UNICANCER

Centre JEAN PERRIN "La science et l'espérance"

Centre Jean Perrin

Centre de Lutte contre le Cancer d'Auvergne

Clermont-Ferrand - France -

Endopredict

Expérience du CJP en 2017

Monaco le 31/01/2018

Frédérique Penault-Llorca, MD, PhD

Liens d’intérêts

- Frédérique Penault-Llorca: consultante pour Abbvie, AstraZeneca, Bayer, BMS, Lilly, Merck, Merck Lifa, Novartis, Pfizer, Roche, Sanofi, Takeda dans le champ de biomarqueurs

Contexte de l'utilisation des signatures en 2018

Tumeur luminales : A: PR >20% and Ki67 <14%

B : PR <20% and/or Ki67 >14%*

- Risques intermédiaires
- Risques élevés pour éviter la chimiothérapie
- Mieux définir le risque de récidive à 5 et 10 ans
- Eviter les sur et sous-traitements
  - Adaptation thérapeutique adjuvante
  - Hormonothérapie vs Hormonothérapie + Chimiothérapie

- Plusieurs tests disponibles – prise en charge RIHN (…..)

* St Gallen A. Goldhirsch Ann Oncol 2013

Particularités du test Endopredict

EndoPredict
(Sividon puis Myriad)

HR+ / HER2- , T1-2, N0

FFPE

qRT-PCR

8 GENES SIGNATURE

PROLIFERATION, OESTROGENES

« LOCAL » TEST

(SPECIAL EQUIPMENT IS REQUIRED)

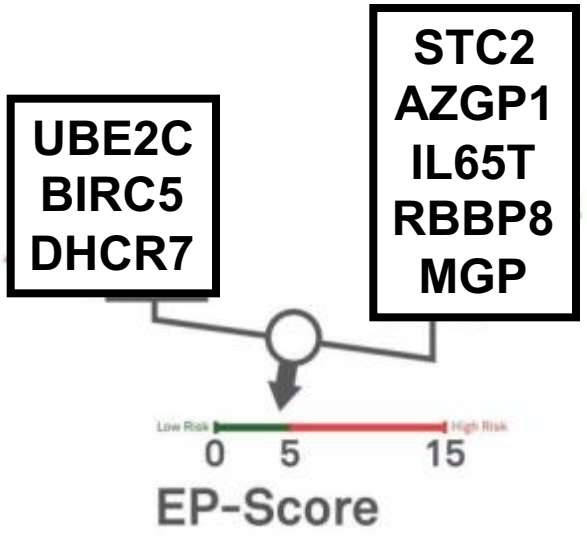
SCORE OF RECURRENCE EP SCORE

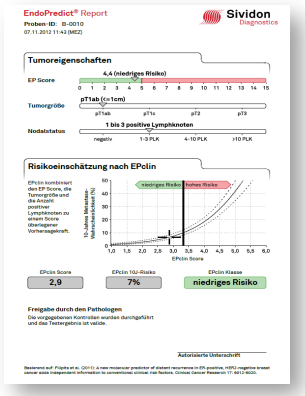
LATE AND EARLY RECURRENCES (5 & 10 YEARS)

PROGNOSIS

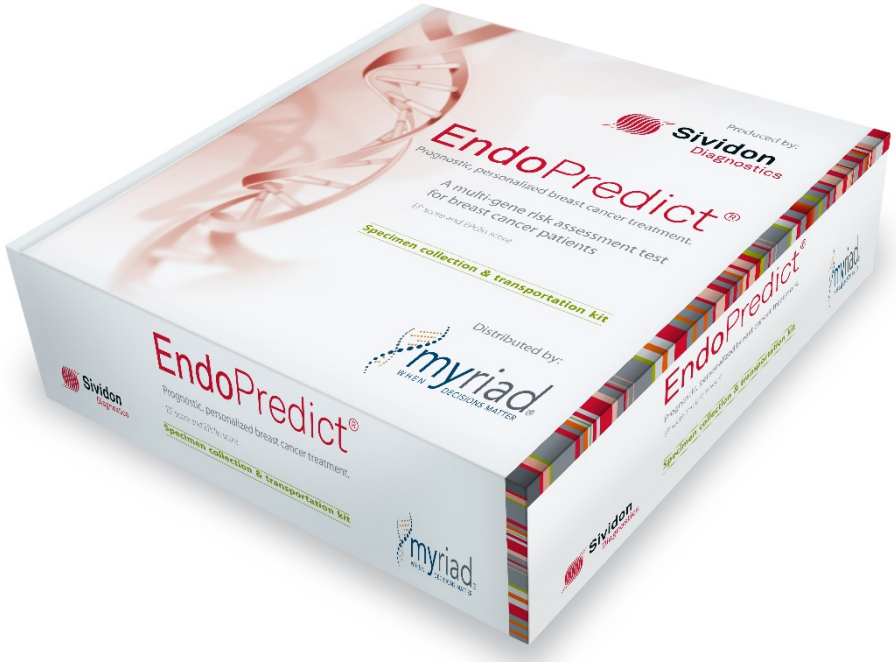
LOW RISK

HIGH RISK





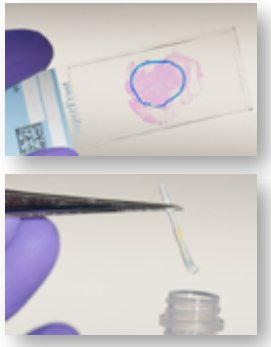
EndoPredict:
2° Generation Gene Expression Test



