The Benefits of Improving Patient Access to Innovative Diabetes Therapies in Middle-Income Countries

Introduction

Rapid economic growth combined with demographic and lifestyle changes in middle-income countries around the world are driving increased demand for high quality health care.[1] In recent years many of these countries have made serious strides toward achieving Universal Health Coverage (UHC).[2] However, in order to stem a growing tide of non-communicable diseases, middle-income countries should continue seeking ways to improve healthcare quality and access for patients across a wide range of socioeconomic status.

Globally, non-communicable diseases (NCDs) – including cardiovascular diseases, cancer, diabetes, and chronic lung diseases – kill 38 million people every year.[3] Nearly three quarters of these deaths occur in low- and middle-income countries.[4] Although some NCDs are preventable and many are treatable, they account for approximately 68% of annual deaths.[5]

Diabetes impacts over 400 million adults globally, 90% of whom suffer from Type 2 diabetes. It accounts for 5 million deaths every year,[6] making it one of the medical diagnoses associated with the highest global disease burdens. This number of cases is growing rapidly – by 2040, nearly 650 million people worldwide will be diagnosed with diabetes.[7] Type 2 diabetes disproportionately impacts low- and middle-income countries, where nearly 80% of diabetes-related deaths occur annually.[8]

In middle-income countries, governments have recognized that the growing burden of Type 2 diabetes presents a significant threat to the health and productivity of their citizens and to their continued economic growth. This report focuses on six middle-income countries: Brazil, China, India, Indonesia, Mexico, and South Africa. In these countries the prevalence of Type 2 diabetes is high and growing in spite of ongoing healthcare system reforms designed to counter this rising burden (Fig. 1 and Table 1).

The development of new treatments for Type 2 diabetes has paralleled the global increase in Type 2 diabetes, and corresponding treatment guidelines have emerged to provide evidence-based standards to guide the selection of appropriate therapies.[9]

With appropriate treatment and disease management, progression of Type 2 diabetes and its associated morbidity and mortality can be prevented or substantially reduced and early interventions can prevent the disease altogether. However, in many middle-income countries the lack of access to consistent, optimal care leads to much higher rates of diabetes-related mortality than is observed in more developed health systems – such as those in the Organization for Economic Cooperation and Development (OECD) – that better integrate access to high quality care and availability of the full range of treatment options throughout the continuum of care (Fig. 2).

Table 1. Type 2 Diabetes Clinical Burden in Select Middle-Income Countries

	2000		2013		2035	
Country	**# of Cases**	**Prevalence**	**# of Cases**	**Prevalence**	**# of Cases**	**Prevalence**
China	20,800,000	1.6%	98,400,000	7.2%	142,700,000	10.1%
India	31,700,000	3.0%	65,100,000	5.1%	109,000,000	6.9%
Indonesia	8,400,000	4.0%	8,500,000	3.4%	14,100,000	4.6%
Brazil	4,600,000	2.6%	11,900,000	5.8%	19,200,000	8.2%
Mexico	2,200,000	2.1%	8,700,000	7.0%	15,700,000	10.2%
South Africa	800,000	1.8%	2,646,000	4.9%	3,900,000	5.8%

Note: Values for 2000 and 2013 are observed; Values for 2035 are projected.

Sources: WHO, Global Health Observatory; World Bank, Population Estimates and Projections Database; Guariguata, L. *et. al.* Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice* 103 (2014): 137-149.

