ESP EQAs: impact on quality improvement

A. Ryška - on behalf of ESP Foundation

The Fingerland Department of Pathology, Charles University Medical Faculty, Hradec Králové, Czech Republic
Concept of targeted therapy

“The ultimate goal of personalised medicine is to define a disease sufficiently to enable identification and treatment of only those patients most likely to respond“
Current landscape of EQA in pathology

• well-established pan-European providers
• well-established national providers
• national programs of interlab comparison
ESP EQA programs

- **RAS** (Colorectal cancer)
- Since 2009 KRAS, 2013 +NRAS
- today **RAS** - mandatory + **BRAF** (optional)

- **Lung**
- since 2012 - ALK IHC + FISH, later EGFR, KRAS
- 2014 - EGFR, ALK, ROS1
- 2015 - technical assessment of IHC slides
- today - **MOL** [EGFR, KRAS(opt), **BRAF** (opt)], **ALK**, **ROS1**, **PDL1**, **METex14**
Issues regarding the participation

• who has to participate
• who is required to participate
• who does participate
• who can afford to participate
One Europe – (at least) two worlds
Biomarkers testing in NSCLC

• survey conducted by the Central European Cooperative Oncology Group (CECOG)
• availability and reimbursement of molecular testing in NSCLC
## Routine testing – tumor types

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<th>EGFR</th>
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<th>ROS1</th>
<th>PD-L1</th>
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- **Green**: Adeno & Co.
- **Yellow**: Adeno + Squamous
- **Gray**: Not tested

Ryska A. et al. The Oncologist 2018;23:1–7
# Testing reimbursement

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- **Green**: Health Insurance (HI)
- **Yellow**: HI - limited
- **Red**: HI/Pharma Pharma
- **Blue**: Not reimbursed
- **Gray**: Not tested

Ryska A. et al. The Oncologist 2018;23:1–7
Issues regarding the participation

• who has to participate
• who is required to participate
• who does participate
• who can afford to participate
• how frequently to participate
• what are the expectations of participants
What exactly do we check in EQA

• biomarker in context of diagnosis?
  • BRAF in NSCLC, BRAF in CRC, BRAF in ctDNA
  • HER2 in breast cancer, HER2 in gastric cancer
Monalisa after one week in USA
What exactly do we check in EQA

• biomarker in context of diagnosis?
  • BRAF in NSCLC, BRAF in CRC, \textit{BRAF in ctDNA}
  • \textit{HER2 in breast cancer, HER2 in gastric cancer}

• \textbf{Result} of the method or \textit{presence} of the biomarker?
Detection of ALK Rearrangement by Immunohistochemistry in Lung Adenocarcinoma and the Identification of a Novel EML4-ALK Variant

Ka-Fai To, MBChB,*‡§ Joanna HM Tong, PhD,*‡§ King SF Yeung, BSc,*‡§ Raymond WM Lung, PhD,*‡§ Peggy PY Law, MPhil,*‡§ Shuk Ling Chau, MPhil,*‡§ Wei Kang, PhD,*‡§ Carol YK Tong, MPhil,*‡§ Chit Chow, PhD,*‡ Anthony WH Chan,* Linda KS Leung, MBBS,*‡ and Tony SK Mok, MBBS,*‡

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<td>+ve (42.5%)</td>
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- 3 methods available
- IHC
- FISH
- RT-PCR
What exactly do we check in EQA

• biomarker in context of diagnosis?
  • BRAF in melanoma, BRAF in CRC, *BRAF in ctDNA*
  • *HER2 in breast cancer, HER2 in gastric cancer*

• Result of the method or presence of the biomarker?
  • even the „same method“ can give dramatically different results – what is the „correct value“?
An issue well known from other disciplines
NSCLC - progression on 1st line TKI

~60% EGFR target alteration

T790M alone, 44%

10%

Bypass Tracks ~20%

SCLC with PI3K ~4%

PIK3CA ~1-2%

BRARER2 Amplification ~1%

No identification AR mechanism ~15-20%

T790M w/EGFR amplification

SCLC alone ~6%

MET amplification ~5%

EMT ~1-2%

Other EGFR point mutations 1-2%

Camidge, D. R. et al. (2014) Acquired resistance to TKIs in solid tumours: learning from lung cancer
EGFR in ctDNA – sensitivity of assays

True positive or false positive?

- EGFR+ patients with progression on 1st line TKI
- Testing of ctDNA with highly sensitive method
- Patients with T790M treated by osimertinib

Hochmair MJ et al. Targeted Oncology (2019) 14:75-83
Correct result of the predictive test - much more than the test itself

• preanalytical issues
• correct diagnosis (!)
• optimal tissue sample (cellularity)
• analytical phase (choice of optimal method, lab's performance)
• interpretation
• reporting - clinical relevance
Differences in staining quality may be massive

Supporting Figure 1. Example of good (top row) and weak (bottom row) ALK IHC staining patterns during the 2018 EQA scheme.

