What is the current state of breast cancer classification?

Giuseppe Viale
European Institute of Oncology
University of Milan
Milan-Italy

Why subtyping?

Breast cancer is a heterogeneous disease:

- Histological features
- Biological characteristics
- Clinical outcome
- Responsiveness to therapies

Need for classification

Juliet:

"What's in a name? That which we call a rose
By any other name would smell as sweet."

Romeo and Juliet (II, ii, 1-2)

The “perfect” classification

- Clinically useful
  - Prognostic/Predictive
- Scientifically accurate
- Applicable
  - Easy to teach, easy to learn
  - Affordable (time and resources)
- Reproducible

Histopathological Classification (WHO, 2012)

- Ductal carcinoma, n.o.s.
- Lobular carcinoma
  - Classic
  - Variants
- Special types
  - Cribriform
  - Tubular
  - Medullary
  - Apocrine
  - Micropapillary
  - Metaplastic
  - Mucinous
  - ……..

20 major types,

18 minor subtypes!

Histopathological Classification

- Highest number of types and subtypes
- Two major types include some 80% of the cases
- It has minimal prognostic/predictive value (clinical utility?)
- Some “special” or “variant” subtypes have clinical implications

Biological Classification
St. Gallen 2007

Highly Endocrine responsive

- High ER & PgR

and

- No HER2 overexpr

and

- Low Ki-67

Non endocrine responsive

- ER & PgR both absent

Incompletely endocrine responsive

- Low ER & PgR

or

- PgR absent

or

- HER2 overexpr

or

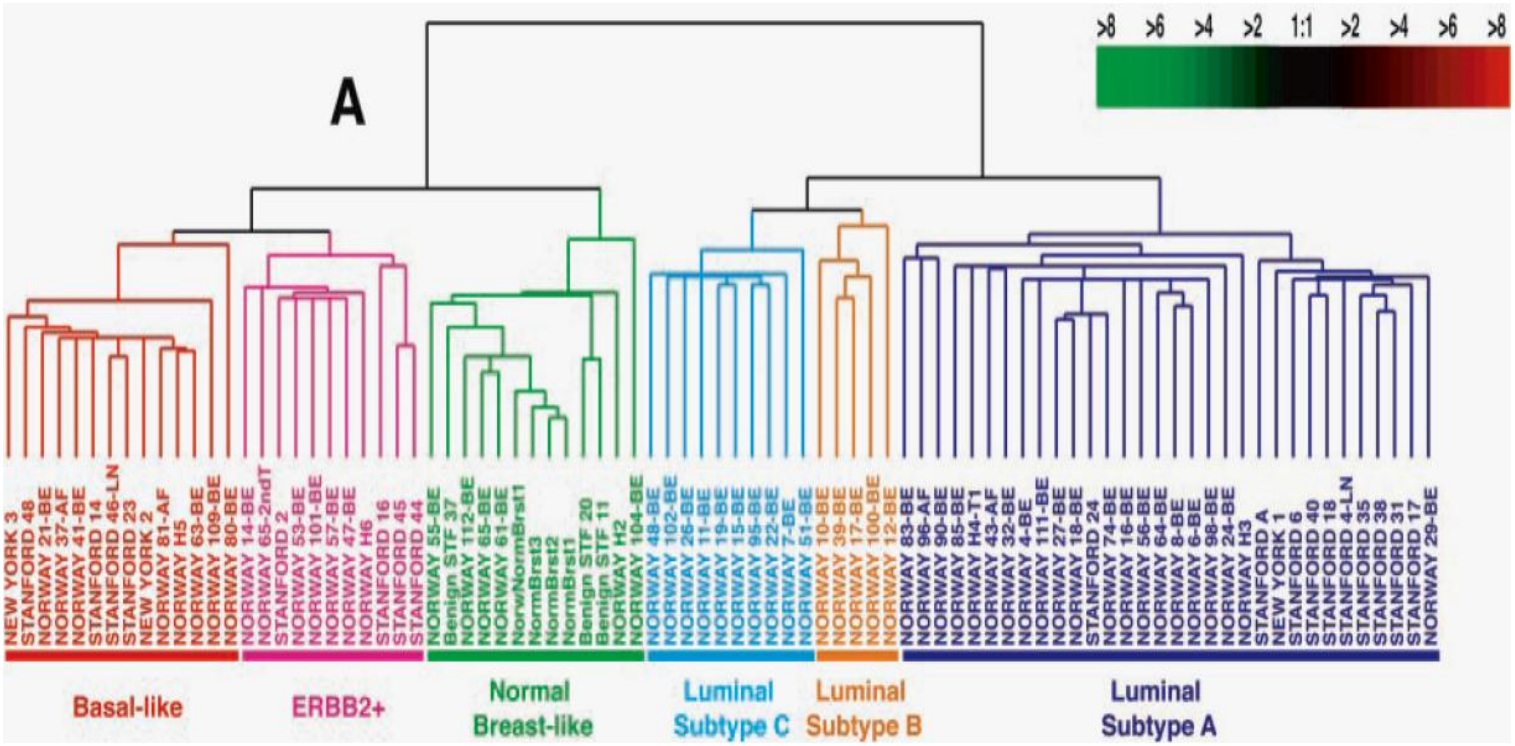
- High Ki-67

Biological Classification

- Kind of “Working formulation for clinical use”
- Lowest number of subtypes