- **Targeted patients**
  -
- **Proven outcomes**
- **Proven prognostic power**

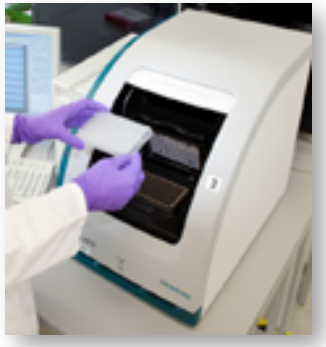
RT-PCR-based EndoPredict
Can be performed in local molecular pathology labs

Tumour sample

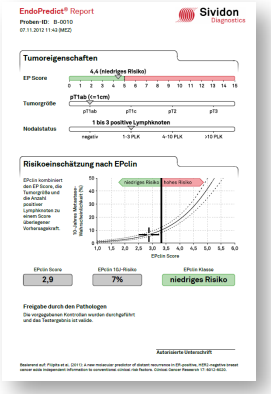


RNA isolation

EndoPredict-Test



Test result



FFPE tissue sample:
- ER +, HER2 -
- 10 µm section
- >30% tumour content (adjacent HE slide)

RNA-Isolation:
- Manually
- Automatically

- 3h for 12 samples

RT-qPCR:
- Pipetting of 96 well plates
- RT-PCR run

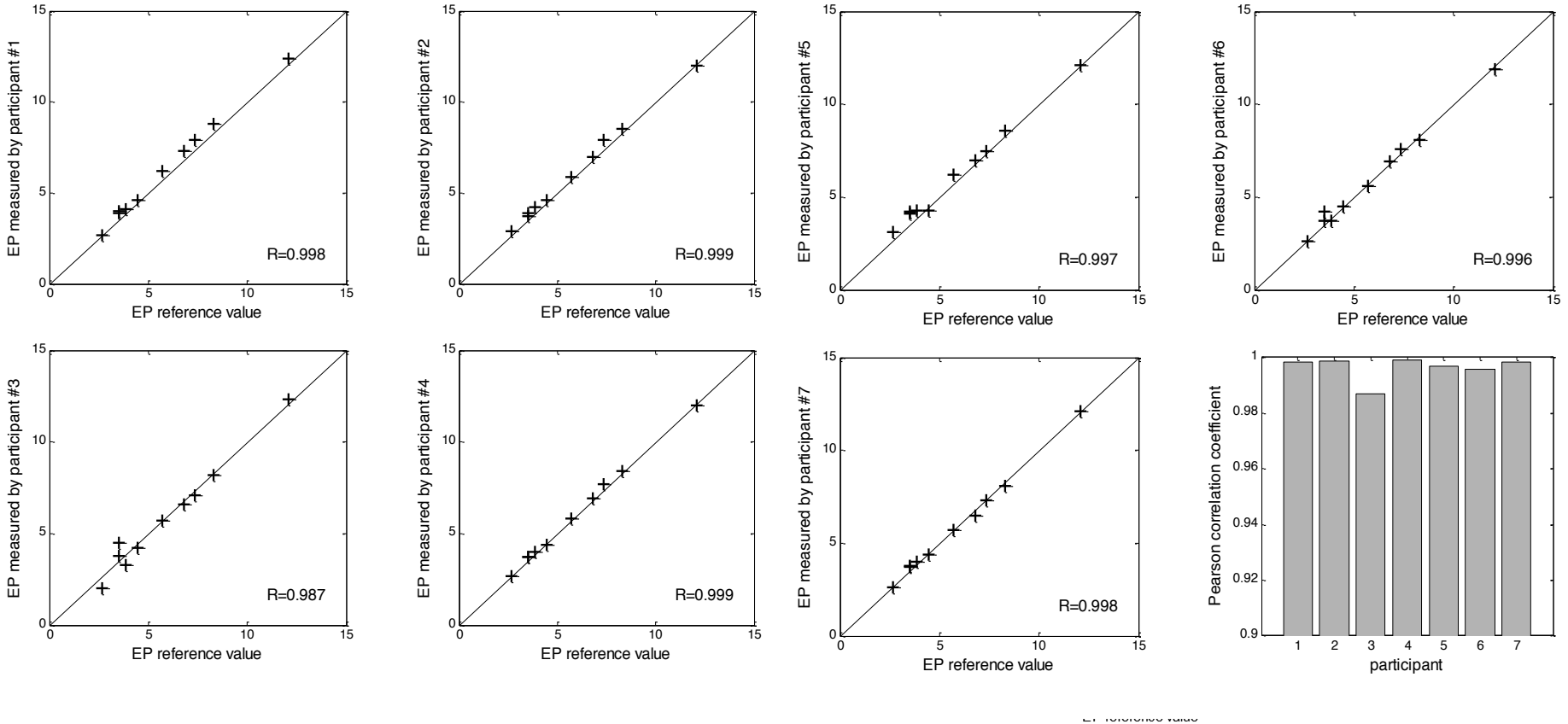
- 2h per plate

Analysis and report:
- Upload in software
- Quality control
- Print-out of report

- 15 min

„Turn-around-Time“ < 8 h

EndoPredict is a highly reproducible test
Shown in analytical verification and round robin trials



