QUELLE ORGANISATION POUR LES ANALYSES GENOMIQUES DANS LE CANCER BRONCHIQUE ?

The French model

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Marseille, France

DISCLOSURE SLIDE

- Honoraria from Astra-Zeneca, Bristol Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann – La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer.

Agenda

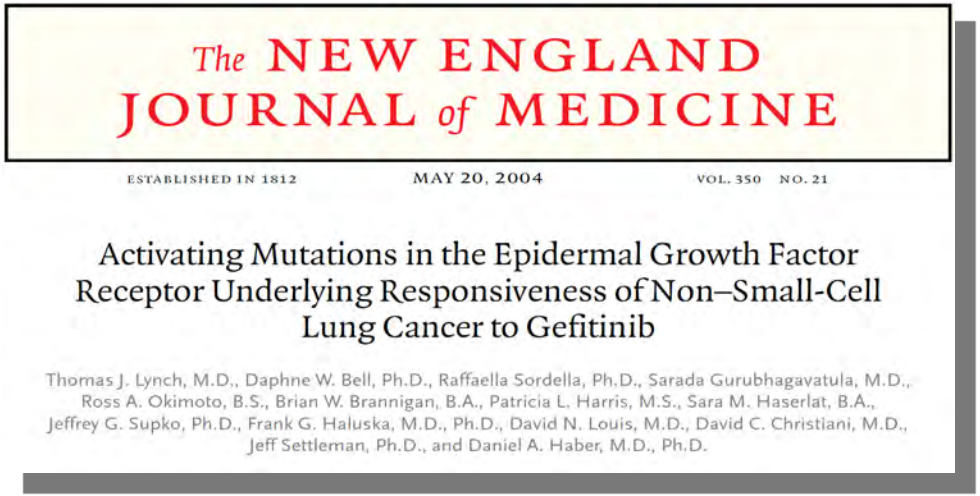
- **Une décade d'innovations**
- **Difficile de rester leader**
- **France Medecine Genomique 2025**
- **Quels défis à surmonter ?**

Agenda

- **Une décade d'innovations**
- **Difficile de rester leader**
- **France Medecine Genomique 2025**
- **Quels défis à surmonter ?**

Background

- **2004**, the advent of actionable molecular alteration in lung cancer



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Lynch T et al, NEJM 2004

The first steps

- **2006**: The French Genetic Centers Network
- Leaded by:
  - **DGOS (Health Ministery)**
  - **INCa (French NCI)**

The first steps

- **2006**: The French Genetic Centers Network
- **Biomarkers assesment for …**
  - Prediction (targeted therapies)
  - Diagnosis
  - Prognostic
  - Residual disease
- **Daily practice**

The first steps

- **2006**: The French Genetic Centers Network
- **Link with research activities**
  - Translational research
  - Clinical trials
    - National Cancer Institute (USA)
    - Drugs Companies

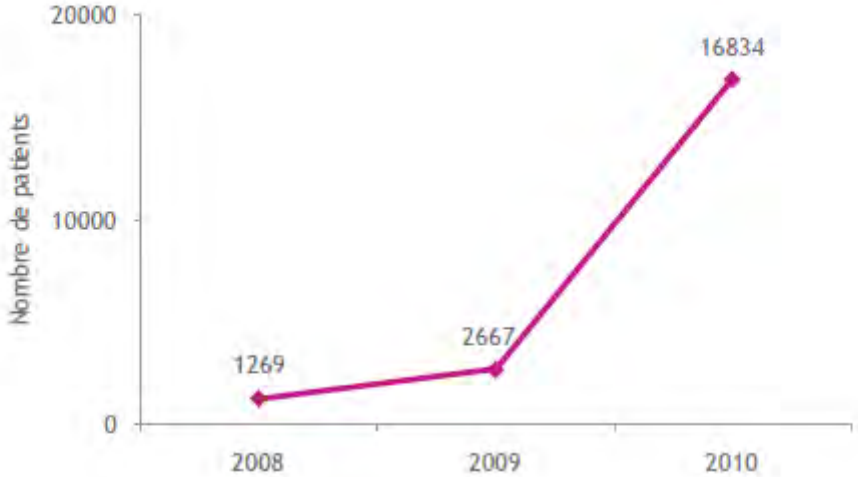
The first steps

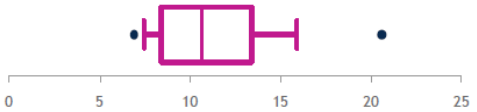
- **2006**: The French Genetic Centers Network
- **Initial Financial Investment (French NCI)**
  - Equipment: **4.7 M€**
  - Recruitment (non MD): **4.0 M€**

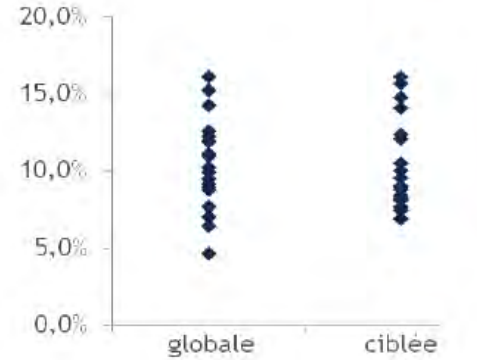
The first steps

- **2008-2009: The time of success**

Évolution du nombre de recherches de mutations de l'*EGFR* dans le cancer du poumon





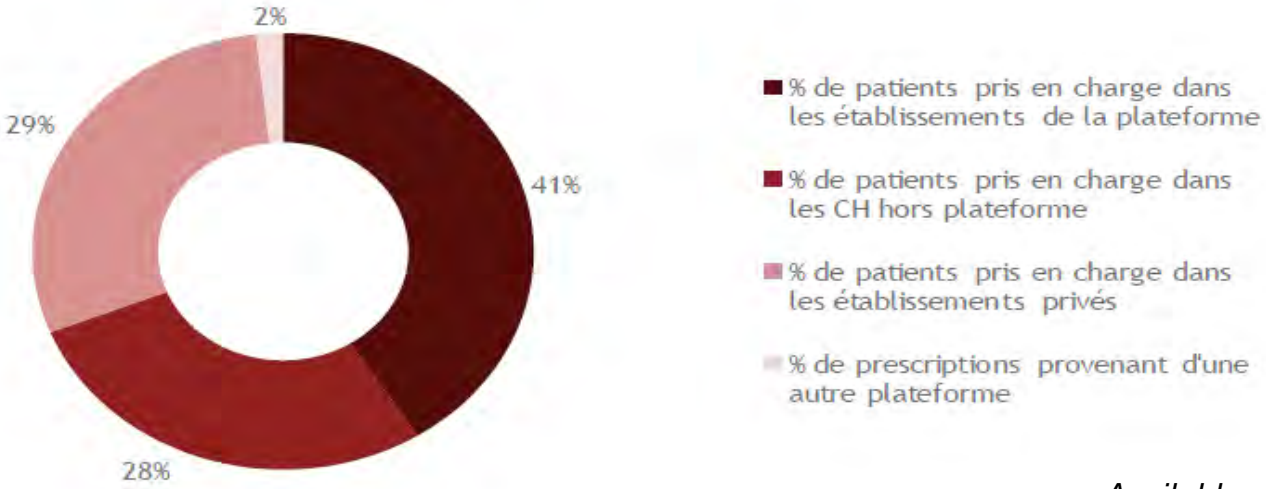


Available at www.e-cancer.fr

The first steps

- **2008-2009: The time of success**

Origine des prescriptions pour la recherche de mutations *EGFR* dans le cancer du poumon (%)



The first steps

- **2008-2009: Quality insurance procedures**
  - Guidelines for molecular alterations assessement in solid tumors

Available at www.e-cancer.fr

The first steps

- **2009: a continuous political support**

Mesure 21

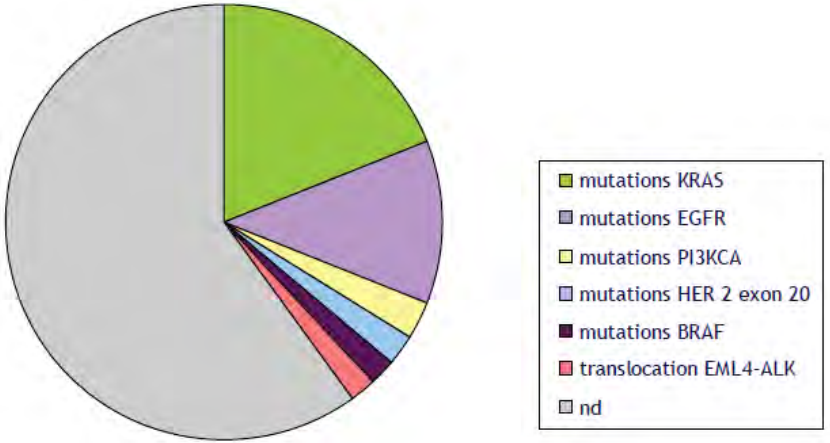
Garantir un égal accès aux traitements et aux innovations.*

action 21.2 : Développer les plateformes de génétique moléculaire des cancers et l'accès aux tests moléculaires.

