EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacogenomics: a long(er) learning curve?

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An agency of the European Union

Agenda

- PGx - shades of grey
- Learning curve/post-marketing evidence development
- Regulatory versus HTA post-marketing information needs
- The toolkit along the learning curve

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Level of individualisation

- Personalised medicine (e.g. autologous cellular therapy)
- Multi-stratified medicine (e.g. CFTR-directed therapy, ca 1800 ‘strata’)
- Binary stratification (e.g. HER2 +/-)

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Shades of grey

Determinants of disease manifestation and treatment response:

- Environment
- Genetic background; modifier genes (genes that modify the clinical outcome of a genetic mutation)
- ‘Stochastic events’ (? ; unknowns)

Brunner HG. NEJM 2012; 367:1350-2; October 4, 2012

CDx don’t tell the whole story about response (e.g. Herceptin <50% response rate)

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Shades of grey

Biomarker:

Single nucleotide polymorphism in the 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR*) gene

Drug:

Statins; retrospective analysis identified two strata of patients, one reached total cholesterol target level in 71.9%, versus 49.0% in the other group.

Clinical utility:

- relatively benign safety profile of statins at appropriate doses,
- benefit–risk positive for both populations?
- Justification for restricting use to higher response stratum?

Donnelly, L. A. et al. *Pharmacogenet. Genomics* **18**, 1021–1026 (2008)

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The drug development / licensing paradigm

Learn - confirm - license

(Re-learn – re/de-license)

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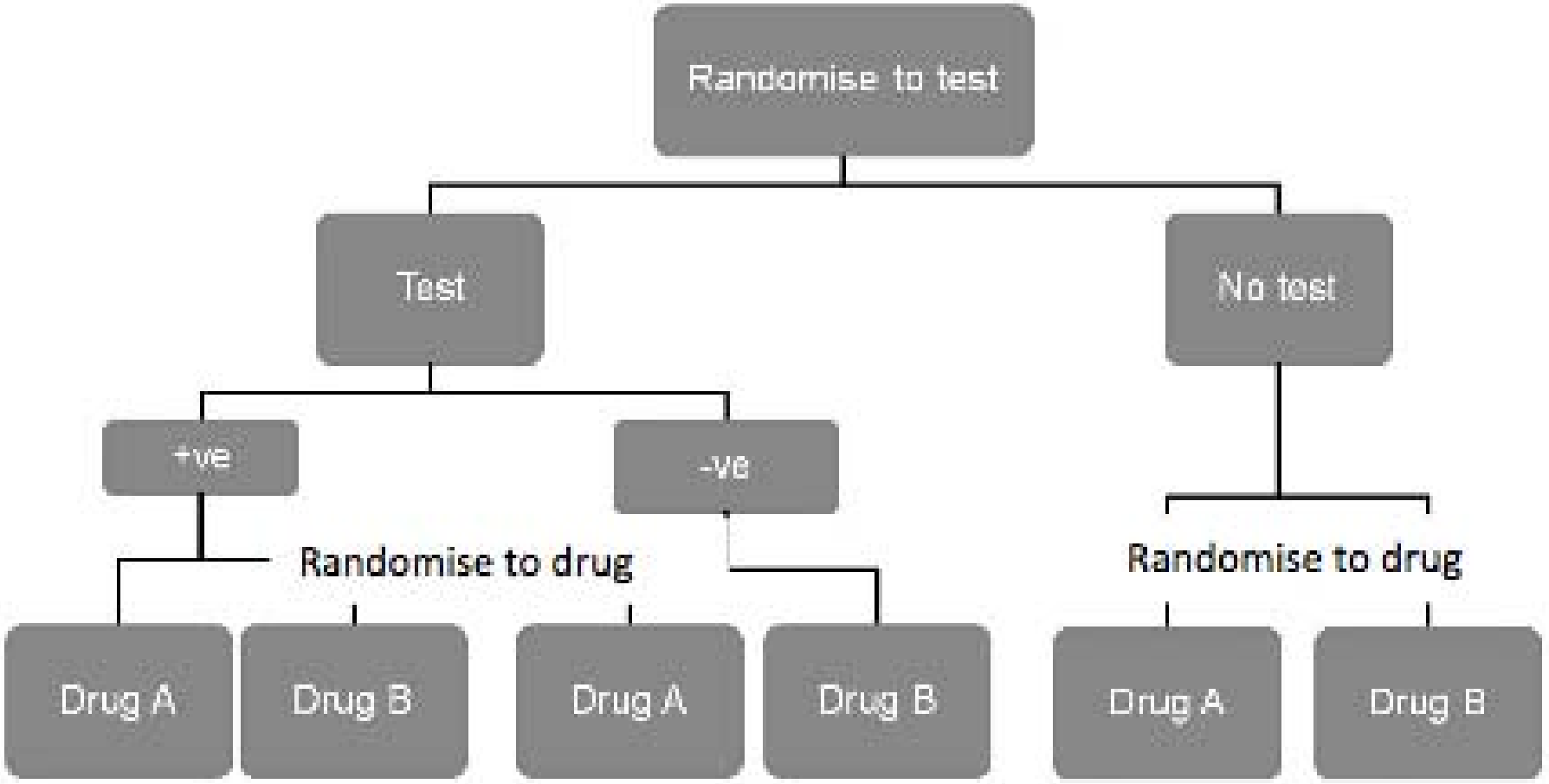
Evidence Development Strategies:

