EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Personalised medicine challenges: hype or hope?

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An agency of the European Union

Outline

European Council definition of Personalised medicine and EU Medicines Agencies network strategy to 2020

EMA: Regulatory science and personalised medicines

European Commission: major initiatives

Few question for discussions

European Council conclusions on PERSONALISED MEDICINE

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C 421/2 EN Official Journal of the European Union 17.12.2015

IV

(Notices)

NOTICES FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

COUNCIL

Council conclusions on personalised medicine for patients

(2015/C 421/03)

European Council DEFINTION OF PERSONALISED MEDICINE

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No commonly agreed definition of the term “personalised medicine”.

Widely understood that personalised medicine refers to a:

- **medical model using characterisation** of individuals' **phenotypes** and **genotypes** (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.

- Personalised medicine relates to the broader concept of **patient-centred care**, which takes into account that, in general, **healthcare systems need to better respond to patient needs**

Council of the European Union

Brussels, 7 December 2015
(OR. en)

15054/15

SAN 428

OUTCOME OF PROCEEDINGS

From:	General Secretariat of the Council
On:	7 December 2015
To:	Delegations
No. prev. doc.:	14393/15
Subject:	Personalised medicine for patients – Council conclusions (7 December 2015)

Delegations will find in the annex the Council conclusions on personalised medicine for patients, adopted by the Council at its 3434th meeting held on 7 December 2015.

Joint EU Medicines Agencies network strategy to 2020

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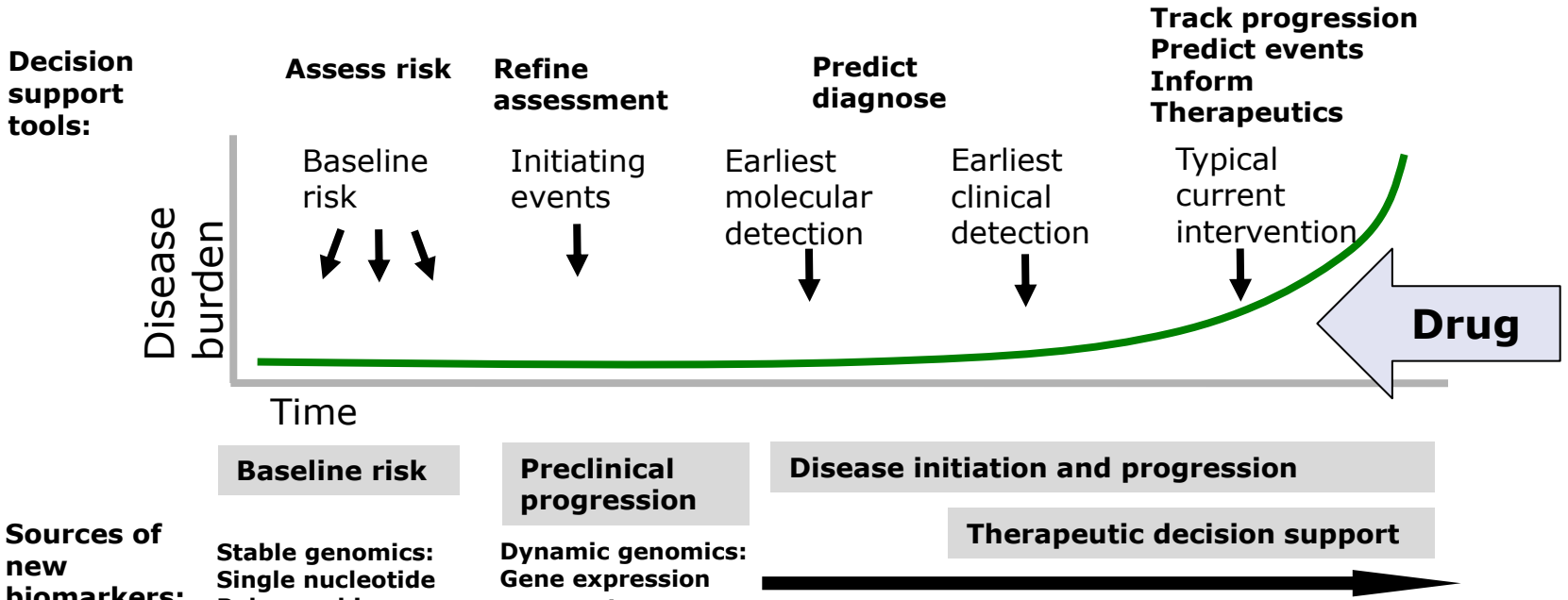
- ….Key objectives....