Figure 1.   Growth of Type 2 Diabetes Burden in Select Middle-Income Countries 2000-2035
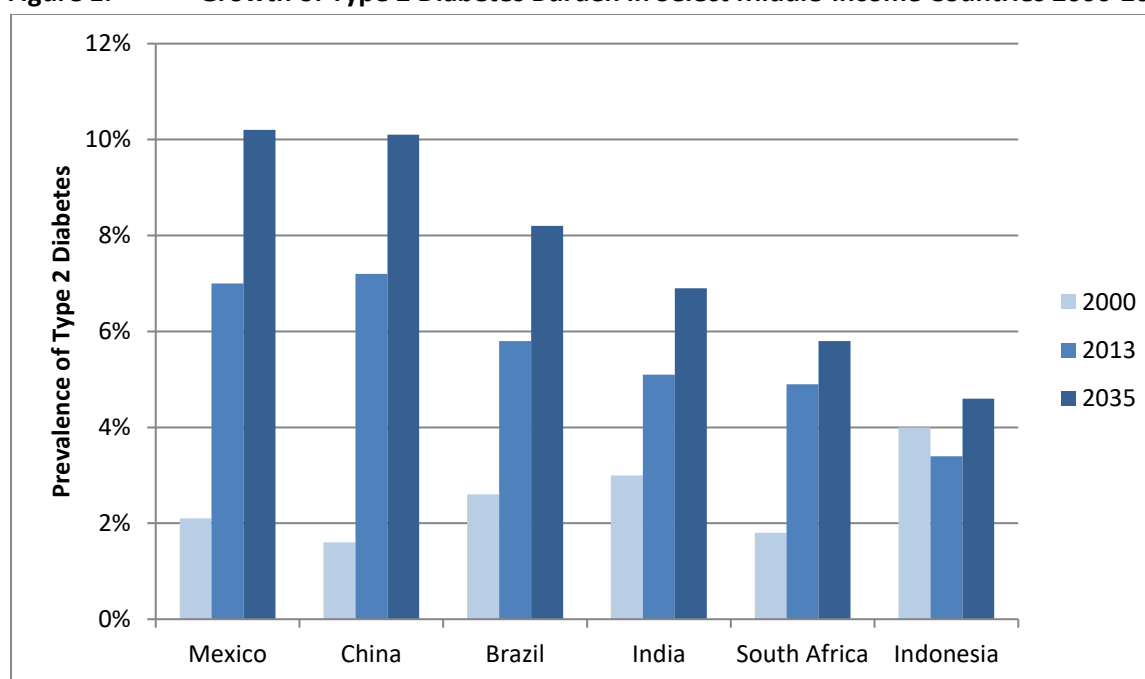
Note: Values for 2000 and 2013 are observed; Values for 2035 are projected.

Sources: WHO, Global Health Observatory; World Bank, Population Estimates and Projections Database; Guariguata, L. *et. al.* Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice* 103 (2014): 137-149.

Figure 2. **Type 2 Diabetes-Related Mortality Select Middle-Income Countries and the Organisation for Economic Co-operation and Development (OECD)**
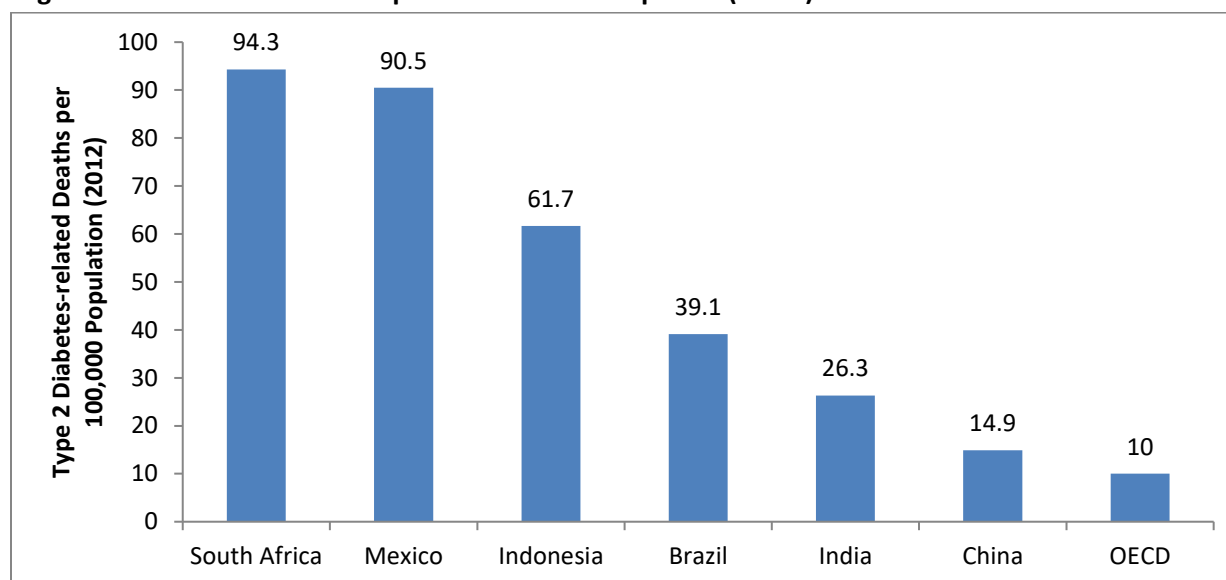
Source: WHO, Global Health Observatory.[i]

