

# Personalized Medicine and Health Economics: Is Small the New Big? A White Paper

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**P**ersonalized medicine incorporates the progress of genome-based knowledge into practice, hugely benefiting patients and health systems [1]. PM can be defined as the tailoring of preventive, diagnostic and therapeutic interventions to the genetic, molecular and other phenotypic characteristics of an individual or population [2]. This may involve genetic or laboratory biomarker information [3,4]. Today the definition is broader and includes products and services that apply the science of genomics and proteomics (directly or indirectly) and capitalize on the trends toward wellness and consumerism to enable tailored approaches to prevention and care. This definition encompasses everything from high tech diagnostics to low tech foods to technologies that enable storage, analysis and linking of patient and scientific data [5].

A 75% increase in investment by the pharma industry in PM research over the last 5 years stimulated interest in these interventions [6], presenting new challenges to health policy

makers regarding the impact of PM on both clinical practice and the health care system. Currently, in most countries including Israel, there are no clear guidelines for industry and reimbursement regulators on coverage and payment for PM technologies. Moreover, social, ethical and regulatory issues need to be discussed and decisions taken to redesign the health care system for personalized medicine. Obviously, this necessitates changes in regulations and health policy to achieve fair and equitable access to new personalized health technologies [7,8]\*.

Many questions have been raised in the last decade regarding PM. A major issue concerns the shift from the one-size-fits-all concept to targeted stratified medicine [9]. In this document we address the impact of personalized medicine on the total national health expenditure including the public/private mix [10], future cost-containment measures, acceptable cost/quality-adjusted life year thresholds, clinical trials, and regulatory and reimbursement mechanisms [11].

## IMPACT OF PM ON THE TOTAL NATIONAL HEALTH EXPENDITURE

Overall, total health care expenditures are likely to rise as patients live longer and costly advanced health technologies continue to be developed [12]. Yet, some argue that health care expenditures will decrease [13]. Personalized medicine promises both higher quality of treatment for individual patients and lower costs in health care [14,15] since patients will be offered only those therapies that are effective for them, and treatments that will not be safe or effective will be avoided and in some cases omitted. Furthermore, companion diagnostics, which facilitates PM, has the potential to decrease costs associated with misdiagnoses, adverse

\*Health Technology: Any intervention that may be used for health, to prevent, diagnose or treat disease or for rehabilitation or long term care. This includes pharmaceuticals, devices, procedures and organizational systems used in health care (INAHTA)

PM = personalized medicine

drug reactions, or delayed treatment benefits, as well as costs associated with the prescription of drugs unlikely to work appropriately given the patient's genome [16]. For example, according to the Personalized Medicine Coalition, \$604,000,000 could be saved by the health care system every year in the United States if patients with metastatic colorectal cancer would undergo genetic testing for the *KRAS* gene prior to treatment [17].

Although medical revolutions require many years to achieve their objectives, the growing number of personalized health technologies that will be introduced into health care systems will raise costs. Generally, some of these new technologies tend to address unmet medical needs and many will replace obsolete generic treatments in small population groups with better performing expensive branded treatments. In addition, the genetic and genomic clinical diagnostics market continues to grow, revealing genetic predispositions and asymptomatic diseases that probably boost health care expenditures. This will probably lead to the development of new drugs or biologic agents that will contribute to the increase in health care expenditures [18].

In the long term, increased efficacy and safety of personalized therapies will offset prices of drugs and decrease costs due to prevention of adverse reactions to conventional drugs, reduction of the high expense of hospitalizations, avoidance of misdiagnosis, early disease intervention, and disease prevention [19].

Personalized medicine could lower overall costs especially if disinvestment is applied to generic therapeutics, medical devices and surgical procedures which we know benefit only a fraction of those who receive them. Unfortunately, current policies do not incentivize the reimbursement of companion diagnostics aimed at identifying those patients already under treatment that is ineffective for them. In addition, it is unlikely that most of these historic effective low cost treatments will be replaced by premium priced new personalized therapies.

