PMD 164 – Impact of HER2 testing quality improvement from a health economic perspective
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Background
Each year in France, more than 50,000 women are newly diagnosed with breast cancer and 90,000 HER2 tests are performed.
For HER2+ breast cancer patients, initiating the right treatment at an early stage increases the chance of survival and the accurate determination of HER2 status is clinically crucial.
Between 2007 and 2014, quality of HER2 testing improved significantly, leading to lower rates of HER2 status misclassified.

Conclusion
As targeted therapies’ offer increases more and more in cancer treatment, besides treatment efficacy, it appears crucial to optimize patients profiling with accurate testing in order to provide the right treatment for the right patient. The HER2 story illustrates and emphasizes the key role of a companion test to efficiently select patients.
HER2 testing interpretation improvement in France over the last 7 years has clearly contributed to reduce the economic burden of tumor misclassification.
Between 2007 and 2014, the decrease of HER2 false-negative rate (from 4% to 2%) and HER2 false-positive rate (from 10% to 7%) saved 542 patient lives and 25 million EUR (€), mainly coming from drug savings.
Continued investment in improving HER2 testing accuracy would ensure therapeutic and economic efficiency of breast cancer treatments. Further analysis could be performed to evaluate the societal cost of HER2 testing inaccuracy.

Objective
In an increasingly challenging environment within the French health care system, payers are interested to discuss the full value of a drug. A structured and standardized methodology was built in order to evaluate the public health impact of HER2 testing interpretation improvement in France since 2007.

Methods
A comprehensive decision tree was built according to HER2 status, diagnosis and disease progression at any stage of breast cancer (early and metastatic stages). Two simulations were conducted for year 2007 and 2014 according to HER2 testing improvement – see Figure 1.
Patients with tumors score of IHC 3+ or IHC 2+/ISH-positive were diagnosed HER 2-positive. Patients with tumor scores of IHC 0, IHC 1+ or IHC 2+/ISH-negative were considered HER2-negative.

Data
Epidemiologic data were obtaining from the French National Cancer Institute (InCa). All breast cancer patients are considered to be tested.
The rate of HER2+ and HER2- are extracted from the “HER France” register developed by the French Association for Quality Assurance in Histopathology and Cytopathology (AFaQAP).
Twice a year, AFaQAP offers laboratories the opportunity to participate to external quality assessment (EQA) of HER2 expression in breast cancer. The rate of HER2 status misclassified (false-positive and false-negative) were assessed using results of EQA based on misreading/mininterpretation rate. Discordance due to technical error is not considered.
Current use of trastuzumab (Herceptin®) and bevacizumab (Avastin®) was assessed using quarterly Roche database for analyzing market shares. Drug efficacy data are based on their Summary of Product Characteristics (SmPC).

Cost
Cost analysis considered intervention costs, costs of premature death, life years lost and drug costs, focused on drug registered on the French costly drug list (like trastuzumab and bevacizumab). No discount rate on costs was applied in the model.
Intervention costs are weighted according to public/private settings (396.37€ in public settings / 304.72€ in private settings).

Results & Discussion
The number of women whose tumors were classified as HER2-positive (FP) was estimated to be 7,700 in 2007 versus 528 in 2014. The corresponding value for women misclassified as HER2-negatives was 10,300 in 2007 versus 826 in 2014 – see Table 1.

The continuous improvement of HER2 testing interpretation between 2007 and 2014 has saved 155 more lives in 2014 than in 2007, and a total of 542 patient lives have been saved over the past 7 years in France. According to average death age by breast cancer in France (72.4 years) and female life expectancy (84 years, www.insee.fr), 6,287 years of life have been saved between 2007 and 2014 – see Table 2.

Table 2: Impact of HER2 testing quality improvement on survival between 2007 and 2014

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Year</th>
<th>N</th>
<th>Life years saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2007</td>
<td>13%</td>
<td>542</td>
</tr>
<tr>
<td>2</td>
<td>2014</td>
<td>6%</td>
<td>25 088 156</td>
</tr>
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Other costs were weighted according to public/private settings (396.37€ in public settings / 304.72€ in private settings).

Whatever the scenario tested, improvement in HER2 testing quality results in more lives saved than the base case scenario (most conservative), showing a minimal gain of 452 lives and a maximum gain of 1,580 lives – see Table 3.

Table 3: Sensitivity analysis

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Conclusion
FP rates were assumed to generate unnecessary trastuzumab costs, a ~6-month increase duration of treatment and no impact on clinical outcomes with similar disease-free survival rates between FP and truly HER2+ patients. FN results mainly lead to a shorter life-expectancy due to lack of targeted therapy and an increased risk of recurrence and progression to metastatic breast cancer (~40% relative risk).
The improvement of HER2 testing interpretation between 2007 and 2017 saved 25 million EUR (€). These savings are mainly the result of HER2 false-negative rate decrease and more than 30% come from Herceptin cost. Cost savings of 4 million EUR (€) were also achieved by intervention cost, at the two breast cancer stages – see Figure 3.

The continuous improvement of HER2 testing interpretation between 2007 and 2014 has saved 155 more lives in 2014 than in 2007, and a total of 542 patient lives have been saved over the past 7 years in France. According to average death age by breast cancer in France (72.4 years) and female life expectancy (84 years, www.insee.fr), 6,287 years of life have been saved between 2007 and 2014 – see Table 2.

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Figure 1: Decision tree of our management according to HER2 status, diagnose and disease progression (IHC: immuno histochemistry/ISH: in situ hybridisation)

Figure 2: Rate evolution of HER2 status misclassified between 2007 and 2014 (source: French Association for Quality Assurance in Histopathology and Cytopathology)

Figure 3: Cost differential at early and metastatic stages of breast cancer between 2007 and 2014 - results of the base-case analysis (in €/Year/Stage, ACC: Annualized Cost Change)