Precision Medicine & Biomarker

EFSPI, Stats Leader Meeting
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Definition
Personalized Medicine

Personalized medicine is a medical procedure that separates patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. The terms **personalized medicine**, **precision medicine**, **stratified medicine** and **P4 medicine** are used interchangeably to describe this concept though some authors and organisations use these expressions separately to indicate particular nuances. [Wikepedia[1]]

- **Personalized medicine:** "Genomics+medical information technology+patient empowerment" (Millenson et al, 2006)

- **Precision medicine:** Integration of molecular research with clinical data from individual patients to develop a more accurate molecular taxonomy of diseases that enhances diagnosis and treatment and tailors disease management to the individual characteristics of each patient. (US Nat Acad of Sciences report, 2011)

- **Stratified medicine:** Use of new molecular insights and molecular diagnostic tests, to better tailor medicines and better manage a patient's disease (Meier-Apt 2012)

- **P4 medicine:** Clinical application of the tools and strategies of systems biology and medicine to quantify wellness and demystify disease for the well-being of an individual. (Hood, 2008)

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Definition
Personalized Medicine – 2nd try

- **Personalised medicine:** Tailor made for an individual patient (drug, regimen,…) A vison, we are not there.

- **Precision medicine:** Identification via multiple markers using predefined schedules and doses

- **Stratified medicine:** Different treatment for selected groups of patients

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Definition
Predictive vs. Prognostic markers

Biomarker A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarker definitions Working group: Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther 69:89-95 (2001))

- **Prognostic marker**: Predict likely course of disease irrespective of treatment in a specified population, e.g. Grading in most type of cancers

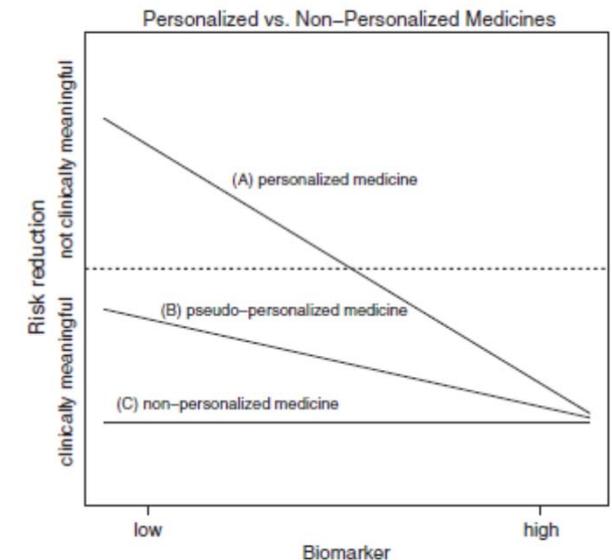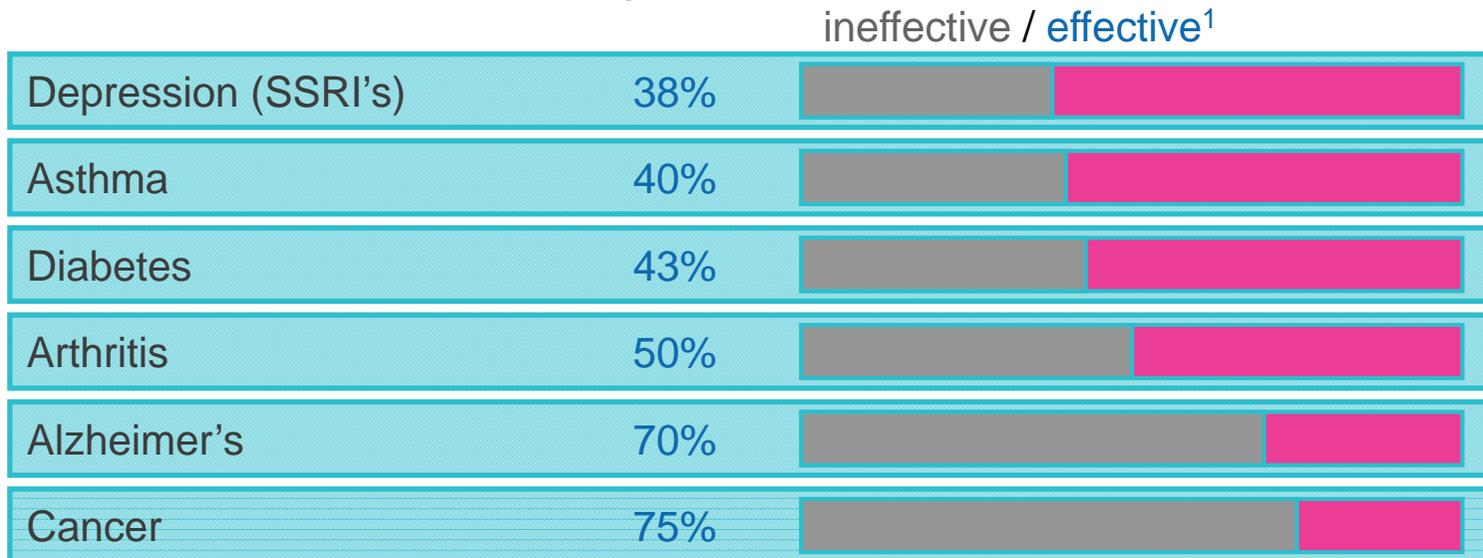- **Predictive marker**: Linked to treatment: predicts likely response to treatment

