を除く）を加えた。

### 2.3 特徴分析[4)]

特徴分析とは、複数の対象文書から、特徴的に出現する形態素や係り受けの表現を抽出する手法である。それぞれの文書に出現する形態素を、出現分布も考慮したうえで、特徴的であると判断できる形態素を抽出することができ、その文書の特徴を把握することができる。また、形態素間の係り受け関係を調べることで、特徴的な表現の抽出も可能となる。

### 2.4 質問形式の自動判定と回答の評判分析[4)]

厚労省法令DBには、様々な通知等に対する質問とその回答をまとめた質疑応答集と呼ばれる文書が、蓄積されている。その文書は、一問一答形式で記載されており、質問の形式は様々である。

質問は大別すると肯定否定を問わない「開かれた質問(Open Question)」と肯定否定を問う「閉ざされた質問（Closed Question)」に分かれる。一般的に、後者の方が、質問内容とその回答が明確にされると考えられる。これについて行政文書としての明確性を示すバロメータになるかどうかを検討するために、質疑応答集に於ける両者の頻度、及びClosed Questionの場合、その回答が明確に肯定否定の形を取っているかを検討する。

まず「開かれた質問(Open Question)」であるか「閉ざされた質問（Closed Question)」であるかを分類するために、以下に示す判定ロジックを作成し、質問形式の自動判定のツールを作成した

〈質問形式の判定ロジック〉

- **質疑応答集より質問文のみを抽出する。**
- **質問文をTMSにより形態素解析を行う**
- **形態素解析後の形態素ファイルを以下の流れで場合分けを行う**
- **分岐1：質問文か、質問文でないか？**
  **・TMS述語属性が「疑問」：[Question]カラムに"Q"**
  **・TMS述語属性が「疑問」でない：[Question]カラムに""(空白)**
- **分岐2：同じ行IDの中に5w1Hの「いつ」「どう」「どの」「何」「どこ」の形態素が含まれるか？（一度でも出現したら、含まれると判断）**
  **・含まれる：[Open Q]カラムに"Open"**
  **・含まれない：[Open Q]カラムに""(空白)**
- 「Open Question」の判定：同じ行IDの最終行の[Open Q]カラムに"Open"のフラグがあれば、「Open Question」と判定
- 「Closed Question」の判定：同じ行IDの最終行の[Open Q]カラムに"Open"のフラグがなく、[Question]カラムに"Q"のフラグがあれば、「Closed Question」と判定
- 「判定不能」の判定：同じ行IDの最終行の[Open Q]カラムに"Open"のフラグがなく、[Question]カラムにも"Q"のフラグがない場合は、「判定不能」と判定

次に、評判分析について説明する。評判分析とは、事前にTMSによって定められた「評価を与える語」(デフォルトでは約3000種類の用語が登録されている）と「形態素間の係り受け関係」に基づいて、文章の中から肯定的・否定的と解釈できる表現を抽出する分析手法である。分析対象となる文を評判判定ルール[4)]に基づいて、「肯定的な文」と「否定的な文」に自動判定することができる。ここでは、質疑応答集の回答部

分に対して評判分析を行うことで、質問に対する回答が、肯定的なのか否定的なのかを自動判定できるか検討する。

## 3　実験１と結果

実験１には、厚労省法令 DB より「コンパニオン診断薬」のキーワードで抽出された以下の３つ文書を対象とした。

① 平成 25 年 07 月 01 日 薬食審査発第 701010 号 「コンパニオン診断薬等及び関連する医薬品の承認申請に係る留意事項について」 ・・・（以下 留意事項文書）

② 平成 25 年 07 月 01 日 事務連絡「コンパニオン診断薬等及び関連する医薬品に関する質疑応答集(Q&A)について」・・・（以下 Q&A 文書）

③ 平成 25 年 12 月 26 日 事務連絡「コンパニオン診断薬及び関連する医薬品に関する技術的ガイダンス等について」・・・（以下 ガイダンス文書）

各々の文書のボリュームは、A4 サイズでそれぞれ

① A4 5 ページ、形態素数（延べ数）は 868 語、形態素数（重複除く）316 語

② A4 4 ページ、形態素数（延べ数）は 541 語、形態素数（重複除く）271 語

③ A4 15 ページ、形態素数（延べ数）は 2369 語、形態素数（重複除く）844 語

であった。詳細は**表 1** に示す。

### 3.1 形態素頻度解析

次に、対象の３文書の形態素頻度解析を行った。その結果、

① 留意事項文書では…「コンパニオン診断薬等」「医薬品」「バイオマーカー」

② Q&A 文書では…「コンパニオン診断薬等」「医薬品」「関連」

③ ガイダンス文書では…「医薬品」「コンパニオン診断薬等」「係る」

の順で形態素の出現頻度が多かった。各文書の上位２０位までの形態素を**表 2** に示す。

### 3.2 特徴分析

ここでは、対象の３文書における特徴的な形態素の抽出を試みた。

特徴語の抽出には、２文字以上であり、かつ各文書で２回以上の出現頻度がある形態素で算出を行った。

また、今回対象となる文書では、形態素の出現頻度が少ないため、その点を考慮して算出方法には「Yates 補正 $\chi$ 二乗値」[4]を用いて算出した。結果は**表 3** 及び**図 1** に示す。

### 3.3 評判分析

Q&A 文書における PMDA の「A：回答」部分に対して、TMS の評判分析を行い、以下の４つに自動判定した。

- positive：肯定的な回答
- negative：否定的な回答
- positive/negative：肯定的・否定的両方の意味を含む回答
- blank：肯定的・否定的どちらの意味も成さない回答

