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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004188
Article Type:	Research
Date Submitted by the Author:	07-Oct-2013
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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Public health
Keywords:	THERAPEUTICS, Molecular aspects < ONCOLOGY, Molecular diagnostics < INFECTIOUS DISEASES

Stratified medicine in European Medicines Agency licensing: a systematic review of predictive biomarkers

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Abstract

Objectives Stratified medicine is often heralded as the future of clinical practice. Key part of stratified medicine is the use of predictive biomarkers, which identify patient subgroups most likely to benefit (or least likely to experience harm) from an intervention. We investigated how many and what predictive biomarkers are currently included in European Medicines Agency licensing.

Methods and eligibility criteria Indications and contraindications of all drugs considered by the EMA and published on their website were screened to identify predictive biomarkers. For all included Biomarker-Indication-Drug (B-I-D) combinations data was collected on: the type of the biomarker, whether it selected a subgroup of patients based on efficacy or toxicity, therapeutic area, marketing status, date of licensing decision, date of inclusion of the biomarker in the indication or contraindication, and on orphan designation.

Results 49 B-I-D combinations were identified over 16 years, which included 37 biomarkers and 41 different drugs. All identified biomarkers were molecular. Six drugs (relating to 10 B-I-D combinations) had an orphan designation at the time of licensing. The identified B-I-D combinations were mainly used in cancer and HIV treatment, but also in hepatitis C and three other indications (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia). In 45 B-I-D combinations biomarkers were used as predictive of drug efficacy and in four of drug toxicity. It appeared that there was an increase in the number of B-I-D combinations introduced each year, however the numbers were too small to identify any trends.

Conclusions Given the large body of literature documenting research into potential predictive biomarkers and extensive investment into stratified medicine, we identified relatively few predictive biomarkers included in licensing. These were also limited to a small number of clinical areas. This might suggest a need for improvement in methods of translation from laboratory findings to clinical practice.

Article summary

Article focus

- To identify predictive biomarkers included in European Medicines Agency licensing
- For identified biomarkers, to investigate their type, the clinical areas in which these biomarkers are used and possible trends over time with regard to the number of new predictive biomarkers considered each year

Key messages

- 49 Biomarker-Indication-Drug (B-I-D) combinations were identified over 16 years, which included 37 biomarkers and 41 different drugs. There appeared to be an increase in the number of B-I-D combinations introduced each year, however the numbers were too small to identify any trends.
- All identified biomarkers were molecular. They were mainly used in cancer and HIV treatment, but also in hepatitis C and three other indications (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia).

Strengths and limitations of this study

- Our research, to our knowledge, provides the first indication of the number and nature of predictive biomarkers included in licensing in Europe using systematic review methodology.
- It is likely that the 49 identified B-I-D combinations do not represent a complete list of predictive biomarkers used in practice, as some could have been considered by national regulatory agencies, particularly for drugs considered before EMA was established in 1995.

Introduction

Drugs are rarely effective in all patients and may be associated with serious adverse events.[1] The challenge of stratified medicine is to identify predictive biomarkers that identify patient subgroups (or strata) with a differential therapeutic response to a linked intervention, allowing more appropriate and effective use of interventions to maximise patient benefit and minimise the occurrence of serious adverse events.[2;3] Predictive biomarkers are defined particular to a treatment for a condition, where biomarker values are associated with differential efficacy or toxicity of that treatment.[4-7] The use of predictive biomarkers promises a more appropriate choice of treatment: it can also help to rationalise funding decisions, avoiding costs of futile treatment and of adverse events. However the additional cost of measuring the marker has to be taken into account. Examples of predictive biomarkers include tamoxifen use in breast cancer, which is prescribed to women who are oestrogen receptor positive,[8] and trastuzumab which is prescribed to those with HER2 overexpression in their tumour.[9]

There is a large body of literature documenting research into potential predictive biomarkers,[10;11] and millions of pounds have been invested into stratified medicine, both in industry and through programs from funding bodies such as the Medical Research Council[12] and Cancer Research UK.[13] We aimed to evaluate the degree to which this investment has led to production of biomarker-treatment combinations ready for use in clinical practice. To explore this question, we have undertaken a systematic review of predictive biomarkers reported in licensing decisions of the European Medicines Agency (EMA).

In our review we aimed to find out how many of the indications and contraindications considered by the EMA define a patient population using a predictive biomarker. We were also interested in the disease areas where predictive biomarkers have been used and any trend over time. It has been hypothesised that stratified medicine has not been implemented in practice as much as expected. This paper provides evidence of the impact of stratified medicine research to date and if less than expected, then this will highlight the need to review the underlying reasons and address the problems.

Methods

We defined a Biomarker-Indication-Drug (B-I-D) combination as the unit of our analysis, relating to the use of a predictive biomarker with a particular drug for a particular condition or disease.[4-7] For toxicity biomarkers where the a biomarkers of drug toxicity may be used in more than one disease area we grouped these into one B-I-D combination.

All drugs listed on the EMA website in either European Public Assessment Reports or Pending Decisions[14;15] (accessed on the 17th of January 2013) were evaluated, together with their indications and contraindications.

Our inclusion criteria were that the biomarker had to:

(i) be used in the indication and/or contraindication of the drug,
(ii) be associated with a particular treatment,
(iii) identify a subgroup of patients with a particular disease eligible for treatment with the drug.

We excluded biomarkers:

(i) associated with a non-therapeutic substance (for example vaccines),
(ii) not used as predictive, including:
    - used for diagnosis, screening or forming part of the disease definition (already established for defining a disease) or established disease subtype,
    - prognostic only (associated with outcome regardless of treatment and not predictive of treatment response[16])
(iii) associated with another treatment (for example the biomarker was not associated with the differential efficacy or toxicity of the drug of interest, but another drug given in combination with the drug of interest).

We have reviewed EMA licensing, as in Europe a centralised drug evaluation by the EMA is required for drugs for treatment of a number of conditions, drugs obtained from biotechnology processes and all drugs used for rare conditions (orphan medicines). Companies can also apply for a centralised marketing authorisation of other drugs.[17] Although the EMA does not license biomarkers, it evaluates drugs in groups defined by predictive biomarkers (for example trastuzumab is licensed for use in HER2 overexpressing breast cancer patients).[18] Our approach is likely to give a broad overview of the impact of predictive biomarkers on treatment selection since 1995 (when EMA was established[19]).

In the first stage of screening all entries were screened by two independent reviewers (MB and KM) to identify those potentially including a predictive biomarker. If an entry was identified by at least one of the reviewers as potentially relevant, it was included in the second stage of screening.

In the second stage of screening, a list of potential B-I-D combinations was created based on the entries identified in the first stage. The list of potential B-I-D combinations was assessed by two independent reviewers (MB and KM) using full inclusion/exclusion criteria, based on the information in the Summary of Product Characteristics (which sets out the position of the drug obtained in the assessment process and summarises its properties and clinical use together with the clinical trial evidence that was considered by the EMA)[20] , the Scientific Discussion (which discusses the properties and clinical evidence in more detail) and additional information from targeted internet searches and expert advice if necessary. Any disagreements were resolved by discussion.

For the included B-I-D combinations data was collected on: the type of the biomarker used as predictive, whether it selected a subgroup of patients based on efficacy or toxicity, therapeutic area, marketing status, date of licensing decision, date of inclusion of the biomarker in the indication or contraindication, and on orphan designation (granted to drugs intended for the treatment of a life-threatening or chronically

debilitating condition which is either affecting no more than 5 in 10,000 people in the EU or when the revenue is unlikely to cover the investment in drug development[21]). To provide a context for our review, we have also collected data on the total number of drugs licensed each year with and without an orphan designation.

Results

Across the 18 year period (1995-2012) we identified 49 B-I-D combinations, including 37 biomarkers and 41 different drugs. The details of the review process are presented in Figure 1. Most of the drugs were authorised, the exceptions being:

- Gemtuzumab ozogamicin (refused)
- Zeldoronic acid (pending)
- Imatinib in the indication for aggressive systemic mastocytosis (withdrawn)
- Amprnavir (withdrawn)
- Nelfinavir (withdrawn)

The number of new B-I-D combinations considered by the EMA each year has increased from zero or one per year in the late nineties, to a maximum of 7 in each of 2011 and 2012 as shown in Figure 2. A predictive biomarker was included in the indication or contraindication at the time when the drug was first licensed for 35 drugs (for one (capecitabine) the date of inclusion of the biomarker was unclear from the documentation, for the remaining drugs the time from the initial licensing decision to the inclusion of a predictive biomarker ranged from one to ten years). The proportion of first licensing decision of all new drugs that included a predictive biomarker increased over time and was close to 10% in 2003, 2004, 2011 and 2012 (Figure 3).

Six drugs associated with a predictive biomarker had an orphan designation at the time of licensing, however for two it was removed at the end of exclusivity period (details reported in

Table 1). One of the six drugs (imatinib) was associated with five different predictive biomarkers in five different indications (Figure 4).

The identified predictive biomarkers were all molecular. Thirty-three biomarkers were used to predict treatment efficacy (details reported in

Table 1) and only four to predict toxicity (Table 2).

Most of the biomarkers were included in indications and contraindications of cancer treatments (26 B-I-D combinations) and viral diseases, mainly HIV (17 B-I-D combinations). The remaining biomarkers were used to stratify metabolic and blood disorders (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia) and appeared in the last two years (Figure 2).

Discussion

Stratified medicine is promoted as key to the future of medicine, and is currently one of the most active areas of clinical research. To our knowledge this review provides the first indication of the number and nature of predictive biomarkers included in licensing in Europe based on the drug indications and contraindications on the EMA website. Forty nine B-I-D combinations were identified. All identified biomarkers were molecular. The identified B-I-D combinations were mainly used in cancer and HIV treatment, with only five used in other disease areas.

It is likely that the 49 identified B-I-D combinations from the EMA database do not represent a complete list of the predictive biomarkers used in practice (some predictive biomarkers could have been considered by national regulatory agencies, particularly for drugs considered before EMA was established in 1995) few are likely to have been omitted, particularly from recent years.[19] Several types of biomarkers were excluded. We did not include biomarkers used for dose adjustments as they do not directly predict efficacy or toxicity (although inappropriate dose adjustment could limit the treatment efficacy or cause adverse events).[22] We also only investigated biomarkers associated with drug treatments. Other biomarkers may be used in practice with non-drug treatments (for example radiotherapy).

The definition of a predictive biomarker can be difficult to apply, as over time predictive biomarkers may become part of a redefinition of the disease or subtype of disease[23] and be classed as diagnostic tests. In our evaluation we excluded diagnostic biomarkers (for example these included factor IX deficiency, or genetic testing for familial lipoprotein lipase deficiency), and biomarkers used to identify an established subtype of a disease (mainly ST segment elevation and non-ST segment elevation myocardial infarction).

The spectrum of diseases where predictive biomarkers have been successfully developed is relatively narrow. This suggests a possible need for more research in other clinical areas. Also the vast majority of the B-I-D combinations were associated with treatment efficacy and only four with toxicity. As adverse events associated with some treatments could be potentially serious and the possibility to screen out patients at high risk prior to commencing treatment would be beneficial. A proportion of the drugs with an associated predictive biomarker identified in our review had an orphan designation. This seems surprising, as convincing evidence to support the use of a drug in a subgroup of patients with a rare

condition might be difficult to obtain, due to the small numbers of patients available to test the hypotheses.

