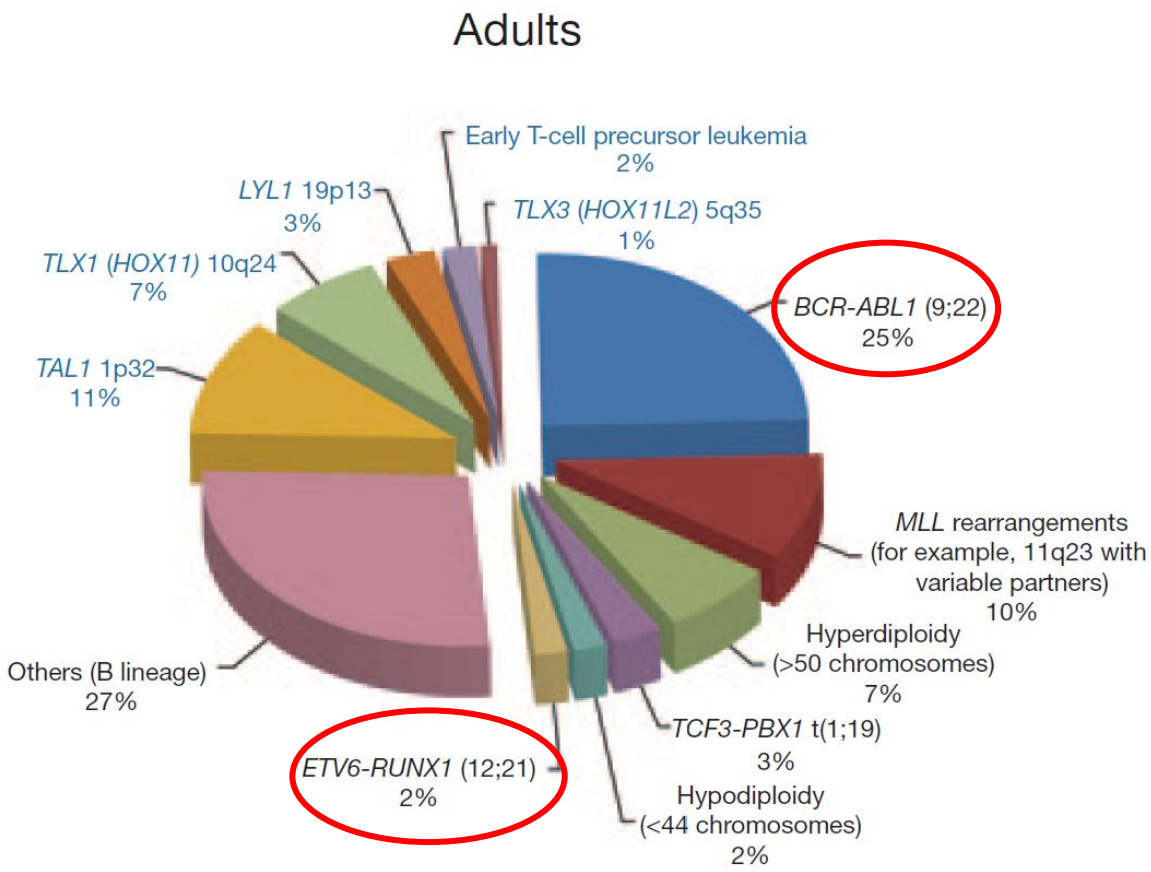
- Στους ενήλικες→ 65%
  - Αντίστοιχα στα παιδιά → 8,2%
- Στα παιδιά → 51.8%
  - Αντίστοιχα στους ενήλικες→ 4,9%

Dowing *et al*., The Pediatric Cancer Genome Project, **Nat Genet**, 2012

Διαφέρει ο καρκίνος ανάλογα με την ηλικιακή ομάδα?- Γενετική Βάση

Συχνότητα της Τ- και Β- Οξείας Λεμφοκυτταρικής Λευχαιμίας (ΟΛΛ) στα παιδιά και στους ενήλικες





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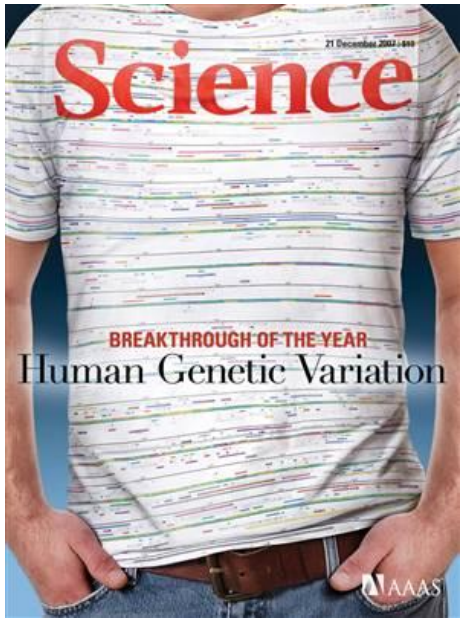
Dowing *et al*., The Pediatric Cancer Genome Project, **Nat Genet**, 2012

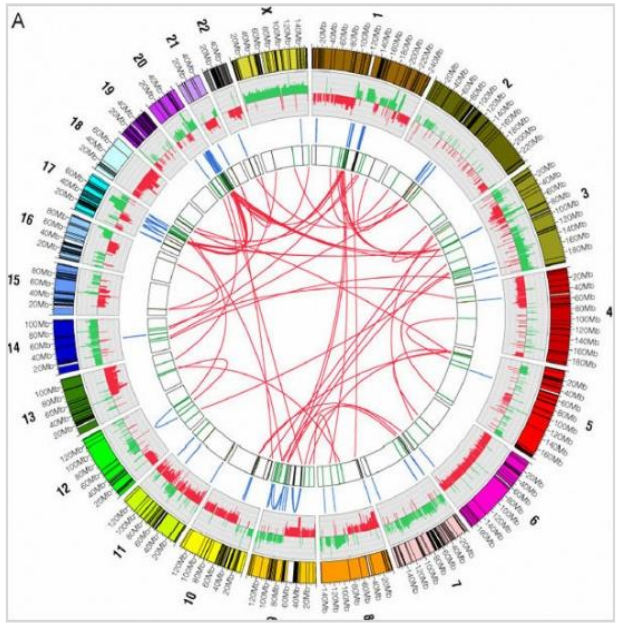
Ορισμοσ

- ‘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*

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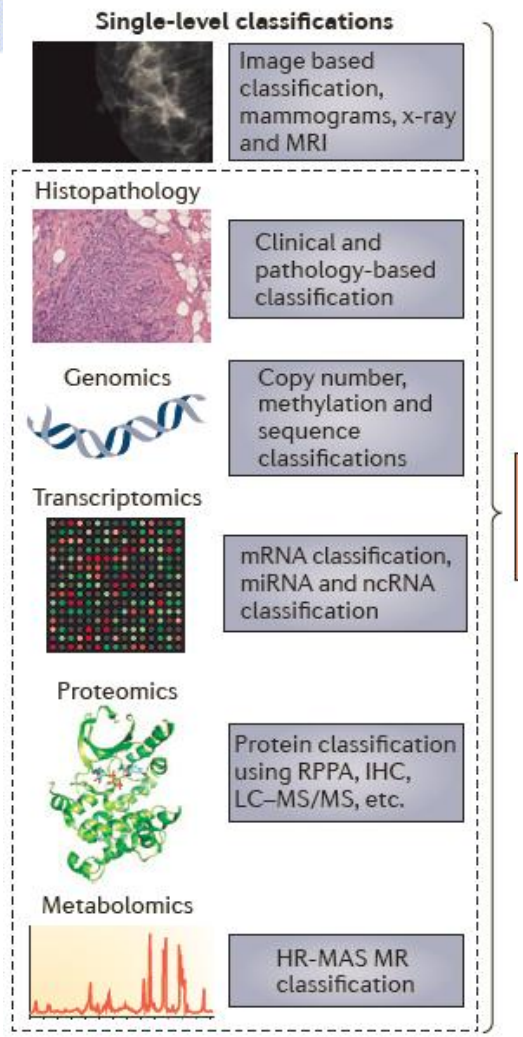
Τα OMICS στην ιατρική ακριβείας



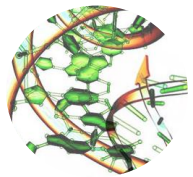
- ΔΙΑΓΝΩΣΗ
- ΔΙΑΣΤΡΩΜΑΤΩΣΗ
- ΘΕΡΑΠΕΙΑ
- ΦΑΡΜΑΚΟΓΕΝΕΤΙΚΗ

Γονιδιωματικη του Καρκινου

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

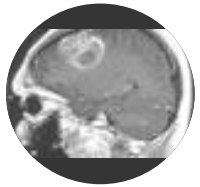
2000

Hallmarks of Cancer **δημοσίευση**



2005

Εγκαινιάζεται το πρόγραμμα Cancer Genome Atlas (TCGA)

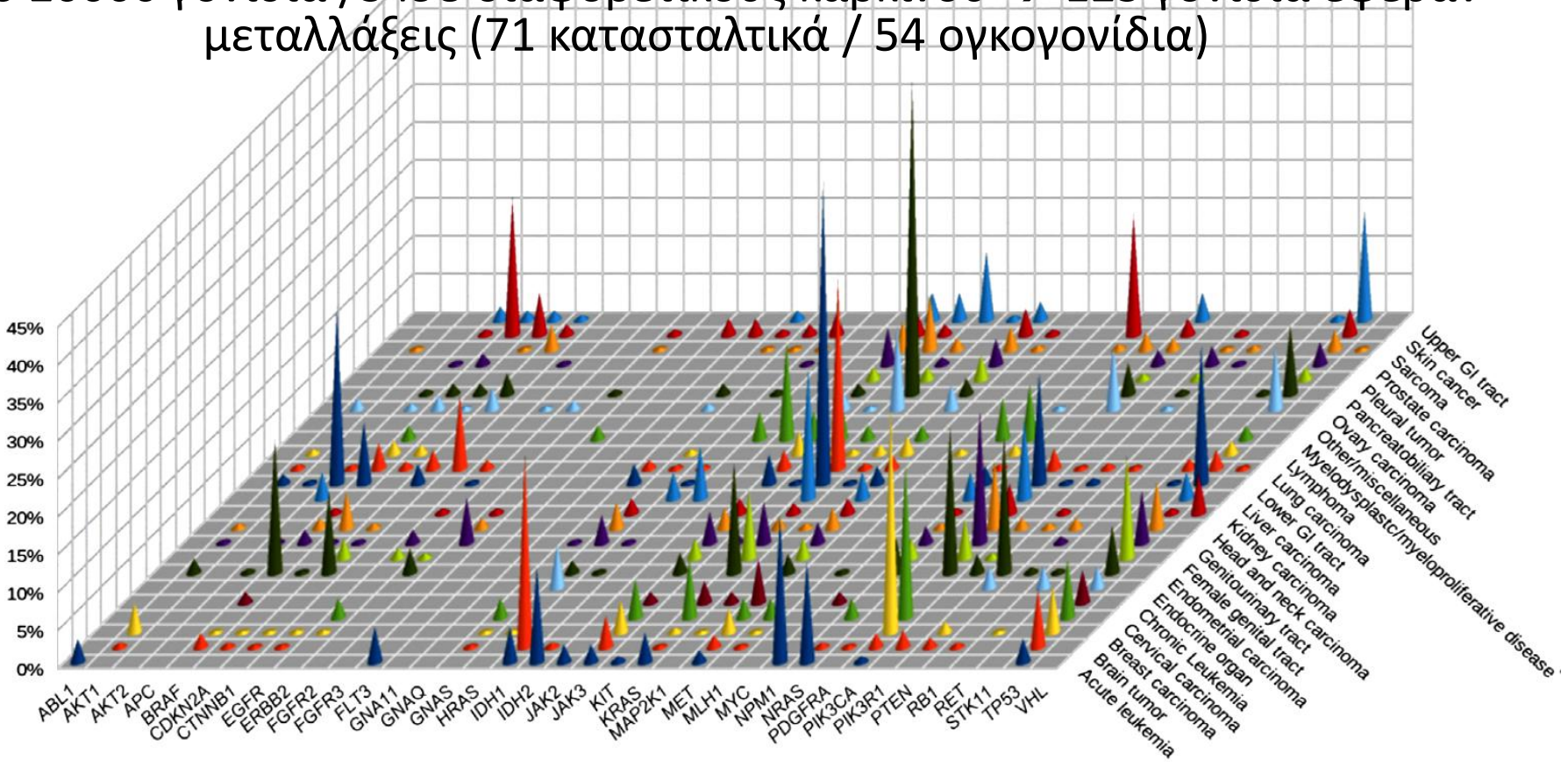


2010-2014

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

Cancer Genetics

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



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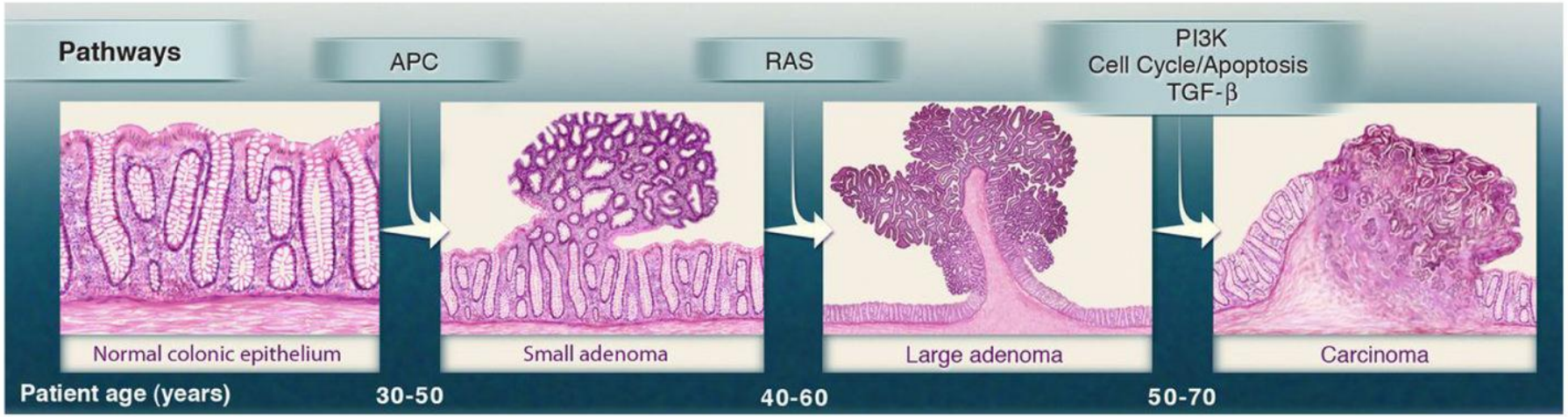
MacConaill, L, et. al., J Mol Diagn 2014, 16: 660-672

Μεταλλαξεισ στην ογκολογια

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



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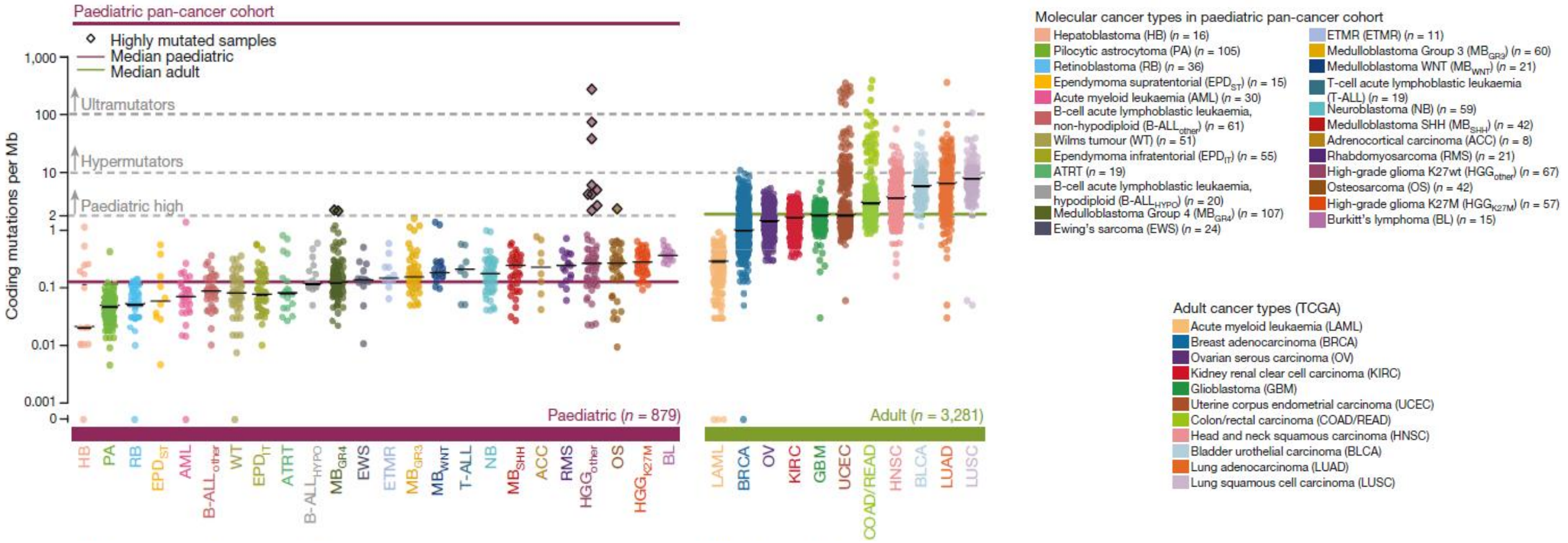
Διαφέρει ο καρκίνος ανάλογα με την ηλικιακή ομάδα?- Αριθμός Μεταλλαγών

Σωματικές παραλλαγές - paediatric pan-cancer cohort



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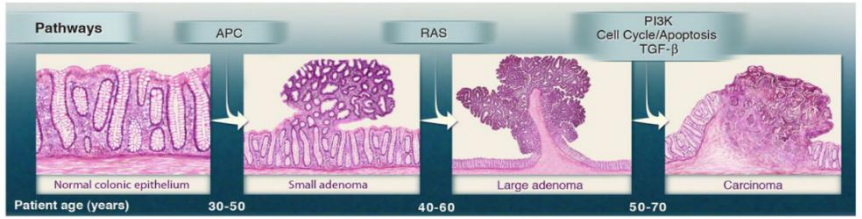
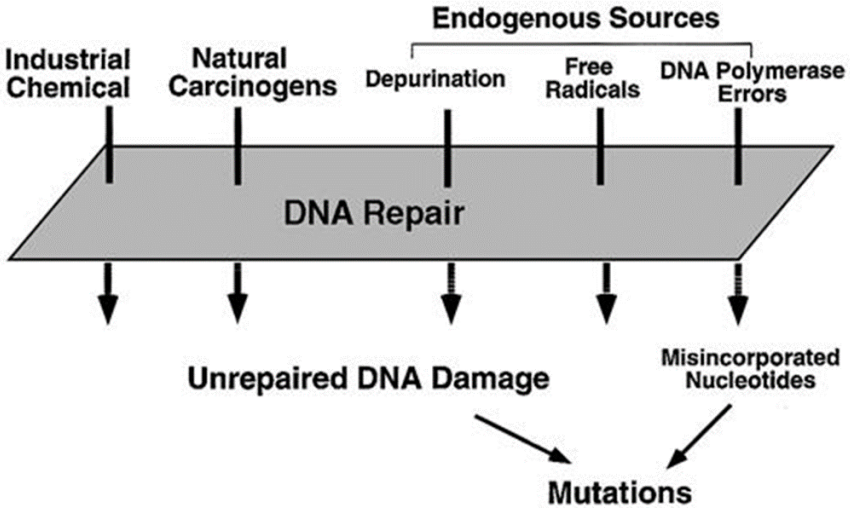
Gröbner *et al*., The landscape of genomic alterations across childhood cancers, **Nature**, 2018