- Tumours with different prognosis in the same category
- Issues of reproducibility

Molecular Classification

Unsupervised analysis of global gene expression patterns unveiled distinct and robust molecular subtypes of breast cancer (496 genes)



Sørlie T et al PNAS 2001

Molecular Classification

- 4-6 subtypes
- Tumours with different prognosis in the same category (e.g., Basal-like)
- Issues of affordability

BL tumors are heterogeneous

- IDC NOS, high-grade
- ILC high-grade, pleomorphic
- Metaplastic, high-grade
- Myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
- Medullary
- Adenoid-cystic
- Metaplastic , low-grade
  - Low grade adenosquamous
  - Fibromatosis-like

Poor prognosis

Good prognosis

When I want to read a good novel I write one!

(Benjamin Disraeli,1804-1881)

'Subtype' *Surrogate IHC markers*	**Type of therapy**	**Notes**
'Luminal A' ***ER and/or PgR positive*** ***HER2 negative, Ki-67 low (<14%)****	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status).
'Luminal B (HER2 neg)' ***ER and/or PgR positive*** ***HER2 negative, Ki-67 high***	Cytotoxics + endocrine therapy	Inclusion and type of cytotoxics may depend on perceived risk and patient preference.
'Luminal B (HER2 pos)' ***ER and/or PgR positive*** ***HER2 positive***	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive **(non luminal)'**	Cytotoxics + anti-HER2	
'Triple negative (ductal)'	Cytotoxics	Consider DNA disrupting agents.
'Special histological types'* **A. Endocrine responsive** **B. Endocrine non responsive**	Endocrine therapy Cytotoxics	Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics.

