End points di Attività- Efficacia ed Enti Regolatori OGGI: e in futuro?

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From drug approval to accessibility: the rules of the game

(there is a method to the madness[1])

- The Goals and the Players:

- **Goal → Approval → Regulatory Agencies (FDA, EMA)**
- **Goal → Reimbursement → Payers (AIFA)**
- **Goal → Accessibility → Guidelines , Recommendations (Scientific Societies, Regional or Local Boards)**

- The Rules:

- **Regulatory Agencies → Efficacy**
- **Payers → Cost Effectiveness**
- **Guidelines (Boards) → Comparative/relative Effectiveness**

[1]W Shakespeare, Hamlet, 1600

«there is a method to the madness»[1]

Drug approval : FDA, EMA

Evidence of Efficacy

Scientific evidence is not enough…

HR	OS control	OS treatment	NNT
0.66	0.97	0.98	**100**
	0.20	0.35	**6.6**

If the sample size is large enough, both scenarios yield statistically significant results, but in the first example you have to treat 100 patients to benefit one

«there is a method to the madness»

Drug reimbursement : AIFA

Cost-effectiveness

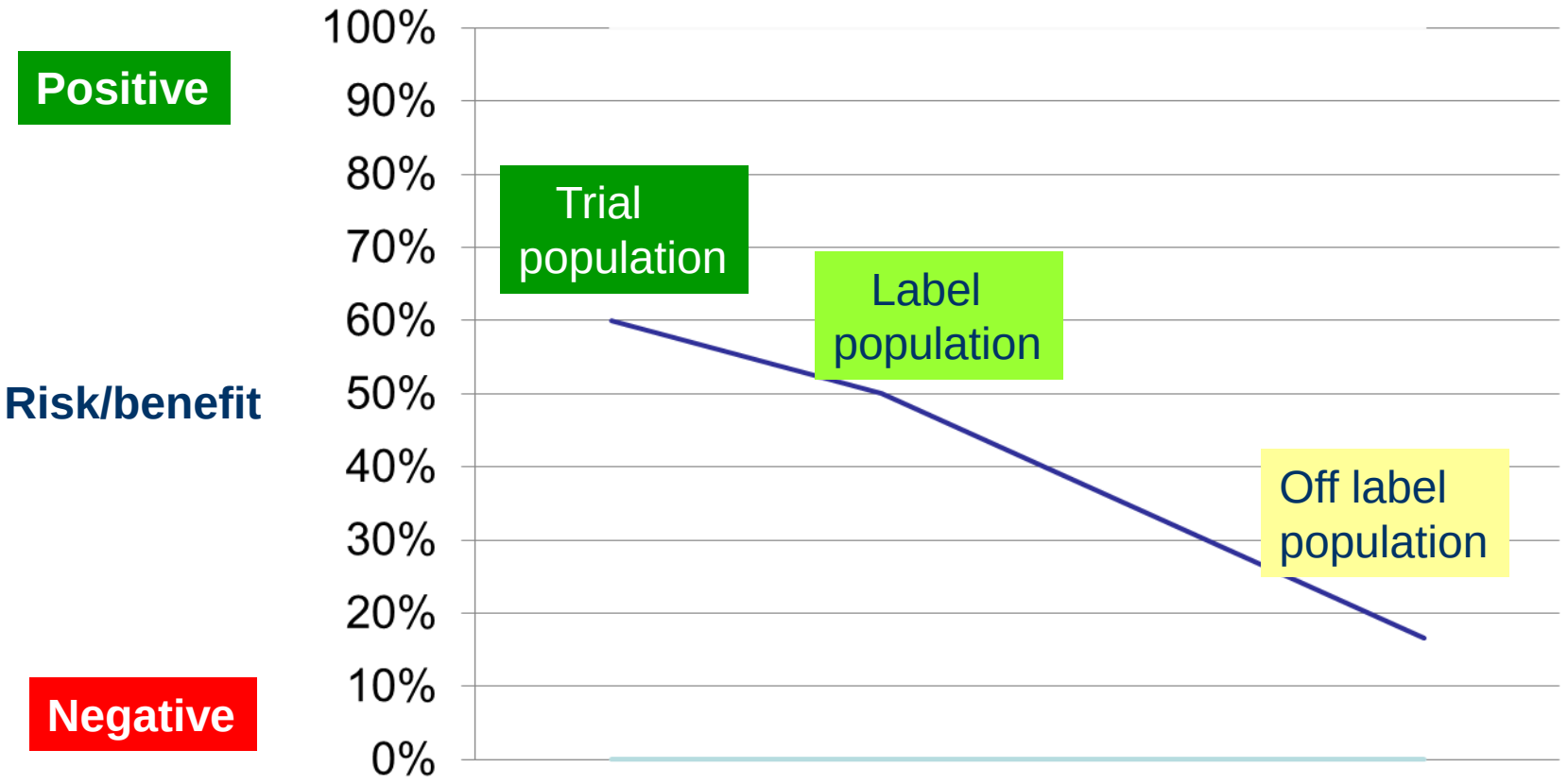
(cost x unit of outcome or value for money)

