Roundtable
Le nuove frontiere della remunerazione del farmaco

Remunerazione del farmaco e personalizzazione delle terapie

Paolo Marchetti

Società Italiana Medicina Personalizzata SIMeP
Italian Society Personalized Medicine ISPeM

Appropriatezza in oncologia (e non solo!)

- **Appropriatezza Scientifica**
  - adeguamento della prestazione ai risultati di studi clinici controllati
- **Appropriatezza Clinica**
  - adeguamento della prestazione ai trattamenti standard codificati dalle società scientifiche (linee guida)
- **Appropriatezza Prescrittiva**
  - adeguamento della prestazione alle indicazioni dell'ente regolatorio nazionale (Note limitative sec le determinazioni AIFA)
- **Appropriatezza Regolatoria**
  - adeguamento della prestazione alle norme indicate dagli enti regolatori regionali
- **Appropriatezza Strutturale**
  - adeguamento strutturale assistenziale alle necessità del paziente che deve ricevere una prestazione clinicamente appropriata

Il quesito centrale

- Fino a che punto l'utilità terapeutica di una nuova e specifica tecnologia o farmaco vale il suo costo e quanto siamo disposti a spendere per un singolo obiettivo clinico?

Il quesito centrale

- Fino a che punto l'utilità terapeutica di una nuova e specifica tecnologia o farmaco vale il suo costo e quanto siamo disposti **ad investire** per un singolo obiettivo clinico?

Migliorare l’utilizzo delle risorse

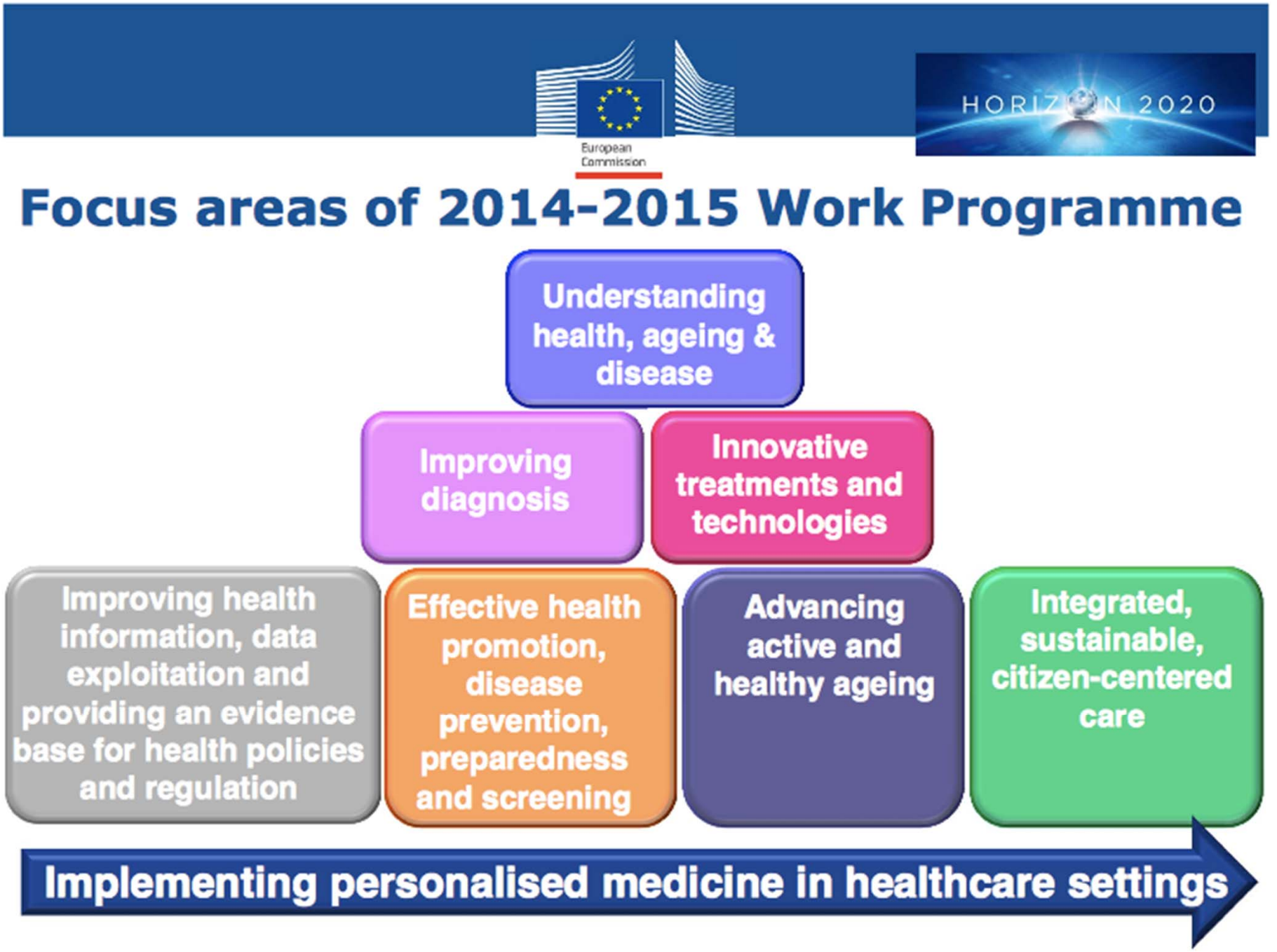
A semantic problem?

- *From “fee for service payment”*
- *To “conditional pricing”*
  - Risk sharing
  - Pay for performance
  - Cost sharing

Personalised cancer management

- Personalised cancer management—giving patients optimum treatment according to their individual circumstances (including genetics) and the molecular characteristics of their tumours—is a key theme for oncologists in general, and in all aspects of medicine.