Mean value of Pearson correlation coefficients: r = 0,996

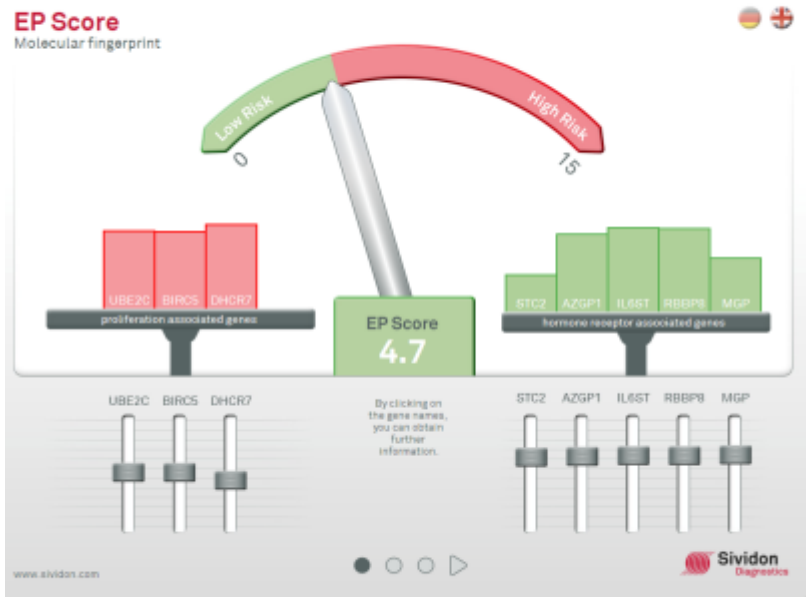
Standard deviation: EP: 1.7% ⟺ Ki67: 30% (Varga et al., 2012)

Denkert et al., 2012

ENDOPREDICT

- **Test avec un marquage CE pour le diagnostic *in vitro* → Applicable depuis le 11 Mai 2015 en France**
- **Test d'expression génique à partir d'un échantillon de tissu tumoral par RT-PCR (ARNm).**
- **Analyse de 8 gènes tumoraux identifiés dans la progression de la maladie**

1 EP Score



Source : endopredict.com

2 EPclin Score

Source : endopredict.com

Les gènes de la signature Endopredict

8 gènes cibles et 3 gènes de référence

-Gène de la Voie de signalisation estrogéno-dépendante :

AZPG1
IL6ST
MGP
RBB8
STC2

~~RE & RP~~

-Voie de la prolifération et apoptose :

BIRC5
DHCR7
UBE2C

~~KI67 HER2~~

RT-PCR

-Gènes de références : CALM2, OAZ1, RPL37A

Score génomique

	1	2	3	4	5	6	7	8	9	10	11	CQ ADN
A	AZGP1 A 20,56	BIRC5 A 27,06	OAZ1 A 22,62	DHCR7 A 26,66	IL6ST A 22,83	MGP A 20,33	CALM2 A 21,34	RBBP8 A 27,35	STC2 A 28,13	UBE2C A 26,73	RPL37A A 19,47	HBB A No Ct
B	AZGP1 A 20,72	BIRC5 A 27,14	OAZ1 A 22,94	DHCR7 A 26,62	IL6ST A 22,84	MGP A 20,58	CALM2 A 21,53	RBBP8 A 27,26	STC2 A 28,19	UBE2C A 26,68	RPL37A A 19,58	HBB A No Ct
C	AZGP1 A 20,84	BIRC5 A 27,17	OAZ1 A 22,67	DHCR7 A 26,54	IL6ST A 22,82	MGP A 20,70	CALM2 A 21,49	RBBP8 A 27,49	STC2 A 28,38	UBE2C A 26,73	RPL37A A 19,70	HBB A No Ct
CQ+	HBB POS 27,00	BIRC5 POS 26,63	OAZ1 POS 22,68	DHCR7 POS 24,29	IL6ST POS 24,08	MGP POS 25,57	CALM2 POS 21,16	RBBP8 POS 26,36	STC2 POS 24,69	UBE2C POS 24,25	RPL37A PO. 18,87	AZGP1 POS 25,81
NTC	AZGP1 NEG No Ct	BIRC5 NEG No Ct	OAZ1 NEG No Ct	DHCR7 NEG No Ct	IL6ST NEG No Ct	MGP NEG No Ct	CALM2 NEG No Ct	RBBP8 NEG No Ct	STC2 NEG No Ct	UBE2C NEG No Ct	RPL37A NE. No Ct	HBB NEG No Ct

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

Score génomique EP-score

0-15 précision de 1% (0.15)

Un algorithme à 3 variables

The EP risk score ranges from 0 to 15; higher values indicate a higher risk of recurrence.

EPclin (s_{clin}), a combined score consisting of the EP risk score and clinical parameters, was constructed from the training set:

$$s_{clin} = 0.35 \cdot t + 0.64 \cdot n + 0.28 \cdot s \qquad \text{(D)}$$

where t codes the tumor size (1: ≤1 cm, 2: >1 to ≤2 cm, 3: >2 to ≤5 cm, and 4: >5 cm) and n the nodal status

Un score Clinique **EPclin Score**

Taille Tumorale pT (1-4)

Statut ganglionnaire pN

Score génomique EP-Score (0-15)

EndoPredict Assay Design

EP Score

RT-PCR

3 Proliferation Genes
UBEC2, BIRC5, DHCR7

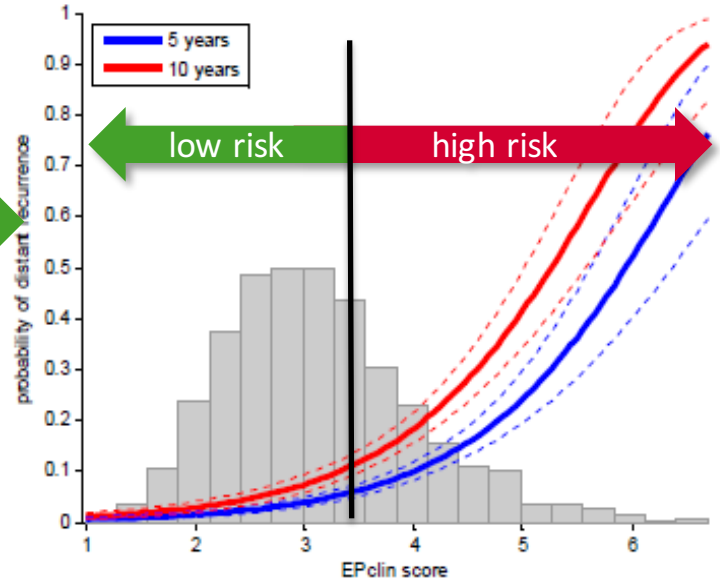
5 Hormone Receptor Genes
STC2, AZGP1, IL6ST, RBBP8, MGP

