UNIVERSITY OF BIRMINGHAM

MRC Hubs for Trials Methodology Research
Midlands Hub

Stratified medicine in practice: Review of predictive biomarkers in European Medicines Agency (EMA) indications

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Objectives

- What predictive biomarkers are included in drug indications in Europe?
- How many are there?
- In what therapeutic areas?
- What is the supporting evidence?

What is a biomarker?

"Biological Marker (Biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

Controlled Clinical Trials 22:485–502 (2001)

What is a predictive biomarker?

- “a marker that predicts the differential efficacy (benefit) of a particular therapy based on marker status”

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- “measured at baseline to identify patients who are likely or unlikely to benefit from a specific treatment”

  Simon R, Cur Breast Cancer Rep (2009) 1:216-221

- used for patient selection for treatment based on the “estimation of probability of response to a particular agent”

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Review of EMA indications

Inclusion criteria

- predictive biomarker
  - associated with the indicated drug
  - differential effectiveness and/or toxicity
- included in the EMA therapeutic indication

Exclusion criteria

- diagnostic and screening biomarkers
- prognostic biomarkers - unless they are also predictive
- biomarkers used for dose adjustments
- biomarkers not identified precisely in the therapeutic indication (e.g. general reference to need of genetic testing, etc.)
- biomarkers associated with another treatment

Review of EMA indications

- Database created October 2010

  One entry for each drug and marketing status

704 entries in the database

- 1
  p
  b
- 2
  E
  int

Trade name	Generic name	Status	Indication
Glivec	imatinib	authorised	Glivec is indicated for the treatment of • adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. • adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. • adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy. • adult patients with relapsed or refractory Ph+ ALL as monotherapy. ...
Glivec	imatinib	withdrawn	Glivec was to be used for the treatment of aggressive systemic mastocytosis in adults. (...) Since patients who have a mutation called D816V in the receptor protein c-Kit were expected to be insensitive to Glivec, the medicine was only to be used in patients who did not have this genetic mutation, or whose mutation status was unknown.

Biomarkers not classed as predictive

- Diagnostic/ screening biomarker

  igovomab (Indimacis 125): *positive diagnosis of relapsing ovarian adenocarcinoma when **serum CA 125** is increased without positive results of ultrasound or computerised tomography scan*

- Biomarker does not identify a subgroup

  interferon alfa-2b (IntronA): *treatment of adult patients with **Philadelphia chromosome** or bcr/abl translocation positive chronic myelogenous leukaemia…*