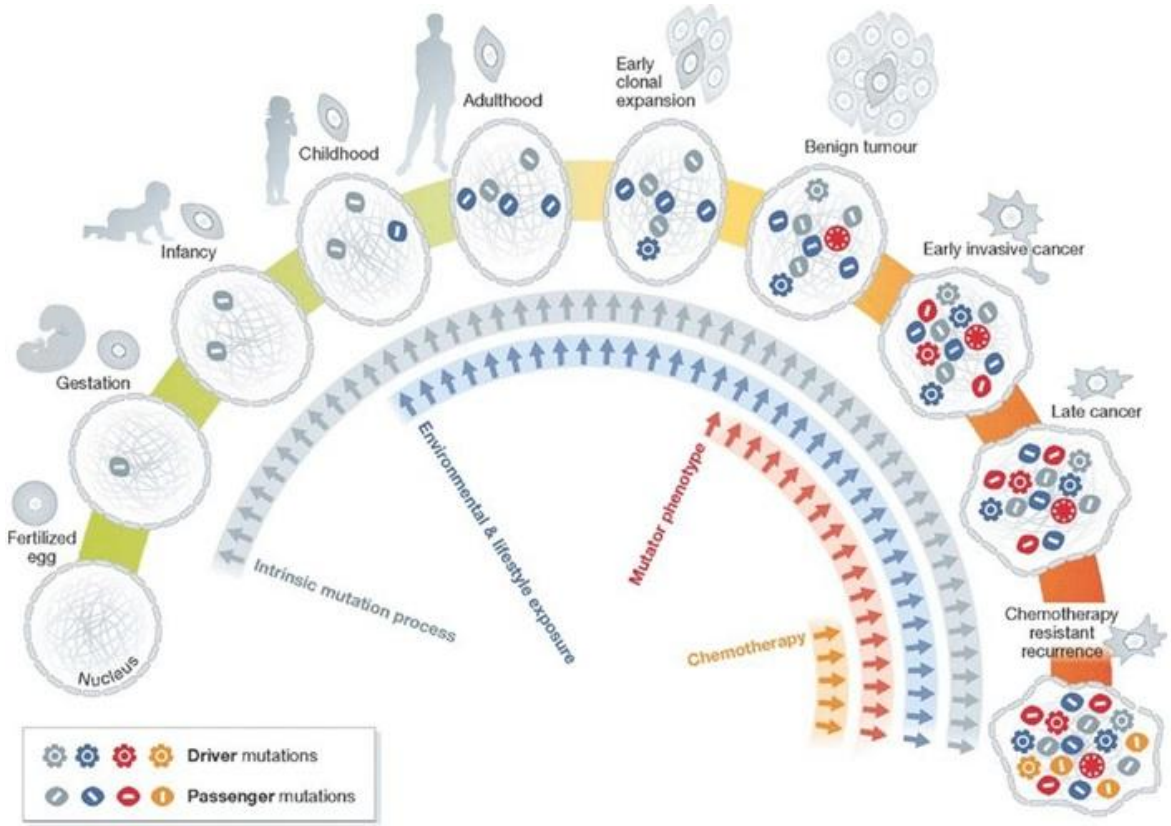
Παιδικής Ηλικίας

- Υπόθεση των 2 χτυπημάτων

Ενηλίκων







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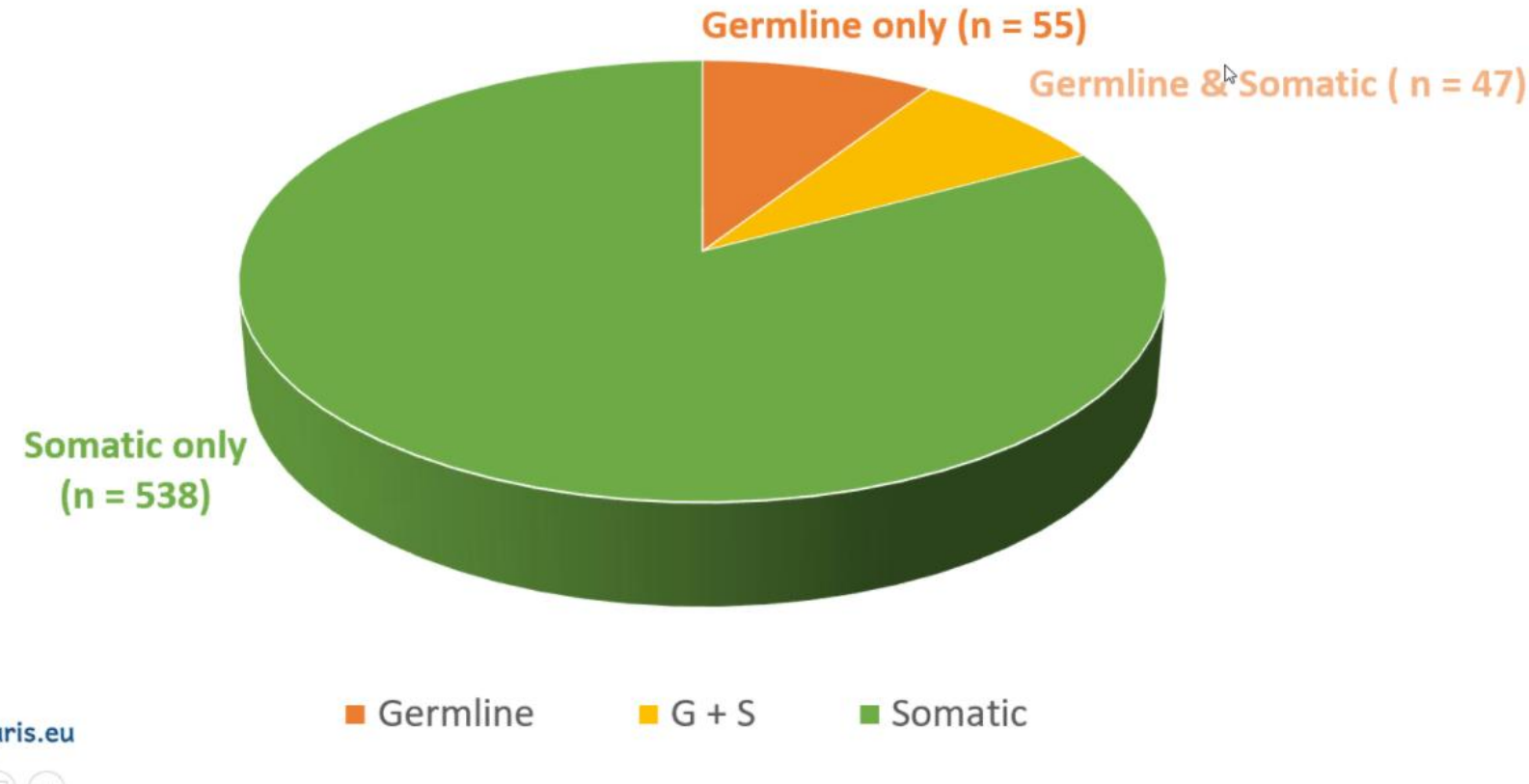
Stratton M, **EMBO Mol Med**, 2013
Loeb KR, **Carcinogenesis,** 2000

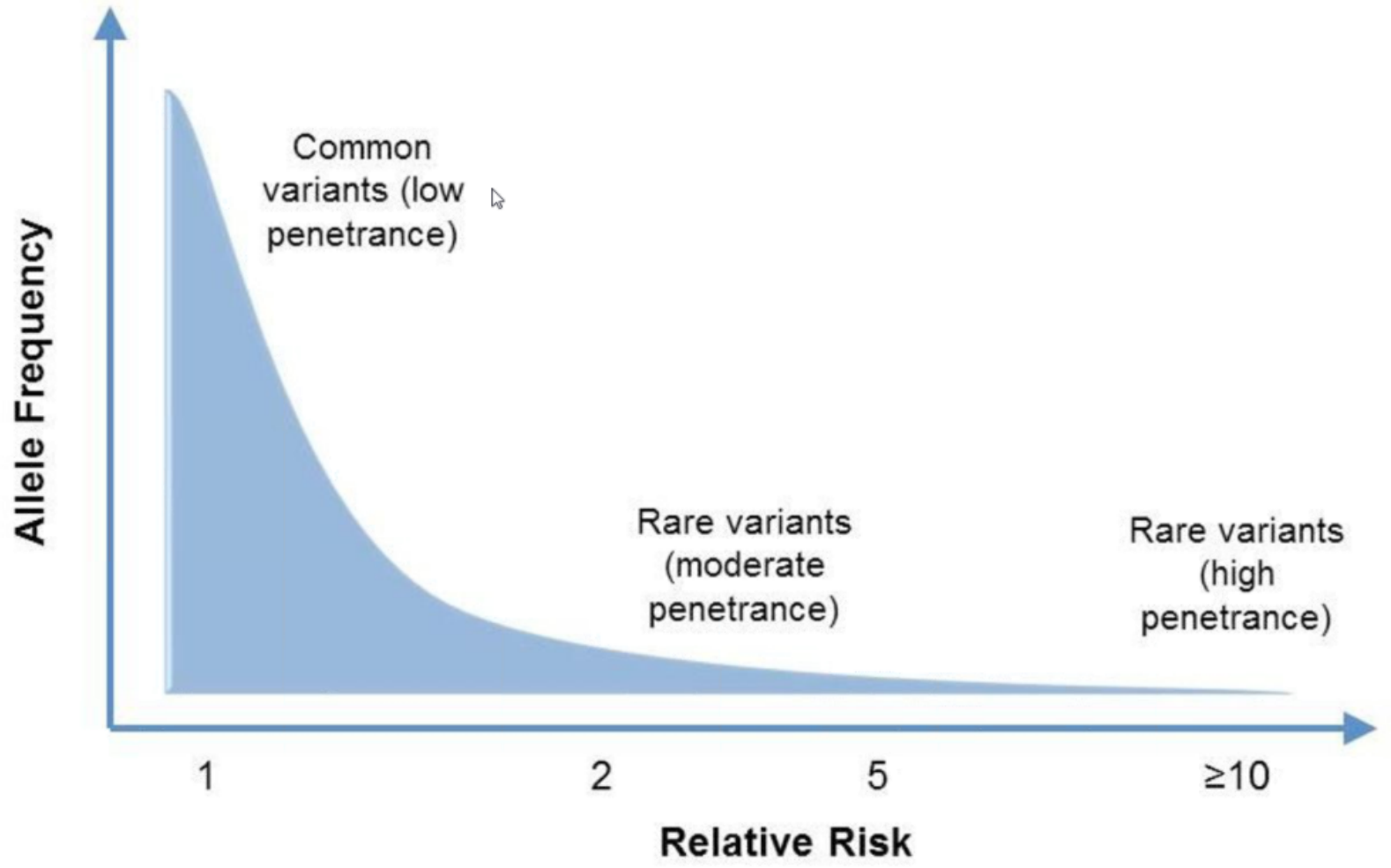
Cancer Gene Census: 640 cancer genes

https://cancer.sanger.ac.uk/census

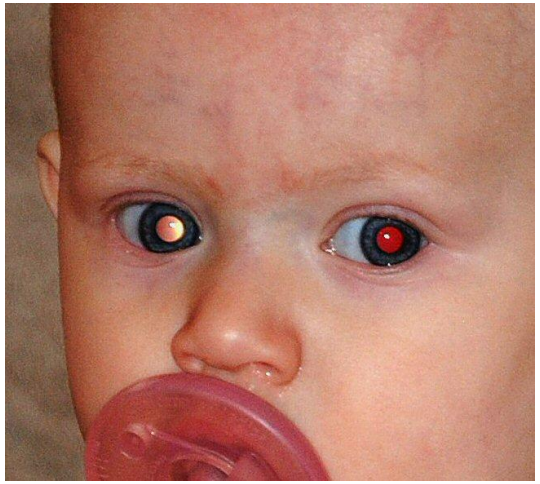


www.genturis.eu

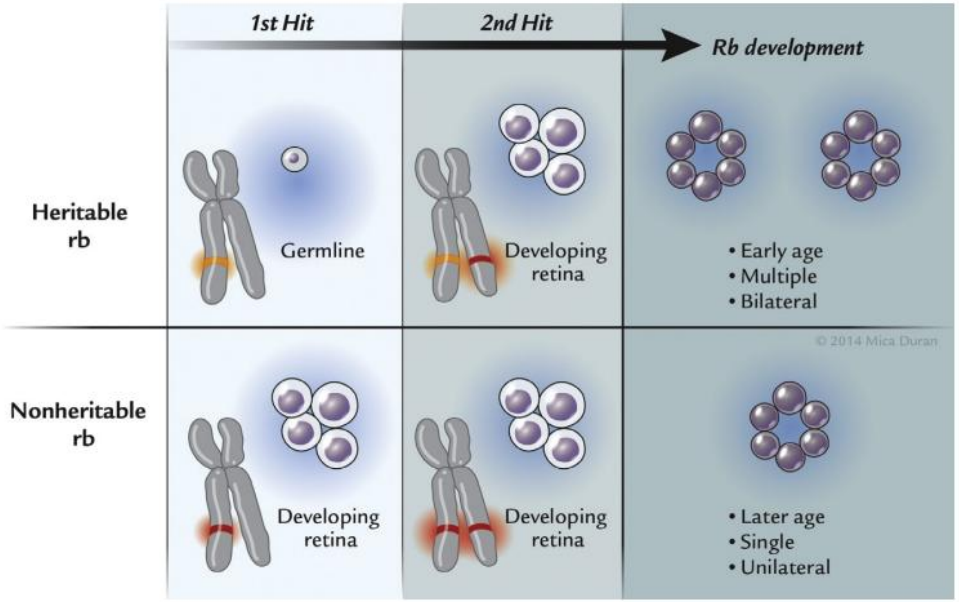
Γονίδια Προδιάθεσης για Καρκίνο



Ρετινοβλάστωμα γονίδιο *RB1*



Η υπόθεση των 2 χτυπημάτων
A. G. Knudson -1971



- *Οικογενές (40%) vs Σποραδικό*
- Κίνδυνος καρκίνου: Ρετινοβλάστωμα (90-95% < 6 ετών), επιφυσιοβλάστωμα (2% <6 ετών)
  - Δευτεροπαθές νεόπλασμα (20% κίνδυνος εφόρου ζωής): οστεοσάρκωμα, σάρκωμα μαλακών μορίων, μελάνωμα

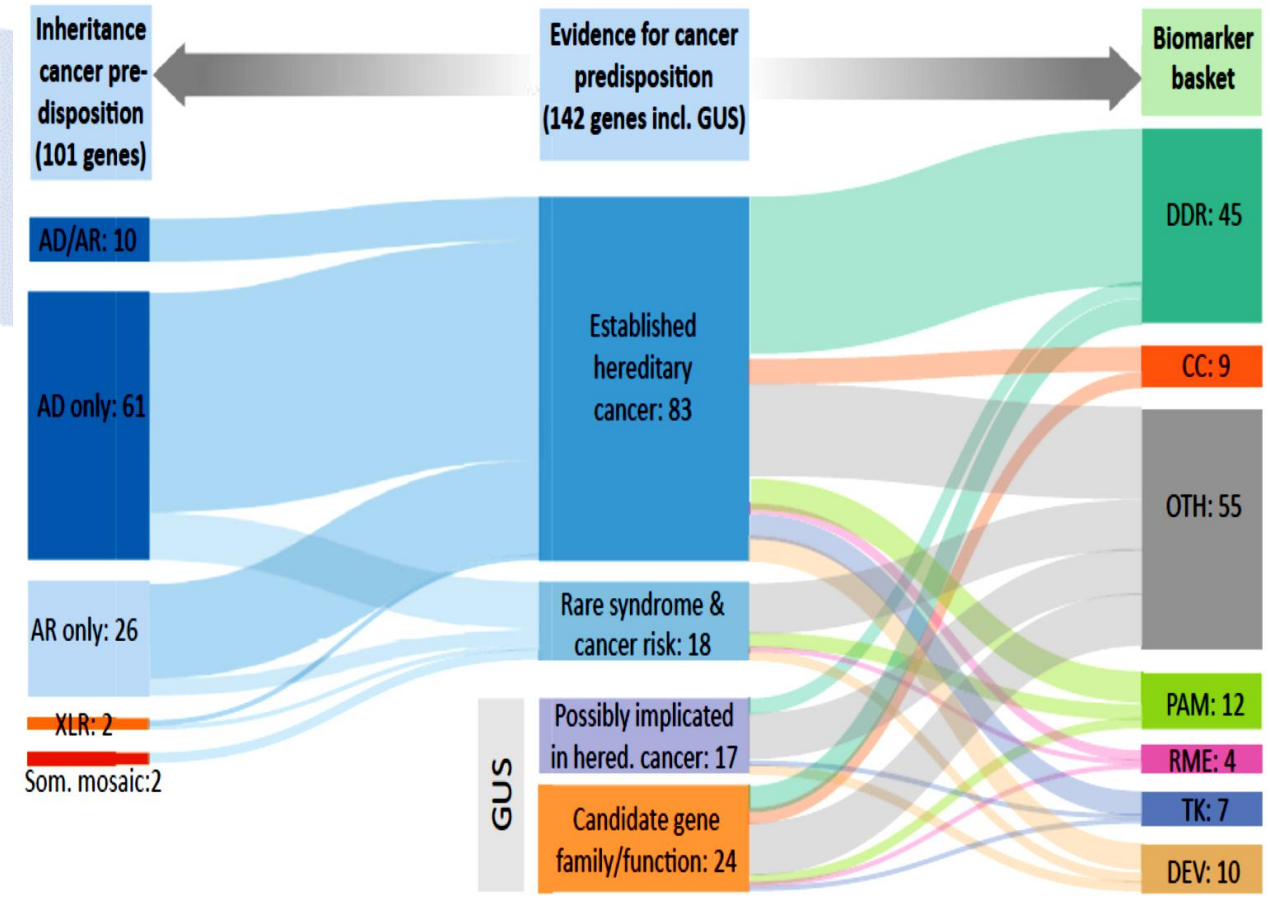
Σύνδρομο Li-Fraumeni

- παραλλαγή/έλλειμμα στο *TP53*
- Διάφοροι τύποι καρκίνου (σαρκώματα, λευχαιμία, Ca μαστού)
- Υποδιπλοειδική ΟΛΛ (50%)
- Αναπλαστικό ραβδομυοσάρκωμα (75%)
- Καρκίνος χοριοειδών πλεγμάτων (50%)
- Καρκίνωμα επινεφριδίων (50%, <15 ετών)
- Καρκίνος μαστού (<30 έτη), επί απουσίας μεταλλάξεων στα *BRCA1/2* (10%)