Our review shows that few predictive biomarkers have been included in licensing relative to the large body of literature documenting numerous potential predictive biomarkers.[10;11] Therefore, in spite of the substantial investment in research, the promise of stratified medicine is not yet being realised to a large extent. The reasons for this might include poor translation of findings of laboratory studies into clinical context, or the failure to identify effective predictive biomarkers and treatments. Even though it is becoming easier and cheaper to gather huge sets of genomic data, its interpretation is challenging, which can potentially hinder translational research. Recognising this, initiatives have been undertaken both in the USA (National Institutes of Health and the FDA) and UK (Medical Research Council) to promote the translation of basic research into clinical practice.[12] Also the availability of datasets such as the Cancer Cell Line Encyclopaedia and a similar UK initiative might contribute to the faster progress of stratified medicine.[24;25] The relatively small number of predictive biomarkers identified in licensing might also indicate the need for more sound methodological standards for biomarker discovery and development.[26]

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Competing interests

All authors declare that they have no financial or non-financial interests that may be relevant to the submitted work.

Author Contributions

KM, JD, RR and LB designed the review. KM and MB carried out the review. Where needed CC and PJ provided clinical advice. All authors contributed to the interpretation of the results, commented on drafts and accepted the final version of this paper.

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

Data sharing

Data sharing: full dataset available from the corresponding author.

Ethical Approval

No ethical approval was required, as the study did not involve collection of patient data

Study funding

This work was funded by the MRC Midlands Hub for Trials Methodology Research at the University of Birmingham (Medical Research Council Grant ID G0800808). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Table 1 Biomarkers predictive of efficacy identified in the review of EMA licensing

Biomarker	Indication	Drug
ALK gene rearrangement	Carcinoma, Non-Small-Cell Lung	Crizotinib (Xalkori)
BRAF V600 mutation	Melanoma	Vemurafenib (Zelboraf)
CCR5 tropism	HIV Infections	Maraviroc (Celsentri)
CD-33 expression*	Leukemia, Myeloid, Acute	gemtuzumab ozogamicin (Mylotarg)‡
EGFR expression	Colorectal Neoplasms	Cetuximab (Erbitux)
EGFR expression	Carcinoma, Non-Small-Cell Lung	Erlotinib (Tarceva)
EGFR mutation	Carcinoma, Non-Small-Cell Lung	Erlotinib (Tarceva)
EGFR mutation	Carcinoma, Non-Small-Cell Lung	Gefitinib (Iressa)
EpCAM expression	CancerAscites	Catumaxomab (Removab)
FIP1L1-PDGFR rearrangement	Hypereosinophilic Syndrome	Imatinib (Glivec)#
G551D mutation in the CFTR gene	Cystic Fibrosis	Ivacaftor (Kalydeco)‡
genotype 1 HCV	Hepatitis C, Chronic	Boceprevir (Victrelis)
genotype 1 HCV	Hepatitis C	Telaprevir (Incivo)
HER2 expression	Breast Neoplasms	Lapatinib (Tyverb)
HER2 expression	Breast Neoplasms	Trastuzumab (Herceptin)
HER2 expression	Stomach Neoplasms	Trastuzumab (Herceptin)
HER2 expression	Breast Neoplasms	Everolimus (Afinitor)
HER2 expression **	Breast Neoplasms	pertuzumab (Perjeta)
Hormone dependency	Prostatic Neoplasms	Degarelix (Firmagon)
Hormone receptor expression**	Breast Neoplasms	zoledronic acid (Zometa)
Hormone receptor expression	Breast Neoplasms	Everolimus (Afinitor)
Kit (CD 117) expression	Gastrointestinal Stromal Tumors	Imatinib (Glivec)#
Kit (D816V) mutation***	Aggressive Systemic Mastocytosis	Imatinib (Glivec)#
KRAS mutation	Colorectal Neoplasms	Cetuximab (Erbitux)
KRAS mutation	Colorectal Neoplasms	Panitumumab (Vectibix)
LPL protein detectable	Hyperlipoproteinemia Type I	alipogene tiparvovec (Glybera)‡
oestrogen receptor expression	Breast Neoplasms	Fulvestrant (Faslodex)
oestrogen receptor expression	Breast Neoplasms	Toremifene (Fareston)
PDGFR gene rearrangements	Myelodysplastic-Myeloproliferative Diseases	Imatinib (Glivec)#
Philadelphia chromosome	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Dasatinib (Sprycel)‡
Philadelphia chromosome	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Imatinib (Glivec)#
t(15;17) translocation	Leukemia, Promyelocytic, Acute	arsenic trioxide (Trisenox)#
viral resistance mutations***	HIV Infections	Amprenavir (Agenerase)
viral resistance mutations	HIV Infections	atazanavir sulphate (Reyataz)
viral resistance mutations	HIV Infections	Darunavir (Prezista)
viral resistance mutations	HIV Infections	efavirenz / emtricitabine / tenofovir disoproxil (Atripla)
viral resistance mutations	HIV Infections	Emtricitabine (Emtriva)
viral resistance mutations	HIV Infections	emtricitabine / rilpivirine / tenofovir disoproxil (Eviplera)
viral resistance mutations	HIV Infections	Enfuvirtide (Fuzeon)

viral resistance mutations	HIV Infections	fosamprenavir calcium (Telzir)
viral resistance mutations	HIV Infections	lopinavir / ritonavir (Kaletra)
viral resistance mutations ***	HIV Infections	Nelfinavir (Viracept)
viral resistance mutations	HIV Infections	rilpivirine hydrochloride (Edurant)
viral resistance mutations	HIV Infections	tenofovir disoproxil fumarate (Viread)
viral resistance mutations	HIV Infections	Tipranavir (Aptivus)

* refused **pending ***withdrawn
‡ drug designated an orphan medicine, # orphan designation has been removed at the end of exclusivity period

Table 2 Biomarkers predictive of toxicity identified in the review of EMA licensing

Biomarker	Indication	Drug
DPD deficiency	Colorectal Neoplasms Colonic Neoplasms Stomach Neoplasms Breast Neoplasms	Capecitabine (Xeloda and generic drugs: Capecitabine Accord; Capecitabine Krka; Capecitabine Medac; Capecitabine Teva)
DPD deficiency	Stomach Neoplasms	tegafur / gimeracil / oteracil (Teysuno)
HLA-B*5701 allele	HIV Infections	Abacavir (Kivexa; Trizivir; Ziagen)*
NADPH reductase deficiency	Methemoglobinemia	Methylthioninium chloride (Methylthioninium chloride Proveblue)

* HLA-B*5701 allele is predictive of hypersensitivity to abacavir, which is present in three three drugs: Kivexa (abacavir / lamivudine); Trizivir (abacavir / lamivudine / zidovudine); Ziagen (abacavir)

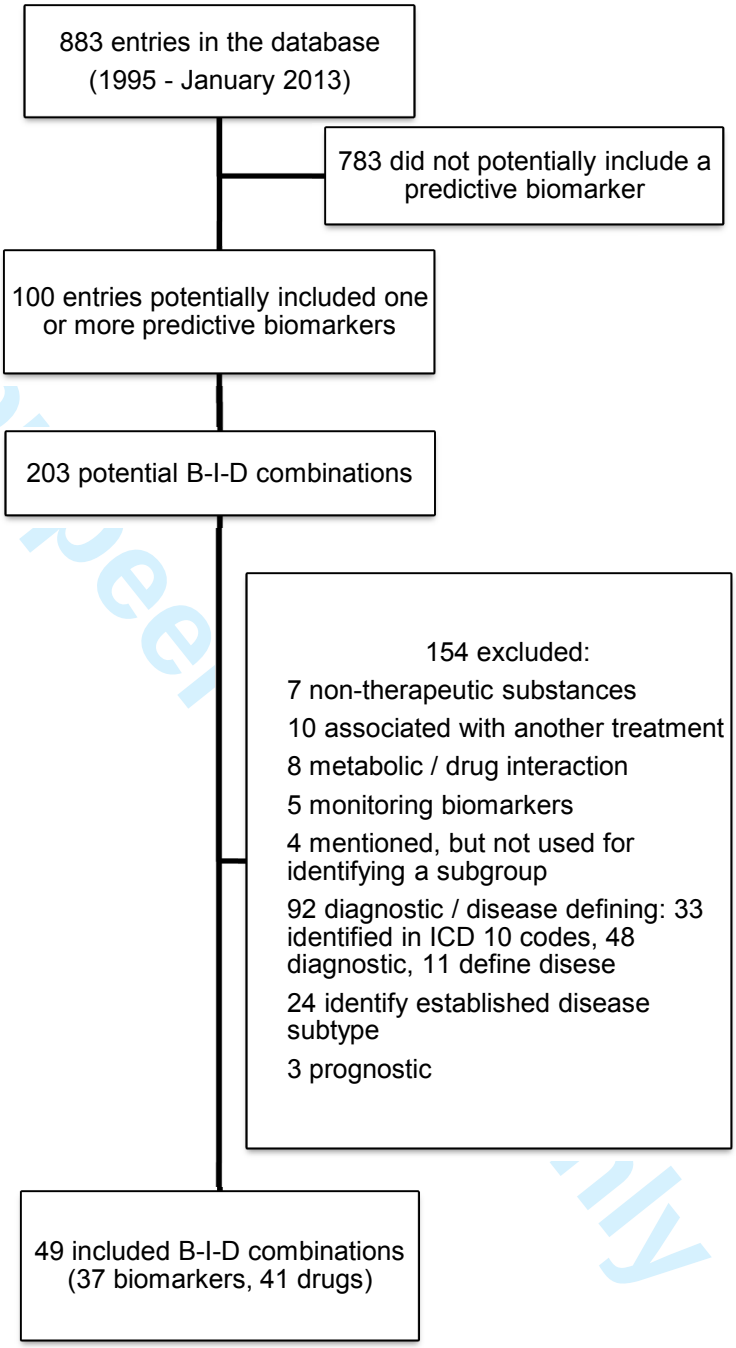


Figure 1 Flow diagram for the systematic review of predictive biomarkeres in EMA licensig