Elements of the cost-effectiveness analysis

- **Severity of the disease**
- **Absolute risk reduction**
- **Safety**
- **Price policy (risk-sharing, PbR)**

Cost-effectiveness is not enough…

The efficacy - effectiveness gap



«there is a method to the madness»

Drug accessibility : recommendations

Comparative-effectivenss

Comparative effectiveness depends from:

- **Availability of other therapeutic options**
- **Efficacy& tolerability in subgroups of patients**

There is a method to the madness, but…. madness provides mad results

- V

THE EUROPEAN DILEMMA

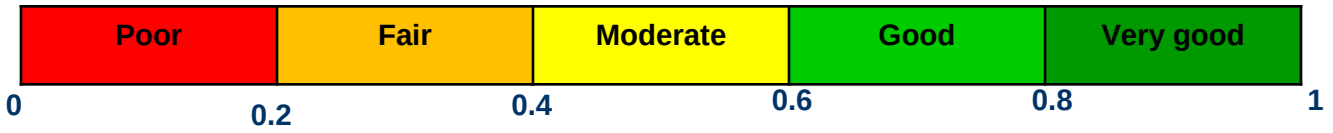
- One central set of standards for drug approval
- One scientific advice
- One application one assessment and one opinion
- One decision valid in 27 EU MS and 3 EFTA countries
- One system for following the medicine on the market
- But **30 independent decisions** about whether the medicine should be made available to patients or not
- Based on **different methodologies and interpretations**

Level of agreement between agencies in the HTA recommendations measured by kappa scores

287 drug-indication pairs collected between 2007-2009

	CDR Canada	NICE England	PBAC Australia	TLV Sweden	SMC Scotland
CDR	-	0.038	0.165	-0.001	0.062
NICE		-	0.178	0.228	0.105
PBAC			-	-0.023	0.132
TLV				-	0.066
SMC					-

Interpretation of kappa score indicators



Source: Nicod E and Kanavos P, 2012

Innovation in oncology at a turning point

- Approval does not guarantee availability of innovative drugs
- Payers increasingly use HTA to decide about reimbursement
- HTAs are done AFTER approval and at national/regional level
- Comparative effectiveness has nothing to do with «personalized» cancer medicine

Innovation in oncology: the way ahead

A «Patient-Centric» Health Care must guarantee three essential elements:

- availability

- affordability

- appropriateness

Neoadjuvant results to accelerate drug approval

The NEW ENGLAND JOURNAL of MEDICINE

Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.