Australian 2010 Draft for Consultation Document

"Level 1: Double Randomized Trial"



The drug development / licensing paradigm

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CDx guided treatments:
Retrospective; Retrofitting; Rescue

Goals of post-marketing requirements

- Test-drug utilisation
- Test performance in real-life
- Impact of new test kits/methodologies
- Clinical utility
- Comparative/relative effectiveness assessment

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Assessing test-drug utilization Example: Herceptin

Background: physician adherence to guidelines

Results:

– HER2 testing occurred in 88% of all newly diagnosed patients, for whom testing is recommended.

– Among those with HER2 testing performed, 21.5% were positive, 77.3% were negative, and 1.2% were unknown.

– Of the 52 patients who used trastuzumab, only 1 did not have documented HER2 overexpression.

– Of the 45 HER2^{+}, 13% did not receive trastuzumab.

Is the test used?

Is the pos/neg ratio similar to clinical trials?

Are the right patients treated?

Barron JJ et al. The Oncologist 2009; 14:760-768

Test performance in real-life

- Assay-performance characteristics may be lab-dependent
- Positive and negative predictive value are population-dependent
- Cut-off values are population-dependent

Impact of new test kits/methodologies

- ‘Approved’ CDx will compete with alternative proprietary test or ‘home-brews’ for same biomarker
- These may screen in or screen out different patients, impacting benefit-risk and cost-effectiveness (e.g. Herceptin and IHC/FISH/CISH)

Clinical utility

Clinical utility: “is the test worth doing?”

