GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ESMO ADVANCED COURSE ON BIOMARKERS FOR PRECISION MEDICINE:

INCIDENTAL FINDINGS IN NGS SEQUENCING

Dr Etienne ROULEAU, Tumor Genetics Lab, Gustave Roussy

Zürich, 28-29 November 2019

DISCLOSURE OF INTEREST

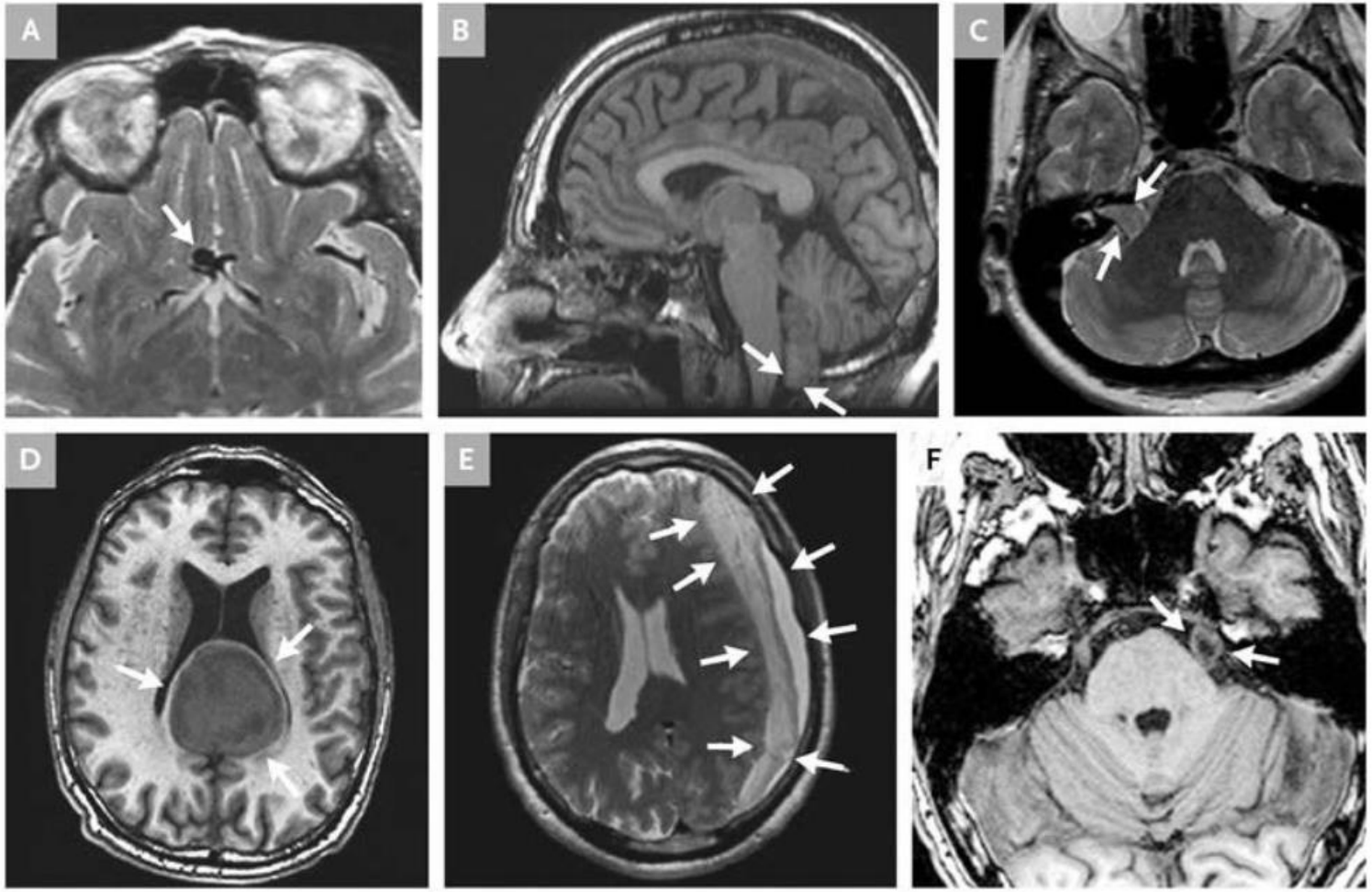
Advisory board and travel : AstraZeneca – BMS

Research grant : AstraZeneca

Advisroy board : Roche – GlaxoWellcome

Non financial interest : president of the GFCO (French somatic geneticists association) – administrator in IQNPath – Founder of the Gen&tiss (French EQA program)

INCIDENTAL FINDINGS – NOTHING NEW



Vernooij, Meike W., M. Arfan Ikram, Hervé L. Tanghe, Arnaud J.P.E. Vincent, Albert Hofman, Gabriel P. Krestin, Wiro J. Niessen, Monique M.B. Breteler, et Aad van der Lugt. « Incidental Findings on Brain MRI in the General Population ». *New England Journal of Medicine* 357, nº 18 (1 novembre 2007): 1821-28.

Asymptomatic brain infarcts (7.2%), cerebral aneurysms (1.8%) and benign primary tumors (1.6%)

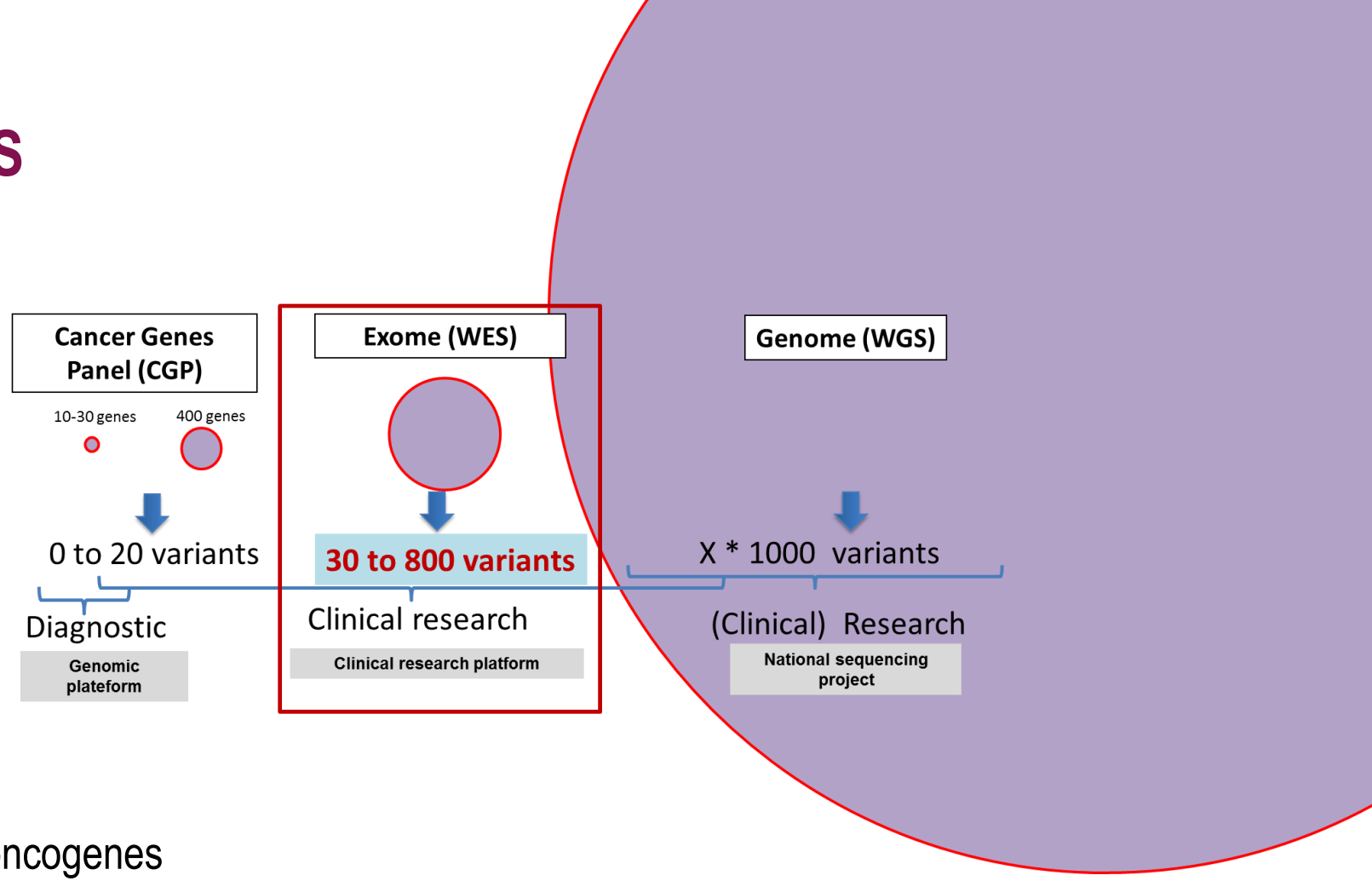
DEFINITIONS

Additional data : results without any direct relation with the initial indication

Incidental data : results without any direct relation, but with a lucky discovery

Secondary data : results without any direct relation, but with an active screening thanks to a gene list

REVOLUTION IN GENOMICS



Tumor testing from hotspot mutations in oncogenes

- ⇒ Expansion to full coding region of oncogenes and tumor supressor genes
- ⇒ Paired tumor-germline analysis or expanded tumor gene panel

