A national project for the quality assessment of breast immunohistochemistry, involving 155 pathology laboratories distributed all over the Italian territory (19 regions), was carried out. The Project lasted one year from December 2014 to December 2015 and it was strongly supported by the Italian Society of Anatomic Pathology (SIAPEC/IAP). Proficiency tests were carried out by the Nordic Immunohistochemical Quality Control (NordiQC) organization. The main aim of the project was to investigate on the general performance of immunohistochemistry (ER, PR and HER2) in the field of breast cancer in the Italian territory, in order to emphasize any difference and give practical support to laboratories in daily practice.

The present review article focused on the description of this extraordinary pioneer Italian experience. Besides NordiQC results, further analysis concerning epidemiology and geographical distribution were done.

Aim of the study was to analyze the general results and to discuss on the benefits that a national quality control program may have if it became a mandatory service provided by the National Health Care System.

In general, the Italian data were in accordance with the general results obtained from the “official” NordiQC HER2, PR and ER assessments. A HER2 scoring consensus between labs and assessor group was achieved in 80% of cases.

Interestingly, what emerges from our study is that no substantial differences exist among the three Italian macro-areas (North, Center and South) in the quality of Immunohistochemistry performed for breast cancer. No statistically significant difference was even found between laboratories that perform more or less than 100 tests/year.

A National Quality Assurance program for breast immunohistochemistry: an Italian perspective

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Key words
Immunohistochemistry • HER2 • Quality control • Italian

Summary

Introduction

Standardization is a tool through which to ensure-safety, reliability and good quality in laboratory activity and pursuing it is essential in everyday medical practice1. In the field of anatomic pathology, immunohistochemistry (IHC) can no longer be considered only a diagnostic tool; it must be taken as a means for medical acts because of its prognostic and predictive properties2. Three main fields, each including numerous steps, take part of this technique and they all need to be standardized: pre-analytical, analytical and post-analytical. Recommendations have been issued involving each of them3-7. To standardize means to conform to a model. Many external proficiency testing (PT) programs8-10 aim to issue recommendations for the analytical steps useful to pur-suit this scope. About one-third of laboratories that participate in these programs achieve optimal results, while one-third are ‘good’ and one-third fail11,12, indicating that PT programs still have a long way to go.

In breast cancer, quantitative immunohistochemical evaluation of Estrogen Receptor (ER), Progesterone receptor (PR), HER2 and Ki67 is essential to address the therapeutic strategy13: identifying hormone responsive and HER2 amplified tumours may ensure patients a life-saving therapy or spare them for useless treatments in case of negative results. It follows that reducing the total number of false positive and false negative results is paramount in order to achieve the maximum of cures at the lowest price in terms of costs and side-effects14. Italy is the 4th-largest national economy in Europe. In 2000 Italy’s Healthcare System was regarded, by World Health Organization’s ranking, as the second best in

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The photos and technical data have been provided by NordiQC.
the world after France. According to the CIA World factbook, Italy has the world’s 14th highest life expectancy. The Italian National Outcomes Program permits measurement of variations in the quality and outcomes of care by region: Italy has the largest internal difference of gross domestic product (GDP) per capita between regions of any European country. Although in theory the entire healthcare system operates under one central ministry of health, the national index score of Italy is a mix of Northern Italian and Rome Green scores, and Southern Italian Red scores, resulting in a lot of Yellows (the performance of the respective national healthcare systems was graded on a three-grade scale for each indicator, where the grades had the meaning of Green = good, Yellow = so-so and Red = not-so-good).

In 2015, the Italian Society of Anatomic Pathology and Cytology (SIAPEC)/ International Academy of Pathology (IAP) promoted a National Quality Control Program on breast cancer IHC, involving 158 Italian labs. PTs were carried out by the Nordic Immunohistochemical Quality Control (NordiQC) organization.

The aim of this study is to present the Italian results of the NordiQCPT, identify regional differences in IHC staining quality and discuss the potential benefits of a National Quality Control program as a mandatory service provided by the National Healthcare System.

Material and methods

In October 2014, a working group was set up by the SIAPEC/IAP to carry out a National Quality Control program on IHC, enrolling 158 Italian laboratories. Out of 20 Italian Regions participated (Fig. 1); Lombardia did not participate because it had already started a similar project independently. Each lab’s referent was contacted both by phone and e-mail and was asked to send by e-mail a signed form (inclusive of contacts, names, addresses and number of HER2 tests/year for 2014). SIAPEC/IAP initiated a collaboration with NordiQC to host and perform the IHC PT. An introductory run named run B19X was established for the 158 Italian labs, identical to the “official” NordiQC run B19 (April 2015) assessing ER and HER2. Subsequently, the Italian labs participated in the “official” NordiQC run B20 (September 2015) for PR and HER2, together with all other NordiQC laboratories (i.e. 525).