**IMPACT OF PM ON THE PUBLIC/PRIVATE EXPENDITURE MIX**

In our uncertain global economy, increasing health care costs is a concern to citizens and decision-makers. Global spending on health care over the last decade has increased at a rate exceeding the rate of economic growth. This fact and the economic crisis of the past decade will strongly reduce government investment for the public welfare and increase the personal liabilities of the population for health care and social security. In the coming years the public system will not have the resources to meet the market demand for personalized medicine, which most probably will be partially borne by the private sector.

These trends in PM will change the “rules of the game” for health care providers, payers, as well as patients who will have a more participative role in their own care [20,21].

Personalized medicine empowers patients to make informed choices and take responsibility for their own health, thereby shouldering the burden of the associated costs. The financial burden may be shared through co-payments, deductibles, co-insurance, prior authorization, and new drug tiers for expensive products.

**APPROACHES AND POLICY REGARDING PM**

- **Establishing coverage and reimbursement policies related to companion diagnostics.** The companion diagnostic is the key “gatekeeper” in determining which patients will benefit from the treatment. PM has the potential to resolve inefficiencies in medical treatment, such as trial-and-error dosing, unnecessary hospitalizations, late diagnoses, and reactive treatments. One of the major reasons for pursuing PM is that the majority of drugs are effective in less than 50% of treated patients. It is in the interest of health care systems to promote the use of pharmacogenetics/pharmacogenomics – genetic and genomics tests designed to identify patient genes as they specifically relate to effectiveness, dosing and potential side effects of specific therapeutic compounds. This will release new information as well as resources, transforming the potential blockbuster drug to a niche product. Application of these tests to reassess drug response in patients already treated and omitting non-responding patients from treatment will release scarce resources to fund new treatments.
- **Applying cost-containment approaches (such as pre-authorization or post-authorization).** To create an agreed national, regional or institutional infrastructure of pre-authorization or post-authorization for very expensive PM drugs, e.g., pharmacogenomics-based treatment prescriptions, will necessitate companion diagnostic testing in advance or impose new companion diagnostics for existing treatments.
- **Constructing and sharing databases.** This will require a great deal of thought: what data will be retrieved, where will they be derived from, what will the appropriate data types and formats be, and how should they be presented to health care staff and patients. More complete and consistent collection and sharing of patient data and retrospective analysis to guide prospective trials and treatment will be needed. Obviously, this requires more than science and technology and may increase costs in the short term due to the establishment of these genetic/genomic databases. But, in the long run, once this infrastructure has been established these formats have the potential to reduce future costs. It will require regulatory, privacy and reimbursement changes to induce the efficient creation and ubiquitous use of such resources.

- **Educating health care staff and providing support.** Health care systems must embark on an aggressive learning curve to educate their health care providers, physicians and nurses in the complex issues raised by genomic and proteomic science. Universities, too, must update their academic programs.
- **Dialogue between stakeholders.** Dialogue and cooperation, in addition to formalized training, should be promoted across the health care industry involving the government, providers, payers and academia, for example, by identifying the most efficient reimbursement methods for diagnostic tests [9,22,23].
- **Moving to value-based payment models.** Uncertainty about the clinical value, safety and cost-effectiveness of new technologies will probably lead stakeholders to gather additional evidence through research and policy options. For instance, Coverage with Evidence Development may be considered in order to generate further, more robust evidence of safety and net health benefit. We expect that health care systems will evaluate viable business models and increase the utilization of value-based payment models, especially risk-sharing schemes. The first risk-sharing agreement through the Israel National List of Health Services was approved in 2010 for the drug sapropterin dihydrochloride (Kuvan<sup>®</sup>, Merck Serono) for patients with phenylketonuria. The core principle agreement included a maximum number of patients eligible to receive Kuvan based on expert opinion, and Merck Serono agreed to bear the extra cost of treatment if the actual use exceeds the agreed number. This pilot agreement will be valid for 3 years, after which it will be reevaluated.