Patient access to appropriate treatment for Type 2 diabetes is thus critically important to improving the health, and by implication, the economic prosperity of these countries. This report highlights the value of improved access to care in middle-income countries with high burden of Type 2 diabetes, which can be achieved through both enhanced care management and increased access to available innovative pharmaceutical products and other treatment resources for patients diagnosed with Type 2 diabetes.

Innovations in Diabetes Treatments

Innovations in the diabetes care paradigm over the past decade include the introduction of two new classes of oral diabetes medications (dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors), glucagon-like peptide-1 (GLP-1) receptor agonists, as well as novel insulin-based products. DPP4-inhibitors and SGLT-2 inhibitors lower blood glucose levels through novel mechanisms of action, allowing for use of these agents in combination with other common diabetes medications.

Potential Benefits of Innovative Diabetes Therapies. Type 2 diabetes is a progressive disease, which means that medications initially effective at controlling a patient's blood glucose may lose efficacy over

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[i] Note: China, India, and Indonesia were not among countries recognized as having "high quality death registration data" from 2012. Values in the table are WHO estimates based on data from available national sources and years other than 2012. For more information regarding methodology and data limitations in the WHO's morbidity data, *see* World Health Organization Department of Health Statistics and Information Systems, "WHO Methods and Data Sources for Country-level Causes of Death 2000-2012," *Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2014.7*, 3-15 (2014). Available at: http://www.who.int/healthinfo/statistics/GlobalCOD_method.pdf.

time. When this occurs, access to additional therapies is critical to maintaining diabetes control.[10] This observation highlights the medical need for new medicines with improved efficacy and safety profiles, including agents that can favorably impact non-insulin parameters, such as weight and blood pressure.[11,12] Improved patient adherence to prescribed regimens is another potential benefit of new diabetes medications. For example, the introduction of second-generation sulfonylurea agents, which are more potent than first-generation agents, allows patients to take smaller and less frequent doses per day. Furthermore, these next generation agents are associated with fewer troublesome side effects and reduced potential for interaction with other commonly used medicines (e.g., aspirin).[13]

More recent advances in targeted therapy for diabetes (e.g., DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists) offer significant clinical advantages. All of these medications act in new ways to treat diabetes in patients whose disease is inadequately controlled on currently available regimens that are anchored by older therapies. DPP-4 inhibitors improve pancreas beta-cell survival, lower risk of hypoglycemia, exhibit weight neutrality, and reduce gastrointestinal side effects and discomfort.[14] A growing number of studies points to the potential benefits of DPP-4 inhibitors for Asian and South Asian populations, including Chinese, Indians, and Indonesians who are characterized by insulin secretory defects, lower beta cell mass, and impaired beta cell function.[15,16] Studies of Chinese, Indian, and Indonesian patients further confirmed DPP-4 inhibitors as an effective alternative to metformin and sulfonylurea.[17]

Long-acting GLP-1 receptor agonists have been shown to significantly decrease body weight, improve glycemic control, and reduce systolic blood pressure.[12] These treatments would be particularly valuable in countries such as Mexico and Brazil where the high rates of patients presenting as overweight or obese drive the rising prevalence of diabetes.[18] Further, the increased potency of GLP-1 receptor agonists in particular has allowed for once-weekly treatments. This has the potential to increase adherence[19] particularly in middle-income countries, where patient navigation and adherence monitoring is made more difficult by significant infrastructure deficiencies and low access to care.[20]

