Utilité clinique des prédicteurs moléculaires

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Question posée

- Est-il licite d’utiliser des tests moléculaires pour ne pas faire de chimiothérapie adjuvante ?

Plan

- Niveau de preuve EGAPP
- Signatures multigéniques
- Ki67
- Perspectives

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group

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Analytical validity

Clinical validity

Clinical utility

ANALYTICAL VALIDITY

A test's ability to accurately and reliably **measure** biomarker of interest

(includes reproducibility, robustness (e.g., resistance to small changes in pre-analytic or analytic variables) and quality control)

CLINICAL VALIDITY

A test's ability to accurately and reliably identify or predict a relevant breast cancer survival endpoint

(= "significativité statistique")

CLINICAL UTILITY

Treatment decision based on a genomic test results in improved clinical outcome

Scenario pour illustrer différence validité clinique et utilité clinique

- Biomarqueur + : 10% rechute à 10 ans
- Biomarqueur - : 30% rechute à 10 ans
- Reproduit dans XX études , significatif en multivarié **= Validité clinique**

- Mais…
- Biomarqueur + / traitement+ : 8% rechute
- Biomarqueur + / traitement-: 10% rechute

- = PAS d'utilité clinique car la valeur pronostique ne permet pas d'éviter des traitements

Plan

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- Signatures multigéniques: recommandations IMPAKT / ESMO
- Ki67
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EVALUATED SIGNATURES

1. 21-gene Recurrence Score (Oncotype Dx®)
2. GENE70 (MammaPrint ®)
3. Genomic Grade Index (GGI, MapQuant Dx®)
4. Breast Cancer Index (BCI)
5. EndoPredict (EP)
6. PAM50 (ROR-S)

LITERATURE SEARCH

- Cross-referencing was performed of identified articles

- Exclusion criteria
  - Cost-benefit studies (healthcare dependent)
  - Neoadjuvant studies (different sampling procedure, addresses prediction not prognosis)
  - *In-silico* analyses (approximate version, uses data from datasets previously analyzed)

ELIGIBLE ARTICLES

Gene Signature	Articles	Unique Patients	Samples from randomized trials (n)
Oncotype Dx	21	6,033	5 *
EndoPredict	1	2,666	2 **
MammaPrint	15	2,440	0
GGI	5	1,841	0
PAM50 (ROR-S)	2	1,496	0
BCI	2	853	1 ***

* ECOGE2197, SWOG8814, NSABP-B20, NSABP-B14, ATAC
** ABCSG-6, ABCSG-8
** * Stockholm Breast Cancer Study Group randomized phase III trial

Validité / Utilité clinique

	oncotype	70 genes	GGI	BCI	PAM50	Endo Predict
Adequate documentations of multivariable regressions - ***N*. Multivariate models** - **Genomic test is significant (*p*<0.05)** - **Added value demonstrated using the likelihood ratio test (*p*<0.05)**	**13** **12** **5**	**13** **12** **2 ***	**4** **4** **0**	**2** **2** **0**	**2** **2** **1**	**2** **2** **2**
Adequate documentation of AUC **Presented the AUC values** - **Presented *P* value for comparison**	**1** **0**	**2** **0**	**0** **0**	**1** **0**	**2** **1 ****	**1** **1**
Reclassification analysis vs. standard risk categories (AOL, NPI, ST Gallen)	**2**	**6**	**0**	**0**	**0**	**0**