For both run B19X and B20, the participating Italian laboratories completed an on-line questionnaire for the protocols used by the individual laboratory for each of the markers evaluated. The protocol data reported by the laboratories were archived in the NordiQC database and used for the subsequent analysis of the assessment results. Two unstained sections for each marker were circulated to the participating laboratories, in order to perform the IHC assays according to their standard protocols as submitted in the questionnaire.

Slides of tissue microarrays (TMAs) from standard processed formalin-fixed, paraffin-embedded (FFPE) tissue were used. Tissue fixation and processing had been carried out according to the recommendations provided by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP).

The TMAs for HER2 IHC (run B19X and B20) included 5 cores (4-5 mm) of 5 different breast carcinomas (Fig. 2). HER2 IHC expression levels were defined by NordiQC by using the three FDA approved kits and antibodies, HercepTest™ Dako, Oracle™ Leica and PATHWAY® Ventana. HER2 amplification status was verified by HER2 fluorochrome in situ hybridization (FISH). HER2 IHC expression levels in the TMAs reflected the range seen in a diagnostic setting and thus included a HER2 IHC 3+ tumour with high level gene amplification, a 2+/3+ tumour with low level gene amplification, a 1+/2+ tumour without gene amplification and two 1+/0+ tumours without gene amplification. The TMAs for ER and PR included cores (4-5 mm) of tonsil, uterine cervix and 4 different breast carcinomas (Fig. 2). Tonsil and uterine cervix were primarily used as positive and negative tissue controls, respectively, for the marker evaluated. Breast carcinomas showed diagnostically relevant expression levels ranging from negative to strong.
The slides stained by the participants were assessed by the NordiQC expert panel consisting of consultant breast pathologists and biomedical scientists, all experienced in IHC PT. Each slide was by consensus marked as optimal, good, borderline or poor, primary based on the precision of the IHC result and concordance to the NordiQC established levels of the target analyte and addressing the technical quality of the IHC staining result. Results evaluated as optimal and good were both considered sufficient, while borderline and poor were considered insufficient. For the latter individually tailored suggestions to improve the staining quality were provided by NordiQC.

HER2 results were considered optimal when all scores for the 5 breast carcinomas were as expected and good if the 3+ HER2 amplified carcinoma or the negative cases showed a 2+ reaction. No patient was misdiagnosed and additional FISH would identify a correct HER2 status. The result was evaluated as borderline if there was a low signal-to-noise ratio compromising the interpretation and poor in case of false negative results (when a 3+ or a 2+ amplified tumor showed a 1+ or 0 reaction) or of false positive (when a 1+ or 0 or a 2+ unamplified tumor showed a 3+ reaction). For ER and PR, the staining was evaluated as optimal when all scores were expected and concordant to the NordiQC reference data. If a reduced proportion of cells was demonstrated in the carcinomas expected to be labelled, but still a positive result was seen in ≥10% of the neoplastic cells, the result was evaluated as good. If a significant reduced analytical sensitivity was observed and ≥ 1 but < 10% of neoplastic cells were identified, the result was evaluated as borderline. In case of a false negative < 1% or false positive staining reaction, the result was evaluated as poor.

Data of ER, PR and HER2 results of Italian labs were extrapolated and compared to the overall data of the NordiQC participants available on the web site (www.nordiqc.org).

The analysis of association between the annual number of HER2 tests performed by each lab and the proportion of sufficient results was carried out with Fisher’s exact test. The same test was used to verify the presence of any difference in geographical distribution of results by diving the labs into three main macro areas: North (labs from Piemonte, Val D’Aosta, Veneto, Friuli Venezia Giulia, Trentino Alto Adige, Emilia Romagna and Liguria), Center (labs from Toscana, Lazio, Umbria, and Marche) and South (labs from Campania, Sicilia, Puglia, Abruzzo, Molise, Sardegna and Calabria). A probability (p) value less than 0.05 was considered statistically significant. All tests were two sided and carried out with GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA).