M. Piccart, Ann Oncology, 2013

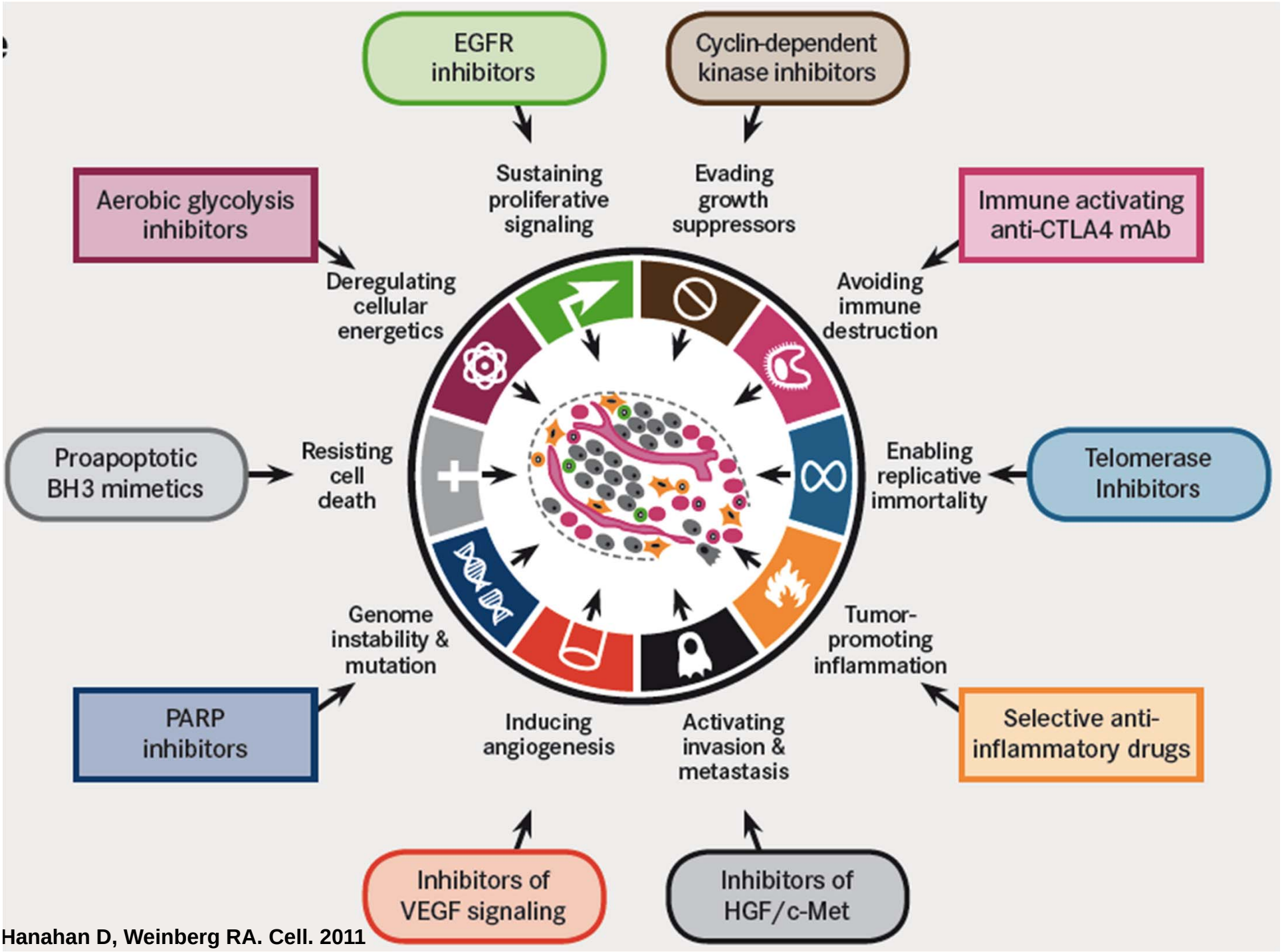


Irene Norstedt, 2014

...and benefit from opportunities

- **Stratified and personalised medicine can deliver better outcomes for patients and potential cost savings**
- **Studies suggest cost savings of 37% for breast cancer and 46% for CVD when a stratified approach is taken**
- **Europe can lead implementation of personalised medicine thanks to favourable conditions**

Hanahan D, Weinberg RA. Cell. 201



Hanahan D, Weinberg RA. Cell. 2011

Personalised cancer management

- From "…omics"
  - Genomics
  - Transcriptomics
  - Proteomics
  - Metabolomics
  - Activomics
  - Targetomics
  - Interactomics
  - Toxgnostics
  - Palliomics

Personalised cancer management

- From "…omics"
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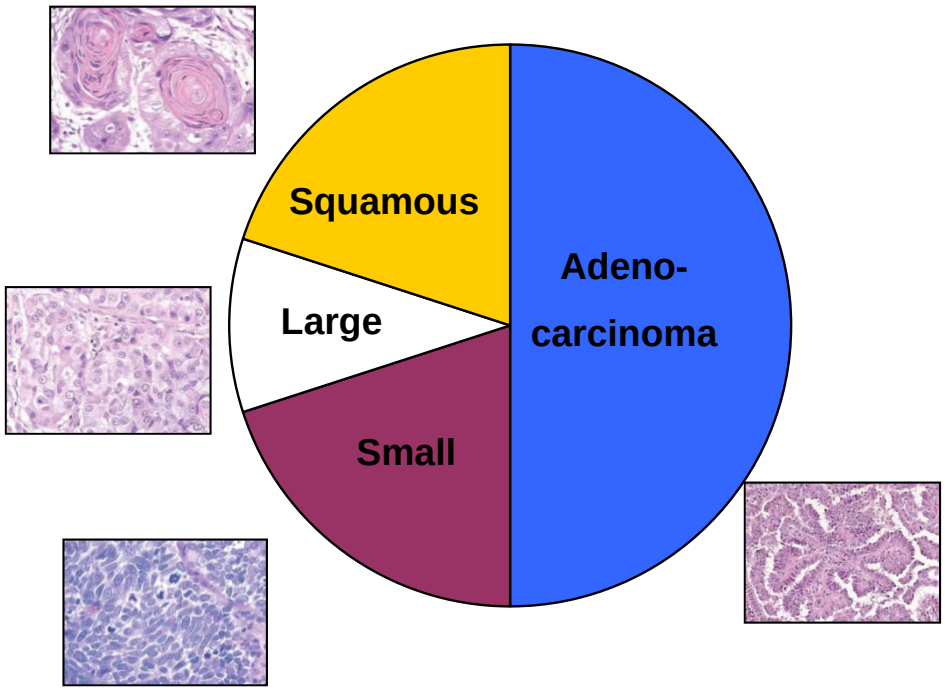
  - Palliomics
- to knowmics