* *Guarante an equal access to treatments and innovations*

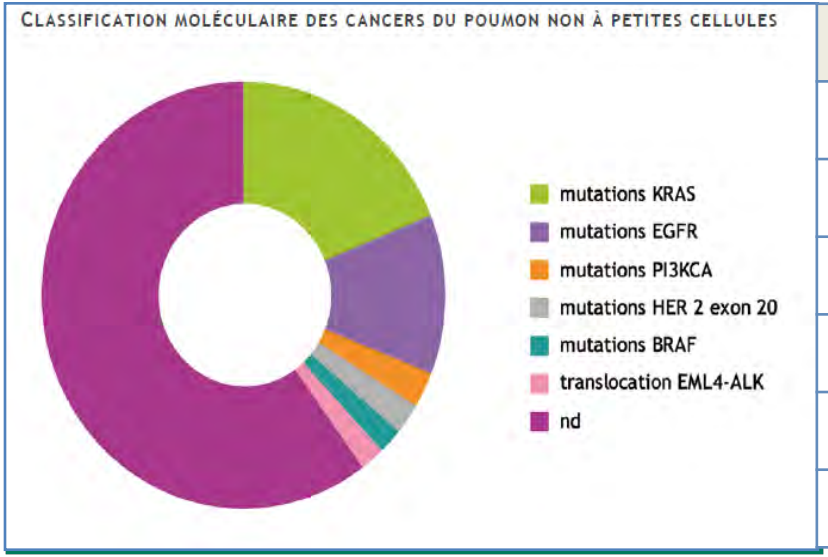
The teens

- **2010**: Increased number of tested genes
  - Anticipate future practices
  - Improve the French participation in clinical trials



The teens

- **2011**: France ahead, on one hand …



Mutation	n	+	Rate (%)
EGFR act. & res.	20761	2009	9.6
KRAS	17153	4358	25.4
BRAF	10017	184	1.8
*EML4/ALK**	4543	208	4.6
Pi3KCA	5329	111	2.1
HER2 Ex. 20	7731	69	0.9

Available at www.e-cancer.fr

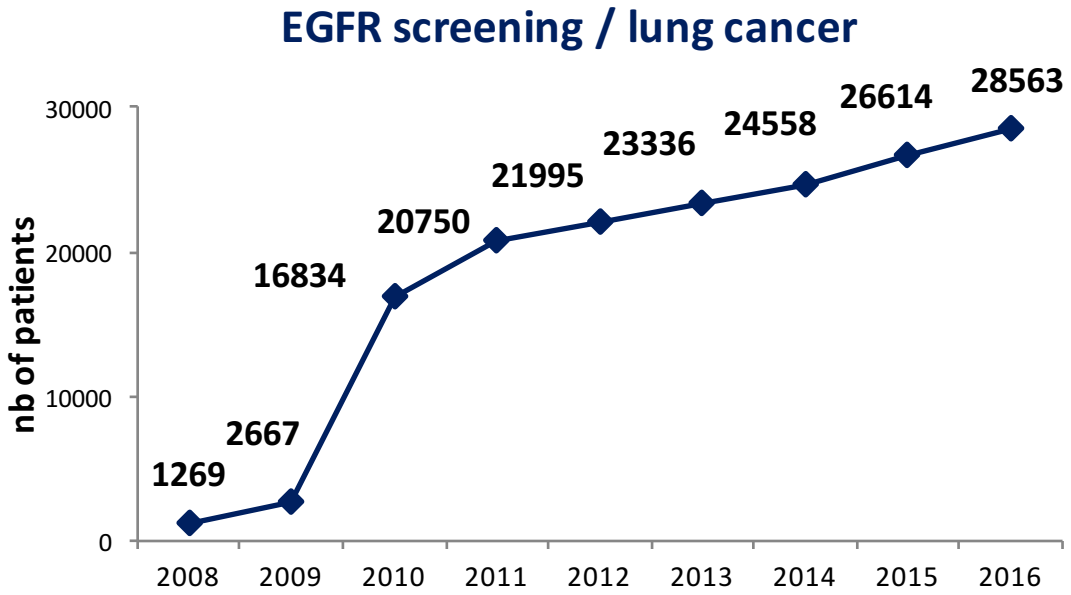
The teens

- **2006-12, a #22 millions Euros investissement**

Plateforme	Estomac	Mélanome	Colorectal		Poumon		TOTAL
	HER2	BRAF	MSI	KRAS	EGFR	ALK	
CHU-CLCC de Strasbourg ; CH de Colmar ; CH de Mulhouse	2 000 €	6 500 €	27 000 €	60 000 €	80 500 €	34 000 €	546 000 €
CHU-CLCC de Bordeaux	3 500 €	29 500 €	232 000 €	140 000 €	235 000 €	99 000 €	1 505 500 €
CHU-CLCC de Clermont-Ferrand	2 000 €	9 500 €	5 000 €	59 000 €	78 500 €	33 000 €	464 500 €
CHU-CLCC de Caen	4 000 €	5 500 €	3 500 €	47 000 €	55 500 €	23 500 €	348 000 €
CHU-CLCC de Dijon	2 000 €	8 500 €	17 000 €	65 000 €	100 000 €	41 000 €	557 000 €
CHU de Brest	12 500 €	9 500 €	16 000 €	25 000 €	74 000 €	31 000 €	411 500 €
CHU-CLCC de Rennes		18 500 €	34 000 €	118 000 €	201 000 €	84 500 €	954 333 €
CHRU de Tours ; CH d'Orléans		7 500 €	30 000 €	81 000 e	83 500 €	35 000 €	451 000 €
CHU-CLCC de Reims		8 000 €	18 000 €	47 000 €	65 000 €	25 500 €	369 500 €
CHU de Besançon		6 000 €	22 000 €	40 000 €	61 500 €	26 000 €	410 500 €
CHU-CLCC de Rouen		11 500 €	38 000 €	85 000 €	97 500 €	41 000 €	578 000 €
AP-HP	5 000 €	54 000 €	198 000 €	405 000 €	544 500 €	229 000 €	4 109 500 €
Institut Curie ; CLCC de Saint-Cloud ; CH de Versailles	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL	49 000 €	370 500 €	824 000 €	2 575 000 €	3 369 500 €	1 381 500 €	21 973 000 €
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CHRU-CLCC de Lille		14 500 €	40 000 e	178 500 €	183 000 €	77 000 €	1 599 333 €
CHU-CLCC de Marseille	4 000 €	19 500 €	21 000 €	138 500 €	236 500 €	99 500 €	1 151 500 €
CHU-CLCC de Nice		15 000 €	6 000 €	76 500 €	68 500 €	29 000 €	492 500 €
CLCC d'Angers		11 500 €	8 000 €	80 000 €	49 000 €	20 500 €	352 500 €
CHU-CLCC de Nantes	2 500 €	26 500 €	46 000 €	57 000 €	102 000 €	43 000 e	598 000 €
CHU d'Amiens			31 000 €	75 000 e	71 500 €		457 000 €
CHU de Poitiers		5 000 €	28 000 €	80 000 €	83 000 €	35 000 €	510 000 €
CHU de Grenoble		4 500 €	4 000 €	40 000 €	95 000 €	40 000 €	438 500 €
CHU-CLCC de Lyon	4 000 €	25 500 €	80 000 €	138 500 €	161 000 €	68 000 €	1 189 500 €
CHU de Saint-Etienne		6 500 €	3 000 €	35 500 €	30 000 €	13 000 e	222 000 €
TOTAL	49 000 €	370 500 €	824 000 €	2 575 000 €	3 369 500 €	1 381 500 €	21 973 000 €