Results

**Run B19x HER2 assessment**

154 labs returned the slides for the evaluation. Of these 79% achieved a sufficient mark (optimal or good) (Tab. I). In 83% of the labs (128/154) the FDA/CE IVD approved assays were used. PATHWAY based on rabbit monoclonal antibody (rmAb) clone (Ventana) was used by 56 laboratories, gaining sufficient results in 84% of cases; the second most used assay was Hercept Test SK001 (Dako), based on a rabbit polyclonal antibody and it was used by 26 laboratories, with a proportion of sufficient marks of 92% (21/26). In both assays the application of optimal protocol settings (suggested by the vendors) ensured a higher pass rate (92% and 96%, respectively). These results were in accordance with those obtained from the “official” NordiQC HER2 assessment in RunB19. Only in 26 cases laboratory developed (LD) assays were used with a proportion of sufficient marks of 70% (18/26).

In 29 cases a poor result was observed. It was mainly due to a 1+ reactivity in an amplified 2+/3+ breast cancer core. Such false negative results were observed in both FDA/CE IVD approved (but modified) and LD assays and typically caused by reduced heat-induced epitope retrieval (HIER) time, short incubation time of the primary antibody and/or less sensitive detection kit (Fig. 3). A scoring consensus between labs and assessor group was achieved in 80% of cases: labs with sufficient staining results achieved a scoring consensus in 93 cases out of 113 (82%) while those with insufficient results in 20 cases out of 28 (71%).

**RunB19x ER assessment**

A total of 151 Italian labs returned the stained slides. In 78 cases (51%) a sufficient mark was achieved (Tab. I). Both concentrated and ready to use (RTU) antibodies were applied. In 101 laboratories, RTU antibodies were used, rmAb clone SP1 (Ventana), in particular (73 labs). Sufficient results were obtained in 95% of cases. Most of poor results (22/29 labs) were obtained with antibody clone 6F11 (Leica/Novocastra) purchased concentrated or in RTU format (6/8 labs) and with antibody clone 1D5 (Dako) concentrated (9/9 labs) or in RTU format (6/8 labs). Demonstration of ER was most challenging in the breast carcinoma core no. 4 (expected weak nuclear staining reaction of 40% of the neoplastic cells) where carefully calibrated protocols were required. Uterine cervical tissue was used as positive control, displaying a moderate to strong nuclear signal in both the squamous epithelium and in the glands but also in stromal cells, except for endothelial and lymphocytic cells. In cases where the positive control stained as expected, core nr. 4 showed reliable reactivity. Core no.3 ER negative breast carcinoma was used to assess the specificity of the protocol: staining of tumour cells in this core was assessed as false positive. The protocol was considered highly sensitive when the signal was detected in normal stromal cells and not only in normal epithelial cells, where a strong signal is expected (Fig. 4).

**RunB20 PR assessment**

123 Italian labs returned the stained slides. In 108 cases (88%) a sufficient mark was achieved (Tab. II). The best
Tab. I. Assessment marks for Run B19x, including tests with ER and HER2 antibodies.

**ER**

<table>
<thead>
<tr>
<th>Concentrated antibodies</th>
<th>N</th>
<th>Vendor</th>
<th>O</th>
<th>G</th>
<th>B</th>
<th>P</th>
<th>Suff*</th>
<th>Suff° OPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb clone 1D5</td>
<td>9</td>
<td>Dako</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mAb clone 6F11</td>
<td>29</td>
<td>Leica/Novocastra</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>22</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>rmAb clone EP1</td>
<td>6</td>
<td>Dako</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>17%</td>
<td>50%</td>
</tr>
<tr>
<td>rmAb clone SP1</td>
<td>2</td>
<td>Thermo/Neomarkers</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

**Ready-to-use antibodies**

| mAb clone 1D5 IR/IS657   | 8  | Dako         | 0  | 1 | 1  | 6  | 13%   | -         |
| mAb clones 1D5+ER-2-123 SK310 | 3  | Dako         | 0  | 0 | 0  | 3  | 0%    | -         |
| mAb clone 6F11 PA0151    | 8  | Leica/Novocastra | 0 | 1 | 1  | 6  | 13%   | -         |
| rmAb EP1 IR/IS084        | 10 | Dako         | 1  | 2 | 3  | 4  | 30%   | 60%       |
| rmAb clone SP1 790-4324/5 | 73 | Ventana      | 43 | 26| 4  | 0  | 95%   | 94%       |
| **Total**                | 151|              | 45 | 33| 16 | 57 |       |           |
| **Proportion**           | 29%| 22%         | 11%| 38%| 51%|    |       |           |