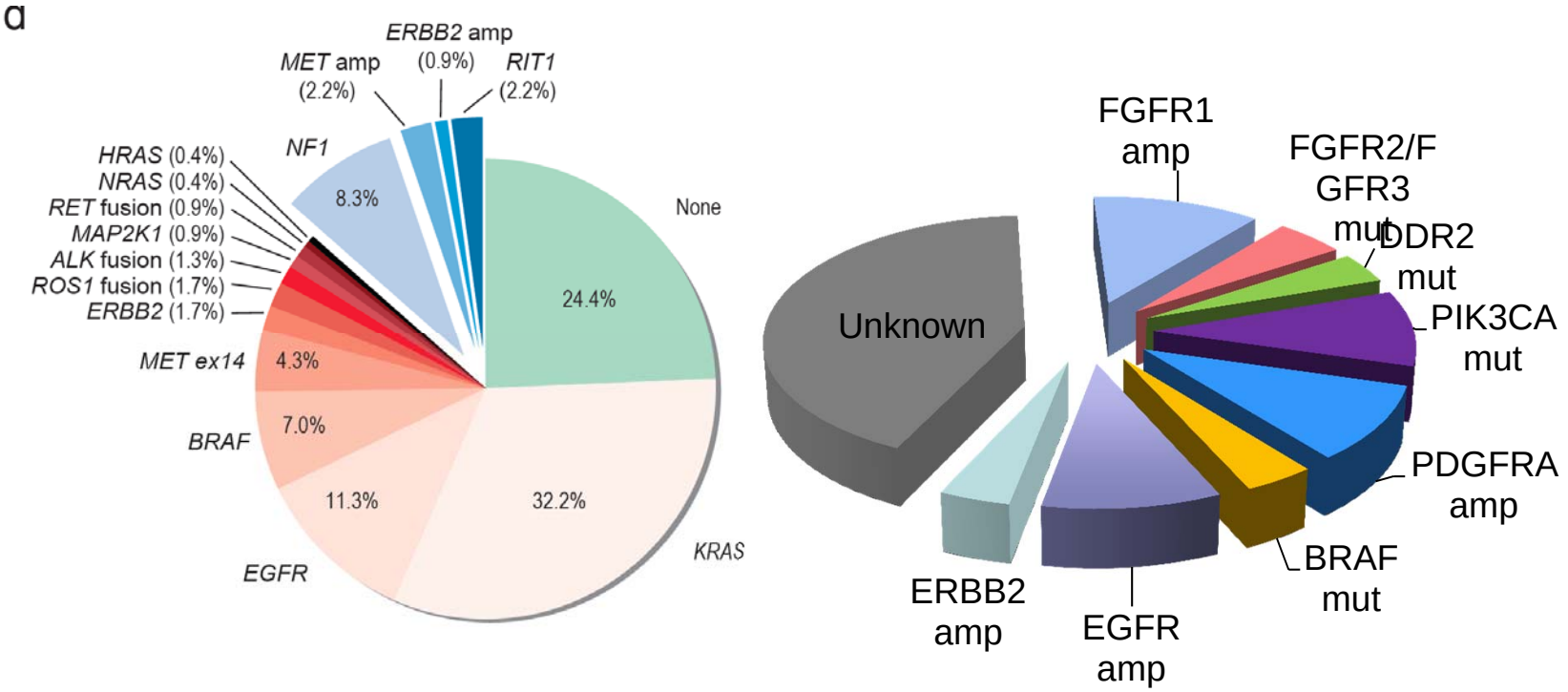
Traditional View of Cancer

Lung Cancer



William Pao, 2012

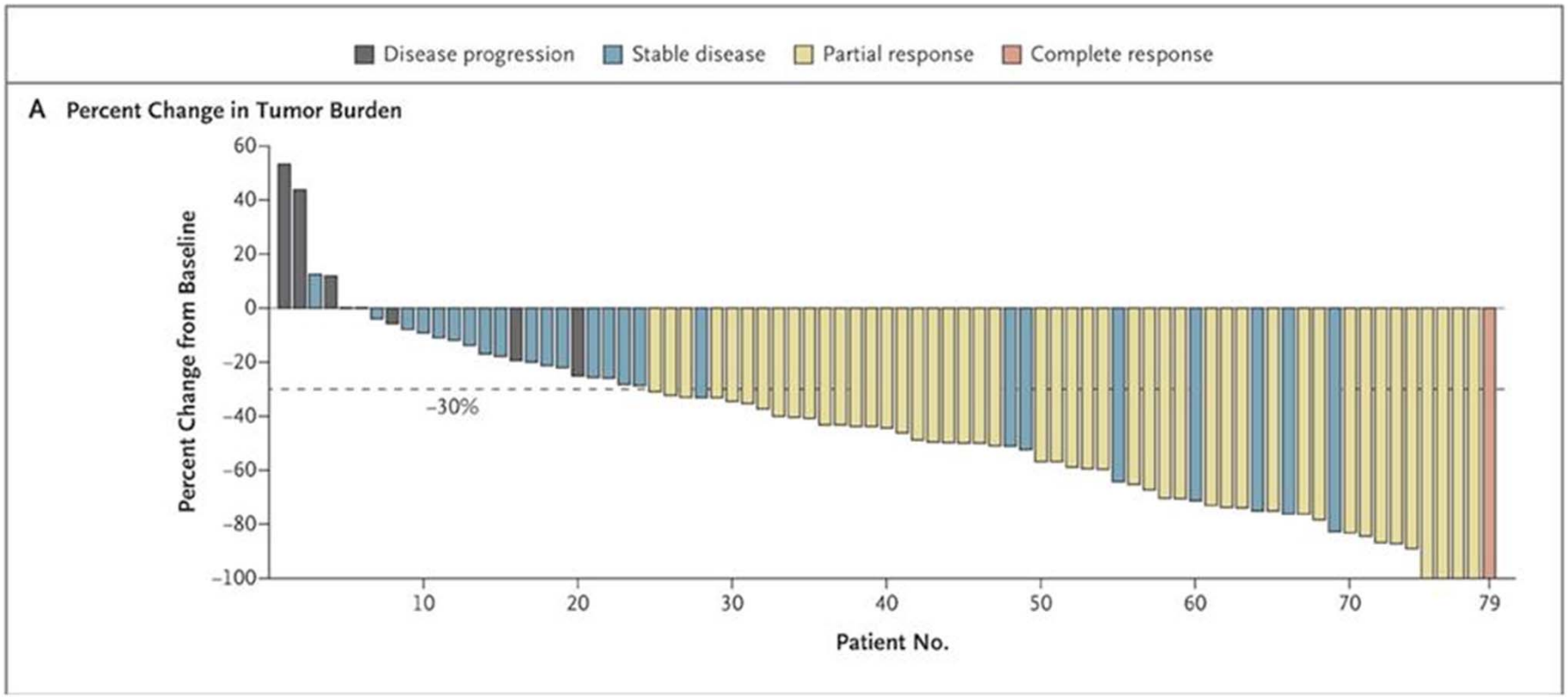