VERY LARGE CANCER GENE PANEL

Table 3: Genes included in the TruSight Oncology 500 panel

DNA content										
ABL1	BRD4	CUX1	FAM175A	GATA6	IGF1	MAP3K13	NOTCH4	POLE	RPTOR	TAF1
ABL2	BRIP1	CXCR4	FAM46C	GEN1	IGF1R	MAP3K14	NPM1	PPARG	RUNX1	TBX3
ACVR1	BTG1	CYLD	FANCA	GID4	IGF2	MAP3K4	NRAS	PPM1D	RUNX1T1	TCEB1
ACVR1B	BTK	DAXX	FANCC	GLI1	IKBKE	MAPK1	NRG1	PPP2R1A	RYBP	TCF3
AKT1	C11orf30	DCUN1D1	FANCD2	GNA11	IKZF1	MAPK3	NSD1	PPP2R2A	SDHA	TCF7L2
AKT2	CALR	DDR2	FANCE	GNA13	IL10	MAX	NTRK1	PPP6C	SDHAF2	TERC
AKT3	CARD11	DDX41	FANCF	GNAQ	IL7R	MCL1	NTRK2	PRDM1	SDHB	TERT
ALK	CASP8	DHX15	FANCG	GNAS	INHA	MDC1	NTRK3	PREX2	SDHC	TET1
ALOX12B	CBFB	DICER1	FANCI	GPR124	INHBA	MDM2	NUP93	PRKAR1A	SDHD	TET2
ANKRD11	CBL	DIS3	FANCL	GPS2	INPP4A	MDM4	NUTM1	PRKCI	SETBP1	TFE3
ANKRD26	CCND1	DNAJB1	FAS	GREM1	INPP4B	MED12	PAK1	PRKDC	SETD2	TFRC
APC	CCND2	DNMT1	FAT1	GRIN2A	INSR	MEF2B	PAK3	PRSS8	SF3B1	TGFBR1
AR	CCND3	DNMT3A	FBXW7	GRM3	IRF2	MEN1	PAK7	PTCH1	SH2B3	TGFBR2
ARAF	CCNE1	DNMT3B	FGF1	GSK3B	IRF4	MET	PALB2	PTEN	SH2D1A	TMEM127
ARFRP1	CD274	DOT1L	FGF10	H3F3A	IRS1	MGA	PARK2	PTPN11	SHQ1	TMPRSS2
ARID1A	CD276	E2F3	FGF14	H3F3B	IRS2	MITF	PARP1	PTPRD	SLIT2	TNFAIP3
ARID1B	CD74	EED	FGF19	H3F3C	JAK1	MLH1	PAX3	PTPRS	SLX4	TNFRSF14
ARID2	CD79A	EGFL7	FGF2	HGF	JAK2	MLL	PAX5	PTPRT	SMAD2	TOP1
ARID5B	CD79B	EGFR	FGF23	HIST1H1C	JAK3	MLLT3	PAX7	QKI	SMAD3	TOP2A
ASXL1	CDC73	EIF1AX	FGF3	HIST1H2BD	JUN	MPL	PAX8	RAB35	SMAD4	TP53
ASXL2	CDH1	EIF4A2	FGF4	HIST1H3A	KAT6A	MRE11A	PBRM1	RAC1	SMARCA4	TP63
ATM	CDK12	EIF4E	FGF5	HIST1H3B	KDM5A	MSH2	PDCD1	RAD21	SMARCB1	TRAF2
ATR	CDK4	EML4	FGF6	HIST1H3C	KDM5C	MSH3	PDCD1LG2	RAD50	SMARCD1	TRAF7
ATRX	CDK6	EP300	FGF7	HIST1H3D	KDM6A	MSH6	PDGFRA	RAD51	SMC1A	TSC1
AURKA	CDK8	EPCAM	FGF8	HIST1H3E	KDR	MST1	PDGFRB	RAD51B	SMC3	TSC2
AURKB	CDKN1A	EPHA3	FGF9	HIST1H3F	KEAP1	MST1R	PDK1	RAD51C	SMO	TSHR
AXIN1	CDKN1B	EPHA5	FGFR1	HIST1H3G	KEL	MTOR	PDPK1	RAD51D	SNCAIP	U2AF1
AXIN2	CDKN2A	EPHA7	FGFR2	HIST1H3H	KIF5B	MUTYH	PGR	RAD52	SOCS1	VEGFA
AXL	CDKN2B	EPHB1	FGFR3	HIST1H3I	KIT	MYB	PHF6	RAD54L	SOX10	VHL
B2M	CDKN2C	ERBB2	FGFR4	HIST1H3J	KLF4	MYC	PHOX2B	RAF1	SOX17	VTCN1
BAP1	CEBPA	ERBB3	FH	HIST2H3A	KLHL6	MYCL1	PIK3C2B	RANBP2	SOX2	WISP3
BARD1	CENPA	ERBB4	FLCN	HIST2H3C	KMT2B	MYCN	PIK3C2G	RARA	SOX9	WT1
BBC3	CHD2	ERCC1	FLI1	HIST2H3D	KMT2C	MYD88	PIK3C3	RASA1	SPEN	XIAP
BCL10	CHD4	ERCC2	FLT1	HIST3H3	KMT2D	MYOD1	PIK3CA	RB1	SPOP	XPO1
BCL2	CHEK1	ERCC3	FLT3	HLA-A	KRAS	NAB2	PIK3CB	RBM10	SPTA1	XRCC2
BCL2L1	CHEK2	ERCC4	FLT4	HLA-B	LAMP1	NBN	PIK3CD	RECQL4	SRC	YAP1
BCL2L11	CIC	ERCC5	FOXA1	HLA-C	LATS1	NCOA3	PIK3CG	REL	SRSF2	YES1
BCL2L2	CREBBP	ERG	FOXL2	HNF1A	LATS2	NCOR1	PIK3R1	RET	STAG1	ZBTB2
BCL6	CRKL	ERRFI1	FOXO1	HNRNPK	LMO1	NEGR1	PIK3R2	RPWD2	STAG2	ZBTB7A
BCOR	CRLF2	ESR1	FOXP1	HOXB13	LRP1B	NF1	PIK3R3	RHEB	STAT3	ZFHX3
BCORL1	CSF1R	ETS1	FRS2	HRAS	LYN	NF2	PIM1	RHOA	STAT4	ZNF217
BCR	CSF3R	ETV1	FUBP1	HSD3B1	LZTR1	NFE2L2	PLCG2	RICTOR	STAT5A	ZNF703
BIRC3	CSNK1A1	ETV4	FYN	HSP90AA1	MAGI2	NFKBIA	PLK2	RIT1	STAT5B	ZRSR2
BLM	CTCF	ETV5	GABRA6	ICOSLG	MALT1	NKX2-1	PMAIP1	RNF43	STK11	
BMPR1A	CTLA4	ETV6	GATA1	ID3	MAP2K1	NKX3-1	PMS1	ROS1	STK40	
BRAF	CTNNA1	EWSR1	GATA2	IDH1	MAP2K2	NOTCH1	PMS2	RPS6KA4	SUFU	
BRCA1	CTNNB1	EZH2	GATA3	IDH2	MAP2K4	NOTCH2	PNRC1	RPS6KB1	SUZ12	
BRCA2	CUL3	FAM123B	GATA4	IFNGR1	MAP3K1	NOTCH3	POLD1	RPS6KB2	SYK	
RNA content*										
ABL1	BCL2	CSF1R	ESR1	EWSR1	FLI1	KIF5B	MSH2	NRG1	PAX7	RAF1
AKT3	BRAF	EGFR	ETS1	FGFR1	FLT1	KIT	MYC	NTRK1	PDGFRA	RET
ALK	BRCA1	EML4	ETV1	FGFR2	FLT3	MET	NOTCH1	NTRK2	PDGFRB	ROS1
AR	BRCA2	ERBB2	ETV4	FGFR3	JAK2	MLL	NOTCH2	NTRK3	PIK3CA	RPS6KB1
AXL	CDK4	ERG	ETV5	FGFR4	KDR	MLLT3	NOTCH3	PAX3	PPARG	TMPRSS2

* The products to evaluate DNA and RNA variants consist of the TruSight Oncology 500 DNA panel and the TruSight Tumor 170 RNA panel.

Panel TruSight Oncology 500

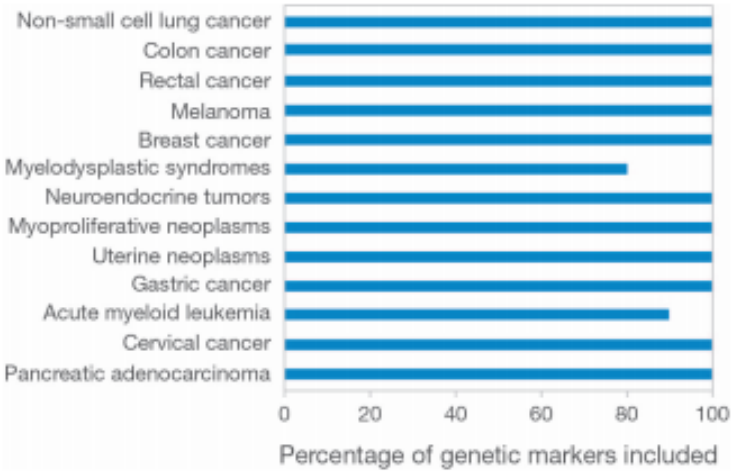


Figure 3: TruSight Oncology 500 content alignment to National Comprehensive Cancer Network (NCCN) guidelines — For each cancer type, the percentage of genetic markers in current NCCN guidelines[3] that are included in the gene panel is indicated.

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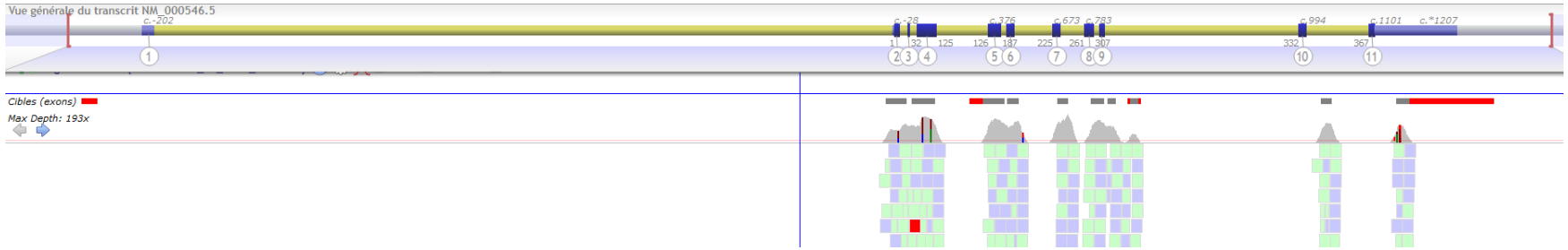
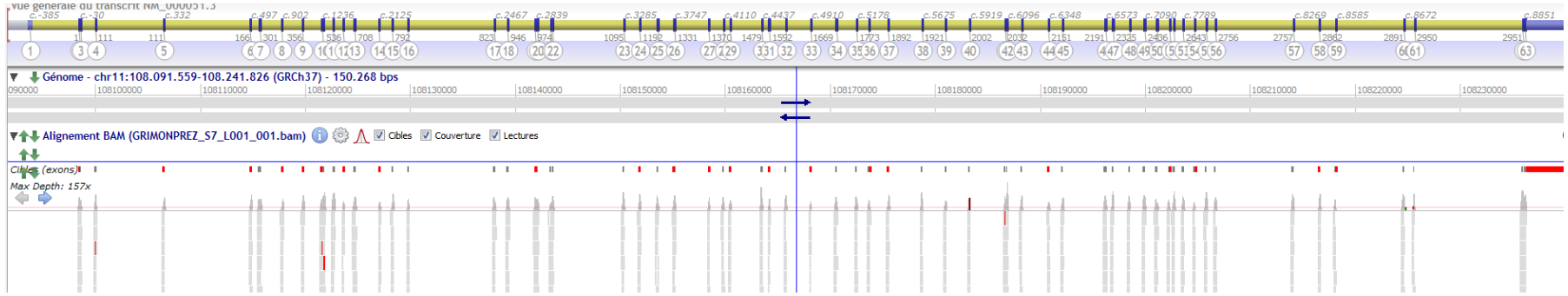
NGS AND SUPPRESSOR GENES