Guidance for Industry

Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

Neo-Adjuvant: A Faster Approach

	Adjuvant	Neo-adjuvant
Number of Patients	thousands	hundreds
Efficacy Endpoint	DFS	pCR
Primary analysis	years after end of recruitment	months after end of recruitment
Trials for suboptimal responders	NA	Yes (adj after PST)
Biological Window	No	Yes
Functional Imaging	No	Yes
Sample Collection	baseline	multiple time points
Cost	+++++	++

Relationship between pCR rate and disease outcome: still many open questions

- **Magnitude of pCR gain that predicts long-term outcome not established:**
  - low pCR rates
  - good prognosis for some non pCRs (lobular, HR+, low grade, minimal RD)
  - lack of targeted therapies (except NOAH trial)

- **Larger pCR differences between treatment arms needed**

- **Relation between pCR and outcome in the different breast cancer subtypes**

- **Paucity of safety data:**
  - small sample size
  - highly selected patient populations
  - highly selected institutions
  - few long term data

Innovation in oncology: the way ahead

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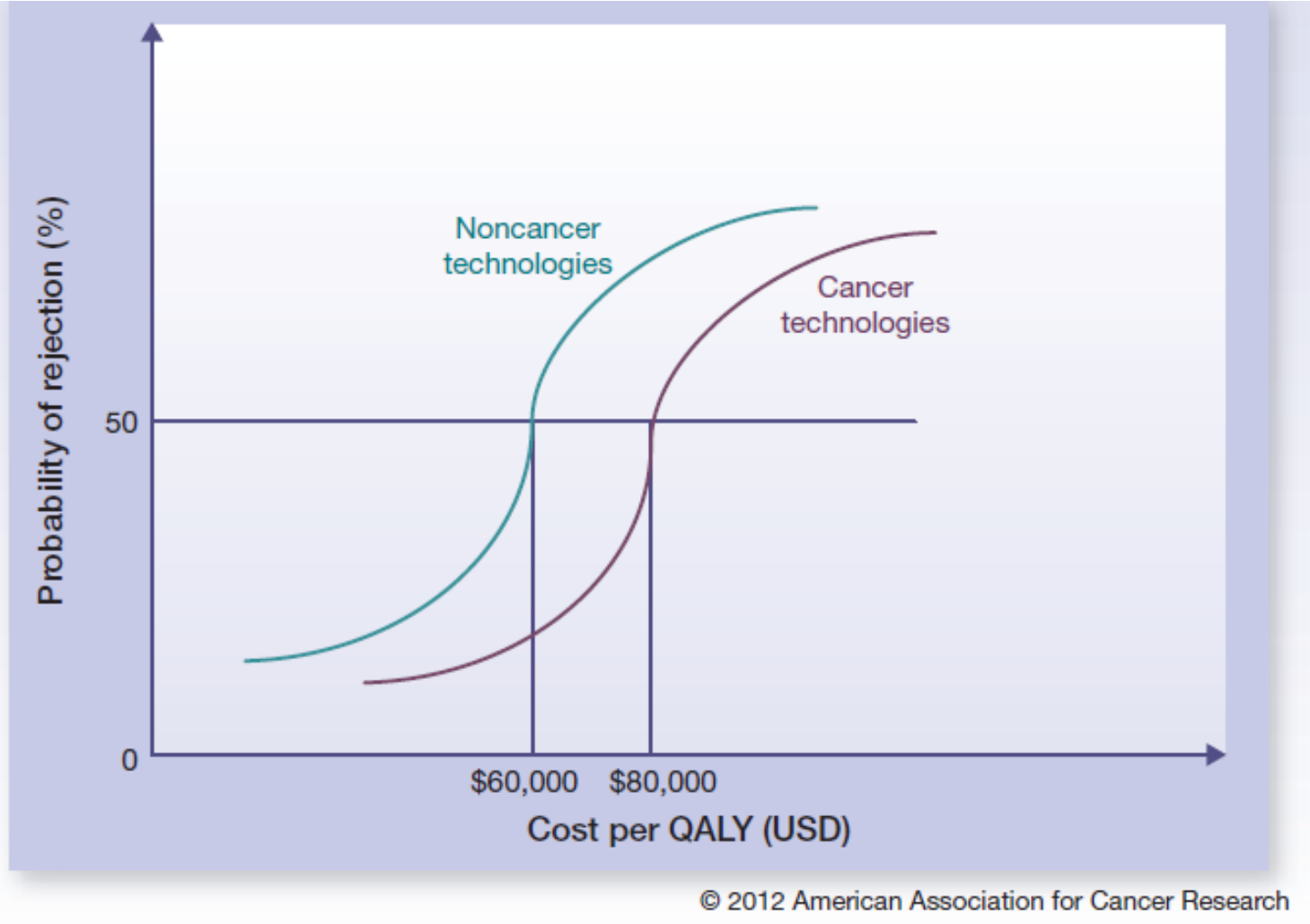
NICE Statement