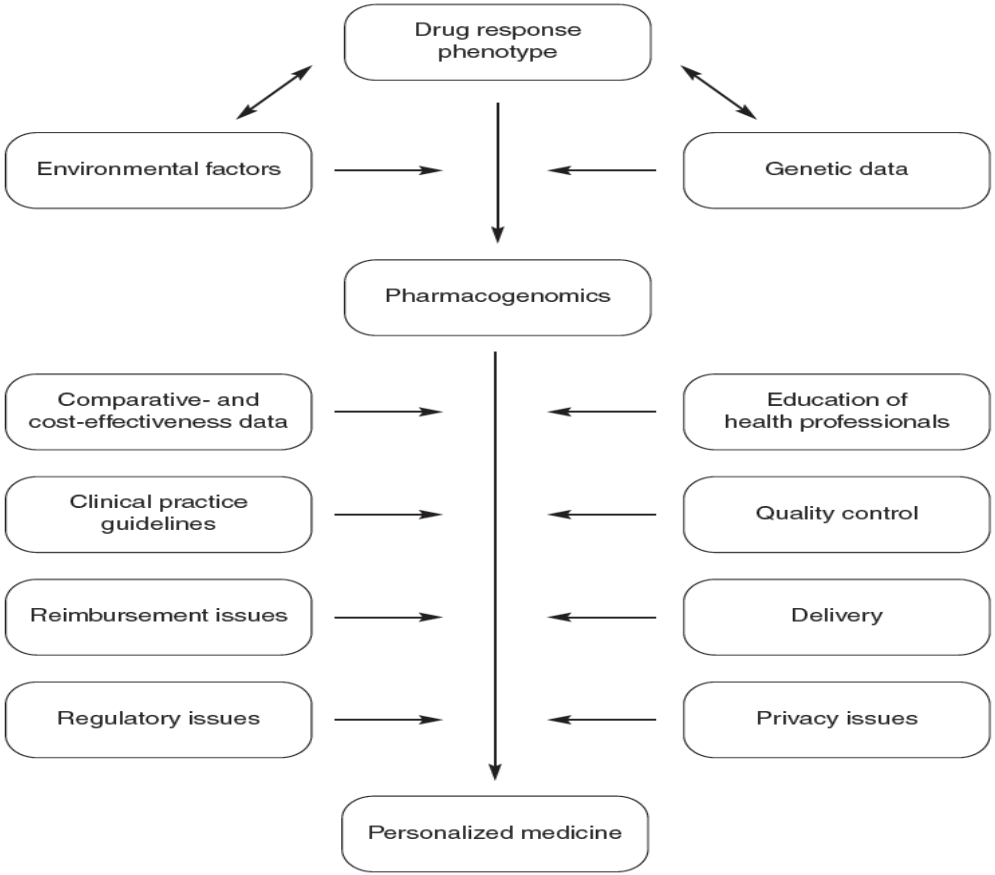
Support patient-focussed innovation and contribute to a vibrant lifescience sector in Europe

Personalised medicine: direction of travel



Source: "Personalized Medicine: Current and Future Perspectives," Patricia Deverka, MD, Duke University, Institute for Genome Sciences and Policy; and Rick J. Carlson, JD, University of Washington