Personalized vs. Non-Personalized Medicines

Fig. 2. Clinical benefit (*i.e.* risk reduction) as a function of biomarker value for three types of medicines. With respect to a clinically meaningful risk reduction (dashed horizontal), line (A) represents a medicine that can be personalized, while lines (B) and (C) represent medicines that do not require personalization.

Definitions of prognostic and predictive according to Buyse et al in Expert Rev. Mol. Diagn. 2011)
Figure from: Mackey HM, Bengtsson T. Sample size and threshold estimation for clinical trials with predictive biomarkers. Contemporary Clinical Trials 36: 664–672, 2013

Why are we doing it?
Major drugs are ineffective for many patients

Indications in which a particular drug class is ineffective
Patient population in %; on average

ineffective / effective[1]

Depression (SSRI's)	38%
Asthma	40%
Diabetes	43%
Arthritis	50%
Alzheimer's	70%
Cancer	75%

Source: Brian B Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine", Vol. 7 (5), 1 May 2001, 201-204.

The end of the 'one-size-fits-all' paradigm in drug treatment ?

[1] Mainly for illustration. Def of effective is a matter of discussion

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The strategy

Three scenarios when developing a new molecule today

- Enriched patient population for sure (for example trastuzumab)
- Potentially enriched patient population defined by a few biomarkers (BM) (for example bevacizumab)
- Enriched population unlikely with/out potential exploratory biomarker analyses (for example rituximab)

"Easy" for the first scenario. Clinical development program nearly unchanged, but additional complexity due to parallel companion diagnostic program and perhaps cutoff selection needed for BM. Whereas the correct selection of the cutoff is a challenge in itself.

Not so easy are the other two scenario. **However, can we ignore the use of precision medicine et al?**

=> **No**, because of patient needs

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Challenges
List of current problems

- Multiplicity
  - Huge problem: Many BMs looked at in one or two studies leading to high rate of false positive.
- Regulatory requirements
  - How much data on BM negative patients required?
  - Qualitative versus Quantitative interactions
  - How much data is required for enrichment decision (only in the positive patitens? what's about date on negative patients?)
- CDx development (≠BM, CDx encompasses: kit components, hardware, software, scoring, cut-offs, etc.)
  - Biomoarker not stable over time
  - Selection of the right cut-off
  - Selection of the right biomarker, challenge of overlapping subsets (multiplicity)
  - BM only available after start of phase II
  - The right time point for a decision on predictive biomarker?
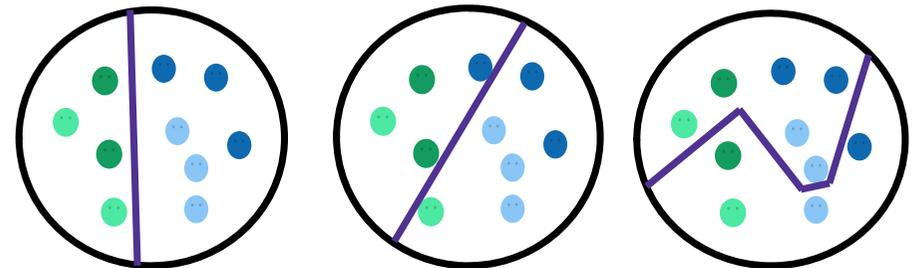
What can we do as statistics leader?
Round table discussion