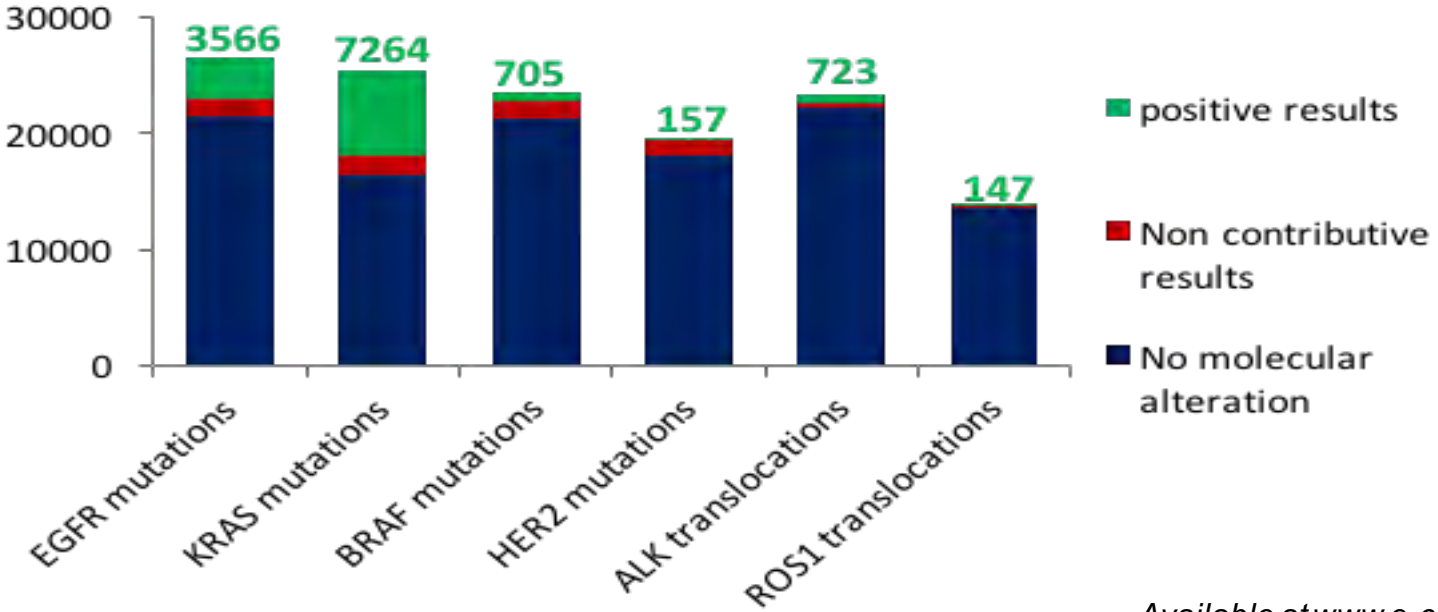
The teens

- **Analyses per year: Ex. *EGFR* (act. & resist.)**



The teens

- **Analyses for Lung Cancer pts in 2016**



Available at www.e-cancer.fr

The teens

- **Analyses per year: >125,000 (2016)**

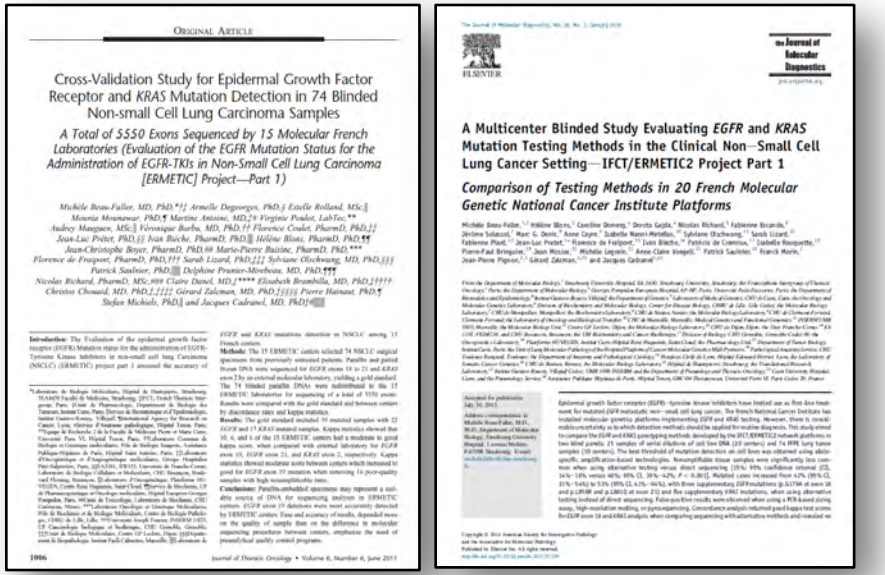
Biomarker	Cancer type	Targeted therapies	#Patients
***KIT* mutations**	GIST	Imatinib	**1 218**
***HER2* amplification**	Breast and gastric cancers	Trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine	**10 832 (B)** **770 (G)**
***RAS* mutations**	Colorectal cancer	Panitumumab, cetuximab	**21 923**
***EGFR* mutations**	Lung cancer	Gefitinib, erlotinib, afatinib, osimertinib	**28 563**
***ALK* translocations**	Lung cancer	Crizotinib, ceritinib, alectinib	**23 434**
ROS1 translocations	Lung cancer	Crizotinib	**17 680**
***BRAF*V600 mutation**	Melanoma	Vemurafenib, dabrafenib, trametinib, cobimetinib	**5 583**
***BCR-ABL* translocation**	Chronic Myeloid Leukaemia/ Acute Lymphoblastic Leukaemia	Imatinib, nilotinib, dasatinib, ponatinib, bosutinib	**9 570**
17p deletion / *TP53* mutation	Chronic Lymphocytic Leukaemia	Ibrutinib, idelalisib	**2 857** **1 808**
***BRCA* mutation**	Ovarian cancer	Olaparib	**1 608**

The teens

- **Both internal and external quality control programs**
  - Mutations EGFR / Lung cancer
  - Mutations KRAS / Colon cancer
  - BCR-ABL / CML
- **ISO15189 certified**

The teens

- **Both internal and external quality control programs**
  - Academic initiatives



ORIGINAL ARTICLE

Cross-Validation Study for Epidermal Growth Factor Receptor and *KRAS* Mutation Detection in 74 Blinded Non-small Cell Lung Carcinoma Samples

A Total of 5550 Exons Sequenced by 15 Molecular French Laboratories (Evaluation of the EGFR Mutation Status for the Administration of EGFR-TKIs in Non-Small Cell Lung Carcinoma [ERMETIC] Project—Part 1)

Michèle Beau-Faller, MD, PhD,*†‡ Armelle Degeorges, PhD,§ Estelle Rolland, MSc,‖ Mounia Mounawar, PhD,¶ Martine Antoine, MD,?# Virginie Poulot, LabTec,** Audrey Maugeon, MSc,‖ Véronique Barbu, MD, PhD,†† Florence Coulet, PharmD, PhD,‡‡ Jean-Luc Prétet, PhD,§§ Ivan Bièche, PharmD, PhD,‖ Hélène Blons, PharmD, PhD,¶¶ Jean-Christophe Beyer, PharmD, PhD,## Marie-Pierre Buzinne, PharmD, PhD,*** Florence de Fraipont, PharmD, PhD,††† Sarah Lizard, PhD,‡‡‡ Sylviane Olschwang, MD, PhD,§§§ Patrick Saulnier, PhD,‖ Delphine Prunier-Mirebeau, MD, PhD,¶¶¶ Nicolas Richard, PharmD, MSc,### Claire Danel, MD,†**** Elisabeth Brambilla, MD, PhD,‡†††† Christos Chouaid, MD, PhD,‡‡‡‡ Gérard Zalcman, MD, PhD,‡§§§§ Pierre Hainaut, PhD,¶ Stefan Michiels, PhD,‖ and Jacques Cadranel, MD, PhD†#‖

Introduction: The Evaluation of the epidermal growth factor receptor (EGFR) Mutation status for the administration of EGFR-Tyrosine Kinase Inhibitors in non-small cell lung Carcinoma (NSCLC) (ERMETIC) project part 1 assessed the accuracy of *EGFR* and *KRAS* mutations detection in NSCLC among 15 French centers.

Methods: The 15 ERMETIC centers selected 74 NSCLC surgical specimens from previously untreated patients. Paraffin and paired frozen DNA were sequenced for *EGFR* exons 18 to 21 and *KRAS* exon 2 by an external molecular laboratory, yielding a gold standard. The 74 blinded paraffin DNAs were redistributed to the 15 ERMETIC laboratories for sequencing of a total of 5550 exons. Results were compared with the gold standard and between centers by discordance rates and kappa statistics.

Results: The gold standard included 39 mutated samples with 22 *EGFR* and 17 *KRAS* mutated samples. Kappa statistics showed that 10, 6, and 6 of the 15 ERMETIC centers had a moderate to good kappa score, when compared with external laboratory for *EGFR* exon 19, *EGFR* exon 21, and *KRAS* exon 2, respectively. Kappa statistics showed moderate scores between centers which increased to good for *EGFR* exon 19 mutation when removing 14 poor-quality samples with high nonamplifiable rates.

Conclusions: Paraffin-embedded specimens may represent a suitable source of DNA for sequencing analyses in ERMETIC centers. *EGFR* exon 19 deletions were most accurately detected by ERMETIC centers. Time and accuracy of results, depended more on the quality of sample than on the difference in molecular sequencing procedures between centers, emphasize the need of preanalytical quality control programs.

ELSEVIER

The Journal of Molecular Diagnostics

jmd.amjpathol.org

A Multicenter Blinded Study Evaluating *EGFR* and *KRAS* Mutation Testing Methods in the Clinical Non–Small Cell Lung Cancer Setting—IFCT/ERMETIC2 Project Part 1

Comparison of Testing Methods in 20 French Molecular Genetic National Cancer Institute Platforms

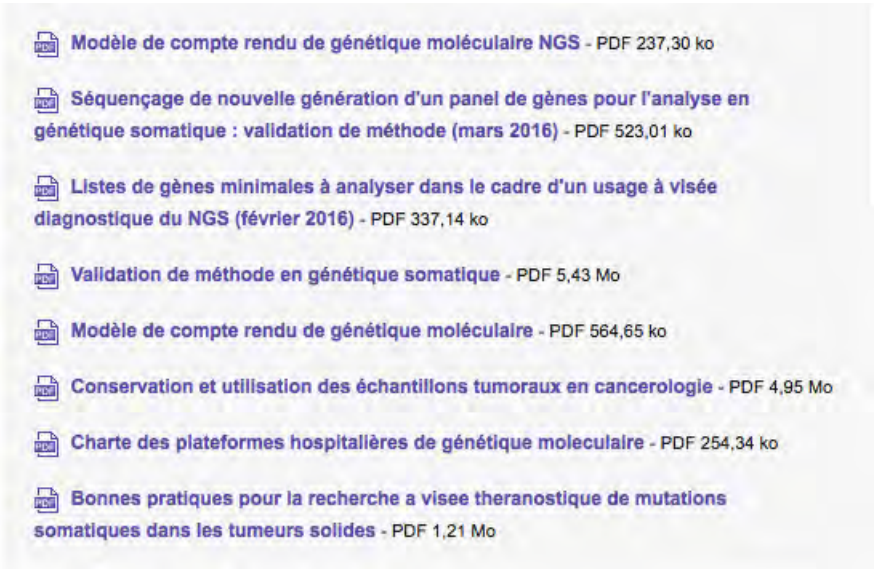
Michèle Beau-Faller,[1,2] Hélène Blons,[3] Caroline Domeng,[4] Dorota Gajda,[5] Nicolas Richard,[6] Fabienne Escande,[7] Jérôme Solassol,[8] Marc G. Denis,[9] Anne Cayre,[9] Isabelle Nanni-Metellus,[10] Sylviane Olschwang,[11] Sarah Lizard,[12] Fabienne Plard,[13] Jean-Luc Pretet,[14] Florence de Fraipont,[15] Ivan Bièche,[16] Patricia de Cremoux,[17] Isabelle Rouquette,[18] Pierre-Paul Bringuier,[19] Jean Mosse,[20] Michèle Laurin,[21] Anne-Claire Voegeli,[22] Patrick Saulnier,[23] Franck Morin,[1] Jean-Pierre Pignon,[24] Gérard Zalcman,[25,26] and Jacques Cadranel[27,28]

Epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors have limited use as first-line treatment for mutated *EGFR* metastatic non–small cell lung cancer. The French National Cancer Institute has installed molecular genetics platforms implementing *EGFR* and *KRAS* testing. However, there is considerable uncertainty as to which detection methods should be applied for routine diagnosis. This study aimed to compare the *EGFR* and *KRAS* genotyping methods developed by the IFCT/ERMETIC2 network platforms in two blind panels: 25 samples of serial dilutions of cell line DNA (20 centers) and 74 FFPE lung tumor samples (10 centers). The best threshold of mutation detection on cell lines was obtained using allele-specific amplification–based technologies. Nonamplifiable tissue samples were significantly less common when using alternative testing versus direct sequencing [35%; 95% confidence interval (CI), 14%–58% versus 46%; 95% CI, 35%–62%; $P < 0.001$]. Mutated cases increased from 42% (95% CI, 31%–54%) to 53% (95% CI, 41%–66%), with three supplementary *EGFR* mutations (p.L858R at exon 18 and p.L861R and p.L861Q at exon 21) and five supplementary *KRAS* mutations, when using alternative testing instead of direct sequencing. False-positive results were observed when using a PCR-based sizing assay, high-resolution melting, or pyrosequencing. Concordance analysis returned good kappa test scores for *EGFR* exon 18 and *KRAS* analysis when comparing sequencing with alternative methods and revealed no

Beau-Faller et al, J Thorac Oncol 2011; Beau-Faller et al, J Mol Diagn 2014

The teens

- **Guidelines**



- ✓ **Methodological validation of new techniques**
- ✓ **Minimal list of genes to be assessed**
- ✓ **Analyses' Reports**
- ✓ **Samples storage**

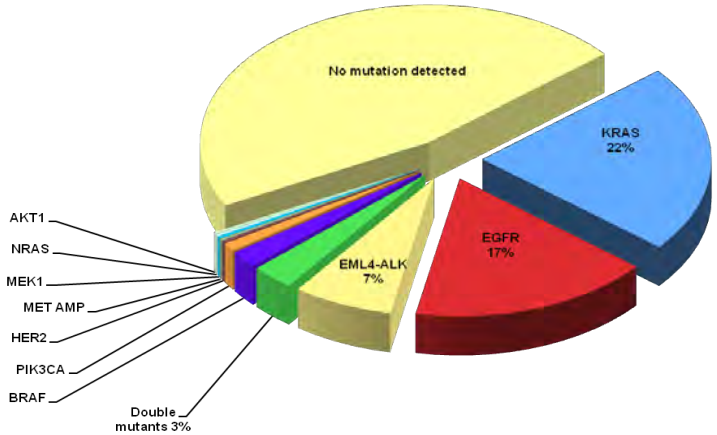
Available at www.e-cancer.fr

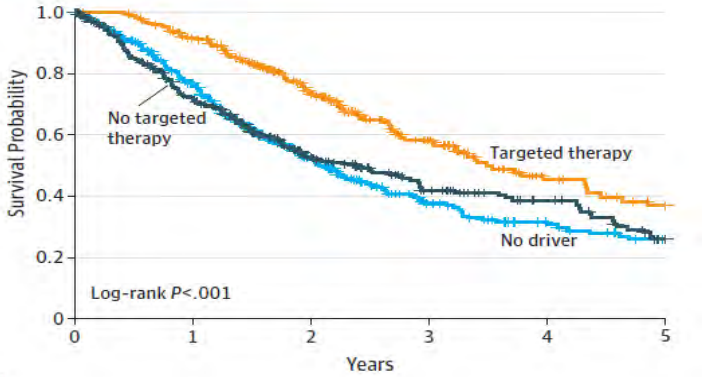
Agenda

- Une décade d’innovations
- **Difficile de rester leader**
- France Medecine Genomique 2025
- Quels défis à surmonter ?

The teens

- **2011**: France in late, on the other hand …
  - Patients' outcomes unknown
  - Conversely to other experiences



