



Arbeitsgemeinschaft
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Humanpharmakologie e.V.

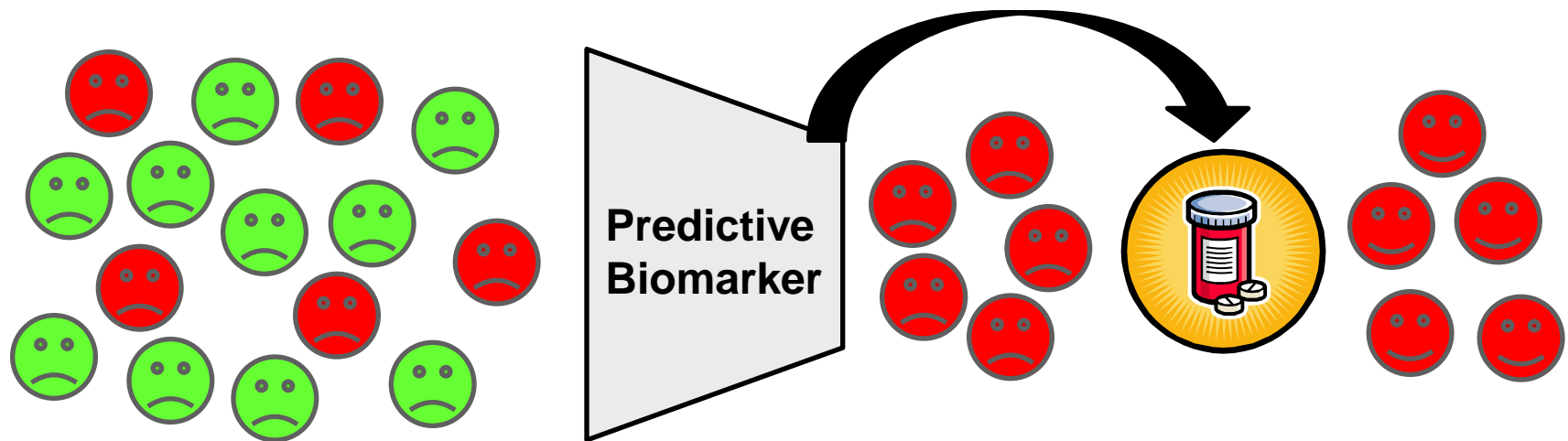
Subject stratification in drug development – getting it right?

Chairmen's introduction:
Concept and impact of stratified medicine

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Concept of Stratified Medicine

- Matching a therapy with specific characteristics of a patient population using predictive biomarkers
- Selecting patients similar to a cohort that has exhibited a differential therapeutic response using a predictive biomarker
- Yielding a therapeutic combined with a companion diagnostic that targets a patient subpopulation for treatment