その判定結果と、PMDA の「回答」部分との判定一致数（一致率）を**表 4** に示す。

## 4 実験２と結果

実験２では、厚労省法令 DB より「質疑応答集」のキーワードで検索した文書の中で、コンパニオン診断薬や医薬品に関連がある「質疑応答集」を平成 25 年制定分と平成 18 年制定分からそれぞれ６文書、計１２文書を抽出し、実験の対象とした。

### 4.1　質問形式の自動判定と評判分析

まず、対象の質疑応答集の12文書から、質問文を抽出した。その結果、平成 25 年制定分の6文書からは81質問文、平成 18 年制定分

の 6 文書からは178質問文が抽出された。文書によって、質問文数が異なっており、最も少ない文書の質問文数は8質問、最も多い文書の質問文数は69質問であった。

次に、これらの質問文が「開かれた質問(Open Question)」であるか、それとも「閉ざされた質問(Closed Question)」であるかを分類するため、前述の自動判定のツールを用いて、分類を試みた。その結果を**表 5** に示す。なお、表の中の質問形式の「願望」とは、TMS による述語属性で「願望」と判定された質問文であり、「〜して頂きたい」といった質問が該当する。また、「その他」の項目には、質疑応答集自体の記載ミスや1つの質問文に複数の質問文がある場合、二者択一の質問文が含まれている。

さらに、これらの質問文の中から、Closed Question の質問文のみを抽出し、その質問文に対応する回答文をTMSの評判分析によって判定した。同様の回答文について、「はい」「いいえ」に準じて回答されているかを目視で確認し、TMS による評判分析の結果と目視で確認した結果の一致数(率)を確認した。

その結果を**表 6**、**表7**に示す。

## 5　考察とまとめ

今回は対象文書に、厚労省法令 DB に登録されている行政文書の中でも CoDx に関連する行政文書としたが、CoDx の分野は比較的新しい分野と言う事もあり、行政文書数は３文書と限られており、テキストマイニングによる分析もごく限られた範囲となった。

まず、実験１において、CoDx に関連する３文書の形態素頻度分析を行った。当然の事ながら３文書において、「コンパニオン診断薬等」という形態素が上位であった。それ以外の形態素は、各々の文書に特徴的なものが上位に示されている。特に、ガイダンス文書の形態素を見てみると、上位に「同等性試験」「臨床試験」「分析法バリデーション」といった技術ガイダンス文書に特徴的な形態素が示されている。

さらに、特徴分析により、対象の文書内において、形態素の出現分布を考慮した分析を行うと、頻度分析では上位に上がっていないが、文書の内容とより関連が深いと思われる特徴的な形態素が上位に示されていた。

以上のことから、文書の特徴を示す形態素を抽出するには、形態素の頻度による分析だけでなく、形態素の出現分布を考慮した分析が重要となる。今後、CoDx に関連する文書数を増やすことで、より特徴的な形態素を特徴分析から抽出することができるようになると思われる。

次に、Q&A 文書の評判分析を行った。回答文の内容と自動判定の結果が一致するかを目視で確認したが、回答の内容と自動判定の結果を一致させることは出来なかった。

この理由としては、今回の回答文が TMS の評判判定のロジックに適合していない事が原因と考えられる。前述の通り、TMS の評判判定は、「評価を与える語」(デフォルトでは約 3000 種類の用語が登録されている)と「形態素間の係り受け関係」に基づいて判定されるが、今回対象とした回答文には、「形態素間の係り受け関係」が存在しない回答文が多数存在していた。具体的には、「差し支えない」「よい」「可能である」といった表現のみの回答文である。これらの回答文だけでも意味は十分通じるのだが、TMS の判定ロジックには、例えば「この方法で差し支えない」というように、形態素

間の係り受け関係がないと、判定することができないため、自動判定が困難となってしまった。

今回のように回答文を自動判定させるには、対象となる行政文書に合わせて、独自の判定ロジックを作成する必要があると思われた。

実験２では、文書をCoDxに関連する文書以外にも拡大し、質疑応答集として１２文書を対象とした。質問文を、TMS で形態素解析し、「Open Question」と「Closed Question」に判定するロジックに当てはめてみたところ、目視での結果と判定ロジックの結果は、高率で一致した。

「判定不能」とされた質問文を見てみると、TMSによる形態素解析の結果、「述語属性」が「疑問」と解析されていない例が複数存在している事がわかった。TMS の形態素解析のロジックを再度確認し修正することで、更に判定制度が向上する可能性がある。また、質問形式の割合は、平成２５年と平成１８年とで差がなく「Open Question」か「Closed Question」が半々程度であった。

次に、「Closed Question」に対応する回答文書に対して、「はい」「いいえ」に準じた回答がなされているかを目視で確認したところ、約３０―４０％の割合でなされていた。ただ、その回答の多くは「差し支えない」「よい」「可能である」といった回答であった。ここでも前回と同様に対象の回答文に対して、評判分析を行ったが、一致率は低値であった。

今回は、厚労省法令DBに公開されているコンパニオン診断薬に関連する行政文書を中心にテキストマイニングを試みた。対象となる文書が限られていたため、分析には限界があった。また、行政文書には、独特な表現や特有の言い回しが多用されており、市販のテキストマイニングツールをそのまま活用するには限界があることも分かった。

現在、厚労省法令DBには、多くの行政文書データが蓄積され続けている。このような文書データを検索・閲覧だけにとどまらず、テキストマイニングの観点から２次利用することは、非常に意義のあることであると考えている。現在のテキストマイニングツールをベースに、行政文書に適した辞書の構築やパラメータの調整、新たな判定ロジックの開発を進めることで、より正確で精度の高い行政文書の分析が可能となると思われた。

## G. 研究発表

１．学会発表

なし

## H. 知的財産権の出願・登録状況

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

参考文献

[1] 鳥山裕司. 医薬関連バイオマーカーの特許出願動向にみる日本の課題. 政策研ニュース 2008；26：22-26.