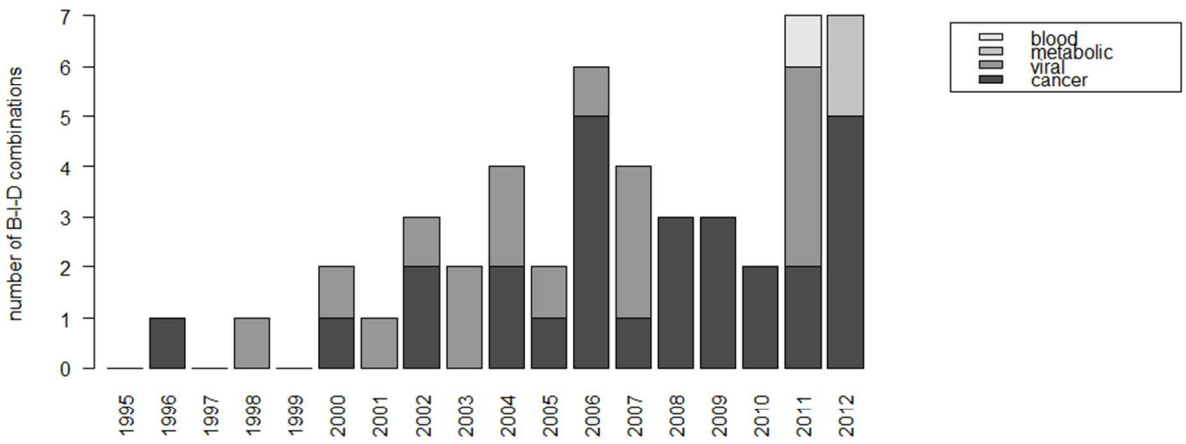
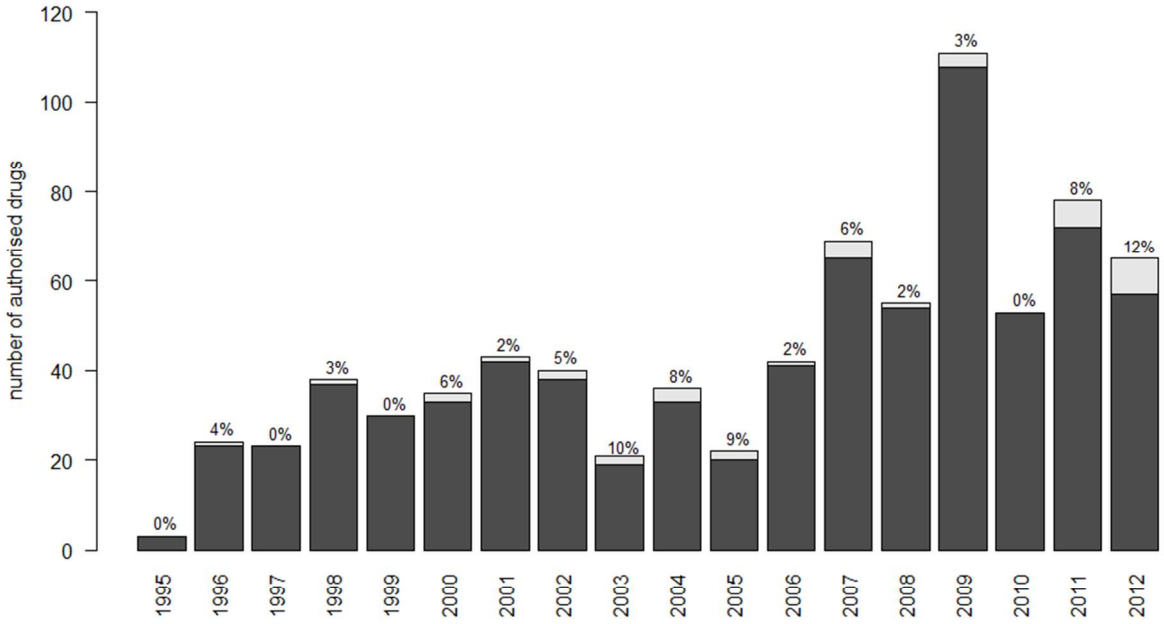


Figure 2 Number of new B-I-D combinations considered each year by disease area



Data for 2012 include 4 generic drugs (capecitabine)

Figure 3 New drugs authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

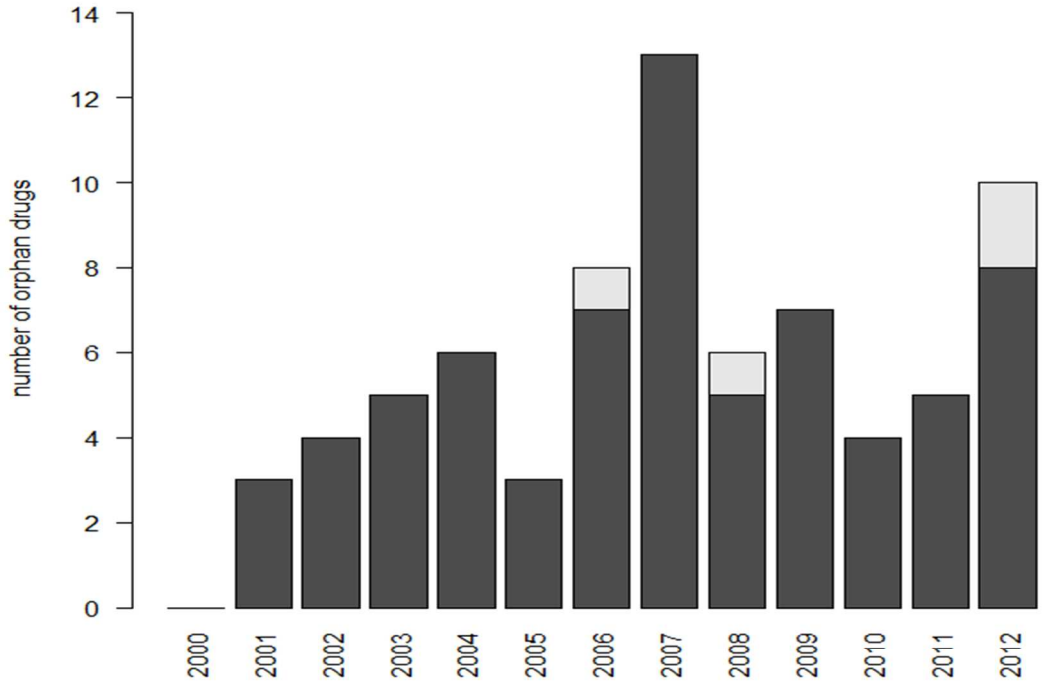


Figure 4 New drugs orphan authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Not applicable
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6-7
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Stratified medicine in European Medicines Agency licensing: a systematic review of predictive biomarkers

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004188.R1
Article Type:	Research
Date Submitted by the Author:	06-Dec-2013
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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Public health
Keywords:	THERAPEUTICS, Molecular aspects < ONCOLOGY, Molecular diagnostics < INFECTIOUS DISEASES

Stratified medicine in European Medicines Agency licensing: a systematic review of predictive biomarkers

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Abstract

Objectives Stratified medicine is often heralded as the future of clinical practice. Key part of stratified medicine is the use of predictive biomarkers, which identify patient subgroups most likely to benefit (or least likely to experience harm) from an intervention. We investigated how many and what predictive biomarkers are currently included in European Medicines Agency licensing.

Methods and eligibility criteria Indications and contraindications of all drugs considered by the EMA and published on their website were screened to identify predictive biomarkers. For all included Biomarker-Indication-Drug (B-I-D) combinations data was collected on: the type of the biomarker, whether it selected a subgroup of patients based on efficacy or toxicity, therapeutic area, marketing status, date of licensing decision, date of inclusion of the biomarker in the indication or contraindication, and on orphan designation.

Results 49 B-I-D combinations were identified over 16 years, which included 37 biomarkers and 41 different drugs. All identified biomarkers were molecular. Six drugs (relating to 10 B-I-D combinations) had an orphan designation at the time of licensing. The identified B-I-D combinations were mainly used in cancer and HIV treatment, but also in hepatitis C and three other indications (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia). In 45 B-I-D combinations biomarkers were used as predictive of drug efficacy and in four of drug toxicity. It appeared that there was an increase in the number of B-I-D combinations introduced each year, however the numbers were too small to identify any trends.

Conclusions Given the large body of literature documenting research into potential predictive biomarkers and extensive investment into stratified medicine, we identified relatively few predictive biomarkers included in licensing. These were also limited to a small number of clinical areas. This might suggest a need for improvement in methods of translation from laboratory findings to clinical practice.

Article summary

Article focus

- To identify predictive biomarkers included in European Medicines Agency licensing
- For identified biomarkers, to investigate their type, the clinical areas in which these biomarkers are used and possible trends over time with regard to the number of new predictive biomarkers considered each year

Key messages

- 49 Biomarker-Indication-Drug (B-I-D) combinations were identified over 16 years, which included 37 biomarkers and 41 different drugs. There appeared to be an increase in the number of B-I-D combinations introduced each year, however the numbers were too small to identify any trends.
- All identified biomarkers were molecular. They were mainly used in cancer and HIV treatment, but also in hepatitis C and three other indications (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia).

Strengths and limitations of this study

- Our research, to our knowledge, provides the first indication of the number and nature of predictive biomarkers included in licensing in Europe using systematic review methodology.
- It is likely that the 49 identified B-I-D combinations do not represent a complete list of predictive biomarkers used in practice, as some could have been considered by national regulatory agencies, particularly for drugs considered before EMA was established in 1995.

Introduction

Drugs are rarely effective in all patients and may be associated with serious adverse events.[1] The challenge of stratified medicine is to identify predictive biomarkers that identify patient subgroups (or strata) with a differential therapeutic response to a linked intervention, allowing more appropriate and effective use of interventions to maximise patient benefit and minimise the occurrence of serious adverse events.[2;3] Predictive biomarkers are defined particular to a treatment for a condition, where biomarker values are associated with differential efficacy or toxicity of that treatment.[4-7] The use of predictive biomarkers promises a more appropriate choice of treatment: it can also help to rationalise funding decisions, avoiding costs of futile treatment and of adverse events. However the additional cost of measuring the marker has to be taken into account. Examples of predictive biomarkers include tamoxifen use in breast cancer, which is prescribed to women who are oestrogen receptor positive,[8] and trastuzumab which is prescribed to those with HER2 overexpression in their tumour.[9]

There is a large body of literature documenting research into potential predictive biomarkers,[10;11] and millions of pounds have been invested into stratified medicine, both in industry and through programs from funding bodies such as the Medical Research Council[12] and Cancer Research UK.[13] We aimed to investigate if this interest in developing stratified medicines has led to production of biomarker-treatment combinations ready for use in clinical practice. To explore this question, we have undertaken a systematic review of predictive biomarkers reported in licensing decisions of the European Medicines Agency (EMA).

In our review we aimed to find out how many of the indications and contraindications considered by the EMA define a patient population using a predictive biomarker. We were also interested in the disease areas where predictive biomarkers have been used and any trend over time. It has been hypothesised that stratified medicine has not been implemented in practice as much as expected. This paper provides evidence of the impact of stratified medicine research to date and if less than expected, then this will highlight the need to review the underlying reasons and address the problems.

Methods

We defined a Biomarker-Indication-Drug (B-I-D) combination as the unit of our analysis, relating to the use of a predictive biomarker with a particular drug for a particular condition or disease.[4-7] For toxicity biomarkers where the a biomarkers of drug toxicity may be used in more than one disease area we grouped these into one B-I-D combination.

All drugs listed on the EMA website in either European Public Assessment Reports or Pending Decisions[14;15] (accessed on the 17th of January 2013) were evaluated, together with their indications and contraindications.

Our inclusion criteria were that the biomarker had to:

(i) be used in the indication and/or contraindication of the drug,
(ii) be associated with a particular treatment,
(iii) identify a subgroup of patients with a particular disease eligible for treatment with the drug.

We excluded biomarkers:

(i) associated with a non-therapeutic substance (for example vaccines),
(ii) not used as predictive, including:
    - used for diagnosis, screening or forming part of the disease definition (already established for defining a disease) or established disease subtype,
    - prognostic only (associated with outcome regardless of treatment and not predictive of treatment response[16])
(iii) associated with another treatment (for example the biomarker was not associated with the differential efficacy or toxicity of the drug of interest, but another drug given in combination with the drug of interest).

We have reviewed EMA licensing, as in Europe a centralised drug evaluation by the EMA is required for drugs for treatment of a number of conditions, drugs obtained from biotechnology processes and all drugs used for rare conditions (orphan medicines). Companies can also apply for a centralised marketing authorisation of other drugs.[17] Although the EMA does not license biomarkers, it evaluates drugs in groups defined by predictive biomarkers (for example trastuzumab is licensed for use in HER2 overexpressing breast cancer patients).[18] Our approach is likely to give a broad overview of the impact of predictive biomarkers on treatment selection since 1995 (when EMA was established[19]).

We created a database of all drugs in the EMA database including the drug name, licensing status, indication and contraindication. In the first stage of screening all database entries were screened by two independent reviewers (MB and KM) to identify those potentially including a predictive biomarker in the indication or contraindication. If an entry was identified by at least one of the reviewers as potentially relevant, it was included in the second stage of screening.