Algorithm

Nodal Status (pN)
+ Tumour Size (pT)

EPClin Score

Cutoff value:
10% distant recurrence (10y)



➔ Two risk groups
➔ Gene selection to predict 10-year outcome

Endopredict summary

Study	Patients population	References
PROGNOSTIC **more than 2000 patients**		
ABCSG 06 et 08	ER+, HER2-, pN- or pN+ Tam 5 yrs or Sequential 5 yrs	Filipits, CCR 2011
ABCSG 06 et 08	Idem but focus on late recurrences	Dubsky, BJC 2013
ATAC	ER+, HER2-, pN- or pN+, menop Tam 5 yrs or AA 5 yrs	Sestak, JNCI 2013
	Focus on late recurrence	Buus, JNCI 2016
GEICAM 9906	ER+, HER2 -, menop or not 6 FEC or 4 FEC then 6 hebdo P	Martin, BCR 2014
PREDICTION No studies…		

Retrospective studies from prospective trials LOE Ib

EP-clinic-score

62% bas risque

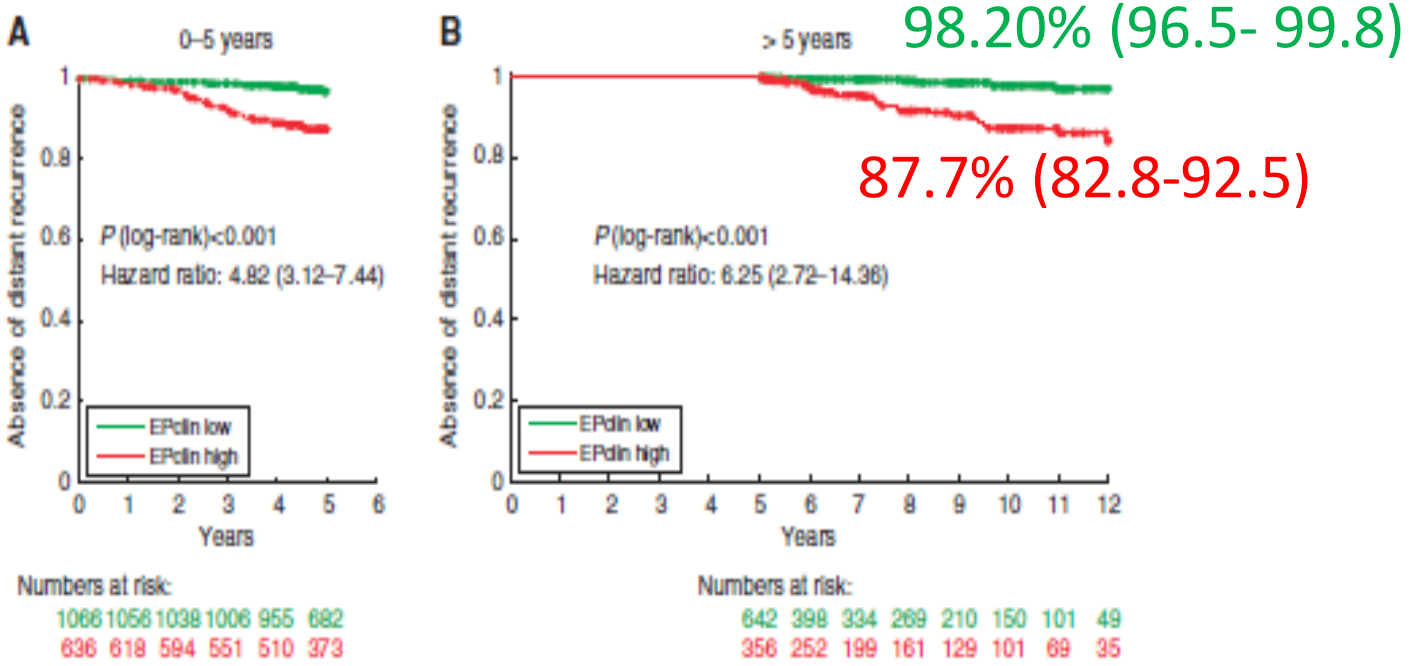


Figure 3. Kaplan–Meier plots. Kaplan–Meier plot of distant recurrence by EPclin groups between (A) 0–5 years of follow-up and (B) 5–10 years of follow-up in the combined ER+ /HER2 – cohort (ABCSG6/8, $n = 1702$). Cutoff point for EPclin was prespecified at 3.3. The numbers in parentheses indicate the 95% CI of the HR.