Furthermore, decision-makers should also consider obligating health care providers to use PGx to optimize drug dose therapies in cases where the test is valid, available and accessible. In 2007, for example, the U.S. Food and Drug Administration recommended genotyping for all patients being assessed for therapy that involved companion diagnostics [24]. Genotyping allows prescription of drug therapy regimens only to individuals expected to benefit from that specific drug at that specific dosage. However, the Centers for Medicare and Medicaid Services state that pharmacogenetic testing for responsiveness to warfarin, whose proponents claim helps guide dosing, has not been shown to improve health outcomes and therefore should not be reimbursed under Medicare except within the confines of a clinical trial specifically designed to demonstrate the clinical effects of such testing (CAG-00400N 4 May 2009) [25].

PGx = pharmacogenetics/pharmacogenomics

#### KEY ASPECTS FOR DECISION-MAKERS REGARDING THE REIMBURSEMENT OF PM

Health decision-makers are continuously requesting additional clinical and economic evidence on the value of new health technologies. With personalized medicine, it will be important to distinguish between “got to have” vs. “nice to know” evidence.

The Israeli reimbursement system, similar to those in many European countries and the USA, may need to change their evaluation procedure for new health technologies and payment policy to accommodate the growing number of PM technologies that are being brought to market. Currently, the reimbursement infrastructures of all European countries are limited in their ability to adequately evaluate and rapidly provide access to PM diagnostics or combined drug and diagnostic products [26].

#### IMPROVING HTA METHODOLOGIES AND FUNDING

For therapies to be successfully ushered through the reimbursement process, payers want evidence that pharmacogenomics-based treatments are clinically significant and cost-effective relative to existing treatments. The concepts of efficacy, safety, and economic efficiency are basic essentials in HTA methodology for approving reimbursement. HTA is mainly used to advise or inform technology-related policy-making, especially health care payers, providers and employers about whether technologies should be included in health benefits plans or disease management programs addressing coverage and reimbursement [27].

As classic HTA and meta-analysis are based on average responses, they are inadequate for PM reimbursement decision-making, which exploits variance in treatment response. Further collaboration across all settings is needed to improve pricing, reimbursement and HTA methodologies to ensure that they implement and reflect the added value of companion diagnostics, thus facilitating the way for PM.

More flexible reimbursement systems and flexible pricing-based models are essential to incentivize companies to develop PM technologies, enable patient accessibility, and reward personalized technologies that demonstrate evidence of value.

#### PROMOTING DECISION-ANALYTIC MODELS

Within the PM framework, decision-analytic models, such as economic evaluations, are likely to play an increasing role in shared decision-making among payers, providers and patients. These models should be transparent; they should define the assumptions on which the economic evaluations are based in terms that are comprehensible for patients and their providers regarding treatment benefits, harms, and costs [28].

HTA = health technology assessment

**SPECIALIST SERVICES ASSESSMENT**

Under current payer policies, many of the services provided by PM specialists (e.g., clinical geneticists, laboratory specialists, genetic consultants) are not eligible for reimbursement or are undervalued. Costs associated with those services should be considered when evaluating the cost of funding a new PM technology, since they have fundamental economic consequences for the health care system [29].

**PATIENT PARTICIPATION IN THE PROCESS OF PM ADOPTION**

Effective integration of PGx testing into clinical care will require attention to patient attitudes. Public attitudes toward PGx testing, ancillary disease risk information and related clinical issues through focus groups were assessed by Haga et al. [30], who reported patients' concerns regarding privacy, confidentiality, and psychological harms associated with ancillary information. Furthermore, focus group participants believed that physicians had a responsibility to disclose ancillary risk information but were concerned about managing and coping with unexpected disease risk information [30]. Lakdawalla et al. [31] stressed the value of hope among patients, especially for long-term survival, despite cost considerations. Some researchers found that 77% of surveyed cancer patients with melanoma, breast cancer, or other solid tumors preferred hopeful gambles to safe bets. Perhaps this will require setting higher thresholds for acceptable cost-effectiveness ratios, notably in the end-of-life context [32].