Frederick Li and Joseph Fraumeni
National Cancer Institute - 1969

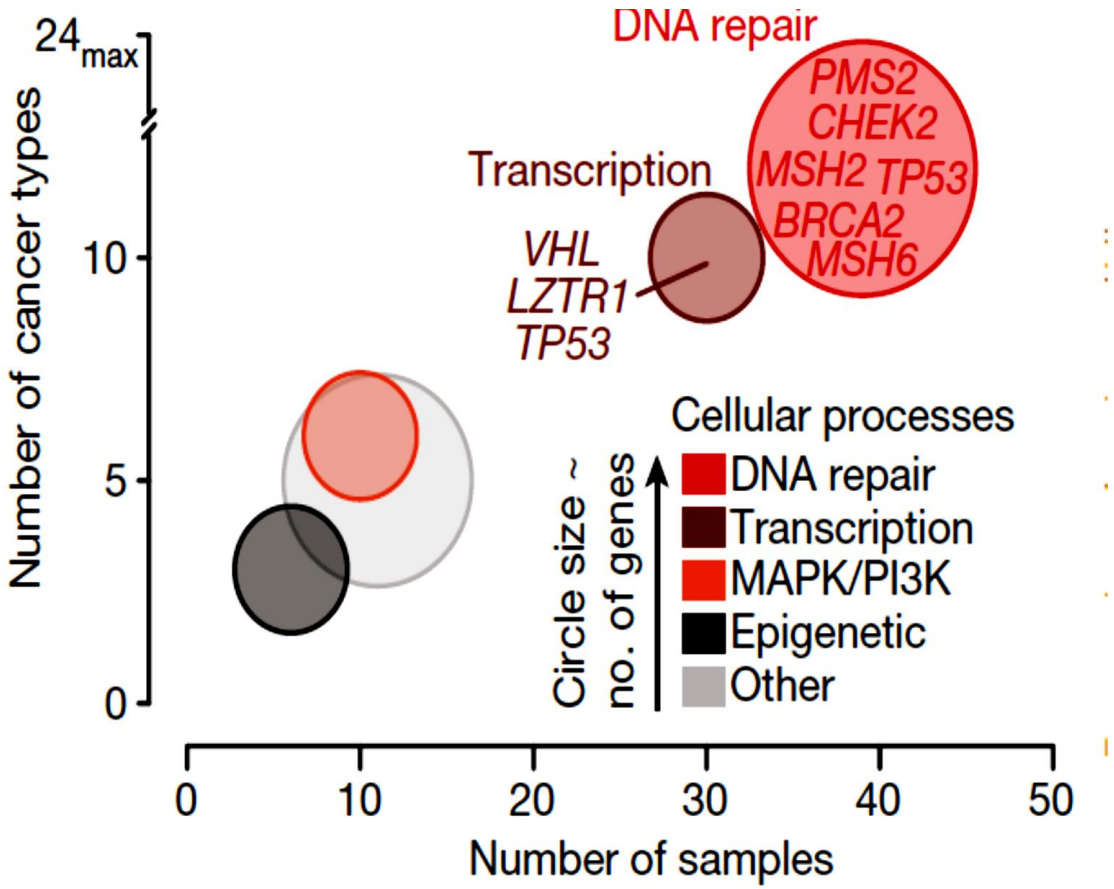
Holmfeldt L, et al. Nat Genet. 2013;45:242-52.
Hettmer S, et al. Cancer. 2014;120:1068-75.
Merino DM, et al. Clin Cancer Res. 2015;21:184-92.

Κυτταρικές διεργασίες που σχετίζονται με CPGs



autosomal dominant; AR, autosomal recessive; CC, cell cycle; DDR, DNA damage repair; DEV, developmental regulation; FR, female ratio (%); GIST, gastrointestinal stromal
tumor; GUS, gene(s) of unknown significance in the context of cancer predisposition; n, number of patients in each subcohort; NSCLC, non-small-cell lung cancer; OTH, other;
PAM, PI3KeAKTemTOR; PNET, primitive neuroectodermal tumor; RME, RAFeMEKeERK; som. mosaic, somatic mosaicism; TK, tyrosine kinases; XLR, X-linked recessive.

Jahn A et al; Annals of Oncology; 2022



Gröbner et al;, 2018 Nature

Τα παιδιά με CPS πρέπει να παρακολουθούνται?

- **Προτείνεται παρακολούθηση:** ≥5% κίνδυνος εμφάνισης καρκίνου τα πρώτα 20 χρόνια ζωής και όταν υπάρχουν τεχνικές αποτελεσματικής παρακολούθησης
- **Δεν προτείνεται:** < 1% κίνδυνος εμφάνισης καρκίνου τα πρώτα 20 χρόνια ζωής.

- Γκρίζα ζώνη- εξατομικευμένη απόφαση: 1% - 5% κίνδυνος στην παιδική ηλικία.

Brodeur M B et al. Clin Cancer Res 2017;23:e1-e5.
Bashford M et al. Genet Med 2019;21:2844.

Genetics inMedicine | ADDENDUM

Addendum: A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

Michael T. Bashford, MD[1], Wendy Kohlman, MS[2], Jessica Everett, MS[3], Ashley Parrott, MS[4] and Toni I. Pollin, MS, PhD[5] for the Practice Guidelines Committee of the National Society of Genetic Counselors and the Professional Practice and Guidelines Committee of the American College of Medical Genetics and Genomics

Genetics in Medicine (2019) 21:2844; https://doi.org/10.1038/s41436-019-0586-y

CCR **PEDIATRIC ONCOLOGY SERIES**

Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson Jr

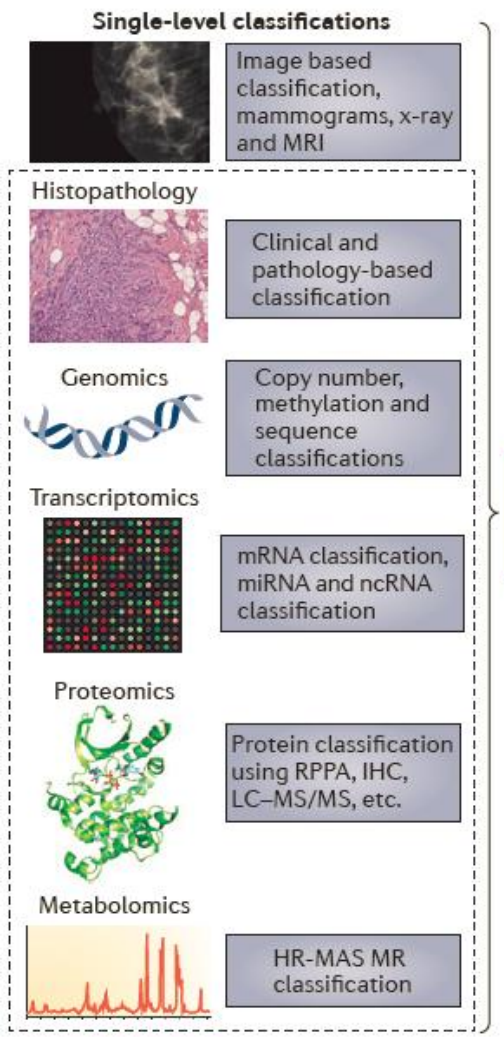
Garrett M. Brodeur[1], Kim E. Nichols[2], Sharon E. Plon[3], Joshua D. Schiffman[4], and David Malkin[5]

Syndrome	Age	Screening
Li-Fraumeni Syndrome	Lifelong	Annual brain and full body MRI, abd US q3-4 months
Beckwith-Wiedemann	Birth- 7 yrs	Every 3-4 month abdominal US and AFP
FAP	10+ years	Annual colonsocopy, endoscopy, eventual colectomy
Pheo/Para		Annual labs, bi-annual whole body MRI
PTEN Hamartoma Tumor Syndrome	7 years	Thyroid screening (US), Colon/breast adulthood
DICER1	3-6 mos	Chest CT (3-6 months and repeat at 3 years, consider CXR between), abd US q3-6 mos, thyroid US (8 yrs)
Rhabdoid Tumor Syndrome	Birth	*Depends on mutation* consider q3 month brain and whole-body MRI to age 5
Retinoblastoma	Birth- 6 yrs	EUA: monthly to age 1, q3 mo. to age 6, brain MRI q3-6 mo. to age 2 then annual to age 6
BMMRD	Birth	Annual brain MRI, annual abd US (1 year), annual CBC (1 year), Colonoscopy (6 yrs), annual whole body MRI (6 years)

Brodeur M B et al. Clin Cancer Res 2017;23:e1-e5.
Bashford M et al. Genet Med 2019;21:2844.

- National Comprehensive Cancer Network guidelines (https://www.nccn.org/professionals/physician_gls/default.aspx).
- GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/).
- https://www.genturis.eu/

The Era of Big Data - Omics



- Diagnosis
- Stratification
- Therapy
- Pharmacogenetics

Molecular Classification in CNS tumors

CNS tumors in AYA

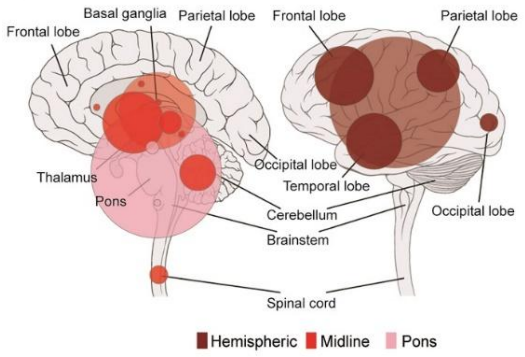
- 3rd most common malignancy after Breast and thyroid Ca
- iGCT: Higher frequency compared to peds

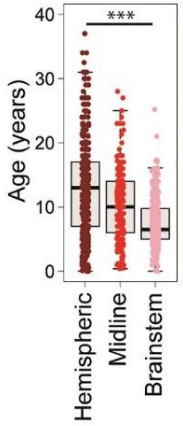
Disease	SNV	Fusions	CNA	Age
LOW-GRADE GLIOMA Pilocytic astrocytoma		KIAA1549-BRAF	7q34 duplication	Child (<15)
Diffuse astrocytoma (incl. IDH mutated tumors)	BRAF V600E IDH1/2, TERT	MYBL1	FGFR TKD, MYB Co-deletion 1p/19q	AYA (15-39)
HIGH-GRADE GLIOMA K27	H3.1 and H3.3 K27M, TP53, ATRX, ACVR1			Child (<15)
G34	H3.3 G34V/R, TP53, ATRX			AYA (15-39)
IDH	IDH1/2, TP53, ATRX			AYA (15-39)
RTK-I	TP53		EGFR amp, PDGFRA amp, chr. 10 loss	Adult (≥40)
Mesenchymal	EGFR, TP53, NF1		CDKN2A del, PDGFRA amp, EGFR amp	AYA (15-39)
PXA-like	BRAF V600E		CDKN2A del	Child (<15)
MEDULLOBLASTOMA Wnt	CTNNB1, TP53, SMARCA4, DDX3X		Monosomy chr. 6	AYA (15-39)
SHH	PTCH1, SUFU, TP53		GLI2 amp, NMYC amp, 10q loss, 9q loss	AYA (15-39)
Group 3	OTX2, DDX3X	PVT1-MYC	i17q, MYC amp, GFI1/GFI1B	Child (<15)
Group 4	KDM6A		i17q, chr. 11 loss, MYCN amp, GFI1/GFI1B	AYA (15-39)
EPENDYMOMA Posterior fossa - PFA			1q gain	Child (<15)
Posterior fossa - PFB				Child (<15)
Supratentorial		C11orf95-RELA YAP1 fusions		Child (<15)
Spinal	NF2		chr. 22q	AYA (15-39)
CRANIOPHARYNGIOMA Adamantinomatous	CTNNB1			Child (<15)
Papillary	BRAF V600E			AYA (15-39)
iGCT	KIT, KRAS, NRAS			AYA (15-39)

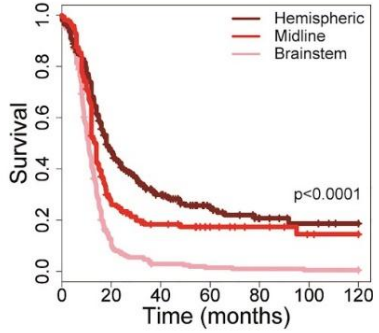
Zapototcky M et al: *Pediatr Blood Cancer.* 2018;**65**:e26861.

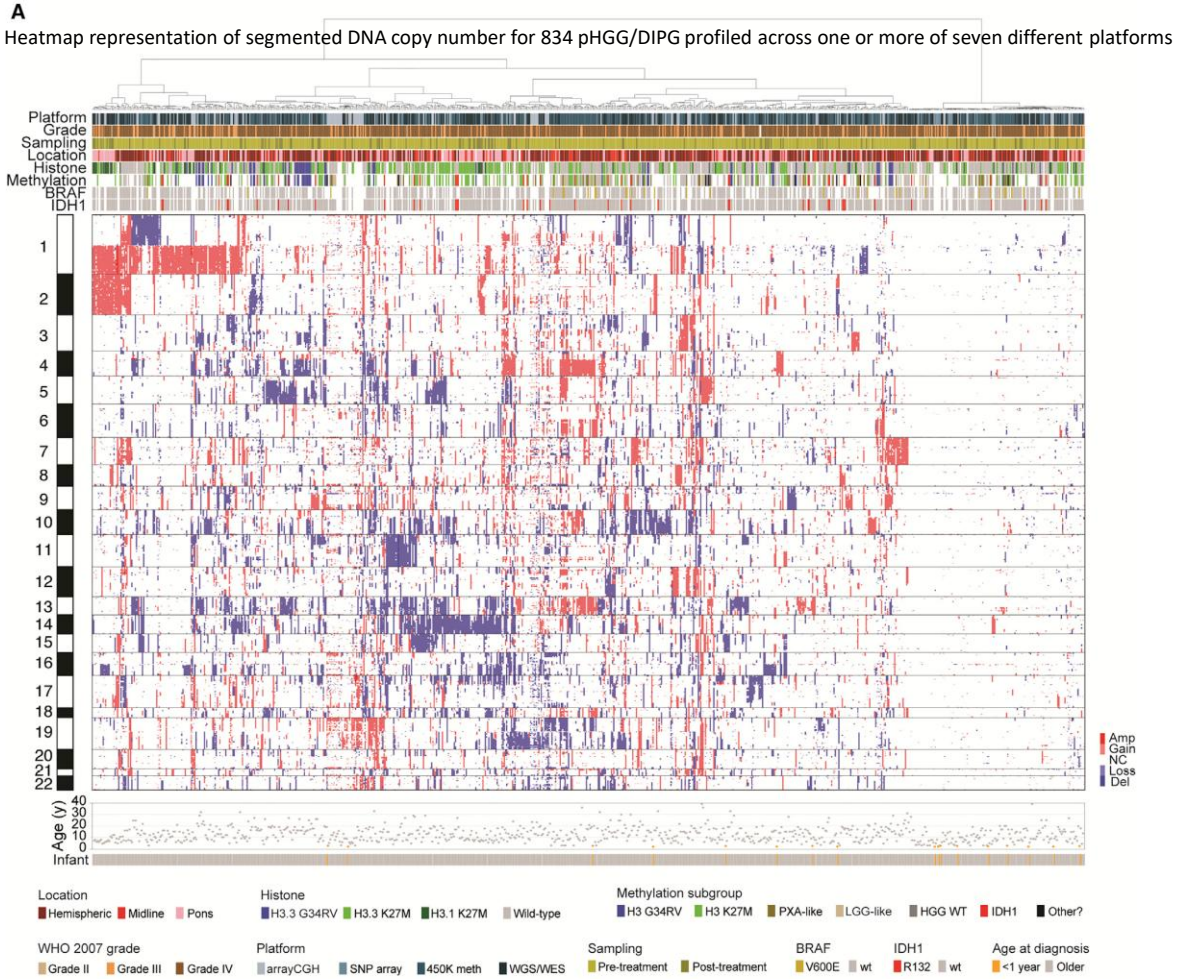
High Grade Gliomas in Pediatric and AYA patients

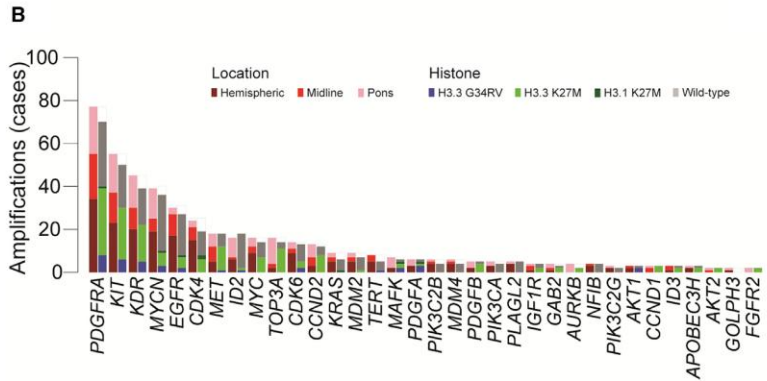
- Integrated molecular meta-analysis
- 1067 unique tumors (pediatrics /AYA)
- Genomic aberrations increase with age
- Prognosis dependent on tumor topography and genetic aberations

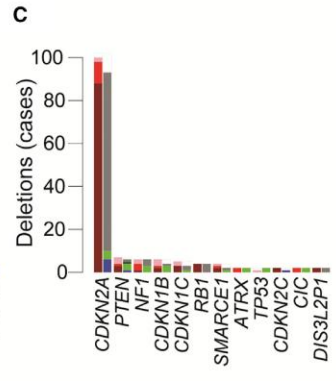












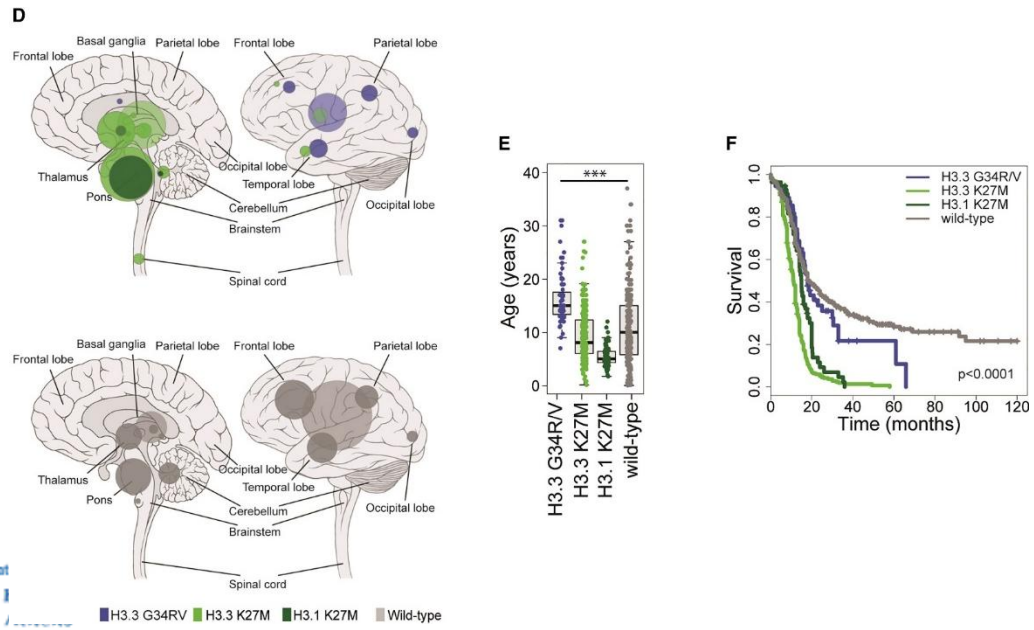
Prof. Antonis Kattamis
National and Kapodistrian University of Athens