- Biomarker associated with another treatment

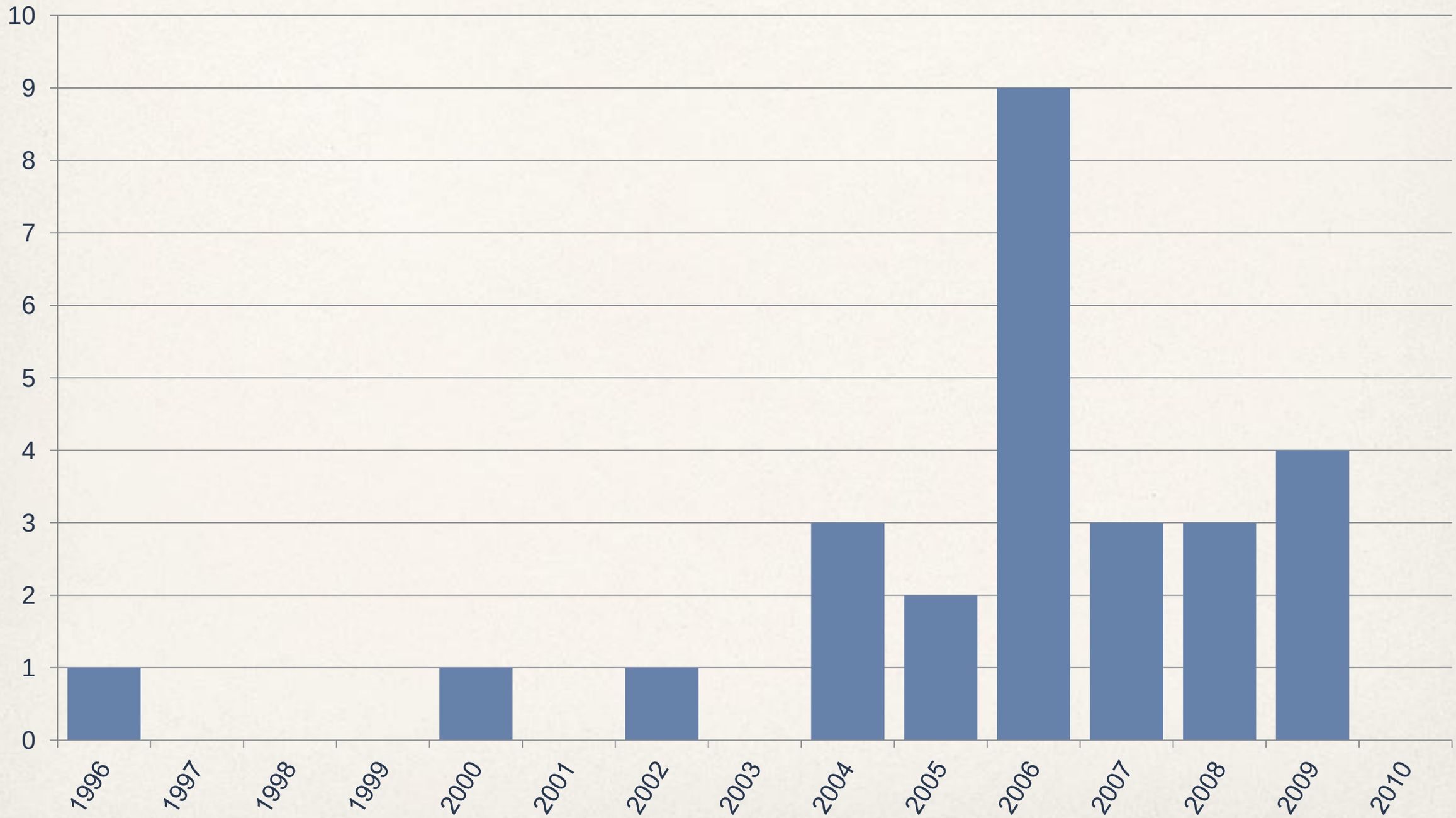
  docetaxel (Docetaxel Winthrop): *in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours **over express HER2** and who previously have not received chemotherapy for metastatic disease...*

- Biomarker not identified precisely

  amprenavir (Agenerase)*: for the treatment of protease inhibitor (PI) experienced HIV-1 infected adults and children above the age of 4 years. Agenerase capsules should normally be administered with low dose ritonavir as a pharmacokinetic enhancer of amprenavir (see sections 4.2 and 4.5). The choice of amprenavir should be based on **individual viral resistance testing and treatment history** of patients ...*

Therapeutic area	Biomarker	Drug
Breast neoplasms	HER2 overexpression/ gene amplification	trastuzumab (Herceptin) lapatinib (Tyverb)
	oestrogen receptor	toremifene (Fareston) fulvestrant (Faslodex)
Cancer Ascites	EpCAM expression	catumaxomab (Removab)
Carcinoma, Non-Small-Cell Lung	EGFR mutations	gefitinib (Iressa)
	EGFR expression	erlotinib (Tarceva)
Colorectal Neoplasms	EGFR expression KRAS mutation	cetuximab (Erbitux) panitumumab (Vectibix)
Gastrointestinal Stromal Tumors	Kit (CD 117) positive	imatinib mesilate (Glivec)
Hypereosinophilic Syndrome	FIP1L1-PDGFRα rearrangement	imatinib mesilate (Glivec)
Leukemia, Myelogenous, Chronic, BCR-ABL Positive	Philadelphia chromosome	imatinib mesilate (Glivec) dasatinib (Sprycel) nilotinib (Tasigna)
Leukemia, Myeloid, Acute	CD-33	gemtuzumab ozogamicin (Mylotarg)
Leukemia, Promyelocytic, Acute	t(15;17) translocation and/or PML/RAR-α gene	arsenic trioxide (Trisenox)
Mastocytosis, Systemic	D816V mutation	imatinib mesilate (Glivec)
Myelodysplastic-Myeloproliferative Diseases	PDGFR gene re-arrangements	imatinib mesilate (Glivec)
Precursor Cell Lymphoblastic Leukemia-Lymphoma	Philadelphia chromosome	imatinib mesilate (Glivec) dasatinib (Sprycel)
Stomach Neoplasms	HER2 overexpression/ gene amplification	trastuzumab (Herceptin)
HIV infection	CCR5 tropism	maraviroc (Celsentri)
	HLA-B*5701 allele	abacavir/lamivudine (Kivexa) abacavir / lamivudine / zidovudine (Trizivir) abacavir (Ziagen)

