# Advances in wilms tumors and neuroblastoma

Dr Malek

# Telomerase maintenance mechanisms (TMM) : biomarker of high(er) risk?

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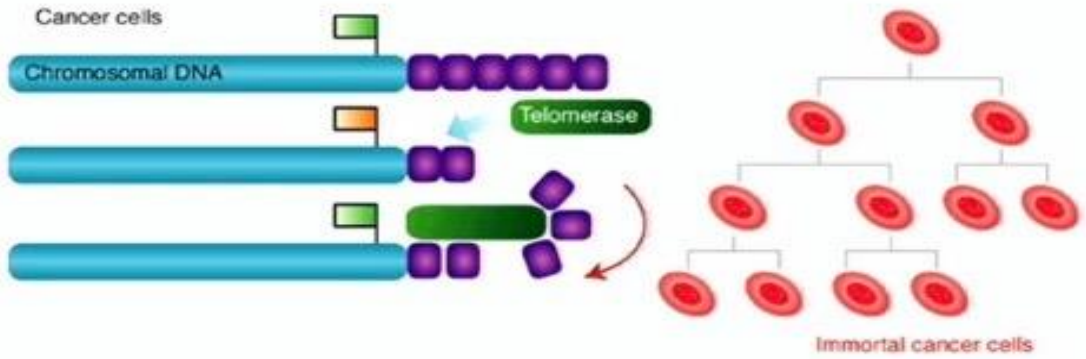


- **Upregulation of TERT (catalytic subunit of the telomerase enzyme) ~85%**
  - Increased expression (MYCNA)
  - TERT promoter mutations
  - TERT Rearrangements
- **Alternative lengthening of telomeres (ALT) ~15%**
  - includes *ATRX* mutations NB
- Evidence for prognostic biomarker

*Cheung , JAMA 2012; Peifer , Nature 2015, Valentijn NatGen2015, Ackermann Science 2018 ,Federico/Dyer,Nat Com 2021, Koneru Can Res 2021)*

# Outline

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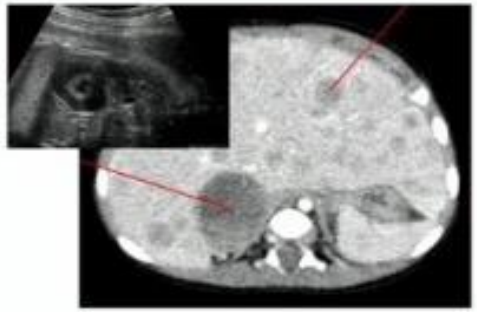
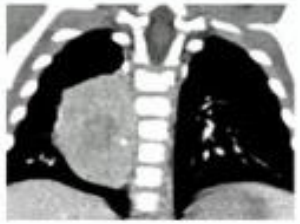
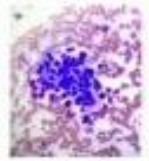
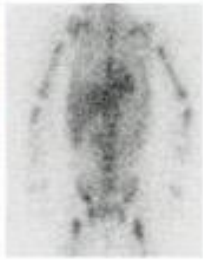
- Types of Biomarkers – definitions
- Historical perspective
- **Integral Biomarkers** currently in use for prognosis, treatment selection
  - Evidence, limitations
- **Biomarkers with early evidence** (*eg* trials)
- Next generation biomarkers (highlights)

# Neuroblastoma heterogeneity
## Prognostic groups (Rx) reflects clinical behavior (biology)



| LOW | INTERMEDIATE | HIGH |
|---|---|---|
| Highest rate of spontaneous resolution/differentiation (95%) | Responsive, curable (even with residual) (>80-90%) | Highly resistant, Metastatic (~ 50%) |
|  |  |    |
| Surgery alone/ observation | Surgery plus chemotherapy (moderate) | Intensive multi-modal treatment |

# Biomarkers in Neuroblastoma

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## Definitions : prognostic vs. predictive

- **Prognostic**- variable that provides information about patient outcome
  - -single biomarkers or combinations of numerous variables (signatures, risk classifiers)
  - -consider context (identified/studied for *all* patients vs subsets, era/treatments)

- **Predictive**- provides information about the effect of a certain intervention
  - -examples: MIBG avid for MIBG therapy; ALK mutation to select for ALK inhibitor treatment
  - -may influence choices of therapy upfront or relapse (*C. Owens, Education talk*)

- **Some biomarkers are both PROGNOSTIC and PREDICTIVE**

# Biomarkers in Neuroblastoma

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·**Timing of biomarkers:** diagnosis, during treatment, at relapse….

·**Types:**

**- Biomarkers (host and/or tumor)-** from DNA, RNA, protein, serum/plasma……

- not all "bio" markers require assay , genes

    - many clinical factors likely are surrogates for "biology"

        -age, stage, image-defined risk factors

*-treatment itself is risk factor*

    *- need to consider the impact of the prognostic factor in context of treatment*

# Prime time now= INTEGRAL Biomarkers

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- **Mostly prognostic markers that are used to:**

- Establish eligibility for trials
- patient risk stratification
- to assign patients to treatment arm

