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Cost of precision medicine at a referral center for cystic fibrosis

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TO THE EDITOR:

We are currently experiencing an exciting period of scientific advances in patient care. Precision medicine and personalized medicine have allowed us to dream of the ability to treat numerous diseases based on their root causes. In cystic fibrosis (CF), the recent integration of precision medicine into routine patient care has enabled the management of CFTR protein expression and has brought hope for the treatment of the disease, with improved quality of life and increased life expectancy.

In CF, precision medicine uses three US Food and Drug Administration-approved drugs, namely ORKAMBI® (lumacaftor/ivacaftor), SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), and KALYDECO® (ivacaftor), all of which are manufactured by Vertex Pharmaceuticals, Inc. (Boston, MA, USA). Substantial clinical benefits have been obtained with a novel combination therapy (VX-659–tezacaftor-ivacaftor) in comparison with placebo, with a change of 14 percentage points in percent predicted FEV_1 (FEV_1%) in individuals with one F508del mutation and one minimal function mutation, as well as a change of 10 percentage points in FEV_1% in individuals with two F508del mutations initially treated with tezacaftor-ivacaftor and subsequently treated with tezacaftor-ivacaftor plus VX-659. In addition, treatment with the triple combination therapy of VX-455–tezacaftor-ivacaftor has been tested in phase I and II clinical trials, with significant improvement in FEV_1%.[1-5]

The outcomes of CF clinical trials have been remarkable. Although the initial results obtained from precision medicine clinical trials showed only a slight improvement in FEV_1% (of < 2-4 percentage points), recent studies have shown a significant improvement in the quality of life and life expectancy of CF patients. However, the economic dimension of precision medicine, including the high cost of developing drugs and running trials, is a barrier to the use and implementation of new therapies. From the discovery of a new molecule to the clinical application of a new drug, high costs are involved. In CF, the final cost of new precision medicine drugs depends on the following: the high cost of clinical trials; lengthy timelines; difficulties in recruiting participants (because the *CFTR* genotype needs to be identified); limited clinical research capacity; strict regulations; administrative barriers; data collection and interpretation; and difficulties in maintaining and monitoring safety. In addition, health care costs rise exponentially when precision medicine is used.

Although the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, National Health Surveillance Agency) is charged with the approval and regulation of pharmaceutical drugs, public health care facilities need further authorization to dispense drugs free of charge to the population. In 2018, the Brazilian government approved the first precision medicine drug for use in CF patients in Brazil. However, the costs must be borne by the patient. The next step should be the support from the public health care system to provide the drug free of charge to all CF patients on the basis of their *CFTR* genotype. However, this raises a controversial question: How much can we afford?

In Brazil, approximately 140 patients at a referral center for CF are eligible for treatment with a precision medicine drug, with total treatment costs estimated at US$ 40,308,420 per year. The classification of *CFTR* mutations was not taken into account because the US Food and Drug Administration did not approve the use of precision medicine drugs for all *CFTR* mutations (Table 1),[6] and the costs were calculated on the basis of the US market in order to provide an international overview of the drug price. Neither our institution nor the public health care system can afford to spend that much on (treating) a single disease. A total financial support of US$ 123,710,785.70 should cover all hospital procedures, including all routine medical consultations. In addition, the cost of treating CF patients amounts to approximately one third of the total cost of maintaining hospital activities.

Some insights can help resolve the controversy over the (estimated) cost of treating a disease and pricing the priceless, i.e., the improvement of health. First, a new drug should be prescribed only for patients who will truly benefit from it, primarily on the basis of the individual response to CF drugs in nasal cell cultures (from patients with *CFTR* and modifier gene variants).[7-10] Second, all *CFTR* genotypes should be identified in order to determine whether precision medicine is feasible. Third, the government and the pharmaceutical industry should discuss costs, benefits, and a partnership for mutual benefit. Fourth, medical societies, as well as patients and their families, together with nongovernmental organizations and researchers, should discuss the possibilities of precision medicine, implementing medication adherence policies and reducing the costs of long-term therapies. Finally, precision medicine should be used in the treatment of other diseases. For example, ataluren

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Table 1. Precision medicine drugs approved for use in the treatment of cystic fibrosis at a referral center in Brazil, as well as an overview of the hospital where the referral center is located.[a]