The mechanism of SGLT-2 inhibitors corrects hyperglycemia independently of insulin, delivering efficacy even in patients with a degree of insulin resistance or loss of beta-cell function. Weight loss and blood pressure reduction associated with the diuretic effect of SGLT-2 inhibitors are also thought to be advantageous.[21] Novel insulins such as detemir and glargine have also demonstrated additional benefit. For example, a study demonstrated that detemir reduced HbA1c to target levels of 7% in 70% of patients, similar to NPH, but without the associated risk of hypoglycemia and weight gain.[22]

Access to Diabetes Treatments in Middle-Income Countries

Access to high quality treatment and disease management for Type 2 diabetes requires a combination of factors to work in coordination including:

- An effective primary care infrastructure for prevention, screening, and diagnosis;
- Evidence-based clinical guidelines to ensure coordinated prevention and appropriate treatment throughout the continuum of care; and

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- Meaningful patient access to the full range of recommended therapies – access to the right medication(s) at the right time in the progressive disease continuum.[23]

In all of the studied countries, governments have committed to develop primary care infrastructure and implement clinical guidelines, though these objectives remain only partially realized.[24] Reimbursement for innovative therapies in these countries is also insufficient to provide appropriate patient access to new treatments.[25]

Primary Care for Diabetes Treatment. The lack of consistent primary care and disease management for Type 2 diabetes was recognized as a challenge in all of the countries we evaluated. As such, their governments have consistently announced reform plans to improve access to primary care and disease management as a key pillar of their efforts to stem the increasing burden of NCDs (Table 2). Patients lacking comprehensive primary care have historically sought care in hospitals on an ad-hoc basis, which results in inconsistent prescribing, as well as lack of follow-up to ensure appropriate lifestyle modification and medication adherence.[26] High quality disease management, in addition to improved access to innovative therapies, would significantly improve clinical and economic outcomes for patients with Type 2 diabetes.[27]

In 2012, China publically recognized the need for action to improve primary care and NCD prevention efforts through the implementation of a National Plan for NCD Prevention and Treatment. [28] This national plan, developed by the Chinese Ministry of Health and fourteen other ministries set a number of measurable targets aimed at improving prevention and monitoring of NCD risk factors at the primary level. A major goal of the plan, specifically related to prevention of Type 2 diabetes was that 80% of primary care hospitals should be equipped to monitor blood glucose levels.

Similarly, India developed its National Action Plan and Monitoring Framework for Prevention and Control of NCDs in 2012 as part of a biennial workplan with the WHO, which sets targets for halting the growth of Type 2 diabetes by 2025 and points to a number of primary care objectives as a means of achieving this goal. Specific commitments to be implemented include the development of NCD prevention clinics at 700 Community Health Centers across India and Type 2 diabetes screening for all persons above the age of 30.[29]

In Indonesia, the Ministry of Health's Directorate published its National Action Plan for the Prevention and Control of NCDs in Indonesia 2015-2019.[30] The plan targets a 10% reduction in levels of hyperglycemia to reduce the burden of Type 2 diabetes. The strategy emphasizes health system strengthening including investment in primary care and improving access to medicines. One pillar of the strategy rests on the development of public awareness and advocacy partnerships, including public-private partnerships.

Brazil's Strategic Action Plan to Prevent and Control NCDs[31] sets specific targets for expanding Type 2 diabetes screening to the primary care setting through community hospitals and pharmacies to 60% of the population. In addition to investing in its primary care infrastructure, the plan also mobilized

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resources to develop a telehealth network allowing for remote provision of primary care to underserved areas. Implementation of the telehealth initiative and the broader primary care infrastructure development plan have been slow however.[32]

In Mexico, the national government included the prevention of NCDs and Type 2 diabetes in particular in its national strategic plan for 2013-2018.[33] The plan sets out specific targets for the reduction of obesity and other risk factors common to Type 2 diabetes, and tasks the Health Ministry and national insurance funds with setting screening targets and requirements for Type 2 diabetes.

 South Africa's National Strategic Plan for the Prevention and Control of Non-Communicable Diseases[34] points to the need for increased investment in training for primary care providers and sets increased screening targets at 5% growth overall and 30% growth in the proportion of screening conducted by primary care providers by 2017.