Keppens C et al. – manuscript in preparation
What do we require

- correct result
- correct and unbiased interpretation
- reporting of the result
- clinical recommendation
Case 1: L18.ALK1 (FISH)

Patient details:
Family name: Partenier
First name: Shalini
DOB: 03/11/1958
Sex: F

Diagnosis
NSCLC. Tumor right upper lobe infiltrating the pleura.
Sample type: FFPE, section of adenocarcinoma
Patient considered for targeted treatment

Molecular Diagnosis
Lung, right upper lobe (FFPE specimen):

Result from Fluorescence In Situ Hybridization:
ALK (break apart probe): No rearrangement

Comment
We use the FISH Abbott break apart probe ALK (Abbott / ref.nr: 06N38-033). The analysis shows no ALK Rearrangement.

Ordering customer, date of order, and electronic signature are integrated into our hospital IT system (pathowin plus) and therefore not added to the reports.
Real world examples (ESP Lung EQA)

How much does the mock report reflect the everyday reality???
Interpretation of test results

• should be given in the report

• suggestions for adequate clinical management and prediction of the effect of the genotype on therapy response

• “In general, NSCLC with this EGFR activating variant respond well to EGFR-TKI therapy.”

• direct patient advice should not be given

• laboratory has not the complete history and clinical data

• country-specific differences

With increasing number of studies, scoring systems and thresholds this becomes incredibly difficult
Threshold of positivity?
50% threshold – PDL1 negative

40%

10% threshold – PDL1 positive
## Scoring of PD-L1 IHC Tests in Lung Cancer

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<th>Antibody (developer) [drug against which the study validated the test]</th>
<th>Cutoff/Threshold</th>
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<td>22C3 (Dako) [pembrolizumab]</td>
<td>1% (used in training group): 1 study [4]&lt;sup&gt;a&lt;/sup&gt; 50% (determined as optimal cutoff): 1 study [4]&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>28–8 (Dako) [nivolumab]</td>
<td>1%: 3 studies [7, 10, 12]&lt;sup&gt;a&lt;/sup&gt; 5%: 2 studies [10, 11]&lt;sup&gt;a&lt;/sup&gt; 10%: 1 study [10]&lt;sup&gt;a&lt;/sup&gt; 50%: 1 study [11]&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>SP263 (Roche) [durvalumab]</td>
<td>25%: 3 studies [7, 14, 28]&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>SP142 (Roche) [atezolizumab]</td>
<td>1%: 2 studies [19, 20]&lt;sup&gt;a&lt;/sup&gt; 5%: 2 studies [19, 20]&lt;sup&gt;a,c&lt;/sup&gt; 50%: 1 study [20]&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>E1L3N (Cell Signaling Technology; reagent provider) [not applicable]</td>
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</table>

<sup>a</sup>Tested in tumor cells.  
<sup>b</sup>Tested in tumor-infiltrating immune cells.  
<sup>c</sup>Tested in tumor stroma
Are the tests replaceable?
HER2 testing in GC using 4B5 and CB11

Biopsies

Resections

Distribution of cases based on clinically used cut-offs for tumor cells (NSCLC, excluding cytology)
Subjectivity of the assessors
Subjective factor - critical in values near the threshold

Negativity ???
<1 % neoplastic cells ???
Issues for the providers

• which markers should be covered
• type of samples (real world x artificial)
  • Heterogeneity x unexpected results
• sources of samples
  • rare mutations, sufficient tissue availability
• selection of samples (which values, mutations, etc.) – overall difficulty of the program/run
• difficulty in long time perspective
## ESP Lung EQA Scheme: overview

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Avg. score: 3.8/5
Avg. score: 3.8/5
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Improvement over time

ESP EQA Lung experience

With increasing experience improves the performance of the lab and reliability of the tests

Impact of EQA on performance of a lab?

- 2012 (KRAS)
- 20% labs
- at least 1/10 samples incorrectly tested
Impact of EQA on performance of a lab?

- 2017 (RAS)
- Labs successfully passing EQA
- 5/274 samples incorrectly tested
Do we have really evidence based data?

• improvement in time – logical (although not automatic), result of EQA?
• no change in performance - does it really mean no improvement?
• overall performance - sum of all participants' results - not the same group!
• accredited vs. non-accredited labs
Issues for the providers

• feedback to individual participants
• feedback to industry (test manufacturers, pharma)
• education of participants
• use of human resources (experts, assessors)
• financial sustainability (fees x expenses, involvement of industry support)
Summary

• EQA in Europe – well established concept
• Extremely valuable results for all parties
• Multiple issues ahead - participation, design of the programs, tissue availability
• None of them is a „killer“, but many are a „pain in the neck“
Now this is not the end. It is not even beginning of the end. But it is, perhaps, the end of the beginning.

W. Churchill