Place potentielle de la génomique dans la prise en charge du cancer du sein

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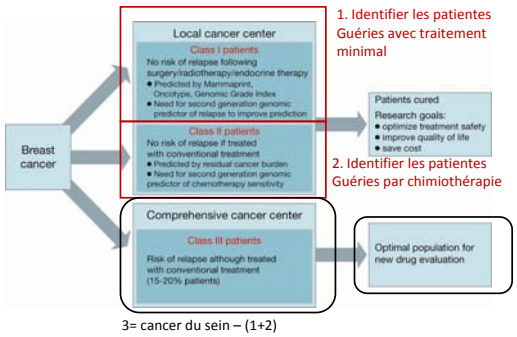
Plan

- Scores multigéniques pour la prise en charge quotidienne du cancer du sein localisé
- Biologie intégrée pour la prise en charge en phase métastatique
- Perspectives: pourquoi les technologies à haut débit vont se développer dans les années à venir ?

Cancer du sein: 3 populations



1. Identifier les patientes Guéries avec traitement minimal

2. Identifier les patientes Guéries par chimiothérapie

3= cancer du sein – (1+2)

Tursz, Nature Reviews Clin Oncol, 2011

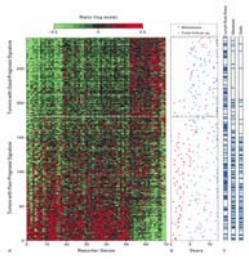
Objectifs des scores multigéniques dans le cancer du sein localisé

- Identifier les patientes guéries sans chimio:
  - Bon pronostic
    - Mammaprint
  - Haute sensibilité de l'hormonothérapie
    - Oncotype DX
    - SET index
- Identifier les patientes guéries par la chimiothérapie
  - Forte sensibilité à la chimiothérapie
    - RCB predictor vs autres (DLD30…)

Mammaprint


Gene expression profiling predicts clinical outcome of breast cancer

70 genes signature
Associated with high risk of metastatic relapse

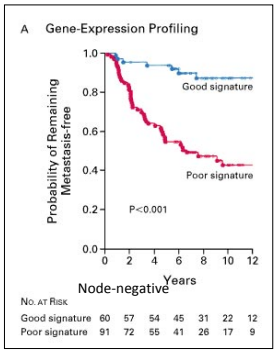


Performances Mammaprint: Validation I

TABLE 4. MULTIVARIABLE PROPORTIONAL-HAZARDS ANALYSIS OF THE RISK OF DISTANT METASTASIS AS A FIRST EVENT.

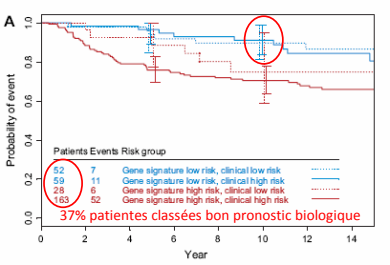
VARIABLE	HAZARD RATIO (95% CI)*	P VALUE
Poor-prognosis signature (vs. good-prognosis signature)	4.6 (2.3–9.2)	<0.001
Age (per 10-yr increment)	0.73 (0.50–1.06)	0.10
Lymph-node status (per positive node)	1.13 (1.03–1.24)	0.01
Diameter of tumor (per cm)	1.56 (1.22–2.0)	<0.001
Tumor grade		0.54
Grade 2 (vs. grade 1)	1.35 (0.61–3.0)	
Grade 3 (vs. grade 1)	1.03 (0.44–2.4)	
Vascular invasion		0.05
1–3 Vessels (vs. 0 vessels)	0.66 (0.30–1.44)	
>3 Vessels (vs. 0 vessels)	1.65 (0.98–2.8)	
Estrogen-receptor expression (per point)†	0.86 (0.56–1.31)	0.48
Mastectomy (vs. breast-conserving therapy)	1.27 (0.79–2.0)	0.32
Chemotherapy (vs. no chemotherapy)	0.37 (0.20–0.66)	<0.001
Hormonal treatment (vs. no hormonal treatment)	0.62 (0.29–1.34)	0.23

*CI denotes confidence interval.
†The log ratio of estrogen-receptor expression was used as a continuous variable.