Table 2.   Government Commitments to Improve Primary Care for Diabetes in Selected Middle-income Countries

Country	Commitments					Implementation Status[35]
	Expansion of Primary Care Infrastructure	Type 2 Diabetes Screening Targets	Obesity and Other Risk Factor Prevention	Objectives for Disease Control Under the National Plan	Other Features	
China[36]	+	+	-	Control blood-glucose levels for 60% of managed patients	80% of community hospitals equipped to monitor blood glucose levels	Partial
India[37]	+	+	+	Halt the rise of uncontrolled diabetes by 2025	Develop and conduct evidence-based public health campaign for early detection and treatment of obesity and diabetes	Partial
Indonesia[38]	+	+	+	Decrease prevalence of patients with uncontrolled blood glucose by 10%	Explicit prioritization of public-private partnerships to raise the profile of NCD prevention and control	Partial
Brazil[39]	+	+	-	-	Expand primary care availability for diabetes treatment and screening to 60% of the population	Partial
Mexico[40]	-	+	+	-	Requires all insured individuals to undergo consultation to identify risk factors, detect diabetes and proceed to treatment	Partial
South Africa[41]	+	+	+	Increase number of patients with controlled blood glucose levels 30% by 2017	Train health workers to identify people at risk and to conduct screening

Increase screening within school health services | Partial |

+ Indicates has made specific commitment. **-** Indicates country has not made specific commitment.

Clinical Guidelines for Diabetes. Clinical guidelines are an important disease management tool for ensuring consistent, evidence-based access to appropriate interventions throughout the continuum of diabetes care. These guidelines are also critical to managing the increasing clinical and economic burden of diabetes on society as well as on individual patients and their families.[42] Local and international medical organizations have developed clinical guidelines to support decision-making on the use of glucose-lowering agents, including oral and injectable agents used either alone or in combination. Guidelines based on clinical evidence are a way to standardize clinical practice, and they can assist in improving healthcare quality and outcomes. The International Diabetes Federation (IDF) is an umbrella organization of over 230 national diabetes associations in 170 countries and territories that represents the interests of people with diabetes and those at risk for developing the disease. In 2005 and 2012, IDF developed global diabetes guidelines through consideration of evidence-informed consensus on a therapeutic algorithm for treating Type 2 diabetes. Screening, diagnosis, and monitoring guidelines have also been developed. However, for this white paper, the focus is pharmacologic therapy and associated recommendations for Type 2 diabetes care. As new therapies receive regulatory approval, guidelines are updated based on clinical evidence to facilitate timely incorporation of innovative treatments in routine patient care.

In all of the studied countries, national treatment guidelines for Type 2 diabetes have been developed either by government agencies or by clinical societies. In China, the most influential treatment guidelines for Type 2 diabetes are maintained by the China Diabetes Society – an organization sponsored by the National Health and Family Planning Commission but headed by clinicians recognized for their expertise. India's National Standard Treatment Guidelines for Type 2 diabetes Mellitus, its most authoritative guidelines, are developed and maintained by the Indian Council of Medical Research (ICMR), a network of clinicians and academics with recognized expertise in treatment of various disease areas. The Indonesian Endocrinology Society, a medical society housed in the University of Indonesia's School of Medicine, maintains its Consensus Guidelines for the Control and Prevention of Type 2 Diabetes Mellitus, which were last updated in 2011.[43] The Brazilian Diabetes Society guidelines are maintained by specialists and aim to adapt current standards of care from leading diabetes societies in the U.S. and Europe. South Africa's most recognized and influential guidelines are developed by the Society for Endocrinology, Metabolism, and Diabetes of South Africa, an organization open to all persons interested in endocrinology, metabolism and diabetes, which develops guidelines through a committee of leading South African endocrinologists.[44] In Mexico, Type 2 diabetes national guidelines are maintained by the Ministry of Health and the Mexican Social Security Institute (IMSS).[45]

As demonstrated in Table 2 below, with the exception of India's National Treatment Guideline, there is significant alignment between the local guidelines and the IDF guideline in terms of the need for innovative biopharmaceutical therapies and novel insulins, although there is some variation with regard to their relative positions in the treatment sequence.