In addition, individual patients may view treatments differently at different ages, in different family circumstances, or from other perspectives. Patients are the end-users of these technologies and their reaction to quality-of-life issues, such as the toxicity of treatment, pain and adverse effects, may also have a powerful impact on the consumption of new technologies.

**ENSURING PATIENT'S ACCESSIBILITY**

Current reimbursement policies fall short of what is needed to ensure that patients have access to personalized therapies, predictive tests for susceptibility to disease, and pharmacogenomics tests for drug responsiveness. The Personalized Medicine Coalition sees fair and equitable payment for diagnostic tests as having a direct impact on patient access to PM. Current coding and payment systems for these tests should be aligned with their technological, clinical and health economic impact. This will force health care systems to establish a more comprehensive policy that promises patients' accessibility to PM [33].

The significant variation in reimbursement and market access systems across Europe creates differentially receptive environments for such technologies [26,34]. Countries like Germany, the UK and France are currently better poised to take advantage of the benefits that these innovations provide by having evolved their reimbursement systems to assess and incorporate these technologies more efficiently. Other coun-

tries with less advanced reimbursement systems will need to adapt to the changing requirements of PM technologies. Furthermore, the pharma industry needs clearer guidance on the evidence requirements across markets to achieve widespread coverage and payment. Additionally, countries making significant investments in the research and development of PM technologies must ensure that their reimbursement systems can evaluate and pay for the resulting innovations once they are commercially available [35].

**COST/QALY THRESHOLD**

PM technologies, the antithesis of the former blockbuster one-drug-fits-all approach, offer the opportunity to improve individual health by delivering the right dose of the right drug to the right patient at the right time, but create challenges for decision-makers about what technologies offer sufficient value to justify the cost of diffusion. However, it suffers from an inhibitory cycle of insufficient economic evidence, leading to under-use, which in turn restricts the supply of data for economic evaluation. Despite the potential benefits of using economic evaluation models in health care decision-making, it is unclear how and to what extent these types of tools are being used to inform decision makers regarding PM-related coverage and treatment decisions by payers, providers and patients.

In February 2012, the UK National Institute for Health and Clinical Excellence (NICE) announced their refusal to recommend the use of three genomics diagnostic tests for breast cancer treatment. This decision was based on the opinion of a panel of experts who found that the tests' proposed advantages varied and that none of the tests were good enough to be included in the guidelines [36]. NICE set an expected standard incremental cost-effectiveness ratio (ICER) of £20,000 (\$31,778) per QALY gained in order for any of these tests to be considered cost-effective when compared to current clinical practice alone or with the Nottingham Prognostic Index\*. None of the results of the economic analyses of genomics diagnostics achieved this threshold. Perhaps this may highlight the need for clarification regarding the evidence required for calculating ICERs and possibly accentuate the need to consider adjusting an appropriate threshold for genomic diagnostic tests. Alan Johnson, then Secretary of State, announced in November 2008 that for end-of-life cancer drugs the threshold could be increased above £30,000 [37].

**CHANGES MANDATED BY THE REGULATORY AUTHORITIES REGARDING PM**

In the field of personalized medicine, a new model should be proposed whereby experts in organizations, the academia and

QALY = quality-adjusted life year

\*The Nottingham prognostic index (NPI) is used to determine prognosis following surgery for breast cancer. Its value is calculated using three pathological criteria: size of the lesion, number of involved lymph nodes, and grade of the tumor.

industry plan studies within a regulatory framework to support authorization and reimbursement for new targeted therapy and biomarkers [38]. One of the functions of the industry should be to communicate with different stakeholders about data required to support product licensure or a new drug indication [39].