Screening for the 10 coding exons in the *TP53* gene

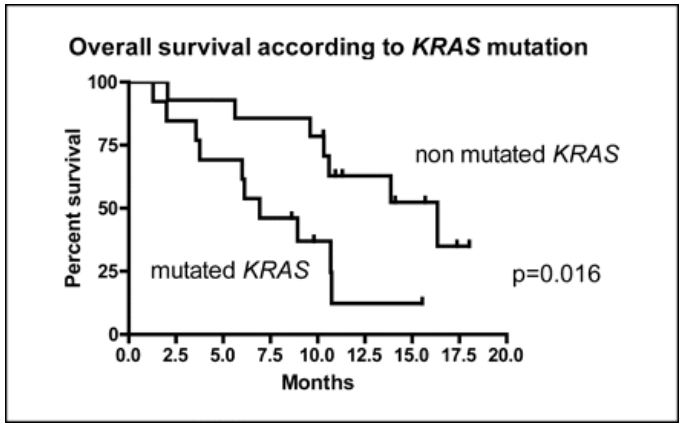


Screening for the 62 coding exons in the *ATM* gene

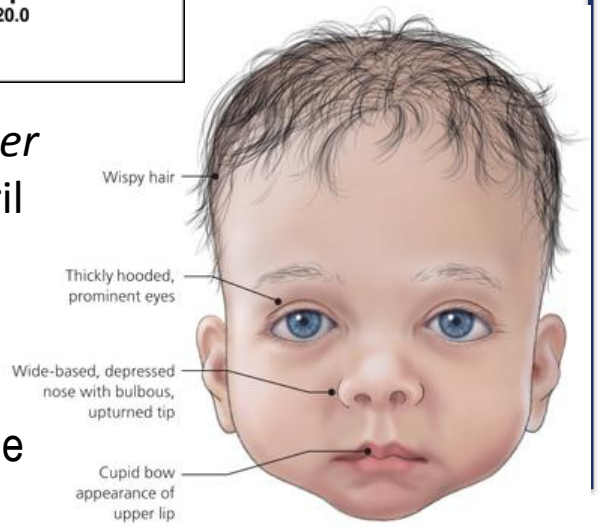


FRONTIER GERMLINE / SOMATIC IS BROKEN

KRAS



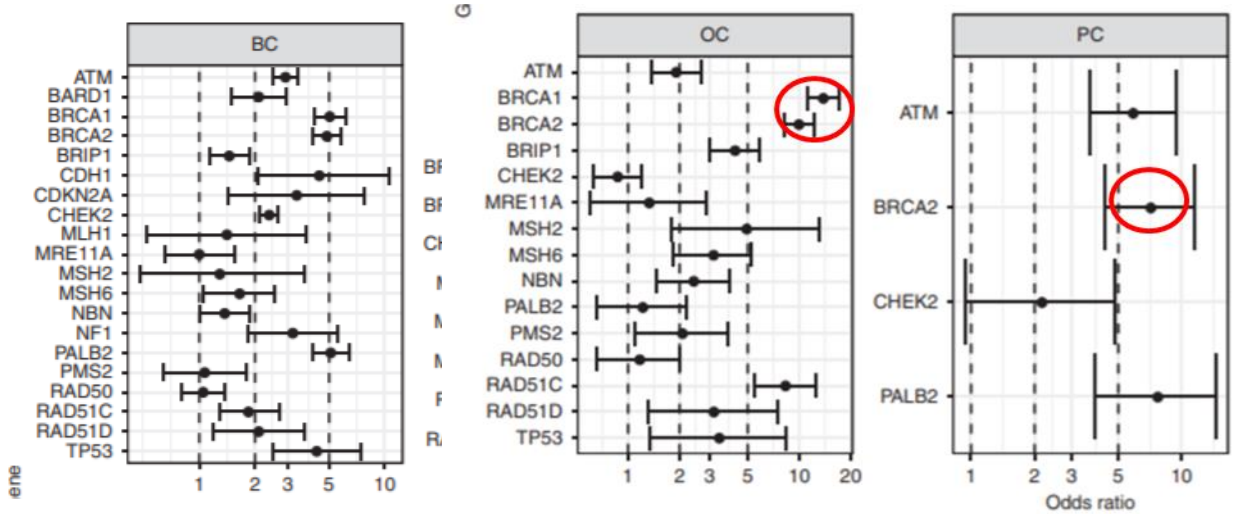
Lièvre, Astrid, et al. *Cancer Research* 66, nº 8 (15 avril 2006): 3992-95.



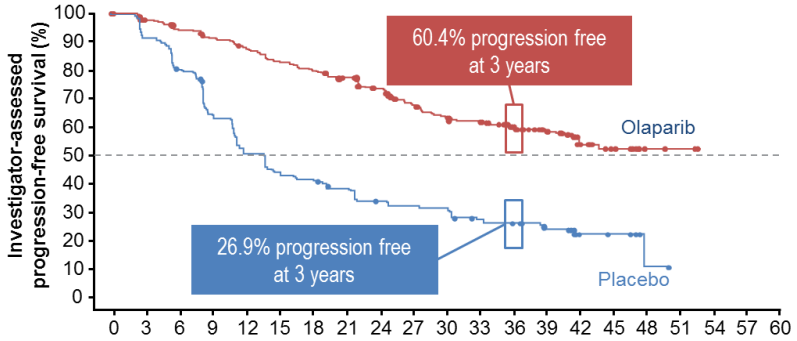
Noonan syndrome

AAFP

BRCA1



LaDuca, Holly et al. *Genetics in Medicine*, 13 août 2019.