In the second stage of screening, a list of potential B-I-D combinations was created based on the entries identified in the first stage. The list of potential B-I-D combinations was assessed by two independent reviewers (MB and KM) using full inclusion/exclusion criteria, based on the information in the Summary of Product Characteristics (which sets out the position of the drug obtained in the assessment process and summarises its properties and clinical use together with the clinical trial evidence that was considered by the EMA)[20] , the Scientific Discussion (which discusses the properties and clinical evidence in more detail) and additional information from targeted internet searches and expert advice if necessary. Any disagreements were resolved by discussion.

For the included B-I-D combinations data was collected on: the type of the biomarker used as predictive, whether it selected a subgroup of patients based on efficacy or toxicity, therapeutic area, marketing

status, date of licensing decision, date of inclusion of the biomarker in the indication or contraindication, and on orphan designation (granted to drugs intended for the treatment of a life-threatening or chronically debilitating condition which is either affecting no more than 5 in 10,000 people in the EU or when the revenue is unlikely to cover the investment in drug development[21]). To provide a context for our review, we have also collected data on the total number of drugs licensed each year with and without an orphan designation.

Results

Across the 18 year period (1995-2012) we identified 49 B-I-D combinations, including 37 biomarkers and 41 different drugs. The details of the review process are presented in Figure 1~~Figure 1~~. Most of the drugs were authorised, the exceptions being:

- Gemtuzumab ozogamicin (refused)
- Zeldoronic acid (pending)
- Imatinib in the indication for aggressive systemic mastocytosis (withdrawn)
- Amprnavir (withdrawn)
- Nelfinavir (withdrawn)

The number of new B-I-D combinations considered by the EMA each year has increased overall from zero or one per year in the late nineties, to a maximum of 7 in each of 2011 and 2012 as shown in Figure 2~~Figure 2~~. This was however not a steady increase, as the number of B-I-D combinations considered by the EMA showed fluctuation between 2000 and 2006, a decrease between 2006 and 2010, followed by an increase in the number in 2011 and 2012. A predictive biomarker was included in the indication or contraindication at the time when the drug was first licensed for 35 drugs (for one (capecitabine) the date of inclusion of the biomarker was unclear from the documentation, for the remaining drugs the time from the initial licensing decision to the inclusion of a predictive biomarker ranged from one to ten years). The proportion of first licensing decision of all new drugs that included a predictive biomarker increased over time and was close to 10% in 2003, 2004, 2005, 2011 and 2012 (Figure 3).

Six drugs associated with a predictive biomarker had an orphan designation at the time of licensing, however for two it was removed at the end of exclusivity period (details reported in

Table 1~~Table 1~~). One of the six drugs (imatinib) was associated with five different predictive biomarkers in five different indications (Figure 4).

The identified predictive biomarkers were all molecular. Thirty-three biomarkers were used to predict treatment efficacy (details reported in

Table 1~~Table 1~~) and only four to predict toxicity (Table 2~~Table 2~~).

Most of the biomarkers were included in indications and contraindications of cancer treatments (26 B-I-D combinations) and viral diseases, mainly HIV (17 B-I-D combinations). The remaining biomarkers were used to stratify metabolic and blood disorders (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia) and appeared in the last two years (Figure 2~~Figure 2~~).

Discussion

Stratified medicine is promoted as key to the future of medicine, and is currently one of the most active areas of clinical research. To our knowledge this review provides the first indication of the number and nature of predictive biomarkers included in licensing in Europe based on the drug indications and contraindications on the EMA website. Forty nine B-I-D combinations were identified. All identified biomarkers were molecular. The identified B-I-D combinations were mainly used in cancer and HIV treatment, with only five used in other disease areas.

It is likely that the 49 identified B-I-D combinations from the EMA database do not represent a complete list of the predictive biomarkers used in practice as some predictive biomarkers could have been considered by national regulatory agencies, particularly for drugs considered before EMA was established in 1995. Also EMA licensing is not compulsory for some disease areas, such as mental health. However a number of drugs with indications in depression of schizophrenia have been considered by the EMA. Therefore we believe that although our approach might not provide a complete list of all predictive biomarkers used in Europe, relatively few are likely to have been omitted, particularly from recent years.[19] The fact that some of the identified B-I-D combinations included biomarkers introduced to an indication of an already licensed drug suggests that at least to some extent we have captured stratification occurring after the initial licensing of a drug. However the actual extent to which this takes place in clinical practice is difficult to evaluate.

Several types of biomarkers were excluded. We did not include biomarkers used for dose adjustments as they do not directly predict efficacy or toxicity (although inappropriate dose adjustment could limit the treatment efficacy or cause adverse events).[22] We also only investigated biomarkers associated with drug treatments. Other biomarkers may be used in practice with non-drug treatments (for example radiotherapy).

The definition of a predictive biomarker can be difficult to apply, as over time predictive biomarkers may become part of a redefinition of the disease or subtype of disease[23] and be classed as diagnostic tests. In our evaluation we excluded diagnostic biomarkers (for example these included factor IX deficiency, or genetic testing for familial lipoprotein lipase deficiency), and biomarkers used to identify an established subtype of a disease (mainly ST segment elevation and non-ST segment elevation myocardial infarction).

The spectrum of diseases where predictive biomarkers have been successfully developed is relatively narrow. This suggests a possible need for more research in other clinical areas. Also the vast majority of the B-I-D combinations were associated with treatment efficacy and only four with toxicity. As adverse events associated with some treatments could be potentially serious and the possibility to screen out patients at high risk prior to commencing treatment would be beneficial. A proportion of the drugs with an associated predictive biomarker identified in our review had an orphan designation. This seems surprising, as convincing evidence to support the use of a drug in a subgroup of patients with a rare condition might be difficult to obtain, due to the small numbers of patients available to test the hypotheses.

It is difficult to provide accurate estimates of the extent of research into potential predictive biomarkers, however it has been suggested in 2011 that the number of publications on different biomarkers (not only predictive) was in the area of 15 000.[10] Another paper published in 2009, which reviewed genetic markers evaluated as potential predictors of response to treatment, found that 541 different genes were investigated as potential predictive biomarkers in 1 668 papers.[11] It can be reasonably expected that this number largely increased since these papers were published. Our review shows that few predictive biomarkers have been included in licensing relative to this large body of literature documenting numerous potential predictive biomarkers. Therefore, in spite of the substantial investment in research, the promise of stratified medicine is not yet being realised to a large extent. The reasons for this might include poor translation of findings of laboratory studies into clinical context, or the failure to identify effective predictive biomarkers and treatments. Even though it is becoming easier and cheaper to gather huge sets of genomic data, its interpretation is challenging, which can potentially hinder translational research. Recognising this, initiatives have been undertaken both in the USA (National Institutes of Health and the FDA) and UK (Medical Research Council) to promote the translation of basic research into clinical practice.[12] Also the availability of datasets such as the Cancer Cell Line Encyclopaedia and a similar UK initiative might contribute to the faster progress of stratified medicine.[24;25] The relatively small number of predictive biomarkers identified in licensing might also indicate the need for more sound methodological standards for biomarker discovery and development.[26]

Competing interests

All authors declare that they have no financial or non-financial interests that may be relevant to the submitted work.

Author Contributions

KM, JD, RR and LB designed the review. KM and MB carried out the review. Where needed CC and PJ provided clinical advice. All authors contributed to the interpretation of the results, commented on drafts and accepted the final version of this paper.

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

Data sharing

Data sharing: full dataset available from the corresponding author.

Ethical Approval

No ethical approval was required, as the study did not involve collection of patient data

Study funding

This work was funded by the MRC Midlands Hub for Trials Methodology Research at the University of Birmingham (Medical Research Council Grant ID G0800808). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Table 1 Biomarkers predictive of efficacy identified in the review of EMA licensing

Biomarker	Indication	Drug
ALK gene rearrangement	Carcinoma, Non-Small-Cell Lung	Crizotinib (Xalkori)
BRAF V600 mutation	Melanoma	Vemurafenib (Zelboraf)
CCR5 tropism	HIV Infections	Maraviroc (Celsentri)
CD-33 expression*	Leukemia, Myeloid, Acute	gemtuzumab ozogamicin (Mylotarg)‡
EGFR expression	Colorectal Neoplasms	Cetuximab (Erbitux)
EGFR expression	Carcinoma, Non-Small-Cell Lung	Erlotinib (Tarceva)
EGFR mutation	Carcinoma, Non-Small-Cell Lung	Erlotinib (Tarceva)
EGFR mutation	Carcinoma, Non-Small-Cell Lung	Gefitinib (Iressa)
EpCAM expression	CancerAscites	Catumaxomab (Removab)
FIP1L1-PDGFR rearrangement	Hypereosinophilic Syndrome	Imatinib (Glivec)#
G551D mutation in the CFTR gene	Cystic Fibrosis	Ivacaftor (Kalydeco)‡
genotype 1 HCV	Hepatitis C, Chronic	Boceprevir (Victrelis)
genotype 1 HCV	Hepatitis C	Telaprevir (Incivo)
HER2 expression	Breast Neoplasms	Lapatinib (Tyverb)
HER2 expression	Breast Neoplasms	Trastuzumab (Herceptin)
HER2 expression	Stomach Neoplasms	Trastuzumab (Herceptin)
HER2 expression	Breast Neoplasms	Everolimus (Afinitor)
HER2 expression **	Breast Neoplasms	pertuzumab (Perjeta)
Hormone dependency	Prostatic Neoplasms	Degarelix (Firmagon)
Hormone receptor expression**	Breast Neoplasms	zoledronic acid (Zometa)
Hormone receptor expression	Breast Neoplasms	Everolimus (Afinitor)
Kit (CD 117) expression	Gastrointestinal Stromal Tumors	Imatinib (Glivec)#
Kit (D816V) mutation***	Aggressive Systemic Mastocytosis	Imatinib (Glivec)#
KRAS mutation	Colorectal Neoplasms	Cetuximab (Erbitux)
KRAS mutation	Colorectal Neoplasms	Panitumumab (Vectibix)
LPL protein detectable	Hyperlipoproteinemia Type I	alipogene tiparvovec (Glybera)‡
oestrogen receptor expression	Breast Neoplasms	Fulvestrant (Faslodex)
oestrogen receptor expression	Breast Neoplasms	Toremifene (Fareston)
PDGFR gene rearrangements	Myelodysplastic-Myeloproliferative Diseases	Imatinib (Glivec)#
Philadelphia chromosome	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Dasatinib (Sprycel)‡
Philadelphia chromosome	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Imatinib (Glivec)#
t(15;17) translocation	Leukemia, Promyelocytic, Acute	arsenic trioxide (Trisenox)#
viral resistance mutations***	HIV Infections	Amprenavir (Agenerase)
viral resistance mutations	HIV Infections	atazanavir sulphate (Reyataz)
viral resistance mutations	HIV Infections	Darunavir (Prezista)
viral resistance mutations	HIV Infections	efavirenz / emtricitabine / tenofovir disoproxil (Atripla)
viral resistance mutations	HIV Infections	Emtricitabine (Emtriva)
viral resistance mutations	HIV Infections	emtricitabine / rilpivirine / tenofovir

		disoproxil (Eviplera)
viral resistance mutations	HIV Infections	Enfuvirtide (Fuzeon)
viral resistance mutations	HIV Infections	fosamprenavir calcium (Telzir)
viral resistance mutations	HIV Infections	lopinavir / ritonavir (Kaletra)
viral resistance mutations ***	HIV Infections	Nelfinavir (Viracept)
viral resistance mutations	HIV Infections	rilpivirine hydrochloride (Edurant)
viral resistance mutations	HIV Infections	tenofovir disoproxil fumarate (Viread)
viral resistance mutations	HIV Infections	Tipranavir (Aptivus)