"We support the general principle that the NHS should pay a price which reflects the additional therapeutic benefit of new drugs. We also share the Government's ambition to ensure that the opinion exists for all new licensed drugs to be offered to those patients who can benefit for them"

provided that the price is a fair reflection of their value

QALY thresolds for cancer and non cancer drugs



B Jonsson, CCR 2013

THE VALUE CATEGORIES IN GERMANY

Institute for Quality and Efficiency in Health Care

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Extent of added benefit: six categories, legal basis

	Criteria in accordance with AM-NutzenV*
major added benefit	*sustained and great improvement ^ (cure, major increase in survival time, long-term freedom from serious symptoms, extensive avoidance of serious side effects)*
considerable added benefit	*marked improvement ^ (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serioussymptoms, relevant avoidance of serious adverse effects, important avoidance of other adverse effects)*
minor added benefit	*moderate and not only marginal improvement ^ (reduction in non-serious symptoms, relevant avoidance of sideeffects)*
added benefit proven, but not quantifiable	
no added benefit hasbeen proven	
less benefit than that of the appropriate comparator	

*Regulation for Early Benefit Assessment of New Pharmaceuticals

^in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

OUTCOMES IN GERMANY

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Our experience

- 21 early assessments
  - Added benefit: 12
    - Major added benefit: none (industry: about 80 %)
    - Considerable: 7
    - Minor: 3
    - Unquantifiable: 2
  - No added benefit: 9
  - Relevant different opinion by GBA in 4 cases
    (2 weighing of endpoints; 2 new information in hearing)
  - Results: IQWiG compatible with those of CVZ, HAS and NICE
    although procedures and criteria are different ….

Examples of considerable benefit: vemurafenib for V600m+ MM
Examples of minor benefit: eribulin for ABC, cabazitaxel for CRPC