Digging into the Lung Cancer Genome



Adenocarcinoma

Squamous Cell carcinoma

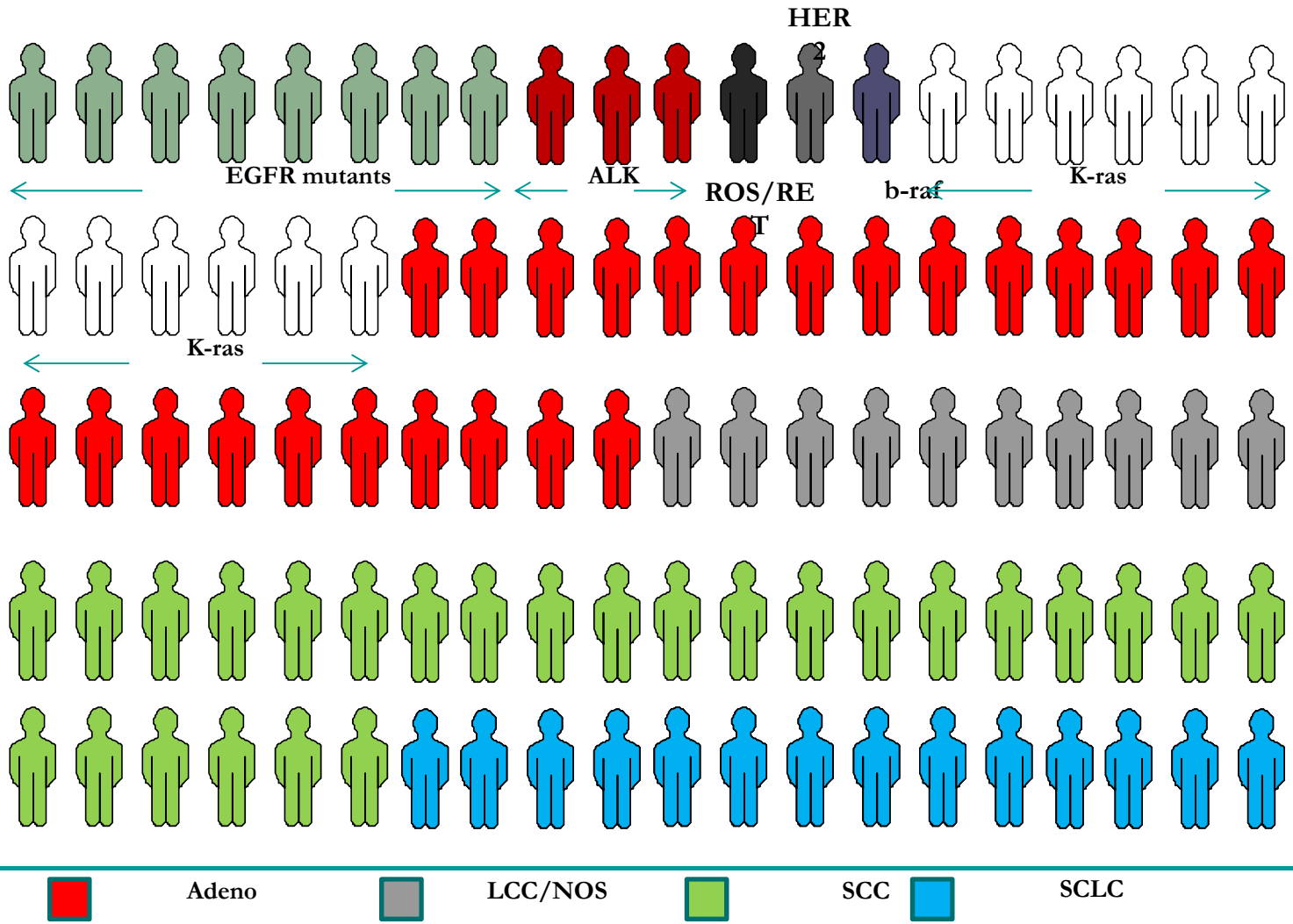
Crizotinib is Clinically Effective in EML4-ALK NSCLC