# Next generation biomarkers-3

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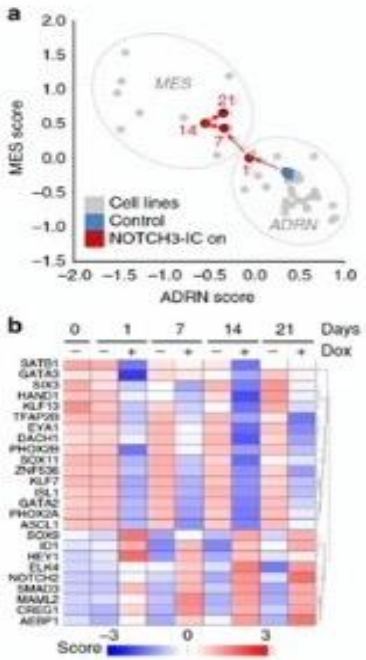
## Adrenergic vs. mesenchymal tumor phenotype

- 2 tumor cell types from distinct lineages; interconversion
- involves super enhancer associated transcription factors
  - Differential gene expression (b)

- Differential chemo and ALK TKI sensitivity
  - Pre-clinical data but ? Future predictive biomarker for Rx

- ? Differences in immune gene activation through epigenetics
  - ? Future predictive biomarker for immunotherapy response
    - *Sengupta Nat Cancer, 2021*




Van Groningen et al, Nat Comm, 2019, Nat Genetics 2017

# ALK = prognostic and predictive

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## Anaplastic Lymphoma Kinase amplification, mutations

- 10-15% of tumors at diagnosis; increased incidence at relapse
- PREDICTS response to ALK tyrosine kinase inhibitors (crizotinib, ceritinib, lorlatinib)
- Differential response based on specific mutation (1245, 1275, 1174)

## ALK alterations occur across all stages, risk groups- ? PROGNOSTIC

- Prognostic in some subsets (*eg MYCN*-A)
- Different results depending on study (and specific subgroup being analyzed)
- Important to study in homogeneous population (single trial)

Mosse, Nature 2008; George, Nature 2008; Bressler Cancer Cell, 2011; Foster CCR 2021,

# Biomarkers- almost prime time -and/or being evaluated prospectively

# DNA content (Ploidy)



- **Hyperdipoidy (DNA index >1) is favorable** (*esp. if < 2yo*)
  - *Bagatell, JCO 2007*

- **Diploid (DNA index =1)** : More malignant NB- more genome instability leading to chromosome changes, translocations (likely includes many tumors with segmental chromosome aberrations, SCA)

- MOSTLY USED TO DISTINGUISH NON-HR PATIENTS, esp infants, toddlers

# LINES Protocol: Impact of SCAs for Risk Assignment

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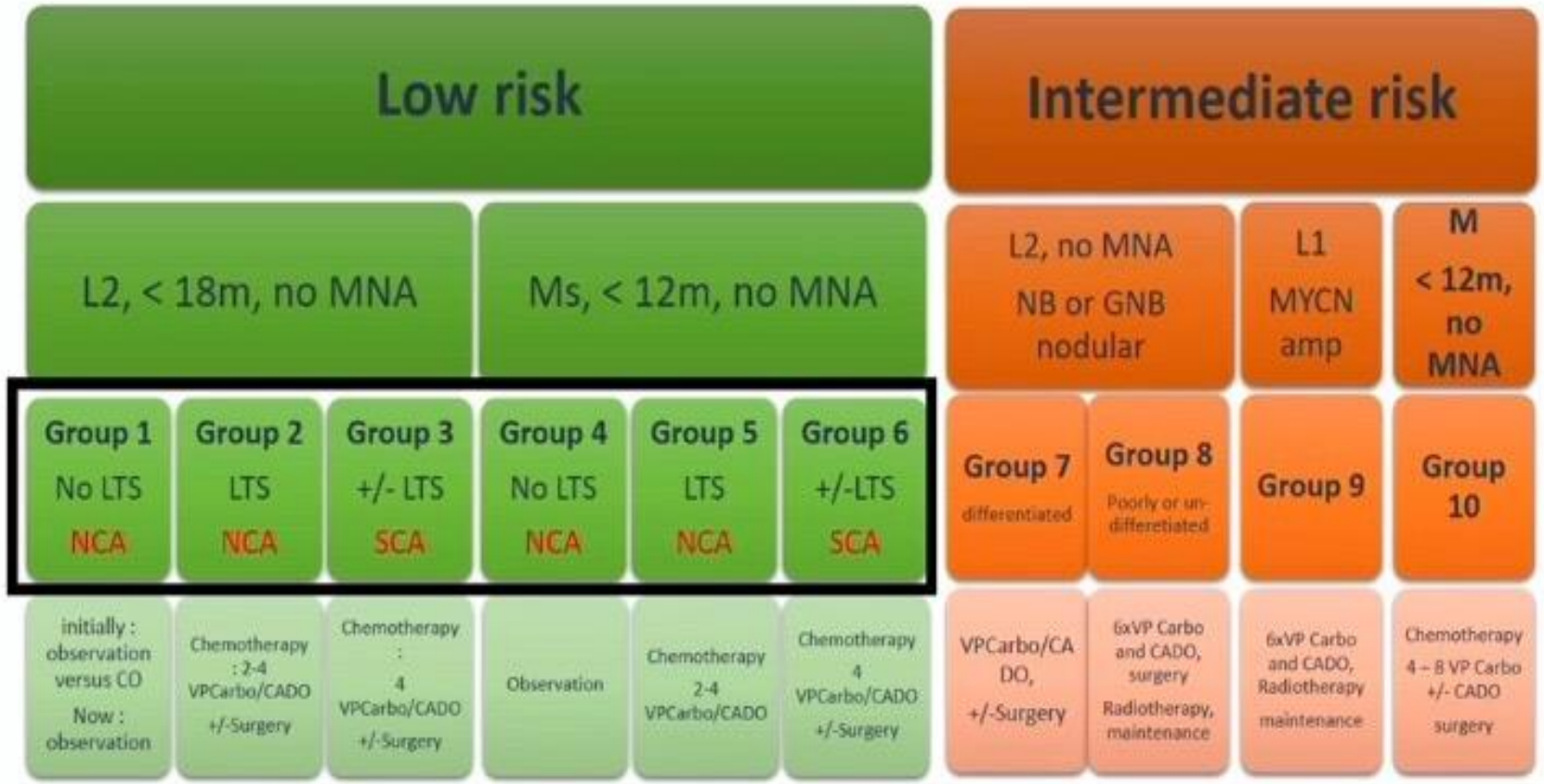
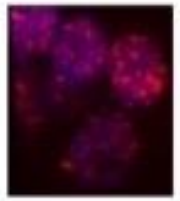