Endopredict

8 cancer-related genes

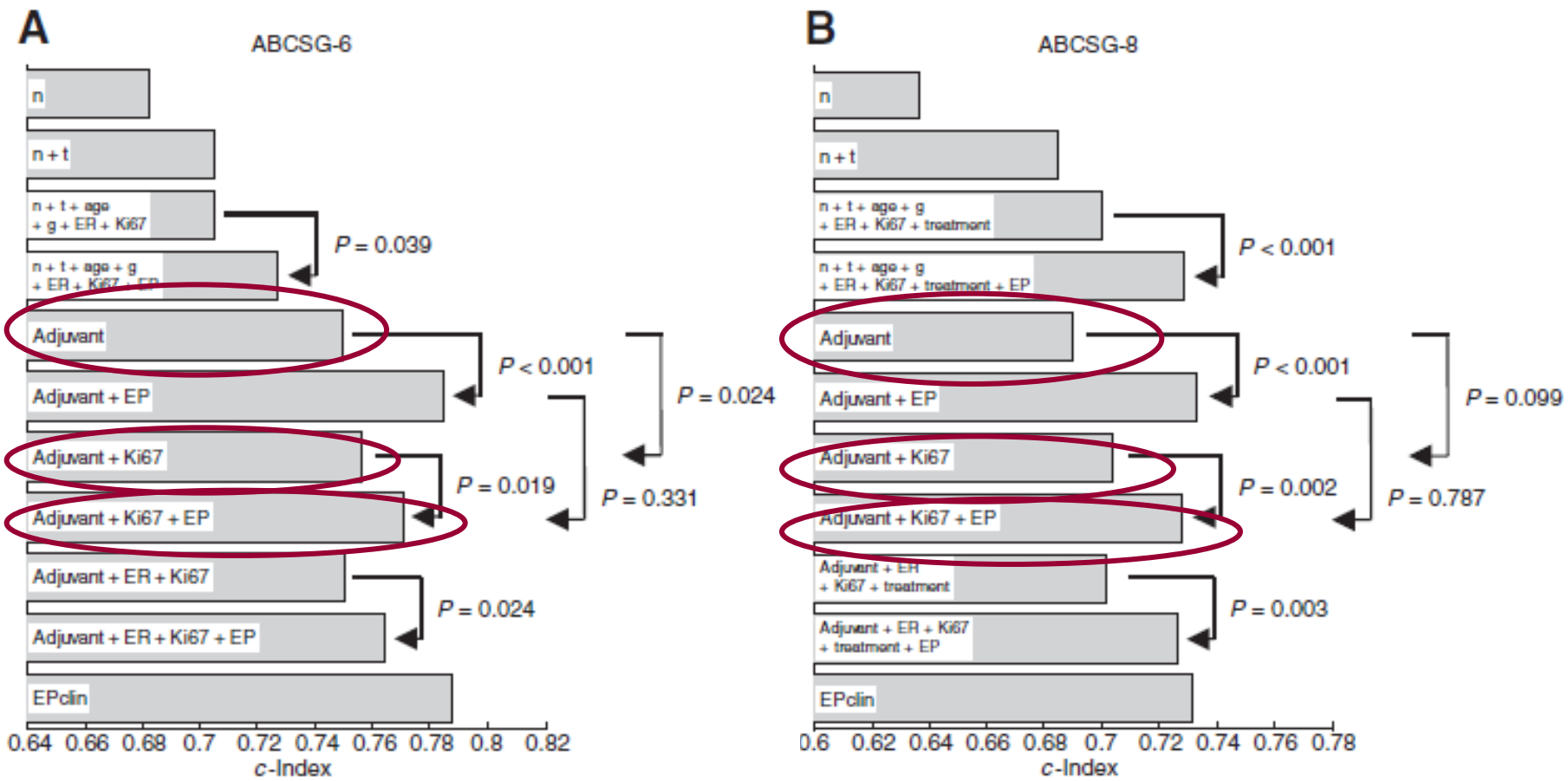
$$
\begin{aligned}
s_u = {} & 0.41 \cdot \Delta C_t(BIRC5) - 0.35 \cdot \Delta C_t(RBBP8) \\
& + 0.39 \cdot \Delta C_t(UBE2C) - 0.31 \cdot \Delta C_t(IL6ST) \\
& - 0.26 \cdot \Delta C_t(AZGP1) + 0.39 \cdot \Delta C_t(DHCR7) \\
& - 0.18 \cdot \Delta C_t(MGP) - 0.15 \cdot \Delta C_t(STC2) - 2.63
\end{aligned}
$$

Table 1. Multivariate Cox proportional hazard models for estimating the contribution of variables to predict distant recurrence

