Pharmacogenetics

Approval gap of pharmacogenomic biomarkers and in vitro companion diagnostics between the United States and Japan

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SUMMARY
What is known and objectives: In vitro companion diagnostic devices (CDx) provide information on pharmacogenomic biomarkers (PGBMs) to enable the safe and effective use of targeted agents for personalized therapy. These devices require specific regulations that strike a balance between scientific evidence and financial burden. The aims were to compare approval of PGBMs and CDx in the USA and Japan and to help inform current discussions on personalized medicine.

Methods: We analysed published documentation from the USA and Japan for CDx and PGBMs, listed by the US Food and Drug Administration (FDA). Aspects evaluated were aim, approval state and therapeutic area. Coverage by the National Health Insurance in Japan was also investigated.

Results and discussion: Thirty-eight PGBMs were listed in the FDA table as of March 2013. In the USA, the aim was efficacy in 55% (21/38). The largest therapeutic area was oncology (39%, 15/38). Fifty-three per cent (20/38) of the PGBMs had a corresponding CDx approved. Of the 38 PGBMs in the FDA table, six had no approved drug in Japan; in 16 of the remaining 32 PGBMs, the aim was efficacy. The largest therapeutic area was oncology (34%, 11/32). Of the 32 PGBMs, 15 were associated with an approved and/or covered CDx, with only 11 having an approved CDx. Four PGBMs had a covered CDx without prior approval in Japan.

What is new and conclusion: Our study confirms that there is still a substantial gap in the approval of PGBMs and CDx between Japan and the USA. Complementary coverage of unapproved CDx by the National Health Insurance, however, is raising access to a similar level in both countries. Because the number of expensive personalized medicines and CDx is increasing, patient access will continue to be an important challenge to healthcare systems in all countries.

WHAT IS KNOWN AND OBJECTIVE
For many years, healthcare professionals have used diagnostic tests to select appropriate treatments for patients or to optimize dosing regimens. Pharmacogenomic biomarkers (PGBMs) can help inform therapeutic decisions in personalized medicine.\(^1\)\(^{-}\)\(^3\) More than 100 drug labels are included in the table of PGBMs published by the US Food and Drug Administration (FDA).\(^4\) In vitro companion diagnostics (CDx) provide information essential for the safe and effective use of targeted therapeutic products.\(^5\) Ethical implementation of personalized medicine, however, requires balancing scientific evidence and financial burden.\(^6\)

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical companies in the USA, Europe and Japan to discuss scientific and technical aspects of drug registration. Harmonization in the development and regulation of PGBMs and CDx, however, remains to be implemented. In July 2011, the FDA issued draft guidance on CDx,\(^7\) whereas the European Medicines Agency (EMA) issued a draft reflection paper\(^8\) focusing on the use of PGBMs in the clinical development of CDx and patient selection. In contrast, the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese counterpart of the FDA and EMA, has not yet issued any document on the development of CDx. Although the FDA and EMA desire co-development of drugs and diagnostics, most approved CDx were not developed concurrently with the drugs concerned.\(^9\)

In addition to approval by a regulatory authority, general use of a CDx requires coverage and reimbursement by health insurers. Coverage decisions are critical factors in patient access to personalized medicine. Policy makers and payers have to make decisions about the financial sustainability of healthcare delivery, whereas regulatory authorities have to optimize access to safe and effective medications.\(^10\) In the USA, FDA approval is not a guarantee of coverage.\(^10\) Lack of evidence for the clinical use of many CDx has led payers to deny or restrict reimbursements.\(^6,11\) For example, the CMS does not routinely cover genotyping for CYP 2C9 and VKORC1\(^12\) in patients being prescribed warfarin. It requires evidence that such testing will deliver improved clinical outcomes.

Assessment of health outcome measures\(^13\) has shown that Japan holds a favourable position in the development of personalized medicine through its industrial, regulatory and reimbursement processes. The National Health Insurance (NHI) in Japan\(^14\) covers virtually all medications and diagnostics approved by the PMDA. Sometimes payers even reimburse for off-label medications and unapproved devices,\(^15\) depending on clinical necessity. Surging healthcare costs, however, are challenging the system. For example, Japanese physicians are struggling with reimbursement for genetic testing.\(^16\)

The objectives of this study were to investigate the differences in approval of PGBMs and CDx in the USA and Japan and to help
inform current discussion on barriers to personalized medicine in both countries. We also evaluated coverage of CDx by the NHI in Japan.

