NEWSLETTER

No. 8 / February 2019

Dr. Kurt R. Müller

Precision Medicine - can we afford it?

Let's face it: affordability of Precision Medicine (PM) is an issue in today's health care environment even if we imagine potential cures with new breakthrough therapies. Obviously, more stratification will lead to superior individual outcomes at justified higher prices. However, what we simple do not know is how all this will sum up and how it could be balanced by potential PM savings. The rapid emergence of drug therapies priced at half to one million intensifies this discussion further. At least within the next 3-5 years, the costs of PM-therapies are expected to be manageable as their costs range between the Generic and the Orphan sales volume. In the long run we need to manage PM as a holistic concept where savings are coming mainly from prevention (Fig. 1) in order to finance targeted therapies.

PRECISION MEDICINE - A HOLISTIC CONCEPT

"Precision Medicine (PM) is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person". This definition has been made by the Precision Medicine Initiative [1] and is pharmaLevers preferred definition. A lot of people associate PM just with genetics, precision therapy and prices. However, this is just one piece of the «PM ecosystem» cf. [2]. Ideally, individual life time risks are identified as early as possible, monitored over time with prompt diagnosis of an emerging disease and followed by a predictive, adaptive treatment pathway. Such an approach with strengthening of preventive measurements is believed to translate into a much more efficient and effective health care system thereby facilitating financing of promising PM-Therapies. Let us keep in mind that human biology, life style and environment account for 89% of mortality [3] and providing genetic risk information to individuals seems not to be effective to create the required behavioral lifestyle changes [4]. The individual benefits derive

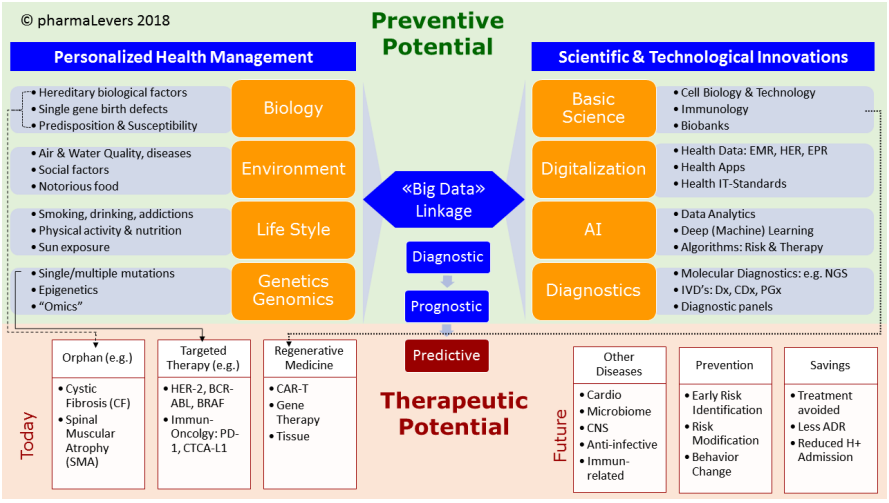

Figure 1: pharmaLevers holistic concept of Precision Medicine

from «Big Data» linkage of Personalized Health Management with Scientific & Technological Innovations (Figure 1). In Switzerland, we are still in the process of setting up the PM infrastructure [5]. It takes time to implement PM with some early successes within three years but most achievements need a time horizon of around five to ten or even more years [6]. Except for single-gene diseases, genetics and genomics deliver no easy answers. There are around 40'000 variants in a exome sequence and most variants are not specific enough to be used for predictions [7]. Furthermore, there are more than 60 million gene expression versions [8]. It seems obvious that successful health care management relies on the combination of multiple interventions; today only 3-13% of cancer patients get treatment based on their genomic analysis [9].

Who will benefit?

Patients
Patients will be able to know and manage their individual increased risk based on genetic profiling. They will have access to more effective therapies or even to new approaches with curative potential. Furthermore, ineffective therapies can be avoided and ADR's can be lowered based on pharmacogenomic drug selection. However, patients' behavioral changes are needed to capture PM's full potential - patients owe society!

Payers & Decision Makers
Eventually, they both will profit from more specific treatments with higher efficacy and probably less ADR and subsequent hospital admissions. P&R is expected to move more in the direction of outcome based payment with more value for money. In addition, the preventive potential by using PM is enormous.

Providers
Physicians simply get closer to their patients' needs with a much broader scope and variety for prevention and targeted therapy.

Industry
We have to differentiate between pharmaceuticals and medical devices companies. The former will normally profit from faster development and review process as fewer and smaller trials will deliver faster efficacy signals. Furthermore, the pharmaceutical industry has the potential to capture the whole value of drug & test. In contrast, the medical devices industry still needs to escape the cost plus coverage trap towards VBP.