Stratification of treatment according to Age, stage (IDRFs), clinical symptoms (LTS)
**LR:** Genomic satus : MYCN, genomic copy number profile
**IR:** pathology

SIOPEN R NET

# *MYCN* status as biomarker



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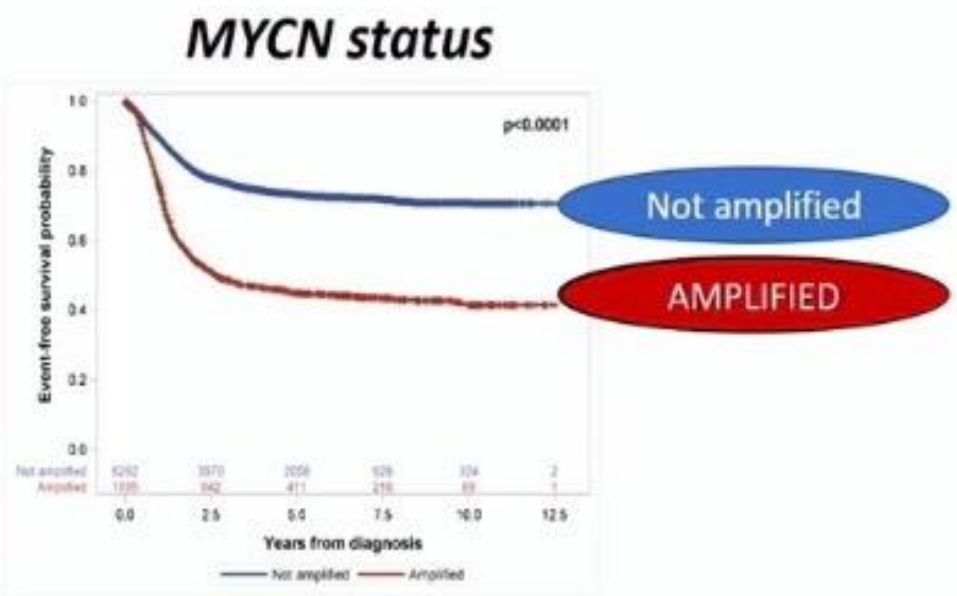


- Correlates with outcome independent of age, stage
- Specific impact in subgroups
  - Loco-regional
  - **Metastatic**
    - For those <12 mo : historically all classified and treated as HIGH RISK
      - *MYCNA* (<30% EFS) vs. *MYCN*-non AMP (80-90%)*
      - Since ~2000 *MYCN*-non-AMP= INTERMEDIATE RISK

*Tonini et al, JCO 1997
ML Schmidt et al, JCO 2000

# Segmental vs Numerical Chromosome Aberrations

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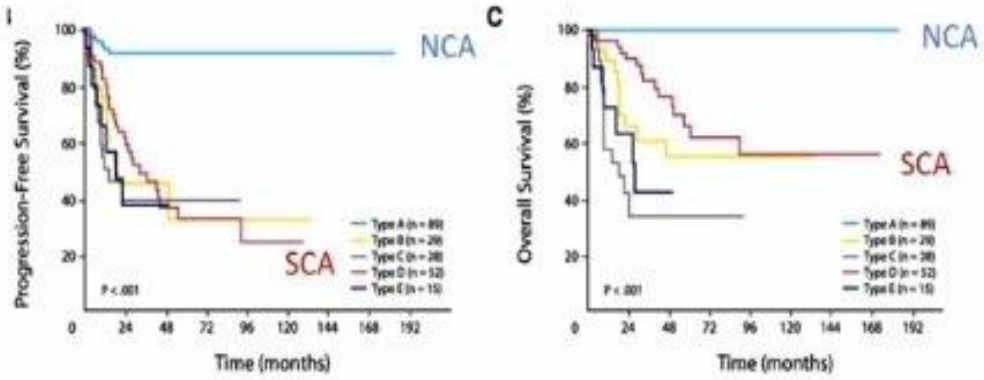





Januoix-Lerosy, *JCO* 2009
George et al *PLOS One* 2017
Schleiermacher, G. *et al. Br J Cancer* **97**, 238-246 (2007)
MANY OTHERS