* refused **pending ***withdrawn
‡ drug designated an orphan medicine, # orphan designation has been removed at the end of exclusivity period

Table 2 Biomarkers predictive of toxicity identified in the review of EMA licensing

Biomarker	Indication	Drug
DPD deficiency	Colorectal Neoplasms Colonic Neoplasms Stomach Neoplasms Breast Neoplasms	Capecitabine (Xeloda and generic drugs: Capecitabine Accord; Capecitabine Krka; Capecitabine Medac; Capecitabine Teva)
DPD deficiency	Stomach Neoplasms	tegafur / gimeracil / oteracil (Teysuno)
HLA-B*5701 allele	HIV Infections	Abacavir (Kivexa; Trizivir; Ziagen)*
NADPH reductase deficiency	Methemoglobinemia	Methylthioninium chloride (Methylthioninium chloride Proveblue)

* HLA-B*5701 allele is predictive of hypersensitivity to abacavir, which is present in three three drugs: Kivexa (abacavir / lamivudine); Trizivir (abacavir / lamivudine / zidovudine); Ziagen (abacavir)

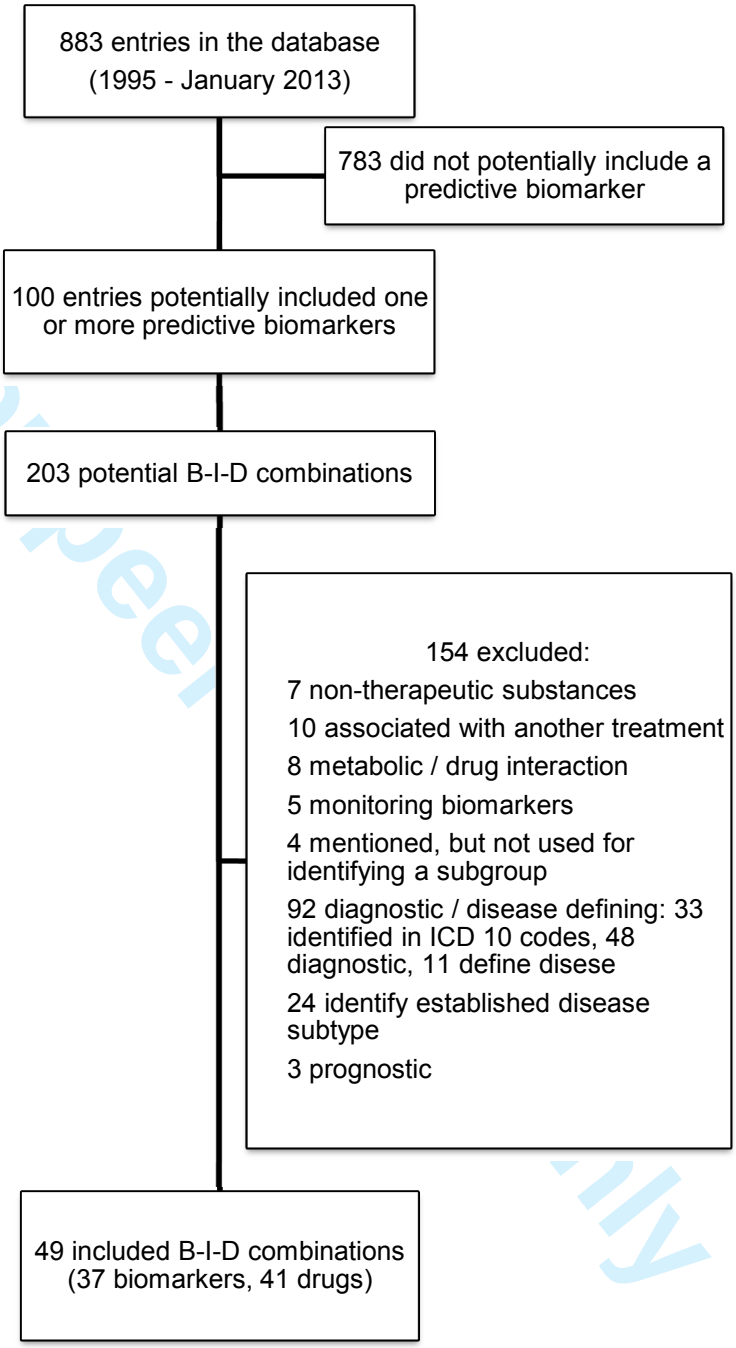


Figure 1 Flow diagram for the systematic review of predictive biomarkers in EMA licensing

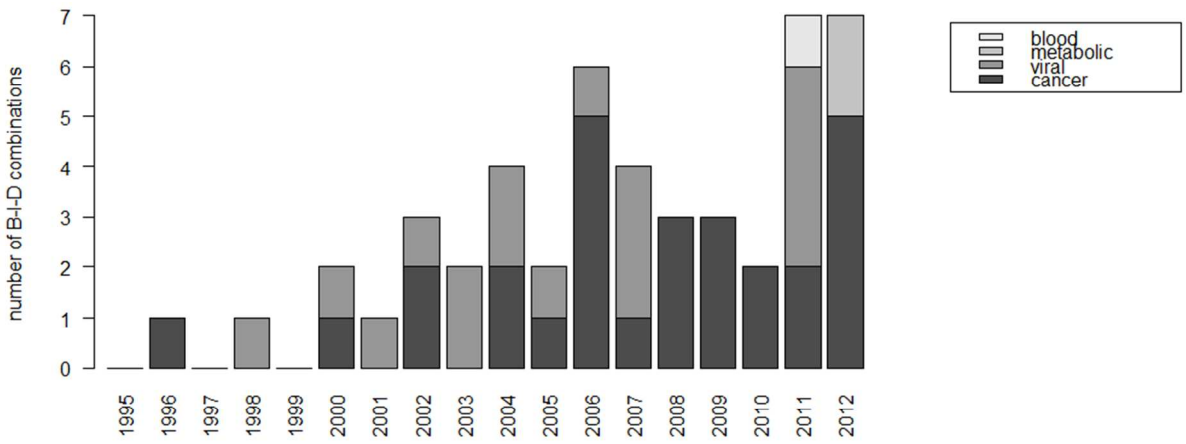
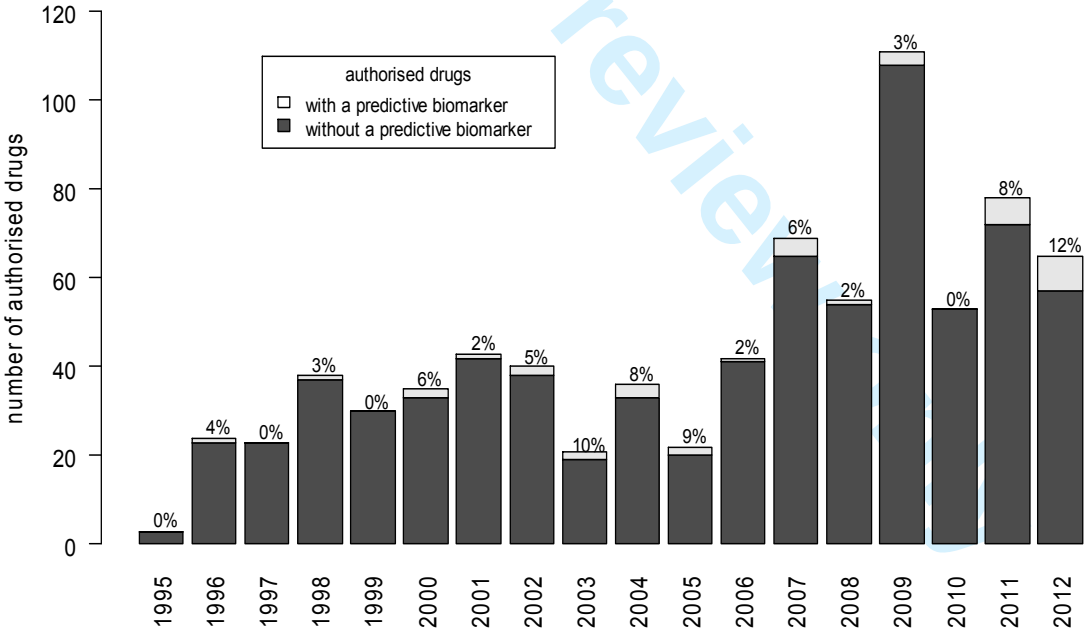


Figure 2 Number of new B-I-D combinations considered each year by disease area (includes biomarkers added after the drug was initially licensed)



Data for 2012 include 4 generic drugs (capecitabine)

Figure 3 New drugs authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

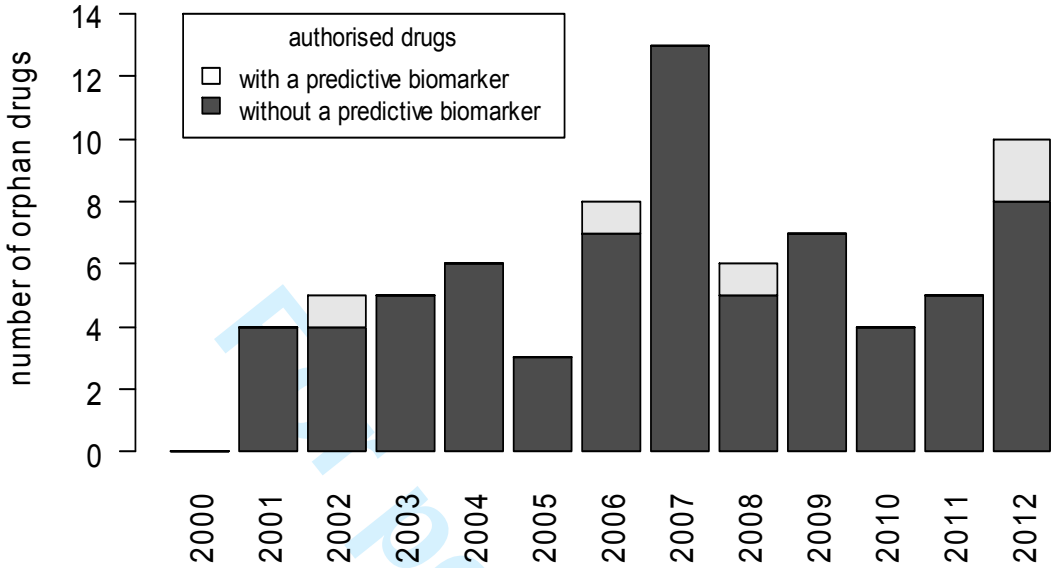


Figure 4 New drugs orphan authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

Stratified medicine in European Medicines Agency licensing: a systematic review of predictive biomarkers

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Abstract

Objectives Stratified medicine is often heralded as the future of clinical practice. Key part of stratified medicine is the use of predictive biomarkers, which identify patient subgroups most likely to benefit (or least likely to experience harm) from an intervention. We investigated how many and what predictive biomarkers are currently included in European Medicines Agency licensing.

Methods and eligibility criteria Indications and contraindications of all drugs considered by the EMA and published on their website were screened to identify predictive biomarkers. For all included Biomarker-Indication-Drug (B-I-D) combinations data was collected on: the type of the biomarker, whether it selected a subgroup of patients based on efficacy or toxicity, therapeutic area, marketing status, date of licensing decision, date of inclusion of the biomarker in the indication or contraindication, and on orphan designation.