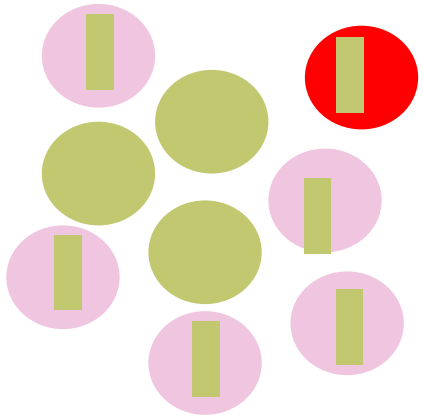


SOLO1

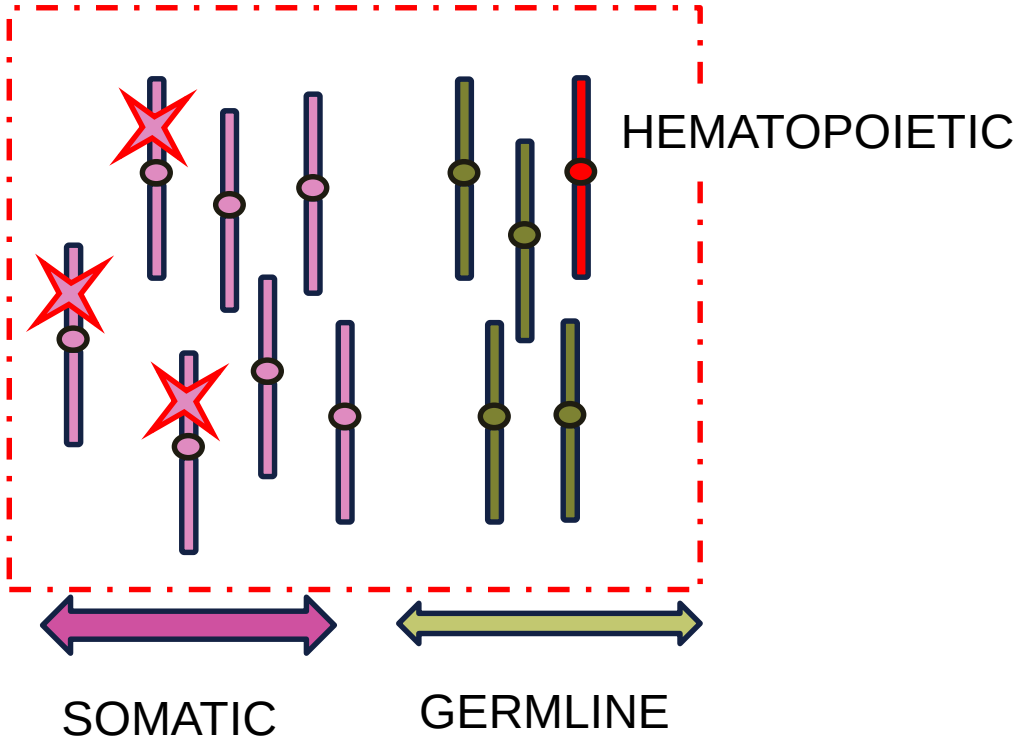
ESMO

HETEROGENEITY IN TISSUE

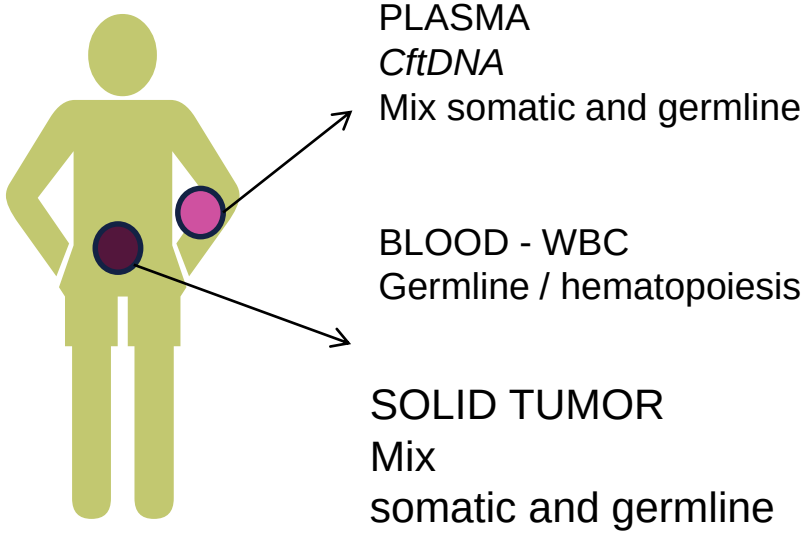
TUMOR



% NEOPLASTIC CELLS



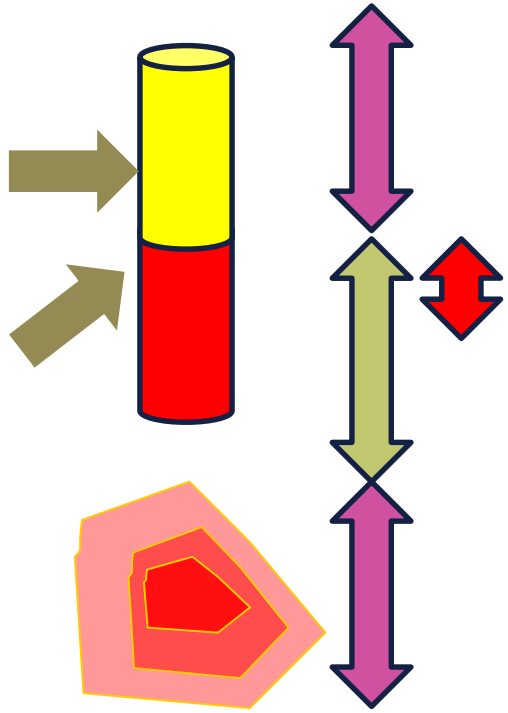
HETEROGENEITY IN SAMPLES



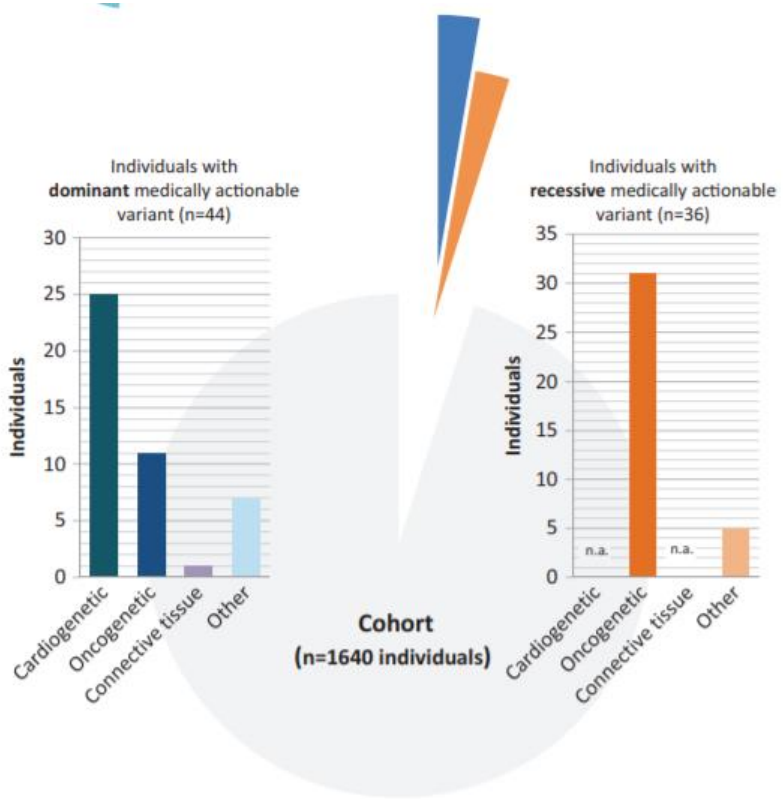
PLASMA
CftDNA
Mix somatic and germline

BLOOD - WBC
Germline / hematopoiesis

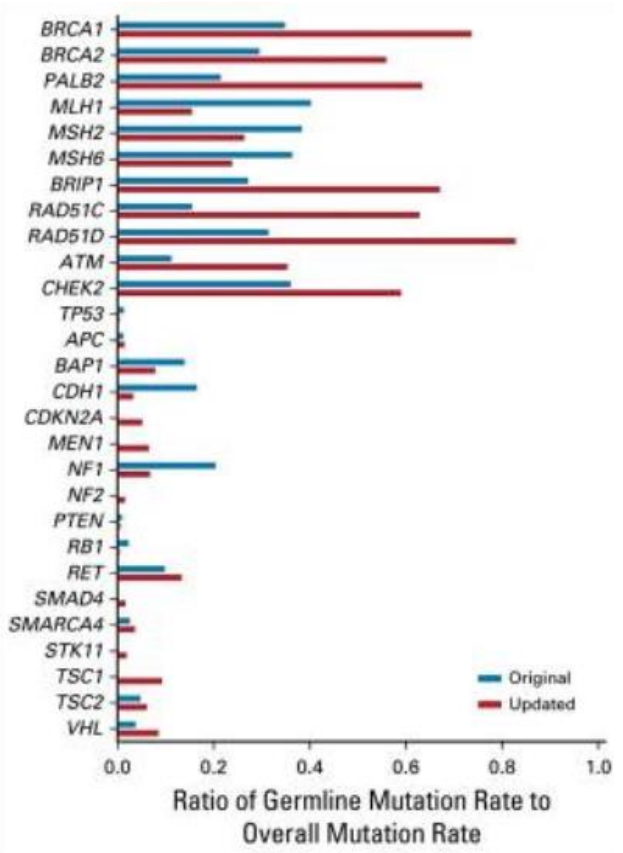
SOLID TUMOR
Mix
somatic and germline



1 IN 38 INDIVIDUALS AT RISK OF A DOMINANT MEDICALLY ACTIONABLE DISEASE



Haer-Wigman, Lonneke, et al. « 1 in 38 Individuals at Risk of a Dominant Medically Actionable Disease ». *European Journal of Human Genetics: EJHG* 27, nº 2 (2019): 325-30..



Mandelker, Diana et al. « The Emerging Significance of Secondary Germline Testing in Cancer Genomics ». *The Journal of Pathology* 244, nº 5 (2018): 610-15..

WHAT IS RELEVANT ?
ACMG INCIDENTAL FINDINGS TO CANCER

All genes

ACMG 59 genes →

Cancer predisposition syndrome
Malignant hyperthermia susceptibility
Ornithine transcarbamylase deficiency
Wilson disease
Familial hypercholesterolemia
Romano-Ward long-QT syndrome types 1, 2,and 3, Brugada syndrome
Arrhythmogenic right ventricular cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Hypertrophic cardiomyopathy, dilated cardiomyopathy
Ehlers-Danlos syndrome, vascular type
Marfan syndrome, Loeys-Dietz syndromes,and familial thoracic aortic aneurysms and dissections

Cancer susceptibility genes

ACMG 25 genes

ESMO 65 genes=> 27 genes

Criteria = actionability

- Penetrance – risk of onset
- Severity of caner
- Availability of clinical management options

Green, Robert C., Jonathan S. Berg, Wayne W. Grody, Sarah S. Kalia, Bruce R. Korf, Christa L. Martin, Amy L. McGuire, et al. « ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing ». *Genetics in Medicine* 15, nº 7 (juillet 2013): 565-74.

« Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the ... - PubMed - NCBI ». 28 november 2019. https://www-ncbi-nlm-nih-gov.proxy.insermbiblio.inist.fr/pubmed/27854360.

ESMO RECOMMANDATIONS

Box 1. Recommendations for genes to be included for germline-focussed analysis and triggering of germline sample laboratory confirmation

	Any tumour type		Associated tumour type only
Tumour arising any age	*BRCA1*	*RAD51C*	*FLCN*
	BRCA2	*RAD51D*	*FH*
	BRIP1	*RET*	*BAP1*
	MLH1	*SDHA*	*POLE*
	MSH2	*SDHAF2*	
	MSH6	*SDHB*	
	PALB2	*SDHC*	
	PMS2	*SDHD*	
	VHL[a]	*TSC2*	
		MUTYH[b]	
Tumour arising age <30 only	*RB1*		*TP53*[c]
	APC		*NF1*

[a]Renal tumours to be excluded.
[b]*MUTYH* should be included for germline-focussed tumour analysis but reporting and germline follow-up testing should only be performed on detection of two pathogenic variants.
[c]Brain tumours to be excluded.

Mandelker, D, M Donoghue, S Talukdar, C Bandlamudi, P Srinivasan, M Vivek, S Jezdic, et al. « Germline-Focussed Analysis of Tumour-Only Sequencing: Recommendations from the ESMO Precision Medicine Working Group ». *Annals of Oncology* 30, nº 8 (1 août 2019): 1221-31. https://doi.org/10.1093/annonc/mdz136.