- **SCAs - loss/gain (SIOPEN-7)- UNFAVORABLE**
  - gain of 1q, 2p, 17q
  - loss of 1p, 3p, 4p, 11q
  - Poor outcome in many otherwise favorable
    - L2, M, ?MS
    - Variable retrospective data/ prognostic impact
- **Numerical (NCAs)- whole chromosome gains/losses –FAVORABLE**
- **Lack of SCA** biomarker identifies patients within non-high risk subsets to DECREASE THERAPY or OBSERVE
  - COG ANBL1232
  - **LINES (SIOPEN)**

# Integral biomarkers- SCA

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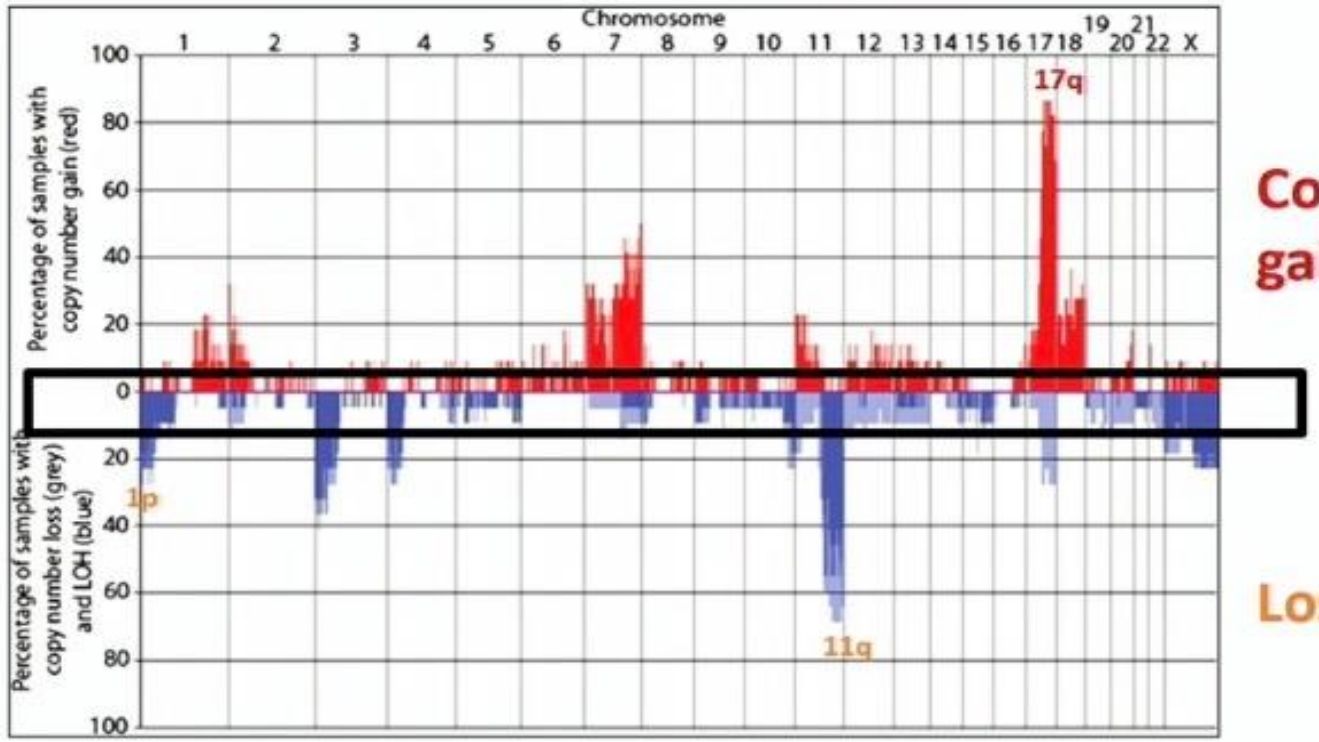
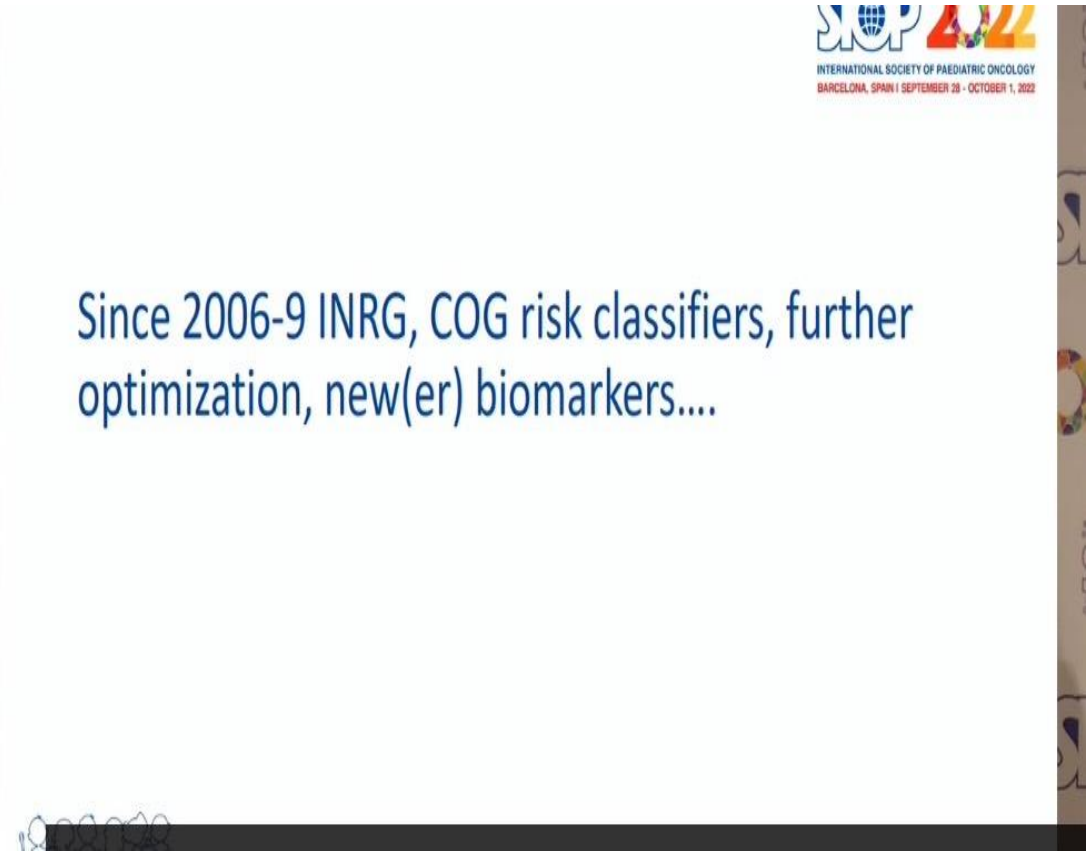
Segmental Chromosome Aberrations = loss/gain of small pieces of chromosomes
(vs. loss/gain of whole chromosomes)