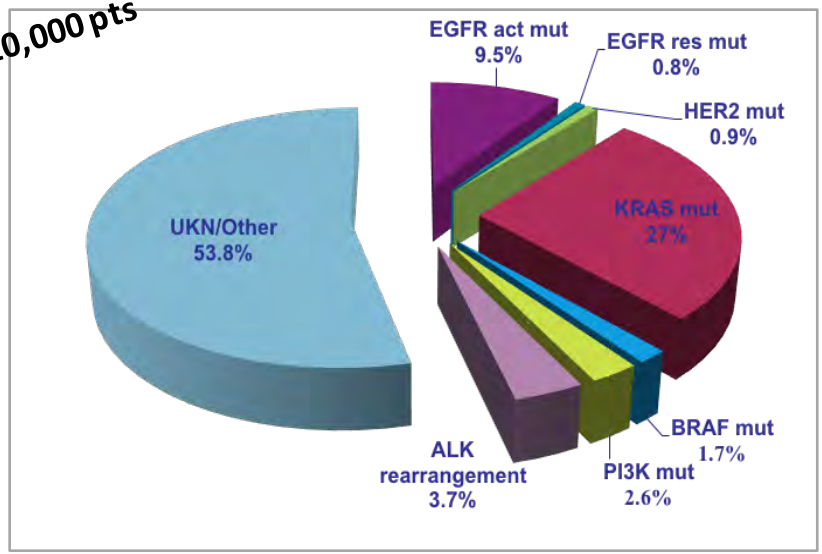


Kris MG et al, ASCO 2011

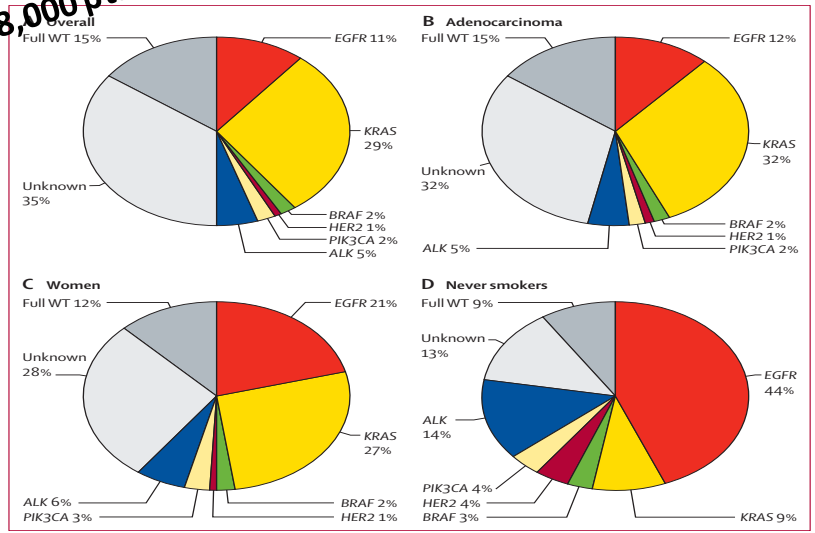
The teens

- **2011-2013**: The biomarkers France project

10,000 pts



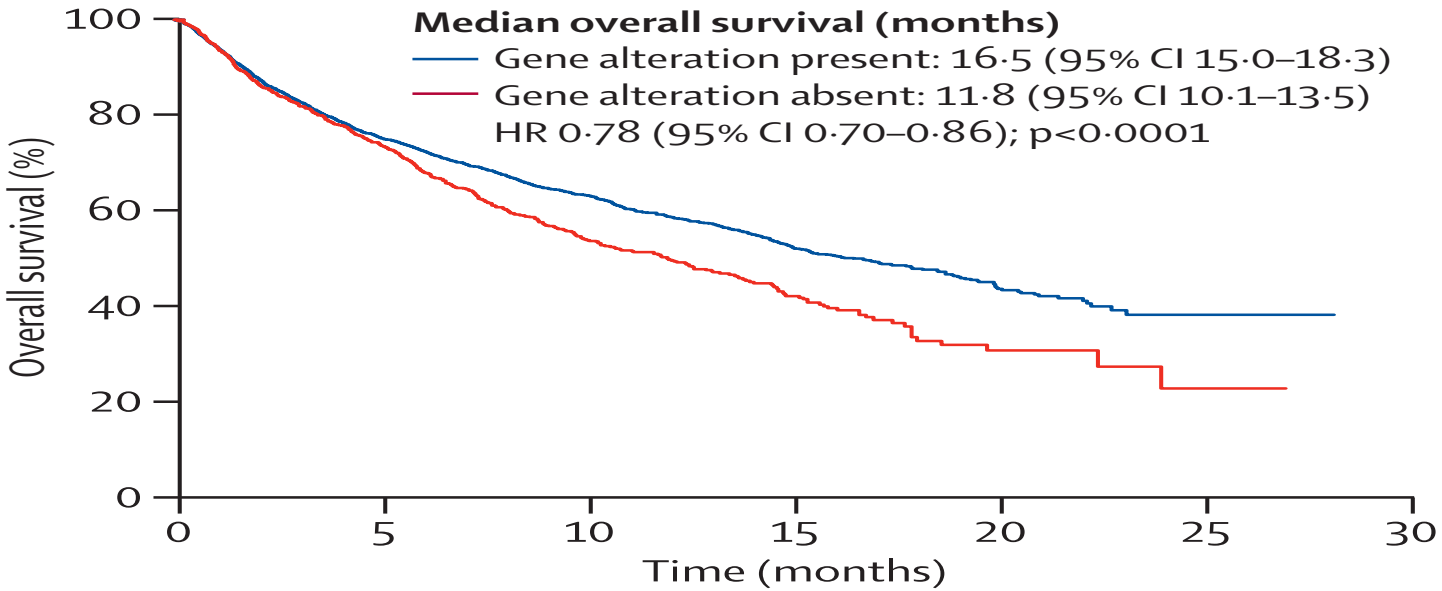
18,000 pts



Barlesi F et al, ASCO 2015; Barlesi F et al, Lancet 2016

The teens

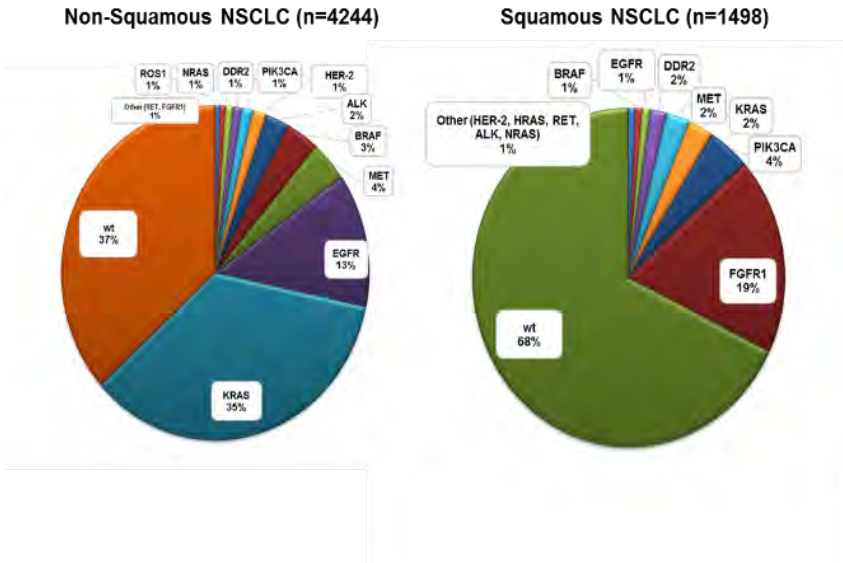
- **2011-2013**: The biomarkers France project

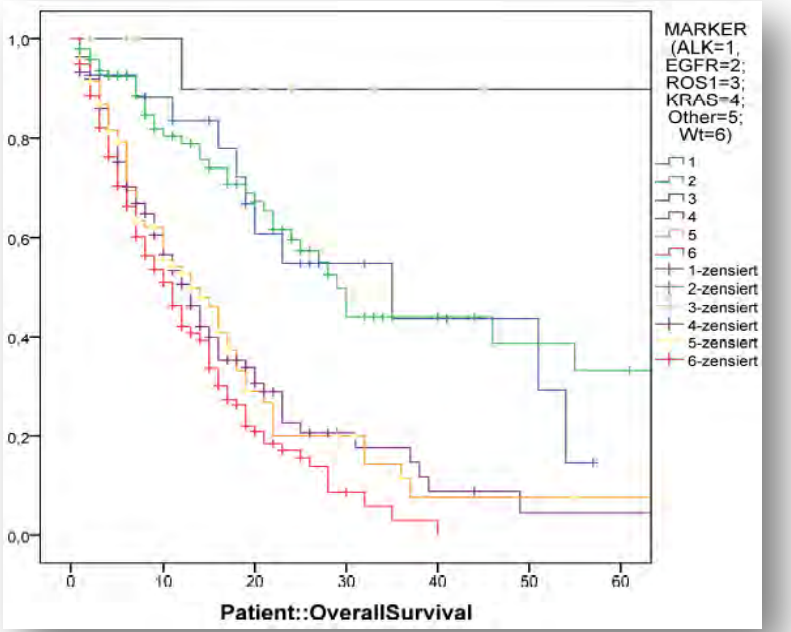


Barlesi F et al, Lancet 2016

The teens

- **2015**: NGS in Germany





Kostenko A et al, ESMO® 2015

The NGS era

- Launched in **2015**
  - Tested since 2013
  - Half of centers in 2016
    - ➢12,000 tumors sequenced in 2016
  - All centers in 2017
  - Iso15189 certified

Minimal NGS panel as per French NCI guidelines

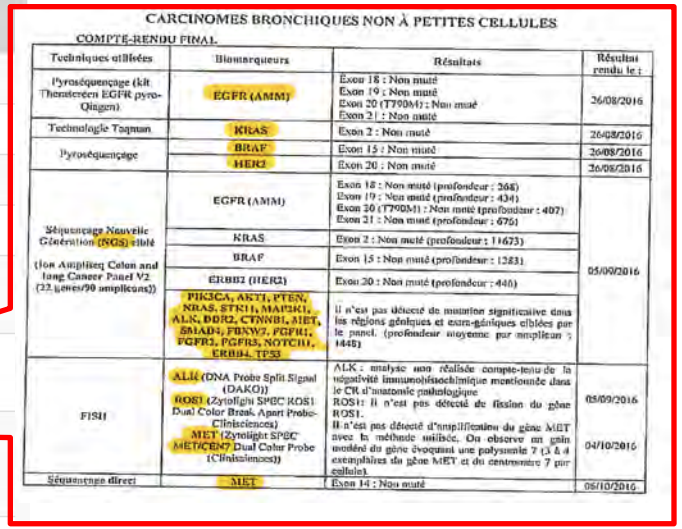
Panel tumeurs solides		
Gène	**Exons / hotspots**	**Transcrit de référence**
AKT1	3	NM_001014431.1
ALK	23+24+25	NM_004304.1
BRAF	11+15	NM_004333.4
EGFR	18+19+20+21	NM_005228.3
ERBB2 (HER2)	20	NM_004448.2
ERBB4	E452K et R393W	NM_005235.2
FGFR2	S252, N549, K659	NM_000141.4
FGFR3	7+9+14 (R248 àS249 et G370 à Y373)	NM_000142.4
HRAS	2+3+4	NM_005343.2
KIT	8+9+11+13+17+18	NM_000222.2
KRAS	2+3+4	NM_033360.2
MAP2K1 (MEK1)	2	NM_002755.3
MET	2 + 14 (de c.2942-63 en 5' à c.3082+20 en 34) à 20	NM_001127500.1
NRAS	2+3+4	NM_002524.3
PDGFRA	12+14+18	NM_006206.4
PIK3CA	9 + 20	NM_006218.2

The NGS era

- Launched in 2015 (ex. Lung Cancer)

Plateformes hospitalières de génétique moléculaire des cancers

Localisation	Marqueur	Année	Nombre de patients	Pourcentage d'altérations moléculaires	Pourcentage de tests non interprétables
Poumon	Mutations BRAF	2015	22988	2.24	9.22
Poumon	Mutations EGFR	2015	26409	12.00	7.59
Poumon	Mutations HER2	2015	20536	0.81	8.95
Poumon	Mutations KRAS	2015	24717	27.71	8.61
Poumon	Translocation ALK	2015	22667	2.84	
Poumon	Translocation ROS1	2015	14268	1.3	
Poumon	panel de mutations par NGS	2015	4405		



CARCINOMES BRONCHIQUES NON À PETITES CELLULES

COMPTE-RENDU FINAL

Techniques utilisées	Biomarqueurs	Résultats	Résultat rendu le :
Pyroséquençage (kit Therascreen EGFR pyro-Qiagen)	EGFR (AMM)	Exon 18 : Non muté Exon 19 : Non muté Exon 20 (T790M) : Non muté Exon 21 : Non muté	26/08/2016
Technologie Taqman	KRAS	Exon 2 : Non muté	26/08/2016
Pyroséquençage	BRAF	Exon 15 : Non muté	26/08/2016
	HER2	Exon 20 : Non muté	26/08/2016
Séquençage Nouvelle Génération (NGS) éllité (Ion Amplieq Colon and lung Cancer Panel V2 (22 gènes/90 amplicons))	EGFR (AMM)	Exon 18 : Non muté (profondeur : 268) Exon 19 : Non muté (profondeur : 434) Exon 20 (T790M) : Non muté (profondeur : 407) Exon 21 : Non muté (profondeur : 675)	05/09/2016
	KRAS	Exon 2 : Non muté (profondeur : 11673)	
	BRAF	Exon 15 : Non muté (profondeur : 1283)	
	ERBB2 (HER2)	Exon 20 : Non muté (profondeur : 446)	
	PIK3CA, AKT1, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, SMAD4, FBXW7, FGFR1, FGFR2, FGFR3, NOTCH1, ERBB4, TP53	Il n'est pas détecté de mutation significative dans les régions géniques et exon-géniques ciblées par le panel. (profondeur moyenne par amplicon : 1445)	
FISH	ALK (DNA Probe Split Signal (DAKO)) ROS1 (Zytolight SPEC ROS1 Dual Color Break Apart Probe-Cliniscience) MET (Zytolight SPEC MET/CEN7 Dual Color Probe (Cliniscience))	ALK : analyse non réalisée compte-tenu de la négativité immunohistochimique mentionnée dans le CR d'anatomie pathologique ROS1: Il n'est pas détecté de fixation du gène ROS1. Il n'est pas détecté d'amplification du gène MET avec la méthode utilisée. On observe un gain modéré du gène évoquant une polysomie 7 (3 à 4 exemplaires du gène MET et du centromère 7 par cellule).	05/09/2016 04/10/2016
Séquençage direct	MET	Exon 14 : Non muté	06/10/2016

Available at www.e-cancer.fr

The NGS era

- A highly competitive field!