CLINICAL SITUATIONS

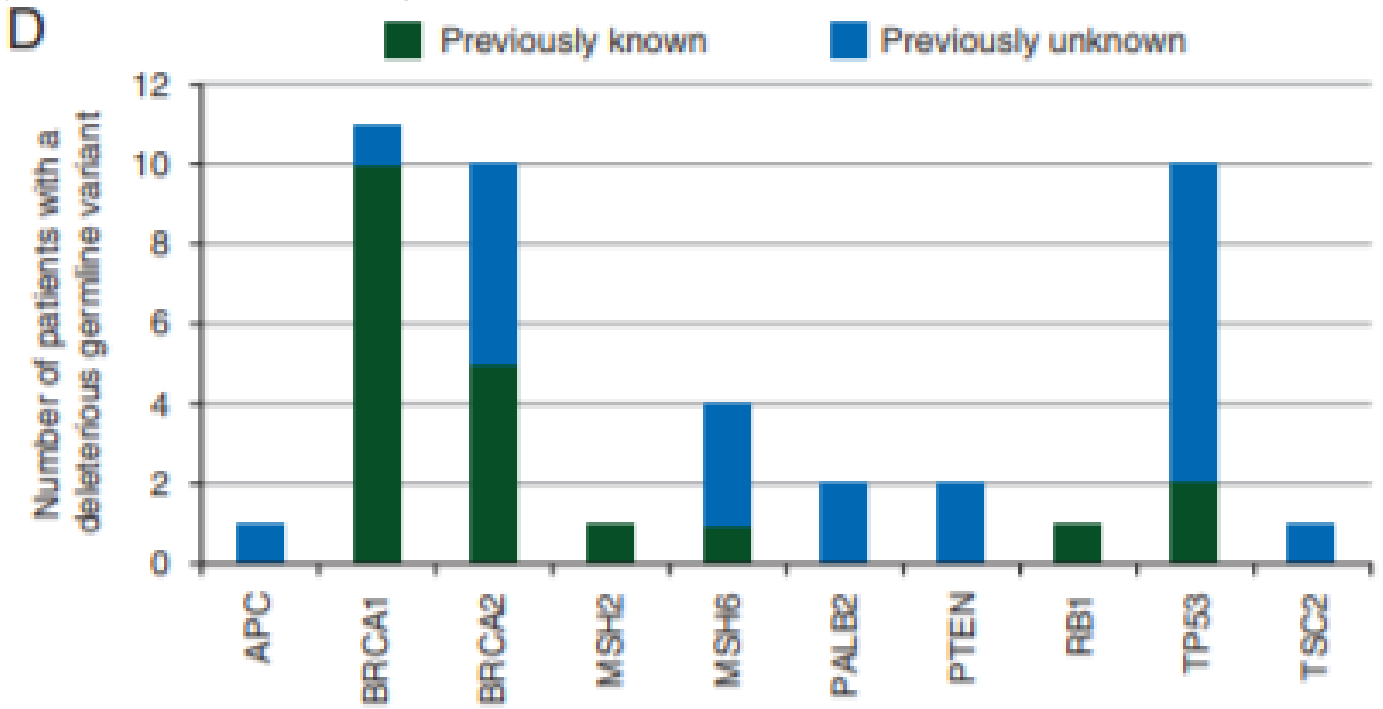
A – Confirmation of a previously identified cancer predisposition syndrome

B- Identification of a cancer predisposition syndrome in an eligible case

C- Identification of a cancer predisposition syndrome in a non eligible case

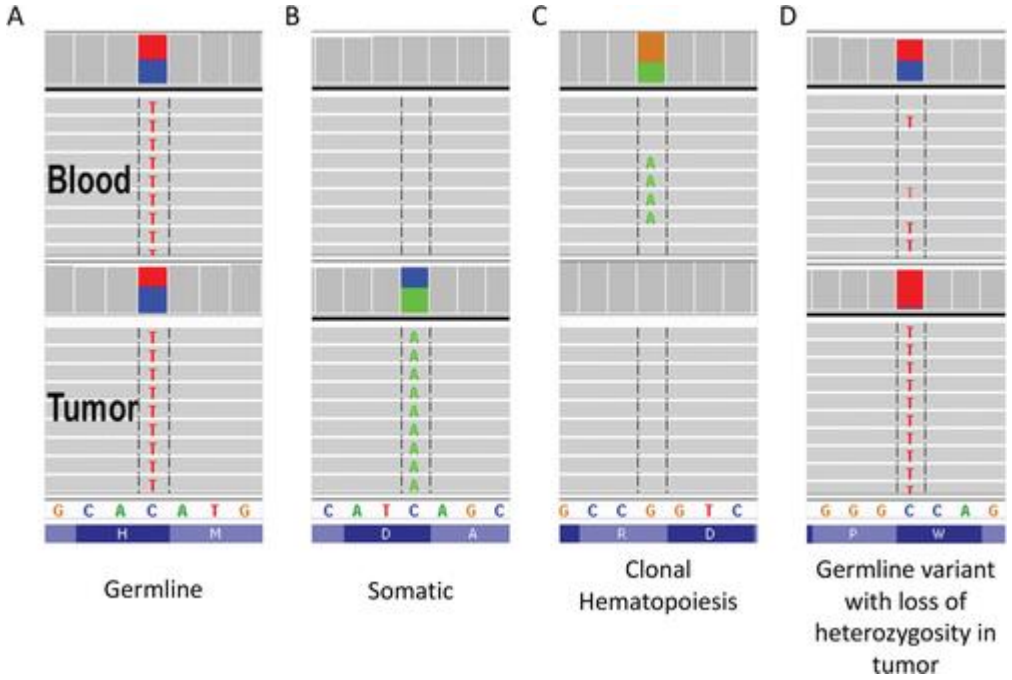
Restriction < 30 years old

- *RB1*
- *APC*
- *NF1*
- *TP53*

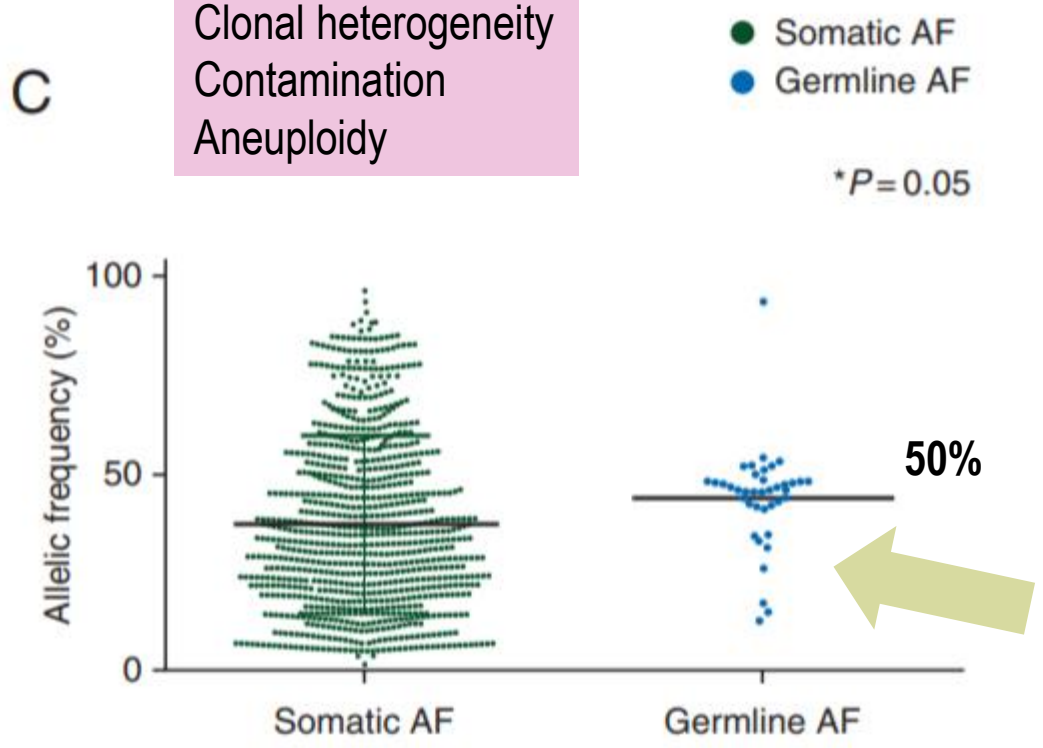


HOW TO IDENTIFY GERMLINE ALTERATION ?

Variant Allele Frequency - VAF



Clonal heterogeneity
Contamination
Aneuploidy

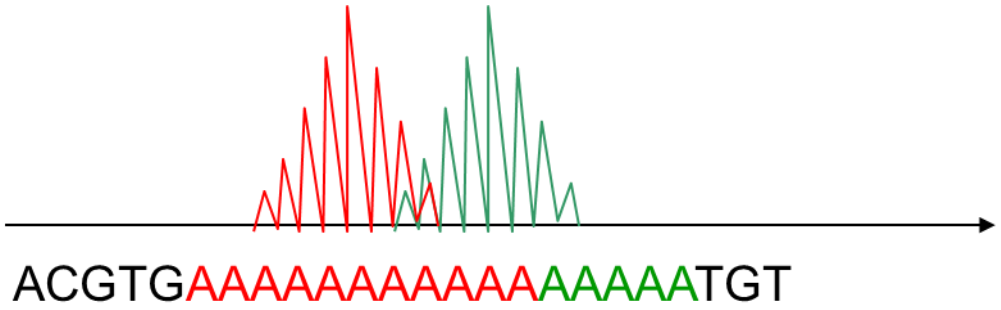


Mandelker, Diana, et Liying Zhang. « The Emerging Significance of Secondary Germline Testing in Cancer Genomics ». *The Journal of Pathology* 244, nº 5 (2018): 610-15..