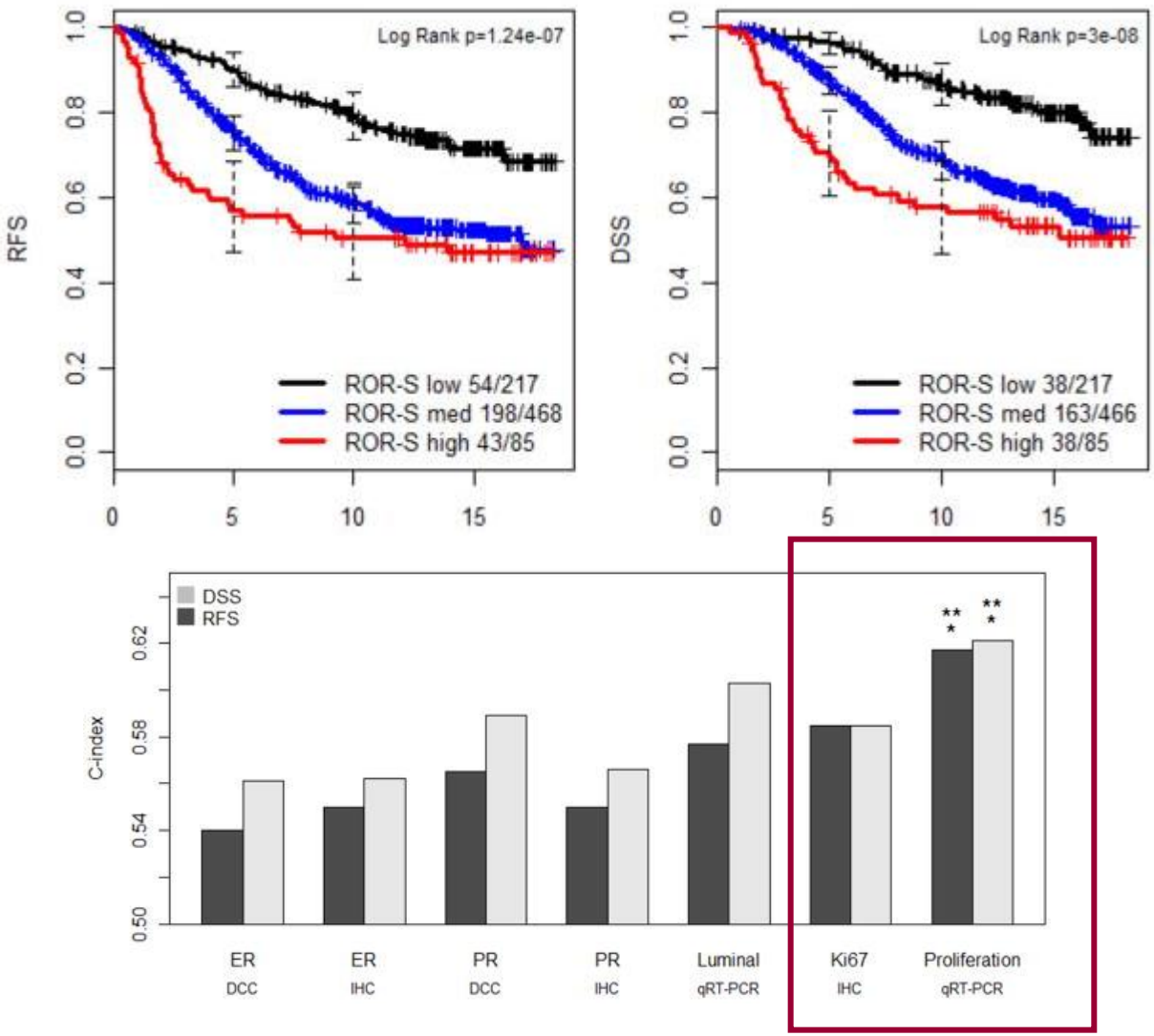
Cox model	Variable	ABCSG-6		ABCSG-8	
		Unit HR (95% CI)	*P*	Unit HR (95% CI)	*P*
Multivariate Cox model	Age	1.00 (0.96–1.04)	0.864	1.02 (0.99–1.04)	0.194
	Tumor size	1.09 (0.70–1.71)	0.704	1.57 (1.15–2.16)	0.005
	Nodal status	2.47 (1.75–3.48)	<0.001	2.32 (1.69–3.20)	<0.001
	Grade	0.81 (0.48–1.37)	0.435	1.09 (0.60–1.99)	0.770
	ER (IHC)	0.90 (0.58–1.40)	0.650	0.97 (0.70–1.34)	0.868
	PR (IHC)	0.83 (0.63–1.10)	0.199	0.94 (0.77–1.15)	0.559
	Ki67	1.03 (1.00–1.06)	0.086	1.00 (0.98–1.02)	0.974
	Treatment arm	–	–	0.78 (0.51–1.19)	0.243
	EP score	1.19 (1.04–1.36)	0.010	1.26 (1.15–1.38)	<0.001
Bivariate Cox model	Adjuvant! score	1.03 (1.02–1.04)	<0.001	1.05 (1.04–1.07)	<0.001
	EP score	1.19 (1.06–1.32)	0.002	1.27 (1.18–1.37)	<0.001