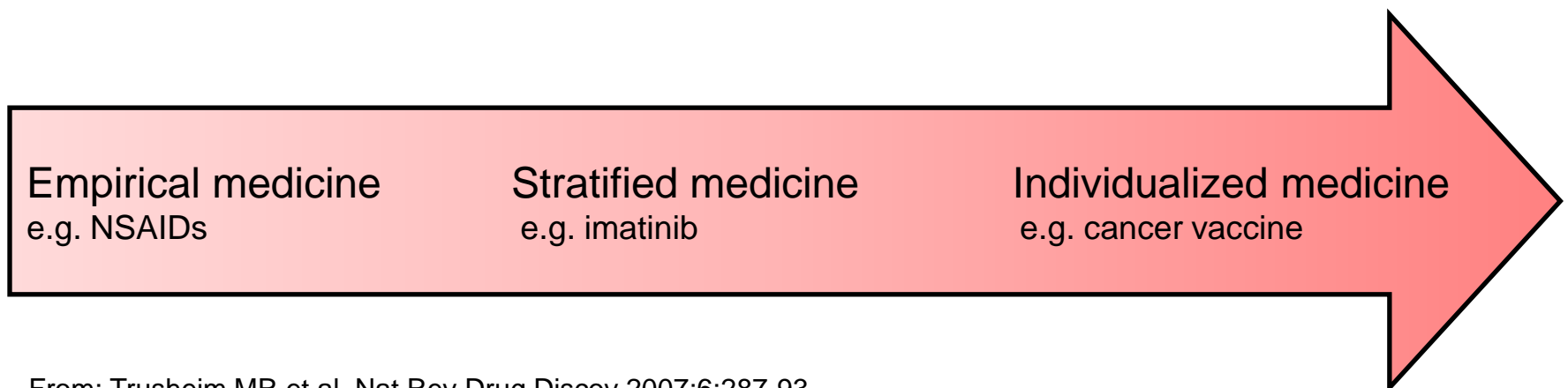


From: Trusheim MR et al. Nat Rev Drug Discov 2011;10:817-33

Prerequisites for Stratified Medicine



- Differential biological mechanisms
 - Indistinguishable clinical presentation of biologically distinct conditions
 - Multiple relevant targets for therapeutic intervention
 - Differential ADME with relation to safety and tolerability
 - Disease adaptiveness leading to treatment resistance
- Multiple treatment options with heterogeneous responses
- Biomarker which is correlated to the differential response



From: Trusheim MR et al. Nat Rev Drug Discov 2007;6:287-93

Biomarkers for Clinical Use



- Biomarker: indicator of a biological process or response
 - Diagnostic biomarker: detect a specific disease (e.g. HCV RNA)
 - Susceptibility biomarker: assess the risk of developing a disease (e.g. BRCA1 – breast cancer)
 - Prognostic biomarker: assess the evolution of a disease (e.g. HbA1C – diabetic complications)
 - Predictive biomarker: assess response to a treatment (e.g. EGFR mutations – NSCLC / gefinitnib)
 - Prognostic + predictive BM: reflects relation of disease and treatment (e.g. HER2 – breast cancer / trastuzumab)

From: European Commission, DG Research – Brussels, 10-11 June 2010, summary report

Stratified Medicine in Clinical Practice - Examples



- Selecting endocrine therapy for estrogen-receptor pos. BRCA
- Matching antibiotic treatment to antibiogram
- Matching HIV therapy to viral load and variant present
- Avoiding carbamazepine in *HLA-B*1502* positive patients
- Avoiding abacavir in *HLA-B*5701* positive patients
- Adapting initial warfarin dose to *CYP2C9* and *VKORC1* status

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

[†]Ranges are derived from multiple published clinical studies. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

From: FDA full prescribing information for COUMADIN (warfarin sodium)

Polygenic Model



Challenge

- Combined result of many genes, each of a small effect

Opportunities

- Mechanism of disease
- Risk of disease
- Classification of disease
- Predict prognosis
- Predict outcome
- Predict toxicity

Stratified Medicine Programme



- Working together with AstraZeneca, Pfizer and the UK government's Technology Strategy Board, we aim to establish the foundations for a national service that will ensure standardised, high quality, cost-effective genetic testing of tumours is available for people with cancer.
- So, as and when targeted treatments become available, patients will be able to choose to have genetic tests that can help doctors decide the most suitable treatment for them. (Service delivery)
- At the same time, by demonstrating it is possible to routinely collect samples from consenting patients, we will build a national database of tumour genetic information, treatments and outcomes that will help researchers design more effective cancer treatments in future. (Research)

Stratified Medicine Programme



- Limited to Cancer
- 3 Phases, Phase 1 (2011-2013):
6 tumour types (Breast, Colorectal, Prostate, Lung, Ovary and Melanoma)
- 9,000 patients will be consented
- 7 Experimental Cancer Medicine Centres (ECMC)
- 3 centralised laboratories performing the genetic tests in a standardised fashion
- £50m TSB funding
- http://science.cancerresearchuk.org/prod_consump/groups/cr_common/@fre/@gen/documents/generalcontent/strat-med-leaflet-techno-hub.pdf