Results 49 B-I-D combinations were identified over 16 years, which included 37 biomarkers and 41 different drugs. All identified biomarkers were molecular. Six drugs (relating to 10 B-I-D combinations) had an orphan designation at the time of licensing. The identified B-I-D combinations were mainly used in cancer and HIV treatment, but also in hepatitis C and three other indications (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia). In 45 B-I-D combinations biomarkers were used as predictive of drug efficacy and in four of drug toxicity. It appeared that there was an increase in the number of B-I-D combinations introduced each year, however the numbers were too small to identify any trends.

Conclusions Given the large body of literature documenting research into potential predictive biomarkers and extensive investment into stratified medicine, we identified relatively few predictive biomarkers included in licensing. These were also limited to a small number of clinical areas. This might suggest a need for improvement in methods of translation from laboratory findings to clinical practice.

Article summary

Article focus

- To identify predictive biomarkers included in European Medicines Agency licensing
- For identified biomarkers, to investigate their type, the clinical areas in which these biomarkers are used and possible trends over time with regard to the number of new predictive biomarkers considered each year

Key messages

- 49 Biomarker-Indication-Drug (B-I-D) combinations were identified over 16 years, which included 37 biomarkers and 41 different drugs. There appeared to be an increase in the number of B-I-D combinations introduced each year, however the numbers were too small to identify any trends.
- All identified biomarkers were molecular. They were mainly used in cancer and HIV treatment, but also in hepatitis C and three other indications (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia).

Strengths and limitations of this study

- Our research, to our knowledge, provides the first indication of the number and nature of predictive biomarkers included in licensing in Europe using systematic review methodology.
- It is likely that the 49 identified B-I-D combinations do not represent a complete list of predictive biomarkers used in practice, as some could have been considered by national regulatory agencies, particularly for drugs considered before EMA was established in 1995.

Introduction

Drugs are rarely effective in all patients and may be associated with serious adverse events.[1] The challenge of stratified medicine is to identify predictive biomarkers that identify patient subgroups (or strata) with a differential therapeutic response to a linked intervention, allowing more appropriate and effective use of interventions to maximise patient benefit and minimise the occurrence of serious adverse events.[2;3] Predictive biomarkers are defined particular to a treatment for a condition, where biomarker values are associated with differential efficacy or toxicity of that treatment.[4-7] The use of predictive biomarkers promises a more appropriate choice of treatment: it can also help to rationalise funding decisions, avoiding costs of futile treatment and of adverse events. However the additional cost of measuring the marker has to be taken into account. Examples of predictive biomarkers include tamoxifen use in breast cancer, which is prescribed to women who are oestrogen receptor positive,[8] and trastuzumab which is prescribed to those with HER2 overexpression in their tumour.[9]

There is a large body of literature documenting research into potential predictive biomarkers,[10;11] and millions of pounds have been invested into stratified medicine, both in industry and through programs from funding bodies such as the Medical Research Council[12] and Cancer Research UK.[13] We aimed to investigate if ~~evaluate the degree to which~~ this ~~investment~~ interest in developing stratified medicines has led to production of biomarker-treatment combinations ready for use in clinical practice. To explore this question, we have undertaken a systematic review of predictive biomarkers reported in licensing decisions of the European Medicines Agency (EMA).

In our review we aimed to find out how many of the indications and contraindications considered by the EMA define a patient population using a predictive biomarker. We were also interested in the disease areas where predictive biomarkers have been used and any trend over time. It has been hypothesised that stratified medicine has not been implemented in practice as much as expected. This paper provides evidence of the impact of stratified medicine research to date and if less than expected, then this will highlight the need to review the underlying reasons and address the problems.

Methods

We defined a Biomarker-Indication-Drug (B-I-D) combination as the unit of our analysis, relating to the use of a predictive biomarker with a particular drug for a particular condition or disease.[4-7] For toxicity biomarkers where the a biomarkers of drug toxicity may be used in more than one disease area we grouped these into one B-I-D combination.

All drugs listed on the EMA website in either European Public Assessment Reports or Pending Decisions[14;15] (accessed on the 17th of January 2013) were evaluated, together with their indications and contraindications.

Our inclusion criteria were that the biomarker had to:

(i) be used in the indication and/or contraindication of the drug,
(ii) be associated with a particular treatment,
(iii) identify a subgroup of patients with a particular disease eligible for treatment with the drug.

We excluded biomarkers:

(i) associated with a non-therapeutic substance (for example vaccines),
(ii) not used as predictive, including:
- used for diagnosis, screening or forming part of the disease definition (already established for defining a disease) or established disease subtype,
- prognostic only (associated with outcome regardless of treatment and not predictive of treatment response[16])

(iii) associated with another treatment (for example the biomarker was not associated with the differential efficacy or toxicity of the drug of interest, but another drug given in combination with the drug of interest).

We have reviewed EMA licensing, as in Europe a centralised drug evaluation by the EMA is required for drugs for treatment of a number of conditions, drugs obtained from biotechnology processes and all drugs used for rare conditions (orphan medicines). Companies can also apply for a centralised marketing authorisation of other drugs.[17] Although the EMA does not license biomarkers, it evaluates drugs in groups defined by predictive biomarkers (for example trastuzumab is licensed for use in HER2 overexpressing breast cancer patients).[18] Our approach is likely to give a broad overview of the impact of predictive biomarkers on treatment selection since 1995 (when EMA was established[19]).

We created a database of all drugs in the EMA database including the drug name, licensing status, indication and contraindication. In the first stage of screening all database entries were screened by two independent reviewers (MB and KM) to identify those potentially including a predictive biomarker in the indication or contraindication. If an entry was identified by at least one of the reviewers as potentially relevant, it was included in the second stage of screening.

In the second stage of screening, a list of potential B-I-D combinations was created based on the entries identified in the first stage. The list of potential B-I-D combinations was assessed by two independent reviewers (MB and KM) using full inclusion/exclusion criteria, based on the information in the Summary of Product Characteristics (which sets out the position of the drug obtained in the assessment process and summarises its properties and clinical use together with the clinical trial evidence that was considered by the EMA)[20] , the Scientific Discussion (which discusses the properties and clinical evidence in more detail) and additional information from targeted internet searches and expert advice if necessary. Any disagreements were resolved by discussion.

For the included B-I-D combinations data was collected on: the type of the biomarker used as predictive, whether it selected a subgroup of patients based on efficacy or toxicity, therapeutic area, marketing

status, date of licensing decision, date of inclusion of the biomarker in the indication or contraindication, and on orphan designation (granted to drugs intended for the treatment of a life-threatening or chronically debilitating condition which is either affecting no more than 5 in 10,000 people in the EU or when the revenue is unlikely to cover the investment in drug development[21]). To provide a context for our review, we have also collected data on the total number of drugs licensed each year with and without an orphan designation.

Results

Across the 18 year period (1995-2012) we identified 49 B-I-D combinations, including 37 biomarkers and 41 different drugs. The details of the review process are presented in Figure 1~~Figure 1~~. Most of the drugs were authorised, the exceptions being:

- Gemtuzumab ozogamicin (refused)
- Zeldoronic acid (pending)
- Imatinib in the indication for aggressive systemic mastocytosis (withdrawn)
- Amprnavir (withdrawn)
- Nelfinavir (withdrawn)

The number of new B-I-D combinations considered by the EMA each year has increased overall from zero or one per year in the late nineties, to a maximum of 7 in each of 2011 and 2012 as shown in Figure 2~~Figure 2~~. This was however not a steady increase, as the number of B-I-D combinations considered by the EMA showed fluctuation between 2000 and 2006, a decrease between 2006 and 2010, followed by an increase in the number in 2011 and 2012. ~~-~~A predictive biomarker was included in the indication or contraindication at the time when the drug was first licensed for 35 drugs (for one (capecitabine) the date of inclusion of the biomarker was unclear from the documentation, for the remaining drugs the time from the initial licensing decision to the inclusion of a predictive biomarker ranged from one to ten years). The proportion of first licensing decision of all new drugs that included a predictive biomarker increased over time and was close to 10% in 2003, 2004, 2005, 2011 and 2012 (Figure 3).

Six drugs associated with a predictive biomarker had an orphan designation at the time of licensing, however for two it was removed at the end of exclusivity period (details reported in

Table 1~~Table 1~~). One of the six drugs (imatinib) was associated with five different predictive biomarkers in five different indications (Figure 4).

The identified predictive biomarkers were all molecular. Thirty-three biomarkers were used to predict treatment efficacy (details reported in

Table 1~~Table 1~~) and only four to predict toxicity (Table 2~~Table 2~~).

Most of the biomarkers were included in indications and contraindications of cancer treatments (26 B-I-D combinations) and viral diseases, mainly HIV (17 B-I-D combinations). The remaining biomarkers were used to stratify metabolic and blood disorders (cystic fibrosis, hyperlipoproteinemia type I, and methemoglobinemia) and appeared in the last two years (Figure 2~~Figure 2~~).

Discussion

Stratified medicine is promoted as key to the future of medicine, and is currently one of the most active areas of clinical research. To our knowledge this review provides the first indication of the number and nature of predictive biomarkers included in licensing in Europe based on the drug indications and contraindications on the EMA website. Forty nine B-I-D combinations were identified. All identified biomarkers were molecular. The identified B-I-D combinations were mainly used in cancer and HIV treatment, with only five used in other disease areas.

It is likely that the 49 identified B-I-D combinations from the EMA database do not represent a complete list of the predictive biomarkers used in practice as ~~(~~some predictive biomarkers could have been considered by national regulatory agencies, particularly for drugs considered before EMA was established in 1995. Also EMA licensing is not compulsory for some disease areas, such as mental health. However a number of drugs with indications in depression of schizophrenia have been considered by the EMA.~~)~~ Therefore we believe that although our approach might not provide a complete list of all predictive biomarkers used in Europe, relatively few are likely to have been omitted, particularly from recent years.[19] The fact that some of the identified B-I-D combinations included biomarkers introduced to an indication of an already licensed drug suggests that at least to some extent we have captured stratification occurring after the initial licensing of a drug. However the actual extent to which this takes place in clinical practice is difficult to evaluate.

Several types of biomarkers were excluded. We did not include biomarkers used for dose adjustments as they do not directly predict efficacy or toxicity (although inappropriate dose adjustment could limit the treatment efficacy or cause adverse events).[22] We also only investigated biomarkers associated with drug treatments. Other biomarkers may be used in practice with non-drug treatments (for example radiotherapy).

The definition of a predictive biomarker can be difficult to apply, as over time predictive biomarkers may become part of a redefinition of the disease or subtype of disease[23] and be classed as diagnostic tests. In our evaluation we excluded diagnostic biomarkers (for example these included factor IX deficiency, or genetic testing for familial lipoprotein lipase deficiency), and biomarkers used to identify an established subtype of a disease (mainly ST segment elevation and non-ST segment elevation myocardial infarction).

The spectrum of diseases where predictive biomarkers have been successfully developed is relatively narrow. This suggests a possible need for more research in other clinical areas. Also the vast majority of the B-I-D combinations were associated with treatment efficacy and only four with toxicity. As adverse events associated with some treatments could be potentially serious and the possibility to screen out patients at high risk prior to commencing treatment would be beneficial. A proportion of the drugs with an associated predictive biomarker identified in our review had an orphan designation. This seems surprising, as convincing evidence to support the use of a drug in a subgroup of patients with a rare condition might be difficult to obtain, due to the small numbers of patients available to test the hypotheses.

