Health Policy xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

A review of international coverage and pricing strategies for personalized medicine and orphan drugs

Irina Degtiar[a,b,*]

[a] Harvard T.H. Chan School of Public Health, 655 Huntington Ave., Boston, MA 02115, USA
[b] University of Michigan, Ann Arbor, School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form 12 August 2017
Accepted 8 September 2017

Keywords:
Precision medicine[MeSH]
Orphan drug production[MeSH]
Insurance, health, reimbursement[MeSH]
Pricing

ABSTRACT

Background: Personalized medicine and orphan drugs share many characteristics—both target small patient populations, have uncertainties regarding efficacy and safety at payer submission, and frequently have high prices. Given personalized medicine's rising importance, this review summarizes international coverage and pricing strategies for personalized medicine and orphan drugs as well as their impact on therapy development incentives, payer budgets, and therapy access and utilization.
Methods: PubMed, Health Policy Reference Center, EconLit, Google Scholar, and references were searched through February 2017 for articles presenting primary data.
Results: Sixty-nine articles summarizing 42 countries' strategies were included. Therapy evaluation criteria varied between countries, as did patient cost-share. Payers primarily valued clinical effectiveness; cost was only considered by some. These differences result in inequities in orphan drug access, particularly in smaller and lower-income countries. The uncertain reimbursement process hinders diagnostic testing. Payer surveys identified lack of comparative effectiveness evidence as a chief complaint, while manufacturers sought more clarity on payer evidence requirements. Despite lack of strong evidence, orphan drugs largely receive positive coverage decisions, while personalized medicine diagnostics do not.
Conclusions: As more personalized medicine and orphan drugs enter the market, registries can provide better quality evidence on their efficacy and safety. Payers need systematic assessment strategies that are communicated with more transparency. Further studies are necessary to compare the implications of different payer approaches.

1. Introduction

Personalized medicine shares many similarities with orphan drugs: drugs that treat diseases affecting small populations. It aims to provide "the right patient with the right drug at the right dose at the right time," which in the context of drugs, in contrast to traditional "one-size-fits-most" therapies, uses an individual's genomic and clinical information to choose an appropriate drug and dose that optimizes efficacy and minimizes adverse events. Personalized medicine stratifies each disease, and its market, into smaller subtypes – a process termed "salami slicing," creating a monopoly environment within each disease subgroup [1,2]. As a result, similar challenges are faced by both orphan drugs and personalized medicine therapies. A small market makes it difficult to accrue sufficient sample sizes for clinical effectiveness studies. Furthermore, given the small market, without high prices, the financial incentives to develop these drugs are limited. However, allowing for high drug prices may make these treatments inaccessible to those needing them. Given these similarities and orphan drugs' longer time on the market, payers may be able to use their experiences with orphan drugs to inform pricing and reimbursement strategies for personalized medicine, a connection which has been little-explored in the literature beyond editorials.

Orphan drugs came into the spotlight with the Orphan Drug Act (ODA) of 1983 in the United States (US), which aimed to address the challenges of developing therapies for rare disease via financial incentives. For drugs targeting diseases that affect less than 200,000 Americans (or those that affect more than 200,000 individuals but aren't expected to recuperate costs of development and marketing), the ODA provides 7-year market exclusivity, tax credits, research grants, and expedited approval [3]. With these combined incentives, in the 20 years following the act, 249 new orphan drugs came to market, compared to the 38 approved prior to 1983 and over

* Corresponding author at: Harvard T.H. Chan School of Public Health, 655 Huntington Avenue, Building 2, 4th Floor, Boston, MA 02115, USA.
E-mail address: idegtiar@g.harvard.edu

http://dx.doi.org/10.1016/j.healthpol.2017.09.005
0168-8510/

600 are FDA-approved as of 2017 [4,5]. The Rare Diseases Act of 2002 further increased research and investment in this field [6]. Similar legislature has been adopted by other countries, such as EC No 141/2000 and No 847/2000 in the European Union (EU) (2000), and legislation in Singapore (1991), Japan (1993), Australia (1997), Taiwan (2000), and South Korea (2003) [7–9]. In the EU, these regulations established the orphan drug designation, created a committee within the European Medicines Agency (EMA), and created marketing and development incentives. Patient advocacy groups such as NORD in the US, EURORDIS in the EU and CORD in Canada have also helped bring orphan diseases into the public research agenda. In 2004, 15 orphan drugs were on the market in the EU; 94 are now authorized as of 2017 [10].

Many of the approved orphan drugs resulted in large net profits to pharmaceutical companies, leading to criticism of the act [11]. This experience highlights the importance of balancing incentives and the importance that payers, in addition to regulatory agencies, play in the market balance. Now, thirty years after the passage of the ODA, most payers admit to being concerned about orphan drugs but having no plan in place to deal with them or economic assessment tools to address their cost [12]. Their lack of strategy stems from a small budget impact and the difficulty of ascertaining value, since small patient sizes make evidence development a challenge and a lack of alternative therapies makes cost-effectiveness analysis difficult.