[2] 厚生労働省法令等データベースサービス. http://wwwhourei.mhlw.go.jp/hourei/.

[3]豊田　裕貴,菰田　文男．特許情報のテキストマイニング,ミネルヴァ書房, 2011

[4] Text Mining Studio バージョン4.2 技術資料, 数理システム, 2013

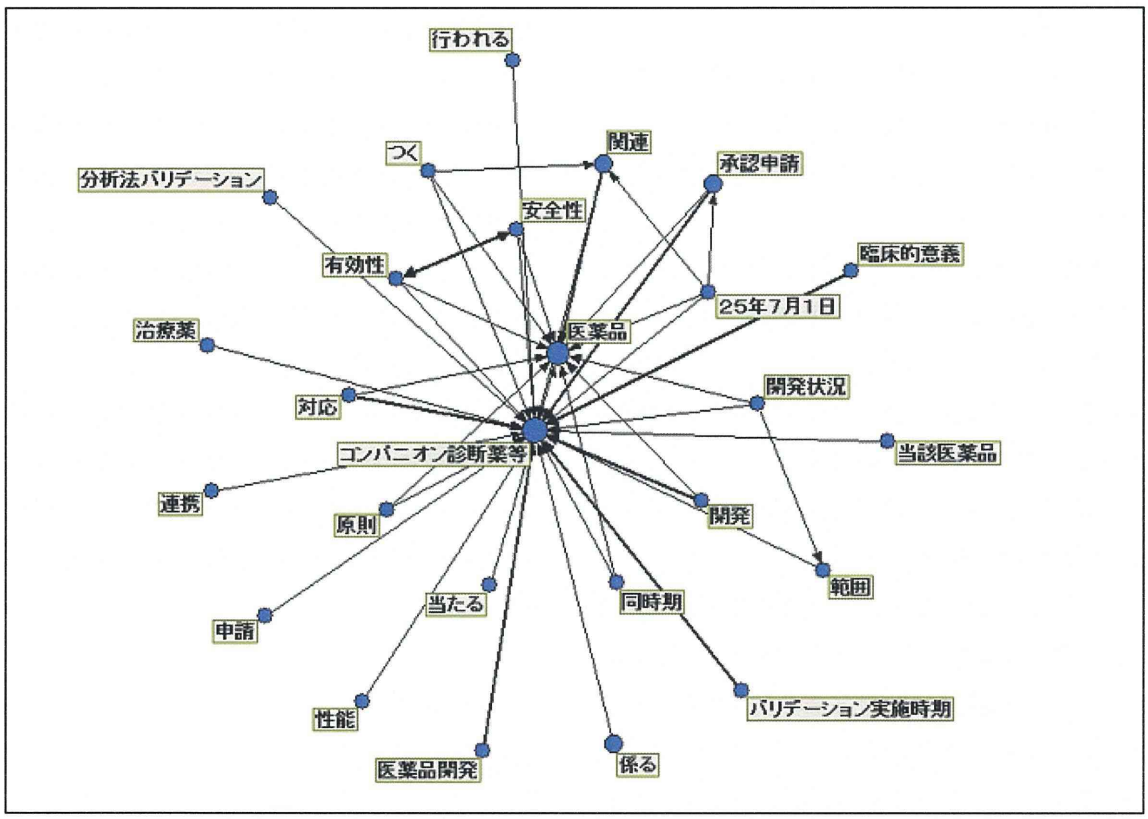


図１：「コンパニオン診断薬等」の形態素に注目したグラフ構造の例

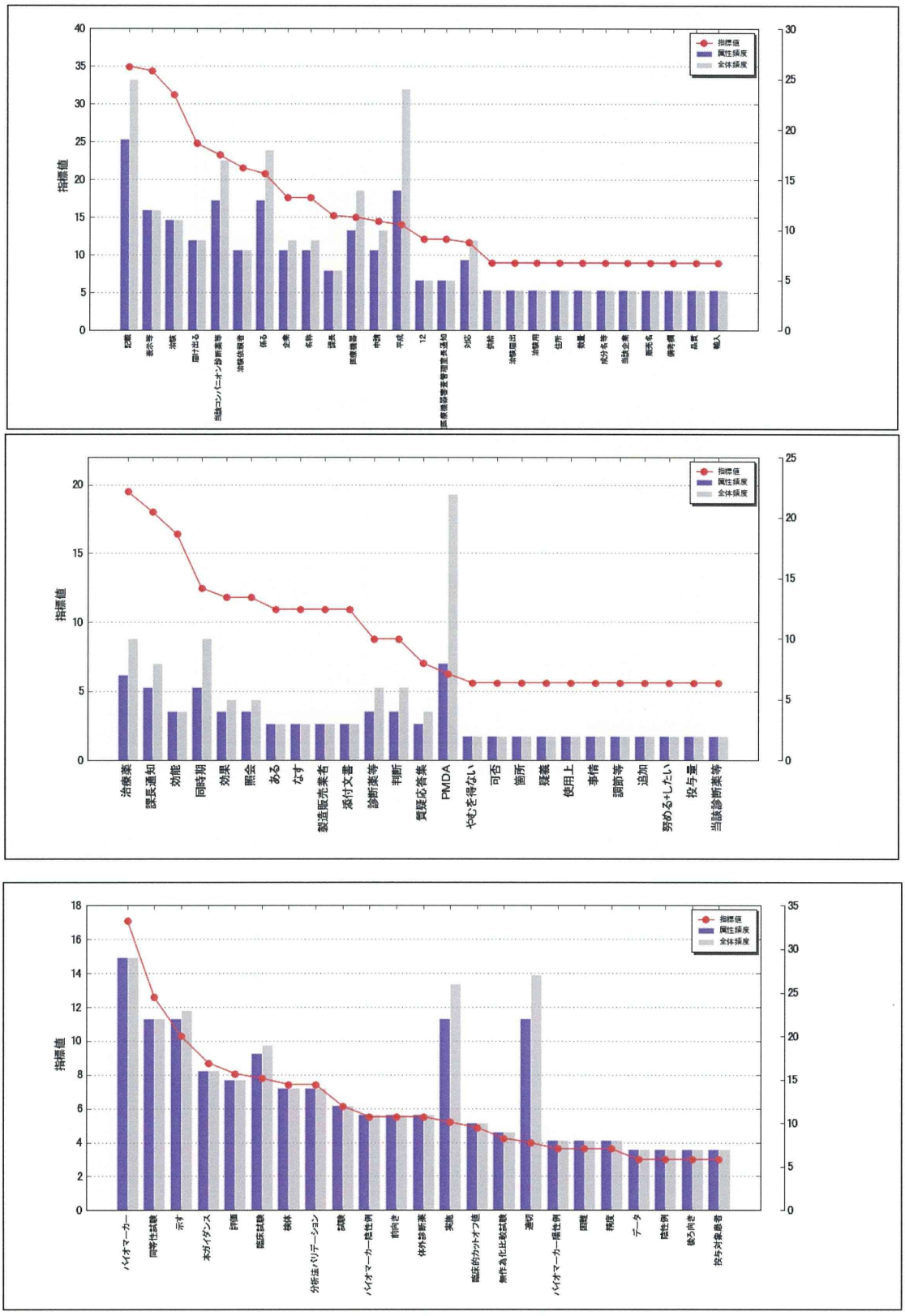


図２：対象の３文書の特徴分析（上位２０位まで）

（上：留意事項文書　中：Q&A 文書　下：ガイダンス文書）

| 項目 | 値 | 品詞 | 出現回数 |
|---|---|---|---|
| 総行数 | 46 | 名詞 | 720 |
| 総文数 | 62 | 動詞 | 65 |
| 平均文長(文字数) | 45.3 | 形容詞 | 1 |
| 延べ単語数 | 868 | 副詞 | 15 |
| 単語種別数 | 316 | 連体詞 | 11 |
| | | 接続詞 | 34 |
| | | 格助詞 | 1 |
| | | 記号 | 21 |

| 項目 | 値 | 品詞 | 出現回数 |
|---|---|---|---|
| 総行数 | 43 | 名詞 | 420 |
| 平均行長(文字数) | 41.7 | 動詞 | 54 |
| 総文数 | 63 | 形容詞 | 12 |
| 平均文長(文字数) | 28.5 | 副詞 | 14 |
| 延べ単語数 | 541 | 連体詞 | 3 |
| 単語種別数 | 271 | 接続詞 | 19 |