**Copy gain**

**Loss**

George , Attiyeh et al, PLOS One 2007 *chleiemacher et al, Br J Ca, 2012*, Janoulix-Lerosy *Ambros et al Clin Ca Res, 2011*, many others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Since 2006-9 INRG, COG risk classifiers, further optimization, new(er) biomarkers....

# Risk Stratification (based on biomarkers) predicts survival--> tailor therapies

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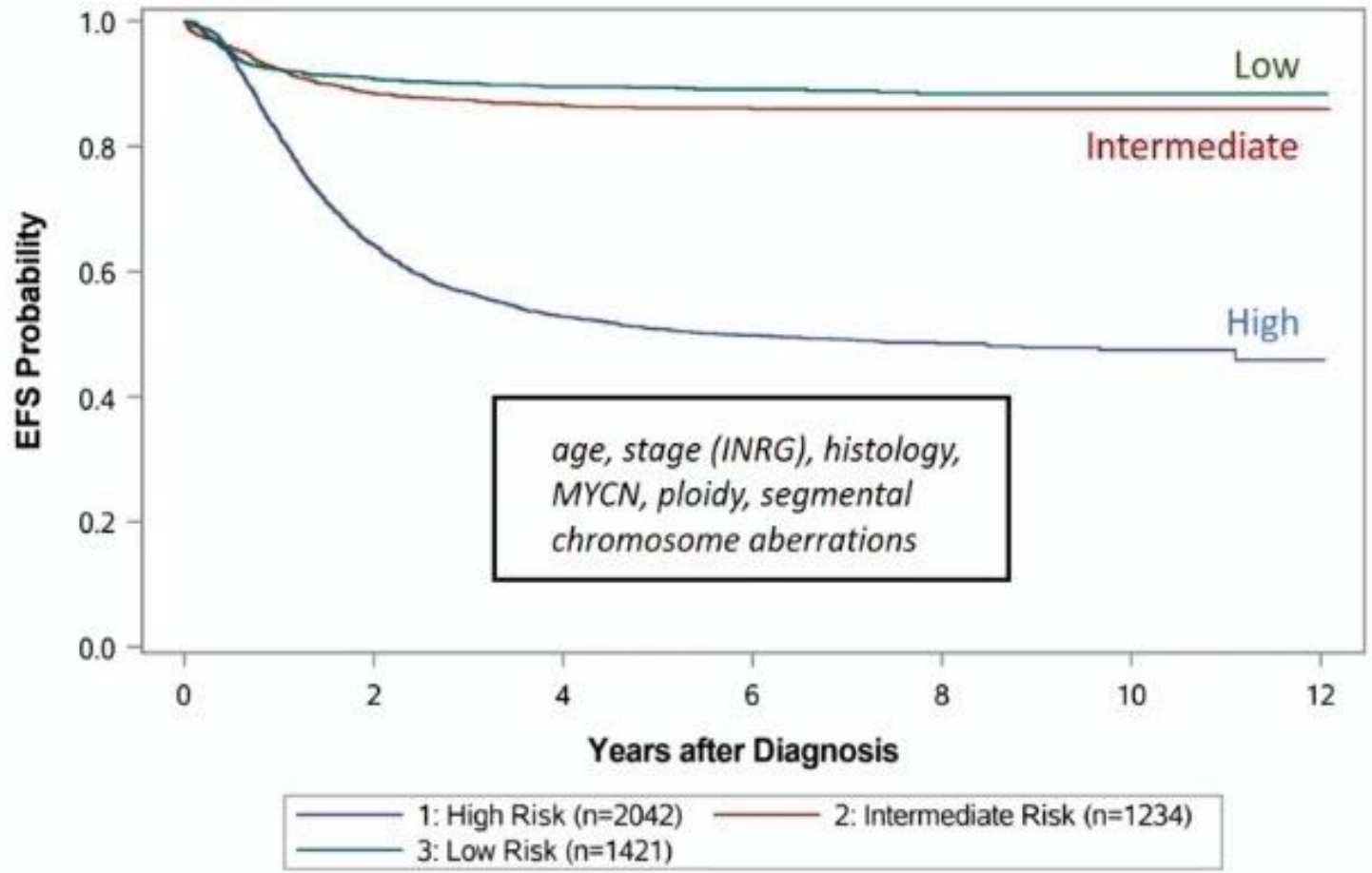