It is difficult to provide accurate estimates of the extent of research into potential predictive biomarkers, however it has been suggested in 2011 that the number of publications on different biomarkers (not only predictive) was in the area of 15 000.[10] Another paper published in 2009, which reviewed genetic markers evaluated as potential predictors of response to treatment, found that 541 different genes were investigated as potential predictive biomarkers in 1 668 papers.[11] It can be reasonably expected that this number largely increased since these papers were published. Our review shows that few predictive biomarkers have been included in licensing relative to the~~i~~s large body of literature documenting numerous potential predictive biomarkers.[~~10;11~~] Therefore, in spite of the substantial investment in research, the promise of stratified medicine is not yet being realised to a large extent. The reasons for this might include poor translation of findings of laboratory studies into clinical context, or the failure to identify effective predictive biomarkers and treatments. Even though it is becoming easier and cheaper to gather huge sets of genomic data, its interpretation is challenging, which can potentially hinder translational research. Recognising this, initiatives have been undertaken both in the USA (National Institutes of Health and the FDA) and UK (Medical Research Council) to promote the translation of basic research into clinical practice.[12] Also the availability of datasets such as the Cancer Cell Line Encyclopaedia and a similar UK initiative might contribute to the faster progress of stratified medicine.[24;25] The relatively small number of predictive biomarkers identified in licensing might also indicate the need for more sound methodological standards for biomarker discovery and development.[26]

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Competing interests

All authors declare that they have no financial or non-financial interests that may be relevant to the submitted work.

Author Contributions

KM, JD, RR and LB designed the review. KM and MB carried out the review. Where needed CC and PJ provided clinical advice. All authors contributed to the interpretation of the results, commented on drafts and accepted the final version of this paper.

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

Data sharing

Data sharing: full dataset available from the corresponding author.

Ethical Approval

No ethical approval was required, as the study did not involve collection of patient data

Study funding

This work was funded by the MRC Midlands Hub for Trials Methodology Research at the University of Birmingham (Medical Research Council Grant ID G0800808). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Table 1 Biomarkers predictive of efficacy identified in the review of EMA licensing

Biomarker	Indication	Drug
ALK gene rearrangement	Carcinoma, Non-Small-Cell Lung	Crizotinib (Xalkori)
BRAF V600 mutation	Melanoma	Vemurafenib (Zelboraf)
CCR5 tropism	HIV Infections	Maraviroc (Celsentri)
CD-33 expression*	Leukemia, Myeloid, Acute	gemtuzumab ozogamicin (Mylotarg)‡
EGFR expression	Colorectal Neoplasms	Cetuximab (Erbitux)
EGFR expression	Carcinoma, Non-Small-Cell Lung	Erlotinib (Tarceva)
EGFR mutation	Carcinoma, Non-Small-Cell Lung	Erlotinib (Tarceva)
EGFR mutation	Carcinoma, Non-Small-Cell Lung	Gefitinib (Iressa)
EpCAM expression	CancerAscites	Catumaxomab (Removab)
FIP1L1-PDGFR rearrangement	Hypereosinophilic Syndrome	Imatinib (Glivec)#
G551D mutation in the CFTR gene	Cystic Fibrosis	Ivacaftor (Kalydeco)‡
genotype 1 HCV	Hepatitis C, Chronic	Boceprevir (Victrelis)
genotype 1 HCV	Hepatitis C	Telaprevir (Incivo)
HER2 expression	Breast Neoplasms	Lapatinib (Tyverb)
HER2 expression	Breast Neoplasms	Trastuzumab (Herceptin)
HER2 expression	Stomach Neoplasms	Trastuzumab (Herceptin)
HER2 expression	Breast Neoplasms	Everolimus (Afinitor)
HER2 expression **	Breast Neoplasms	pertuzumab (Perjeta)
Hormone dependency	Prostatic Neoplasms	Degarelix (Firmagon)
Hormone receptor expression**	Breast Neoplasms	zoledronic acid (Zometa)
Hormone receptor expression	Breast Neoplasms	Everolimus (Afinitor)
Kit (CD 117) expression	Gastrointestinal Stromal Tumors	Imatinib (Glivec)#
Kit (D816V) mutation***	Aggressive Systemic Mastocytosis	Imatinib (Glivec)#
KRAS mutation	Colorectal Neoplasms	Cetuximab (Erbitux)
KRAS mutation	Colorectal Neoplasms	Panitumumab (Vectibix)
LPL protein detectable	Hyperlipoproteinemia Type I	alipogene tiparvovec (Glybera)‡
oestrogen receptor expression	Breast Neoplasms	Fulvestrant (Faslodex)
oestrogen receptor expression	Breast Neoplasms	Toremifene (Fareston)
PDGFR gene rearrangements	Myelodysplastic-Myeloproliferative Diseases	Imatinib (Glivec)#
Philadelphia chromosome	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Dasatinib (Sprycel)‡
Philadelphia chromosome	Precursor Cell Lymphoblastic Leukemia-Lymphoma	Imatinib (Glivec)#
t(15;17) translocation	Leukemia, Promyelocytic, Acute	arsenic trioxide (Trisenox)#
viral resistance mutations***	HIV Infections	Amprenavir (Agenerase)
viral resistance mutations	HIV Infections	atazanavir sulphate (Reyataz)
viral resistance mutations	HIV Infections	Darunavir (Prezista)
viral resistance mutations	HIV Infections	efavirenz / emtricitabine / tenofovir disoproxil (Atripla)
viral resistance mutations	HIV Infections	Emtricitabine (Emtriva)
viral resistance mutations	HIV Infections	emtricitabine / rilpivirine / tenofovir disoproxil (Eviplera)
viral resistance mutations	HIV Infections	Enfuvirtide (Fuzeon)

viral resistance mutations	HIV Infections	fosamprenavir calcium (Telzir)
viral resistance mutations	HIV Infections	lopinavir / ritonavir (Kaletra)
viral resistance mutations ***	HIV Infections	Nelfinavir (Viracept)
viral resistance mutations	HIV Infections	rilpivirine hydrochloride (Edurant)
viral resistance mutations	HIV Infections	tenofovir disoproxil fumarate (Viread)
viral resistance mutations	HIV Infections	Tipranavir (Aptivus)

* refused **pending ***withdrawn
‡ drug designated an orphan medicine, # orphan designation has been removed at the end of exclusivity period

Table 2 Biomarkers predictive of toxicity identified in the review of EMA licensing

Biomarker	Indication	Drug
DPD deficiency	Colorectal Neoplasms Colonic Neoplasms Stomach Neoplasms Breast Neoplasms	Capecitabine (Xeloda and generic drugs: Capecitabine Accord; Capecitabine Krka; Capecitabine Medac; Capecitabine Teva)
DPD deficiency	Stomach Neoplasms	tegafur / gimeracil / oteracil (Teysuno)
HLA-B*5701 allele	HIV Infections	Abacavir (Kivexa; Trizivir; Ziagen)*
NADPH reductase deficiency	Methemoglobinemia	Methylthioninium chloride (Methylthioninium chloride Proveblue)

* HLA-B*5701 allele is predictive of hypersensitivity to abacavir, which is present in three three drugs: Kivexa (abacavir / lamivudine); Trizivir (abacavir / lamivudine / zidovudine); Ziagen (abacavir)

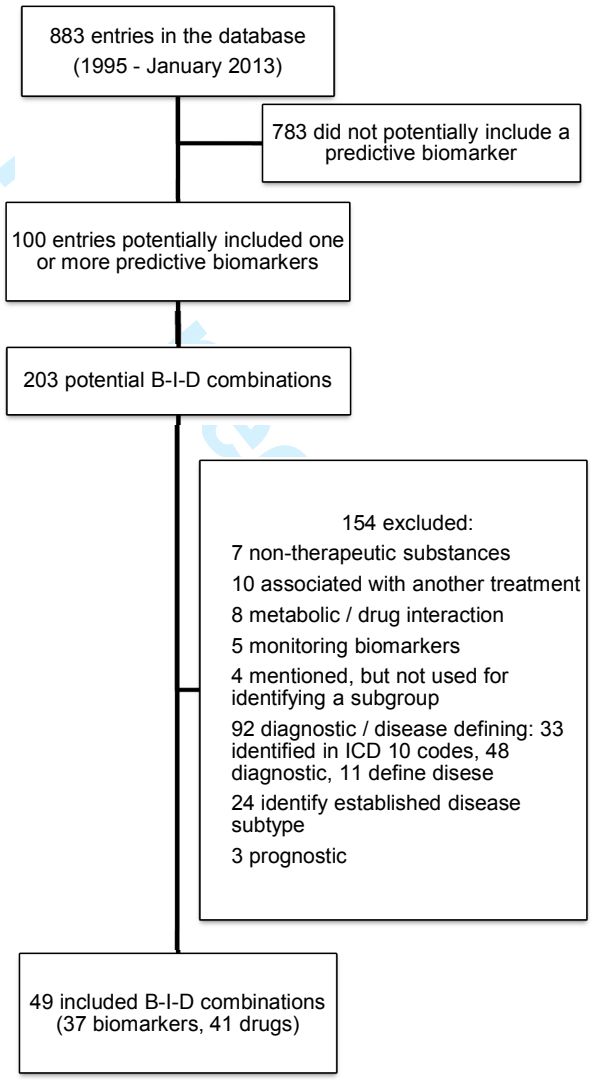


Figure 1 Flow diagram for the systematic review of predictive biomarker~~e~~s in EMA ~~licensig~~licensing