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Table 3. Comparison of National Treatment Guidelines for Type 2 Diabetes in Select Middle-Income Countries

Therapeutic Class	2012 IDF Guideline	National Guidelines					
		China	India	Brazil	South Africa	Mexico	Indonesia
Metformin	First-Line	First-Line	First-Line	First-Line	First-Line	First-Line	
Sulfonylurea	Alternative First-Line	Alternative First-Line	Alternative First-Line	Alternative First-Line	Alternative First Line	Alternative First-Line	Alternative First-Line
α-glucosidase inhibitor			Alternative Second-Line	N/A		N/A	
Sulfonylurea	Second-Line	Second-Line	N/A	Second-Line	Second-Line	Second-Line (in combination with metformin)	
α-glucosidase inhibitor	Alternative Second-Line		Alternative Second-Line	N/A		N/A	
Thiazolidinedione (TZD)			Second-Line	N/A		Alternative First-Line	
Dipeptidyl peptidase-4 inhibitor: sitagliptin / saxagliptin / linagliptin / alogliptin			N/A	Alternative Second-Line	Alternative First-Line	Alternative First-Line	
SGLT-2 inhibitor*: canagliflozin / dapagliflozin / empagliflozin	Alternative Second-Line	N/A			Alternative Second-Line	N/A	N/A
NPH (insulin) (e.g. Humulin N)	Third-Line (used alone or in combination with metformin)	Third Line (basal+/- prandial insulin/premix insulin analogue = 4th line)	Third-Line	Third Line			Third-Line
Glargine (insulin) (Lantus)						Third-Line	Third-Line
Detemir (insulin) (Levemir)							Third-Line
Biphasic (insulin) (e.g. Humalog Mix50; NovoMix)		Fourth-Line			Third-Line (in combination with metformin and sulfonylurea)	N/A	Third-Line
GLP-1 receptor agonists (Victoza – liraglutide)	Alternative Third-Line	N/A	N/A	Alternative Second-Line	Alternative Second-Line	Alternative Second-Line (in combination with metformin)	Third-Line
Or addition of third oral agent (α-glucosidase inhibitor, DPP-4, TZDs)		N/A	N/A	Third-Line	Third-Line	N/A	Alternative Second-Line

Note: N/A indicates that this molecule is not mentioned in the guideline.

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Although international and local clinical treatment standards are in alignment, guidelines are not consistently followed, either due to lack of physician education or lack of availability of certain therapies. In India, the national treatment standard is not recognized as authoritative. The lack of a nationally recognized guideline drives wide variance in clinical practice and a recognized "clinical inertia," or delay in intensifying disease management, including initiation of insulin therapy, when patients fail to achieve evidence-based treatment goals.[46,47] In Indonesia general practitioners have a high awareness of national treatment guidelines. However, adherence of the practitioners to the guidelines' recommendations is low in practice, because of a lack of insurance coverage for internationally accepted screening standards and a lack of reimbursement for therapies such as first generation sulfonylurea therapies.[48] Similarly, in Brazil, inconsistency with regard to the availability of first-line treatments such as metformin across regions drives lower adherence to national primary care guidelines.[49] Adherence to second, third and fourth-line treatment recommendations is hindered by a lack of patient access to specialist care and low levels of reimbursement for newer treatments.[50] In South Africa, studies have shown that clinicians adhere to national treatment guidelines in primary care settings less than 60% of the time, citing overwhelming case loads and a lack of screening and diagnostic resources as well as weak linkages to specialist care.[51]

Availability of Innovative Diabetes Therapies. Although innovative therapies have the potential for important clinical and economic impacts, lengthy regulatory approval processes significantly delay their availability to clinicians and patients in all of the studied countries.[52] Even when diabetes therapies are available for use in middle-income countries, often restrictions on reimbursement exist which limit access to these medicines.[53] Many newer medicines are not reimbursed at all.[54] When medications are absent from national formularies or restrictions are placed on their reimbursement, patient access to meaningful coverage for these therapies is impeded. Table 4 summarizes approval and reimbursement status of agents included in the most recent IDF guidelines.

