Molecular pathology practice in Europe: how we do it

The French organisation

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Who performs MP in France?

- Pathologists (MD), molecular geneticists (MD, PharmD), biologists (MD, PharmD)
- Only one quarter of MP is performed by pathologists
- There is no legal authorization to practice somatic MP (in contrast to molecular oncogenetics for hereditary mutations)
- There is no legal authorisation or special degree/diploma to perform MP for pathologists or molecular geneticists or biologists
- But according to accreditation requirements, you must prove you have training/degree in this field (a molecular pathology PhD is good!)
- Hence, by default, MP is considered to be part of medical biology
How is MP done? (Sanger, NGS, ready to use/automatic devices)

• In France, MP is performed in solid tumors (for targeted therapies), haematopathology, sarcoma and cerebral tumor diagnosis

• MP started with Sanger, then SNaPshot, RealTime PCR, Pyrosequencing and now NGS: NGS was stimulated by INCa in order to provide “NGS to everyone in need”

• Automatic devices (such as Ydilla®) are more and more used for their rapidity or simplicity (small labs)
Since 2006 a program has been developed in France to facilitate the assessment and use of Biomarkers for patients with targetable cancers (with actionable driver mutation)

The French Project: Centralization/Regionalization, free access for patients, evaluation and quality control

Accelerating progress To face cancers
Ensuring equity of access to innovation France organisation of molecular centres for personalised medicine

Provides nationwide molecular diagnostic tests

The programme is operated by INCa/Ministry of Health since 2006

- **Objectives**
  - Perform molecular testing for all patients;
  - Whatever the healthcare institution status (public hospitals, private hospitals etc.);
  - Perform high quality tests;
  - **Leukemia and solid tumors**

- **28 regional centres**
  - Partnerships between several laboratories located in University hospitals and cancer centres
  - Regional organization
  - Cooperation between pathologists and biologists
  - Quality control schemes
  - Accredited according to ISO 15189 standard (COFRAC)
MP acts are not part of the French National Social Security system
Since 2006, MP was initially financed by INCa and then by the Ministry of Health through annual funding adjusted to annual activity reports
Then in 2015, a great idea emerged …
The « Référentiel des actes Innovants Hors Nomenclature (RIHN) » set up by the DGOS (Direction Générale de l'Offre de Soins)
RIHN: principles

Two lists of biology/pathology acts not covered by the Social Security system
- "Liste complémentaire", list of biology/pathology acts, already medically validated waiting for SS reimbursement
- RIHN, list of new innovative acts, to be evaluated in a 3 to 5 year period, and then sent for SS reimbursement
- Each act has a "cost" in € (indicative valuations)

<table>
<thead>
<tr>
<th>Code acte liste complémentaire</th>
<th>Libellé de l'acte de la liste complémentaire/RIHN</th>
<th>Valorisation maximale</th>
</tr>
</thead>
<tbody>
<tr>
<td>N501</td>
<td>Recherche de la mutation BRAF V600 par technique moléculaire</td>
<td>116,10 €</td>
</tr>
<tr>
<td>N504</td>
<td>Séquençage EGFR : 4 exons</td>
<td>315,90 €</td>
</tr>
<tr>
<td>N523</td>
<td>Forfait mutationnel cancer colorectal métastatique (KRAS/NRAS) 6 exons</td>
<td>440,10 €</td>
</tr>
<tr>
<td>N452</td>
<td>Forfait séquençage haut débit (NGS) &lt; 20 kb</td>
<td>882,90 €</td>
</tr>
</tbody>
</table>
Great ideas are not always successful!

Initially, the RIHN system was simple

- Each year (N), the MP platform will produce the test free of charge for all medical centres in the region
- In January N+1, MP platforms will declare the number of tests produced in N
- In June N+1, the platform will receive funding

But...

The amount of money provided for the RIHN/Liste Complémentaire is stable and limited (380,1 M €)

Today, fewer than 10 acts have moved from the LC to the SS system

So the demand is more than the budget allows

In 2017, France produced
- 370 M € “liste complémentaire”
- 300 M € “RIHN”

So the state for 2018 funding has granted only 53.5% of the amount of money declared by each platform resulting in tsunamis in hospital finance departments which decided to charge all the different medical centres!

Now it is a “FarWest” setting: everyone tries to perform MP at a lower cost than the RIHN reference in order not to lose money

“NGS for every one” is now compromised, hospitals prefer simple less expensive tests (Snapshot)
Are MP results part of the pathology report?

- It depends...
- Usually not
- INCa has proposed a standardized MP report

https://www.e-cancer.fr/Professionnels-de-sante/Les-therapies-ciblees/Les-plateformes-de-genetique-moleculaire-des-cancers/Le-programme-d-assurance-qualite-des-plateformes
What about accreditation according to ISO 15189 standard?