**HER2**

<table>
<thead>
<tr>
<th>FDA/CE IVD approved HER2 assays</th>
<th>N</th>
<th>Vendor</th>
<th>O</th>
<th>G</th>
<th>B</th>
<th>P</th>
<th>Suff.</th>
<th>Suff. OPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATHWAY rmAb clone 485, 790-2991</td>
<td>56</td>
<td>Ventana</td>
<td>45</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>85%</td>
<td>92%</td>
</tr>
<tr>
<td>CONFIRM, rmAb clone 485, 800-4493</td>
<td>10</td>
<td>Ventana</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>80%</td>
<td>89%</td>
</tr>
<tr>
<td>CONFIRM, rmAb clone 485, 800-2996</td>
<td>1</td>
<td>Ventana</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>HercepTest SK001</td>
<td>26</td>
<td>Dako</td>
<td>21</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>HercepTest K5207</td>
<td>15</td>
<td>Dako</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>HercepTest K5204</td>
<td>7</td>
<td>Dako</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>Oracle mAb clone CB11, TA9145</td>
<td>13</td>
<td>Leica</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>38%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Antibodies for laboratory developed HER2 assays, conc. antibody**

<table>
<thead>
<tr>
<th>N</th>
<th>Vendor</th>
<th>O</th>
<th>G</th>
<th>B</th>
<th>P</th>
<th>Suff.</th>
<th>Suff.OPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb clone CB11</td>
<td>4</td>
<td>Leica/Novocastra</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Cell Marque Biocare</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Thermo/NeoMarkers</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>pAb clone A0485</td>
<td>14</td>
<td>Dako</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>79%</td>
</tr>
</tbody>
</table>

**Antibodies for laboratory developed HER2 assays, RTU**

<table>
<thead>
<tr>
<th>N</th>
<th>Vendor</th>
<th>O</th>
<th>G</th>
<th>B</th>
<th>P</th>
<th>Suff.</th>
<th>Suff.OPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb clone CB11, RTU-CB11</td>
<td>1</td>
<td>Leica/Novocastra</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>mAb clone CB11, 237M-18</td>
<td>1</td>
<td>Cell Marque</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>pAb E2441</td>
<td>1</td>
<td>Spring Bioscience</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>154</td>
<td></td>
<td>110</td>
<td>13</td>
<td>2</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td><strong>Proportion</strong></td>
<td>71%</td>
<td>8%</td>
<td>1%</td>
<td>20%</td>
<td>79%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Proportion of sufficient stains; ° Proportion of sufficient stains with optimal protocol settings only
results were obtained with concentrated mouse monoclonal antibodies clone PgR636 (Dako), clone 16 (Leica), their RTU counterparts and clone PgR 1294. In 60 laboratories rabbit monoclonal antibody clone 1E2 (Ventana) was used, in 48 (80%) a sufficient result was obtained. In most poor cases a false positive nuclear staining was present in ≥ 10% of cells in the tonsil (Fig. 5). The Italian data were in accordance with the general results of the RunB20 (see www.nordiqc.org).

**RunB20 HER2 assessment**

A total of 122 Italian labs returned the slides. A pass rate of 79% (96/122) was achieved (Tab. II). Insufficient results were characterized by false negative staining reaction (85%, 22/26), mainly observed as 0/1+ in the 2+ HER2 gene amplified breast carcinoma core. In other insufficient assays poor signal-to-noise ratio, im-
paired morphology or excessive counterstaining made the interpretation difficult. The FDA/CE-IVD approved HER2 assays PATHWAY and CONFIRM from Ventana and HercepTest (SK001) from Dako were the most successful. Laboratory developed assays were less successful.

A scoring consensus was achieved in 84% of cases. Italian data were in accordance with the general results of the RunB20 (see www.nordiqc.org).

Comparison of Italian Laboratories

Data on the average number of HER2 tests/year were available for 122 laboratories: it ranged from 36 to 1570 tests/year. Laboratories were divided into 4 groups on the base of their performance status (Fig. 6), from < 100 tests/year to > 400 tests/year. In each of them the number of sufficient (optimal/good) and insufficient results was examined. No statistically significant differences were found among these groups ($p = 0.4368$; $\chi^2 = 2.72$).

The application of the Fisher’s exact test revealed the absence of any statistically significant difference in the proportion of sufficient results of HER2, ER and HER2 score consensus among the three Italian macro areas (North, Center and South), except for PR that gave more sufficient results in the North than in the South and the Center (Fig. 7).