FOUNDATIONONE

CURRENT GENE LIST[5]

FoundationOne identifies all classes of alterations in each of the genes listed below. As a pan-cancer test, FoundationOne is designed to interrogate the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer. These genes are known to be somatically altered in solid cancers based on recent scientific and clinical literature.

CURRENT GENE LIST

ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C19orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter region)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	HSP3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	

SELECT REARRANGEMENTS

ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

FOUNDATION 360

73-Gene Panel

Complete Sequencing of Covered Exons*

Point Mutations (SNVs) (73 Genes)							Indels (23 Genes)		Amplifications (CNVs) (18 Genes)		Fusions (6 Genes)
AKT1	ALK	APC	AR	ARAF	ARID1A	ATM	ATM	APC	AR	BRAF	ALK
BRAF	BRCA1	BRCA2	CCND1	CCND2	CCNE1	CDH1	ARID1A	BRCA1	CCND1	CCND2	FGFR2
CDK4	CDK6	CDKN2A	CTNNB1	DDR2	EGFR	ERBB2	BRCA2	CDH1	CCNE1	CDK4	FGFR3
ESR1	EZH2	FBXW7	FGFR1	FGFR2	FGFR3	GATA3	CDKN2A	EGFR	CDK6	EGFR	NTRK1
GNA11	GNAQ	GNAS	HNF1A	HRAS	IDH1	IDH2	ERBB2	GATA3	ERBB2	FGFR1	RET
JAK2	JAK3	KIT	KRAS	MAP2K1	MAP2K2	MAPK1	KIT	MET	FGFR2	KIT	ROS1
MAPK3	MET	MLH1	MPL	MTOR	MYC	NF1	MLH1	MTOR	KRAS	MET	
NFE2L2	NOTCH1	NPM1	NRAS	NTRK1	NTRK3	PDGFRA	NF1	PDGFRA	MYC	PDGFRA	
PIK3CA	PTEN	PTPN11	RAF1	RB1	RET	RHEB	PTEN	RB1	PIK3CA	RAF1	
RHOA	RIT1	ROS1	SMAD4	SMO	STK11	TERT**	SMAD4	STK11			
TP53	TSC1	VHL					TP53	TSC1			
				** includes TERT promoter region			VHL				

*Exons selected to maximize detection of known somatic mutations. List available upon request

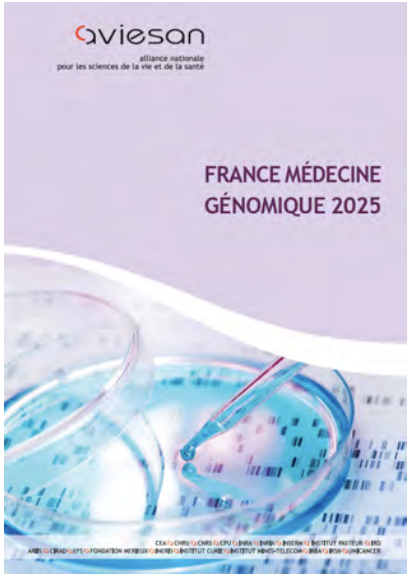
Available at companies' websites

Agenda

- Une décade d'innovations
- Difficile de rester leader
- **France Medecine Genomique 2025**
- Quels défis à surmonter ?

The WES era

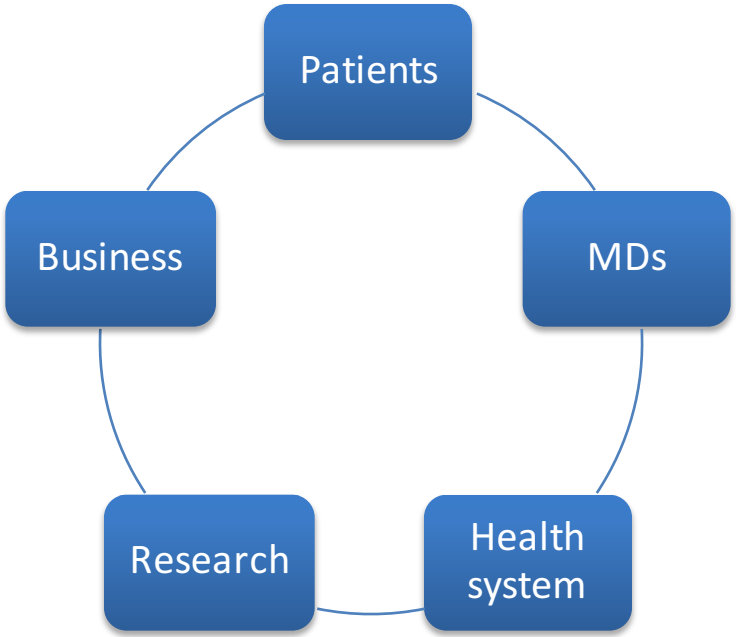
- **2016**: France Medecine Genomique 2025 call
  - 12 genetic centers
  - Put France ahead again
  - Prepare the use of genomic medicine
  - Developp business based on scientific and technical innovations



Available at www.solidarites-sante.gouv.fr

The WES era

- **2016**: France Medecine Genomique 2025 call



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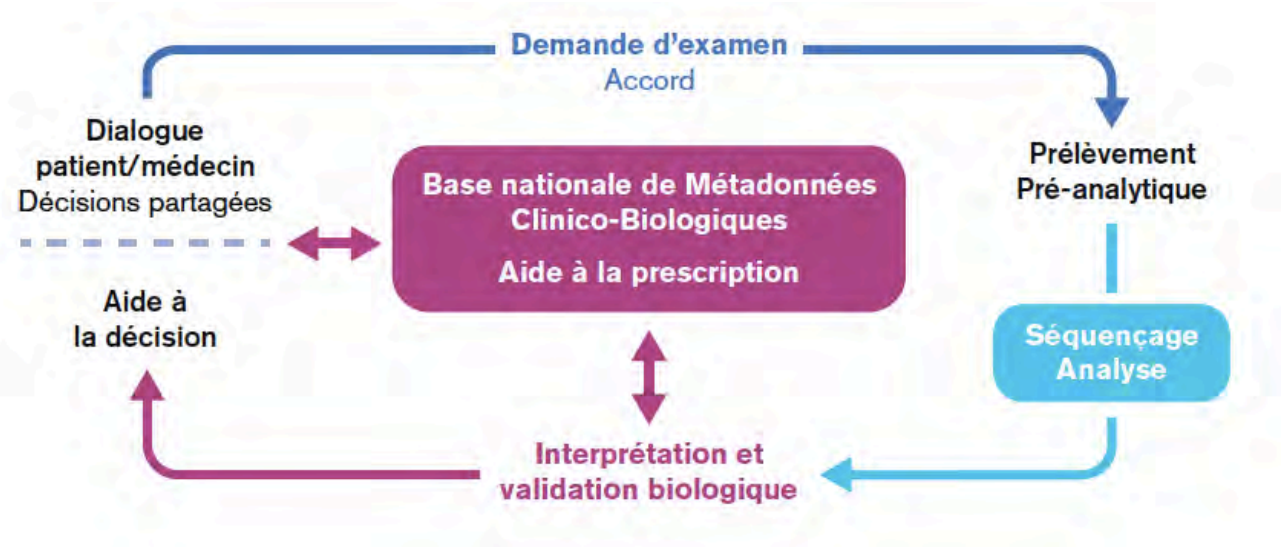
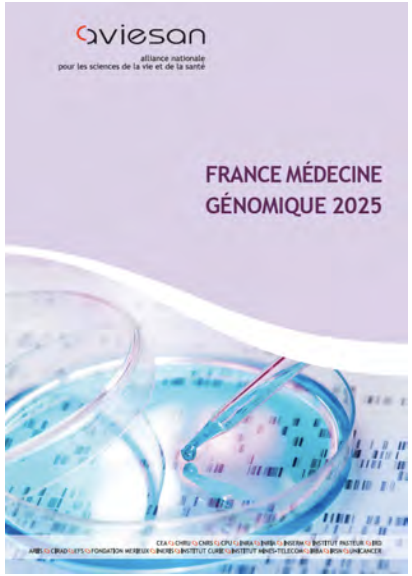
The WES era