> 1500 patients screened to identify 83

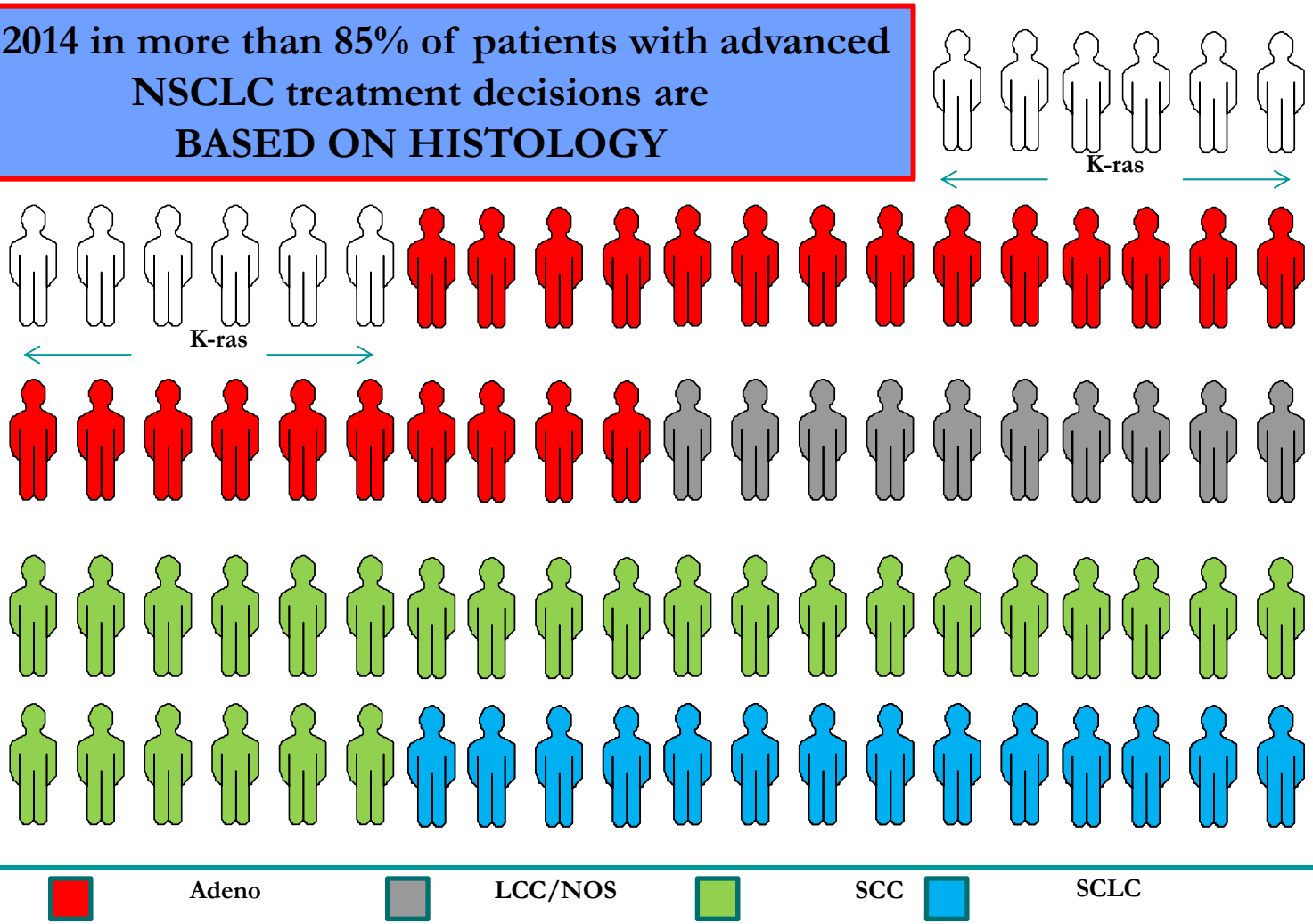
Kwak et al. NEJM 2010

2002-2014 – Changes in the therapeutic landscape of stage IV lung cancer



2002-2014 – Changes in the therapeutic landscape of stage IV lung cancer

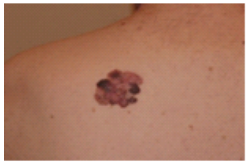
In 2014 in more than 85% of patients with advanced NSCLC treatment decisions are BASED ON HISTOLOGY



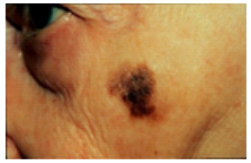
Traditional View of Cancer

Oncogenic Driver Mutations Impact Anticancer Therapy

Melanoma



Arising from Skin Without Chronic Sun Damage



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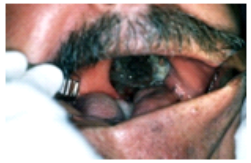
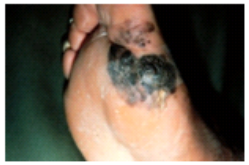
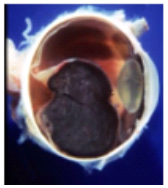