Personalised Medicines: healthcare challenges



P T. 2011 July; 36(7): 412-416, 419-422, 450. PMCID: PMC3171815 Pharmacogenomics in Clinical Practice Reality and Expectations, C. Lee Ventola, MS

Direct spend on cancer care across Europe

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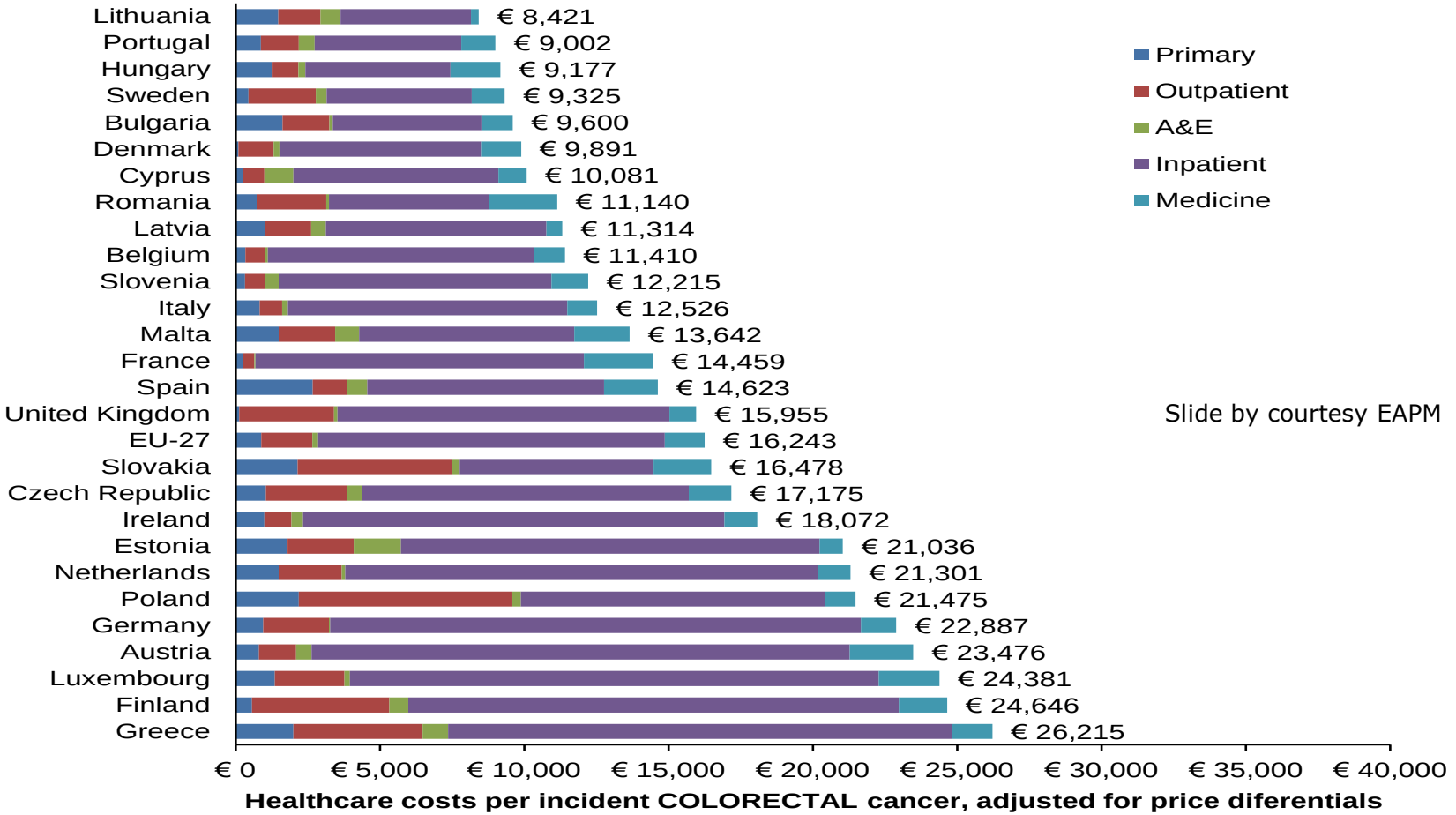