ECONOMIC UNCERTAINTY OF PRECISION MEDICINE MAKES ADEQUATE REIMBURSEMENT DIFFICULT

Despite the ongoing hype around PM, its market impact is still limited. A recent scoping review has identified 344 academic papers with regulatory barriers [10]. A Swiss thesis from 2018 confirms the existing barriers and disincentives for PM [11]. So far, coverage of «one test-one drug» target therapy was manageable with the existing population-based P&R process. However, in the near future, we will be faced with the coverage challenge for individual patient profiles along complex treatment algorithms, digital health applications and multiple omic-based tests cf. [12].

"With the rising importance and budget impact of precision medicine, the current pricing and coverage approach will need to be redefined" [13]. "Stakeholders indicate that the paramount challenge to Precision Medicine is reimbursement, not scientific and technical hurdles" [14].

Keep in mind that just in oncology there are currently 1'502 PD-1/L1 studies of which 1'105 are combinations [15]. This raises two questions; first the evidence for small fragmented populations and second the increasing price for PM-therapies.

"You can be sure that anything custom is more expensive than anything standard" [16]. The economic consequences of PM remain unclear, at this point. In the non-treated population more patients are likely to be diagnosed but less of them may be treated as we can increasingly identify non-responders. In the treated population, the number of responders is expected to increase whereas the number of non-responders is expected to decline (Figure 2). Black stripes stand for a targeted precision therapy which numbers will steadily increase over time.

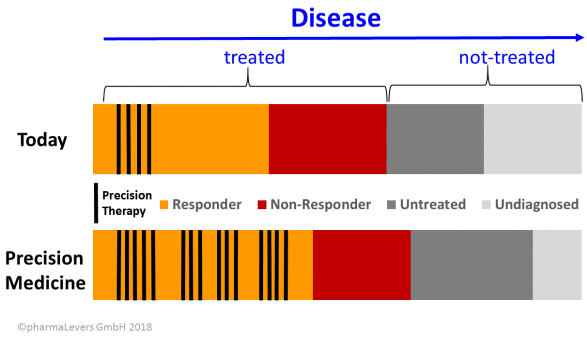

Figure 2: How PM may affect disease management

Today, we simply do not know the economic consequences of Precision Medicine. Health care may become more sustainable or may collapse as a result of affordability issues. This uncertainty is expected to aggravate the current reimbursement challenges, especially for VBP.

As the economic consequences of PM remain unclear, we still stick to current value assessment methods for targeted therapies which basically need a joint assessment of biomarker test and drug. Again, we have a dilemma as PM can be both; cost-effective or not cost-effective cf. [17], [18], [19]. However, the results for pharmacogenomic and pharmacogenetic test-guided therapies are much more positive [20].
Clinical decision making is getting more dynamic and complex with e.g. patient profiling based on panel diagnostics (NGS). As a consequence, economic modelling is getting more demanding and shifting from cohort to patient level where DES-models may be more appropriate than Markov-models [21].

How to meet the reimbursement challenge?

We have learned that reimbursement and not science or technology is the single most important barrier to Precision Medicine.

The current P&R setting is still population based and sufficient to cope with existing targeted therapies. However, complexity is believed to dramatically increase through numerous new diagnostic tests, PM-drug combinations and different, fast changing treatment algorithms. It remains to be seen whether comparators are still drugs or clinical pathways. To demonstrate clinical utility may become mandatory for drugs too as currently for diagnostics.

Probably the only suitable way to deal with the increasing uncertainty about Efficacy-Appropriateness and Cost-Effectiveness is to move towards an adaptive P&R process. Ideally, this would be like real-options with the flexibility to e.g. expand, abandon, wait, contract or switch. Obviously, we can't manage health care like a financial business as all stakeholders need much more stability.

We already have the tools of flexible P&R with Market Access Agreements such as conditional reimbursement, coverage with evidence development, outcome based risk sharing models and simple financial tools. We just have to use them more frequently and adapt them over time. We should keep in mind that the overlap between the marketing authorization and the P&R process needs to be strengthened. We probably have to accept the concept of early try and error. Finally, all starts with openness and flexible thinking.

CHANGES ARE NEEDED FOR REIMBURSEMENT

Precision Medicine constitute a fundamental conceptual change (Table 1) in the way how clinical and coverage decisions should be made. The current regulatory environment has hardly kept pace with this development and the population-based concept is still mostly in place.