- Status at your company
  - Roles and responsibilities (e.g. separate group)
  - Special competence centre?
- What can we influence / what can't we influence?
- What should we do / what shouldn't we do
- What's your strategy / which approaches do you choose?
- BM work still manageable within your company or do we need approaches across companies / academia?
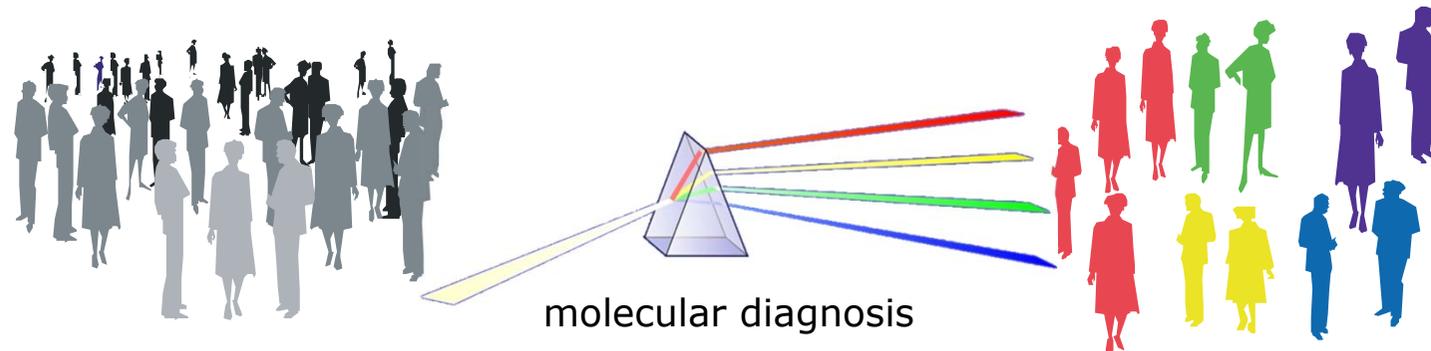
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Summary of discussions and action items

- Table 1
- …..

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Backup

A good therapy starts with a good diagnosis

Stratified Medicine

Use of new molecular insights and molecular diagnostic tests,
to better tailor medicines and better manage a patient's disease

molecular diagnosis

Increasingly, treatment will be tailored to selected patient
groups defined by molecular markers – biomarkers !

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Classification by clinical application

Preventive	• Identification of people at high risk of developing a particular disease • Assist in risk assessment
Diagnostic (Disease)	• Enabling early detection of a disease before clinical symptoms occur • Potentially enabling intervention at an earlier and more curable stage
Prognostic (Disease)	• Confer ability to stratify the risk of disease progression for patients receiving a particular therapy (disease outcome), which may allow for more aggressive therapy in patients with poorer prognosis
Predictive	• Identification of patients who will respond to a specific therapeutic product (treatment outcome), thereby providing guidance on the choice of therapy • Identification of patients' susceptibility to certain side-effects of treatment.
Therapeutic	• Monitoring disease response during a patient's therapy, with the potential for adjusting levels of intervention (e.g. dose) as required
Other (e.g. Pharmaco-dynamic)	• Improving understanding of the MoA of a drug or biological pathway • Used in drug development to determine PK/PD, target activity, effectiveness and safety of developmental candidates

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Guidance documents

Draft guidance: Enrichment strategies for clinical trials to support approval of human drugs and biological products (FDA 2012)

Reflection paper on methodological issues asociated with pharmacogenomic biomarkers in relation to clinical development and patient selection (EMA 2011)

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