SIOP Europe
the European Society for Paediatric Oncology

International Childhood Cancer Awareness Day

Data Linkage of Clinical Trial Data to Research Biomaterial Repositories

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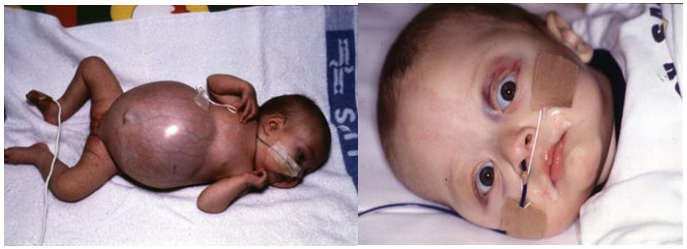
The Case of Neuroblastoma – A Rare Cancer of Childhood!

- Population-based data from Cancer Registries participating in RARECARE:

  Gemma Gatta: European Journal of Cancer (2012) 48, 1435 ff

  - **About 2000 new embryonal cancers every year in EU27**
  - **Annual incidence rate of 4 per million**
    (1.8 neuroblastoma, 1.4 nephroblastoma, and 0.5 retinoblastoma);
  - **91% of cases in patients under 15 years**

- Cancer of the sympathic nervous system
- Adrenal glands, but also in nerve tissues in neck, chest, abdomen, pelvis
- 50% before the age of 2 years
- 50% wide spread dissemination at diagnosis
- It is a disease exhibiting extreme heterogeneity – Biology is key!
  - Low-risk disease most common in infants and good outcomes are common with observation only or surgery
  - High-risk disease is difficult to treat successfully even with intensive multi-modal therapies.



A Case for International Collaboration !
International Neuroblastoma Risk Group (INRG) Data

2004: INRG Task Force established

(52 investigators from US, Europe, Japan, Australia) to develop a consensus approach to *pre-treatment* risk stratification

Methods:

- **"Double Pseudonymisation" of Clinical Trials and Research Data Sets** (via a honest broker = trusted third party)

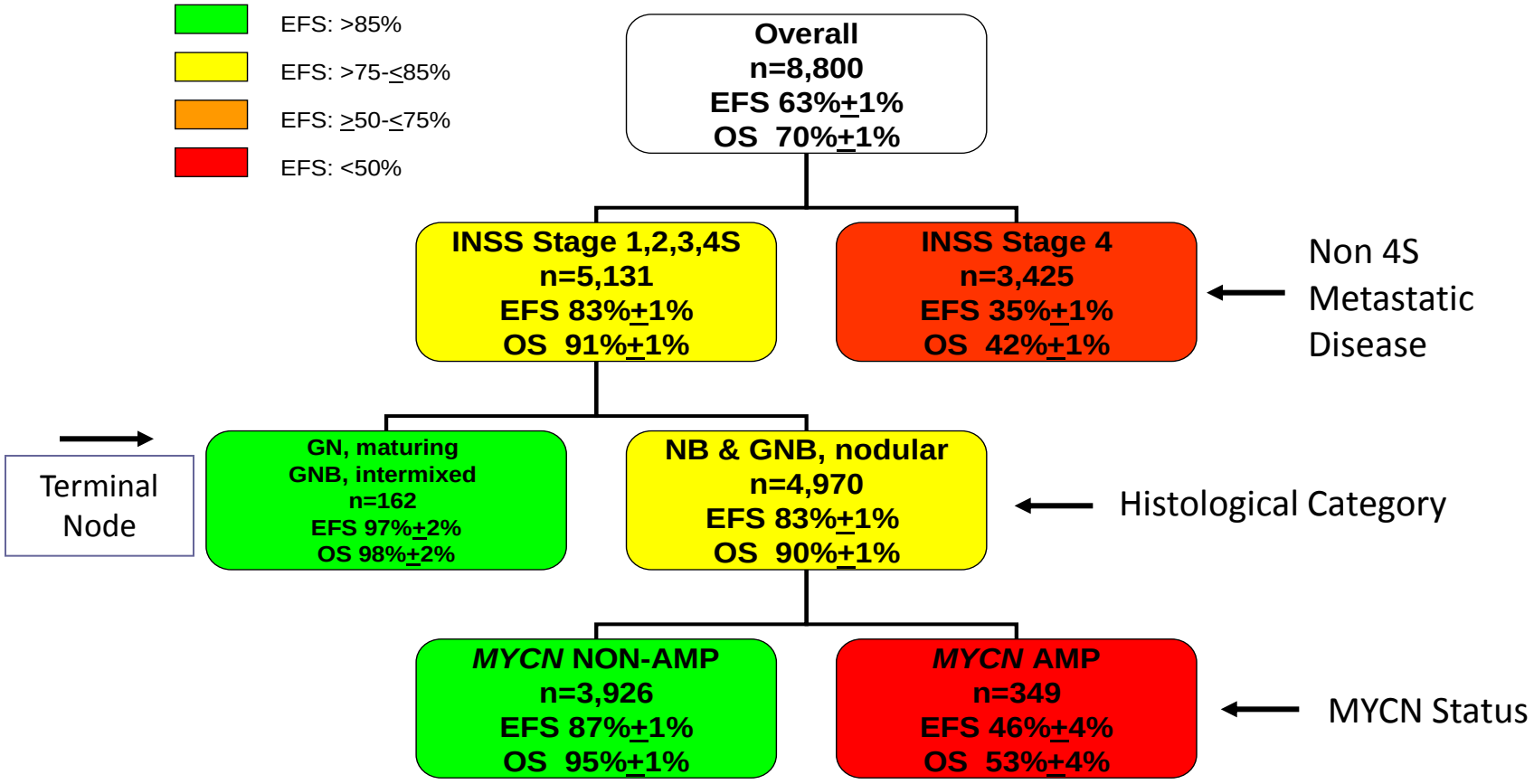
- **Data collected on 8,800 unique patients** diagnosed between 1990-2002 and treated on studies from COG, SIOPEN, GPOH, JANB and JINCS with follow-up to 2004
  - Demographics
  - 36 prognostic markers (Genetic markers: 1p, 11q, MYCN, ploidy)
  - Treatment
  - Outcome (EFS, OS)