# Biomarkers : Risk Classification

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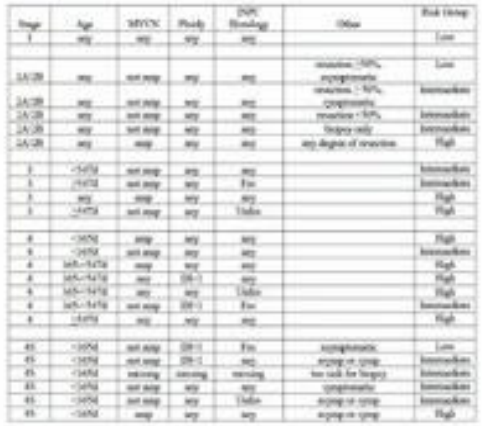
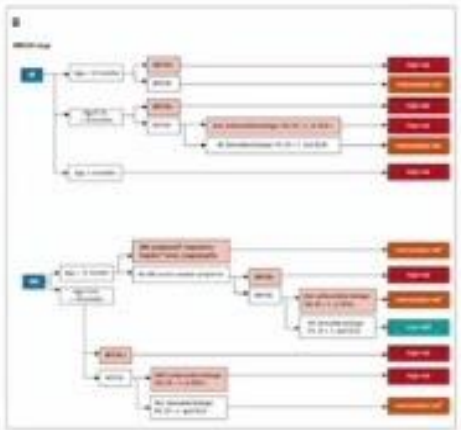
Independent prognostic markers used alone or with other variables by COG and INRG classifiers to assign RISK group (low, intermediate, high) and determine eligibility for cooperative group clinical trials

- ***MYCN* status, histology, ploidy (DNA index)** used (together w/ age, stage)



**COG**: 2006



**COG**: v2, 2021

| | INRG Stage | Age (months) | Histologic Category | Grade of Tumor Differentiation | MYCN | 11q Aberration | Ploidy | Pretreatment Risk Group |
|---|---|---|---|---|---|---|---|---|
| loco-regional | L1/L2 | | GN maturing; GNB intermixed | | | | | A Very low |
| | L1 | | Any, except GN maturing or GNB intermixed | | NA | | | B Very low |
| | | | | | Amp | | | K High |
| | L2 | < 18 | Any, except GN maturing or GNB intermixed | | NA | No | | D Low |
| | | | | | | Yes | | G Intermediate |
| | | > 18 | GNB nodular; neuroblastoma | Differentiating | NA | No | | E Low |
| | | | | | | Yes | | H Intermediate |
| | | | | Poorly differentiated or undifferentiated | NA | | | |
| | | | | | Amp | | | N High |
| metastatic | M | < 18 | | | NA | | Hyperdiploid | F Low |
| | | < 12 | | | NA | | Diploid | I Intermediate |
| | | 12 to < 18 | | | NA | | Diploid | J Intermediate |
| | | < 18 | | | Amp | | | O High |
| | | > 18 | | | | | | P High |
| | MS | < 18 | | | NA | No | | C Very low |
| | | | | | | Yes | | Q High |
| | | | | | Amp | | | R High |

**INRGdb.org**: 2009

CHILDREN'S ONCOLOGY GROUP

INRG

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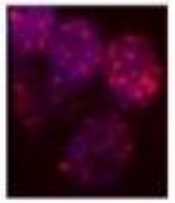
# *MYCN* status as biomarker



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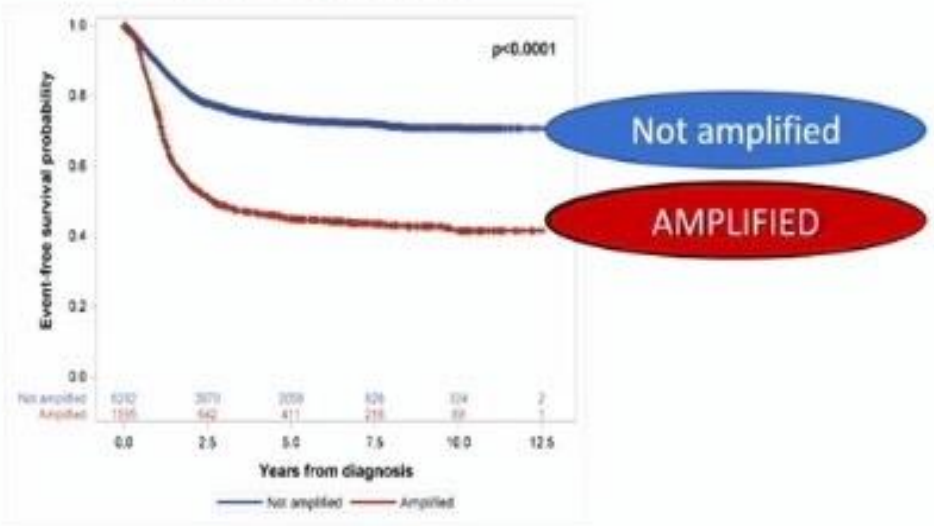