**METHODS**

**Study design**

This was a cross-sectional study of documents published on the FDA’s and PMDA’s websites as of March 2013. PGBMs approved only in Japan, for example HLA-A*310117 and CCR4, were not included in this study because we used the FDA table as the reference.

**Data sources**

PGBMs were listed in the Table of Pharmacogenomic Biomarkers in Drug Labels on the FDA’s website. We also obtained US CDx data from the FDA’s database of 510(k) Premarket Notification and Premarket Approval. Japanese CDx data were obtained

**Table 1. Approval in the USA and Japan of pharmacogenomic biomarkers and corresponding in vitro companion diagnostics**

| Biomarker                        | Aim      | Therapeutic area                | US CDx approval | JPN drug approval | JPN CDx approval | JPN CDx coverage |
|----------------------------------|----------|---------------------------------|-----------------|-------------------|------------------|------------------|
| ALK                              | Efficacy | Oncology                        | A               | A                 | A                | A                |
| Antithrombin III deficiency       | Safety   | Haematology                     | A               | A                 | A                | C                |
| Apoprotein E2                     | Efficacy | Metabolic and endocrinology     | U               | A                 | U                | NC               |
| BRAF                             | Efficacy | Oncology                        | U               | U                 | U                | NC               |
| C-Kit                            | Efficacy | Oncology                        | A               | A                 | U                | C                |
| CCR5                             | Efficacy | Antivirals                      | U               | A                 | U                | NC               |
| CD20 antigen                      | Efficacy | Oncology                        | A               | U                 | A                | C                |
| CD25                             | Efficacy | Oncology                        | U               | U                 | U                | NC               |
| CD30                             | Efficacy | Oncology                        | A               | U                 | U                | NC               |
| CFTR (G551D)                     | Efficacy | Pulmonary                       | A               | U                 | U                | NC               |
| Chromosome 5q                     | Efficacy | Haematology                     | U               | A                 | C                |
| CYP1A2                           | Monitoring | Gastroenterology               | U               | U                 | U                | NC               |
| CYP2C19                          | Monitoring | Two or more areas             | A               | A                 | A                | NC               |
| CYP2C9                           | Monitoring | Two or more areas             | A               | U                 | A                | NC               |
| CYP2D6                           | Monitoring | Two or more areas             | A               | A                 | A                | NC               |
| DPD                              | Safety   | Two or more areas               | U               | A                 | U                | NC               |
| EGFR                             | Efficacy | Oncology                        | A               | A                 | A                | C                |
| ERBB2 (HER2)                     | Efficacy | Oncology                        | A               | A                 | A                | C                |
| Estrogen receptor                | Efficacy | Oncology                        | A               | A                 | A                | C                |
| Estrogen/progesterone receptor   | Efficacy | Oncology                        | A               | A                 | A                | C                |
| Factor V Leiden                  | Safety   | Two or more areas               | A               | U                 | U                | NC               |
| FIP111-PDGFRζ                    | Efficacy | Oncology                        | U               | A                 | U                | C                |
| G6PD                             | Safety   | Two or more areas               | A               | U                 | A                | NC               |
| HGPRT                            | Safety   | Transplantation                 | U               | A                 | U                | NC               |
| HLA-B1*1502                      | Safety   | Neurology                       | U               | A                 | U                | NC               |
| HLA-B1*5701                      | Safety   | Antivirals                      | U               | A                 | U                | NC               |
| IL28B                            | Efficacy | Antivirals                      | U               | A                 | U                | NC               |
| KRAS                             | Efficacy | Oncology                        | A               | A                 | A                | C                |
| LDL receptor                     | Efficacy | Metabolic and endocrinology     | U               | A                 | U                | NC               |
| NAT1 / NAT2                      | Safety   | Two or more areas               | U               | A                 | U                | NC               |
| PDGFR                            | Efficacy | Oncology                        | U               | A                 | U                | NC               |
| Ph1/BCR-ABL                      | Efficacy | Oncology                        | U               | A                 | A                | C                |
| PML/RARα translocation           | Efficacy | Two or more areas               | U               | A                 | U                | NC               |
| Prothrombin F2 mutation          | Safety   | Oncology                        | A               | A                 | U                | NC               |
| TPMT                             | Safety   | Two or more areas               | U               | A                 | U                | NC               |
| UCD                              | Safety   | Two or more areas               | U               | A                 | U                | NC               |
| UGT1A1                           | Safety   | Two or more areas               | A               | A                 | A                | C                |
| VKORC1                           | Monitoring | Haematology                    | A               | U                 | A                | NC               |

