A new paradigm with old challenges? Ethical implications of personalized medicine

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PM: field with (analytically) no clear boundary ⇒ object of inquiry??

(Preliminary) definition:

*Personalized (or individualized) medicine* tries to identify individual (molecular biological) factors that allow to better predict risk of disease and intended/unintended effects of interventions.

Goal:

*Prevention, diagnostic, prognostic and therapy tailored to the individual*

De facto: patient subgroups ⇒ *stratified medicine*
Methodological Challenges

• Not clearly defined, very heterogeneous field
  ➔ *individual adjustment of considerations necessary*

• Early stage of development: „visions“, but no broad practical application yet
  ➔ *anticipative technology assessment*

• “PM is in” – hype about PM
  ➔ *realistic assessment of possibilities of PM necessary*

  ➔ *Early, preliminary assessment of ethical implications*

  ➔ Many ethical challenges are not specific for PM!
Basic concept of PM: conceptually convincing

- If PM improves (evidence-based!) the effectiveness, safety and efficiency of health care delivery, promoting PM is an *ethical imperative*!

But: (potential) ambivalence of biomedical progress

- Assessment of ethical, legal, social & economic implications of PM

- Goal: ethically acceptable *development* and *application* of PM

- Cave: dominance of biological explanations!
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<td>individual level</td>
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<td>Prediction/Prevention</td>
<td>Therapy</td>
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<tr>
<td>• Informed consent for add-on-studies</td>
<td>• Implication of predictive information about health risks?</td>
<td>• Higher risks due to insufficient testing (small groups of patients)?</td>
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<td>• Informational self-determination</td>
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<td>• Overemphasis of individual responsibility for health</td>
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<td>societal level</td>
<td>• Allocation of research resources</td>
<td>• Discrimination of „bad risks“</td>
<td>• Cost impact? =&gt; Access, distributive justice</td>
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<td>• Study design (patient relevant outcomes)</td>
<td>• (Access, distributive justice)</td>
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Modified according to Schleidgen 2011
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## Distributive justice: 4 levels

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Level 1: Allocation of resources into PM (vs. other alternatives)

- Central issue: high public and private investment in PM \(\Rightarrow\) right priorities?
  - Directed towards priority health needs of the population?
  - Higher health gain if resources are invested in other approaches?
  - Does it take into account existing inequalities in health status?

Policy options:

(1) Explicit priority setting in public funding for research

- Health care needs in an ageing society (chronic diseases, multi-morbidity)
- Priority for disadvantaged (sub-)populations
- Potential for improving health status in population
- Priority for common diseases?
- Cost-effectiveness (efficiency) – anticipative assessment possible?

(2) Incentives for pharmaceutical companies to invest in areas with high priority
Level 2: Resource allocation within PM

- Investment in profitable areas ⇒ populations with rare (genetic) profile are neglected ⇒ "orphan populations"
- Neglect of vulnerable, already disadvantaged subpopulations
- Research with patient subgroups beyond PM neglected ⇒ higher risks through insufficiently tested interventions

Policy options

- Incentives for investments by pharmaceutical industry in "orphan populations" (cf. current orphan drug regulation)
- More public research funding in (genetically) rare patient populations
- Challenge: increasing number of "orphan drugs" ⇒ increasing public spending necessary ⇒ limits? priorities?
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Justice requires: General & equal access to personalized medicine

Central question: *Will health care become more or less expensive with PM?*

**Optimistic scenario:** *Cost savings* through targeted therapies with a higher effectiveness and less side effects

**Pessimistic scenario:** *cost increase* due to additional (biomarker) diagnostic, high costs for R&D and production of PM for small populations ("niche busters")

*Cost increase* ⇒ (potentially) limited access for less affluent patients with less comprehensive insurance coverage ⇒ Creation of new & aggravation of existing inequalities (on a national and global scale!)
Cost-effectiveness depends on several factors:

- Size of target population
- Number & cost of biomarker tests (i.e. test strategy)
- Likelihood of modified treatment decision due to diagnostic
- Cost impact of modified treatment decision

Cost-effectiveness varies considerably! (Wong et al. 2010)

Individual assessment of C/E-ration for each PM intervention

Shape the cost-effectiveness of PM!

HNPCC-screening: between 20,000€ and 1,500,000€/LYS depending on test strategy! (Mayer & Rogowski 2011)

Challenge (e.g. in oncology):

- Small incremental benefit ⇒ bad cost-effectiveness (HER-2 & Trastuzumab: $125,000/QALY [Elkin et al. 2004])
- Does the (small) additional benefit (at the end of life) justify the high costs?
Cost-benefit-assessment requires valid *benefit* assessment!

At the time of licensing of the drug: benefit under routine conditions difficult to assess

- Studies for licensing: usually assess efficacy under ideal conditions
- Selected, not representative samples
- Surrogate endpoints instead of patient relevant endpoints (⇒ overall survival, quality of life)
- No head-to-head comparison with standard treatment
- Incomplete data transparency (reporting & publication bias)

⇒ Requirements for a needs oriented and fair allocation & distribution are often not met!
Policy options

(1) First: Improve benefit assessment
- Independent, publicly financed clinical studies after licensing of the drug (patient relevant outcomes)
- (Initially) coverage only in clinical studies („coverage with evidence development“)
- (Germany: benefit assessment according to AMNOG too early!)

(2) Then: Cost-benefit assessment (CEA/CUA)
- Price negotiations with pharmaceutical industry
- Limited of coverage of interventions with bad incremental C/E-ratio
- Goal: unlimited access to real innovations for all patients, exclusion of „pseudo innovations“

Problem in Germany (& other countries): so far no open socio-political discourse on setting limits fairly in the hc system!
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Discrimination of patient subgroups through *secondary* information of PM about

- risk of disease, prognosis, treatment effectiveness
- Categorization: „good responder“ ⇔ „non-responder“, „difficult to treat“

**Fairness implications:**

- Restricted access to health care interventions
- Restricted access to health insurances or higher premiums
- Disadvantages in other areas (e.g. employment)
- Stigmatization of subpopulations

**Policy options**

- Restrictive regulation of access to sensitive (genetic) information (e.g. only physician & patient, patient controls access)
- Informed consent for testing: Information about (indirect) risks
Personalized medicine has (potentially) ethical implications

- most are not specific for PM
- depend on application of individualized strategies

**Individualized prediction & prevention:** mainly challenges on the individual level (excess diagnostic information!)

**Individualized treatment:** mainly challenges on societal level

- Allocation of research resources into/within PM
- Distribution of PM interventions (cost-effectiveness!)

No general rejection of PM, but

1. „Monitoring“ of ethical implications
2. Implement policies to ensure ethically acceptable development and application of PM

Shape the development in the field of PM!
Finally...

I would like to thank

• *your* for your attention

• *my colleagues* in the BMBF-collaborative research project for their input
  • Sebastian Schleidgen (ethics)
  • Elisabeth Meyer/Wolf Rogowski (economics)
  • Simone von Hardenberg/Nikola Wilman (law)

Further Information: [www.igv-ethik.de](http://www.igv-ethik.de)
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Contact: marckmann@lmu.de