Factors prognostic of event-free survival were identified using survival tree regression

Will we need to go back to every single patient/parent for **„specific" and „explicit" consent** in the future ?

Secondary Use of Data to built the "The INRG Classification System"

Survival Tree Regression: Top Level – New Insights!



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Benefits of Secondary Use of Data
"The INRG Classification System"

- 7 factors identified that were highly statistically significant and also considered clinically relevant
  - Non 4S Metastatic Disease
  - New Age Cut Point: < 18 months vs. ≥18 months]
  - Histological Category – Ganglioneuroma, ganglioneuroblastoma – intermixed vs. neuroblastoma, ganglioneuroblastoma – nodular
  - Grade of Tumour Differentiation
    differentiating vs. undifferentiated or poorly differentiated
  - 3 Biological Factors
    - *MYCN* status
    - Presence/absence of 11q aberration
    - Ploidy (≤ 1.0 versus >1.0)

Such efforts rely on a „ broad" **One-Time Only Consent** !
- Trying to trace back patients absorbs enormous time and resources
- Likely to result in loss of data or abandoned research

Benefits of Secondary Use of Data

The INRG Classification System

- Ensures that children diagnosed with neuroblastoma in any country are stratified into homogenous pre-treatment groups
- Facilitates the comparison of risk-based clinical trials conducted in different regions of the world
- Enhances our ability to develop international collaborative studies

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The Issue:
Need for Secondary Use of Data

Collaborative and shared research

- INRG data are available for investigator-initiated data mining studies
- Approximately 30 research projects completed or still ongoing
- Analysis conducted by INRG statisticians
- Published in high profile journals

  - DuBois et al., Ped. Blood Cancer, 2008
  - Bagatell et al., J Clin Oncol, 2009
  - Moroz et al., Eur. J Cancer, 2010
  - Taggart et al., J Clin Oncol, 2011
  - Baruchel et al., Eur J Cancer, 2011
  - London et al., J Clin Oncol, 2011
  - Schleiermacher et al., Br. J. Cancer 2012
  - And more…

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One Example of many…
Achievements of the INRG Biology Committee

British Journal of Cancer (2009) 100, 1471 – 1482

www.bjcancer.com

International consensus for neuroblastoma molecular diagnostics: report from the International Neuroblastoma Risk Group (INRG) Biology Committee

PF Ambros*,[1], IM Ambros*,[1], GM Brodeur[2], M Haber[3], J Khan[4], A Nakagawara[5], G Schleiermacher[6], F Speleman[7], R Spitz[8], WB London[9], SL Cohn[10], ADJ Pearson[11] and JM Maris*,[2]

[1]CCRI, Children's Cancer Research Institute, Vienna, Austria; [2]Center for Childhood Cancer Research, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, PA, USA; [3]Children's Cancer Institute Australia, Sydney, Australia; [4]National Cancer Institute, Bethesda, MD, USA; [5]Chiba Cancer Center Research Institute, Japan; [6]Institut Curie, Paris, France; [7]Centre for Medical Genetics, Ghent, Belgium; [8]University of Cologne, Germany; [9]Children's Oncology Group Statistics and Data Center, University of Florida, Gainesville, FL, USA; [10]The University of Chicago, Chicago, IL, USA; [11]Section of Paediatrics, Institute of Cancer Research and Royal Marsden Hospital, Surrey, UK

- Development of precise definitions
- Standardisation of techniques
- Proposition of standard operating procedures for the determination of genetic markers used for treatment stratification (MYCN)

Continued Need for Secondary Use of Data and Follow UP!

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Limitations of original INRG Data

- **Original INRG Data Base outdated!**
  - **Consists of prognostic factors identified > 30 years ago**
  - More **recent whole genome data** generated by labs around the world are not included in the database (GWAS, array cGH, omic signatures, NGS)

- **GOAL**
  - Transform the originally flat-field application housing the INRG data
  - Use new technology facilitating links with other databases (i.e. biobank data, genomic data, …)
  - Create an Interactive INRG database (iINRGdb)

The future potential of biomarker and mode of actions discovery rely on
Data Linkage and Patient Traceability !
Does not work with anonymised data sets !