Personalized medicine faces many of the same challenges, often compounded with the added cost and complexity of a "companion diagnostic" that tests a much larger base population for therapy eligibility. In less than a decade, personalized medicine expanded from just 13 approved personalized medicine treatments and diagnostics in 2006 to 113 in 2014 in the US [13]. Former President Obama's Precision Medicine Initiative of 2015 sought to prioritize technology-driven biomedical advances and create a million-person database to facilitate future research [14]. With the rising importance – and budget impact – of personalized medicine, the current pricing and coverage approach will need to be redefined. More clarity is needed on different pricing and coverage strategy alternatives and their implications. Payers' experience with orphan drug reimbursement can be used to inform the decision-making process for personalized therapies targeting small populations.

Existing literature provides an overview of strategies for orphan drugs and personalized medicine individually but has not yet reviewed evidence across both for shared learning. Nor has there been a comprehensive summary of orphan drug or personalized medicine reimbursement and pricing strategies' impacts on three of the major stakeholders: patients, manufacturers, and payers. This review hence seeks to summarize and compare evaluation tools and criteria used by different countries for making coverage and pricing decisions for personalized medicine and orphan drugs. It presents both public and private payers' coverage and pricing strategies and evidence on implications for therapy development incentives, payer budgets, and therapy access and utilization. The combined perspective aims to inform how payer strategies could adopt in the face of the changing market.

2. Methods

A literature review was conducted to compare payers' (1) evaluation criteria, (2) pricing and coverage strategies, and (3) patient cost-sharing for orphan drugs and personalized medicine therapies, as well as these strategies' implications for (4) therapy development incentives, (5) payer budgets, and (6) therapy access and utilization. The search was conducted in PubMed, the Health Policy Reference Center (HPRC), and EconLit. Presence of the following keywords in the abstract, title, or (for HPRC) subject terms was used to identify relevant articles, through a combination of (1 OR 2) AND 3:

1. Personalized medicine OR pharmacogenetics [MeSH] OR personalized healthcare OR precision medicine OR targeted therapies OR individualized medicine [MeSH].
2. Orphan drug OR orphan drug production [MeSH].
3. Pricing OR payer* OR coverage OR insurance [MeSH] OR reimbursement.

Filters were included to ensure that studies were published in English prior to February 28, 2017 and had an abstract. This search was supplemented by an ad-hoc search of the grey literature in Google Scholar and a review of references in identified articles. Because definitions of orphan drugs and personalized medicine can vary by country and region, papers were included if their authors described the therapy/therapies as an "orphan drug", treating a "rare" disease, individualizing treatment based on a patient's genomics, predicted response or risk, pertaining to "precision medicine" or to pharmacogenetics. Studies were included if they presented primary data and pertained to personalized medicine or orphan drug therapy evaluation criteria used by payers, coverage and pricing strategies, where they have been implemented, and/or their impact on therapy development incentives, payer budgets, and therapy access and utilization. Studies' titles and abstracts were first screened; relevant studies' full text was then screened for addressing the above criteria.

Information was abstracted with respect to (a) publication details (author, title, year, journal, author affiliations, study funding source); (b) study design (study type, country or area, subjects, sample size); (c) payer strategy (evaluation criteria, other aspects of coverage/pricing strategy, patient share of costs, whether the payer is public or private); (d) impacts of payer strategy on therapy development incentives, payer budgets, therapy access and utilization; and (e) additional author recommendations. This review first summarizes payer strategies discussed in literature then presents available evidence on their implications.

3. Results

A total of 656 non-duplicate articles were identified through PubMed, HPRC, EconLit, Google Scholar, and reference reviews. Of these, 245 passed the title and abstract screen. In a full-text screen, 176 were excluded for being irrelevant, providing no primary evidence, or not being in English, leaving 69 articles summarized in this review. Fig. 1 presents a PRISMA diagram of the search. Appendix Tables A1 and A2 of supplementary material provide a detailed summary by study of payer strategies and their implications, respectively, as well as publication details and study design.

3.1. Study designs

These studies reviewed strategies across 42 countries: the US, Australia, Canada, all 27 EU Member States, Norway, Iceland, Switzerland, Israel, the Philippines, Singapore, Malaysia, Indonesia, Vietnam, Thailand, Taiwan, and South Korea. 40 studies pertained to orphan drugs; 29 pertained to personalized medicine, and none discussed both. 39 studies discussed only public insurance systems, 13 discussed only private systems, and 17 discussed both. 49 discussed payer strategies: 35 presented data on therapy evaluation criteria, 36 discussed coverage and pricing strategies, and 9 discussed patient cost-sharing. 47 mentioned the impacts of these strategies, of which 11 mentioned implications on therapy development incentives, 20 on payer budgets, and 34 on therapy access and

Please cite this article in press as: Degtiar I. A review of international coverage and pricing strategies for personalized medicine and orphan drugs. Health Policy (2017), http://dx.doi.org/10.1016/j.healthpol.2017.09.005