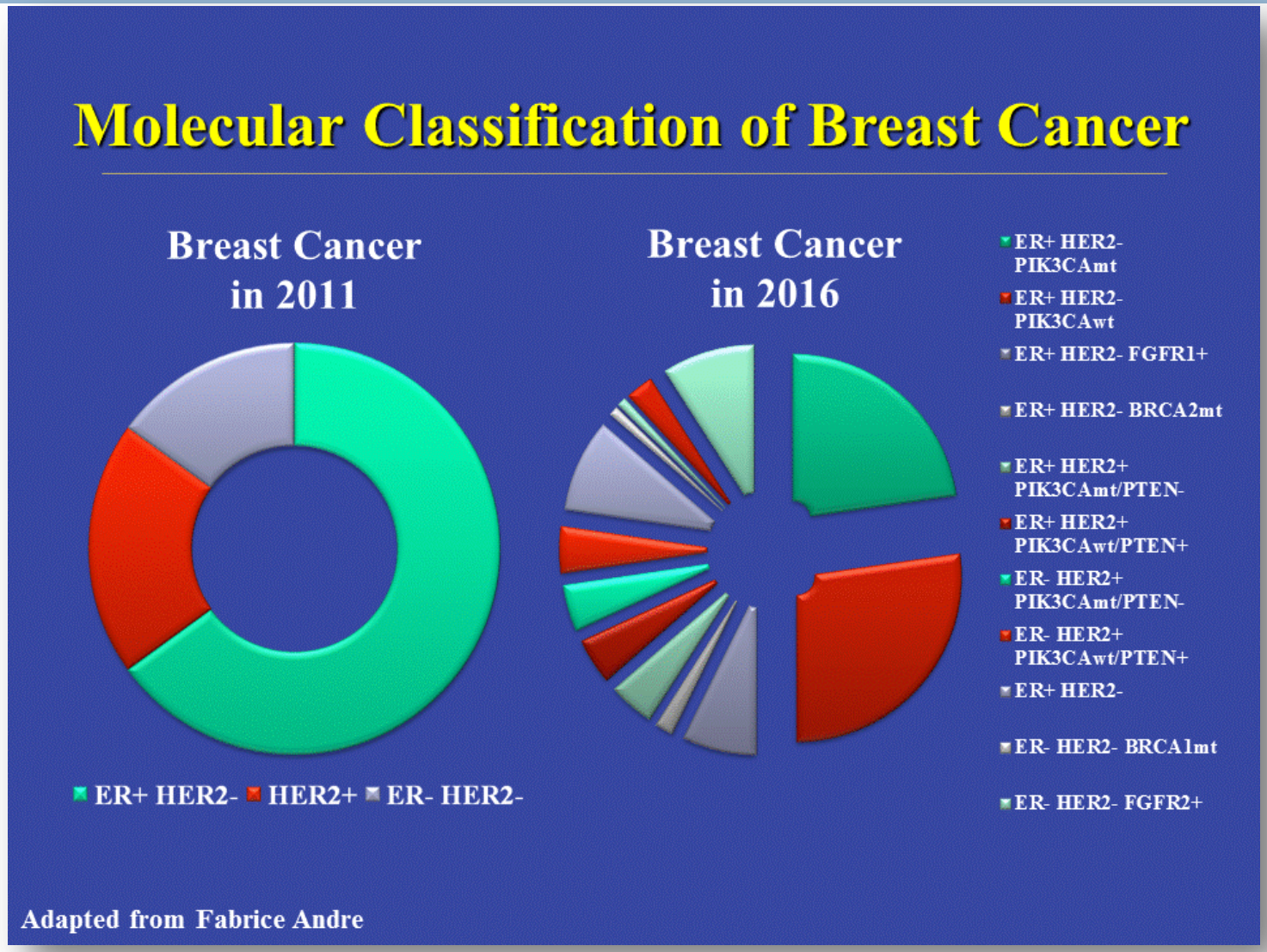
A clinically useful classification for a personalized cancer medicine: premises

- Genetic aberrations exist in human malignancies
- Some of them “drive” oncogenesis and tumour progression
- These genetic aberrations are potentially “druggable”
- There are tolerable and effective medicinal compounds to target these aberrations

Personalized Cancer Medicine: where are we in Breast Cancer?

- Somatic genetic aberrations are responsible for approximately 90% of breast cancers
- Multiple regions of gene copy gain (17q12)
- High-frequency somatic point mutations
  - TP53 (44%); PIK3CA (26%); CDH1 (19%)
- Low-frequency recurrent point mutations in druggable target genes (KRAS,BRAF,EGFR)
- Additional low-frequency mutations (PTEN, AKT1, …)