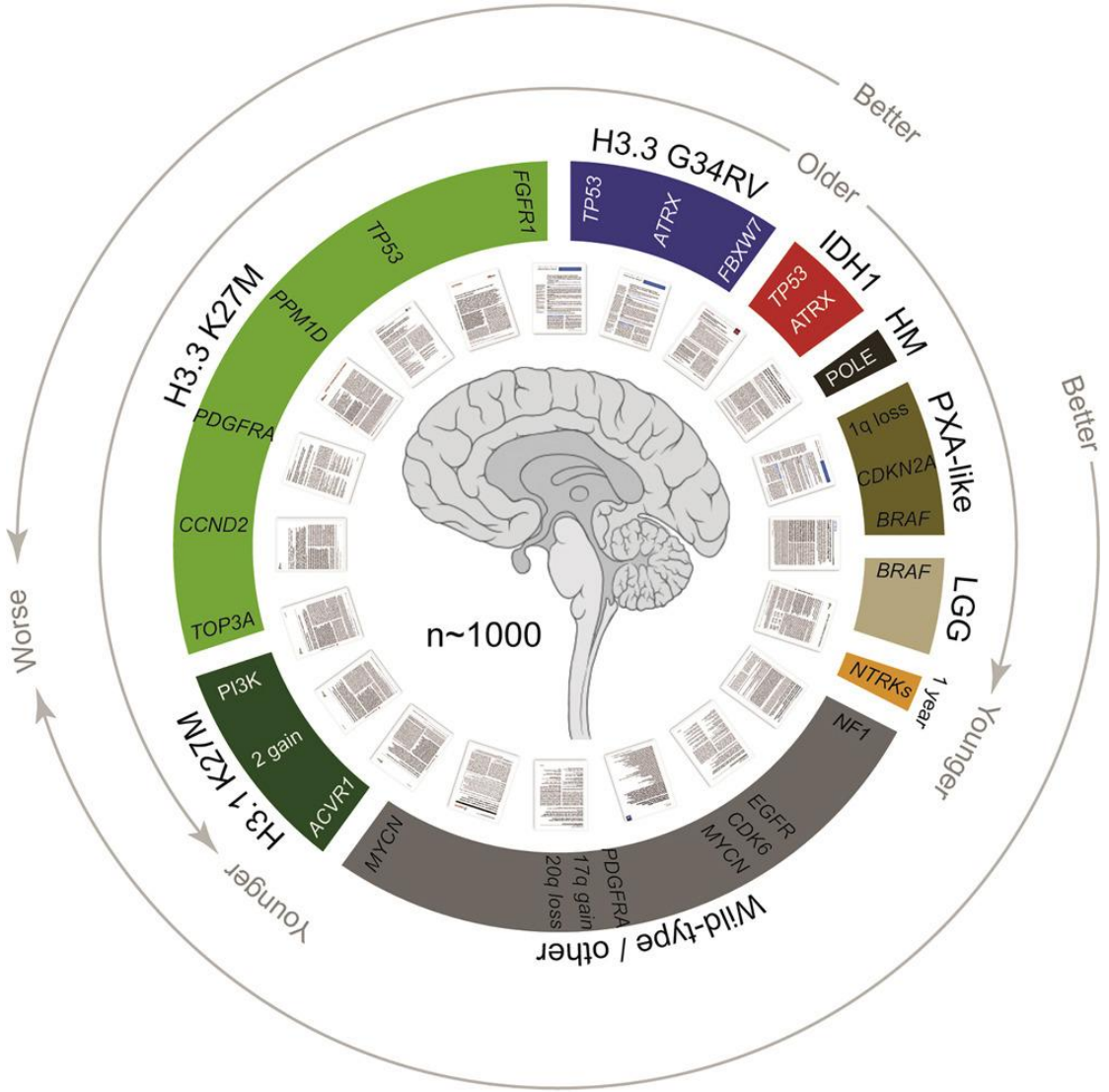
Mackay et al. Cancer Cell 2017 32, 520-537.e5DOI: (10.1016/j.ccell.2017.08.017)

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

AYA patients have Characteristic Genetic Alterations:

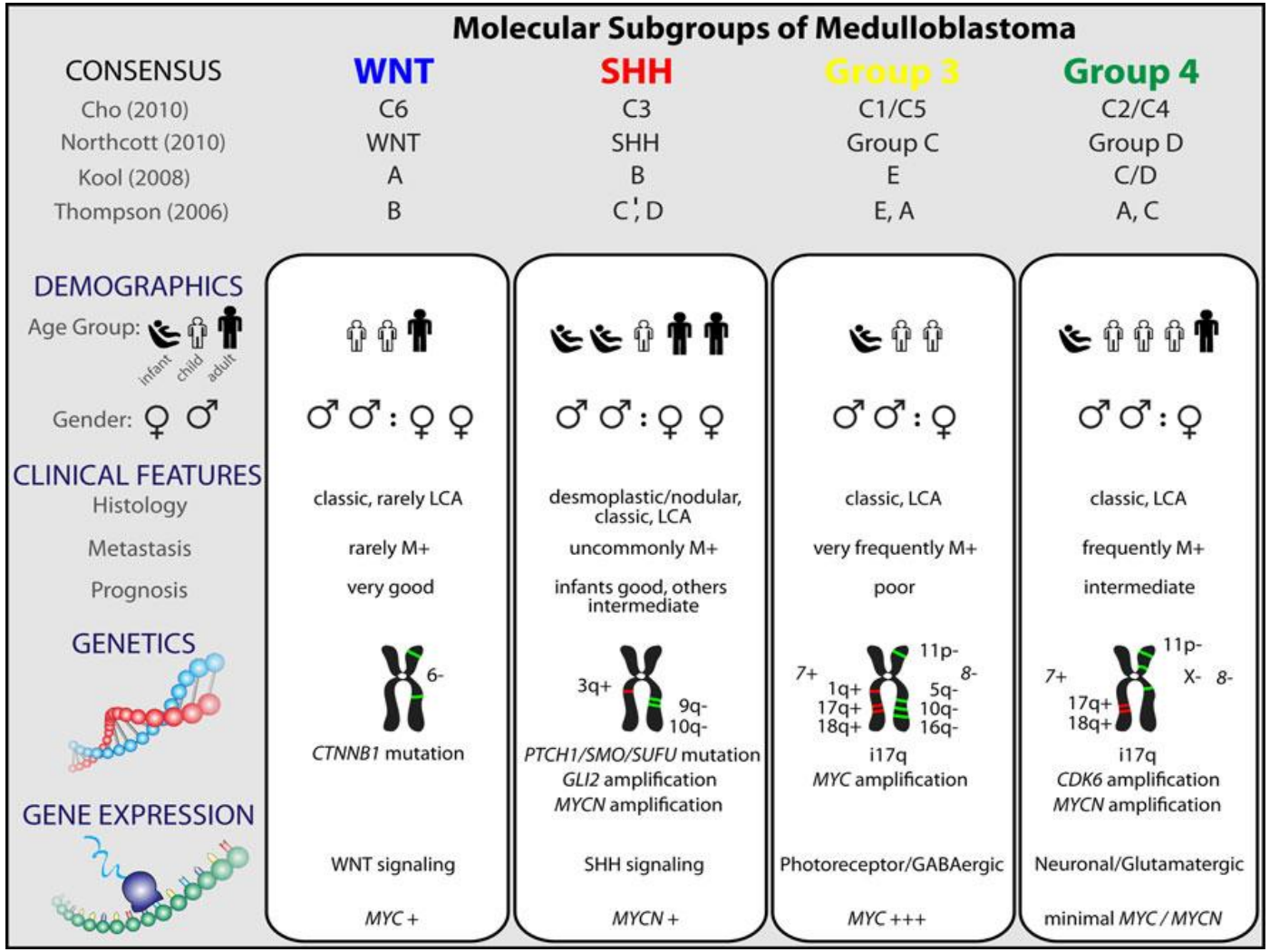
- H3.3 G34RV
- Rarely H3.3 K27M . No H3.1 K27M
- Mutated epidermal growth factor receptor (EGFR)
- *MYC* and *MYCN* amplifications not usually seen
- frequent isocitrate dehydrogenase 1 (*IDH1*) or *IDH2* mutations





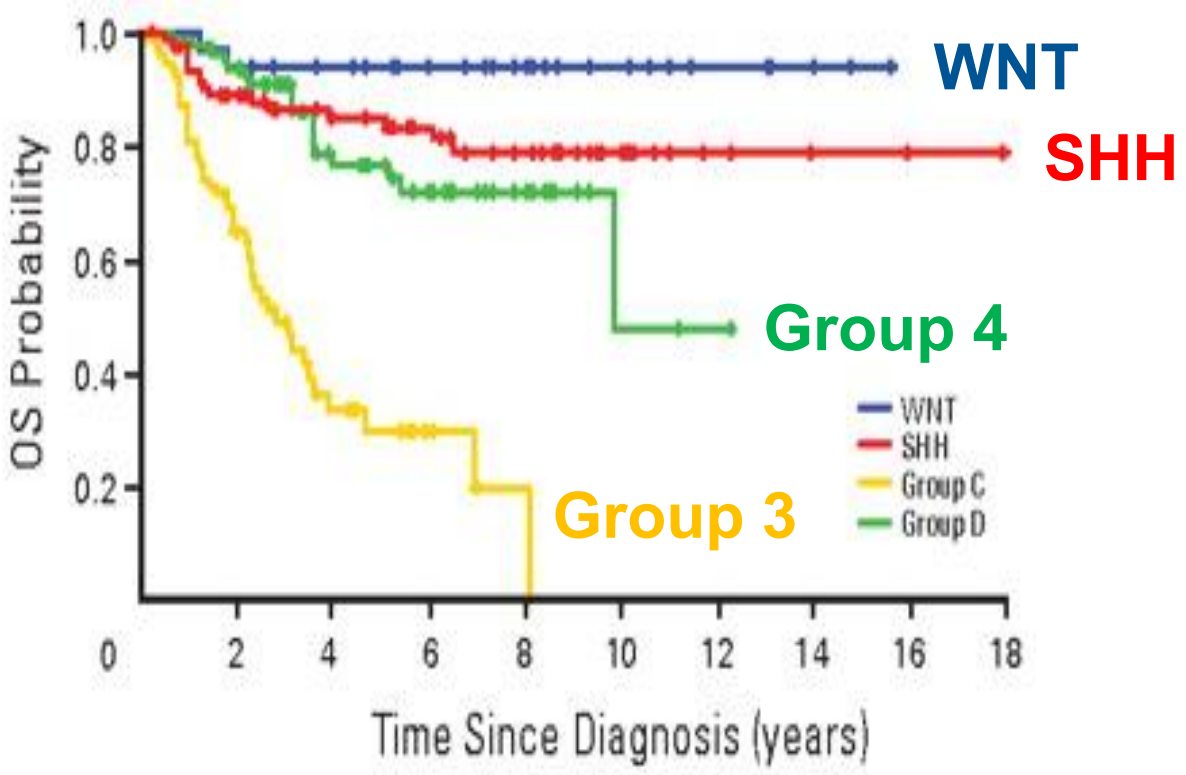
Mackay et al. Cancer Cell 2017 32, 520-537.e5DOI: (10.1016/j.ccell.2017.08.017)

Embryonal Tumors-Medulloblastoma



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

Subgroup Influences Prognosis



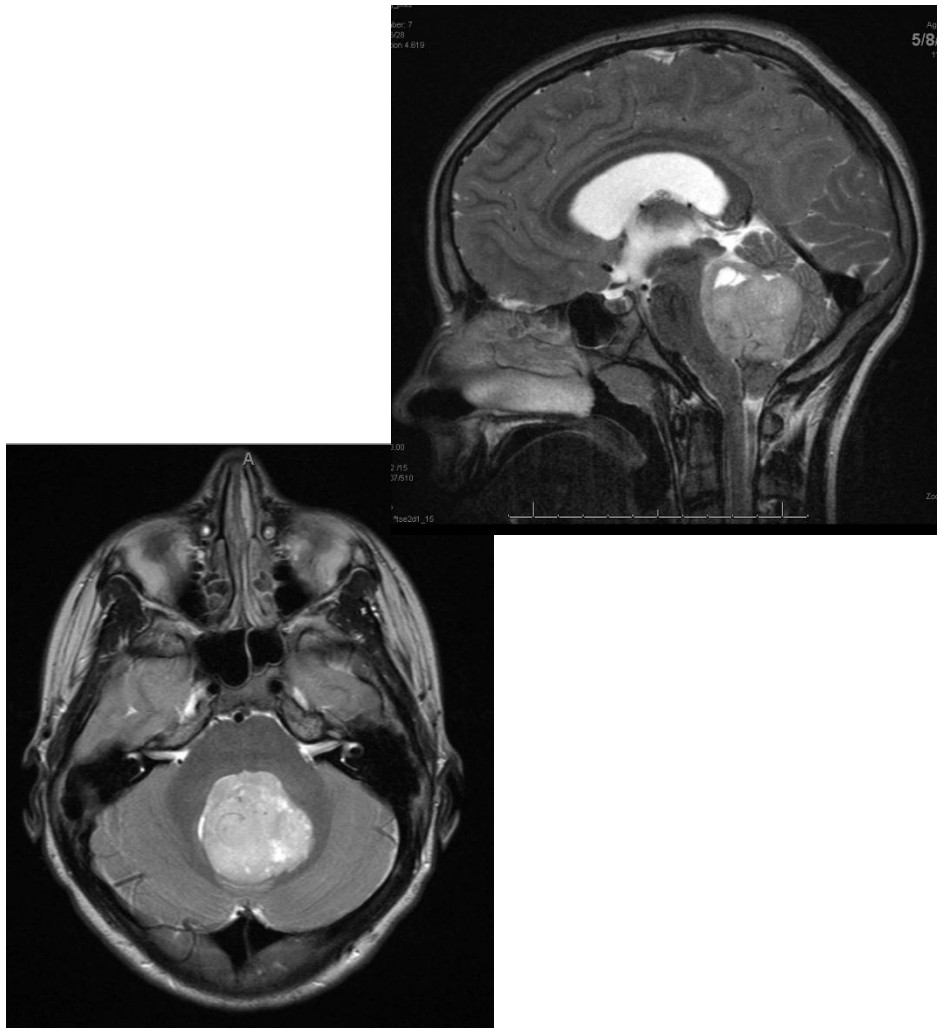
Medulloblastoma in AYA

- 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*

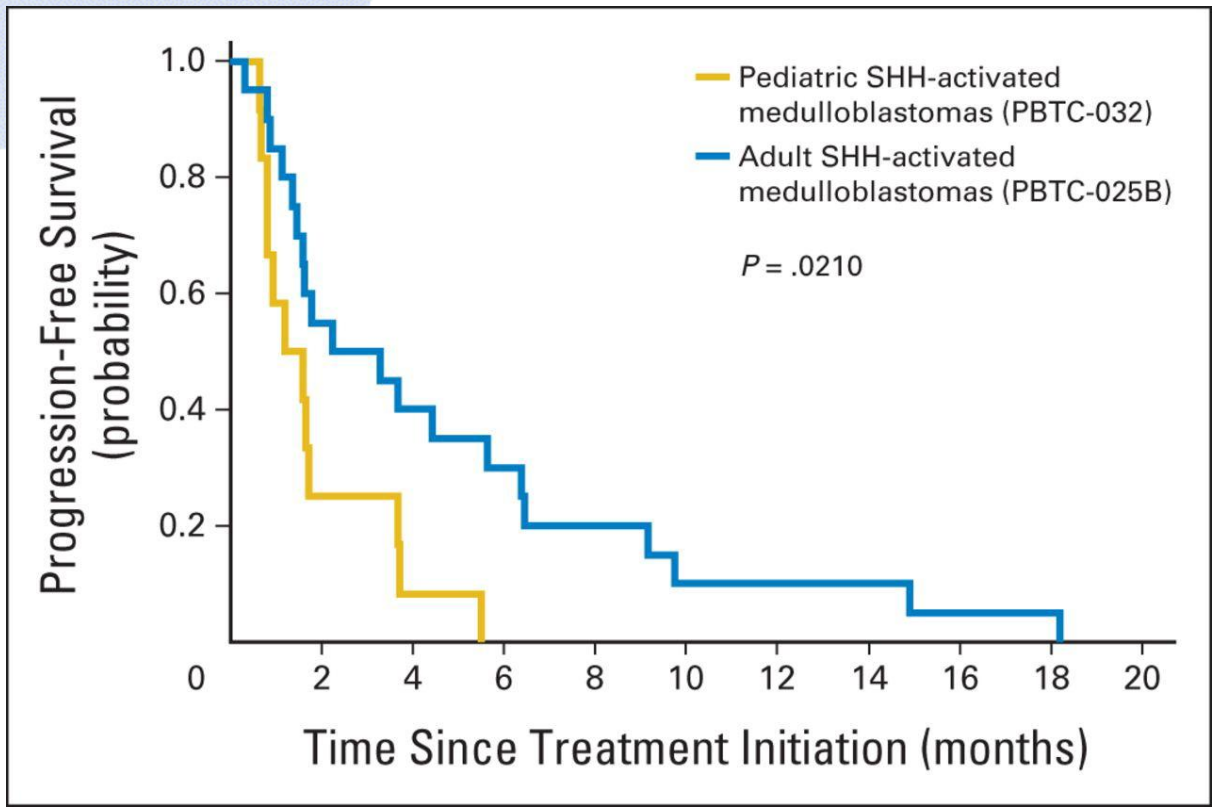
Northcott et al. J Clin Oncol 2011;29:1408

Medulloblastoma / μυελοβλαστωμα

- Most common CNS malignancy
- 20% of primary CNS tumors
- Mean age of presentation: 3-4 years
- CNS metastasis in 30 %
- Can have extraneural mets