Discussion

Quantification of immunohistochemical reactivity is an important goal to be pursued in the era of the “next generation IHC”, as the implementation of the targeted cancer therapy has introduced a predictive role for tissue markers. Accurate quantification requires method of high quality both in terms of sensitivity and specificity. Several organizations (NordiQC, UK NEQAS ICC, RCPAQAP, cIQc) work internationally and have long time experiences on programs based on expert panel-based qualitative assessment systems. PT in IHC aims to examine the analytical outcome of the staining and to relate any difference to the antibodies, protocol parameters and stainerplat forms. The optimization of the analytical phase is a compelling issue also due to intra-observer and inter-observer variability of the interpretation of the staining results. The lack of reproducibility of scoring by pathologists is being addressed by digital algorithms applied to computer assisted image analysis, whose effects have yet to be explored.
In our study, HER2 scores for the multi-tissue sections of 80-84% of participants were in concordance with the NordiQC assessor group that used ASCO/CAP 2013 interpretation guidelines. The proportion was slightly lower than other previous runs in NordiQC. The greatest discrepancy was recorded for the case with an intermediate staining reaction.

Breast cancer represents worldwide the most frequent cancer with an estimated incidence for women in Italy in 2012 of 31.21% and a mortality rate of 17.05% 22. Worldwide, an increase of deaths due to this disease is being recorded mainly in less developed countries where the correct management of the disease must deal with poor financial sources 23. Sophisticated diagnostic and therapeutic tools are available only in large specialized centers which, however, serve a small portion of patients. Due to this, the 2015 St Gallen International Expert Consensus 13 agreed on prioritizing IHC as a valid surrogate of molecular testing in defining clinically useful subgroups of breast cancer. Four main cancer subgroups may be highlighted: triple negative, ER negative and HER2 positive, ER positive and HER2 positive, and ER positive and HER2 negative (luminal type A and B) 24 25. Great uncertainty stands in the best treatment of luminal types 26-28: it strongly depends on the level of ER expression, the certainty of HER2 negativity and the proliferation index. It follows that the accuracy of these immunohistochemical tests allows to address the right therapeutic choices, hence the right management of founds and resources.

Italy is the European country with the largest internal difference of GDP/capita between internal regions 29 with the GDP of the poorest region being only 1/3 of that of Lombardia (the richest). Furthermore, a high variation in the quality and outcomes of care by region is registered 30. The Euro Health Consumer Index in 2015 evaluated the performance of healthcare provision from a consumer viewpoint. Although the Italian healthcare system is formally under the guidance of one central ministry of health, the national Index score of Italy was
influenced by the optimal performance of regions from the North of Italy and Rome and the poor services offered by most of the regions from the South of Italy. The most alarming datum was the substantial flow across regions of patients seeking better quality care; generally they move from the south to the north of the country. What emerges from our study is that no substantial differences exist among the three Italian macro-areas (North, Center and South) in the quality of IHC performed for breast cancer. No statistically significant difference was even found between laboratories that perform more or less than 100 tests/year.

In Italy, each region independently organizes procedures of accreditation to safeguard the quality of healthcare system. A voluntary system of accreditation is also possible whereby it comes out that in regions with higher GDP/capita a woman affected by breast cancer has more chances than in other regions.

Results coming from our project have shown that the overall pass rate of HER2 in RunB19x (79%) was similar to the 86% pass rate in the “official” RunB19. However, these results are significantly lower than those observed by the NordiQC in the previous runs of the same module (see www.nordiqc.org). It is well known that laboratories participating in the same run more than once show an improvement of performance. Quality assessment programs have proven efficient over time and should be a required step in the management of IHC laboratories, especially in the context of predictive markers. The evaluation of the expression of ER and PR receptors and HER2 on tissue is the starting point that initiates a complex process made up of resources (drugs, staff, facilities) and funds. Accurate HER2 testing is essential because of the severe adverse events that may be provoked by HER2-directed therapies in case of their inappropriate administration. Furthermore, cost analyses have shown that incorrect HER2 tests may also have relevant economic consequences.

For this reason the assessment of quality should represent a service offered by the National Healthcare System. Virtuous countries are those where quality certifications are well regulated and mandatory. The effort made by the SIAPEC/IAP with this experience must be seen as the starting point for a project to be carried out and it gave the opportunity to portray the Italian setting that is arranged in a context with several organizational, socio-cultural and geographical diversities compared to other European countries.

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