Table 4. Comparison of Approval and Reimbursement for Type 2 Diabetes in U.S. Middle-Income Countries

Therapeutic Class	2012 IDF Guideline	U.S.[ii] (FDA Approval Year)	Reimbursement					
			China	India	Indonesia	Brazil	South Africa	Mexico
Metformin	First-Line	Yes (1994)	Yes	Yes	Yes	Yes	Yes	Yes
Sulfonylurea	Alternative First-Line	Yes (1958)	Yes	Yes	Yes	Yes	Yes	Yes
α-glucosidase inhibitor		Yes (1995)	Yes	No	Yes	No	No	Yes
Sulfonylurea	Second-Line	Yes (1958)	Yes	Yes	Yes	Yes	Yes	Yes
α-glucosidase inhibitor	Alternative Second-Line	Yes (1995)	Yes	No	Yes	No	No	Yes
Thiazolidinedione (TZD)		Yes (1999)	Yes	Yes	Yes	No	No	Yes
Dipeptidyl peptidase-4 inhibitor:								
sitagliptin		Yes (2006)	No	No	No	No	No	No
saxagliptin		Yes (2009)	No	No	No	No	No	No
linagliptin		Yes (2011)	No	No	No	No	N/A	No
alogliptin		Yes (2013)	No	No	N/A	N/A	N/A	No
SGLT-2 inhibitor:								
canagliflozin	*Alternative Second-Line (US ONLY)**	Yes (2013)	N/A	No	N/A	No	N/A	No
dapagliflozin		Yes (2014)	N/A	N/A	N/A	No	N/A	No
empagliflozin		Yes (2014)	N/A	N/A	N/A	No	N/A	No
NPH (insulin) (e.g. Humulin N)	Third-Line *(used alone or in combination with metformin)*	Yes (1982)	Yes	No	Yes	Yes	Yes	Yes
Glargine (insulin) (Lantus)		Yes (2000)	Yes	No	Yes	Yes	No	Yes
Detemir (insulin) (Levemir)		Yes (2005)	Yes	No	Yes	Yes	No	No
Biphasic (insulin) (e.g. Humalog Mix50; NovoMix)		Yes (1996)	Yes	Yes	Yes	No	No	Yes
GLP-1 receptor agonists (Victoza – liraglutide)	Alternative Third-Line	Yes (2010)	No	No	No	No	No	No
Or addition of third oral agent (α-glucosidase inhibitor, DPP-4, TZDs)		Yes	Yes	Yes	Yes	No	No	Yes

Notes: "Yes" indicates the drug is approved and reimbursed; "No" indicates the drug is approved and not reimbursed; "N/A" means the product is not available in the country. For India, "Yes" indicates that the drug is included on most of India's state level formularies on a population-weighted basis. India does not currently provide national level public reimbursement for medicines.

Sources: IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015); FDA, Drugs@FDA Database.

[ii] U.S. Reimbursement is defined as the availability of agents through Medicare using the 2015 Medicare Formulary Reference File as the U.S. does not have a national drug list

As Table 4 shows, there is strong alignment between international and national clinical guidelines regarding appropriate treatment algorithms for patients with Type 2 diabetes. These algorithms include the incorporation of new therapeutic classes. However, new classes of medicines face higher regulatory and reimbursement hurdles in the studied countries as compared to the United States. The largest gap in availability of innovative therapies is observed in second-line therapies, which include new sulfonylureas, DPP-4, and SGLT-2 medicines. Indeed, only 25% of these new medicines were reimbursed in China, Indonesia, Mexico, and Brazil, while South Africa and India do not offer public reimbursement for any innovative second-line therapies. India provides public coverage for medicines only on a limited basis and coverage varies from state to state. It does not provide coverage for any of the innovative therapies listed in the table.[55]

Even when therapies are included in national formularies, they may not be covered in all regions within a country due to localized and/or fragmented public reimbursement systems. In China, for example, provinces make their own reimbursement lists which may vary as much as 15% from the national list for urban residents.[56] In some cities, particularly in China's wealthier costal region, patients enjoy coverage beyond what is specified by the NRDL. In contrast, rural patients, who fall under the New Rural Cooperative Medical Insurance Scheme (NRCMS), often have to pay out-of-pocket for medicines because the benefits provided by the NRCMS are much more limited.[57] In Mexico, the two largest insurance schemes (Mexican Social Security Institute (IMSS) and Institute for Social Security and Services for State Workers (ISSSTE)) offer varying coverage, and this inconsistency is compounded at the hospital level.[58] As previously stated, inconsistent access to treatments throughout the treatment paradigm negatively impacts clinician adherence to treatment guidelines, ultimately limiting patient access to appropriate care.