Drug[b]	n	Monthly cost/ patient	Annual cost/ patient	Total annual cost
ORKAMBI® or SYMDEKO®[c]	57	US$ 26,880	US$ 322,560	US$ 18,385,920
ORKAMBI®	76	US$ 21,583	US$ 259,000	US$ 19,884,000
KALYDECO®	5	US$ 28,675	US$ 344,100	US$ 1,720,500
ORKAMBI® or KALYDECO®[d]	2	US$ 21,583	US$ 259,000	US$ 518,000
Total				US$ 40,308,420
Overview of the hospital where the referral center is located				
Financial support (university and health care system)		US$ 123,710,785.70 (R$ 460,000,000.00)[e]		
Number of hospital beds		419		
Number of beds in the adult ICU		409		
Number of beds in the pediatric ICU		56		
Bed occupancy rate		85%		
Number of hospitalizations		14,442 per year		
Number of medical specialties		47 (580 subspecialties)		
Number of patients receiving emergency room treatment		69,573 per year		
Number of patients receiving outpatient treatment		373,574 per year		
Geographic area of coverage		~100 cities (~5,000,000 inhabitants)		
Number of visitors		~10,000 per day		
Number of operating rooms		16		
Number of surgical procedures		15,509 per year		
Number of transplants		485 per year[f]		
Number of medical records since the first year of the hospital's inception		1,000,000		
Number of new records		~150 per day		
Number of laboratory tests		2,529,209 per year (more than 300 different types of tests)		
Number of radiological examinations		146,375 per year		
Number of nuclear medicine examinations		9,532 per year		
Number of radiotherapy cycles		47,906 per year		
Hospital pharmacy		2,313,771 units of medication + 843,265 saline bottles		
Number of blood bags used		6,730 per month		
Number of surgical gloves used		2,500,000 per year		
Number of thermometers used		60 per month		
Amount of water consumed		9,227 m^3 per month		
Amount of oxygen consumed		35,715 m^3 per month		
Number of hospital sheets used		2,000 per day		

[a]Adapted from Pereira.[6] [b]ORKAMBI®: lumacaftor/ivacaftor as 100 mg/125 mg and 150 mg/188 mg granule packets for children ≥ 2 years of age or 100 mg/125 mg and 200 mg/125 mg tablets for children ≥ 6 years of age; SYMDEKO®: tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 75 mg for patients ≥ 12 years of age with the F508del/F508del genotype; KALYDECO®: ivacaftor 150 mg, approved for use in individuals ≥ 2 years of age with at least one copy of a class III variant (E56K, G178R, S549R, K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N, R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, or D1152H). The prices of all three medications have been established by the manufacturer (Vertex Pharmaceuticals, Inc., Boston, MA, USA). [c]Values calculated for SYMDEKO®. [d]Values calculated for ORKAMBI®. [e]Calculated on the basis of the exchange rate on July 27, 2018 (US$ 1.00 = R$ 3.718). [f]No lung transplants were performed at our facility during that period. Note: At this writing, the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, National Health Surveillance Agency) has yet to approve the use of SYMDEKO® in the country. Because of that, we used the drugs approved by the US Food and Drug Administration protocol and their age recommendation for drug use in order to facilitate the comparison of our findings with those of other studies.

has been discontinued for the treatment of CF, but it is still prescribed for the treatment of Duchenne muscular dystrophy and Becker muscular dystrophy caused by nonsense mutations in the *DMD* gene.

Precision medicine gives us hope, and genome editing tools are being investigated for the treatment of CF. In the long run, gene therapy will be used as a treatment model for CF.

Is precision medicine cost-effective? Is the heavy upfront investment legitimate? What is the total cost of innovation: developing and releasing a new drug and the moral issue of pricing and profit? This letter is a reflection on the application of new therapies (using CF as model) and their financial impact on health care systems. In addition, this letter invites patients, civil society, governmental officials, and the pharmaceutical

industry to discuss the major outcomes of new therapies and markers, including quality-adjusted life years.

The *CFTR* gene was described as the cause of CF in 1989. Since then, we have dreamed of treating the root cause of the disease. We have made remarkable progress with research on phenotype variability, *CFTR* variants, and modifier genes, and we should continue to research and translate these findings into new diagnostic methods and therapies. Although high costs can be a barrier, they can be overcome through the collaborative input of all involved parties. We believe in the promise of precision medicine to improve quality of life and life expectancy, and our efforts should be geared toward allowing precision medicine to reach its full expectations.

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