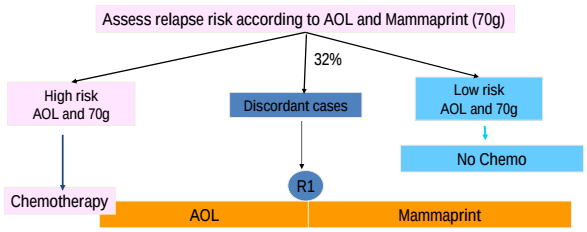
Van de Vijvers, NEJM, 2002

Performances Mammaprint: Validation II



Buyse, JNCI, 05

Prospective validation of genomic signature: EORTC-BIG MINDACT TRIAL



n=6000

Onco *type* DX™ 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

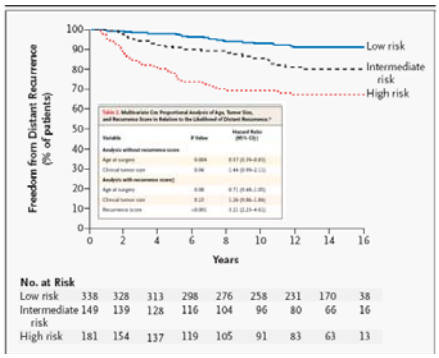
HER2
GRB7
HER2

REFERENCE
Beta -actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

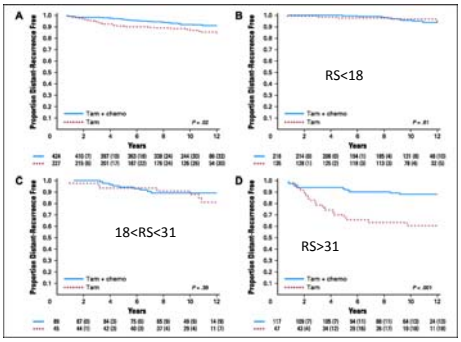
Category	RS (0 -100)
Low risk	RS <18
Int risk	RS >18 and <31
High risk	RS >31

Oncotype DX: Validation I: ER-positive disease (NSABP-B14)



Paik NEJM 2004

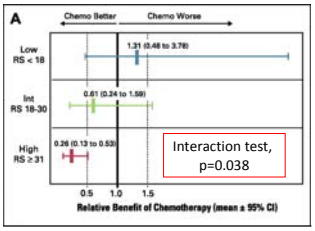
Oncotype DX: Validation II (NSABP-B20)



Paik, JCO, 2006

Predictive value for efficacy of adjuvant chemotherapy

NSABP-B20 trial



Paik, JCO, 2006

Concordant data with SWOG 8814 (Albain, Lancet Oncol, 2009)

Oncotype: Summary of data

- >3000 patients analyzed (4 from randomized trials)
  - *NSABP-B14 (NEJM, 04), NSABP-B20 (JCO, 06),* Kaiser studies (Breast Cancer Res), *SWOG-8814 (Lancet Oncol, 2009), Trans ATAC (SABCS, 08),* Japanese study (ASCO breast, 09)
- Concordant data:
  - Prognostic parameter
  - Risk of metastatic relapse <10% if RS<18 and N0
  - Predictive parameter for the efficacy of suboptimal chemotherapy
- Missing data:
  - Comparison with optimal IHC score
  - Efficacy of taxanes in RS<18 not evaluated
  - Prospective validation (ongoing TAILORx, accrual done)

Summary

- Genomic test identify a population of breast cancer patients who present <10% risk of distant relapse
- 3 questions:
  - Is this level of evidence enough to deny chemotherapy to patients ?
  - Do they perform better than standard parameters ?
  - How to improve it ?

3 questions

- Is this level of evidence enough to deny chemotherapy to patients ?
  - Retrospective studies vs randomized trial
- Do they perform better than standard parameters ?
- How to improve it ?