Slide by courtesy EAPM

Personalised medicines utility

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- Promote and protect individuals health:
  - identify patients who are most likely to benefit → patient selection
  - identify patients likely to be at increased risk for sADR (Abacavir)
  - identify patient for intensified monitoring e.g. during initiation of treatment
  - monitor and adjust treatment (e.g. schedule, dose, discontinuation, DDI)
- Promote Patient-centred sustainable health with targeted treatment, early intervention and prevention: HTA/Payers/PH Authorities promoting and embracing the opportunity?

Outlook: targeted therapies on the increase

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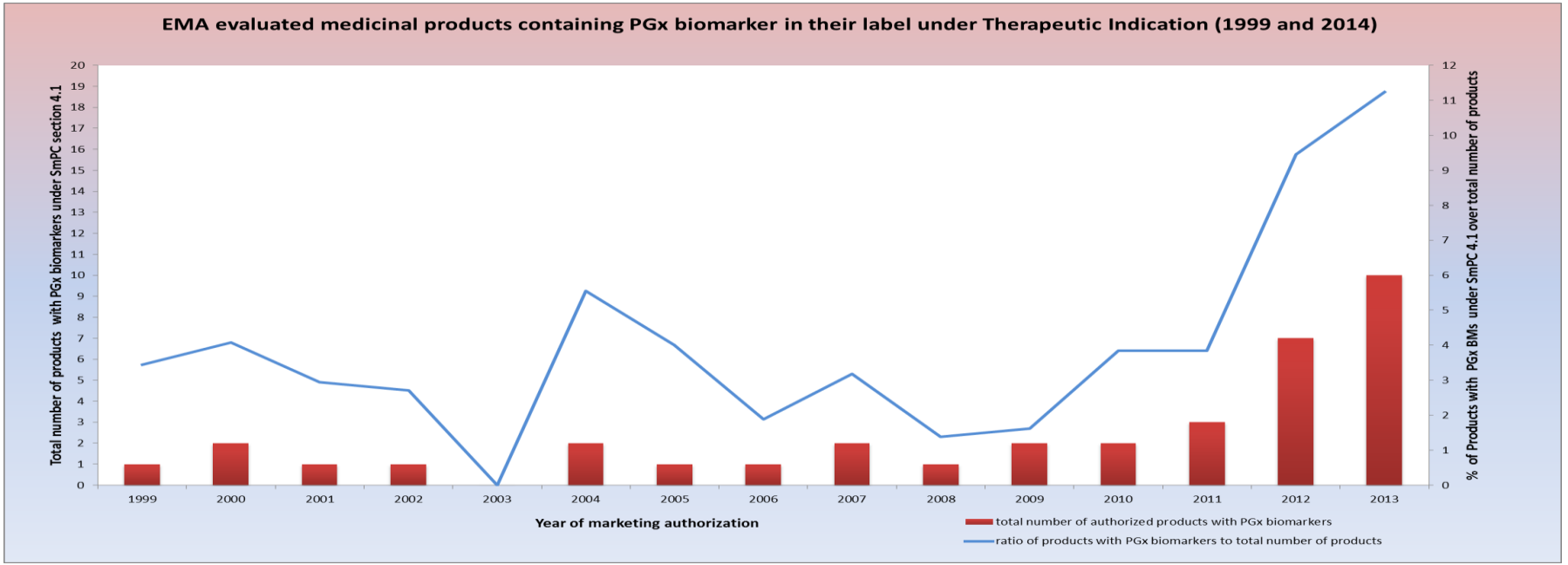
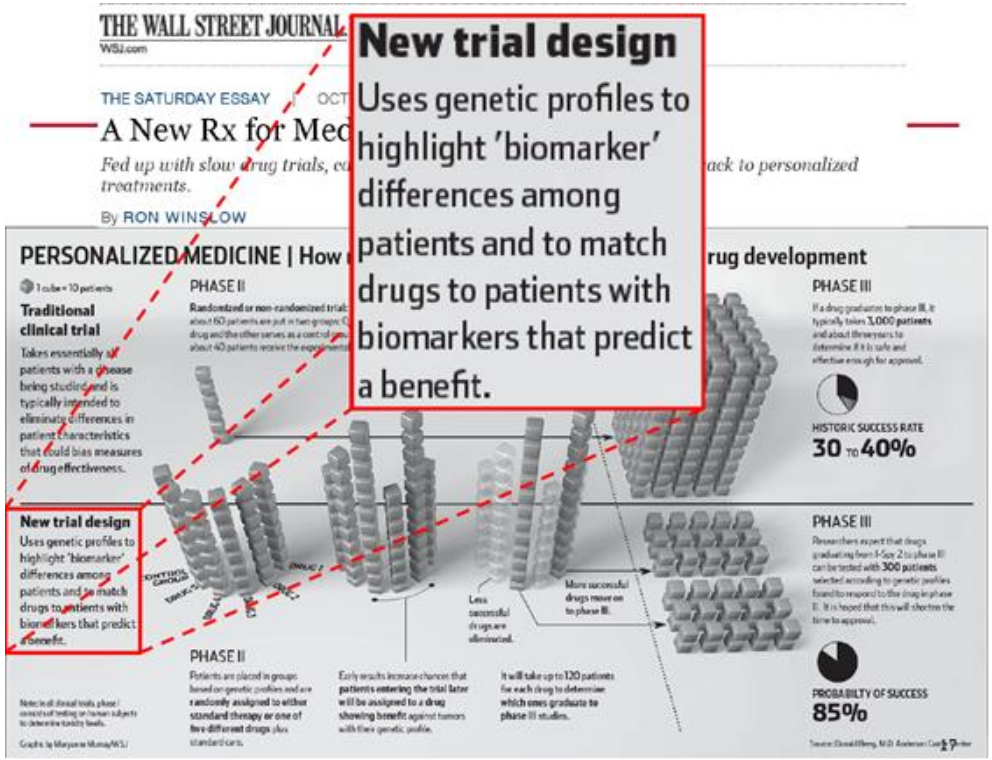
Figure 2: Number of medicinal products and ratio of medicinal products containing a genomic biomarker (gene) in their product label under "Therapeutic Indication" per year.