Woodcock J. Clin Pharmacol Ther 2010; 88: 765

Reflection paper on PG biomarkers. EMA/446337/2011

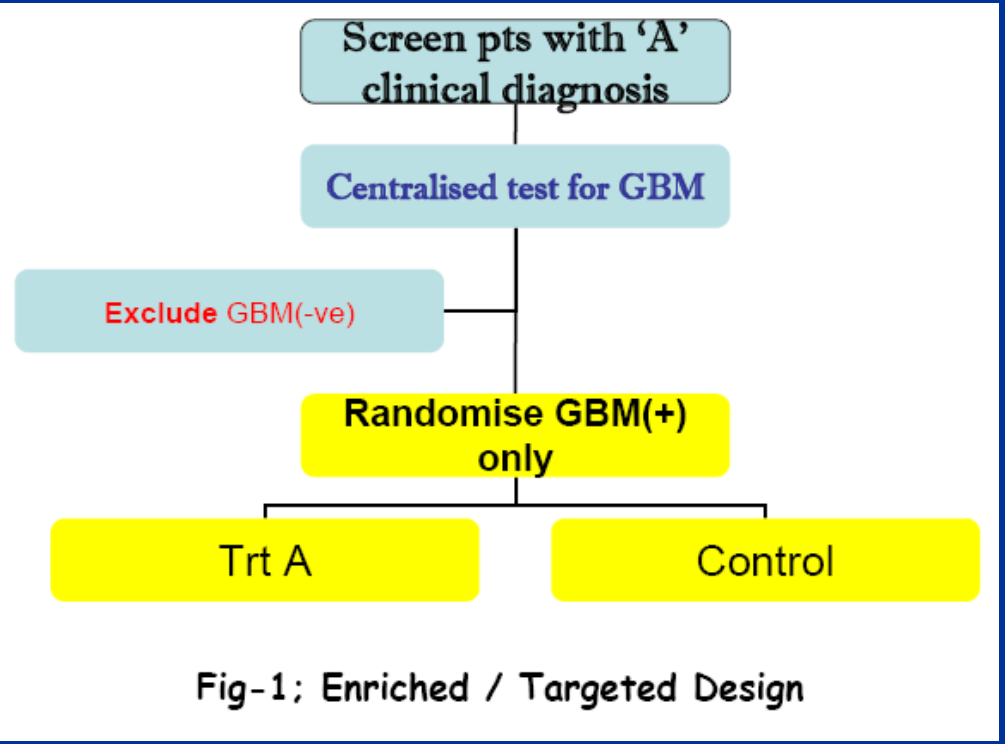
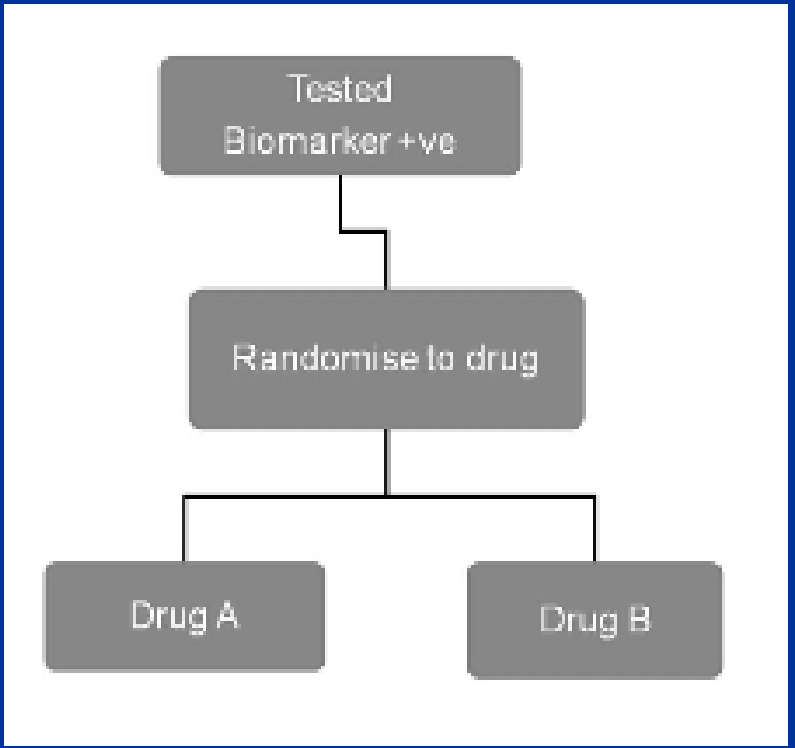


Fig-1; Enriched / Targeted Design

Australian Document: “Level 3: Randomized trial of drug only”



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Clinical utility

Clinical utility: “is the test worth doing?”

Post-licensing research plan will depend on licensing pathway

(e.g. determination of negative predicative value, case study: Ivacaftor*, effective in CF patients with G551D mutation, but not F508del mutation, other 1800 mutations?)

* cystic finbrosis transmembrane conductance regulator (CFTR)potentiator

Relative Effectiveness

Some specifics may vary, (e.g. pos/neg ratio in a given population may impact on cost-effectiveness)…

but fundamental information needs about relative effectiveness are not much different for CDx guided and non-stratified therapies

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Regulatory - HTA framework for post-marketing requirements?

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	Regulators' needs	HTAs' needs
Treatment yes/no decision	++	++
Stratification for maximum Efficacy (to optimise CE)	(+)/-	++
Test-drug Utilisation	++	++
Performance of drug in combination with new test (kit)	++	++
Relative Effectiveness	(+)/-	++

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A timely initiative

"Methodologies for post authorisation safety and efficacy/effectiveness studies regarding PG and BM related issues (for adverse drug reactions and for lack of effectiveness) in the post marketing setting."

Concept paper on …PG methodologies in the pharmaco-vigilance evaluation of medicinal products; 15 Dec 2011; EMA/CHMP/917570/2011

"…stringent evidentiary requirements in the post marketing (post authorisation) era"

Reflection paper on pharmacogenomic biomarkers … EMA/446337/2011

The drug development / licensing paradigm

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Lifecycle approach to research and licensing

Thank you!

(EMA, Canary Wharf, London)

Research 101

- Temperature
- Concentration of substrate
- Concentration of inhibitor
- …

Experiment: all factors except one are kept constant