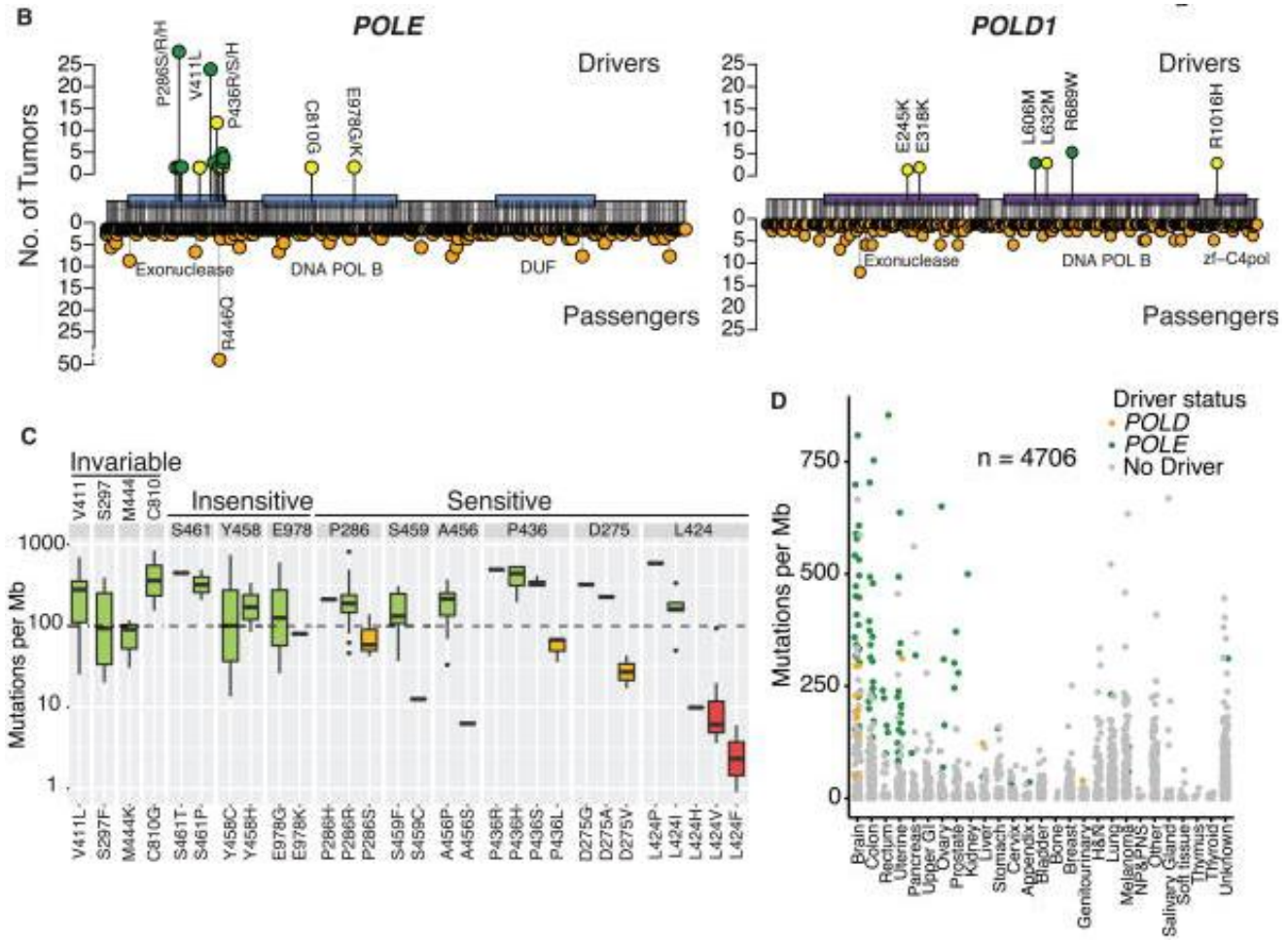
Meric-Bernstam, F., L. Brusco, M. Daniels, C. Wathoo, A. M. Bailey, L. Strong, K. Shaw, et al. « Incidental Germline Variants in 1000 Advanced Cancers on a Prospective Somatic Genomic Profiling Protocol ». *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 27, nº 5 (2016): 795-800.

INDIRECT IDENTIFICATION
CASE OF HYPERMUTATED CANCER

Indirect findings to germline mutation



Signature can lead to germline testing



Campbell, Brittany B., Nicholas Light, David Fabrizio, Matthew Zatzman, Fabio Fuligni, Richard de Borja, Scott Davidson, et al. “Comprehensive Analysis of Hypermutation in Human Cancer.” *Cell* 171, no. 5 (November 16, 2017):.

RECOMMANDATIONS TO CONFIRM

1- Adequat classification of the variants

restriction to class 4 and 5 / high actionability

2- Appropriate germline sample for validation

3- Validation in specialist genetic labs

4- Reference to a specialist genetics service for the follow-up and management of the familly

Mandelker, D, M Donoghue, S Talukdar, C Bandlamudi, P Srinivasan, M Vivek, S Jezdic, et al. « Germline-Focussed Analysis of Tumour-Only Sequencing: Recommendations from the ESMO Precision Medicine Working Group ». *Annals of Oncology* 30, nº 8 (1 août 2019): 1221-31.

CHIP – MOSAICISM - TUMOR

GERMLINE

Decrease in the limit of detection => low VAF under 50%

- post-zygotic mosaicism

DE NOVO mutation (ex. TP53 / APC)

contribution to LFS of de novo mutations to at least 14% (1)

SOMATIC

- Age acquired clonal mosaicism (2-3)
- Treatment related clonal mosaicism

CLONAL HEMATOPOIESIS MUTATIONS

1- Renaux-Petel, Mariette,, et al. « Contribution of de Novo and Mosaic TP53 Mutations to Li-Fraumeni Syndrome ». *Journal of Medical Genetics* 55, nº 3 (2018): 173-80.

2-Coombs, Catherine C., et al. « Identification of Clonal Hematopoiesis Mutations in Solid Tumor Patients Undergoing Unpaired Next-Generation Sequencing Assays ». *Clinical cancer research : an official journal of the American Association for Cancer Research* 24, nº 23 (1 décembre 2018): 5918-24.

3-Suehara, Yasuhito et al « Mutations Found in Cell-Free DNAs of Patients with Malignant Lymphoma at Remission Can Derive from Clonal Hematopoiesis ». *Cancer Science* 110, nº 10 (octobre 2019): 3375-8

CLINICAL RELEVANCE

Classification – only pathogenic / likely pathogenic variant

Plon, Sharon E, et al. « Sequence Variant Classification and Reporting: Recommendations for Improving the Interpretation of Cancer Susceptibility Genetic Test Results ». Human Mutation 29, nº 11 (novembre 2008): 1282-91

Classification of variant	Description	Likelihood of Being Pathogenic
Class 5	Pathogenic	>95%
Class 4	Likely pathogenic	>90%
Class 3	Variant of unknown significance	10-90%
Class 2	Likely benign	<10%
Class 1	Benign	<5%

Germline mutation is not systematically related to the disease

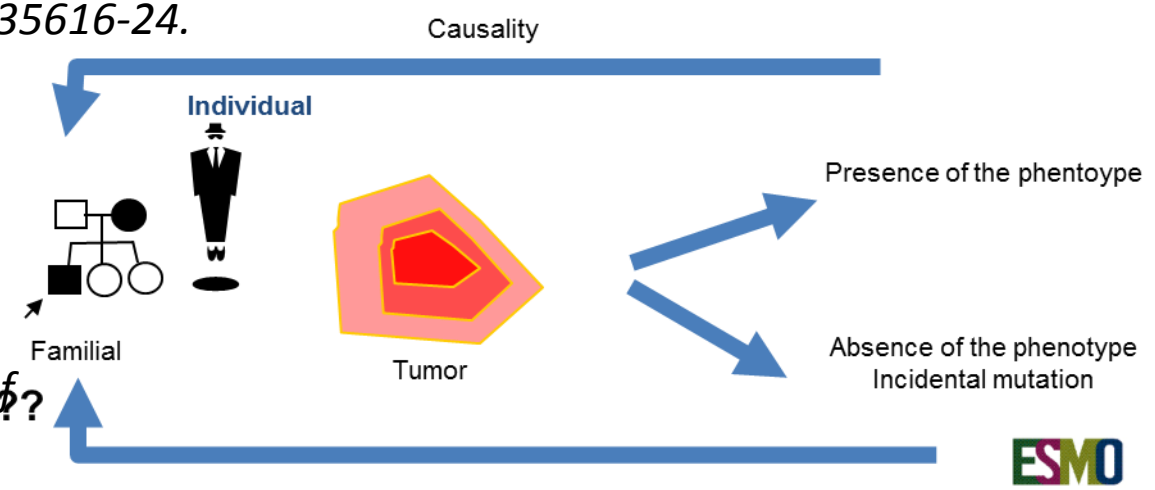
Curtit, Elsa, Vanessa Benhamo, Nadège Gruel, Tatiana Popova, Elodie Manie, Paul Cottu, Odette Mariani, et al. « First Description of a Sporadic Breast Cancer in a Woman with BRCA1 Germline Mutation ». Oncotarget 6, nº 34 (3 novembre 2015): 35616-24.

Incidental germline mutation and risk related

General population of women : 0.64% germline mutation

42% not have a first-degree relative with cancer

Rowley, Simone M., et al. « Population-Based Genetic Testing of Asymptomatic Women for Breast and Ovarian Cancer Susceptibility ». Genetics in Medicine: 21, nº 4 (2019): 913-22.



LIMIT OF THIS DETECTION

Variant validation – discrepancy between somatic / germline geneticist

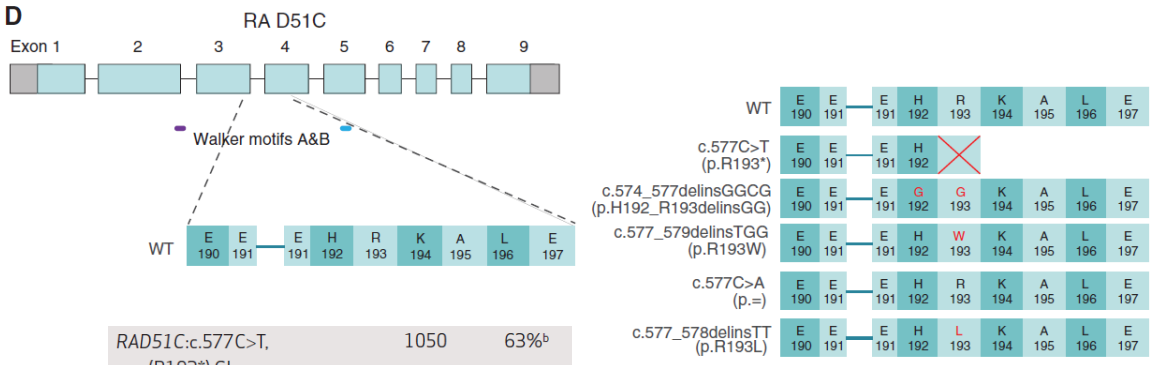
"Pathogenic variants on TGP test results were found to differ 13% and 5% of the time compared with ClinVar interpretations and germline test results"
Moody, Emily W., Jennie Vagher, Whitney Espinel, David Goldgar, Kelsi J. Hagerty, et Amanda Gammon. « Comparison of Somatic and Germline Variant Interpretation in Hereditary Cancer Genes ». *JCO Precision Oncology*, nº 3 (30 octobre 2019): 1-8. https://doi.org/10.1200/PO.19.00144.