Inclusion of predictive biomarkers in indication by year



Supporting evidence: Study designs – initial review

- 135 studies
- **Design**
  - Often unclear (56 studies)
  - Most frequent:
    - enrichment (targeted) design (58 studies)
    - subgroup analysis (19 studies)
- 1 stratified design (SATURN, erlotinib for NSCLC)
- 1 marker-strategy design (PREDICT-1, abacavir for HIV infection)

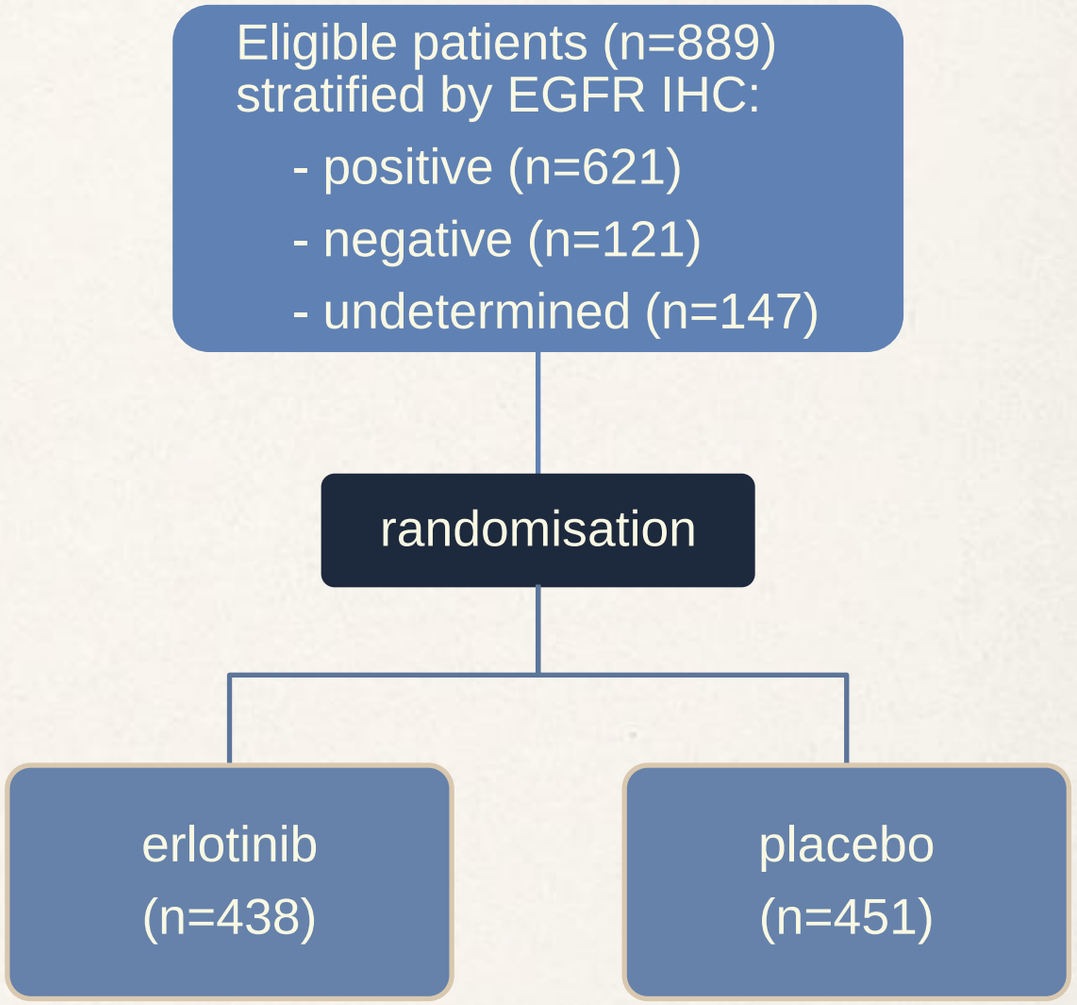
FURTHER WORK IN PROGRESS

SATURN: stratified design

- population: patients with non-small-cell lung cancer; non-progressive after first-line chemotherapy

