DISCLOSURE OF INTEREST

Advisory board and travel: AstraZeneca – BMS
Research grant: AstraZeneca
Advisory 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


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
Tumor testing from hotspot mutations in oncogenes
- Expansion to full coding region of oncogenes and tumor suppressor 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

Panel TruSight Oncology 500

Non-small cell lung cancer
Colon cancer
Rectal cancer
Melanoma
Breast cancer
Myelodysplastic syndromes
Neuroendocrine tumors
Myeloproliferative neoplasms
Uterine neoplasms
Gastric cancer
Acute myeloid leukemia
Cervical cancer
Pancreatic adenocarcinoma

Percentage of genetic markers included

Data source: illumina

* The products to evaluate DNA and RNA variants consist of the TruSight Oncology 500 DNA panel and the TruSight Tumor 150 RNA panel.
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**

Overall survival according to KRAS mutation

- Non mutated KRAS
- Mutated KRAS

p=0.016


**BRCA1**


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Noonan syndrome

AAFP

SOLO1

60.4% progression free at 3 years

26.9% progression free at 3 years

ESMO
HETEROGENEITY IN TISSUE

TUMOR

% NEOPLASTIC CELLS

HEMATOPOIETIC

SOMATIC

GERMLINE
HETEROGENEITY IN SAMPLES

PLASMA
CtDNA
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


WHAT IS RELEVANT?
ACMG INCIDENTAL FINDINGS TO CANCER

All genes
ACMG 59 genes

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

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

ESMO RECOMMENDATIONS

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

INDIRECT IDENTIFICATION
CASE OF HYPERMUTATED CANCER

Indirect findings to germline mutation

ACGTGAAAAAAAAAAATGT

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- Adequate 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 family

CHIP – MOSAICISM - TUMOR

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)


3- Suehara, Yasuhiro 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, n° 11 (novembre 2008): 1282-91

Germline mutation is not systematically related to the disease


Incidental germline mutation and risk related

General population of women : 0.64% germline mutation
42% not have a first-degree relative with cancer

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”

Technology dependancy – VAF estimation / coverage

Other mechanisms of inactivation – large rearrangements – splicing events

Loss of germline allele – reversion - inactivation
Kondrashova O et al. Secondary Somatic Mutations Restoring \(<\!\!\!<i>\text{RAD51C}\!\!\!\!\!\>\) and \(<\!\!\!<i>\text{RAD51D}\!\!\!\!\!\>\) Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. Cancer Discov. 2017 Sep;7(9):984-998.

NOT ALL CANCERS ARE EQUIVALENT

ON – Tumor
OFF - Tumor

Table 2. Characteristics of patients with pathogenic germline variants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>Patients with pathogenic germline variants, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis</td>
<td>50</td>
<td>45* (6.6%)</td>
</tr>
<tr>
<td>Personal history of more than one cancer</td>
<td>72 (7%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Tumor types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>251</td>
<td>17 (6.8%)</td>
</tr>
<tr>
<td>TNBC</td>
<td>86</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>HER2+</td>
<td>24</td>
<td>2 (8.5%)</td>
</tr>
<tr>
<td>HR+</td>
<td>141</td>
<td>9 (6.4%)</td>
</tr>
<tr>
<td>Colon</td>
<td>156</td>
<td>6 (3.5%)</td>
</tr>
<tr>
<td>Brain</td>
<td>152</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>139</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>95</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td>Ovary</td>
<td>36</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>171</td>
<td>6 (3.5%)</td>
</tr>
</tbody>
</table>

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


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, n° 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

Lung cancer
3.8% of pathogenic germline variants
**SELECTION OF ADVANCED DISEASE**

### Colorectal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyps</td>
<td>0.8%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3.8%</td>
</tr>
</tbody>
</table>


### Prostate

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer BRCA2 Inclusion – young age</td>
<td>1.2%</td>
</tr>
<tr>
<td>Prostate cancer BRCA2 Inclusion – advanced metastatic cancer</td>
<td>5.3%</td>
</tr>
<tr>
<td>Other genes</td>
<td>11.8%</td>
</tr>
</tbody>
</table>


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
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

CONCLUSION

Cancer Genomics and Inherited Risk
Zsofia K. Stadler, Kasminian 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