Retrospective studies vs randomized trials

Strength:

Quick implementation of biomarkers

Weaknesses:

Cannot allow concluding that a population DONOT benefit from a treatment

DO not QUANTIFY the medical usefulness of a biomarker

Strength:

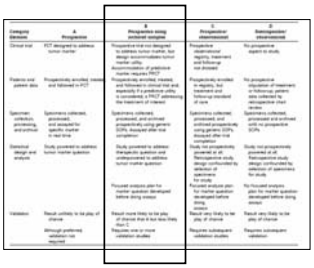
Allow concluding that a population DONOT benefit from a treatment

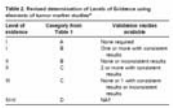
QUANTIFY the medical usefulness of a biomarker

Weaknesses:

SLOW implementation of biomarkers

Levels of evidence (Simon-Hayes)





Consistent retrospective data from prospective clinical studies could define a level I evidence….
pending a prospective validation, like observational cohort (speaker's opinion)

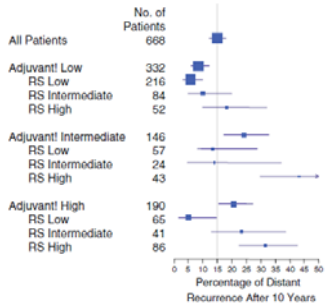
3 questions

– Is this level of evidence enough to deny chemotherapy to patients ?
  - Retrospective studies vs randomized trial

– Do they perform better than standard parameters ?

– How to improve it ?

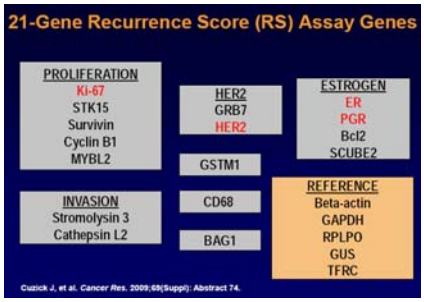
Does Recurrence score add to conventional parameters ?
I: adjuvant online



Recurrence score is adding information to AOL

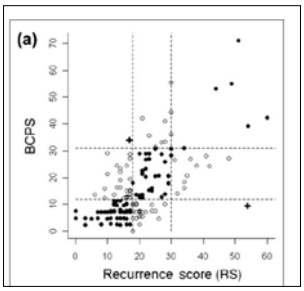
Tang, BCRT

Does Recurrence score add to conventional parameters ?
I: « optimal » IHC score (ER, PR, Her2, KI67)



Since RS includes ER, PR, Her2 and KI67, does it provide additional information ?

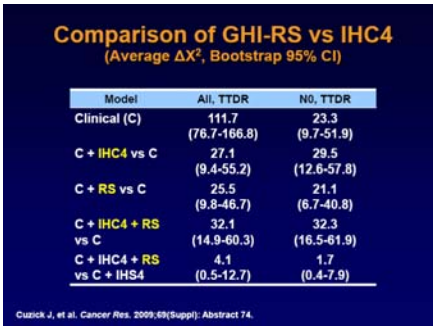
Correlation between RS and (ER, PR, Her2, proliferation)



RS correlates with standard pathological parameters but…
the level of correlation is not high

The Oncotype DX Recurrence Score Is Correlated With a Composite Index Including Routinely Reported Pathologic Features

Comparison between RS and IHC4



Does RS provide additional information as compared to standard parameters ?

Comparison with AOL: Yes

Comparison with ER/PR/Her2/KI67 : this is NOT the righ question since:

the level of evidence for KI67 is not I, at least for the prediction to adjuvant chemotherapy

Current status : the equivalency between RS and (ER,PR,Her2,KI67), together with the predictive value of KI67 are still research hypotheses

3 questions

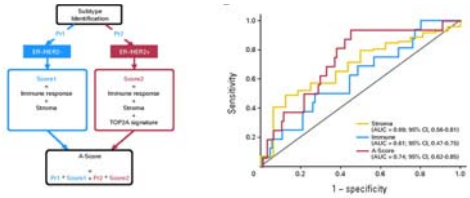
- Is this level of evidence enough to deny chemotherapy to patients ?
  - Retrospective studies vs randomized trial
- Do they perform better than standard parameters ?
- How to improve it ?