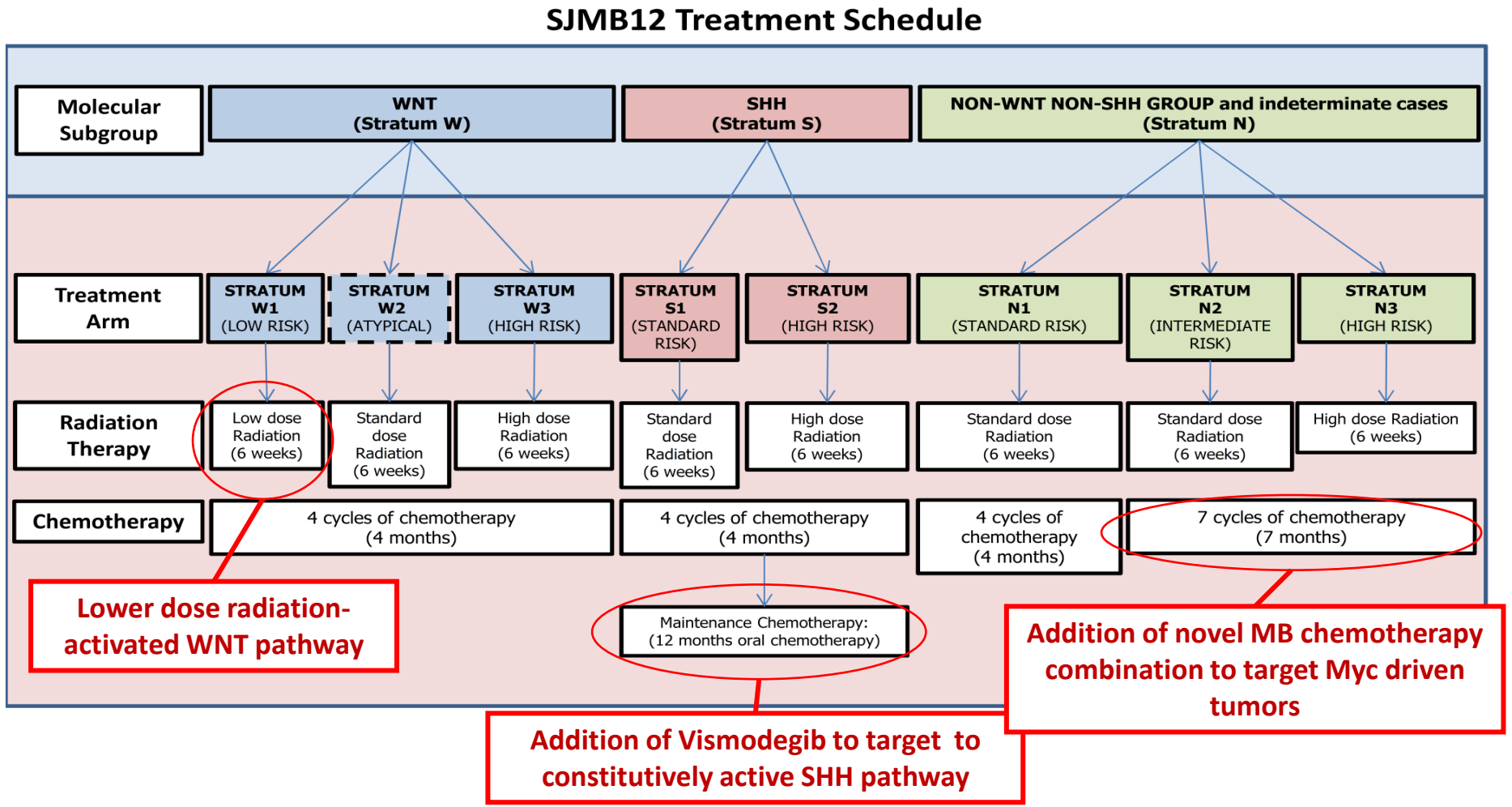
Progression-free survival of adults with sonic hedgehog (SHH) –subgroup Recurrent medulloblastoma (SHH-MB; blue line) versus pediatric patients with SHH-MB (gold line) treated with Vismodegib



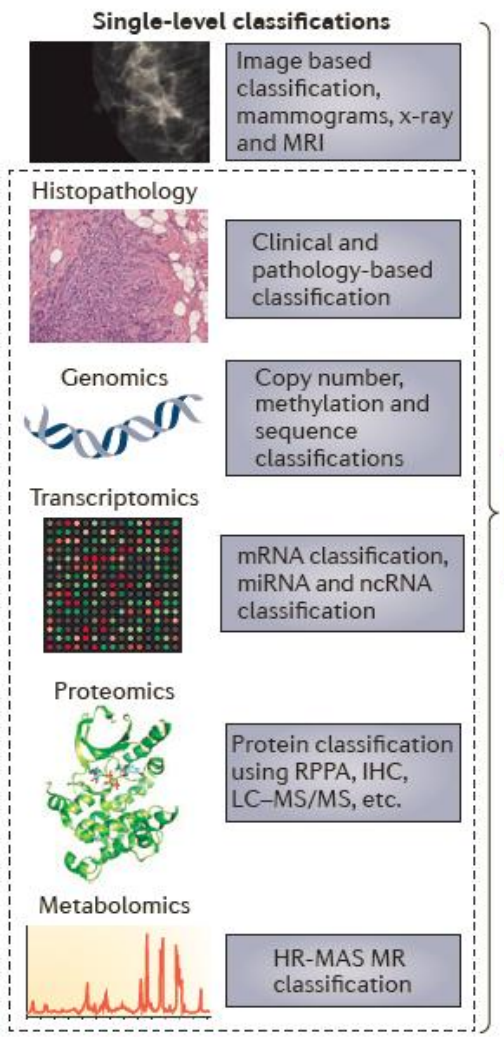
More common in adults:
aberrations in *PTCH1* accompanied favorable outcomes
aberrations of *GLI2* or *SUFU and* Increased pp53 expression → non response

Giles W. etal ; Journal of Clinical Oncology 2015 332646-2654.

Molecular and Risk Adapted Therapy



The Era of Big Data - Omics



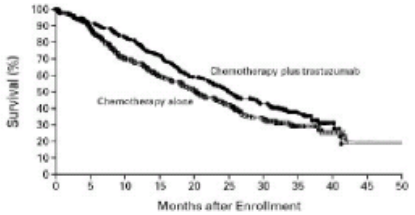
- Diagnosis
- Stratification
- Therapy
- Pharmacogenetics

ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

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

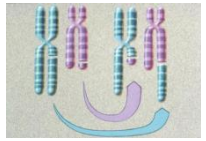
1997

1ο Στοχευμένη rituximab



1998

Trastuzumab εναντι HER2+ Ca μαστού



2001

Imatinib

FDA

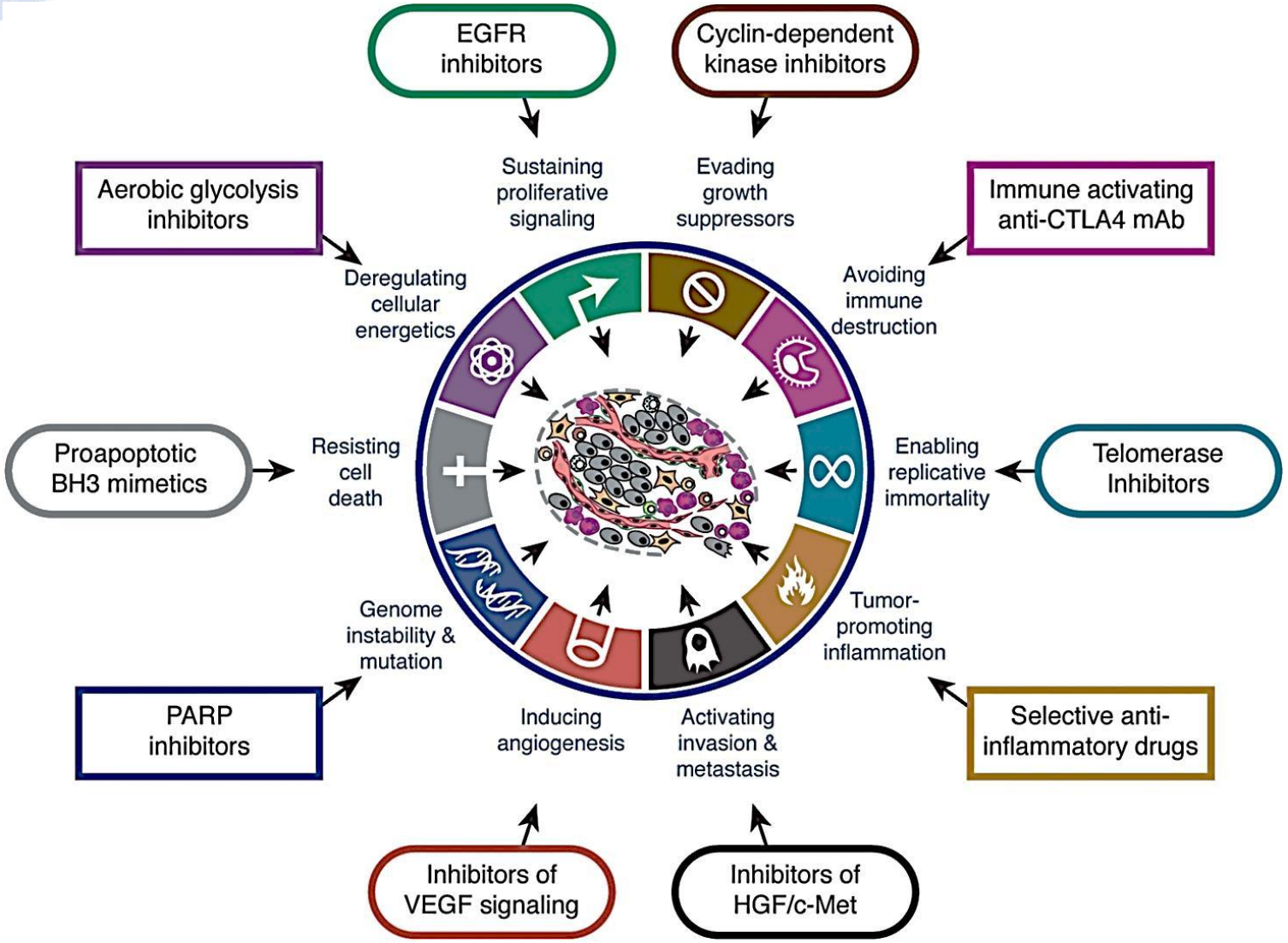
1997-2016

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



Prof. Antonis Kattamis
National and Kapodistrian University of Athens
EST. 1837

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

Precision Medicine: Targeted Therapy

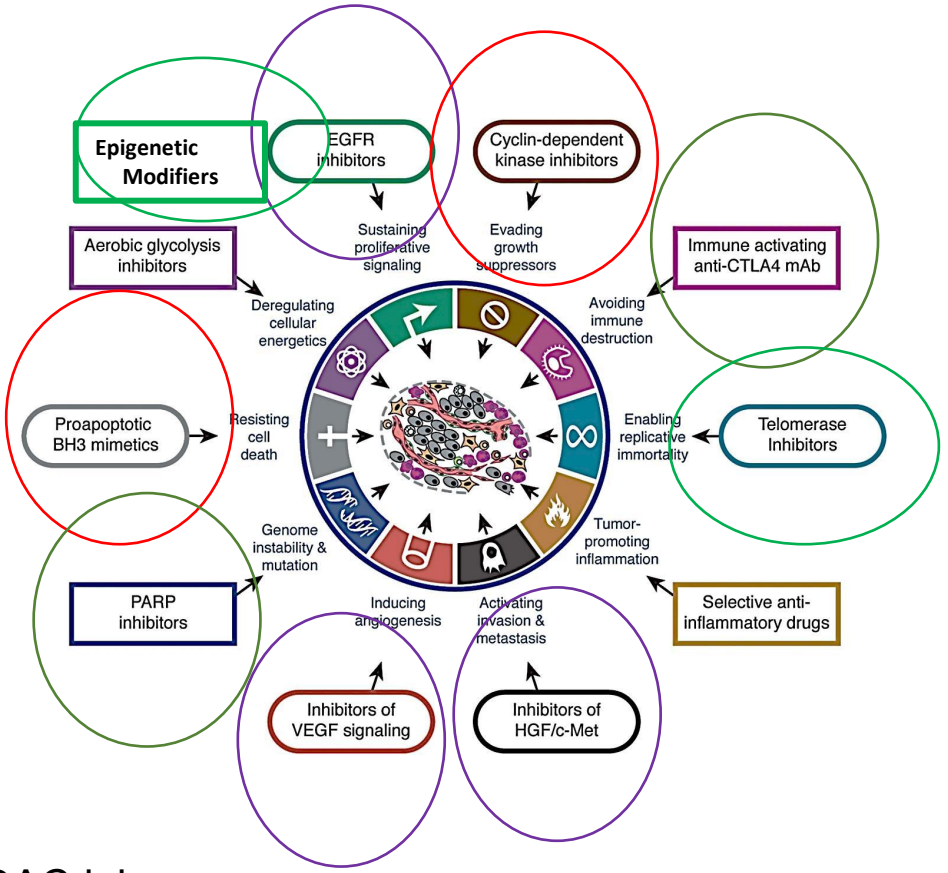
Most actionable events:

- **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

Gliomas in Children

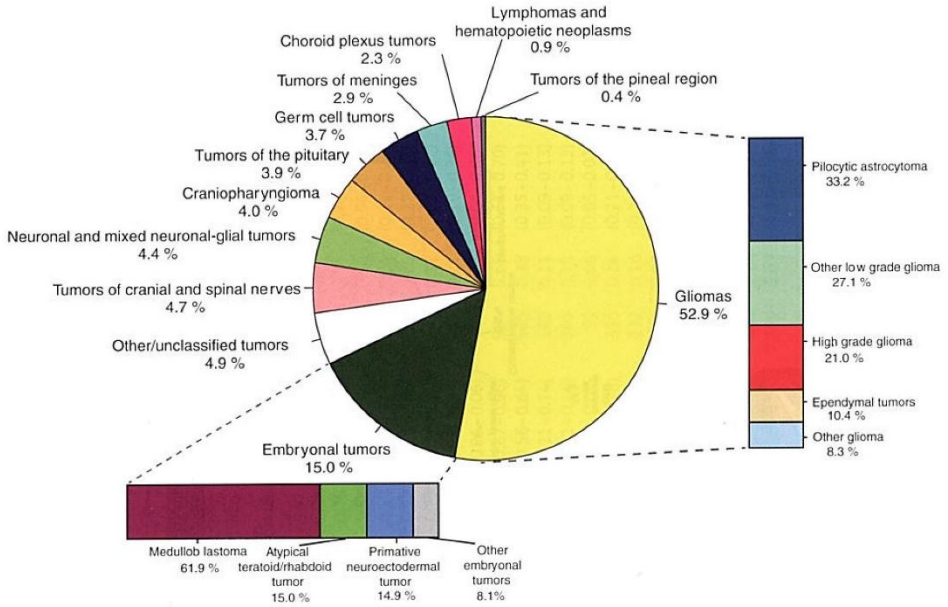
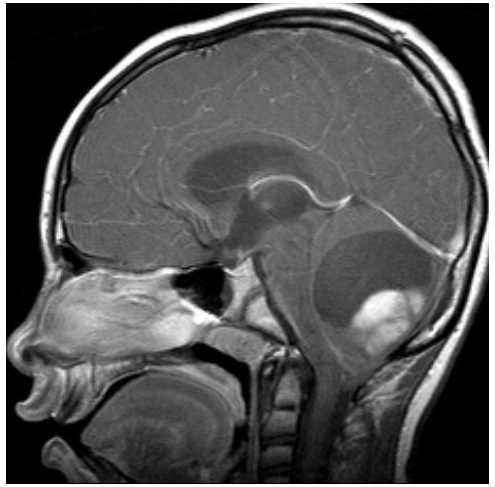
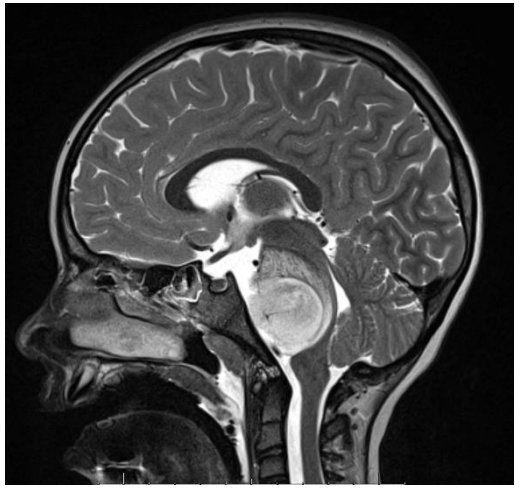


Fig. 8. Distribution of All Primary Brain and CNS Tumors by Histology Groupings (0–14 Years) (N = 16,044) (CBTRUS 2007–2011)