Arising from Mucosal Surfaces



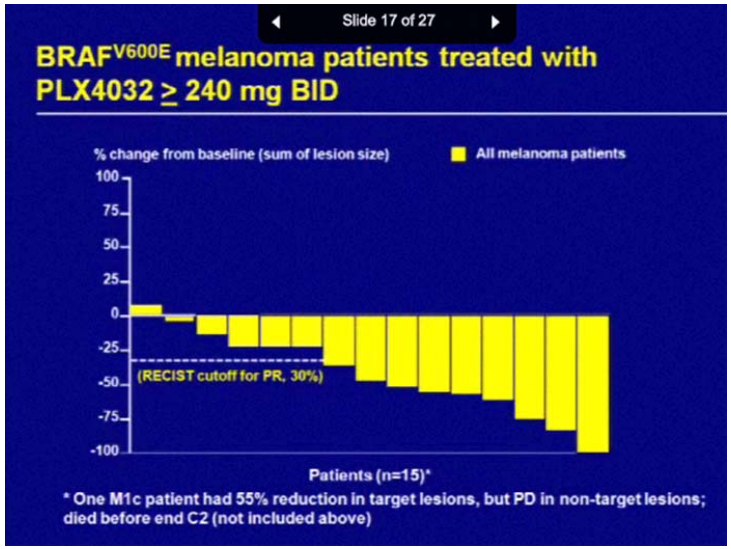
Arising from Acral Surfaces



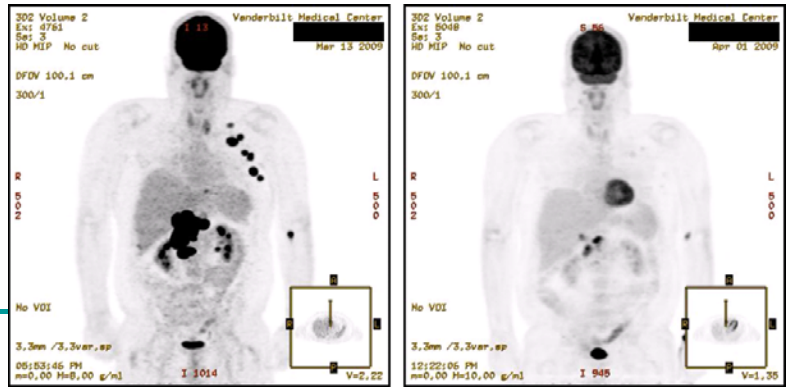
Uveal Melanoma

William Pao, 2012

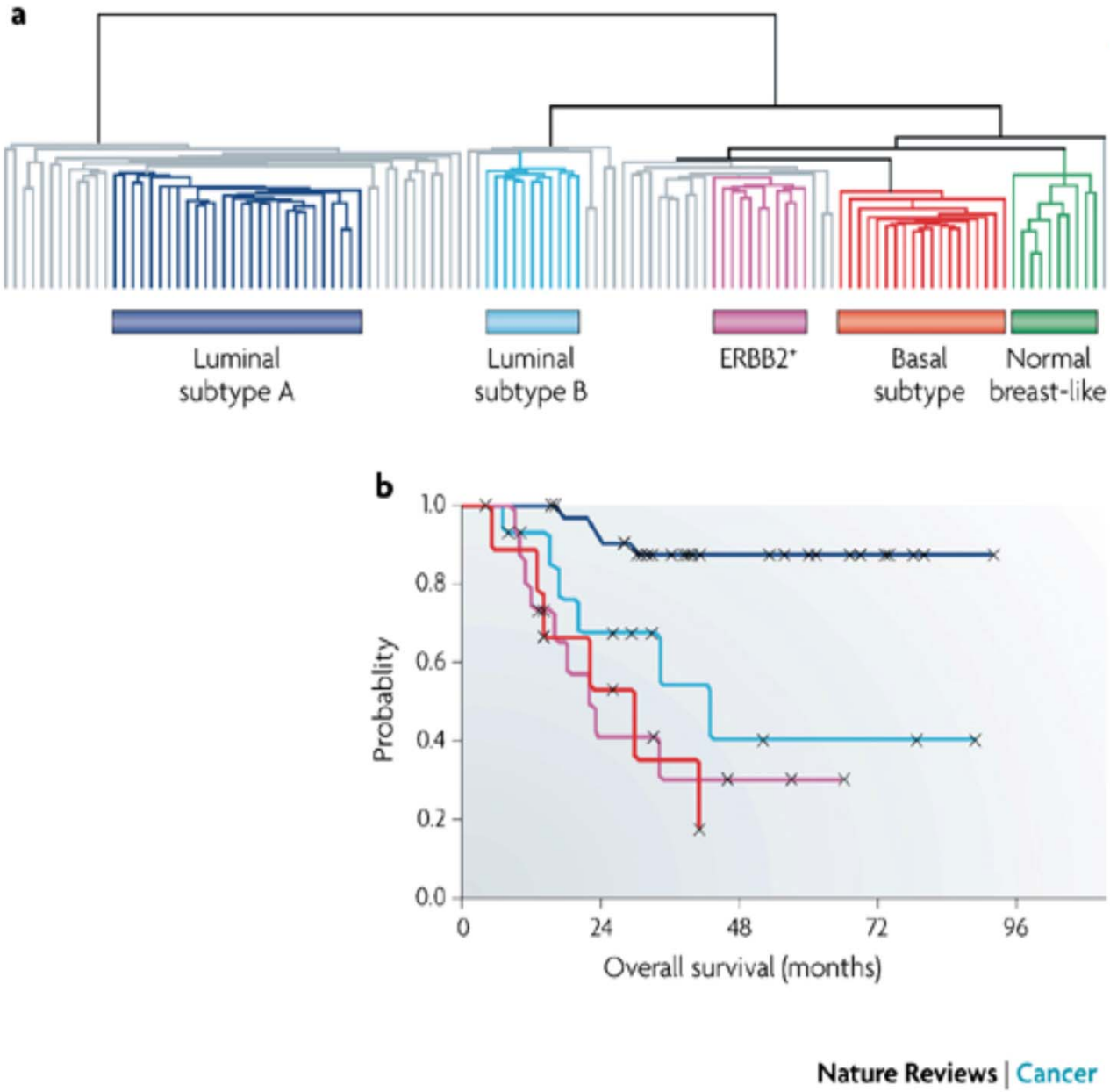
Melanoma



Ph II Trial PLX-4032 PASCO '09



Modelling breast cancer: one size does not fit all



The prognostic outcomes for each subtype of IDC are shown as overall survival. The ERBB2+ and basal subtypes demonstrate the worst prognoses, whereas the luminal subtype A shows the most favourable outcome. Recently, it has been demonstrated that the prognostic outcomes of the subtypes were not different when a pathologically complete response to therapy was achieved.

Tracy Vargo-Gogola1 & Jeffrey M. Rosen, Nature Reviews Cancer 7, 659-672 (September 2007)

A need for biomarkers for treating depression

Drugs/doses

SSRIs (first line)

SNRIs

TCA

Serotonin ligands

Lithium augmentation

Trial-and-Error

>30% non-responders

Takes 3-4 weeks to know

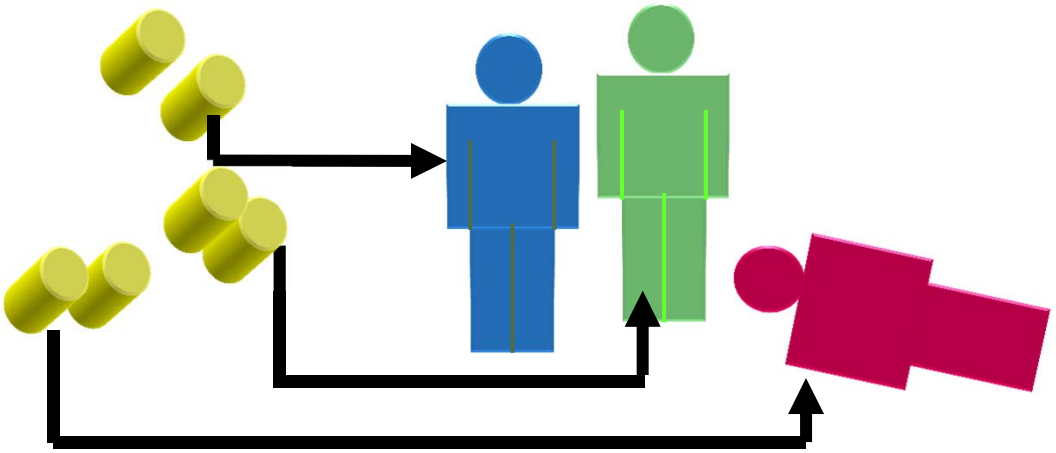
Patient suffering

+Suicide risk
+Huge societal costs

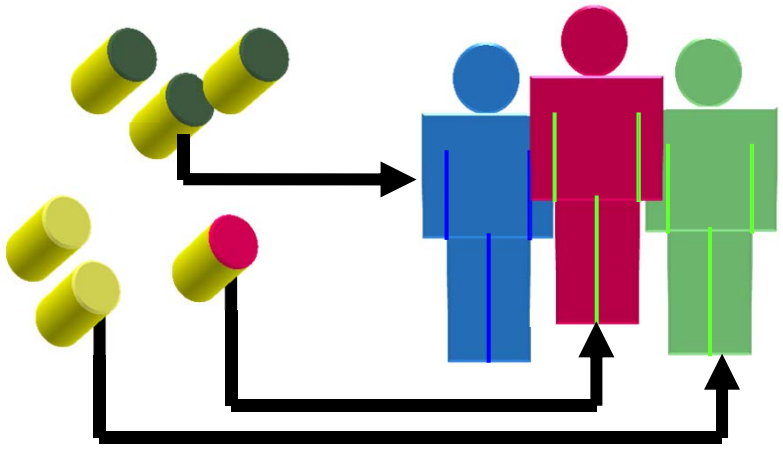
Personalised cancer management

- The Patient, not only the tumor!