- **2016**: France Medecine Genomique 2025 call





Available at www.solidarites-sante.gouv.fr

The WES era

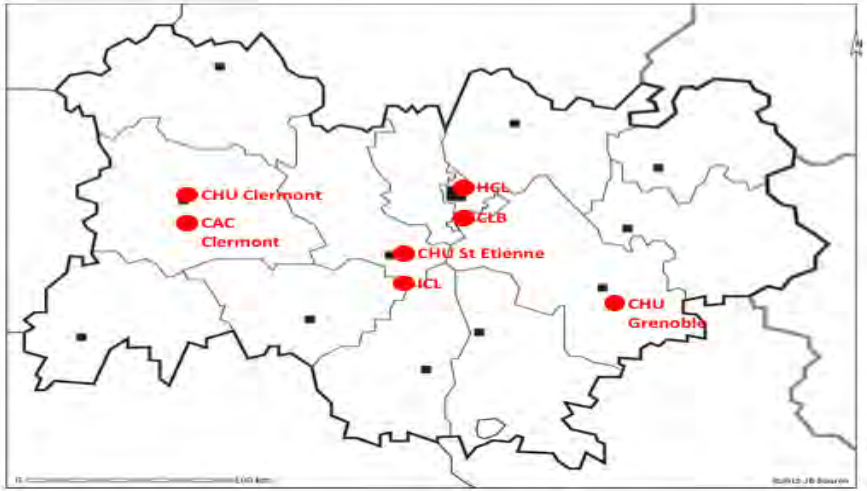
- **2020 objectives**:
  - 235,000 WES / year
    - **175,000 tumors**
  - All data collected at 1 national center
  - Creation of a CRefIX dedicated to
    - Innovations
    - Link to industries

Available at www.solidarites-sante.gouv.fr

The WES era

The SEQOiA project

The AURAGEN project



200 to 300 Millions Euros of budget over the next 5 years

The WES era

- **The AURAGEN project:**
  - **PF unique multisite** *(Clermont-Ferrand, Grenoble, Lyon, St Etienne)*
  - **Validation prescription / collecte prélèvements / conditionnement / envoi** *(Clermont-Ferrand, Grenoble, Lyon, St Etienne)*
  - **Extraction ADN-ARN** *(envoi ADN possible)*
  - **Totale automatisation du pré STHD** *(Lyon)*
  - **Analytique = séquençage THD** *(illumina X Five ou X ten)*
  - **Cluster de calcul & stockage des données** *(Grenoble)*
  - **Interprétation des données** *(Clermont-Ferrand, Grenoble, Lyon, St Etienne)*
  - **Lien avec le parcours de soin**

Courtesy Frederique Penault-Llorca

Agenda

- Une décade d'innovations
- Difficile de rester leader
- France Medecine Genomique 2025
- **Quels défis à surmonter ?**

The challenges

'… those oncologists who practice precision oncology are **two steps ahead of the data**—and the history of medicine has taught us that is an uncertain place to stand.'

Prasad et al, Lancet Oncology 2016

The challenges

Available @ https://www.ibm.com/watson/health/oncology-and-genomics/genomics/

The challenges

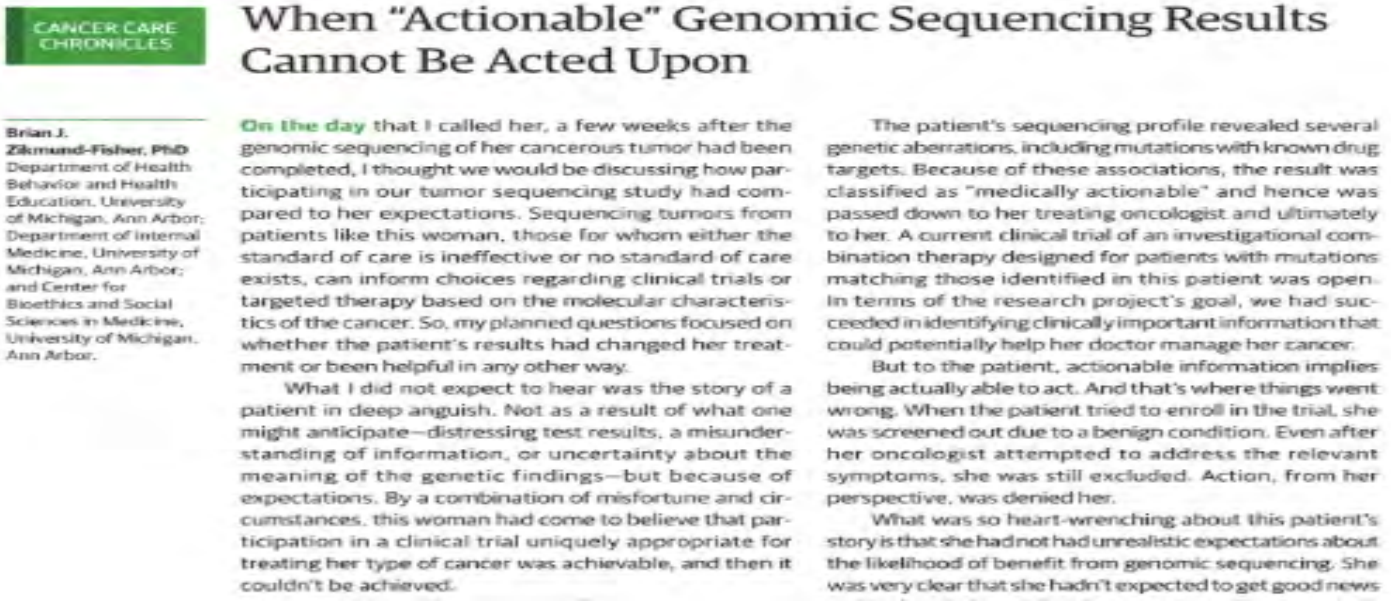
- How **many** actionnable molecular alterations?

	MOSCATO, n (%)	SAFIR02lung, n (%)	MATRIX trial, n (%)
Pts included	1036	686	3099
Pts w successful biopsy (%)	844 (81)	460 (67)	1664 (53)
Pts w actionable target (%)	411 (39)	297 (43)	731 (23)
Pts w targeted treatment **(%)**	199 **(19)**	110 **(16)**	458 **(15)**

Massard C et al, Cancer Discov 2017; SAFIR trial (data as of Sep 2017); courtesy G Middelton (data as of July 2016)

The challenges

- Beside the numbers … **a patient**



CANCER CARE CHRONICLES

When "Actionable" Genomic Sequencing Results Cannot Be Acted Upon

Brian J. Zikmund-Fisher, PhD
Department of Health Behavior and Health Education, University of Michigan, Ann Arbor; Department of Internal Medicine, University of Michigan, Ann Arbor; and Center for Bioethics and Social Sciences in Medicine, University of Michigan, Ann Arbor.

On the day that I called her, a few weeks after the genomic sequencing of her cancerous tumor had been completed, I thought we would be discussing how participating in our tumor sequencing study had compared to her expectations. Sequencing tumors from patients like this woman, those for whom either the standard of care is ineffective or no standard of care exists, can inform choices regarding clinical trials or targeted therapy based on the molecular characteristics of the cancer. So, my planned questions focused on whether the patient's results had changed her treatment or been helpful in any other way.

What I did not expect to hear was the story of a patient in deep anguish. Not as a result of what one might anticipate—distressing test results, a misunderstanding of information, or uncertainty about the meaning of the genetic findings—but because of expectations. By a combination of misfortune and circumstances, this woman had come to believe that participation in a clinical trial uniquely appropriate for treating her type of cancer was achievable, and then it couldn't be achieved.

The patient's sequencing profile revealed several genetic aberrations, including mutations with known drug targets. Because of these associations, the result was classified as "medically actionable" and hence was passed down to her treating oncologist and ultimately to her. A current clinical trial of an investigational combination therapy designed for patients with mutations matching those identified in this patient was open. In terms of the research project's goal, we had succeeded in identifying clinically important information that could potentially help her doctor manage her cancer.

But to the patient, actionable information implies being actually able to act. And that's where things went wrong. When the patient tried to enroll in the trial, she was screened out due to a benign condition. Even after her oncologist attempted to address the relevant symptoms, she was still excluded. Action, from her perspective, was denied her.

What was so heart-wrenching about this patient's story is that she had not had unrealistic expectations about the likelihood of benefit from genomic sequencing. She was very clear that she hadn't expected to get good news

Zikmund-Fisher BJ. JAMA Oncol 2017

The challenges

- What is the **benefit** of precision medicine?