| | | 記号 | 19 |

| 項目 | 値 | 品詞 | 出現回数 |
|---|---|---|---|
| 総行数 | 164 | 名詞 | 1872 |
| 総文数 | 223 | 動詞 | 186 |
| 平均文長(文字数) | 38.1 | 形容詞 | 31 |
| 延べ単語数 | 2369 | 副詞 | 52 |
| 単語種別数 | 844 | 連体詞 | 27 |
| | | 接続詞 | 121 |
| | | 記号 | 80 |

表１：対象の３文書の基本情報（上：留意事項文書　中：Q&A 文書　下：ガイダンス文書）

| 形態素 | 品詞 | 品詞詳細 | 頻度 |
|---|---|---|---|
| 医薬品 | 名詞 | 一般 | 20 |
| コンパニオン診断薬等 | 名詞 | 一般 | 19 |
| 係る | 動詞 | 自立 | 13 |
| 平成 | 名詞 | 固有名詞 | 13 |
| 記載 | 名詞 | サ変接続 | 10 |
| 1 | 名詞 | 数 | 9 |
| 2 | 名詞 | 数 | 9 |
| 旨 | 名詞 | 一般 | 9 |
| 治験 | 名詞 | 一般 | 9 |
| 届け出る | 名詞 | 一般 | 9 |
| 医療機器 | 名詞 | 一般 | 8 |
| 関連 | 名詞 | サ変接続 | 8 |
| 承認申請 | 名詞 | 一般 | 8 |
| また | 名詞 | 一般 | 7 |
| 行う | 動詞 | 自立 | 7 |
| 取り扱う | 名詞 | 一般 | 7 |
| 対応 | 名詞 | サ変接続 | 7 |
| 必要 | 名詞 | 一般 | 7 |
| 開発 | 名詞 | サ変接続 | 6 |
| 開発状況 | 名詞 | 一般 | 6 |