Technology dependancy – VAF estimation / coverage

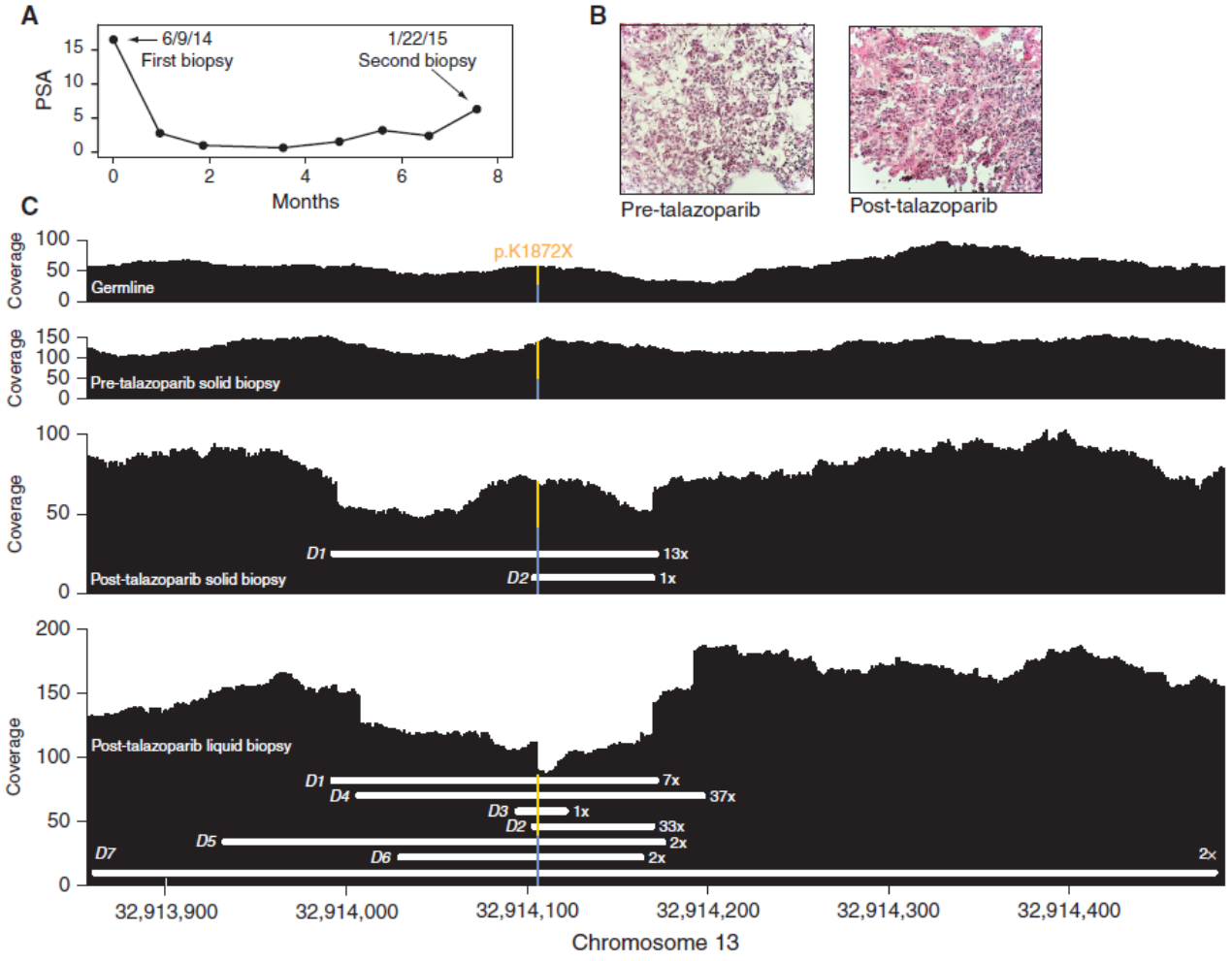
Other mechanisms of inactivation – large rearrangements – splicing events

Loss of germline allele – reversion - inactivation

REVERSION



RAD51C:c.577C>T, p.(R193*) GL	1050	63%[b]
RAD51C:c.577_579delinsTGG, p.(R193W) 2° MUT	1050	10%[b]
RAD51C:c.577C>A, p.(=) 2° MUT	1050	7%[b]
RAD51C:c.574_577delinsGGCG, p.(H192_R193delinsGG) 2° MUT	1021	3%[b]
RAD51C:c.577_578delinsTT, p.(R193L) 2° MUT	1050	2%[b]



Kondrashova O et al Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. Cancer Discov. 2017 Sep;7(9):984-998

Quigley D, et al.
Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors. Cancer Discov. 2017 Sep;7(9):999-1005.

NOT ALL CANCERS ARE EQUIVALENT

ON – Tumor

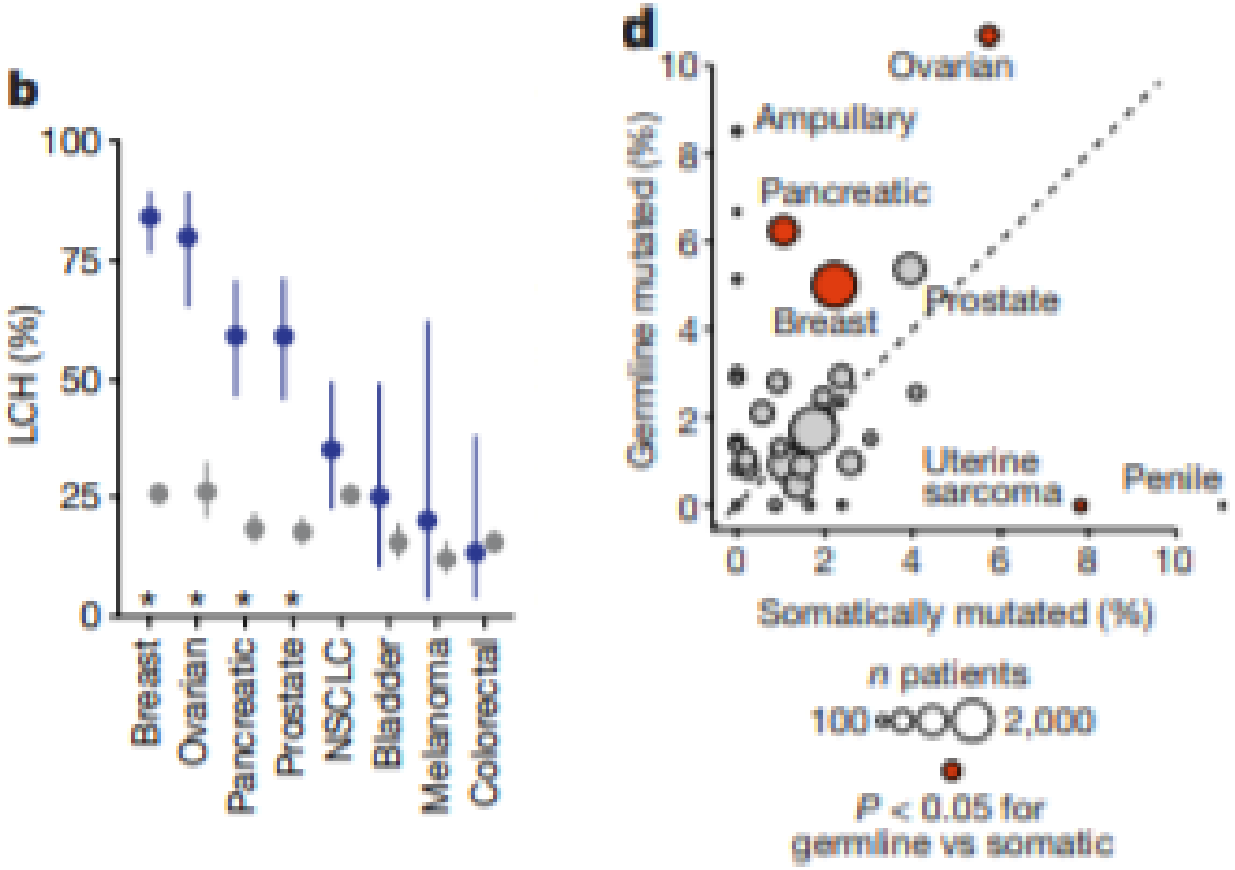
OFF - Tumor

Table 2. Characteristics of patients with pathogenic germline variants

	All patients	Patients with pathogenic germline variants, *N* (%)
Median age at diagnosis	50	45*
Personal history of more than one cancer	72 (7%)	3 (7%)
Tumor types		
Breast	251	17 (6.8%)
TNBC	86	6 (7%)
HER2+	24	2 (8.5%)
HR+	141	9 (6.4%)
Colon	156	6 (3.8%)
Brain	152	3 (2.0%)
Melanoma	139	3 (2.2%)
Sarcoma	95	3 (3.2%)
Ovary	36	5 (14%)
Other	171	6 (3.5%)

*$P = 0.01$ by unpaired two-tailed *t*-test.
TNBC, triple-negative breast cancer.

Meric-Bernstam, F., et al. *Annals of Oncology Oncology* 27, nº 5 (2016): 795-800.



Jonsson, Philip, Chaitanya Bandlamudi, Michael L. Cheng, Preethi Srinivasan, Shweta S. Chavan, Noah D. Friedman, Ezra Y. Rosen, et al. « Tumour Lineage Shapes BRCA-Mediated Phenotypes ». *Nature* 571, nº 7766 (juillet 2019): 576-79.

NOT ALL CANCERS ARE EQUIVALENT

Renal cancer

16% in advanced stage III or IV)Renal Cell Carcinoma

Carlo, Maria I., Semanti Mukherjee, Diana Mandelker, Joseph Vijai, Yelena Kemel, Liying Zhang, Andrea Knezevic, et al. « Prevalence of Germline Mutations in Cancer Susceptibility Genes in Patients With Advanced Renal Cell Carcinoma ». *JAMA Oncology* 4, nº 9 (01 2018): 1228-35.

Ovarian cancer – high grade serous carcinoma

~30% germline mutations in HR genes

1- KP Pennington Clin Cancer Res; 20(3) February 1, 2014

2- Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016 Jun;60:49-58

Lung cancer

3.8% of pathogenic germline variants

Tian, Panwen, Xiangyang Cheng, Zhengyi Zhao, Yuzi Zhang, Celimuge Bao, Yanyan Wang, Shangli Cai, Guowei Ma, et Ying Huang. « Spectrum of Pathogenic Germline Mutations in Chinese Lung Cancer Patients through Next-Generation Sequencing ». *Pathology Oncology Research: POR*, 12 novembre 2019.