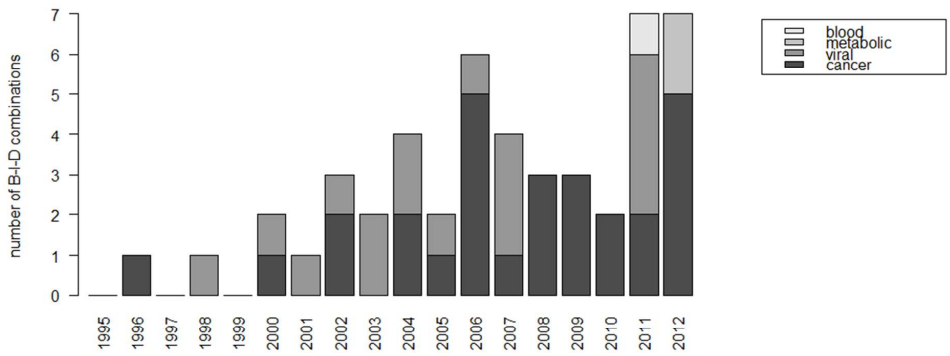
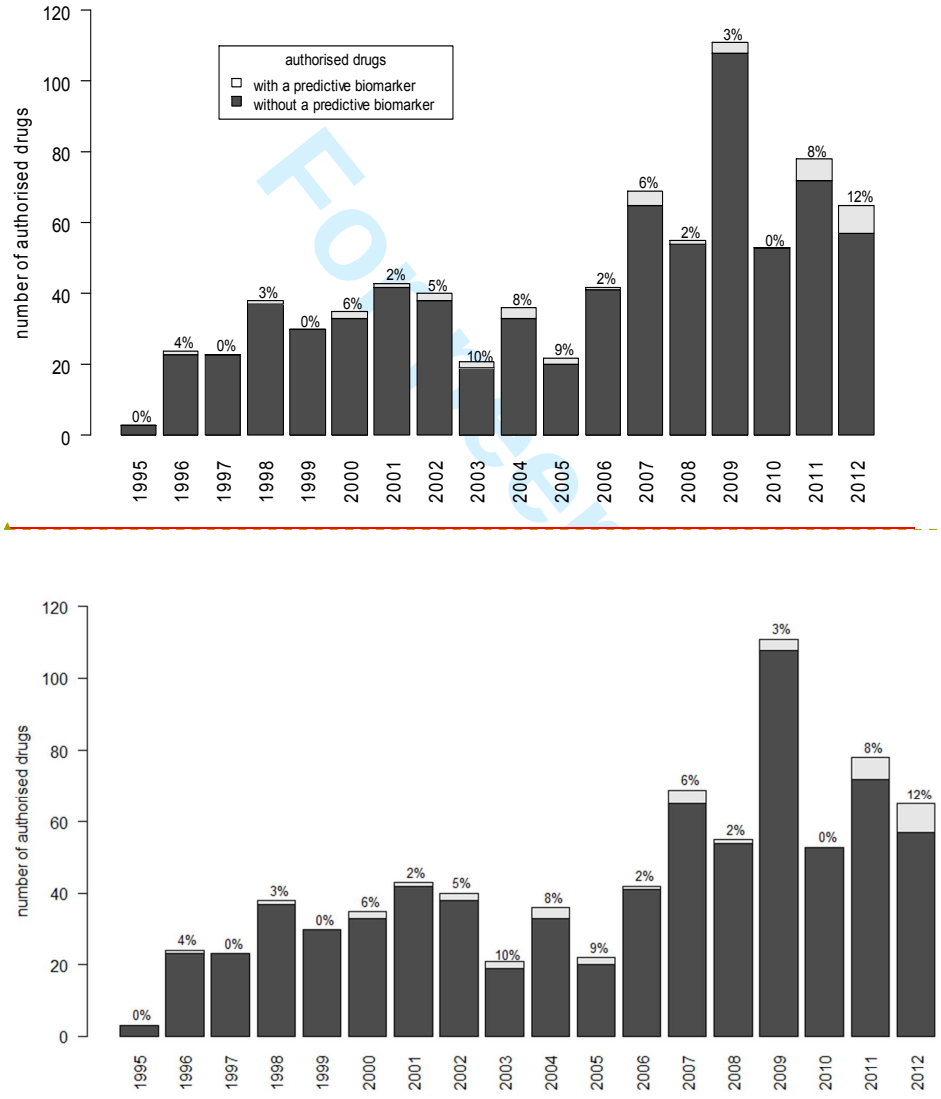


Figure 2 Number of new B-I-D combinations considered each year by disease area (includes biomarkers added after the drug was initially licensed)



Data for 2012 include 4 generic drugs (capecitabine)

Figure 3 New drugs authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

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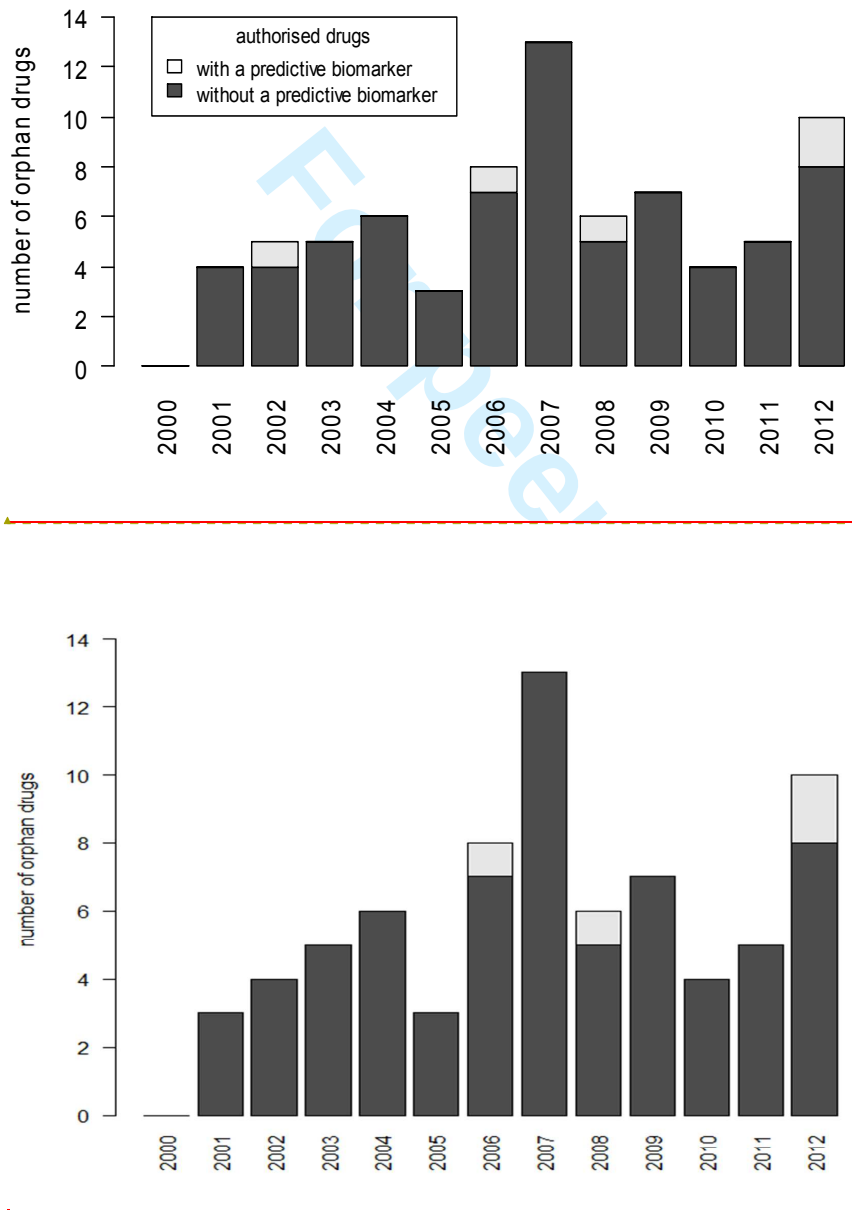

Figure 4 New drugs orphan authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

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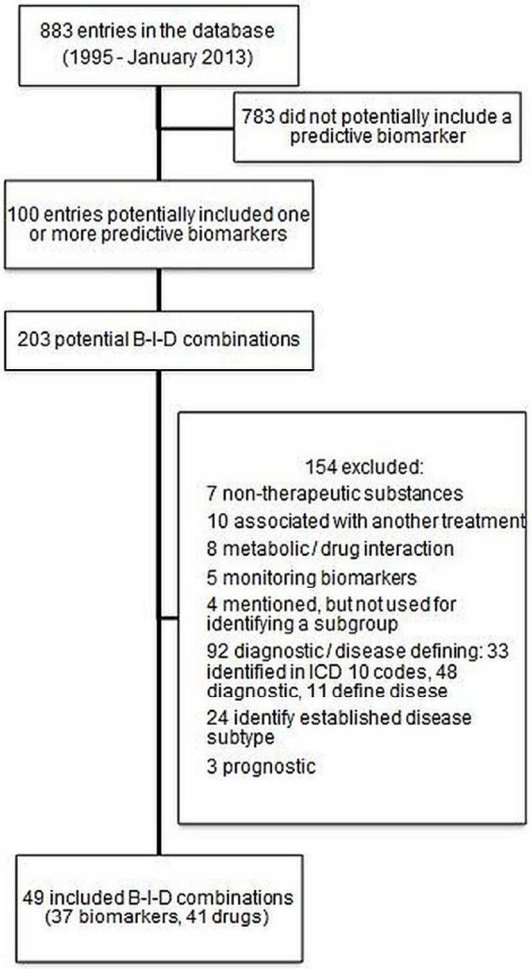

Figure 1 Flow diagram for the systematic review of predictive biomarkers in EMA licensing

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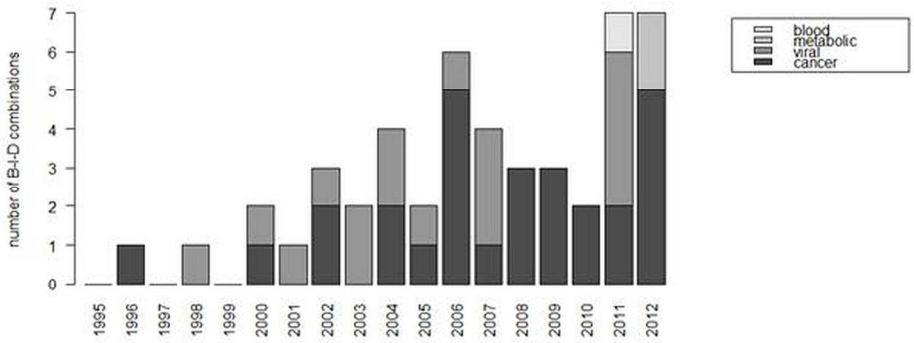
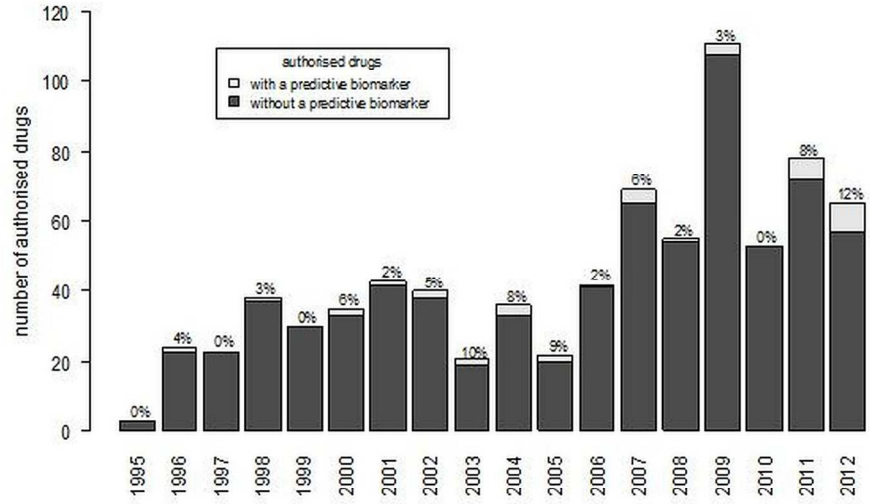


Figure 2 Number of new B-I-D combinations considered each year by disease area (includes biomarkers added after the drug was initially licensed)

151x90mm (300 x 300 DPI)



Data for 2012 include 4 generic drugs (capecitabine)

Figure 3 New drugs authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

123x90mm (300 x 300 DPI)

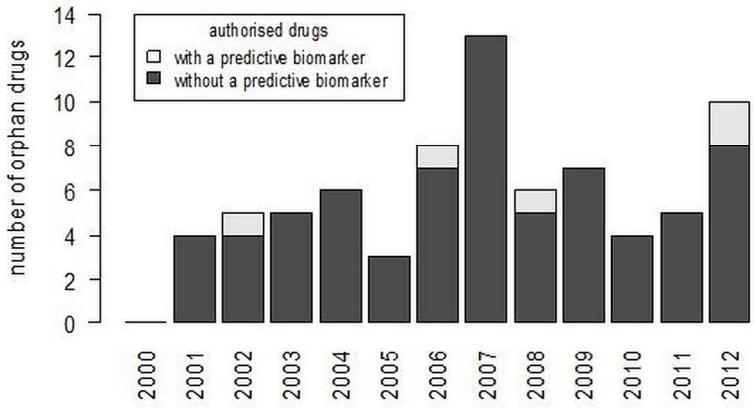


Figure 4 New drugs orphan authorised each year with and without a predictive biomarker in the indication or contraindication (excludes biomarkers added after the drug was initially licensed)

148x90mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Not applicable
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6-7
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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