Allow the identification of pts with an excellent prognosis

After 5 yrs, for whom it should not be necessary to prolounge hormonal TT

For the other Hormonotherapy might not be the best TT option

Les études d’impact

ENDOPREDICT ADENDOM AT CJP

- ADENDOM study *(started January 2016)*
  - Objective

    Evaluation of the impact of the Endopredict® on treatment decision

  - Population
    - N0
    - ER+
    - HER2-

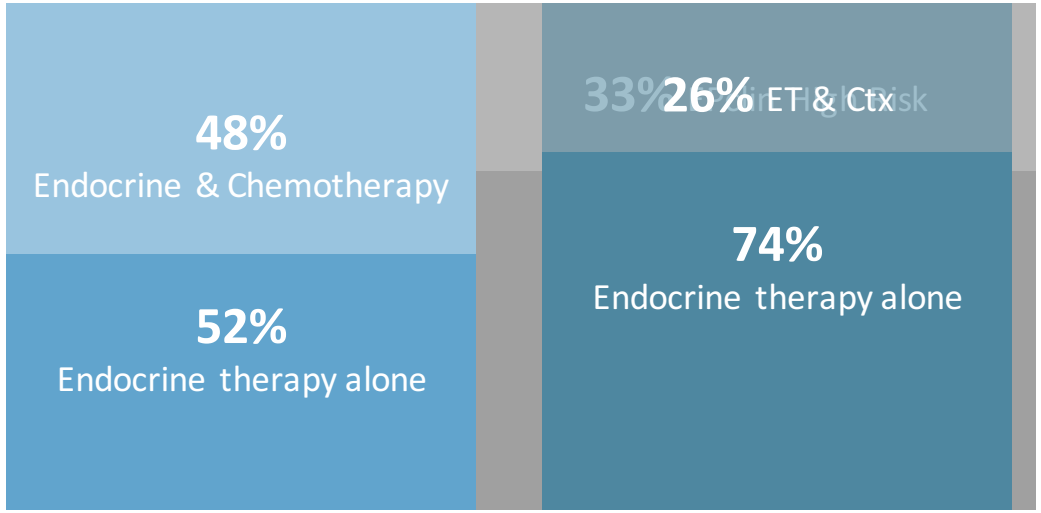
  - 202 patients tested
    - No technical failure
    - 67 pts HIGH RISK(33%)
    - 135 pts LOW RISK (67%)

Low RISK ER+/HER2- population
33% HIGH RISK

ADENDOM Study France (N=201)

9% N1mic
17% G3

EndoPredict changed therapy decisions in **35.8%** of patients



Changes in therapy aligned with test result

- EndoPredict avoided chemotherapy in 28.4% of patients
- EndoPredict resulted in additional chemotherapy in 7.5% of patients

EndoPredict Decision Impact Studies

Country/City	Berlin	Munich	Clermont-Ferrand	Brighton
Publication/ Conference	PlosOne	PlosOne	SABCS 2016	ASCO/ESMO 2017
Year	2013	2017	2016	2017
First author	Mueller et al.	Ettl et al.	Penault-Llorca et al.	Bloomfield et al
# patients	167	395	201	149
EPclin risk class				
Low risk	47%	63%	67%	50%
High risk	54%	37%	33%	50%
Nodal status				
N0	62%	77%	91%	Unknown
N+	38%	23%	9%	Unknown
Therapy Change	37.7%	43%	35.8%	36.9%
Net Reduction CT	-13.1%	-33%	-20.9%	+0.7%

- All studies resulted in a similar proportion of therapy change
- 3 out of 4 studies showed substantial reduction of chemotherapy
  - UK study: substandard presentation of result without any information about clinical characteristics of patients ➔ not comparable with other studies

Net reduction in Chemotherapy in Prospective Recurrence Score® Utility Studies

Multigene assay / country	Study design	Number of patients	Net reduction of chemotherapy use in the study*
Oncotype DX Breast Recurrence Score® Test / EU Meta-Analysis [1]	Meta-analysis, prospective, multicenter	527	**–21 %**
Oncotype DX Breast Recurrence Score Test / Germany [2]	Prospective, multicenter	366	**–33 %**
Oncotype DX Breast Recurrence Score Test / Switzerland [3]	Prospective, multicenter	222	**–13 %**

** in the total study population*

1. Albanell et al, EJC 2016; 2. Eiermann et al, Annals Oncol 2012; 3. Pestalozzi et al, BMC Cancer 2017; 4. Bloomfield et al. ASCO 2017 abstr e12002

Expérience du Centre Jean Perrin et d’autres CLCC

ENDOPREDICT CJP UNIRAD study

- UNIRAD study *(started, June 2015 ➔ 2019)*
  - Objective

Evaluation of DFS benefit at 2 years of Afinitor® after a standard treatment in ER+ HER2- negative EBC

  - Population
    - Invasive early breast cancer (any T)
    - Primary surgery
    - ER+
    - HER2-
    - **<u>EP clin score ≥ 3.3</u>**

  - 434 patients tested
    - No technical failure
    - **373 pts HIGH RISK (86%)**
    - **61 pts LOW RISK (14%)**

High RISK ER+ HER2- population
➔86% HIGH RISK

ENDOPREDICT au CJP depuis le RIHN

En global :

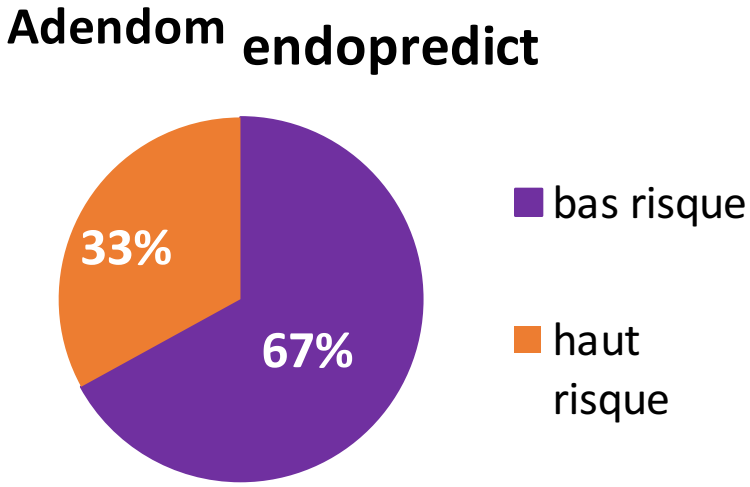
- Nbr de cas : 432
- Risque Elevé :246 cas soit 57%
- Risque Faible : 186 cas soit 43%