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  - **Metastatic**
    - For those <12 mo : historically all classified and treated as HIGH RISK
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      - Since ~2000 *MYCN*-non-AMP= INTERMEDIATE RISK

*Tonini et al, JCO 1997
ML Schmidt et al, JCO 2000

# Current independent prognostic markers- integral

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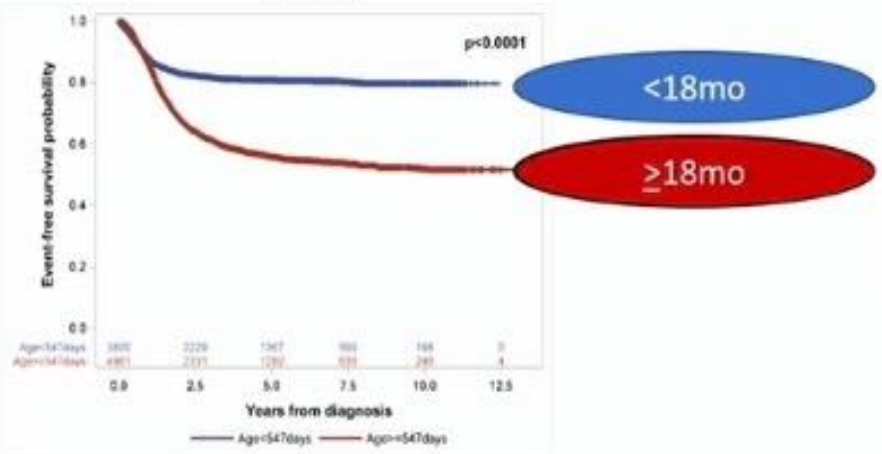
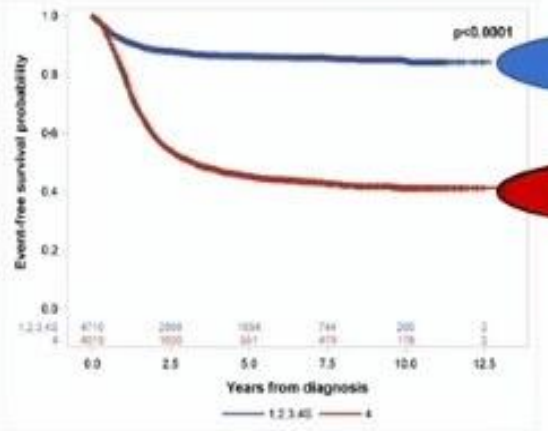
## AGE




<18mo

≥18mo

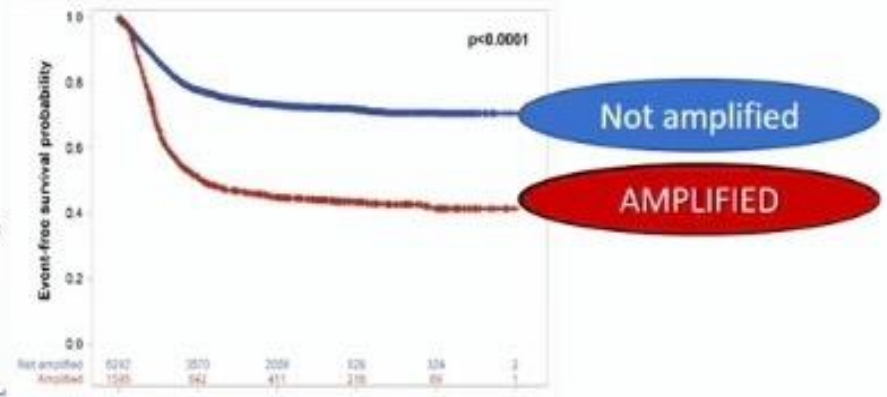
## STAGE (INSS)




stage 1,2,3,4s

stage 4
metastatic

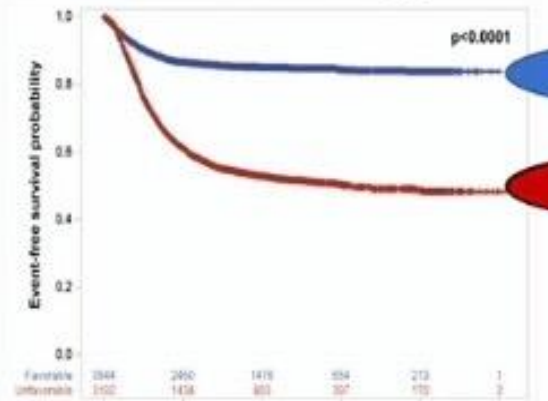
## *MYCN status*




Not amplified

AMPLIFIED

## Histology




favorable

unfavorable

**INRGdb.org**
**(N >20,000)**
*INRG, COG data;*
*Sokol et al, JCO 2020*

# RISK CLASSIFICATION (~1971)

Courtesy of A. Evans, P. Adamson

Reprinted from CANCER, Vol. 27, No. 2, February 1971. 