| 形態素 | 品詞 | 品詞詳細 | 頻度 |
|---|---|---|---|
| コンパニオン診断薬等 | 名詞 | 一般 | 18 |
| 医薬品 | 名詞 | 一般 | 10 |
| 関連 | 名詞 | サ変接続 | 7 |
| 必要 | 名詞 | 一般 | 7 |
| PMDA | 名詞 | 固有名詞<br>組織 | 6 |
| 課長通知 | 名詞 | 一般 | 6 |
| 記 | 名詞 | 一般 | 5 |
| 行う | 動詞 | 自立 | 5 |
| 範囲 | 名詞 | 一般 | 5 |
| 1 | 名詞 | 数 | 4 |
| 診断薬等 | 名詞 | 一般 | 4 |
| 相談 | 名詞 | サ変接続 | 4 |
| 当該医薬品 | 名詞 | 一般 | 4 |
| 同時期 | 名詞 | 一般 | 4 |
| 望ましい | 形容詞 | 自立 | 4 |
| 目的 | 名詞 | 一般 | 4 |
| 用いる | 動詞 | 自立 | 4 |
| ある | 動詞 | 自立 | 3 |
| 医療機器 | 名詞 | 一般 | 3 |
| 可能 | 名詞 | 形容動詞<br>語幹 | 3 |

| 形態素 | 品詞 | 品詞詳細 | 頻度 |
|---|---|---|---|
| コンパニオン診断薬等 | 名詞 | 一般 | 44 |
| 医薬品 | 名詞 | 一般 | 33 |
| 2 | 名詞 | 数 | 25 |
| バイオマーカー | 名詞 | 一般 | 21 |
| 関連 | 名詞 | サ変接続 | 20 |
| 示す | 動詞 | 自立 | 20 |
| 用いる | 動詞 | 自立 | 20 |
| 適切 | 名詞 | 形容動詞語幹 | 19 |
| 1 | 名詞 | 数 | 18 |
| 3 | 名詞 | 数 | 18 |
| 実施 | 名詞 | サ変接続 | 18 |
| 同等性試験 | 名詞 | 一般 | 18 |
| 必要 | 名詞 | 一般 | 15 |
| 臨床試験 | 名詞 | 一般 | 15 |
| 評価 | 名詞 | サ変接続 | 14 |
| また | 名詞 | 一般 | 13 |
| 分析法バリデーション | 名詞 | 一般 | 13 |
| 本ガイダンス | 名詞 | 一般 | 12 |
| 検体 | 名詞 | 一般 | 11 |
| 試験 | 名詞 | 一般 | 11 |

表２：対象の３文書の形態素頻度解析（上位２０位まで）
（上：留意事項文書　中：Q&A 文書　下：ガイダンス文書）

| | 留意事項の文書 | 指標値 | Q&Aの文書 | 指標値 | ガイダンスの文書 | 指標値 |
|---|---|---|---|---|---|---|
| 1 | 記載 | 39.316 | 治療薬 | 20.122 | バイオマーカー | 15.566 |
| 2 | 表示等 | 37.944 | 課長通知 | 18.578 | 同等性試験 | 11.417 |
| 3 | 治験 | 34.414 | 効能 | 16.84 | 示す | 9.19 |
| 4 | 届け出る | 27.368 | 同時期 | 12.908 | 本ガイダンス | 7.884 |
| 5 | 当該コンパニオン診断薬等 | 26.182 | 効果 | 12.143 | 評価 | 7.298 |
| 6 | 治験依頼者 | 23.854 | 照会 | 12.143 | 臨床試験 | 6.912 |
| 7 | 係る | 23.497 | ある | 11.22 | 検体 | 6.713 |
| 8 | 企業 | 19.603 | なす | 11.22 | 分析法バリデーション | 6.713 |
| 9 | 名称 | 19.603 | 製造販売業者 | 11.22 | 試験 | 5.546 |
| 10 | 医療機器 | 17.047 | 添付文書 | 11.22 | バイオマーカー陰性例 | 4.966 |
| 11 | 課長 | 16.854 | 診断薬等 | 9.069 | 前向き | 4.966 |
| 12 | 平成 | 16.321 | 判断 | 9.069 | 体外診断薬 | 4.966 |
| 13 | 申請 | 16.257 | 質疑応答集 | 7.253 | 臨床的カットオフ値 | 4.387 |
| 14 | 12 | 13.375 | PMDA | 6.579 | 実施 | 4.327 |
| 15 | 厚生労働省医薬食品局審査管理課医療機器審査管理室長通知 | 13.375 | やむを得ない | 5.771 | 無作為化比較試験 | 3.811 |
| 16 | 対応 | 13.13 | 可否 | 5.771 | バイオマーカー陽性例 | 3.238 |
| 17 | 開発状況 | 10.105 | 箇所 | 5.771 | 困難 | 3.238 |
| 18 | 供給 | 9.923 | 疑義 | 5.771 | 精度 | 3.238 |
| 19 | 治験届出 | 9.923 | 使用上 | 5.771 | 適切 | 3.2 |
| 20 | 治験用 | 9.923 | 事情 | 5.771 | データ | 2.67 |

表３：対象の３文書の特徴分析（上位２０位まで抜粋）

| 判定結果 | TMS判定 | 回答一致率 |
|---|---|---|
| positive | 6 | 0% |
| negative | 0 | 0% |
| positive and negative | 1 | 0% |
| not positive and not negative | 2 | 0% |
| 合計 | 9 | 0% |