Innovation in oncology: the way ahead

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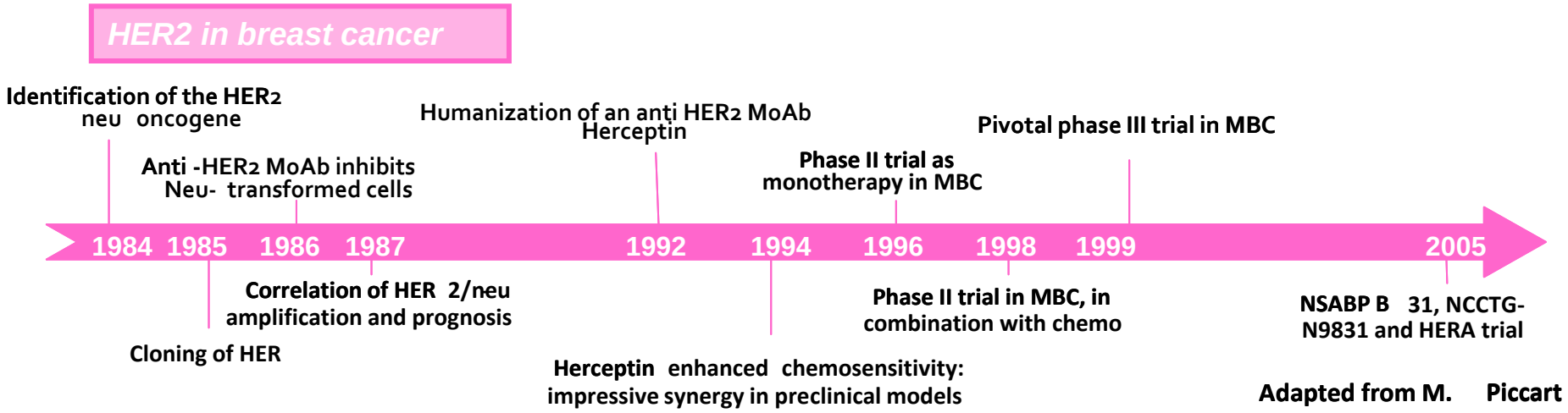
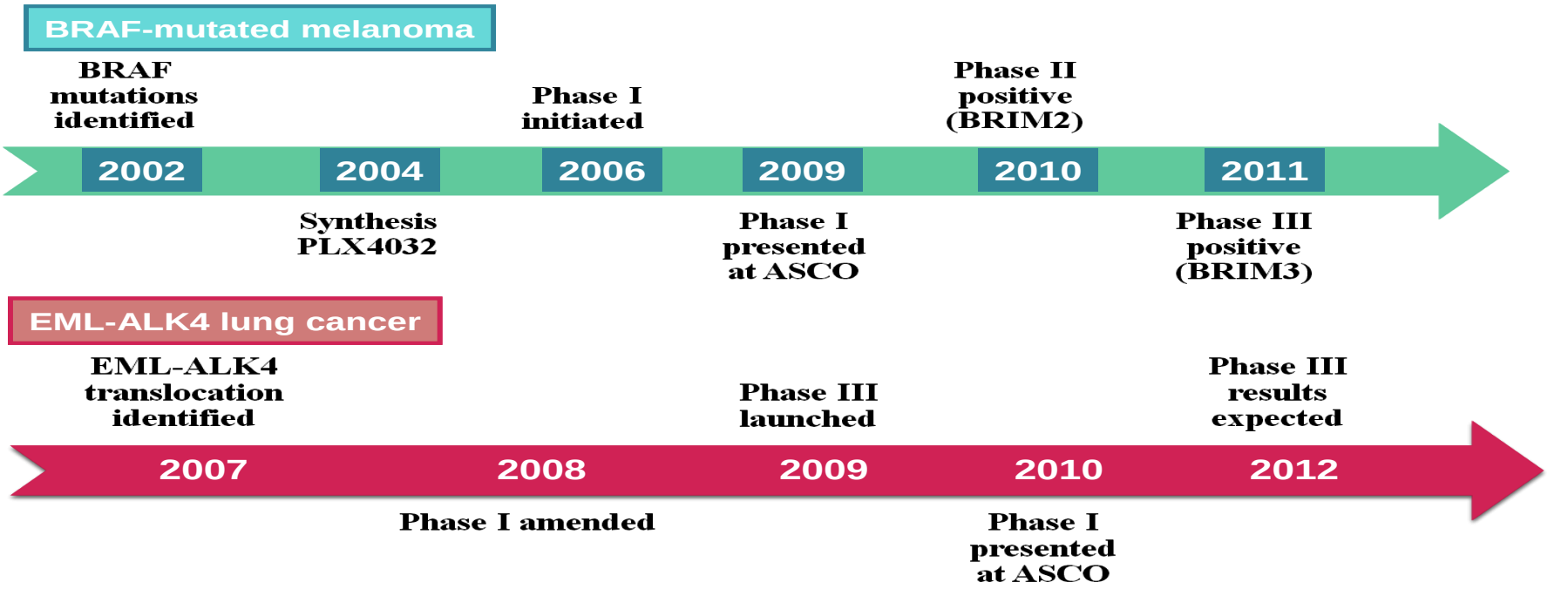
Targeted agents and Companion Diagnostics