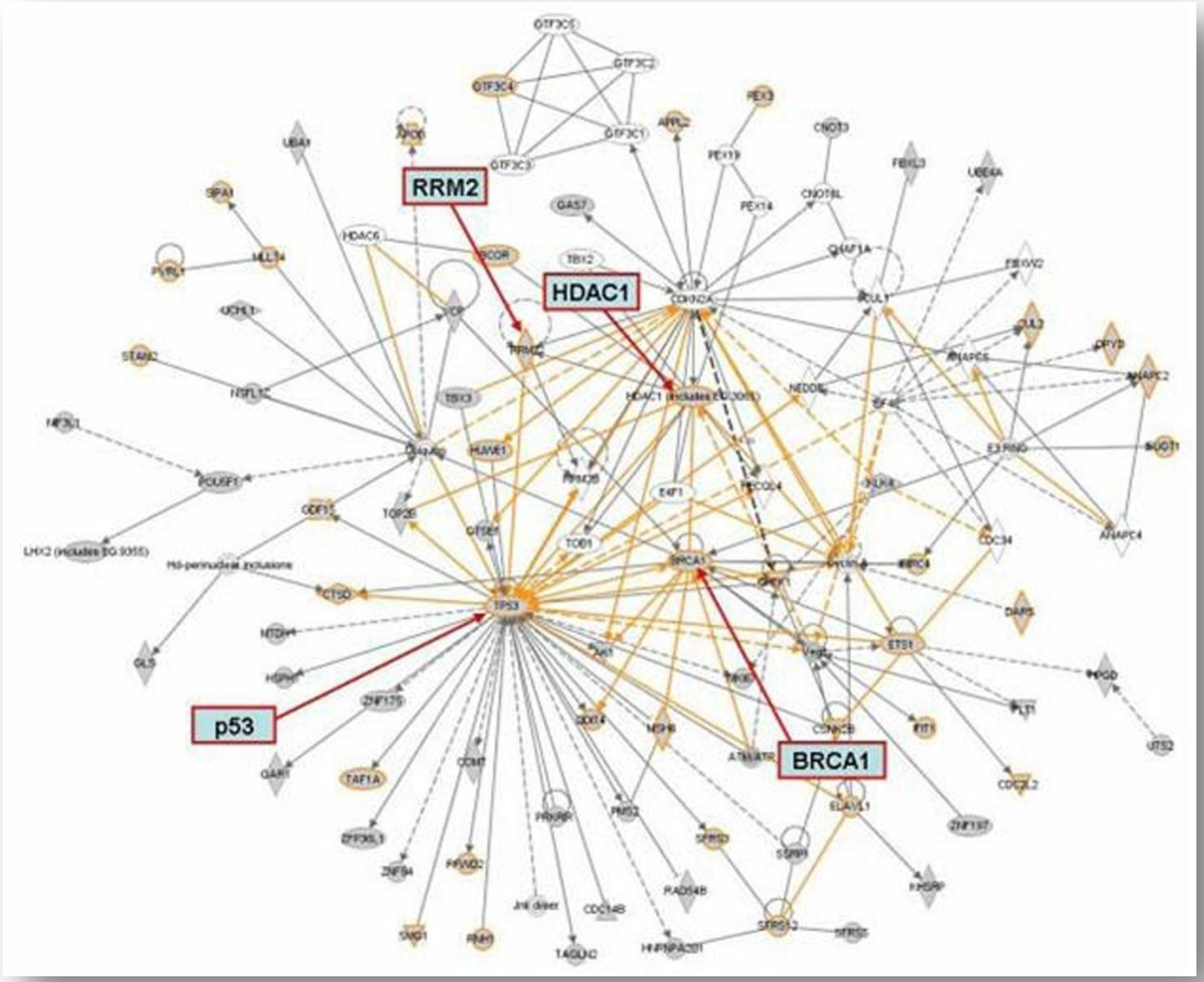
A New Molecular Classification?



Targeted Therapy?

- Targeting one (or a few) “target genes” is not enough
- There is extensive cross-talk (positive and negative) among the different biological pathways
- Inhibition of one gene may activate other gene(s)
- It is necessary to better understand the complexity of human genome

Ingenuity Pathway Analysis: The “Hubs”