Filiptis, Clin Cancer Res, 2012

Endopredict



ROR: PAM50 gene classifier



Nielsen, Clin Cancer Res, 2010

IMPAKT GUIDELINES

1. ANALYTICAL VALIDITY

According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing

IMPAKT GUIDELINES

2. CLINICAL VALIDITY

According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing

While other signatures showed evidence of determining prognosis, the panel believes that more data on analytical validity is required to reach a robust conclusion on their clinical validity

IMPAKT GUIDELINES

3. CLINICAL UTILITY

According to EGAPP criteria, the panel grades
NONE of the signatures as convincing

Prospective trials are ongoing
Differences in N0 v.s. N+

Recommendations/ Guidelines	Year	Signatures Evaluated	Statement
ASCO 2007	2007	Oncotype MammaPrint Rotterdam GS Breast cancer gene expression ratio	- Oncotype CAN be used for prognosis in ER+ N0, Tam treated BC - MAY be used for CT utility -Other GS under investigation for prognosis and utility
French	2009	Oncotype MammaPrint uPA-PAI-1	- Level II "Oncotype, prognosis ER+ N0" - Level II "Oncotype, prediction " ER+, CMF"
EGAPP	2009	Oncotype MammaPrint H:I ratio test	- Inadequate analytic validity "all" - Adequate clinical validity "Oncotype" - Inadequate clinical utility "all"
St Gallen	2011	Oncotype MammaPrint	-Oncotype MAY be used to predict CT utility -Mammaprint- insufficient data
NICE (draft guidelines)	2012	Oncotype MammaPrint Mammastrat IHC4	-Oncotype- Clinical validity established but NO convincing Clinical Utility - Mammaprint/Mammastrat- insufficient data - IHC4- needs further investigation

Pourquoi le panel n’a-t-il pas coté les tests « clinically useful » ?

- Cf scenario initial: bonne valeur pronostique mais aucune preuve que la population de bon pronostic ne bénéficie pas de façon minime de la chimio

Peut-on prescrire un test s'il est « clinically valid » mais n'a pas démontré de « medical usefulness » ?

- Oui… si la patiente est informée du risque pris

- NON à large échelle dans un contexte de santé publique en l'absence de données de cohorte ou d'essai randomisé