CDx, in vitro companion diagnostics; JPN, Japanese; ALK, anaplastic lymphoma kinase; A, approved; C, covered; SERPINC1, serpin peptidase inhibitor, clade C (antithrombin), member 1; U, unapproved; NC, not covered; BRAF, v-raf murine sarcoma viral oncogene homolog B1; C-Kit, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog; CCR5, chemokine receptor type 5; CD, cluster of differentiation; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ERBB2 (Her2), v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2 (human epidermal growth factor receptor 2); FIP111-PDGFRζ, FIP1-like 1-platelet-derived growth factor receptor alpha fusion gene; G6PD, glucose-6-phosphate dehydrogenase; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; HLA, human leucocyte antigen; IL, interleukin; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; LDL, low-density lipoprotein; NAT, N-acetyltransferase; PDGFR, platelet-derived growth factor receptor; Ph1/BCR-ABL, Philadelphia chromosome/breakpoint cluster region-Abelson tyrosine kinase; PML/RARα, promyelocytic leukaemia/retinoic acid receptor alpha; TPMP, thiopurine S-methyltransferase; UCD, urea cycle disorders; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; VKORC1, vitamin K epoxide reductase complex, subunit 1.
from the PMDA label data of in vitro diagnostics. We obtained US drug approval data of these drugs from Drugs@FDA and Japanese drug approval data from the PMDA website’s section on new drug approval. We obtained Japanese coverage data of CDx from the NHI database.

Evaluation and analysis
The aim of each PGBM was evaluated according to the FDA guidance as follows. Efficacy is to identify patients who are most likely to benefit from a particular therapeutic product; safety is to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with a particular therapeutic product; monitoring is to monitor responses to treatment for the purpose of adjusting treatment (e.g. schedule, dose and discontinuation) to improve safety or effectiveness. We used Fisher’s exact test to determine the relationship between the aim (efficacy/safety and monitoring) and therapeutic area (oncology/non-oncology) on the approval status of the CDx. A P value <0.05 was regarded as statistically significant.

RESULTS AND DISCUSSION
Characteristics of PGBMs
Detailed information on the PGBMs and corresponding CDx in Tables S1 (online only). Table 1 shows the 38 PGBMs listed in the FDA table as of March 2013. The aims of the PGBMs included 21 tables.

RESULTS AND DISCUSSION

| Pharmacogenomic biomarker aim | Available | Unavailable | Available | Unavailable |
|------------------------------|-----------|-------------|-----------|-------------|
| Efficacy                     |           |             |           |             |
| Safety                       |           |             |           |             |
| Monitoring                   |           |             |           |             |
| Total                        | 20        | 18          | 15        | 17          |

CDx, in vitro companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.

Approval gap of CDx between the USA and Japan
Twenty of the PGBMs (53%) had a corresponding CDx approved in the USA. Of the 20 PGBMs with an approved CDx in the USA, only three [ALK, ERBB2 (HER2) and BRAF] showed successful drug diagnostic co-development. In the other 17 PGBMs, the drug and its CDx were approved separately. Table 2 shows the aim of each PGBM and whether a CDx was approved.

Table 2. Aims of pharmacogenomic biomarkers with or without an in vitro companion diagnostic device available in the USA and Japan

| Pharmacogenomic biomarker aim | Available | Unavailable | Available | Unavailable |
|------------------------------|-----------|-------------|-----------|-------------|
| Efficacy                     |           |             |           |             |
| Safety                       |           |             |           |             |
| Monitoring                   |           |             |           |             |
| Total                        | 20        | 18          | 15        | 17          |

CDx, in vitro companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.

was not associated with whether the aim of the PGBM was efficacy, safety or monitoring (P = 0.64). Table 3 shows the therapeutic area of each PGBM and whether a CDx was approved. The percentage of oncology PGBMs with an available CDx (73%, 11/15) was significantly higher than that of non-oncology PGBMs with an available CDx (39%, 9/23, P = 0.041).