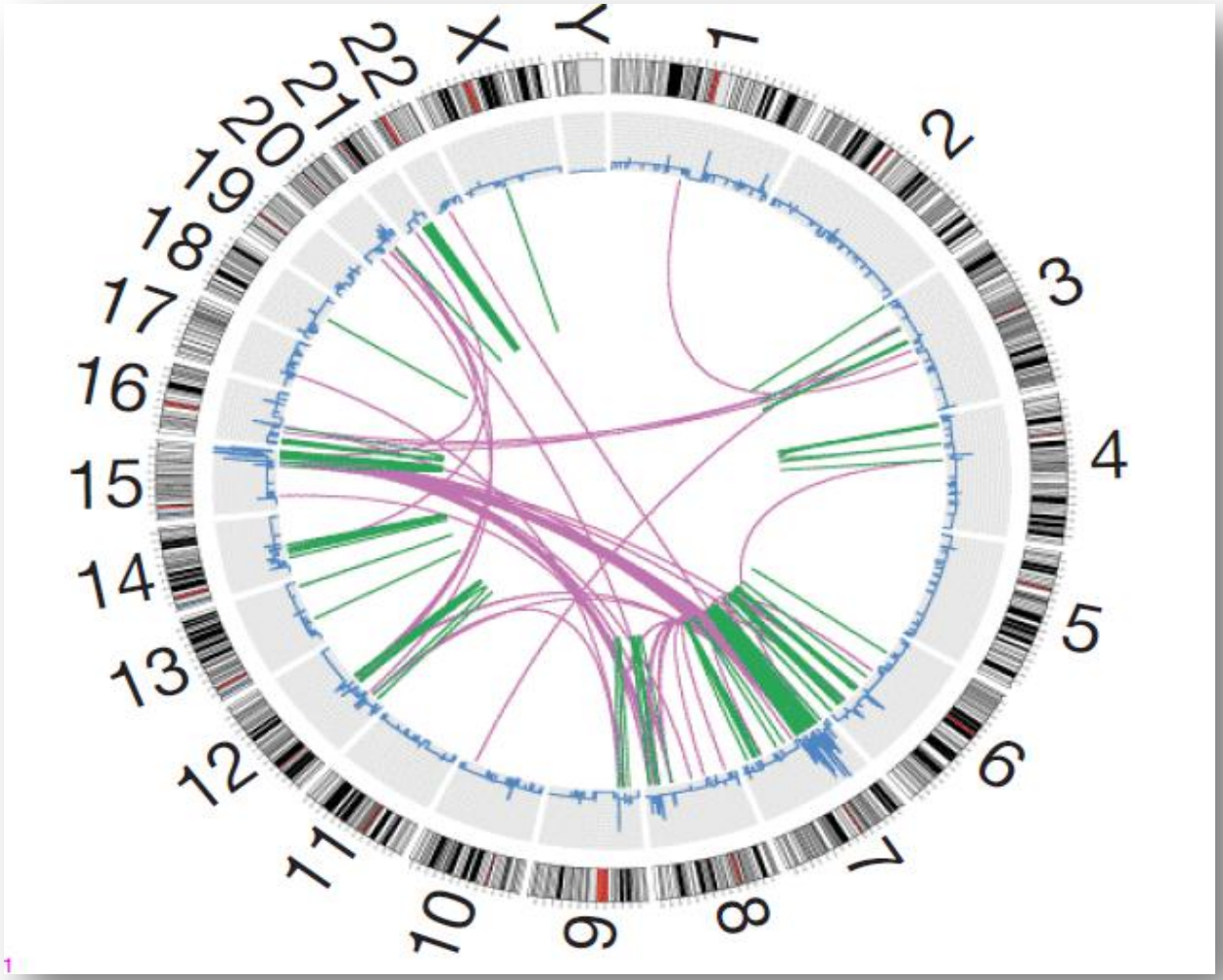


Delta's domestic route map

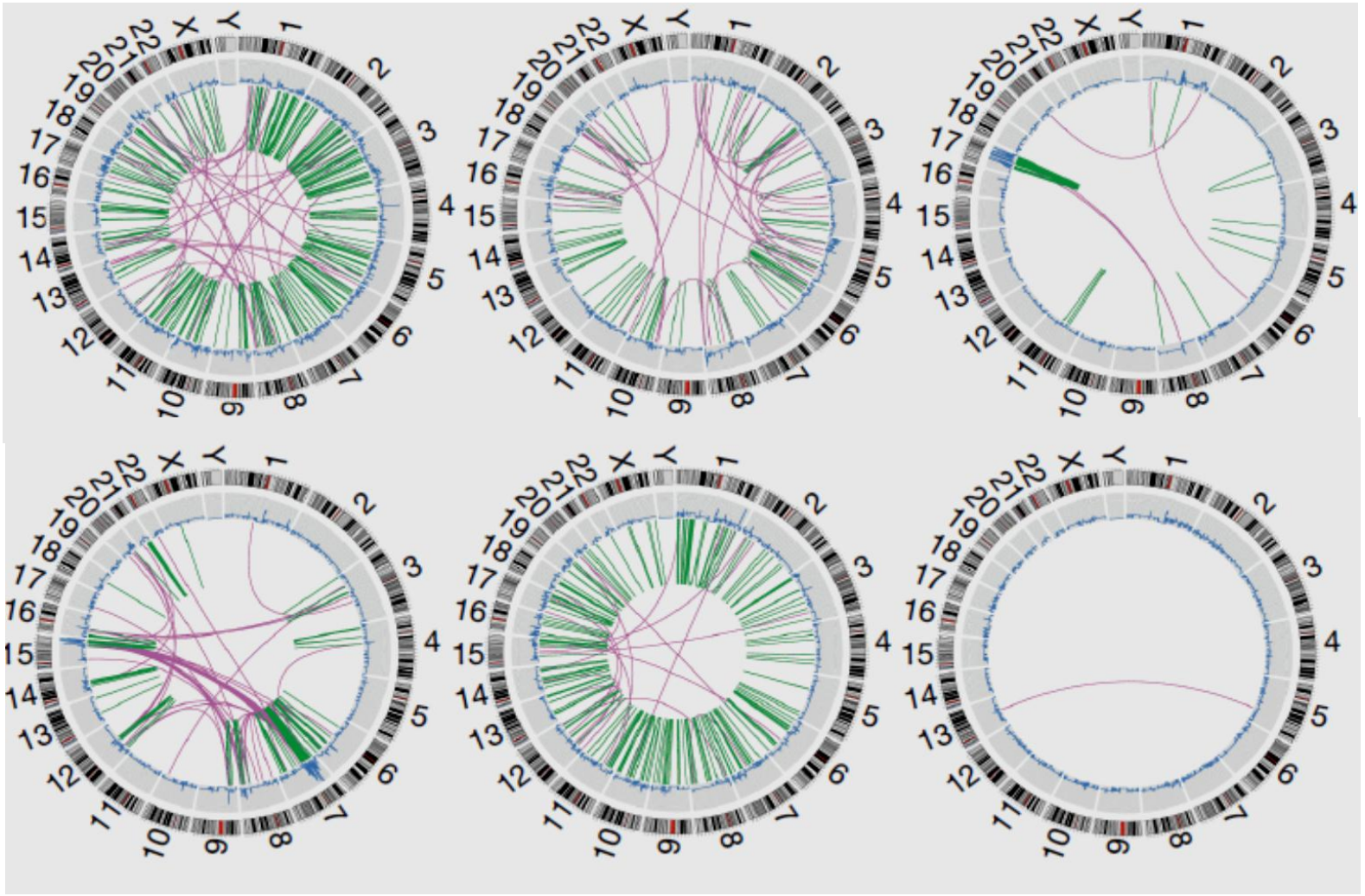
Targeted Therapy?

- Targeting one (or a few) “target genes” is not enough
- There is extensive cross-talk (positive and negative) among the different biological pathways
- Inhibition of one gene may activate other gene(s)
- It is necessary to better understand the complexity of human genome

Circos plot: The new genomic map



The classification of tomorrow?



The complexity of the issue

- Each tumour is different from the others (personalised therapy)
- Tumours change during progression
- There is striking heterogeneity within a given tumour (genetic map of individual tumour cells)
- Is this universe too large to be explored?

Epilogue

- No classification -taken alone- is “perfect”
  - Enthusiasm for the novel assays
  - Biotech pressure
- Clinical, morphological, immunohistochemical and molecular data should be integrated into a single classification scheme with definite prognostic/predictive value