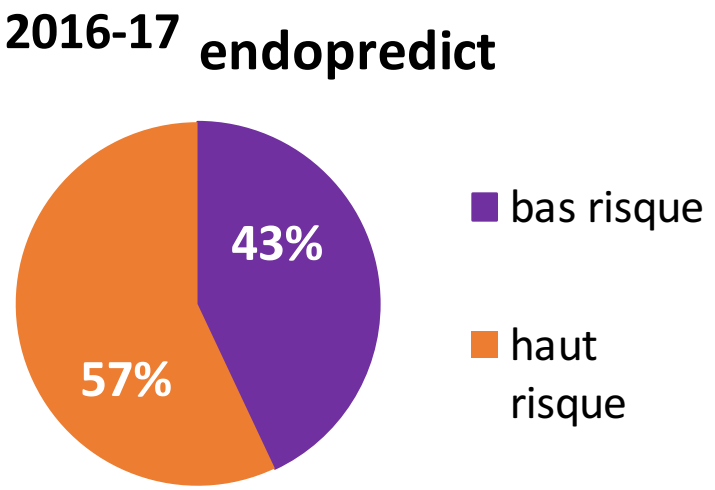
En 2016:

- Nbr de cas : 176
- Risque Elevé : 88 cas soit 50%
- Risque Faible : 88 cas soit 50%

2017 (dec-septembre):

- Nbr de cas :256
- Risque Elevé :158 cas soit 62%
- Risque Faible : 98 cas soit 38%





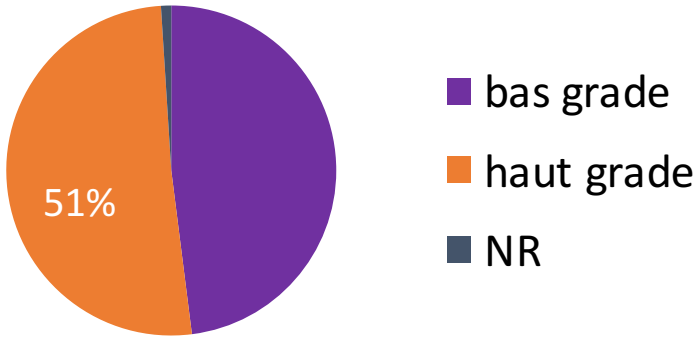
Au CJP
Mai à décembre 2017
317 tests

	N = 317	%
Mean Age	58 yrs [29-91]	
Menopausal		
Yes	43	75%
No	14	25%
Unknown	260	
pT1	14	5%
pT1ab	34	11%
pT1c	147	**48%**
pT2	95	**31%**
pT3	12	4%
pT4	1	0%
pN0	213	**73%**
pN1	77	**26%**
pN2	1	0%
unknown	26	
SBR Grade 1	45	15%
SBR Grade 2	243	**78%**
SBR Grade 3	23	7%
NC	6	
ER (IHC)	Mean % of + cells = 94% [56-100]	100% positive
NC	N = 61 (19%)	
PR (IHC)	Mean % of + cells = 70% [0-100]	93% positive (≥10)
NC	N = 82 (26%)	
Proliferation (**Ki67** / % IHC)	Mean = 18% [1-50]	142 ≥ 15% (64%)
NC	N = 96 (30%)	**105 ≥ 20% (48%)**