Potential solutions to capture specific information that would encompass ER, He2, Ki67

- Higher number of events in training set (Michiels, Lancet, 2005)
- Population more homogenous regarding clinical/molecular characteristics (Andre, Pusztai, Nat Clin Pract Oncol, 2006) : develop predictors within molecular classes
- Tests developed to provide additional information to clinico-pathological characteristics
- New technologies (+ complementarity) (Desmedt, EJC, 2009)
- Supported by functional studies (Ioannidis, PLoS Med, 2005)

Development A-score

139 patients, ER-negative breast cancer, treated with neoadjuvant epirubicine
Which functional pathway is predictive ?



Add value as compared to standard parameters but…
One could argue that this score could be assessed by TOP2A FISH and lymphocytes infiltrates

Primary goal of GE arrays: discovery to be transferred onto clinics with simple tool
GE for clinics: more precise, more reproducible

Desmedt C et al. JCO 2011;29:1578-1586 JOURNAL OF CLINICAL ONCOLOGY

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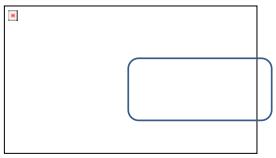
- Identifier les patientes guéries par la chimiothérapie
  - Forte sensibilité à la chimiothérapie
    - RCB predictor vs autres (DLD30…)

Problématique des scores de chimiosensibilité

DLD30 gene predictor
(Hess, J Clin Oncol, 2006)

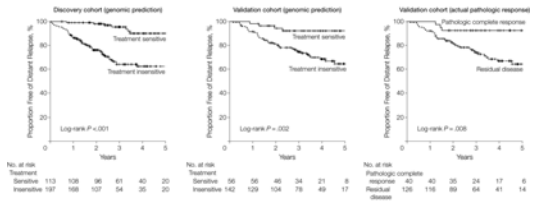


mauvaise valeur prédictive positive

Ne permettent pas d'identifier
un groupe de patientes guéries

Peut-on mettre au point un prédicteur génomique avec forte valeur prédictive positive qui permette d'identifier un groupe de patientes GUERIES par la chimio ?

Kaplan-Meier Estimates of Distant Relapse–Free Survival According to Genomic Predictions (Before Treatment) as Treatment Sensitive or Treatment Insensitive and to Pathologic Response (After Treatment) as Pathologic Complete Response or Residual Disease



Hatzis, C. et al. JAMA 2011;305:1873-1881

JAMA

Algorithme possible pour l'intégration des tests génomiques à la pratique clinique

GUERIES

NON GUERIES:
Utilisation des tests génomiques
Pour l'identification de cibles
thérapeutiques

Plan

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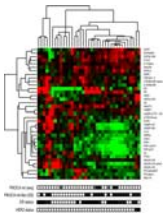
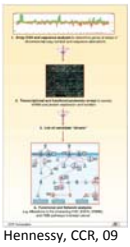
Genomic predictors for treatment efficacy: targeted therapies

Functional pathways



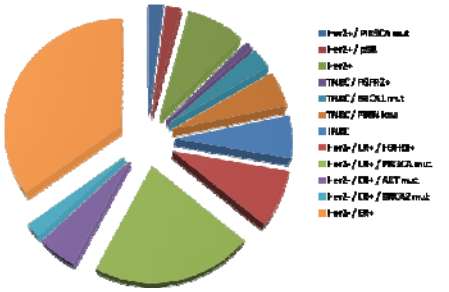
Quantification of PI3K activation / GE array
Loi, PNAS, 2010

Target detection



B. Hennessy, CCR, 09

Molecular segmentation of breast cancers



Breast cancer includes **rare** molecular segments characterized by a specific molecular alteration

Starting point

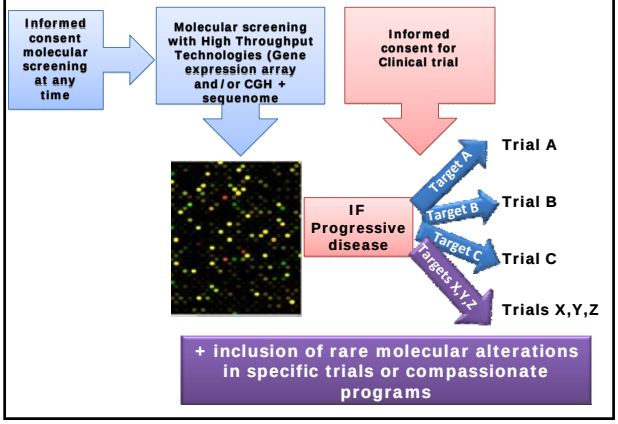
A high number of molecular alterations are RARE