## A PROPOSED STAGING FOR CHILDREN WITH NEUROBLASTOMA

*Children's Cancer Study Group A*

AUDREY E. EVANS,* GIULIO J. D'ANGIO,† AND JUDSON RANDOLPH‡

A clinical staging of patients with neuroblastoma is proposed. Such staging is desirable to aid in estimating the prognosis and to be able to evaluate the efficacy of differing therapeutic regimens by analyzing results obtained in comparable groups of patients. That the suggested staging is practical is illustrated by the ease with which 100 children with neuroblastoma, entered in previous studies by Children's Cancer Study Group A, were staged using the criteria described. Short-term survival data of this small sample demonstrated, in addition, that the proposed staging appears to be of help in estimating the

Staging=
1st prognostic biomarker

# Risk Classification based on prognostic clinical factors and biomarkers

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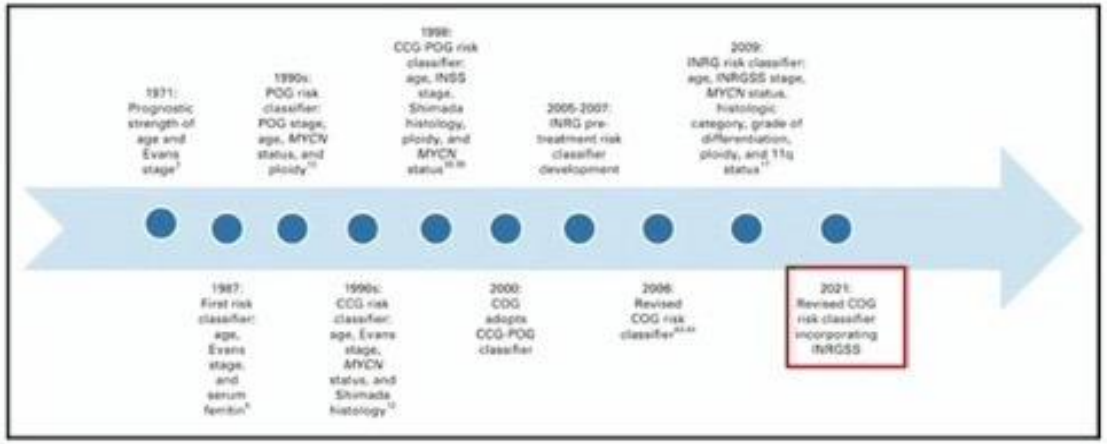


| Risk Factor | POG Classifier 1990-2000 | CCG Classifier Before 2000 | COG Classifier 2000 | COG Classifier 2006 | INRG Classifier 2009 | COG Classifier 2021 |
|---|---|---|---|---|---|---|
| Age (< 12 months, ≥ 12 months) | RA | RA | RA | | | |
| Age (< 18 months, ≥ 18 months) | | | | RA | RA | RA |
| POG stage | RA | | | | | |
| Evans stage | | RA | | | | |
| INSS stage | | | RA | RA | | |
| INRGSS stage | | | | | RA | RA |
| Ploidy | RA | | RA | RA | RA | RA |
| MYCN status | RA | RA | RA | RA | RA | RA |
| VMA/HVA | MD | MD | MD | | | |
| INPC (Shimada histology) | | RA | RA | RA | | TBD |
| Histologic category | | | | | RA | TBD |
| Grade of differentiation | | | | | RA | TBD |
| MKI | | | | | | TBD |
| Serum LDH | MD | MD | MD | | | |
| Serum ferritin | MD | MD | MD | | | |
| Symptomatic | | | | RA | | RA |
| Extent of primary tumor resection | | | | RA | | RA |
| 1p LOH | | | RS | TS | | |
| 11q LOH | | | RS | TS | RA | |
| IDRFs | | | | RS | | |
| MRP | RS | | | | | |
| NGF | RS | | | | | |
| TrkA receptors | RS | | | | | |
| $p^{75\ NTR}$ receptors | RS | | | | | |
| 14q LOH | RS | | | | | |
| 17q gain | RS | | | | | |
| SCAs (1p, 3p, 4p,11q loss and 1q, 2p, 17q gain) | | | | | | RA |
| TMM (ALT, TERT) | | | | RS | RS | RS |
| ALK | | | | TS | | TS |
| RAS/MAPK | | | | RS | RS | RS |
| RNA expression signatures | | | | RS | RS | RS |

Abbreviations: ALK, anaplastic lymphoma kinase; ALT, alternative lengthening of telomeres; CCG, Children's Cancer Group; COG, Children's Oncology Group; HVA, homovanillic acid; IDRF, image-defined risk factor; INPC, International Neuroblastoma Pathology Classification; INRG, International Neuroblastoma Risk Group; INRGSS, International Risk Group Staging System; INSS, International Neuroblastoma Staging System; LDH, lactate dehydrogenase; LOH, loss of heterozygosity; MD, criteria used to monitor disease response; MKI, mitosis-karyorrhexis index; MRP, multidrug resistance protein; NGF, nerve growth factor; $p^{75\ NTR}$, p75 neurotrophin receptor; POG, Pediatric Oncology Group; RAS/MAPK, Ras mitogen-activated protein kinase; RA, criteria used for risk assignment; RS, criteria collected for research studies; SCA, segmental chromosome

JCO® Clinical Cancer Informatics

**Tailoring Therapy for Children With Neuroblastoma on the Basis of Risk Group Classification: Past, Present, and Future.**

Liang, Wayne; MD, MS; Federico, Sara; London, Wendy; Naranjo, Arlene; Irwin, Meredith; Volchenboum, Samuel; MD, PhD; Cohn, Susan

JCO Clinical Cancer Informatics. 4:895-905, December 2020.
DOI: 10.1200/CCI.20.00074