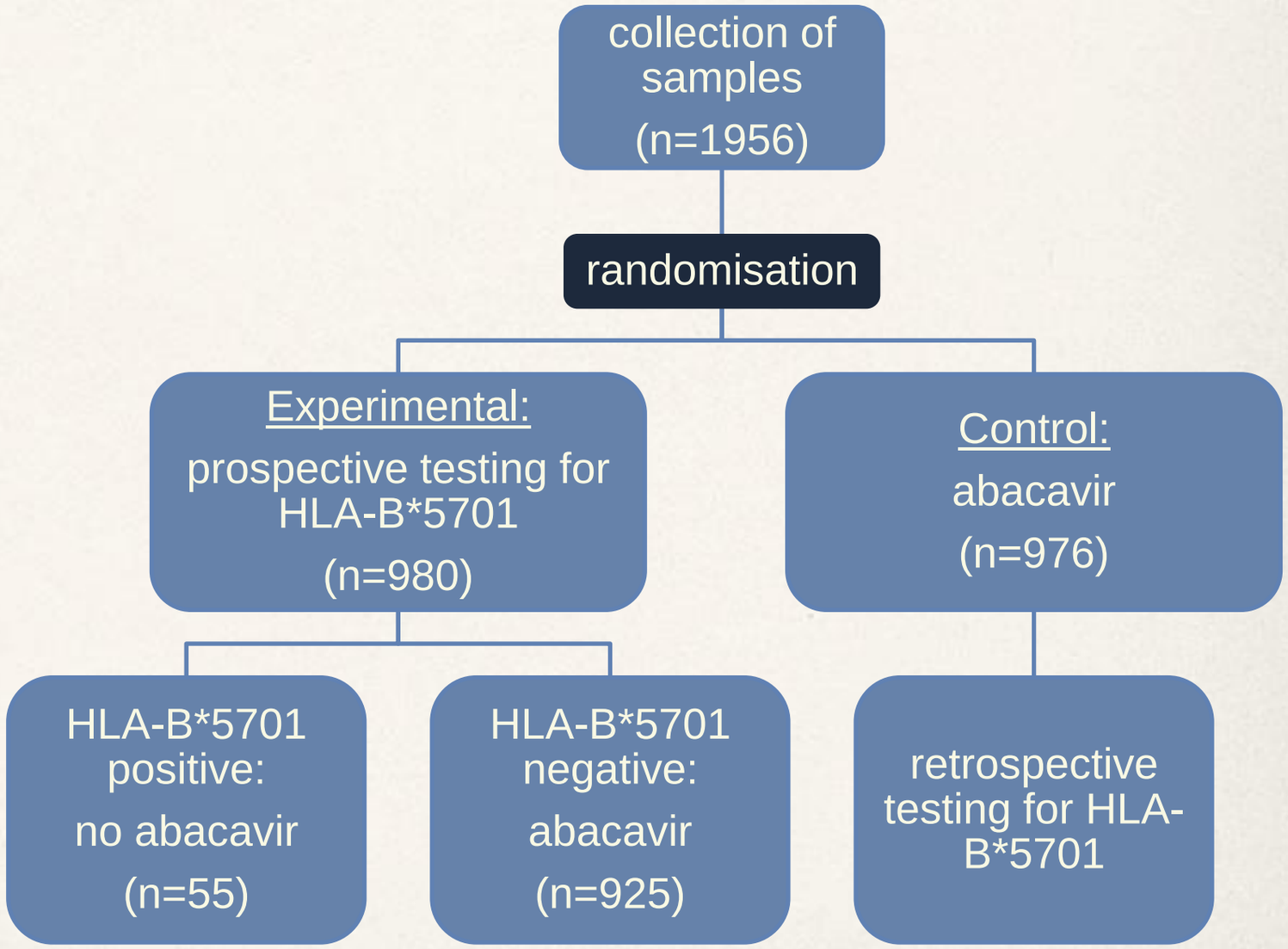
- is erlotinib more effective in EGFR+ patients?

- two primary analyses: progression free survival in the overall population and in patients with EGFR IHC positive tumors



PREDICT-1: biomarker strategy design

- population: patients with HIV infection
- is HLA-B*5701 allele associated with hypersensitivity reaction to abacavir
- Compare reduction in incidence of hypersensitivity reaction (experimental vs. control)



Limitations

- Definition of a predictive biomarker
- Only drugs reviewed
- Only EMA - drugs licensed after 1995
- Only indications checked – biomarkers possible in contraindications
- Dose adjustment biomarkers were not considered relevant

Conclusions

- Relatively few predictive biomarkers identified
- Also in rare diseases
- Therapeutic areas – limited to cancer and HIV infection
- Study designs – mainly enrichment (targeted) design and subgroup analyses – can have serious limitations
- Further work: examine evidence in more detail