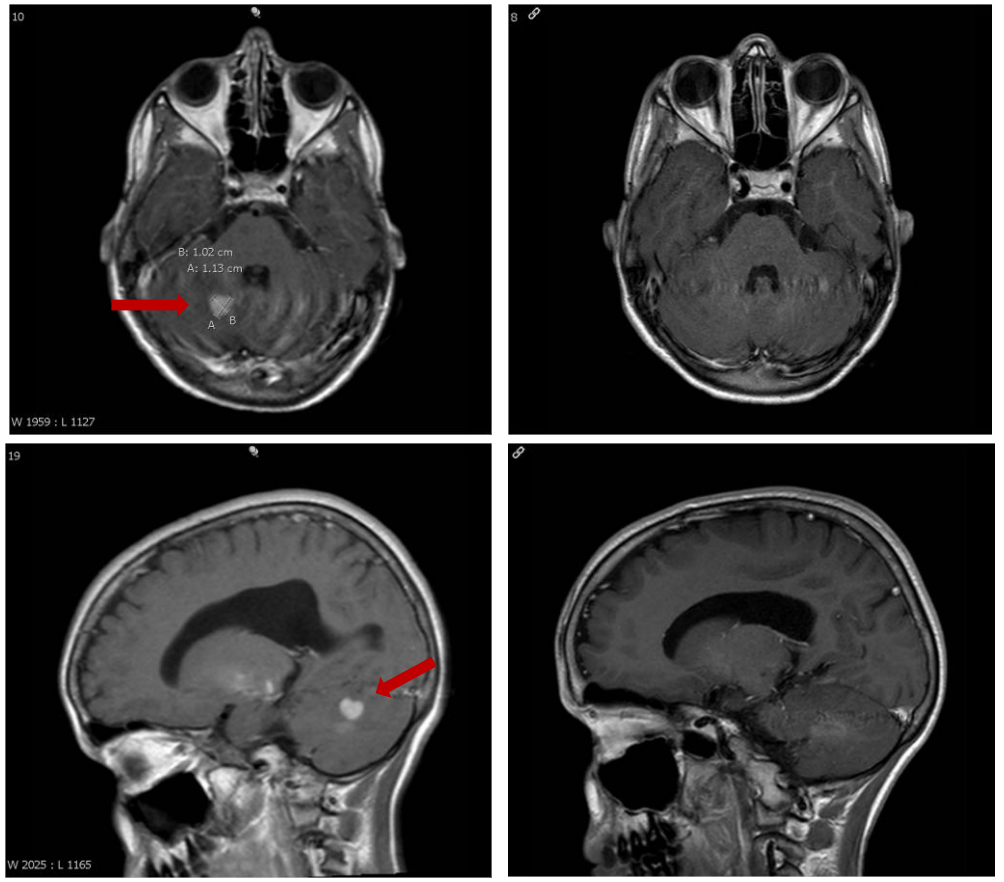
Pilocytic astrocytoma
OS 10yr > 97%



Pontine glioma
OS 5yr < 1%

Ostrom et al., Neuro-Oncology 2014

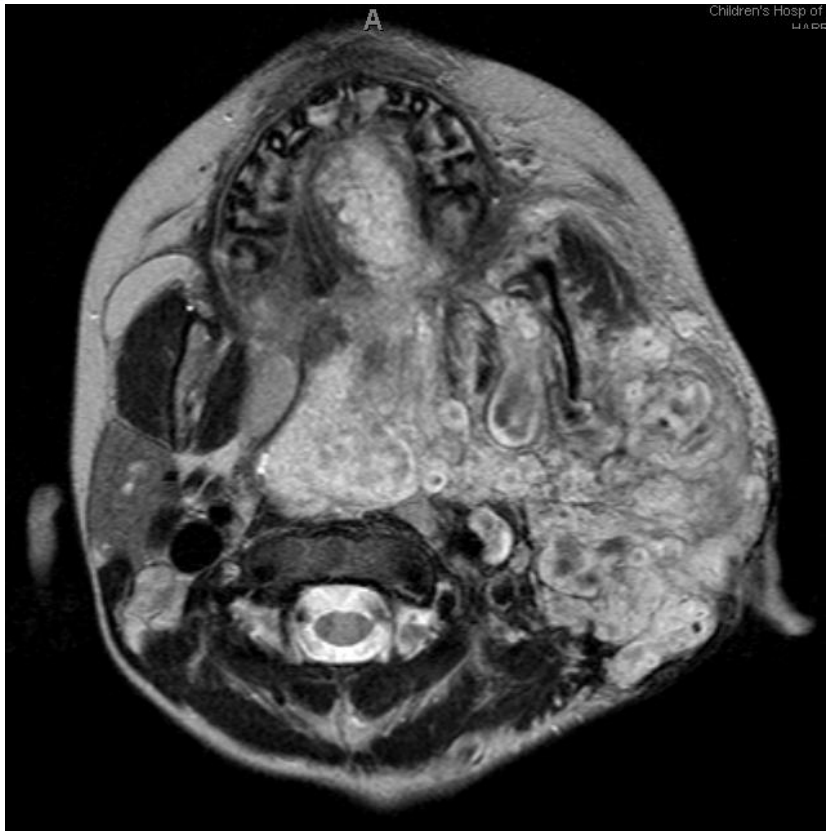
Response to *BRAF(V600E)* inhibitor



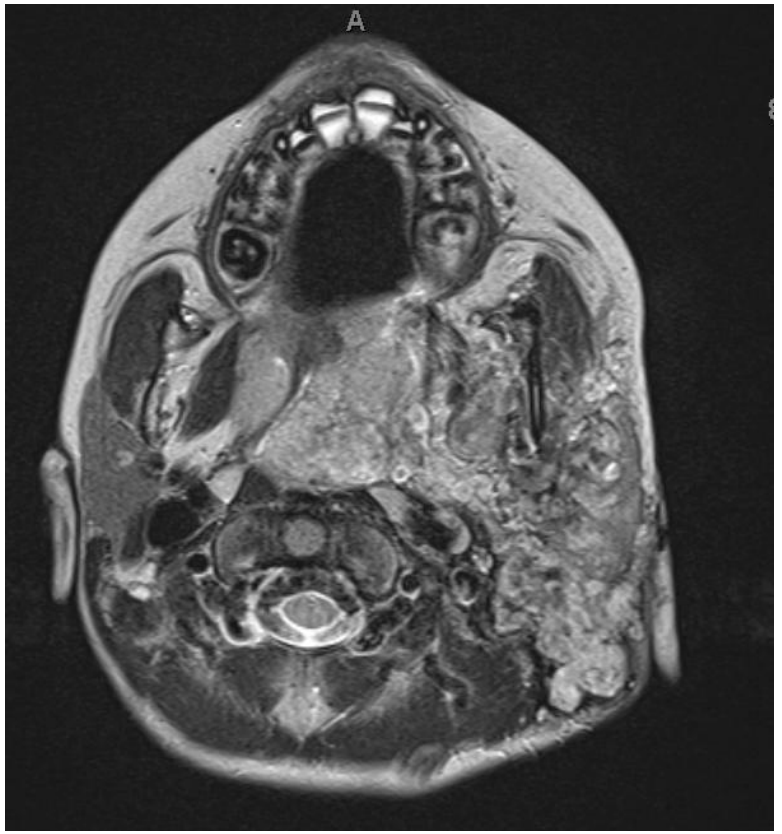
Pre-Vemurafenib Vemurafenib - 2 months

Response to MEK inhibitor

(Phase 1 clinical trial for gliomas and plexiform neurofibromas)



Pre-Trametinib

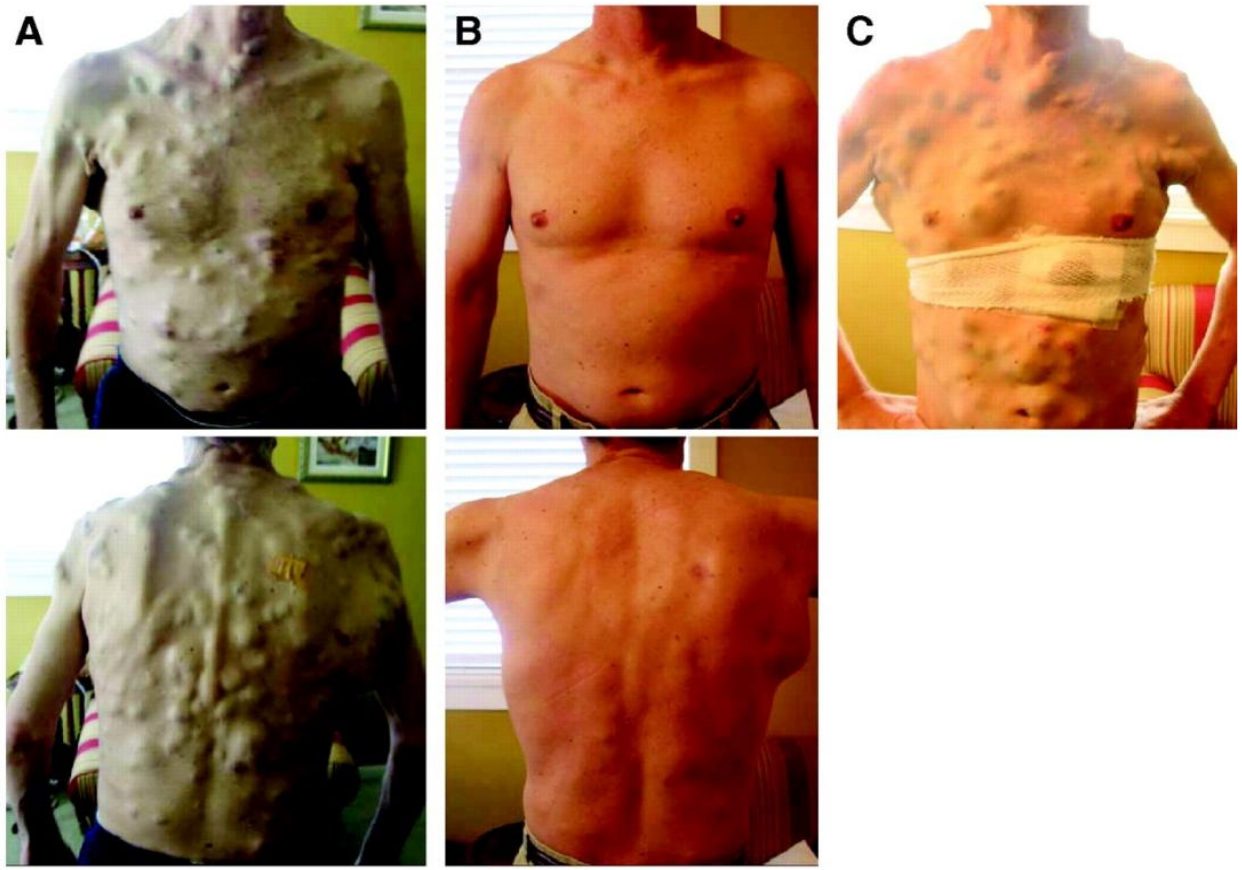


Trametinib - 8 months

Ιατρικη ακριβειασ

Στοχευμένη θεραπεία αποτυγχάνει λόγω πολυπλοκότητας της νεοπλαστικής εξεργασίας

.

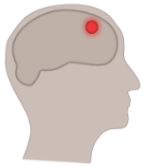


Source: Wagle, N et al. Dissecting Therapeutic Resistance to RAF Inhibition in Melanoma by Tumor Genomic Profiling. JCO August 1, 2011 vol. 29 no. 22 3085-3096

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

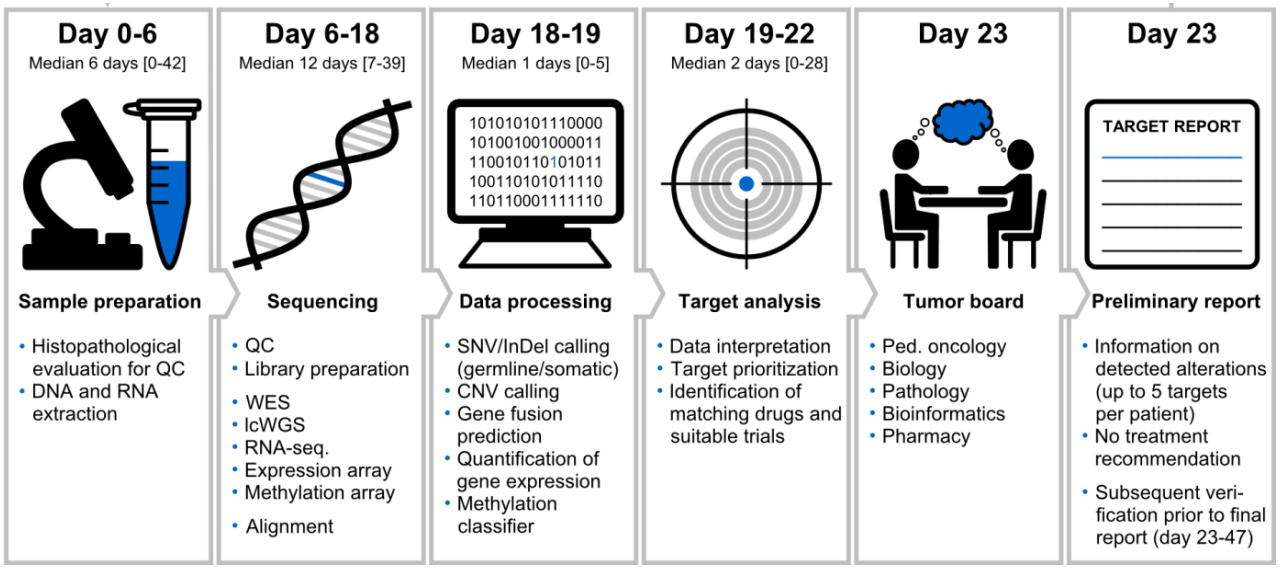
(Epi-)Genomic profiling ⟵  ⟶ Co-clinical Drug Screening

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

image-based high-content drug profiling

Ιατρικη Ακριβειας

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

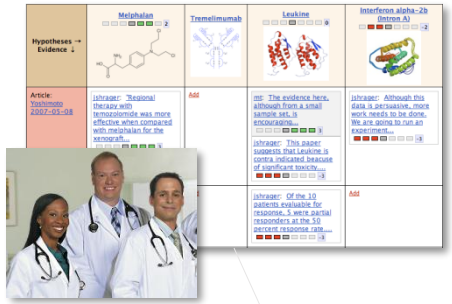


Graph adapted from Worst BC et al. *EJC* 2016

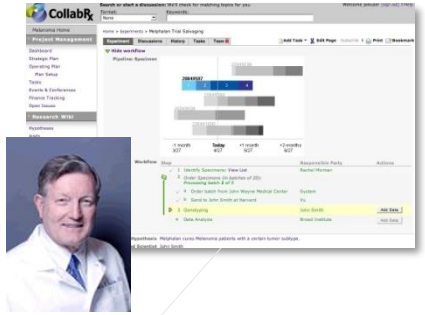
Η εποχή των Μαζικών Δεδομένων

Επιστήμονες

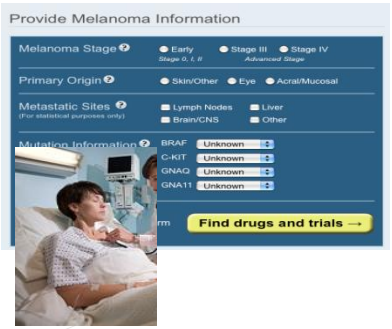
Κλινικοί Ερευνητές



Ιατροί

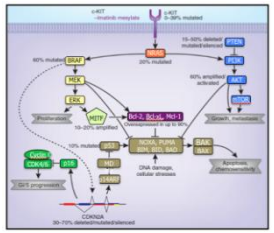


Ασθενείς

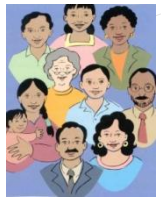


Data

Rapid Learning System

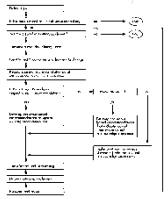


Μοριακά Μοντέλα Ασθενειών

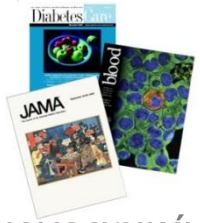


Μελέτες

Θεραπείες

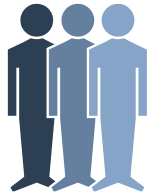


Κατευθυντήριες Οδηγίες



Βιβλιογραφικά Δεδομένα

Tests

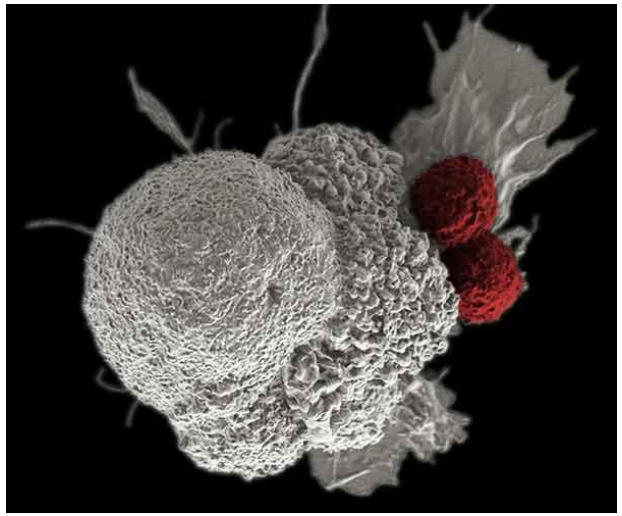


Περιπτώσεις

Prof. Antonis Kattamis
National and Kapodistrian University of Athens
EST. 1837

Ανοσοθεραπεια

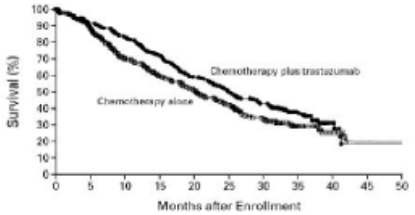
- ‘Απλά’ MoAbs
- MoAbs συνδεδεμένα με τοξίνη
- MoAbs που διεγείρουν ανοσολογική απάντηση



ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ

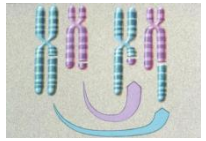
1997

1° Στοχευμένη rituximab



1998

Trastuzumab εναντι HER2+ Ca μαστού



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Imatinib

FDA

1997-2016

100+ FDA-approved Στοχευμένη θεραπείας

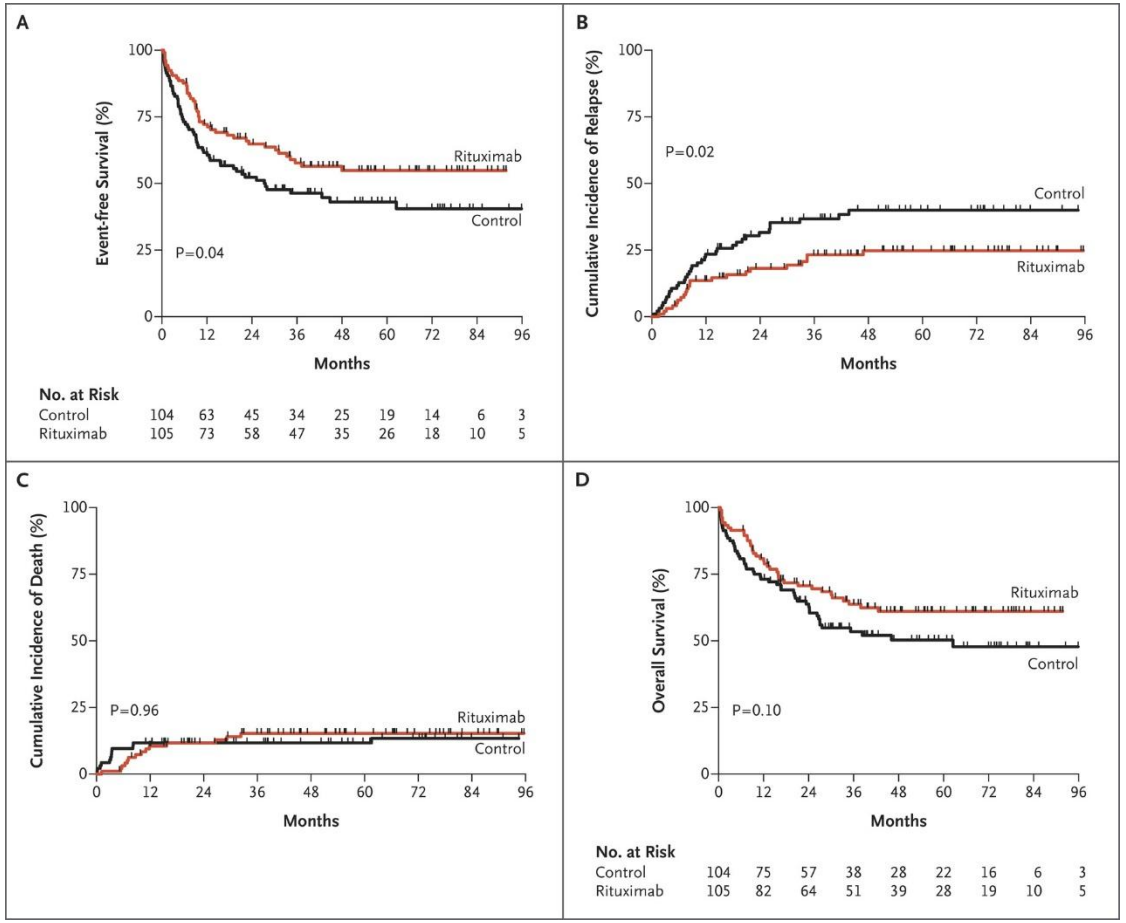
CancerProgress.Net

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

RITUXIMAB

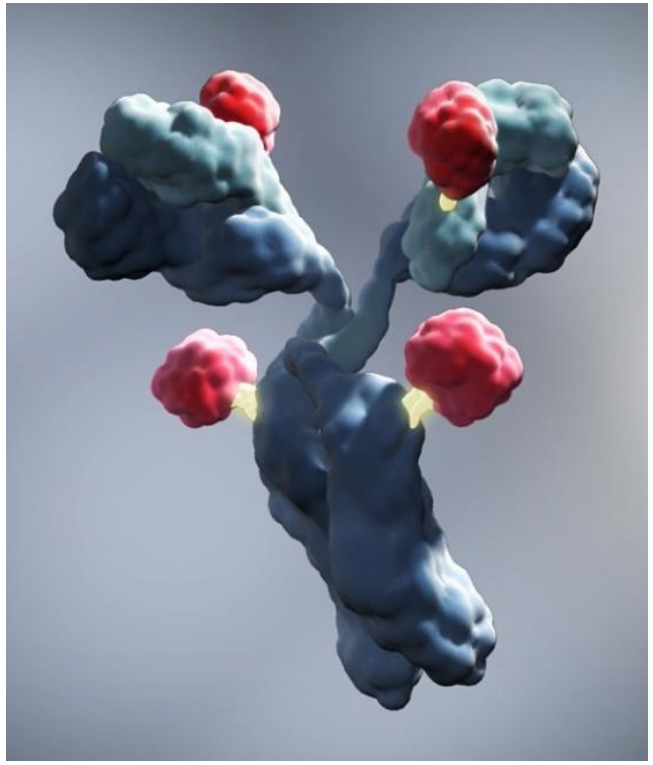
- Rituximab (mabthera) chimeric anti-CD20 monoclonal antibody
- Relapsed or refractory, CD-20 positive, B-cell, low-grade or follicular NHL
- B-cell νεοπλασίες συχνά ως κ 1η γραμμης
  - BURKITT
  - EBV-LPD
  - LYMPHOCYTIC PREFOMINANCE HL
- και στα αυτοάνοσα νοσήματα