#### THE FDA

In July 2011 the FDA issued a Draft Guidance (“Guidance”) to assist companies to develop a therapeutic product that depends on the use of such a device/test for the product’s safe and effective use, and to develop a companion diagnostic device intended for use with a corresponding therapeutic product [40]. The following recommendations were issued:

- **Recommended regulatory process.** The FDA recommends contemporaneous development of a drug and its corresponding diagnostic device. If the device and its test results are essential for the drug’s safety and efficacy, the FDA will not approve the product or use of the product with the device if the FDA has not also approved/cleared the device itself. However, the FDA will retain discretion to approve a drug for use with a companion device, even if the FDA has not yet approved/cleared the device, expecting it to be performed subsequently.
- **Investigational use.** A diagnostic device used to make treatment decisions in a clinical trial is considered to be an investigational device (IVD) unless the device is used in a manner that is already approved/cleared. The diagnostic test will be considered a significant risk device if it is used to make critical treatment choices that pose serious risks to health, safety or welfare of the patient (e.g., testing mutations in *BRCA1/2*). In such situations, the device sponsor must comply with investigational device exemption (IDE) regulations.
 

A diagnostic device and therapeutic product may be studied in the same investigational study, as long as the study meets IDE and investigational new drug (IND) regulations. The Draft Guidance also recommends that the device sponsor and the therapeutic product sponsor submit information about the proposed IVD companion diagnostic device in a pre-IND submission.
- **Labeling.** The Draft Guidance also addresses labeling of therapeutic products that depend on a diagnostic test. Existing FDA regulations indicate that product labeling must include information relating to relevant laboratory tests. Where appropriate, the Indications and Usage section of a label must define the patient subpopulation that would be treated with the drug. If a diagnostic test is

essential for monitoring beneficial or adverse effects of a therapeutic product, the Warnings and Precaution section must identify the type of test necessary for monitoring effects. Labeling must include information about the type of device (i.e., intended use of the device) rather than a specific manufacturer’s device. Moreover, if the FDA approves/clears a companion diagnostic device after it approves a relevant therapeutic product, the product label must be amended to incorporate such information.

#### CONCLUSIONS

As Raju Kucherlapati, professor of Genetics at Harvard Medical School and one of the researchers behind the Human Genome Project, wrote in the PricewaterhouseCoopers report on the impact of personalized medicine: “Implementation of personalized medicine is going to result in better outcomes for patients, and I truly believe there is going to be reduced cost. It’s happening today, it’s not some time in the future. This is going to be the normal practice as we move forward.”

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FDA = U.S. Food and Drug Administration

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**Capsule**

**Rev-erb-α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy**

The nuclear receptor Rev-erb-α modulates hepatic lipid and glucose metabolism, adipogenesis and the inflammatory response in macrophages. Woltdt et al. show that Rev-erb-α is highly expressed in oxidative skeletal muscle and that its deficiency in muscle leads to reduced mitochondrial content and oxidative function, as well as upregulation of autophagy. These cellular effects resulted in both impaired mitochondrial biogenesis and increased clearance of this organelle, leading to compromised exercise capacity. On a molecular level, Rev-erb-α deficiency resulted in deactivation of the Lkb1-Ampk-Sirt1-Ppargc-1α signaling pathway. These effects were recapitulated

in isolated fibers and in muscle cells after knockdown of the gene encoding Rev-erb-α, *Nr1d1*. In complementary experiments, Rev-erb-α overexpression in vitro increased the number of mitochondria and improved respiratory capacity, whereas muscle overexpression or pharmacological activation of Rev-erb-α in vivo increased exercise capacity. This study identifies Rev-erb-α as a pharmacological target that improves muscle oxidative function by modulating gene networks controlling mitochondrial number and function.

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Eitan Israeli

**“It is a glorious thing to be indifferent to suffering, but only to one’s own suffering”**

Robert Lynd (1879-1949), Irish journalist and Sinn Fein activist