Of the 32 PGBMs approved in Japan, 15 (47%) were associated with an approved and/or covered CDx, with only 11 having an approved CDx. The four PGBMs with an unapproved but covered CDx in Japan are c-kit, chromosome 5q, FIP1L1-PDGFRα and PML/RARα translocation. The four PGBMs for which a CDx is available in the USA, but not approved in the USA, were chromosome 5q, FIP1L1-PDGFRα, Ph1/BCR-ABL and PML/RARα transloca-

Table 3. Therapeutic areas of pharmacogenomic biomarkers with or without an in vitro companion diagnostic device available in the USA and Japan

| Therapeutic area | Available | Unavailable | Available | Unavailable |
|------------------|-----------|-------------|-----------|-------------|
| Antivirals       | 0         | 3           | 0         | 3           |
| Gastroenterology | 0         | 1           | 0         | 0           |
| Haematology      | 2         | 1           | 2         | 1           |
| Metabolic and endocrinology | 0         | 2           | 0         | 2           |
| Neurology        | 0         | 1           | 0         | 1           |
| Oncology         | 10        | 4           | 9         | 2           |
| Pulmonary        | 0         | 0           | 0         | 0           |
| Transplantation  | 0         | 1           | 0         | 1           |
| Two or more      | 0         | 5           | 4         | 7           |
| Total            | 20        | 18          | 15        | 17          |

CDx, in vitro companion diagnostics.
Availability in the USA signifies approval, whereas availability in Japan signifies approval and/or coverage.
CDx for CYP2C19 and CYP2D6 are approved, but not covered in Japan. A CDx for CD20 antigen is approved and covered, although the corresponding drug, rituximab, has not been introduced in Japan, probably because rituximab, indicated for the treatment of patients with CD20-positive B-cell non-Hodgkin lymphoma, is already approved in Japan.

Table 2 shows the aim of the 32 PGBMs according to the availability of the CDx (i.e. whether it is approved and/or covered). The percentage of PGBMs aiming at efficacy and with an available CDx (69%, 11/16) was significantly higher than that of PGBMs aiming at safety or monitoring (25%, 4/16, \( P = 0.016 \)). Table 3 shows the therapeutic area of the 32 PGBMs according to the availability of a CDx. The percentage of oncology PGBMs with an available CDx (82%, 9/11) was significantly higher than that of non-oncology PGBMs with an available CDx (29%, 6/21, \( P = 0.006 \)).

Our study confirmed that there is still a substantial approval gap for PGBMs and CDx between Japan and the USA. Approval gaps between the two countries were also observed for neurologica26 and psychiatric drugs.27 When we focused on oncology, however, there was no approval gap for CDx. The percentage of oncology PGBMs that had an approved CDx was 73% (11/15) in the USA and 82% (9/11) in Japan. This is probably because the drug lag has been markedly reduced in oncology28 where PGBMs play an important role.

Complementary coverage by the National Health Insurance to close the approval gap

Although the percentage of PGBMs with an approved CDx was lower in Japan (34%, 11/32) than in the USA (50%, 19/38), availability (i.e. the percentage of CDx approved or covered) was similar in Japan (47%, 15/32). This is because although four PGBMs, chromosome 5q, c-kit, FIP1L1-PDGFRα and PML/RARα translocation, were associated with unapproved CDx, they were covered and reimbursed by the NHI. The reason for this is unclear although testing for these four PGBMs is specified as required in the Japanese labels of the corresponding drugs25 and in the relevant guidelines.29 We could not provide data on coverage or reimbursement of CDx in the USA because the healthcare reimbursement and payment system in the USA is much more complex30 than that of the NHI in Japan. Coverage and reimbursement for a CDx are separate from and more multifaceted than for the corresponding drug in the USA.6,30

WHAT IS NEW AND CONCLUSION

Our study confirms that there is still a substantial gap in the approval of PGBMs and CDx between Japan and the USA. However, complementary coverage of an unapproved CDx by the NHI has increased availability to Japanese patients to a level similar to that of US patients. Caution should be exercised, however, because of the marked differences in the two healthcare systems. Because the number of expensive and targeted personalized medicine drugs and CDx is increasing, patient access will continue to be an important challenge to healthcare systems of all countries.

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CONFLICT OF INTEREST

The authors report no conflict of interest in this work.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Information on the pharmacogenomic biomarkers and corresponding in vitro companion diagnostics. It includes the type of biomarker, approved assay method, disease or molecule in focus, CDx target, and corresponding drugs.

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