«

SELECTION OF ADVANCED DISEASE

Colorectal

Polyps
0,8%

→

Colorectal cancer
3,8%

Gordon, Adam S.,, et al. « Rates of Actionable Genetic Findings in Individuals with Colorectal Cancer or Polyps Ascertained from a Community Medical Setting ». *The American Journal of Human Genetics* 105, nº 3 (5 septembre 2019): 526-33..

Prostate

Prostate cancer
BRCA2
Inclusion – young age
1,2%

→

Prostate cancer
BRCA2
Inclusion – advanced metastatic cancer
5,3%
Other genes – 11,8%

Kote-Jarai, Z., D et al. « BRCA2 Is a Moderate Penetrance Gene Contributing to Young-Onset Prostate Cancer: Implications for Genetic Testing in Prostate Cancer Patients ». *British Journal of Cancer* 105, nº 8 (11 octobre 2011): 1230-34.
Pritchard, Colin C., Joaquin Mateo, Michael F. Walsh, Navonil De Sarkar, Wassim Abida, Himisha Beltran, Andrea Garofalo, et al. « Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer ». *The New England Journal of Medicine* 375, nº 5 (4 août 2016): 443-53.

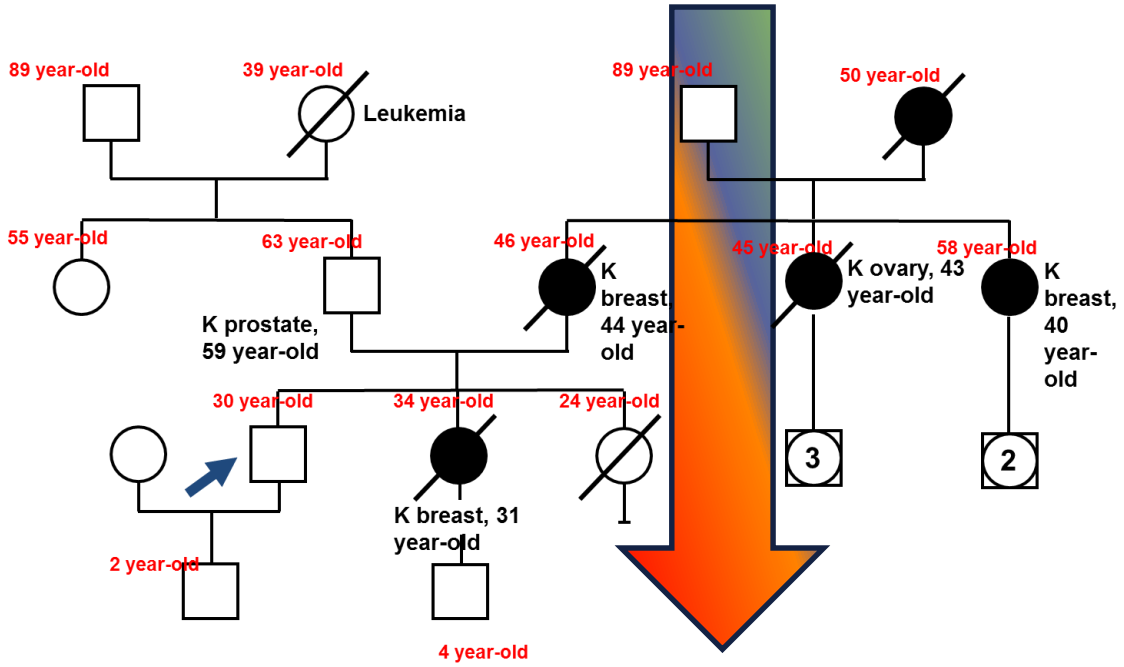
WHY UNCLASSIFIED VARIANT SHOULD BE TAKEN INTO ACCOUNT ?

Assessment of variants is done only for high-risk families and only for this level of risk

Process of variant assessment :

- High-risk family and co-segregation
- Histological data
- Functional data (RNA, protein)
- Co-occurrence (no bi-allelic *BRCA1*, rare bi-allelic *BRCA2*)
- Somatic signature

NEUTRAL
« Class 1 »



CAUSAL
« Class 5 »

PATIENT PREFERENCES AND REGULATION

No explicit consent for tumor testing

Oncologist / pathologist initiative

Germline testing = specific organization / authorization

Strict or list regulation on incidental findings

Preferences

- 99% interest for secondary germline variants (1)
- 94% interest for germline actionable variants (4)
- 77% for serious but preventable disease (2)
- 56% for serious but unpreventable disease (2)
- 49% for unknown significance variants (2)

Questions

- Right to know
- Information quality
- Clinical utility
- Asymptomatic to at risk
- Psychological impact
- Familial impact

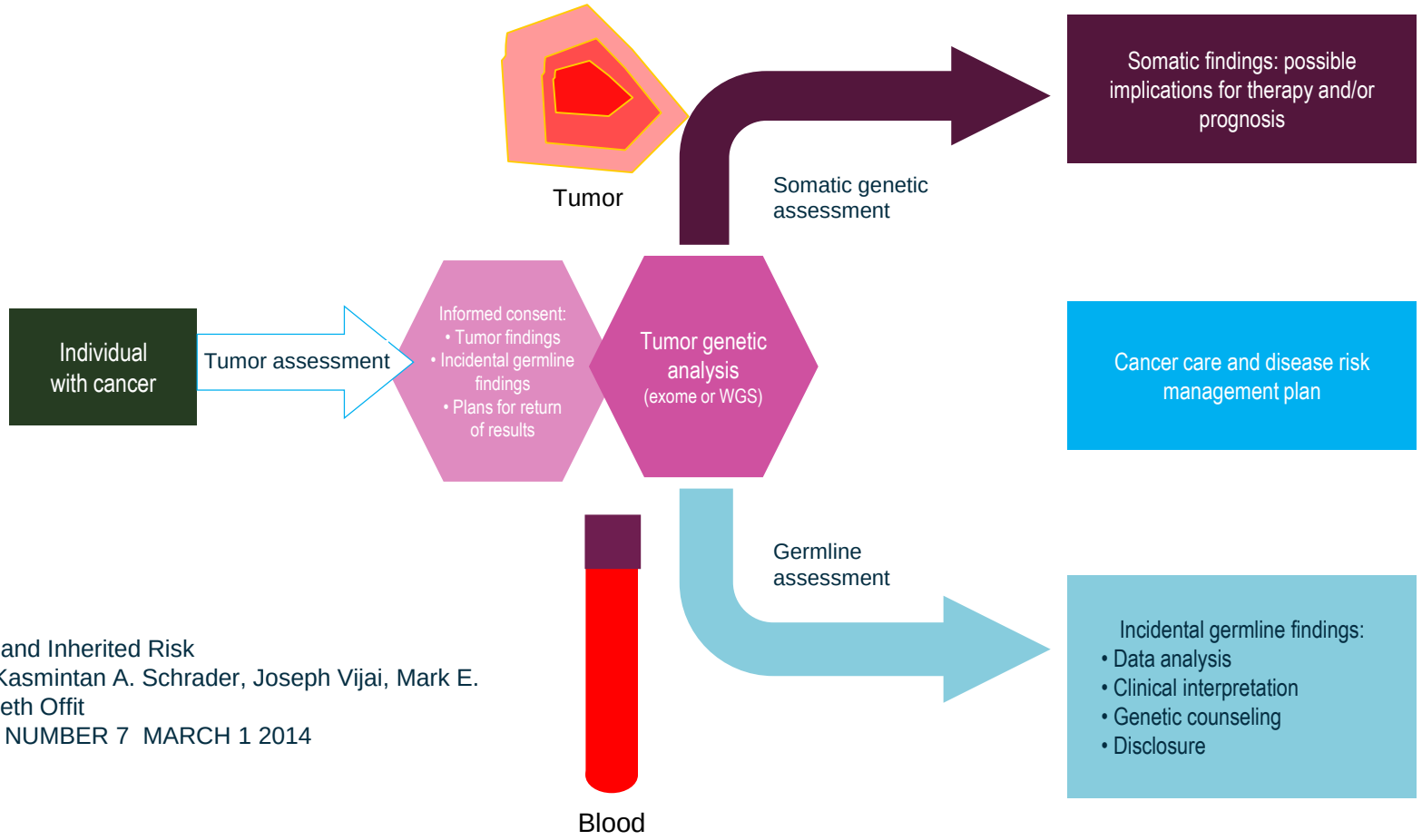
1- Yusuf, Rafeek A., Deevakar Rogith, Shelly R. A. Hovick, Susan K. Peterson, Allison M. Burton-Chase, Bryan M. Fellman, Yisheng Li, Carolyn McKinney, Elmer V. Bernstam, et Funda Meric-Bernstam. « Attitudes toward Molecular Testing for Personalized Cancer Therapy ». *Cancer* 121, nº 2 (15 janvier 2015): 243-50

2- Yushak, Melinda L., Gang Han, Sara Bouberhan, Lianne Epstein, Michael P. DiGiovanna, Sarah S. Mougalian, Tara B. Sanft, et al. « Patient Preferences Regarding Incidental Genomic Findings Discovered during Tumor Profiling ». *Cancer* 122, nº 10 (2016): 1588-97.

3- Hamilton, Jada G., Elyse Shuk, Margaux C. Genoff, Vivian M. Rodríguez, Jennifer L. Hay, Kenneth Offit, et Mark E. Robson. « Interest and Attitudes of Patients With Advanced Cancer With Regard to Secondary Germline Findings From Tumor Genomic Profiling ». *Journal of Oncology Practice* 13, nº 7 (2017): e590-601.

4- Stjepanovic, Neda, Tracy L. Stockley, Philippe L. Bedard, Jeanna M. McCuaig, Melyssa Aronson, Spring Holter, Kara Semotiuk, et al. « Additional germline findings from a tumor profiling program ». *BMC Medical Genomics* 11 (9 août 2018).

CONCLUSION



Cancer Genomics and Inherited Risk
Zsofia K. Stadler, Kasmintan A. Schrader, Joseph Vijai, Mark E. Robson, and Kenneth Offit
JCO VOLUME 32 NUMBER 7 MARCH 1 2014

CONCLUSION

- Real impact of the incidental findings in tumor molecular screening
- Extension of the gene screening related to drugs / clinical trials
- Need for specific process in MTB to take them into account
- Need for specific patient information and/or consent

BE PREPARED !

THANK YOU FOR YOUR ATTENTION

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