Some of the drugs (or combination) under development target these rare events

Implication: there is a risk of falsely conclude that a new targeted agent does not work if the trial does not include a minimum number of patients with a specific molecular alteration

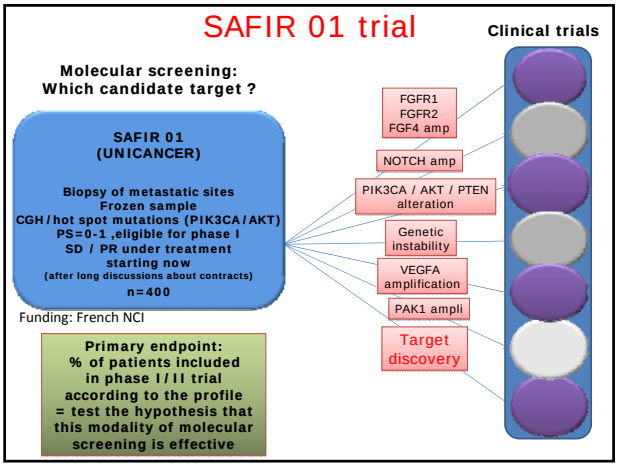
Need for molecular enrichment in phase I / II trials

High throughput technologies for molecular screening



+ inclusion of rare molecular alterations in specific trials or compassionate programs

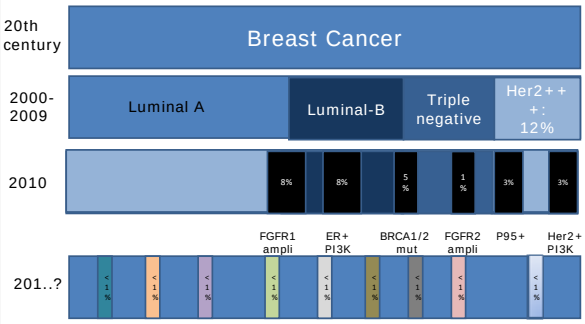
SAFIR 01 trial



Funding: French NCI

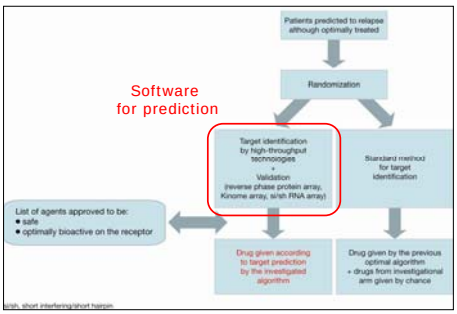
Primary endpoint:
% of patients included in phase I / II trial according to the profile = test the hypothesis that this modality of molecular screening is effective

The problem:
Further molecular segmentation in breast cancers



Are genomic-oriented phase II trials testing drugs still feasible ?
What could be the next generation of trials in the metastatic setting ?

??? Solution ???:
Test the algorithm for prediction, no longer the drugs



Tursz et al, Nature Reviews Clin Oncol, 2011

Clinical programs molecular selection: Phase I/II trials enrichement

The project: Virtual cell project

- SAFIR01
- MOSCATO
- MSN
- PAIR

Institut de cancérologie GUSTAVE ROUSSY

Passion for innovation POWERED BY DASSAULT SYSTEMES

Development of database: Common rules for success / failure of targeted agents

Algorithm for Prediction: what are the Bioinformatic rules to Predict sensitivity to targeted agents

n=1500

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Perspectives

- Reproductibilité / industrialisation
- Niveaux de preuve supérieurs car capacité financière à mener les études
- Le multiplex évite la mise au point puis la réalisation de multiples bioassays
- Permet de prédire les cibles thérapeutiques