The number of pharmacogenomic biomarker in EU product label have been steady between 1999 and 2010 and since then gradually increasing in recent years. Initially, they have been intended for information only, progressing into becoming one of the important determinant for selection of patients likely to benefit from treatment and "more" individualised dose selection. Biomarker information may also be included in the labelling in case of negative selection (i.e., if the biomarker is used to select a population unlikely to respond) or in case of uncertainty about the value of the biomarker but where a negative selection is suspected, e.g. vandetanib.

Biomarkers and stratified medicines: more efficient clinical trials



Genomics stratified medicines and clinical trials

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Table 4. Studied patient population (biomarker positive and/or negative) in pivotal clinical trial leading to initial marketing authorisation

PGx biomarker	*Active substance*	*Patient population studied in pivotal trial for initial MAA*
HLA-B*5701	Abacavir (Ziagen) Abacavir/lamivudine (Kivexa) Abacavir/lamivudine/zidovudine (Trizivir)	HLA-B*5701 positive and negative (not tested at time of MAA)
CD30	Brentuximab vedotin (Adcetris)	CD30 positive only
HER2	Everolimus (Afinitor) Trastuzumab (Herceptin) Lapatinib (Tyverb) Pertuzumab (Perjeta) Trastuzumab emtansine (Kadcyla)	HER negative only HER positive only
RAS	Panitumumab (Vectibix) Cetuximab (Erbitux)	Wild-type and mutant
EGFR	Cetuximab (Erbitux) Gefitinib (Iressa) Erlotinib (Tarceva) Afatinib (Giotrif)	EGFR positive only EGFR positive and negative EGFR positive only
ALK	Crizotinib (Xalkori)	ALK-positive and negative
BRAF V600	Vemurafenib (Zelboraf) Dabrafenib (Tafinlar)	BRAF V600 mutation positive only
BCR-ABL	Imatinib (Glivec) Dasatinib (Sprycel) Nilotinib (Tasigna) Bosutinib (Bosulif) Imatinib (actavis, accord, medac, teva) Ponatinib (Iclusig)	Philadelphia chromosome (bcr-abl) positive (Ph+) only Bioequivalence studies T315I+ mutation only
Kit CD117	Imatinib (Glivec)	Kit (CD 117) positive only
CFTR *G551D*	Ivacaftor (Kalydeco)	G551D positive mutation only
FIP1L1-PDGFR	Imatinib (Glivec)	FIP1L1-PDGFRα positive rearrangement only
T315I	Ponatinib (Iclusig)	T315I positive mutation only
RET mutation	Vandetanib (Caprelsa)	RET mutation positive and negative
PML/RAR-α	Arsenic trioxide (Trisenox)	t(15;17) translocation and/or PML/RAR-α positive and negative

Pharmacogenomic information in drug labels: European Medicines Agency perspective The Pharmacogenomics Journal (2015), 1 – 10

Towards Personalised Medicines: regulatory science challenges

- Benefit/risk evaluation and regulatory decision making:
  - Retrospective analyses versus BM utility prospective validation/subgroups
  - Multiplicity issues
  - Handling of missing data
  - Studies in BM-negative patients: why and when are they needed?

- Emerging new clinical trials designs:
  - Adaptive designs
  - Umbrella and Basket trials
  - Algorithm based trials

- Possibility of using data derived from several independent studies? Pre-competitive research, Open science and new (BIG) data sources
- **HTAs acceptance**?

Personalised Medicines: regulatory science challenges

Oversight of the quality and use of molecular tests in the life-cycle of stratified medicines (Implementation of Guidelines on PG and PK, Good Genomic Practices, Guidelines on genomic BM and drugs co-development, PG methodology in PhVG ICH E18 genomic samples and data handling, etc.)

Consider methodology implication for drug clinical development of Next Generation Sequencing (NGS) for clinical use

⇒ analysis of a panel of genes (short term)

⇒ analysis of whole exome or genome (medium term)

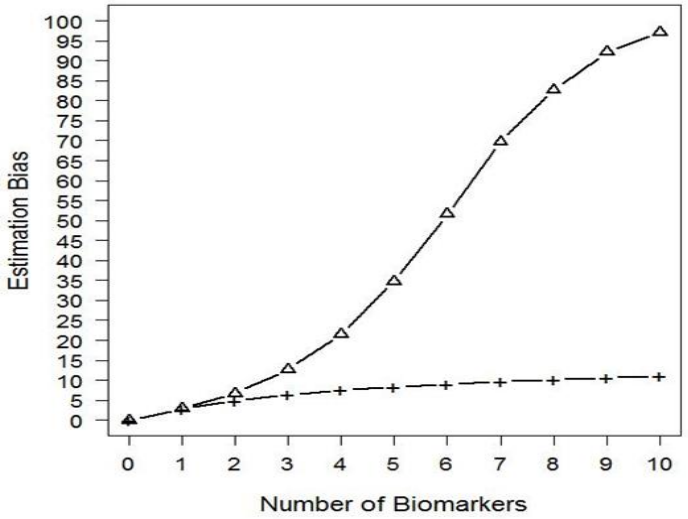
⇒ Large Unbiased Sequencing (long term)