- Χρήση στην Β-ΟΛΛ !
- Χαμηλότερες αντιδράσεις στην Asp
- St. Jude Children's Research Center, Total XVII,



Maury S et al
N Engl J Med 2016; 375:1044-1053

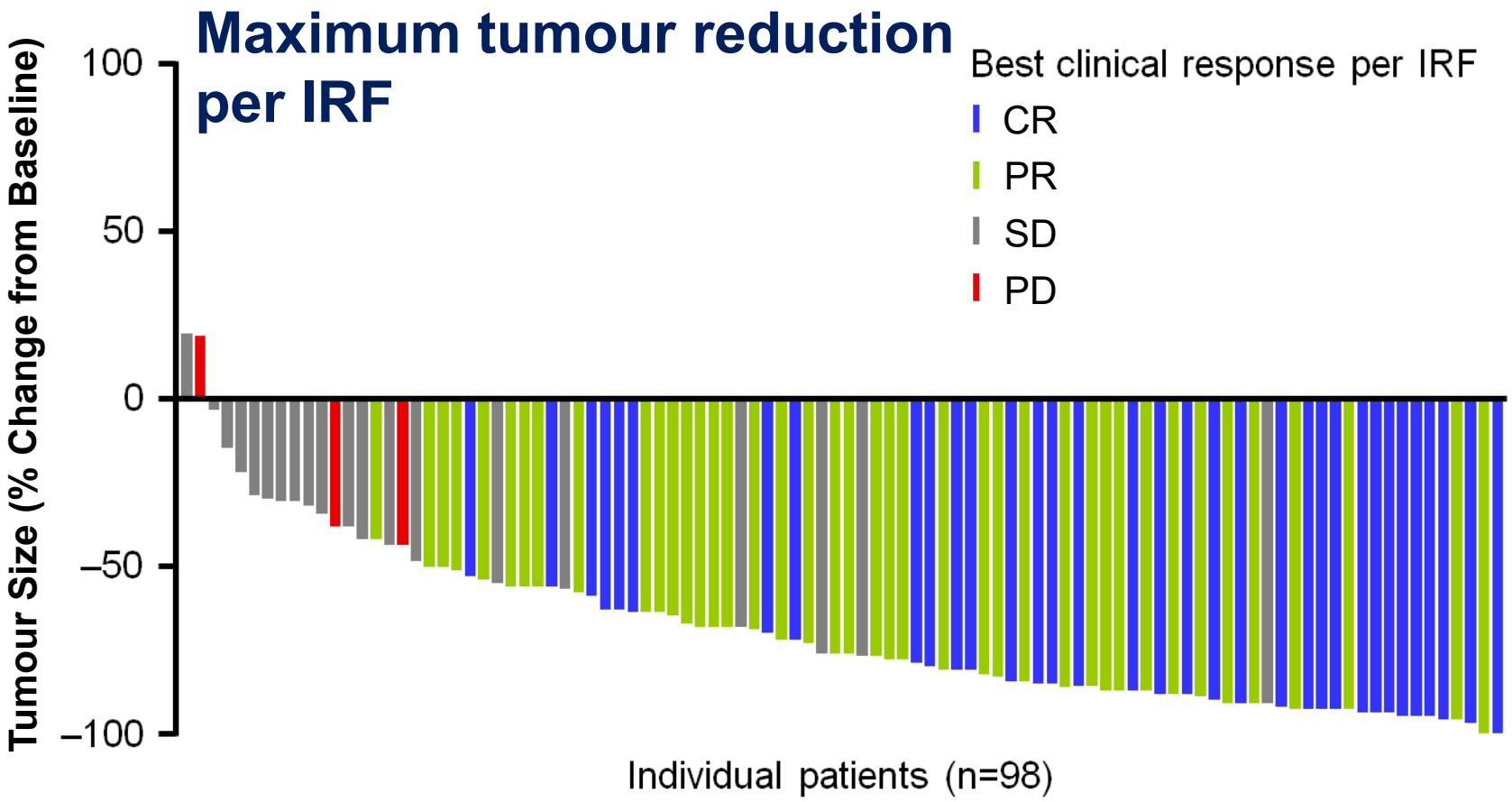
BRENTUXIMAB VEDOTIN



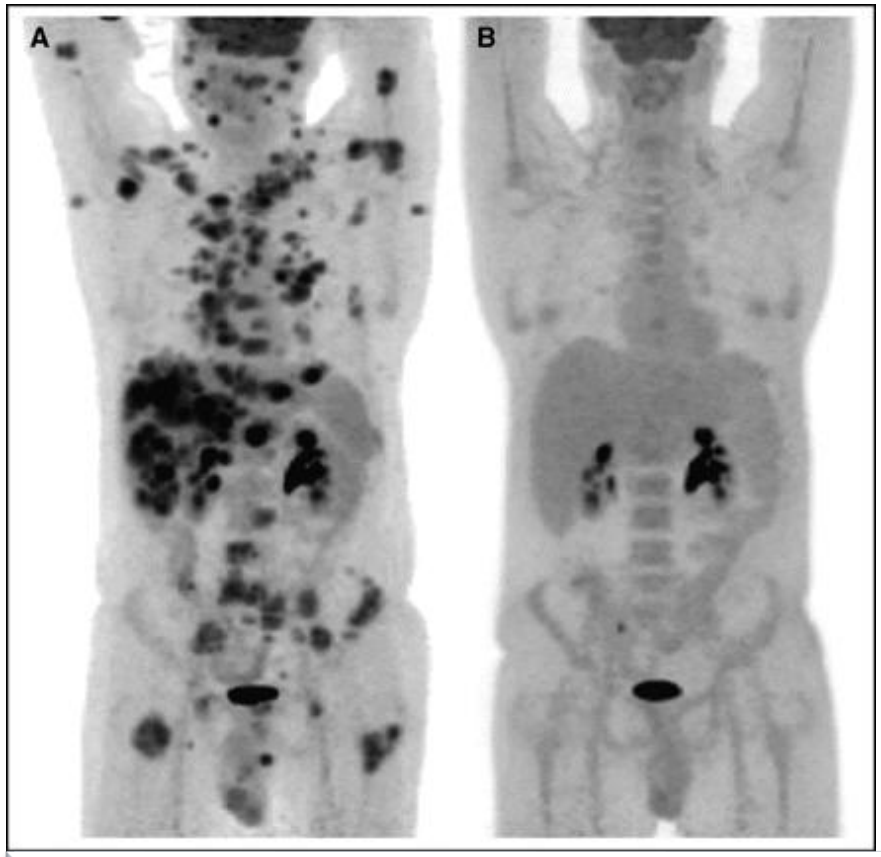
Σύζευγμα αντισώματος-φαρμάκου (ADC):

- 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

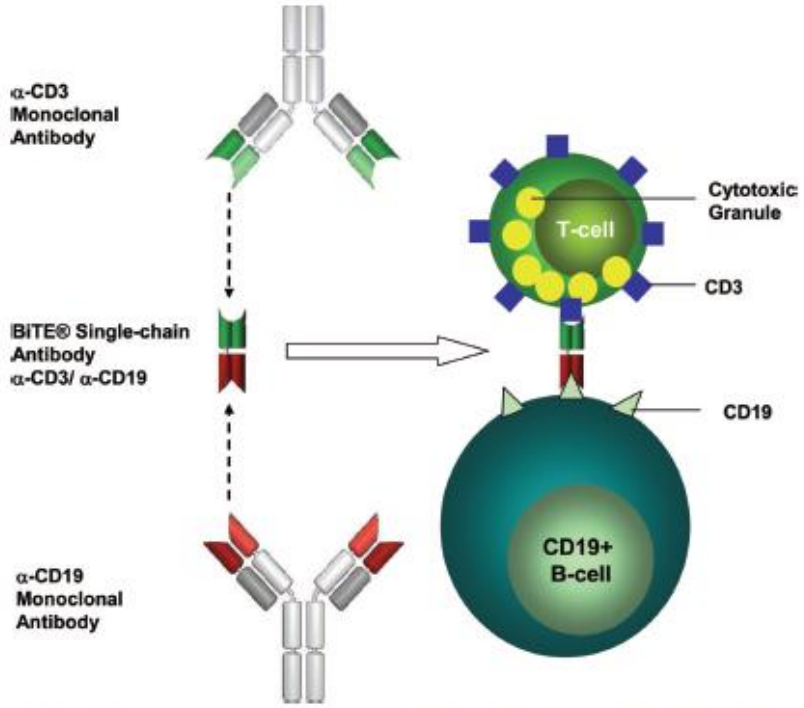


Figure 1. Single-chain antibody blinatumomab redirects CD3+ T cells to kill CD19+ B cells.

- 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

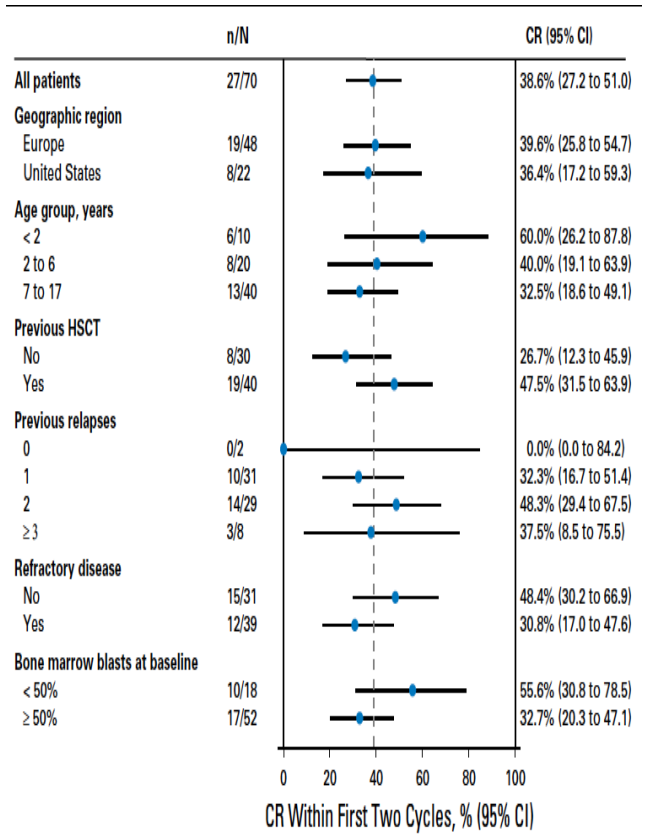
  Side effect profile very different from cytotoxic chemotherapy
  - Causes lymphopenia but no significant anemia, thrombocytopenia or neutropenia
  - Very low incidence of serious infections
  - Unique CNS toxicities including hallucinations and seizures

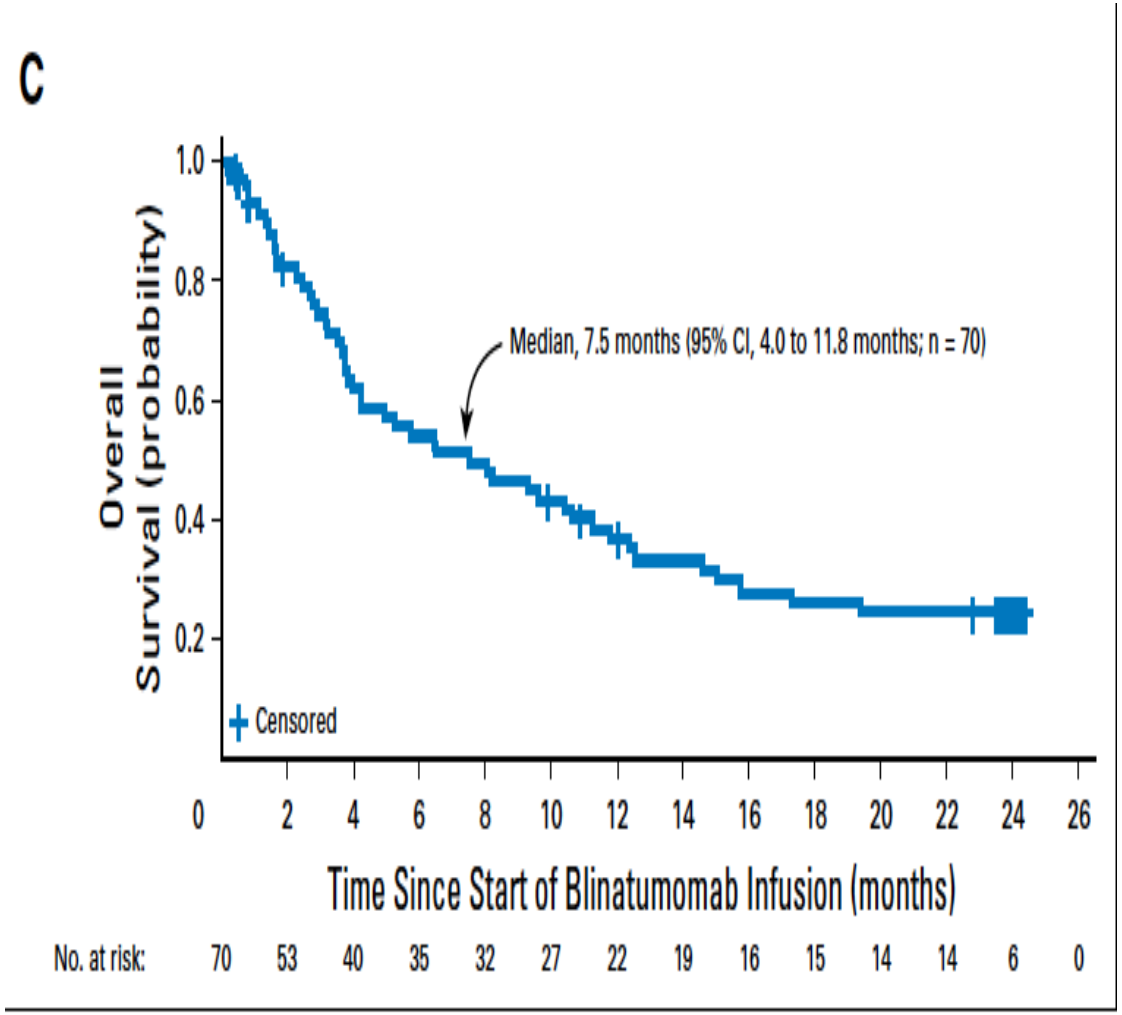
VOLUME 34 · NUMBER 36 · DECEMBER 20, 2016