Table 1: Comparison of Population- and Precision Medicine-based approaches

	Population based	Precision based	Consequences
Disease	• Symptom based • Subgroups driven by response • Large populations	• Molecular based • Subgroups driven by biology • Small populations	• Targeting the cause • New classification of disease • Predictive Medicine
Economics	• Value spread across responders & non-responders [22] • Drug value • Comparators	• Value concentrated among responders [22] • (Test+Drug) value • Algorithms	• Lower NNT • Joint assessment • Assess pathways
Coverage	• Average efficacy • Cohort evidence • Safety is empirical • Uniform pricing	• Selective efficacy • Patient evidence • Safety is selective • Dynamic pricing	• Improved outcome • From RCT to RWE • Less ADR & H^+ • Adaptive VBP

The Swiss Federal Office of Public Health has issued a report about the expected challenges of PM [19] – some are listed below:

- Assessment of efficacy, appropriateness and cost-effectiveness with small number of cases and high drug prices e.g. oncology
- Managed Entry Agreements (MEA) are rarely employed
- Diagnostic tests need to prove clinical utility which means they must change the clinical pathway
- Preventive analyses need legal provision and positive listing
- Biomarker profiling is a medical service whereas other diagnostic tests must be listed on the positive list of analyses
- Evaluation and assessment process for drug & medical devices differ in terms of requirements, process and decision making

Most of the current PM-therapies are in the field of oncology. Some people may argue that such therapies are sufficiently covered with today's regulations by using more or less orphan drug criteria cf. [13]. However, in the near future, the number of genomics biomarkers will increase dramatically leading to many PM-combinations of which some will get standards and others will be out-innovated quickly. Fragmentation of the patient population will increase, evidence levels will become limited and prices will ceiling affordability. Furthermore, it is believed that many clinical pathways are going to compete for patients. Economic assessment of pathways has to deal with different payment systems for medical services, medical devices and pharmaceuticals.

How should Payers and Decision Makers deal with this overwhelming level of uncertainties? Innovative Market Access Agreements are needed more than ever to enable patients' timely access to innovations.

Especially for potentially curative therapies as e.g. CAR-T or Gene Therapy innovative pricing, financing and payment systems are required. One key issue will be how to manage upfront payment [23]. Overall adaptive processes are needed cf. [24].

A bright future

Precision Medicine will learn us more about the cause of a disease and the reasons for different individual outcomes. The concept of cure will become an achievable target not only for a small number of patients.
Furthermore, both healthy and unhealthy persons will have the chance to know their short and life time risks for serious diseases. They will get a fair chance to reduce their risks by adapting their life style and behaviors.
Precision Medicine will no longer be confined to oncology. The PM-concept will change how auto-immune, cardiovascular, infectious or metabolic diseases are diagnosed and treated. Early intervention in the pre-chronic phase will translate into tremendous economic savings for the benefit of the society. Patients' odysseys of chronic disease without diagnosis can be stopped or will never happen.
Precision Medicine will go together with digitalization at an evolutionary speed, leading to a high amount of efficiency and quality gains.
To move forward in the direction of above «vision» we have to accept the rising level of uncertainty. Easy to say but difficult to handle with the current health care spending ceiling.

How to find us:

pharmaLevers GmbH
Mittlere Bühnenbergstrasse 16
CH-4665 Oftringen
+41 62 798 04 33
+41 79 636 63 96

kurt.mueller@pharmalevers.com
https://www.pharmalevers.com
https://twitter.com/pharmalevers