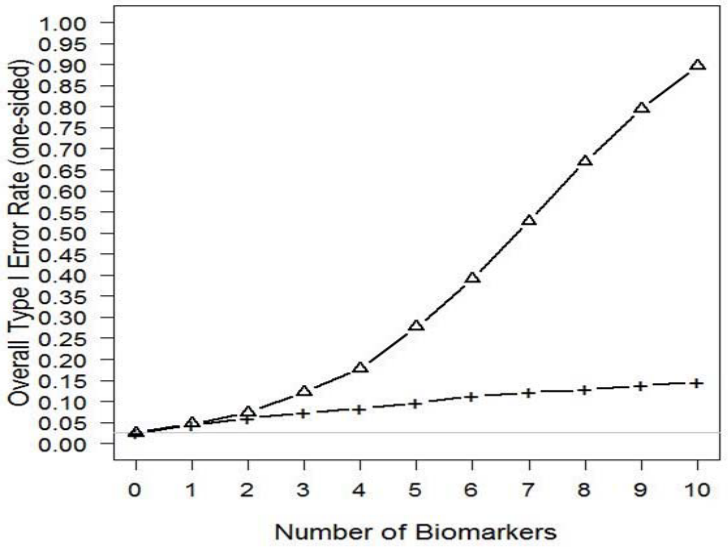
Personalised Medicines: regulatory science challenges

From single genomic biomarkers (as drug targets)

-→ to multiple biomarkers (pts profiling)

→ increased estimation bias and type I error





△ All BM+ combinations

\+ BM+ subgroups

M. Posch (2012) EMA workshop on pharmacogenomics: from science to clinical care (acknowledgments: A. Graf)

Comparison of test results possible?

pembrolizumab (Keytruda)
anti-PD1 IgG4 (humanized)
MSD/Dako
22C3 mouse
tumor cells (stroma?)
melanoma ≥ 1%
NSCLC: ≥1%/≥50%

nivolumab (Opdivo)
anti-PD1 IgG4 (human)
BMS/Dako
28-8 rabbit
tumor cells
≥1%/≥5%

Biomarkers in Personalised Medicines: challenges

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Qualitative/quantitative: meaning of PD-L1 positive?

- variability of antibody used, protocols
- tumor surface staining and/or infiltrating lymphocytes
- threshold for PD-L1 positivity by IHC
- performance metrics CDx – detection and cut-off limits, sensitivity, specificity, reproducibility

Specimen?

- archival tissue or recent - FFPE or fresh; resection or biopsy; intratumoral heterogeneity?
- time point: before start of therapy? on-treatment 1, 2 3 m

Exclusion of PD-L1 negative in CTs?

- Preliminary data % benefit? predictive claims (BM-restricted indication?)
- alternatives for indication? design (mono vs. combo)?

Extrapolations across indications/treatment lines?

EMA network and personalised medicines development

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- Patients' priorities and active role to interventional trials with personalised medicines: what has changed with omics, how it is perceived, what are the needs and the preferences to address the implications for individual and family?
- HCPs' role in primary and secondary care: how to responsibly participate in clinical research and improve the interface with research communities (to validate new biomarkers, new pre-clinical and clinical methodologies)?
- Patients and HCPs support to the development of Clinical (big) data gathering tools for early access to personalised medicines, the development of prescription support tools and the longitudinal profiling of the individuals(both clinical status and tests for personalised medicines).
- Role of P and HCP in the evaluation, with regulators, HTAs, payers, and stakeholders, of the impact of personalised medicines on PH: how to define at an early stage the value(s) of personalised medicines?
- Is it Personalised Medicine a tool towards a sustainable health care?


Thanks for your attention