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





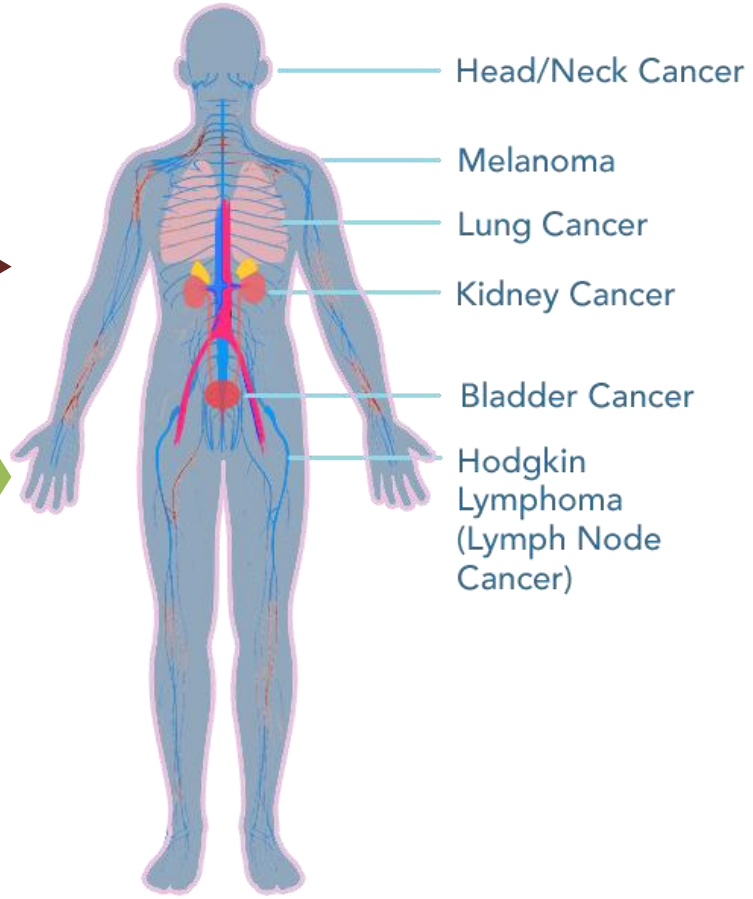
Η ΑΝΟΙΞΗ ΤΗΣ ΑΝΟΣΟΘΕΡΑΠΕΙΑΣ

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

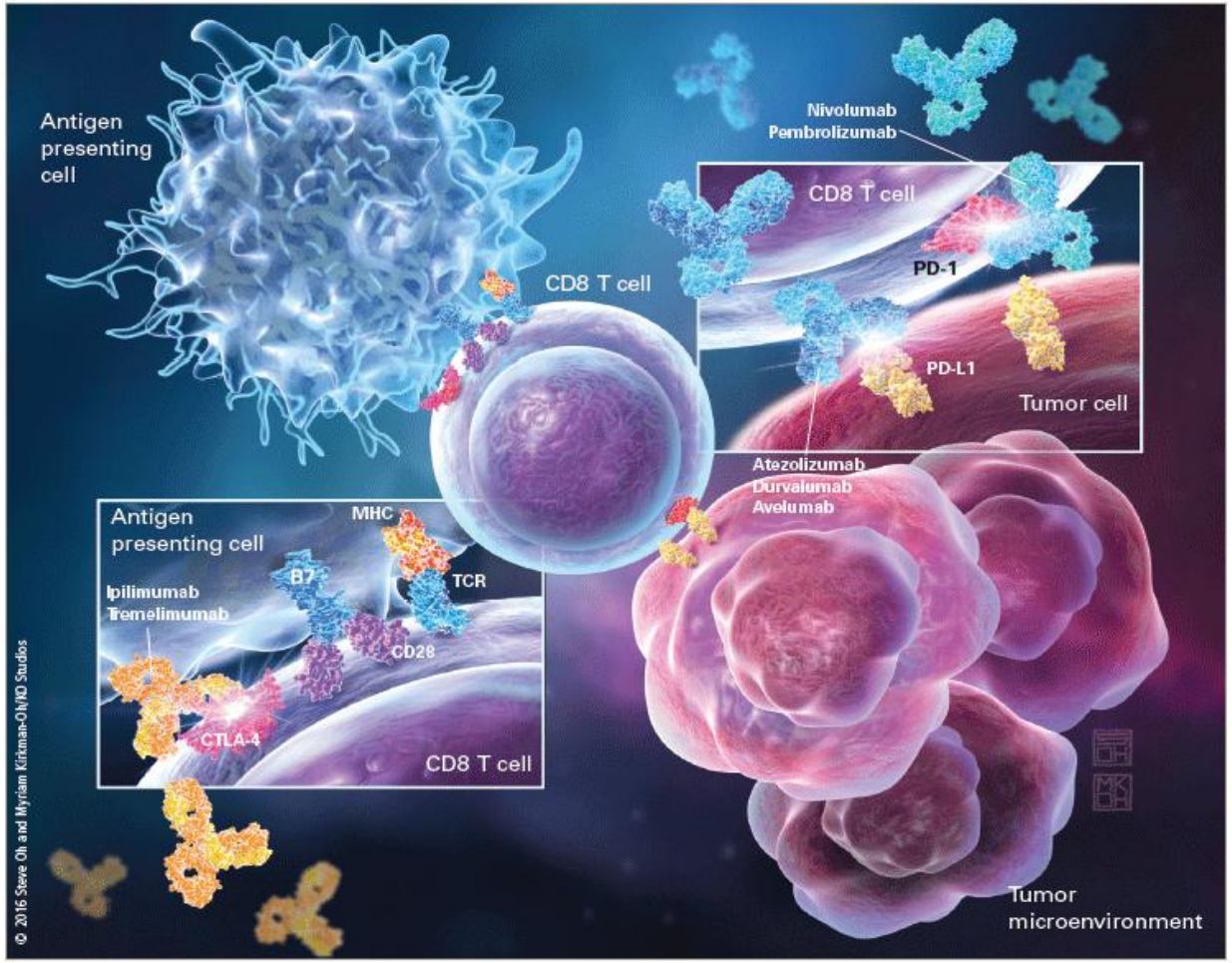
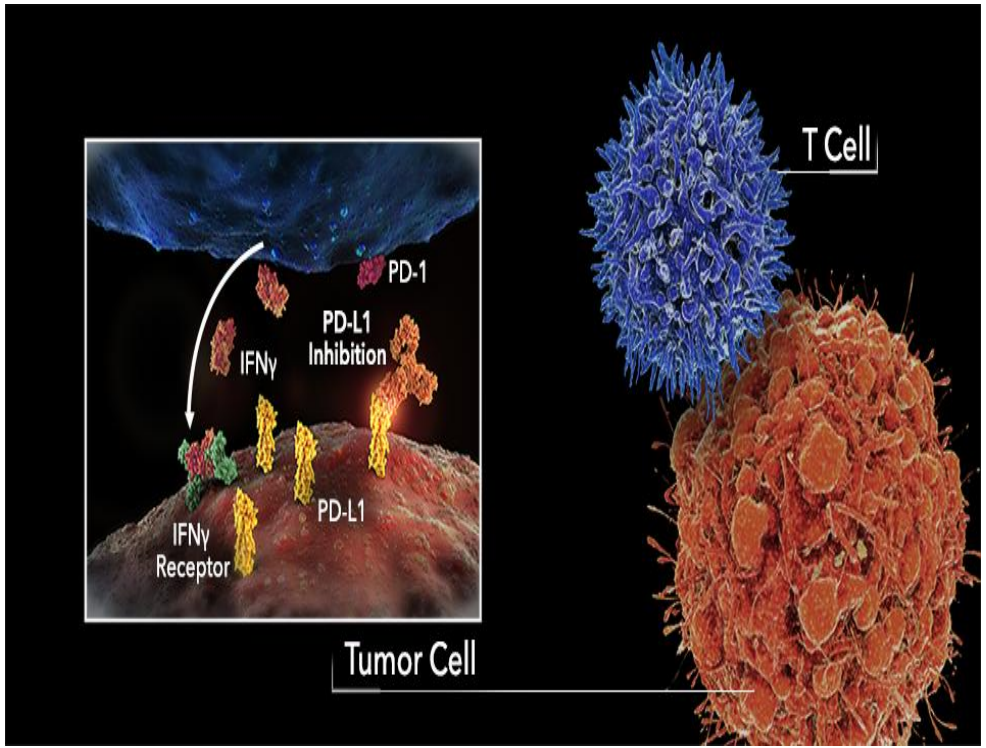


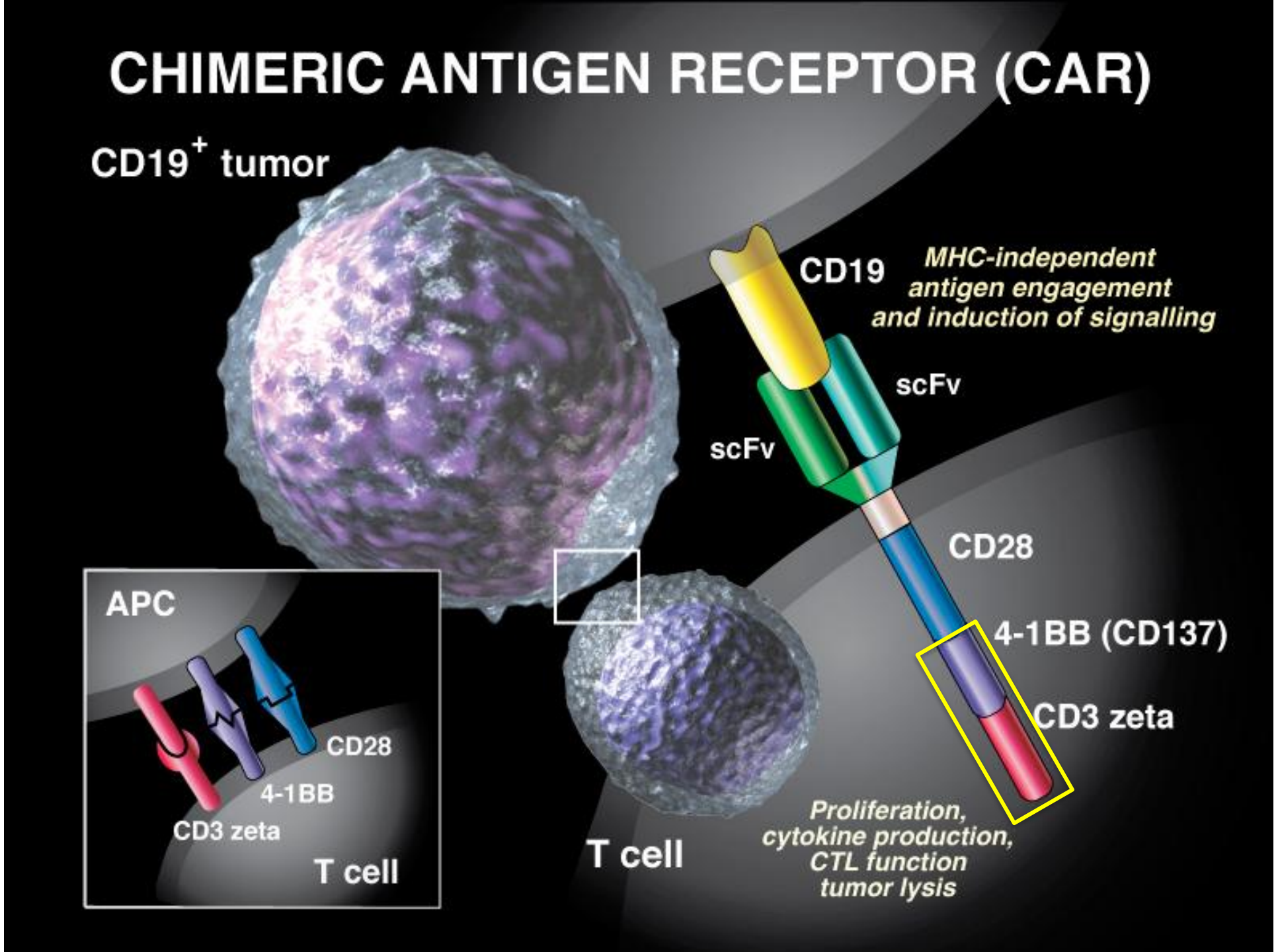
Figure. Immune Checkpoint Inhibition Mechanisms of Action Relevant to Lung Cancer Immunotherapy—T cells

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



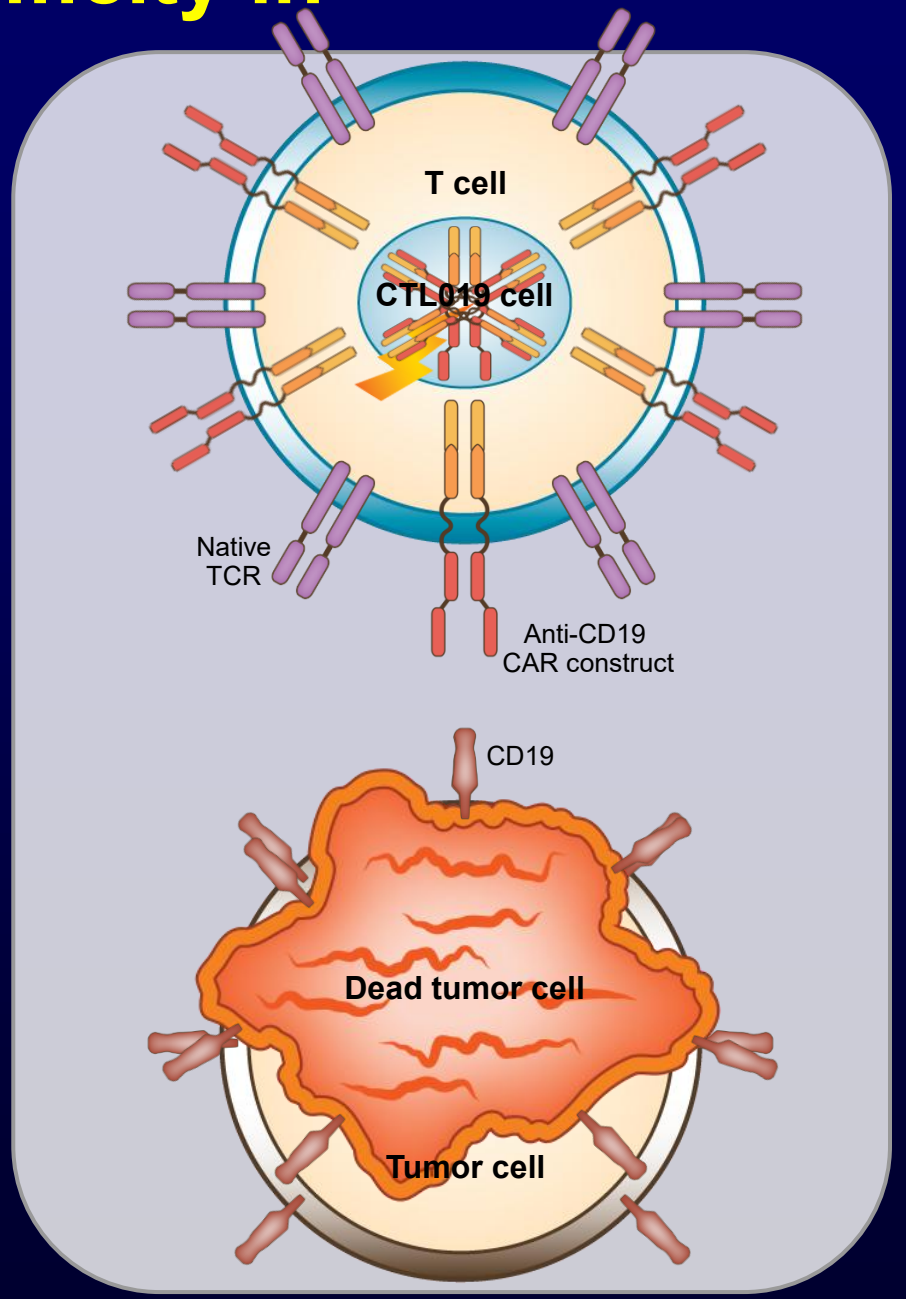

CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent
antigen engagement
and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation,
cytokine production,
CTL function
tumor lysis

Redirecting T cell Specificity in CTL019 cells

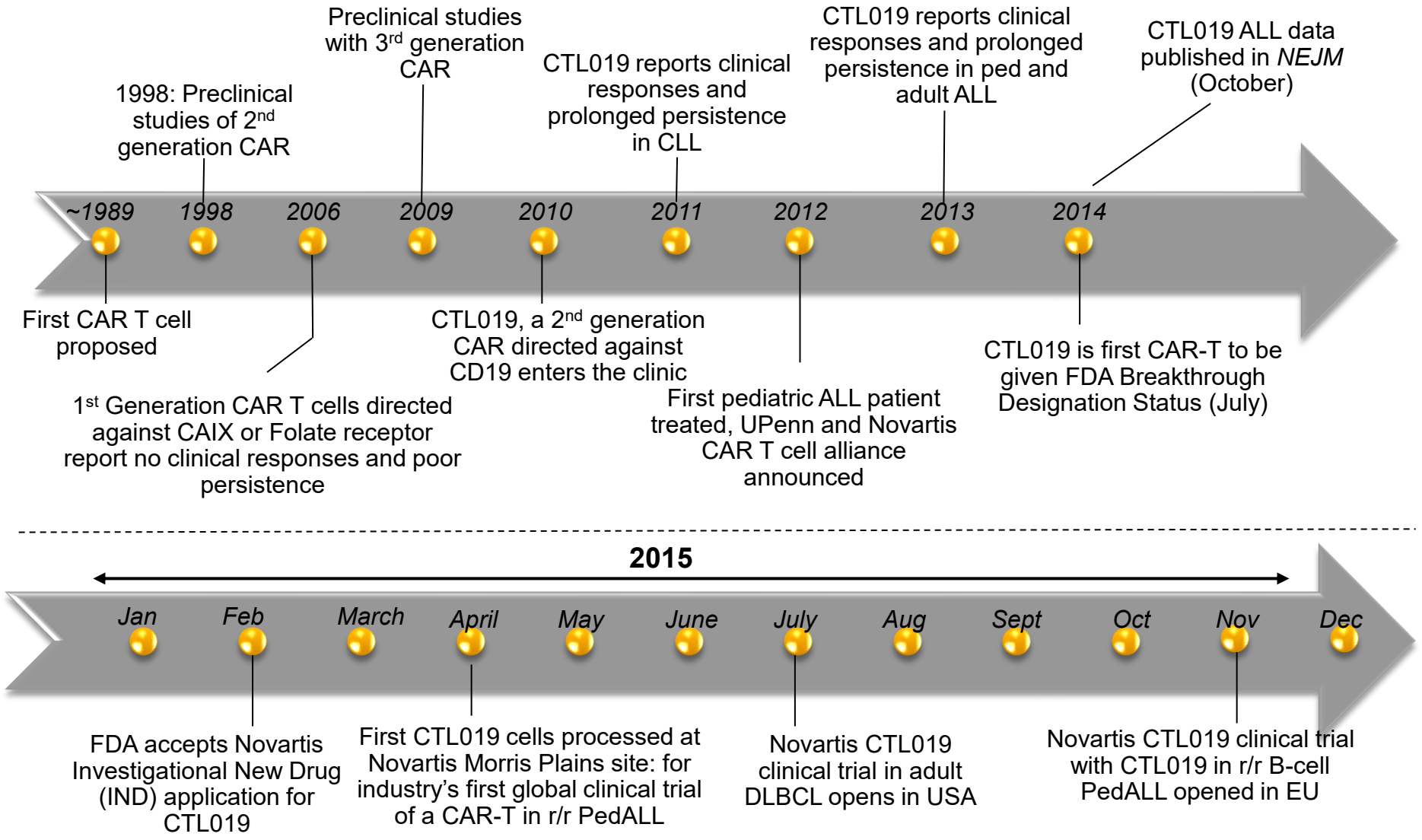
Goals for modern, highly active cell therapy:

- Proliferation – high level of in vivo proliferation correlates with high response rates
- Persistence – longer term persistence may allow longer term disease control.

Length of persistence needed for long-term disease control is unknown



Chimeric Antigen Receptor (CAR) T-Cell Therapy: Timeline



Infusion

Persistence

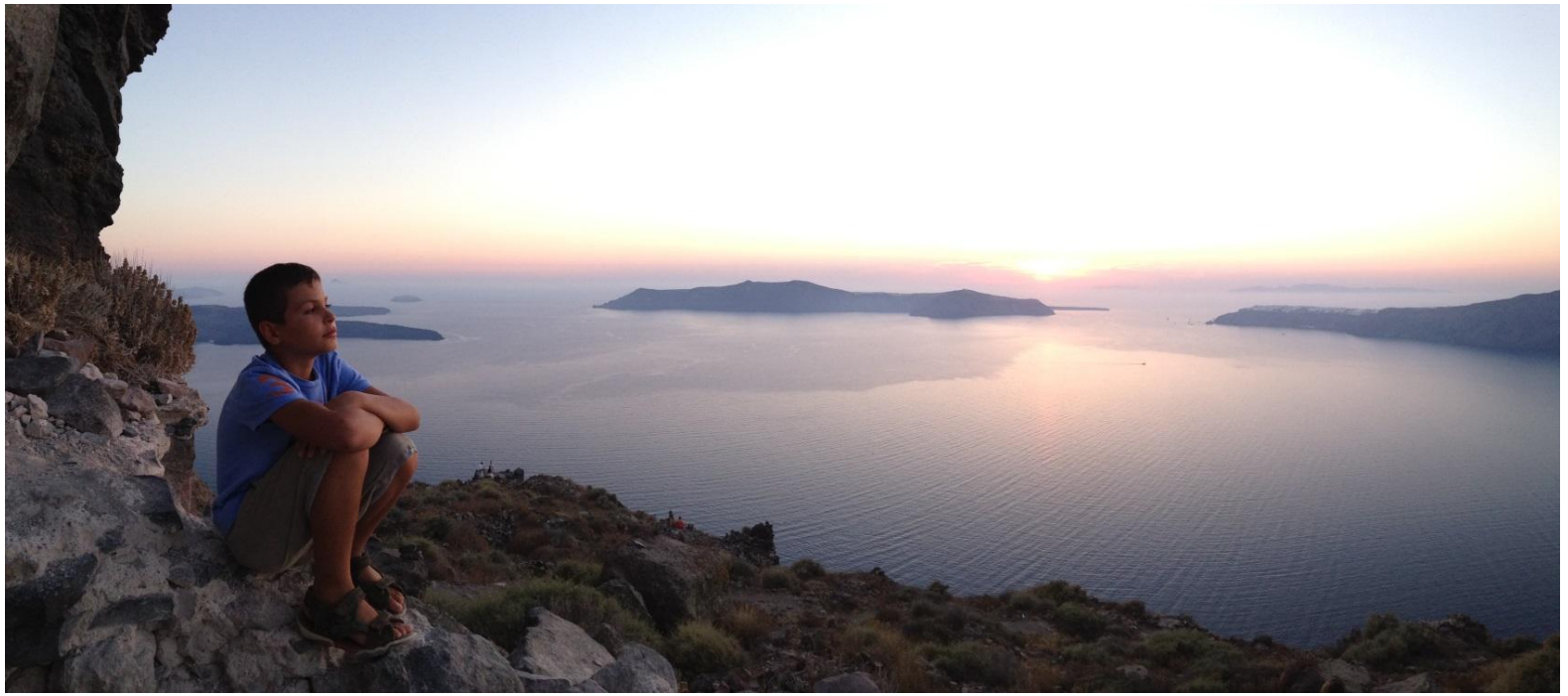
Stephan Grupp
Shannon Maude
Amanda DiNofia
Lisa Wray
David Barrett
Colleen Callahan
Diane Baniewicz
Amy Barry
Claire White
Brooke Leibfield
Lauren Vernau
Laura Motley
Vik Shenoy
Nick Kawchak
Beth McBride
Veronica Little
Deborah Barnebei

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