The drug at the right dose



Avoid
Toxic Death



Prevent toxicities
Optimize
Intensify treatment

Prevention of 5-FU-induced toxicities using pretherapeutic DPD deficiency screening

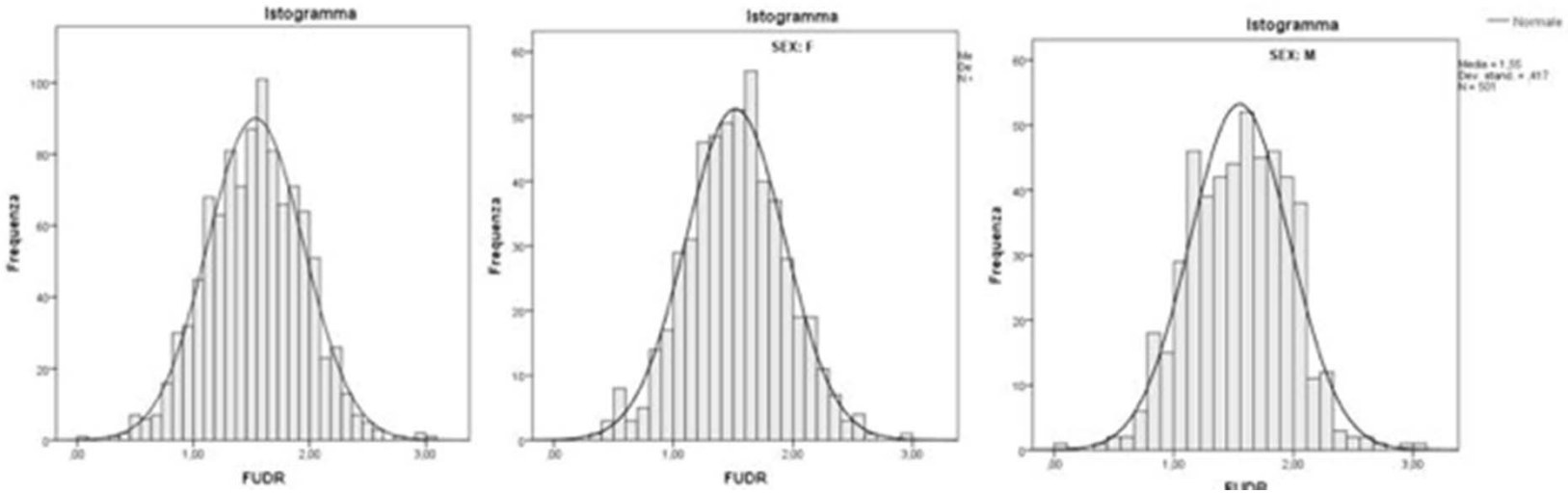
- Early severe toxicities (25% after the first cycle) or death (0.3% = 200 patients/year in France or in Italy; 1,300 in USA (Bamat M, *ASCO* 2011)
- Related to an asymptomatic DPD deficiency
- Complete DPD deficiency = multi-organ toxicity (diarrhea, mucositis, deH_2O, coma,…)
- Autosomal Codominant (DPD deficient families)

Pharmacokinetic (PK) guided optimization of 5-fluorouracil dosing in the treatment of patients with colorectal cancer

- Growing evidence suggests that BSA-based 5-FU dosing has several limitations, and that PK-guided dosing of 5-FU improves clinical efficacy with reduced toxicity.
- 5-FU dosing based on BSA results in sub-optimal 5-FU exposure levels for the majority of patients (81%).
- PK-guided dose adjustment of 5-FU appears to be a practical and feasible approach to personalize optimal 5-FU exposure with potential for application in routine clinical practice.

Association of poor metabolism and ultra-rapid metabolism of 5-fluorouracil with severe toxicity in a colorectal cancer patients cohort (n=1010)

- Fluoropyrimidine based chemotherapy represents the most common first line chemotherapy for colo-rectal cancer, but up to 30% of patients develop severe toxicity leading to reduced dosage, delayed drug administration and therapy discontinuation.



F. Mazzuca, P. Marchetti et al., in press

UGT1A1 genotyping for predicting toxicities in aCRC Pts treated with irinotecan (IRI)-based regimens

- Considering UGT1A1 genotype along with other clinical factors is important for managing pts undergoing IRI-based regimens.

W Ichikawa et al., ASCO 2013

The Rome Sant'Andrea Hospital Model Experienced benefits

- Monitoring of drug-related risks: more effective prevention of adverse drug effect;
- Selection of optimal therapy;
- Reduction of trial-and-error prescribing;
- Exclusion of unnecessary/ineffective drugs;
- Longitudinal patient evaluation with therapeutic drug monitoring;
- Increased patient compliance with therapy.

P Marchetti et al., submitted

Oncological genomic road map. Diagnosis-specific chemotherapic drugs, complementary therapy and pain control drugs (up to 100 SNPs). Available panels

- NSCLC (NON-SMALL CELLS LUNG CANCER)
- SCLC (SMALL CELLS LUNG CANCER)
- CRC (COLORECTAL CANCER)
- BREAST CANCER
- OVARIAN CANCER
- STOMACH CANCER
- PROSTATE CANCER
- PANCREATIC & BILIARY TRACT CANCER
- HEPATOCELLULAR CARCINOMA
- ENDOMETRIAL CANCER
- CERVICAL CANCER
- BLADDER & UROTELIAL CANCER
- TESTICULAR CANCER
- ANAL CANCER
- RENAL CANCER
- MELANOMA
- SARCOMA

Personalized Medicine delivered to patients: The Rome Sant'Andrea Hospital Model

Drug metabolism assay
***ex-vivo* 5-fluorouracil degradation rate**

Therapeutic Drug Monitoring
PACLITAXEL DOCETAXEL OXALIPLATINO MITOTANO LENALIDOMIDE CAPECITABINE NASTROZOLE EXEMESTANO FULVESTRANT DETROZOLO 5-ALPHAFLUOROBETAALANINA CICLOFOSFAMIDE METOTREXATO PAZOPANIB REGORAFENIB SORAFENIB IMATINIB SUNIPINIB TAMOXIFENE CABAZITAXEN BLEOMICINA RIZOTINIB DECARBAZINA AXITINIB DOXORUBICINA GEFITINIB ISOFOSFAMIDE IRINOTECAN

Statins PGX (up to 19 SNPs)
Trombophilic and cardiologic risk (up to 15 SNPs)
Anticoagulants PGX (up to 25 SNPs)
AMD risk (up to 15 SNPs)
Hearing loss risk (up to 16 SNPs)
Oxidative stress profile (up to 22 SNPs)
Vitamin B12 absorbtion (up to 15 SNPs)

Psychiatric genomics and *TDM* road map: receptor, metabolism and transporter profiles (up to 35 SNPs)