Evolution of Techniques

New datasets, using new technologies, have been generated!

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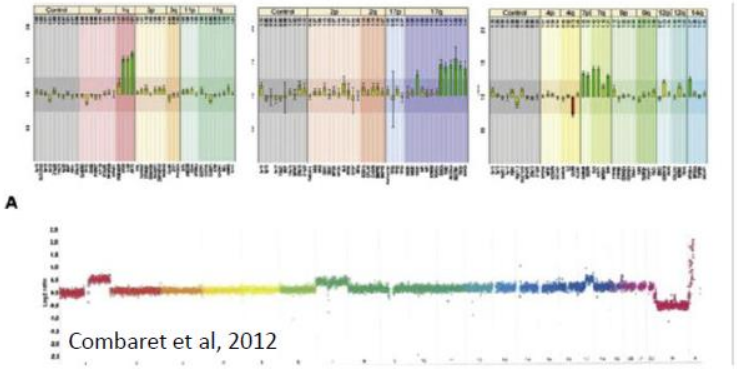

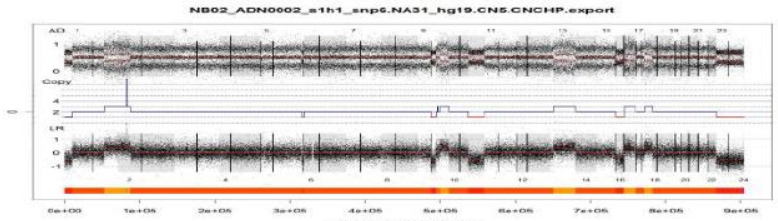

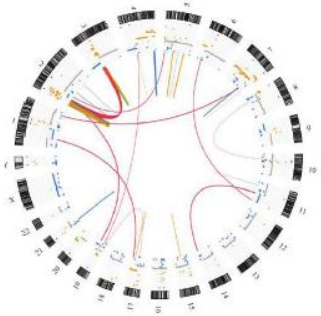

Technique	N° of features
MLPA	100 loci (Ambros et al 2011)
aCGH	4k – 1000k
SNP (SNP6, cytoscanR)	> 1 Mio
Sequencing data Whole exome Whole genome	Coding sequence

Next Steps: Expansion Phase

New datasets, using new technologies, have been generated!

- DNA copy number profiles (array CGH, SNParrays)
- Somatic mutations (NGS techniques)
- Coding gene expression profiles
- miRNA and non coding gene expression profiles
- Methylation and other epigenetic profiles

} Tumor sample

- Genomics of peripheral samples (ctDNA)

} Peripheral samples (blood, bone marrow

- Germline genomics

} Constitutional

- **Currently updating outcome data and expanding data fields on existing patients** (race, ethnicity, sex, second malignancies, etc)
- **Adding data on new patients after approval from Cooperative Group Chairs**

The Need: Large Scale Data Integration in Rare Diseases

i.e. “An Interactive iINRGdb” – under construction

- Fostering research in Biomarker Discovery & Mode of Actions
- Basis for Innovative Drug Development
- Basis for “Personalized Medicine” approaches in Rare Diseases

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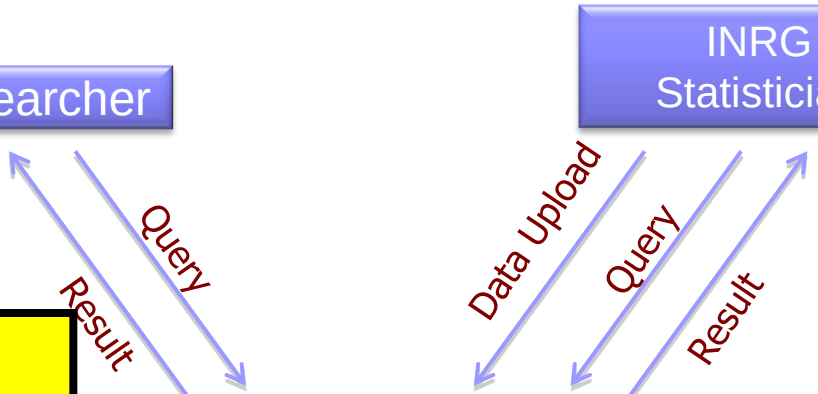
Impact of DPR

NEED TO MAINTAIN RESEARCH IN RARE DISEASES

- **One-time “broad” consent**
- **Pseudonymisation**
- **Safe- Guard Measures**



Acknowledgments
INRG Task Force

- **Co-Chairs - Andrew D. J. Pearson, U.K. and Susan L. Cohn, USA**
- Investigators: pediatric oncologists, biologists, statisticians, pathologists, surgeons, radiologists, and young investigators
- Investigators were assigned to chair one of 4 committees:
  - Surgery (Tom Monclair)
  - Statistics (Wendy London)
  - Biology (Peter Ambros)
  - Metastatic Disease (Kate Matthay)
- INRG investigators
- The Forbeck Foundation – Sponsor of the 2005 INRG Conference
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