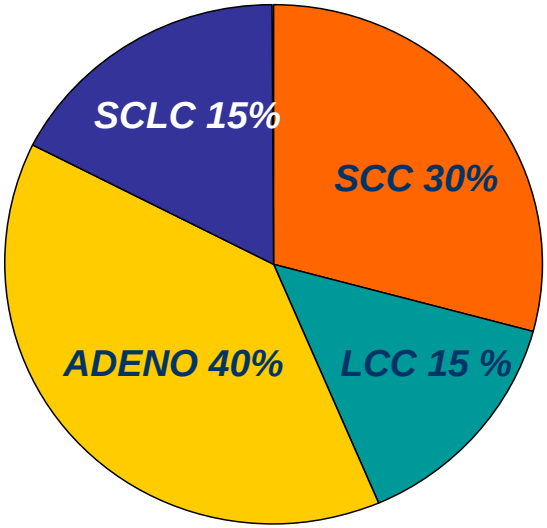


Accelerated Clinical Translation

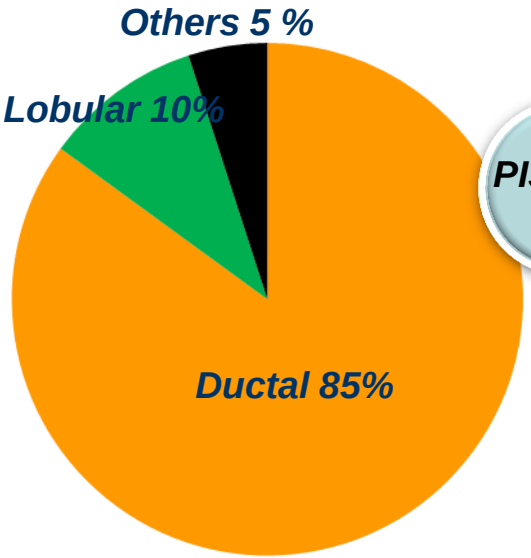


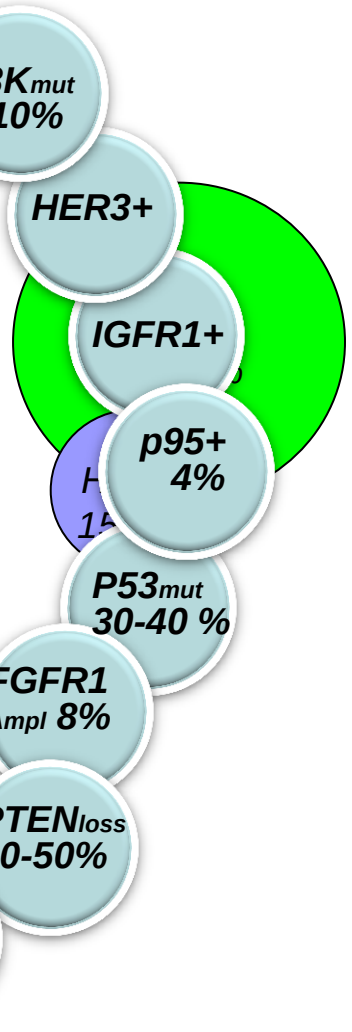
Lung and Breast Cancer: from Histology to molecularly characterized diseases