CLOMIPRAMINE, DOTIEPINE, TRIMIPRAMINE, TRANYLCYPROMINE, MECLOBEMIDE, SELEGILINE, ISOCARBOXAZIDE, PHENELZINE, CITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VENLAFAXINE, DULOXETINE, MIRTAZAPINE REBOXETINE, BUPROPION, BUSPIRONE, CHLORPROMAZINE, THIORIDAZINE, MESORIDAZINE, LEVOMEPROMAZINE, LOXAPINE, MOLINDONE, PERPHENAZINE , TIOTIXENE, TRIFLUOPERAZINE, HALOPERIDOL, FLUPHENAZINE, DROPERIDOL, ZUCLOPENTHIXOL, PROCHLORPERAZINE, AMISULPRIDE, ARIPIPRAZOLE DEIDROARIPIPRAZOLO, ASENAPINE, BLONANSERINA, CLOTIAPINE, CLOZAPINE, ILOPERIDONE, RISPERIDONE / 9-OH RISPERIDONE, SULPIRIDE, ZIPRASIDONE, ZOTEPINA, BENPERIDOLO, BROMPERIDOLO, CLORPROTIZENE, FLUPENTHIXOL , FLUSPIRILENE, MELPERONE, PERAZINA, PIPAMPERONE, PIMOZIDE, QUETIAPINE, DOXEPIN, OLANZAPINE, ROTIGOTINE

Personalized Medicine delivered to patients: The Rome Sant'Andrea Hospital Model

Neurological genomics and *TDM* road map: receptor, metabolism and transporter profiles (up to 35 SNPs)

FELBAMATE GABAPENTIN HYDANTOIN LOSIGAMONE RUFINAMIDE STIRIPENTOL TIAGABINE ZONISAMIDE VIGABATRIN LEVETIRACETAM LAMOTRIGINE OXCARBAZEPINE / 10-OH CARBAZEPINA LACOSAMIDE

Psychiatric metabolomics
The kinurenine fingerprint

TRYPTOPHAN, KYNURENINE, KYNURENIC ACID, 3-OH KYNURENINE, XANTHURENIC ACID, ANTHRANILIC ACID, 3-OH ANTHRANILIC ACID, QUINOLINIC ACID

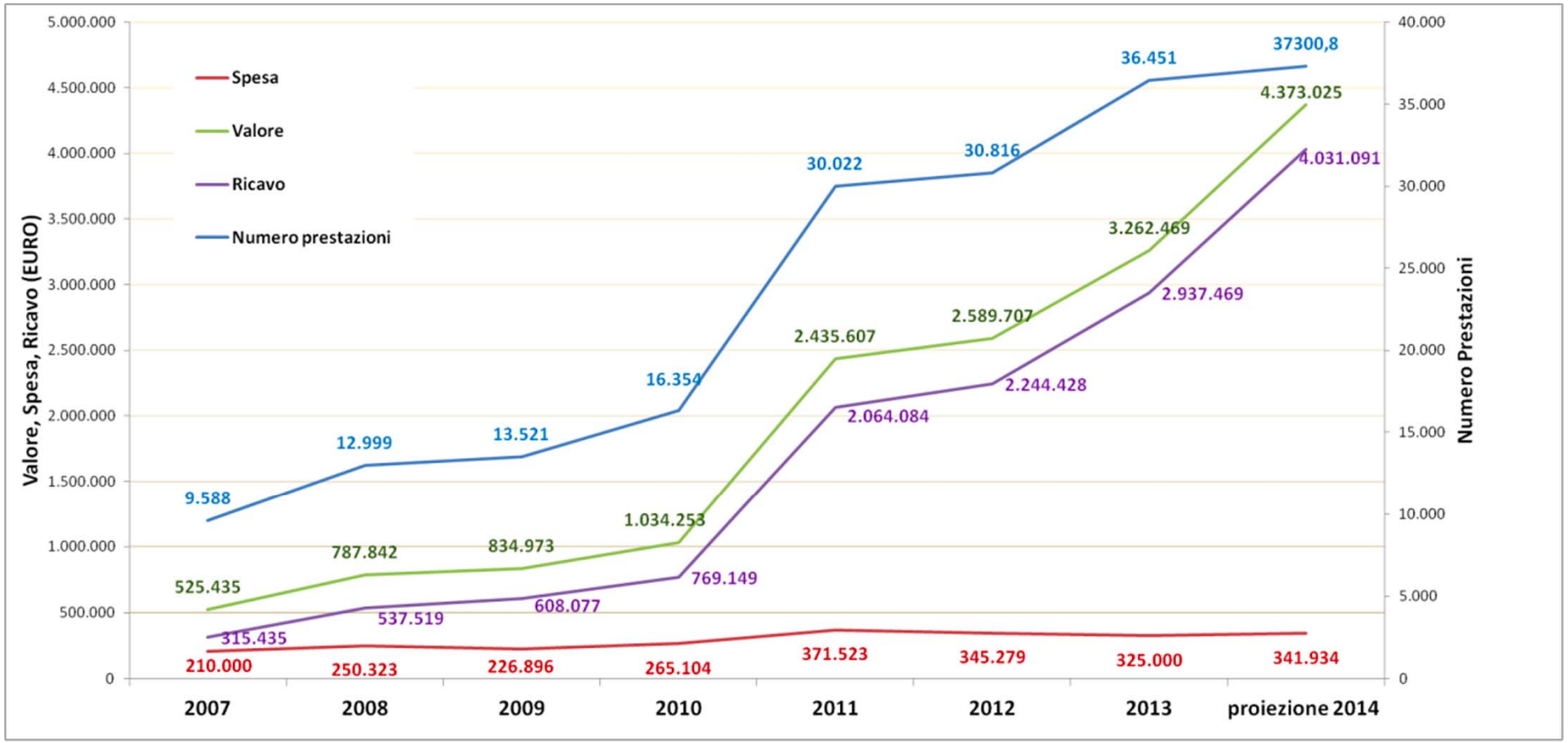
Functional metabolomics
Intestinal permeability evaluation

LACTULOSE-TO-MANNITOL RATIO
SUCRALOSE
SUCROSE

The gambling risk

genomic, neuropsychological, personological assay
Dinamic integration of 5 SNPs and 3 psycometric scale by RICOGA 1.0 algoritim ®

Relazione tra spesa e produttività del DiMA nel periodo 2007-2014



H2020 and beyond: skip discrepancy between theory and practice of Personalized Medicine

- Personalized Medicine has been widely depicted as a striking innovation, able to reform the standard approach to disease management, replacing the one-size-fits-all scheme of medicine with a single-patient-sized medical intervention…

M. Simmaco, P. Marchetti et al., 2014

H2020 and beyond: skip discrepancy between theory and practice of Personalized Medicine

… according to the following rules:

- monitoring of disease risks and more effective prevention;
- early intervention;
- selection of optimal therapy;
- reduction of trial-and-error prescribing and reduction of adverse drug reactions;
- exclusion of unnecessary drugs;
- therapeutic drug monitoring and disease progression/remission monitoring;
- increased patient compliance with therapy.

M. Simmaco, P. Marchetti et al., 2014