表４：Q&A 文書の回答部分の自動判定一致率

| 質問形式 | | 目視による確認 | | | | | 合計 | 自動判定一致率 |
|---|---|---|---|---|---|---|---|---|
| | | open | closed | 願望(open) | 願望(closed) | その他 | | |
| 自動判定 | Open | 35 | 0 | 0 | 0 | 1 | 36 | 97% |
| | closed | 0 | 38 | 0 | 1 | 0 | 39 | 97% |
| | 判定不能 | 0 | 0 | 4 | 0 | 2 | 6 | *** |
| 合計 | | 35 | 38 | 4 | 1 | 3 | 81 | *** |
| 目視一致率 | | 100% | 100% | 0% | 100% | *** | | |

| 質問形式 | | 目視による確認 | | | | | 合計 | 自動判定一致率 |
|---|---|---|---|---|---|---|---|---|
| | | open | closed | 願望(open) | 願望(closed) | その他 | | |
| 自動判定 | open | 55 | 1 | 1 | 0 | 12 | 69 | 80% |
| | closed | 1 | 74 | 0 | 0 | 4 | 79 | 94% |
| | 判定不能 | 13 | 2 | 11 | 0 | 4 | 30 | *** |
| 合計 | | 69 | 77 | 12 | 0 | 20 | 178 | |
| 目視一致率 | | 80% | 96% | 8% | #DIV/0! | *** | | |

表５：上段 平成２５年の質疑応答集６文書　下段 平成１８年の質疑応答集６文書

・質問形式の「願望」とは、TMS による述語属性が「願望」と判定された質問文であり、「～して頂きたい」といった質問が該当する。

・「その他」には、質疑応答集の記載ミスや１つの質問文に複数の質問文がある場合、二者択一の質問文が含まれる。

| Closed Qestion に対する回答 | 「はい」「いいえ」に準ずる回答 | それ以外 | 合計 |
|---|---|---|---|
| 平成25年質疑応答集 | 15(39%) | 23(61%) | 38 |
| 平成18年質疑応答集 | 27(35%) | 50(65%) | 77 |

表６：対象の質疑応答集での”Closed Question”に対応する回答文の割合

| Closed Qestion<br>に対する回答 | 「はい」「いいえ」に<br>準ずる回答文 | 評判分析一致数<br>（率） |
|---|---|---|
| 平成25年質疑応答集 | 15 | 3(8%) |
| 平成18年質疑応答集 | 27 | 9(11%) |

表７：対象の質疑応答集での「はい」「いいえ」に準ずる回答文に対する評判分析との一致数

# Ⅲ. 発表論文

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## Pharmacogenetics

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

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***Keywords:*** **biomarkers, drug approval, *in vitro* diagnostic devices, personalized medicine, pharmacogenomics, USFDA**

## 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,[5] whereas the European Medicines Agency (EMA) issued a draft reflection paper[7] 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.[8]

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.[9] In the USA, FDA approval is not a guarantee of coverage.[8,10] 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

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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*3101[17] and CCR4,[18] were not included in this study because we used the FDA table[4] as the reference.

### *Data sources*

PGBMs were listed in the Table of Pharmacogenomic Biomarkers in Drug Labels on the FDA's website.[4] We also obtained US CDx data from the FDA's database of 510(k) Premarket Notification[19] and Premarket Approval.[20] 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 | C |
| Antithrombin III deficiency (SERPINC1) | Safety | Haematology | A | A | A | C |
| Apoprotein E2 | Efficacy | Metabolic and endocrinology | U | A | U | NC |
| BRAF | Efficacy | Oncology | A | 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 | U | 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 | A | U | 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 | A | U | NC |
| FIP1L1-PDGFRα | Efficacy | Oncology | U | A | U | C |
| G6PD | Safety | Two or more areas | A | A | U | NC |
| HGPRT | Safety | Transplantation | U | A | U | NC |
| HLA-B*1502 | Safety | Neurology | U | A | U | NC |
| HLA-B*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 | C |
| 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 | A | U | 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); FIP1L1-PDGFRα, 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.



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from the PMDA label data of *in vitro* diagnostics.[21] We obtained US drug approval data of these drugs from Drugs@FDA[22] and Japanese drug approval data from the PMDA website's section on new drug approval.[23] We obtained Japanese coverage data of CDx from the NHI database.[24]

### *Evaluation and analysis*

The aim of each PGBM was evaluated according to the FDA guidance[5] 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 PBGMs and corresponding CDx in Tables S1 (online only). Table 1 shows the 38 PGBMs listed in the FDA table as of March 2013.[4] The aims of the PGBMs included 21 (55%) for efficacy, 12 (32%) for safety and five (13%) for monitoring. Therapeutic areas with PGBMs included antivirals (3; 8%), gastroenterology (1; 3%), haematology (3; 8%), metabolic and endocrinology (2; 5%), neurology (1; 3%), oncology (15; 39%), pulmonary (1; 3%), transplantation (1; 3%) and two or more areas (11; 29%).

Of the 38 PGBMs in the FDA table, six did not have related approved drugs in Japan (Table 1). These included BRAF (vemurafenib), CD20 antigen (tositumomab), CD25 (denileukin diftitox), CD30 (brentuximab vedotin), CFTR (ivacaftor) and CYP1A2 (dexlansoprazole). Both biological and non-biological factors can affect regulatory decisions. For example, a much lower incidence of cystic fibrosis and melanoma in Japan compared with the West could discourage the makers of ivacaftor and vemurafenib to file an application to the PMDA.[3] Denileukin diftitox and tositumomab, which were approved for lymphoma by the FDA in 1999 and 2003, respectively, remain unavailable both in the EU and Japan probably because better treatment modalities are available now.