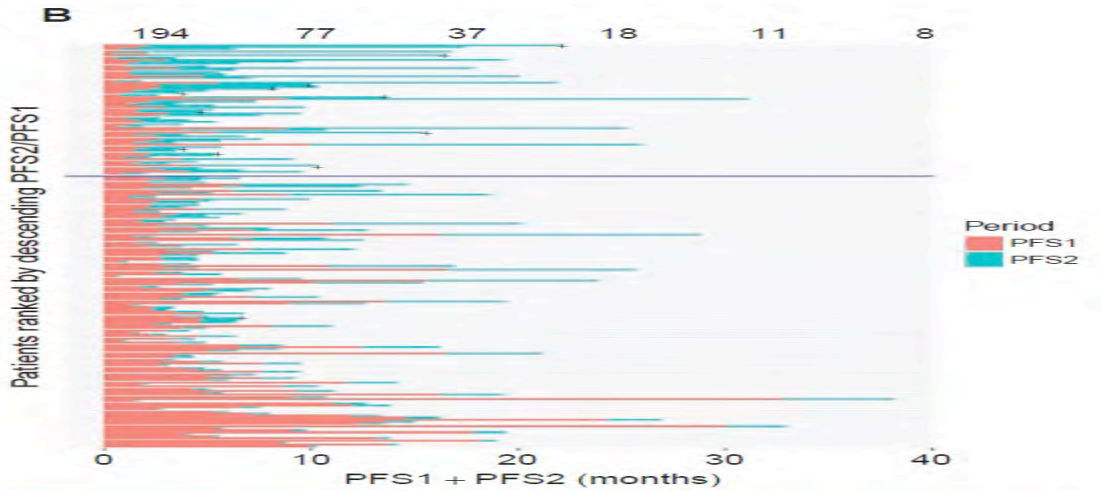
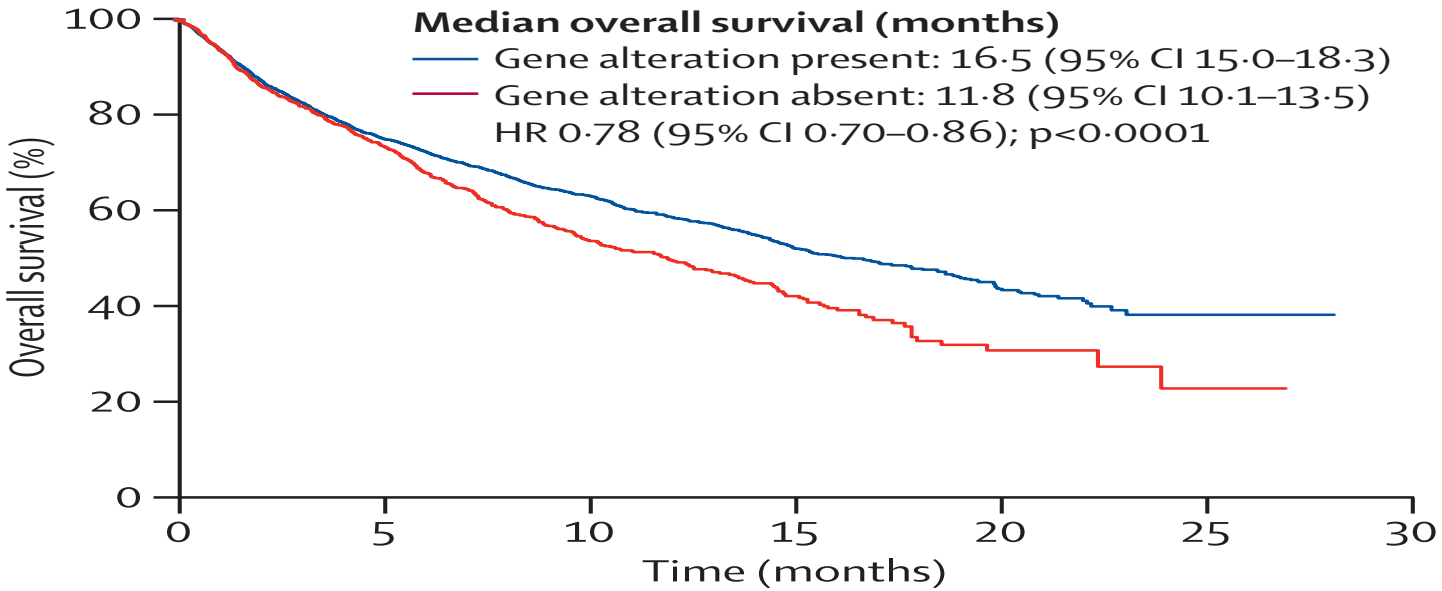


Figure 3. Efficacy on primary endpoint. **A,** Kaplan–Meier curve of PFS2/PFS1. Crosses denote censored data. Green line denotes PFS2/PFS1 > 1.3. **B,** Individual PFS1 and PFS2 times, ordered by descending PFS2/PFS1 (n = 194). Crosses denote censored data. Patients above the blue horizontal line have PFS2/PFS1 > 1.3.

Massard C et al, Cancer Discov 2017

The challenges

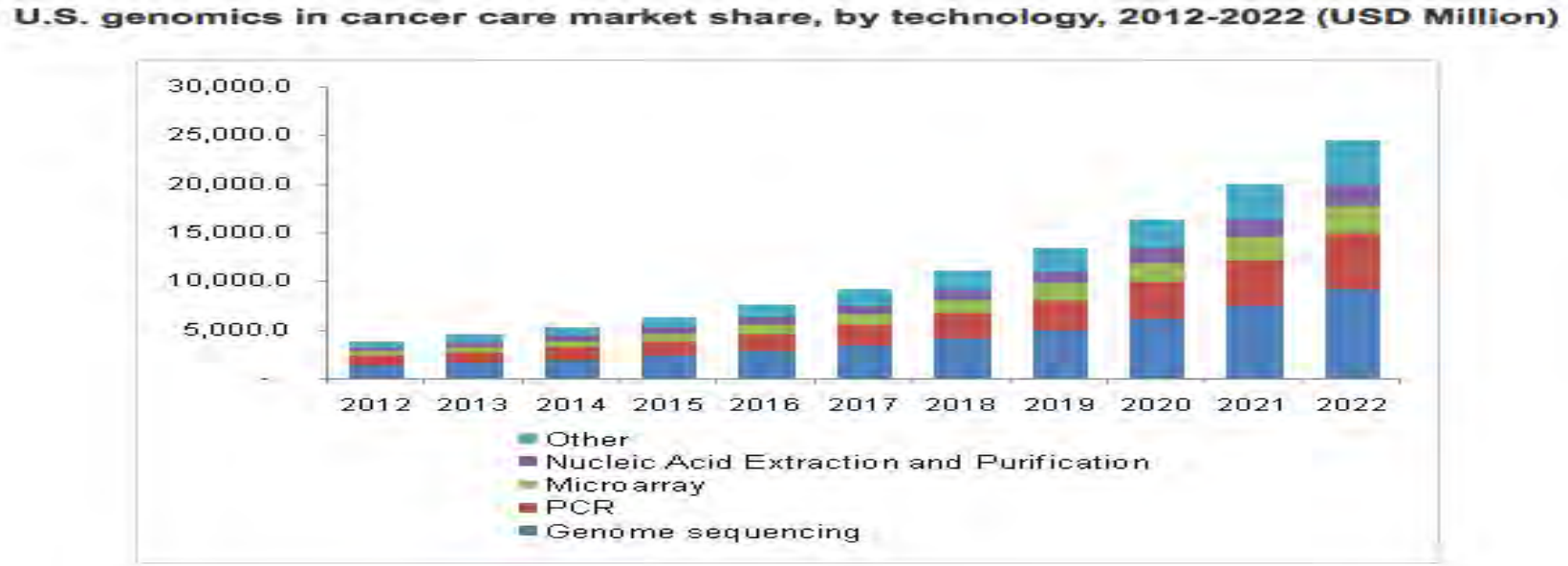
- What is the **health gain?**



Barlesi F et al, Lancet 2016

The challenges

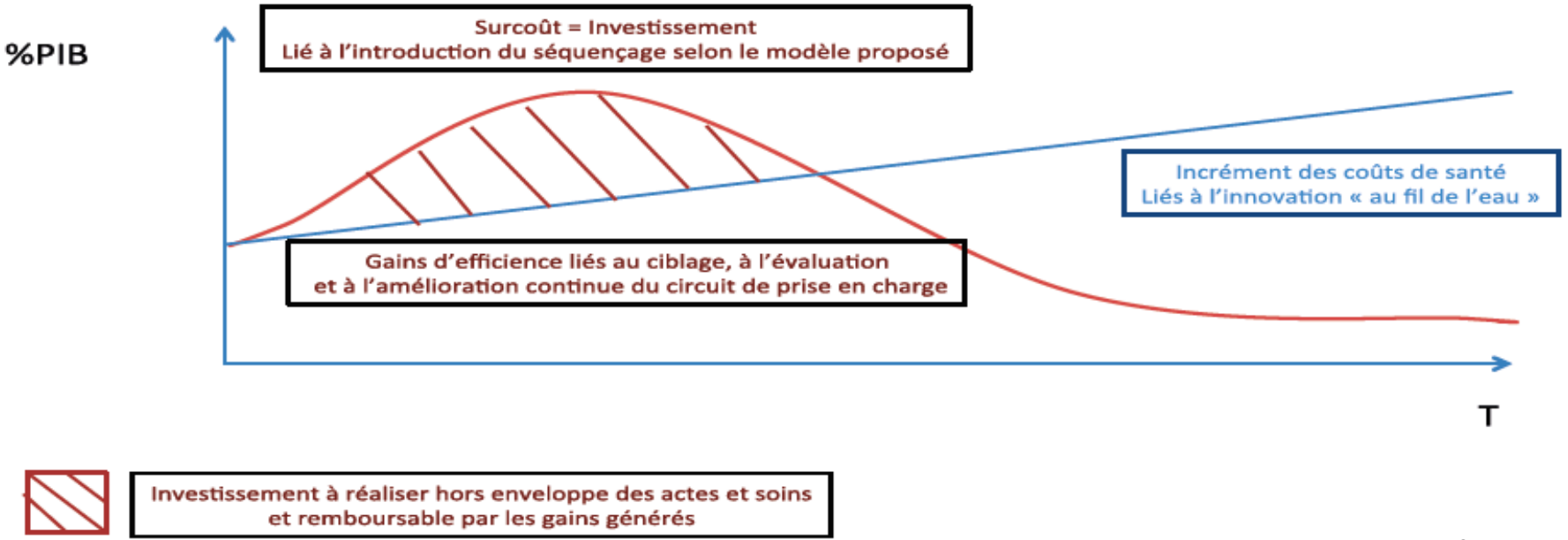
- A huge **business**!



Available at http://www.grandviewresearch.com/industry-analysis/genomics-in-cancer-care-market

The challenges

- How to cover the **cost** of the NGS / WES?



Conclusions

- A model based on
  - A **nationwide access** to genotyping
  - A link to **research**
- A **new step** starting in 2017
- A survival impact and an economic model that remain **to be demonstrated**

Acknowledgements

- French Intergroup for Thoracic Oncology (IFCT)
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