Lung Cancers

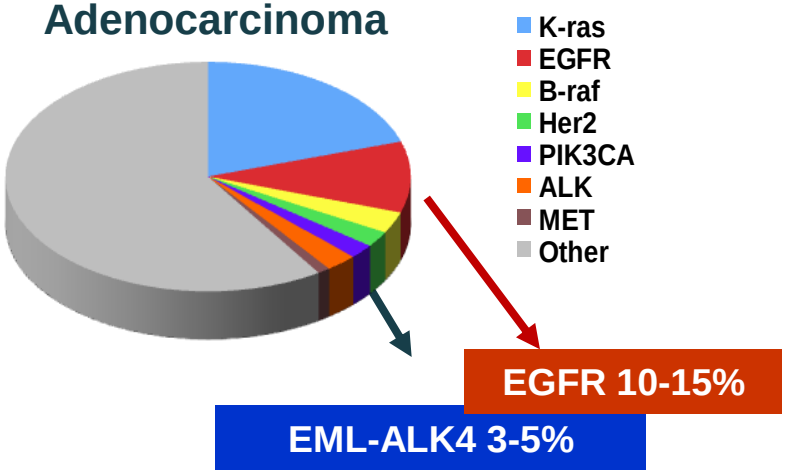


Breast Cancers



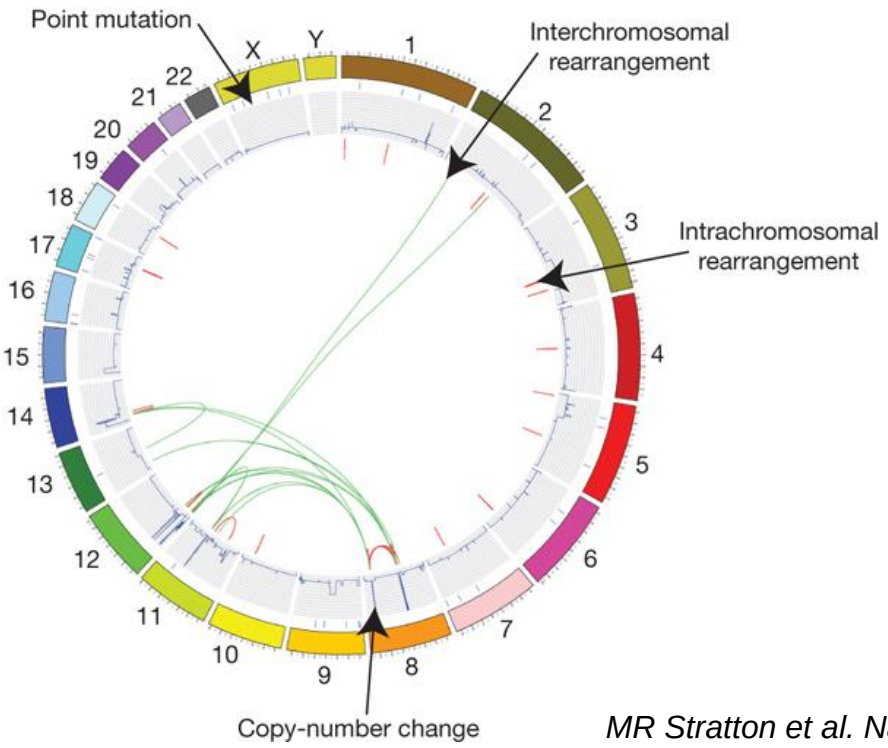


Somatic Mutations in Adenocarcinoma



Promise & Challenges: Progress in Genome Sequencing

Yesterday	**Months**	**Uninterpretable**	**Clinic**	**$$$$**
Today	**Days**	**Interpretable with human genome**	**Clinic**	**$$$**
Tomorrow	**Hours**	**Interpretable with human genome**	**Clinic ?**	**$$**



Pasche B, Absher D. JAMA. 2011;305:1596.

Circos Plots

*MR Stratton et al. Nature **458**, 719-724 (2009) doi:10.1038/nature07943*

End points of Efficacy and Regulatory Agencies: the challenges ahead

- **from «does it work?» to «is it worth?»**
- **Joint HTA/Regulatory advice**
- **Post-marketing studies to determine relative effectiveness**
- **Access to tissue: primary, mets, CTCs**
- **Access to Multigene Platforms**
- **Umbrella Trials with multiple Pharma Companies**
- Examples:
- Dabrafenib for BRAF mut NSCLC, 11,000 screened: 23 enrolled
- Xalkori – crizotinib- 4.300 screened pts to randomize 347 pts