Of the remaining 32 PGBMs in Japan, the aims were efficacy in 50% (16/32), safety in 38% (12/32) and monitoring in 12% (4/32) (Table 2). The therapeutic areas were antivirals in 9% (3/32), haematology in 9% (3/32), metabolic and endocrinology in 6% (2/32), neurology in 3% (1/32), oncology in 34% (11/32), transplantation in 3% (1/32) and two or more areas in 34% (11/32) (Table 3).

### *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.[25] 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. Approval

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

| | USA | | Japan | |
|---|---|---|---|---|
| | CDx | | CDx | |
| Pharmacogenomic biomarker aim | Available | Unavailable | Available | Unavailable |
| Efficacy | 11 | 10 | 11 | 5 |
| Safety | 5 | 7 | 2 | 10 |
| Monitoring | 4 | 1 | 2 | 2 |
| 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.

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

| | USA | | Japan | |
|---|---|---|---|---|
| | CDx | | CDx | |
| 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 | 11 | 4 | 9 | 2 |
| Pulmonary | 1 | 0 | 0 | 0 |
| Transplantation | 0 | 1 | 0 | 1 |
| Two or more | 6 | 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.

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 covered in Japan, but not approved in the USA, were chromosome 5q, FIP1L1-PDGFRα, Ph1/BCR-ABL and PML/RARα transloca-

tion. 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, tositumomab, 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, $P = 0{\cdot}016$). 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, $P = 0{\cdot}006$).

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 neurological[26] 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 oncology[28] 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 drugs[23] 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 complex[10,12] 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.

## REFERENCES

1. Li-Wan-Po A. Pharmacogenetics and personalized medicine. *J Clin Pharm Ther*, 2012;**37**:617–619.
2. Shimazawa R, Ikeda M Differences in pharmacogenomic biomarker information in package inserts from the United States, the United Kingdom and Japan. *J Clin Pharm Ther*, 2013;**38**:468–475.
3. Shimazawa R, Ikeda M. Are there any differences in the regulations of personalised medicine among the US, EU, and Japan? *Br J Clin Pharmacol*, 2013;**75**:1365–1367.
4. U.S. Food and Drug Administration. *Table of Pharmacogenomic Biomarkers in Drug Labels*. Available at: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm (accessed 5 March 2013).
5. U.S. Food and Drug Administration. *Draft Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices*. Available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm (accessed 23 September 2013).
6. Meckley LM, Neumann PJ. Personalized medicine: factors influencing reimbursement. *Health Policy*, 2010;**94**:91–100.
7. European Medicines Agency. *Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection*. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108672.pdf (accessed 23 September 2013).
8. Cohen J, Wilson A, Manzolillo K. Clinical and economic challenges facing pharmacogenomics. *Pharmacogenomics J*, 2013;**13**:378–388.
9. Kaa K. Medicare challenges and solutions–reimbursement issues in treating the patient with colorectal cancer. *J Manag Care Pharm*, 2007;**13**:S19–S26.
10. Radensky P. Reimbursement challenges with *In vitro* diagnostic tests: Fitting a square peg in a round hole. Food and Drug Law Institute Update. Available at: http://www.mwe.com/info/pubs/radensky0708.pdf (accessed 23 September 2013).
11. Tufts Center for the Study of Drug Development. Lack of clinically useful diagnostics hinder growth in personalized medicines. *Tufts CSDD Impact Report*, 2011;**13**.



Journal of Clinical Pharmacy and Therapeutics Published by John Wiley & Sons Ltd

12. Centers for Medicare and Medicaid Services. *Decision Memo for Pharmacogenomic Testing for Warfarin Response (CAG-00400N)*. Available at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=224&IsPopup=y&NCDId=333&NcaName=Pharmacogenomic+Testing+for+Warfarin+Response&ncdver=1&bc=AAAAAAAAEAAA& (accessed 23 September 2013).
13. World Health Organization. *World Health Statistics*. Available at: http://www.who.int/gho/publications/world_health_statistics/en/index.html (accessed 23 September 2013).
14. Ministry of Health, Labour and Welfare. *Overview of Medical Service Regime in Japan*. Available at: http://www.mhlw.go.jp/bunya/iryouhoken/iryouhoken01/dl/01_eng.pdf (accessed 23 September 2013).
15. Health Insurance Claims Review and Reimbursement Services. *Reimbursement list of off-label uses (Japanese)*. Available at: http://www.ssk.or.jp/shinsajoho/teikyojirei/ika.html (accessed 23 September 2013).
16. Fujiwara Y. Genomics, health care, and society. *N Engl J Med*, 2011;**365**:2339.
17. Ozeki T, Mushiroda T, Yowang A *et al.* Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet*, 2011;**20**:1034–1041.
18. Tobinai K, Takahashi T, Akinaga S. Targeting chemokine receptor CCR4 in adult T-cell leukemia-lymphoma and other T-cell lymphomas. *Curr Hematol Malig Rep*, 2012; **7**:235–240.
19. U.S. Food and Drug Administration. *510(k) Premarket Notification*. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm (accessed 23 September 2013).
20. U.S. Food and Drug Administration. *Premarket Approval (PMA)*. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm (accessed 23 September 2013).
21. Pharmaceuticals and Medical Devices Agency. *Labels of in vitro diagnostic devices (Japanese)*. Available at: http://www.info.pmda.go.jp/tsearch/html/menu_tenpu_base.html (accessed 23 September 2013).
22. U.S. Food and Drug Administration. *Drugs@FDA*. Available at: http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/ (accessed 23 September 2013).
23. Pharmaceuticals and Medical Devices Agency. *Drug approval database (Japanese)*. Available at: http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit? (accessed 23 September 2013).
24. Ministry of Health, Labour and Welfare. *National Health Insurance database 2012 (Japanese)*. Available at: http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/iryouhoken15/index.html (accessed 23 September 2013).
25. Fierce Medical Devices: Companion Diagnostics. *The Future of Medicine*. Available at: http://www.fiercemedicaldevices.com/offer/companion_diagnostics (accessed 23 September 2013).
26. Shimazawa R, Ikeda M. Delays in neurological drug development in Japan. *Intern Med*, 2011;**50**:1565–1568.
27. Shimazawa R, Kusumi I, Ikeda M. Delays in psychiatric drug development in Japan. *J Clin Pharm Ther*, 2012;**37**:348–351.
28. Sinha G. Japan works to shorten "drug lag", boost trials of new drugs. *J Natl Cancer Inst*, 2010;**102**:148–151.
29. National Comprehensive Cancer Network. NCCN Guidelines. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 23 September 2013).
30. Quinn B. Medicare and biomarkers–What does the future look like? *Drug Discov*, 2010;**7**:27–29.