CJP : Mai à décembre 2017: 317 tests

endopredict

Données nationales 2016

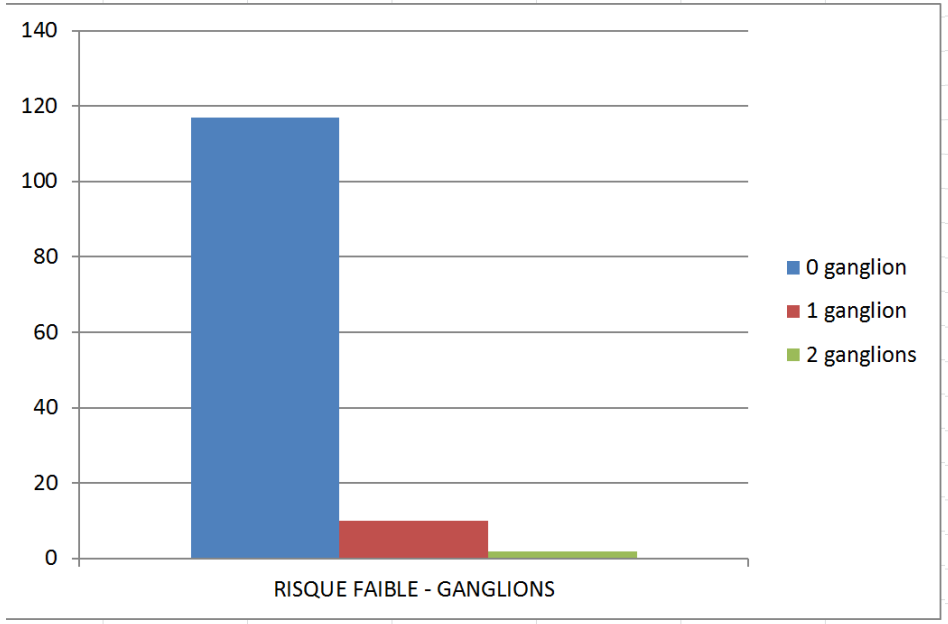


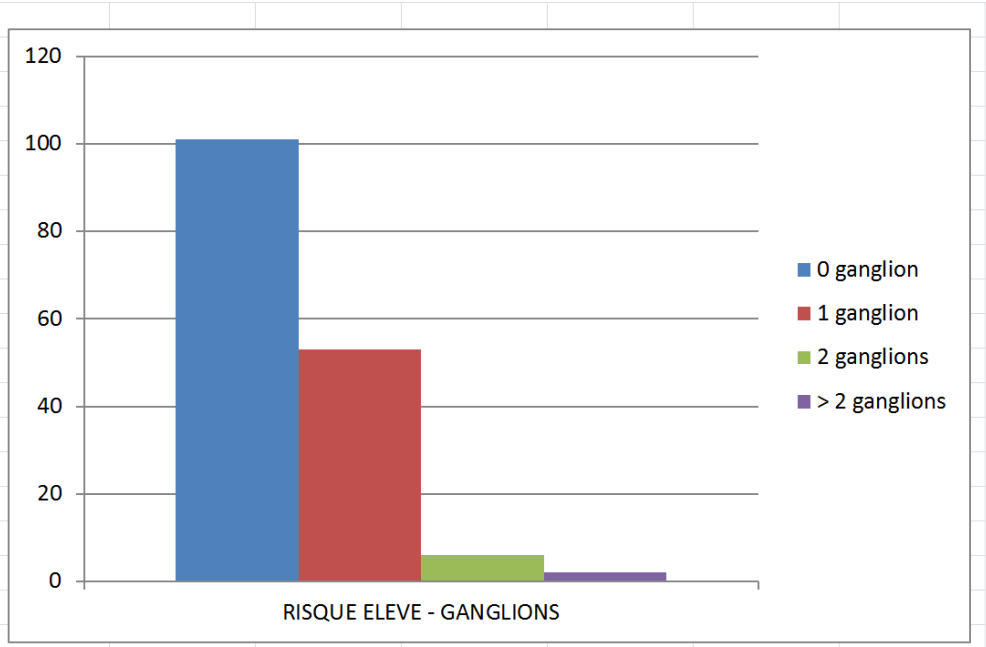
CRITERIA		Threshold
SCORE Mean ET	3,54 0,65	3,3
10 years risk of reccurence mean ET	14,3% [3-51] 8,7%	10%
EP CLIN **Low** **High** **ND**	**147** **167** **3**	**47%** **53%**

Endopredict: sur 294 cas : 165 HR soit 56%

- 70N+ soit 23.8%, dont ➔22 mi
- **Nb de cas entre 3.2 et 3.4** : 41 dont 8N+ parmi lesquels 4mi
- **Nb de cas entre 3.1 et 3.5** : 80 dont 15N+ parmi lesquels 8mi

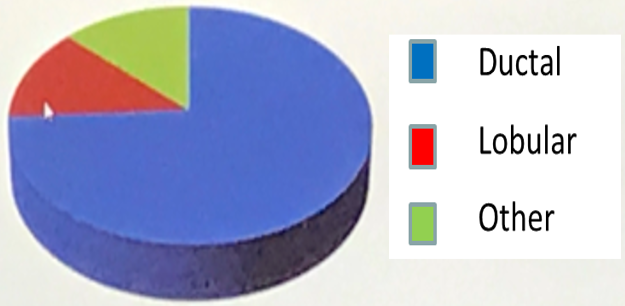
Expérience CJP





Types histologiques des cas testés avec Endopredict

TOTAL N = 69 patientes



Données Institut Curie
A Vincent-Salomon SFSPM 2017

56/44

Corrélations anatomo-cliniques ENDOPREDICT 2017

Critères		RISQUE FAIBLE N = 39 patientes		RISQUE ELEVE N = 30 patientes	
Taille	pT1	30	77	21	70
	pT2	9	23	9	30
Grade	I	6	15,4	1	3,3
	II	30	77	23	76,7
	III	3	7,6	6	20
Index mitotique	faible	28	71,8	14	46,7
	modéré	10	25,7	9	30
	fort	1	2,5	7	23,3
Emboles	Absence	30	77	25	83,3
	Présence	9	23	5	16,7
Classification moléculaire en IHC	luminal A	24	61,5	10	33,3
	luminal B	15	38,5	20	66,7

Résultats des tests Endopredict

	Nb patientes	%	
Risque faible	39	56%	
Risque élevé	30	44%	⇨ Prescription de chimiothérapie

IGR Experience (Endopredict)