• MP is part of medical biology, so accreditation to ISO 15189 is mandatory

• In 2020, every centre performing MP must be fully accredited by the French authority (COFRAC)

• Each test (ie. SNaPshot, NGS etc.) must be accredited

• When fully accredited, MP Practitioners (Pathologists or Biologists) will be qualified to perform MP
How are pathologists trained for MP?

• “Older” Pathologists can do a special training for MP (Inter University Diploma), with a one month internship on an INCa platform.

• Since 2018, young pathology residents started to do a 6 month internship on an INCa platform with annual national E-learning and national exam.

• No specific training (to my knowledge) for biologists...
How many MP tests are performed in a year? Description of these tests

MOLECULAR TESTING for Cancers in FRANCE: a nationwide project, 2017 report

- 81000 patients were molecularly tested
- 45000 molecular tests by NGS
- Access to 35 targeted therapies
Predictive tests for targeted therapy prescription

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cancer type</th>
<th>Targeted therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCR-ABL</strong></td>
<td>Chronic Myeloid Leukemia/Acute Lymphoblastic</td>
<td>Imatinib, nilotinib, dasatinib, ponatinib, bosutinib</td>
</tr>
<tr>
<td><strong>ABL</strong> translocation</td>
<td>Leukemia</td>
<td></td>
</tr>
<tr>
<td><strong>KIT and PDGFR</strong></td>
<td>GIST</td>
<td>Imatinib, nilotinib, dasatinib</td>
</tr>
<tr>
<td><strong>mutations</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>HER2</strong></td>
<td>Breast and gastric cancers</td>
<td>Trastuzumab, lapatinib (breast)</td>
</tr>
<tr>
<td><strong>amplification</strong></td>
<td></td>
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<tr>
<td><strong>RAS</strong></td>
<td>Colorectal cancer</td>
<td>Panitumumab and Cetuximab</td>
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<tr>
<td><strong>mutations</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>EGFR</strong></td>
<td>Lung cancer</td>
<td>NIB</td>
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<tr>
<td><strong>mutations</strong></td>
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<tr>
<td><strong>ALK-ROS</strong></td>
<td>Lung cancer</td>
<td>NIB</td>
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<tr>
<td><strong>translocations</strong></td>
<td></td>
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<tr>
<td><strong>BRAPV600</strong></td>
<td>Melanoma</td>
<td>Vemurafenib, dabrafenib</td>
</tr>
</tbody>
</table>

**SOLID TUMORS TESTED in 2019**
- Breast cancer
- Ovarian cancer
- Stomach cancer
- Gastrointestinal stromal tumors (GIST)
- Colorectal cancer
- Melanoma
- Lung cancer
- Sarcomas
- Neuroblastoma
- Glial tumors
A search for EGFR activating mutations was carried out for 28,151 patients.

A search for EGFR mutations on circulating tumor DNA was carried out in 4,358 patients. An ALK rearrangement search was carried out in 20,042 patients.

17,718 patients had translocation research of ROS1.

The search for mutations of EGFR and other oncogenes (KRAS, BRAF, HER2, PI3KCA, etc.) was carried out by NGS for 18,022 patients.
MOLECULAR TESTING for Cancers in FRANCE: a nationwide project, 2008-2017 progression

Lung ADK

28,151 patients
MOLECULAR TESTING for Cancers in FRANCE: a nationwide project, 2017 report (NGS)

45000 Molecular tests by NGS

Saved from: http://lesdonnees.e-cancer.fr/Themes/Soins/Les-tests-de-genetique-somatique/Les-tests-de-genetique-somatique
- What about collaboration with commercial solutions as Foundation Medicine, Myriad Genetics ...
  Clinicians are very fond of these tests and could ask for them to be performed. But these tests should not be reimbursed by the RIHN system as they are not performed by a French Pathologist or Biologist.

- What is the involvement of the pharmaceutical industry?
  Helpful, but not allowed by law to fund any theranostic tests related to their drugs.

- Are Liquid Biopsies part of MP practice?
  Yes, and are more and more used especially in lung tumors (diagnostic, resistance mutations etc)
Conclusion

• In France, MP is performed for all patients in need
• But for how long, considering the current difficulties of reimbursement by the Ministry of Health (RIHN)?
• Young pathologists will be (well) trained and will use MP in their daily practice

To coin a phrase, MP is part of Pathology!
Carrefour Pathologie 2019
4 au 7 novembre
Palais des Congrès Paris

• Sessions médico-techniques les 5 et 6 novembre sur les thèmes de la sénologie et du workflow
• Sessions INSERM le 7 novembre
• Sessions AIP le 7 novembre sur le thème de la microbiopsie ganglionnaire
• Le programme détaillé est en ligne sur www.carrefour-pathologie.org
Thank you for your attention