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- Ki67: marqueur de prolifération, corrélé grade, RE, Her2.
  - Intérêt dans les grade 2 / RE+ / Her2- ?
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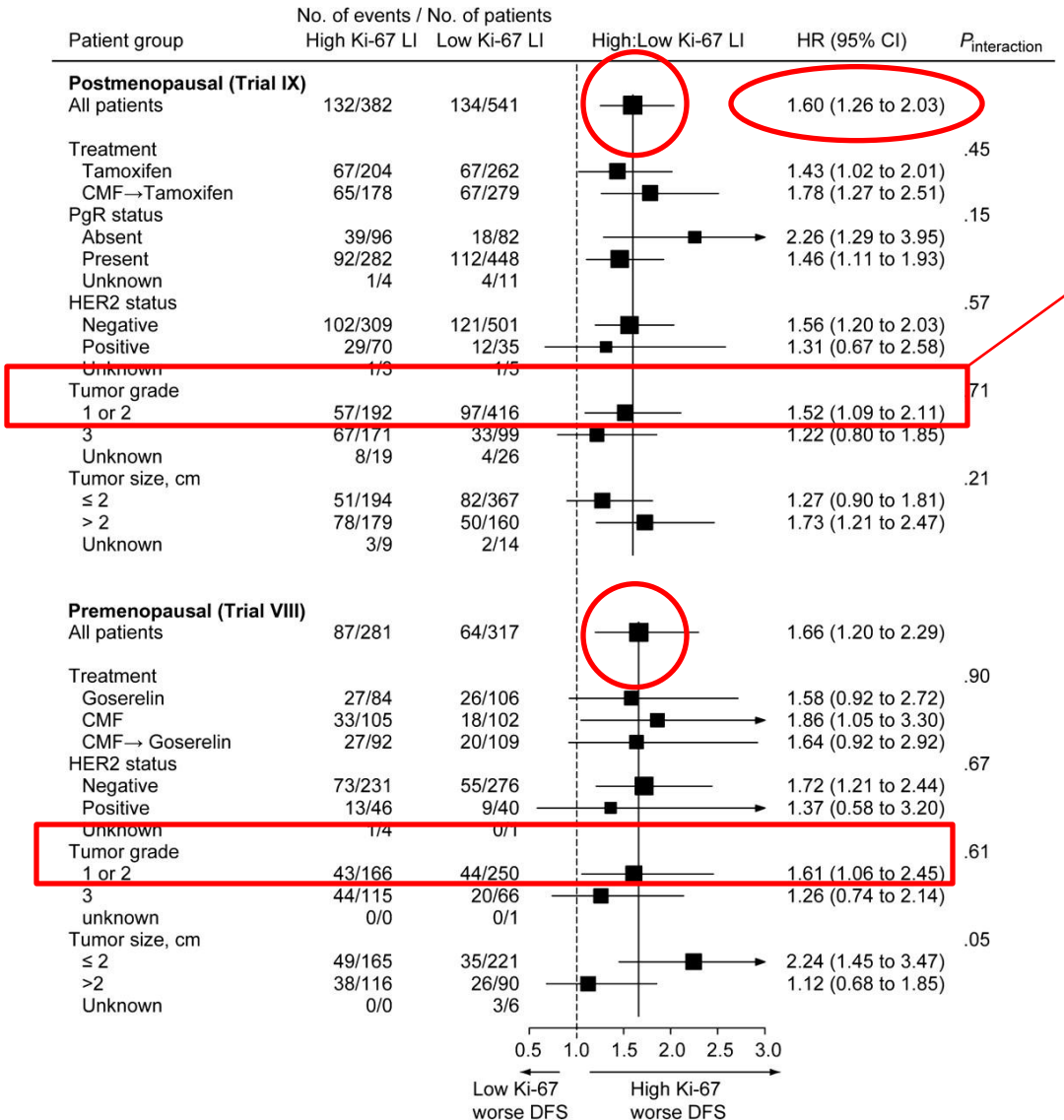
Prognostic value in ER+ disease: IBCSG VIII/IX



30% of the ER+ / grade I-II have high Ki67
HR for relape:1.5

Modest
prognostic value

Viale, JNCI, 2008

Prognostic value of Ki67 expression: BIG1-98

	Letrozole		Tamoxifen	
	Events	Total (%)	Events	Total (%)
All patients	122	1,361 (9.0)	181	1,324 (13.7)
Ki-67 LI				
Low (≤ 11%)	56	730 (7.7)	66	703 (9.4)
High (> 11%)	66	631 (10.5)	115	621 (18.5)

Total: **171 / 1324 (13%)**

Modest prognostic value

Viale, J Clin Oncol, 2008

Ki67 and efficacy of adjuvant chemotherapy

		Trials	n	method	Interaction test
1st generation	Viale G JNCI 2008	IBCSG VIII and IX	1521	IHC	p=0.90 (IX) p=0.45 (VIII)
1st generation	Paik S JCO 2006	NSABP-B20	651	RT-PCR	p=0.17
2nd generation	Bartlett Lancet Oncol 2010	NEAT / BR9601	1941	IHC	p=0.95
3rd generation	Penault-llorca F JCO 2009	PACS01	700	IHC	p=0.10
3rd generation	Dumontet Clin Cancer Res 2011	BCIRG001	1350	IHC	Non significant

Ki67 : Summary

- Modest prognostic value
- **NO** evidence that it could be a predictive biomarker for the efficacy of adjuvant chemotherapy
- **NO EVIDENCE** of clinical utility (IMPAKT guidelines)

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Conclusion

- **Ki67 :**
  - valeur pronostique modeste
  - pas de valeur prédictive démontrée
  - Pas de démonstration de l’utilité clinique
  - Mauvais outil de décision « per se »

- **Signatures génomiques:**
  - valeur pronostique
  - Pas de démonstration de l’utilité clinique

Perspectives

- TAILORx / MINDACT : résultats sous peu
- Nécessité de bâtir de nouveaux modèles d'implémentation de biomarqueurs (cohortes avec remboursement conditionnel)
- Endopredict / ROR : prometteurs
- IHC4: prometteur mais en cours de validation
- Nécessité de QUANTIFIER le bénéfice attendu de ne pas faire de chimiothérapie : coût , toxicités , qualité de vie (CANTO)