M Lacroix-Triki SFSPM November 2017

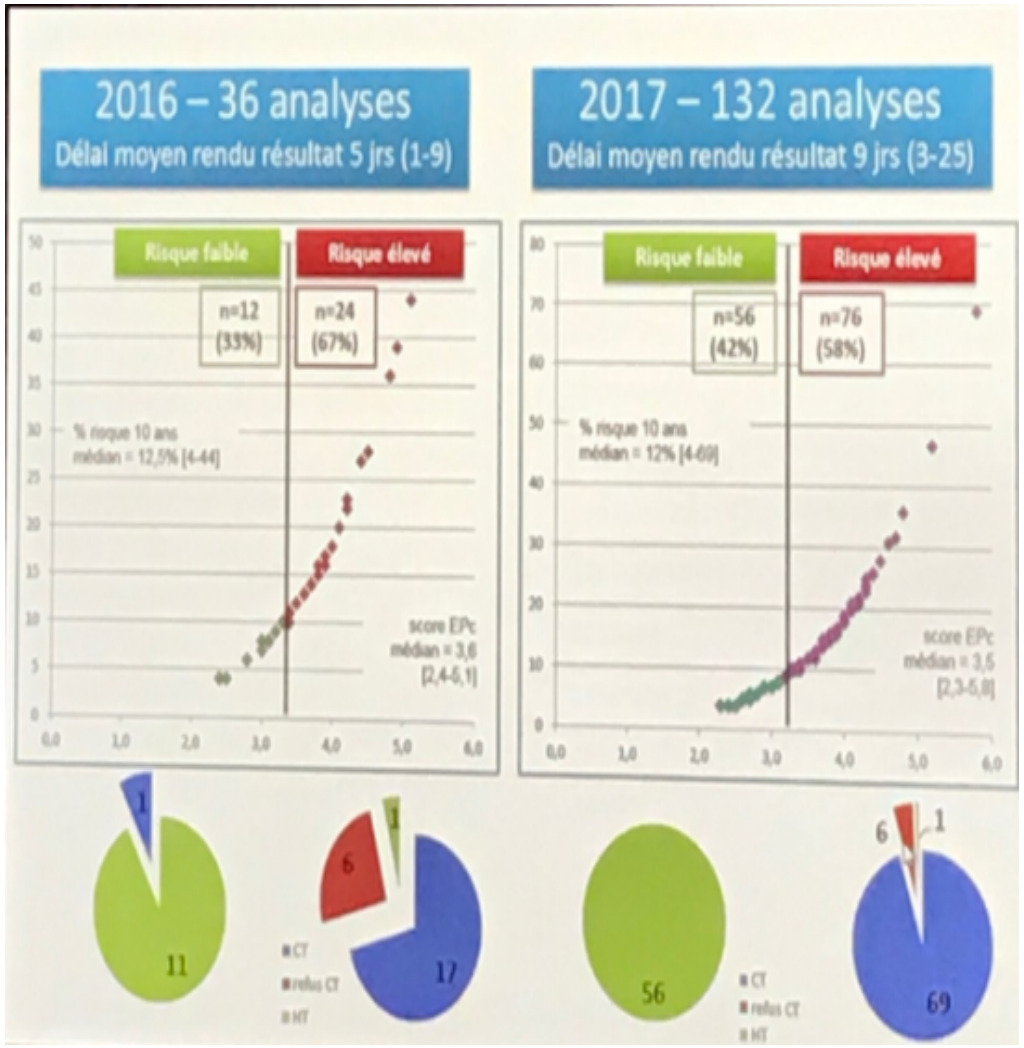
168 patients

65% postmeno

pT1c – pT2 (>90%)

pN0 (>70%)

grade II/III (>90%)



33/67%

2016 : Average Time to results 5 days (1 to 9)
36 cases (Median risk at 10 years : 12,5 %)
Median EPclin score : 3,6 (2,4 – 5,1)
➔ **Chemo : 67% ;**
6 patients refused chemo, 1 HT

42/58%

2017 : Average to results 9 days (3 to 25)
132 cases (Median risk at 10 years : 12 %)
Median EPclin score : 3,5 (2,3 – 5,8)
➔ **Chemo : 58% ;**
6 patients refused chemo, 1 HT

Conclusion

Conclusions

- Test bien implanté et simple à réaliser
- Toujours interpréter avec les données de EP Score et EP clin et discuter les cas proches de la cut off
- Importance de constituer des registres
- Incertitudes quant au financement RIHN et aux modalités « déclaration par le centre prescripteur ».

Critères de vraie vie pour utilisation Endopredict in RIHN : COHORTE

- Cancer du sein invasif ER + (ER≥ 10% par IHC), HER2- (0, 1+, ou ni non amplifié ni équivoque par FISH) pT1b / c, pT2, pN0 - pN1mique, pN1 (1 à 3 N)
  - Avec: PR <20%
  - ou luminal de grade 1 à 2 avec Ki67> 10% ou index mitotique (IM) 2 à 3
  - ou grade luminal 3 avec Ki67 <30% ou score IM 1 à 2

- En dehors de ces situations le test peut être prescrit après des discussions en RCP en particulier pour les femmes préménopausées ou pour décider d'une prolongation du traitement hormonal après 5 ans
- Un registre national est en place

	EndoPredict	Oncotype DX	MammaPrint	Prosigna
Manufacturer	myriad WHEN DECISIONS MATTER	Genomic Health LIFE. CHANGING.	agendia	nanoString TECHNOLOGIES
Launch	2011	2004	2005	2013
Test generation	2nd	1st	1st	2nd
Assay Platform	RT-qPCR	RT-qPCR	Microarray	nCounter
Type of tissue	FFPE	FFPE	FFPE / fresh	FFPE
Molecular analysis	12-Gene Molecular Score	21-Gene Assay	70-Gene Assay	50-Gene Assay
Indications	Prognostic ER+, HER2- N0/N+	Prognostic ER+, HER2-; N0/N+	Prognostic stage I-II; N0/N1-3; <5cm; ER+ or ER-; HER2- or HER2+	Prognostic postmenopausal stage I-II; ER+ N0/N+
Clinical Parameters	Yes (T + N)	No	No	Yes (T)
Results	10-year risk of recurrence	10-year risk of recurrence; benefit of chemo	5-year risk of recurrence; benefit of chemo	10-year risk of recurrence
Late Metastasis	Yes	No	No	Yes
Added value to Ki67	Yes	No	No	Yes
Risk categories	Low, high	Low, intermediate, high	Low, high	Low, intermediate, high
Guidelines	ESMO, St. Gallen, ASCO, EGMT, AGO	ESMO, St. Gallen, ASCO, EGMT, AGO, NCCN	ESMO, St. Gallen, ASCO, EGMT, AGO	ESMO, St. Gallen, ASCO, EGMT, AGO
Notable Cohort(s)	TransATAC, ABCSG6&8	NSABP B-20, SWOG8814, TAILORx, TransATAC	MINDACT	TransATAC, ABCSG8
Prospective Trials	UNIRAD (ongoing) RESCUE (ongoing)	TaILORx (low risk gr, 5y)	MINDACT (5y)	OPTIMA (ongoing)
CE-IVD marked	yes	No	Yes	Yes
FDA cleared	no	no	yes	yes