REFERENCES

1. Ghr.nlm.nih.gov. What is precision medicine? [Internet]. Genetics Home Reference. Available from: https://ghr.nlm.nih.gov/primer/precisionmedicine/definition
2. Ginsburg GS, Phillips KA. Precision medicine: From science to value. Health Aff. 2018;37(5):694–701.
3. Dever GEA. MODEL FOR HEALTH POLICY ANALYSIS * The purpose of this paper is to develop an innovative epidemiological model that may be used in policy analysis of health programs I-2 , 13]. Soc Indic Res. 1976;2:453–66.
4. Doble B, Schofield DJ, Roscioli T, Mattick JS. The promise of personalised medicine. Lancet [Internet]. 2016 Jan;387(10017):433–4. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00176-8/fulltext
5. Meier-Abt P, Lawrence AK, Selter L, Vayena E, Schwede T. The Swiss approach to precision medicine. Swiss Med Wkly. 2018;(January):1–8.
6. Hudson K et al. The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine: Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH [Internet]. 2015. Available from: https://acd.od.nih.gov/documents/reports/DRAFT-PMI-WG-Report-9-11-2015-508.pdf
7. Biesecker LG, Nussbaum RL, Rehm HL. Distinguishing Variant Pathogenicity From Genetic Diagnosis. JAMA [Internet]. 2018 Oct 15;19(2):249–55. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2018.14900
8. Cerrato P, Halamka J. Realizing the Promise of Precision Medicine: The role of patient data, mobile technology, and consumer engagement. 1st Editio. Academic Press; 2018. 218 p.
9. Tannock IF, Hickman JA. Limits to Personalized Cancer Medicine. N Engl J Med. 2016 Jan 5;375(13):1289–94.
10. Knowles L, Luth W, Bubela T. Paving the road to personalized medicine: recommendations on regulatory, intellectual property and reimbursement challenges. J Law Biosci [Internet]. 2017;(November):453–506. Available from: http://academic.oup.com/jlb/article/doi/10.1093/jlb/lsx030/4584308
11. Bosshard K. Law and Economics of Personalized Medicine: Institutional Levers to Foster the Translation of Personalized Medicine. [Wiesbaden]: Springer Fachmedien Wiesbaden GmbH; 2018.
12. Love-Koh J, Peel A, Rejon-Parilla JC, Ennis K, Lovett R, Manca A, et al. The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. Pharmacoeconomics [Internet]. 2018;(0123456789). Available from: http://link.springer.com/10.1007/s40273-018-0686-6
13. Degtiar I. A review of international coverage and pricing strategies for personalized medicine and orphan drugs. Health Policy (New York) [Internet]. 2017;121(12):1240–8. Available from: https://doi.org/10.1016/j.healthpol.2017.09.005
14. Pothier KC. Personalizing Precision Medicine: A Global Voyage from Vision to Reality. 1st Edition. Hoboken, NJ 07030, USA: John Wiley & Sons, Inc; 2017. 261 p.
15. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol. 2018;29(1):84–91.
16. Kern LM. PERSPECTIVE : PART I: CAN WE AFFORD PRECISION MEDICINE ? SGIM Forum [Internet]. 2018;41(8):1–2. Available from: https://www.sgim.org/File Library/SGIM/Resource Library/Forum/2018/SGIM-August-1.pdf
17. Paris V, Colbert A, Delaunay N. Achieving the promise of precision medicine. In: New Health Technologies: Managing Access, Value and Sustainability [Internet]. OECD Publishing; 2017. p. 159–82. Available from: https://www.oecd-ilibrary.org/social-issues-migration-health/managing-new-technologies-in-health-care_9789264266438-en
18. Hatz MH, Schremser K, Rogowski WH. Is Individualized Medicine More Cost-Effective? A Systematic Review. Pharmacoeconomics [Internet]. 2014 May 27;32(5):443–55. Available from: http://link.springer.com/10.1007/s40273-014-0143-0
19. BAG. Aktuelle Entwicklungen in der datengetriebenen Medizin und die damit verbundenen Herausforderungen und Aufgaben für das BAG. Bericht der Arbeitsgruppe Personalisierte Medizin des BAG [Internet]. 2017. Available from: https://www.bag.admin.ch/bag/de/home/medizin-und-forschung/biomedizinische-forschung-und-technologie/masterplan-zur-staerkung-der-biomedizinischen-forschung-und-technologie/personalisierte-medizin.html
20. Plöthner M, Ribbentrop D, Hartman JP, Frank M. Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany. Adv Ther. 2016;33(9):1461–80.
21. Degeling K, Koffijberg H, IJzerman MJ. A systematic review and checklist presenting the main challenges for health economic modeling in personalized medicine: towards implementing patient-level models. Expert Rev Pharmacoeconomics Outcomes Res [Internet]. 2017;17(1):17–25. Available from: https://doi.org/10.1080/14737167.2017.1273110
22. Garrison LP, Towse A. Value-based pricing and reimbursement in personalised healthcare: Introduction to the basic health economics. J Pers Med. 2017;7(3).
23. EPFL IRGC. The Economics of Precision Medicine. A Risk-Governance Perspective. [Internet]. Lausanne. EPFL International Risk Governance Center; 2018. Available from: https://infoscience.epfl.ch/record/256776/files/The economics of precision medicine.pdf
24. Barker R. Bioscience - Lost in Translation? [Internet]. Vol. 1. Oxford University Press; 2016. Available from: http://www.oxfordmedicine.com/view/10.1093/med/9780198737780.001.0001/med-9780198737780

Market Access Consulting (P&R, HEOR, HTA, Policy)
Strategic Insights, Innovative Pricing Strategy, Cause/Effect-Relationship, Second Opinion, Managed Entry Agreements, Precision Medicine, Healthcare Policy, HTA scoping & analysis, BAG- Submission, Value Dossier, Stakeholder Management, Pharmacoeconomics, Negotiation Analysis, Value-Testing, Budget-Impact, Payer Marketing, Patient Engagement.