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# Differences in pharmacogenomic biomarker information in package inserts from the United States, the United Kingdom and Japan

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## SUMMARY

***What is known and objective:*** **The provision of pharmacogenomic information in drug package inserts (PIs) has become more common in recent years. The content of PIs can be tailored to meet specific requirements of the target populations. Our objective was to identify, assess and report on differences in pharmacogenomic information in PIs from the United States (USA), the United Kingdom (UK) and Japan.**

***Methods:*** **Package inserts were obtained from the US Food and Drug Administration (FDA) Table of Pharmacogenomic Biomarkers in Drug Labels on 1 October 2012. Corresponding PIs were obtained concurrently from Japan and the UK. We compared the pharmacogenomic information included, where the information was located, the therapeutic class of the drug, the type and purpose of the biomarker and the initial US approval year.**

***Results and discussion:*** **One hundred eighteen PIs were included in the FDA table. Of the 118 PIs, 29 provided information on drug targets, 69 on metabolizing enzymes and 20 on other aspects. Genomic biomarkers were described in 71 PIs from the UK and 44 from Japan. Consistency in labelling across the three jurisdictions was greater in the 'Indications' section of the PIs than that in the 'Precautions' section. There appears to be greater concordance across countries for the biomarker information in the 'Indications' sections (UK 65% and Japan 48% relative to the US information) than that in the 'Precautions' sections (UK 41% and Japan 17%).**

***What is new and conclusion:*** **There are substantial differences in the pharmacogenomic information included in PIs from the USA, the UK and Japan. The differences varied according to the PI sections, and type and purpose of the biomarkers. The differences appeared to vary according to the strength of the evidence supporting use of the biomarkers. Further analyses are necessary to determine the causes of these differences.**

## WHAT IS KNOWN AND OBJECTIVE

Individual differences in drug efficacy and patients' susceptibility to adverse effects are well recognized. Studying the genomic basis of these differences can help clinicians to optimize therapy and reduce adverse drug reactions.

The United States (US) Food and Drug Administration (FDA) released their 'Guidance for Industry: Pharmacogenomic Data Submissions' document in March 2005 to help drug developers understand the agency's policies and processes for accepting and using pharmacogenomics data.[1] Similarly, the FDA created a 'Genomics' web portal, providing up-to-date regulatory and background information on genomics in relation to drug efficacy, safety, pharmacokinetics, pharmacodynamics and dosage.[2] Among other regulatory activities, the FDA attempts to incorporate genomic information into drug labels by requiring the revision of existing labels on the basis of clinical findings or the inclusion of appropriate wording in drug labels of new products. A list of pharmacogenomic biomarkers identified in the context of approved drug labels can be found on the FDA's website.[3] The FDA's European counterpart, the European Medicines Agency (EMA), has similarly published a variety of scientific guidelines on pharmacogenomics.[4]

Drug package inserts (PIs) represent the most fundamental tool for providing information on approved drugs to healthcare professionals and for promoting proper use of the drugs. The contents of PIs can be tailored to meet the requirements of the target populations and take local guidance into consideration.

The availability of pharmacogenomic information presented in PIs has been investigated in recent years in the United States, Europe and Japan.[5–10] Findings showed that 121 of the 1200 PIs from the United States released over the period 1945–2005 contained pharmacogenomic information.[5] In the European Union, the PIs from approximately 20% of the 584 products reviewed by EMA as of 2011 contained genomics information to personalize their use.[10] In Japan, 32 of 199 PIs (16%) reviewed by the Pharmaceutical Medical Device Agency (PMDA) from 2002 to 2006 included pharmacogenomic information.[8] However, there have been few comparisons of the pharmacogenomic information in PIs between countries.[9] We selected the United States, the United Kingdom (UK) and Japan for our comparison because of similarities in their drug regulations, as all three are members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The UK, like Japan, has a national health service that controls drug cost reimbursement.[11]

The aim of the current study was to investigate differences in information on genomic biomarkers in PIs from the United States, the UK and Japan. The findings should provide a basis for further regulatory standardization and highlight justifiable population-specific differences in pharmacogenomic information in PIs.

## METHODS

A list of pharmacogenomic biomarkers in PIs from the United States is available from the FDA website.[3] PIs from the United

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