Availability is also restricted at the hospital level in many of the countries, compounding the problem of inconsistent availability. For example, hospital formularies in China frequently do not feature medications that are included on the National and Provincial reimbursement lists.[59] Similarly, although healthcare and medications are officially intended to be provided to patients covered by Mexico's IMSS and ISSSTE insurance funds free of charge, patients are frequently forced to purchase drugs 100% out of pocket at retail pharmacies due to supply shortages, insufficient funding for outpatient treatment, and delivery delays.[60]

Overall, reduced access to the full spectrum of available diabetes therapies can result in suboptimal therapy and corresponding long-term increases in morbidity and mortality, significantly impacting the utilization of health resources for patients, their families, and the government.[61]

Impact of Access Barriers to Innovative Type 2 Diabetes Therapies

Clinical and Economic Impact of Diabetes and Comorbidities. Delayed access and reimbursement for innovative diabetes treatments can reduce physicians' ability to provide optimal individualized therapy thereby contributing to the high burden of diabetes. Well-documented complications of inadequately

controlled diabetes include microvascular complications such as nephropathy, retinopathy, and neuropathy, as well as macrovascular complications such as cardiovascular disease.[62]

In China, hypertension and diabetic retinopathy are the most significant comorbidities with Type 2 diabetes, with nearly 35% of Chinese diabetics having hypertension and 23% having diabetic retinopathy, a progressive retinal disease leading to blindness.[63] Recent studies in India report that neuropathy affects nearly one quarter of Type 2 diabetes patients, as does hypertension.[64] Over 20% of Indian diabetics suffer from nephropathy and over 16% from retinopathy.[65] Studies in Indonesia show that over 42% of Indonesian Type 2 diabetes patients suffer from retinopathy, over 60% from hypertension, and as many as 25% from incipient nephropathy.[66] South African patients showed relatively high rates of tuberculosis and HIV/AIDS infections, as well as diabetic nephropathy, micro- or macroalbumineria.[67] The main complications of diabetes in Mexico include nephropathy, cardiovascular disease, retinopathy, neuropathy and peripheral vascular disease.[68]

Globally, diabetes and its comorbidities are estimated to cost as much as $1.4 trillion every year. By 2040 this estimate rises to nearly $1.8 trillion.[69] Figure 3 below demonstrates the substantial direct medical costs caused by the high burden of Type 2 diabetes in the studied countries.

Table 5: Annual Cost of Diabetes Relative to Total Health Expenditure in Select Middle Income Countries (2015)

Country	Age-adjusted Diabetes Prevalence (1)	Adults with Diabetes (1)	Total Annual Diabetes Expenditure, Int $ PPP (1)	Annual Diabetes Expenditure per Diabetes Patient, Int $ PPP (1)	Total Annual Health Expenditure per Person, Int $ PPP (2)	Relative Health Expenditure Premium for Diabetes Patients
Brazil	8%	14,250,800	$29,185,638,400	$2,048	$1,454	141%
China	16%	109,649,100	$89,912,262,000	$820	$646	127%
India	10%	69,188,600	$22,970,615,200	$332	$215	154%
Indonesia	9%	10,021,400	$4,720,079,400	$471	$293	161%
Mexico	10%	11,463,800	$16,691,292,800	$1,456	$1,061	137%
South Africa	7%	2,286,000	$3,968,496,000	$1,736	$1,121	155%

As the prevalence of diabetes increases in middle-income countries, so will the number of patients that have diabetes-related complications or co-morbidities. The myriad of expensive complications stemming from inadequately controlled diabetes drive extremely high direct and indirect costs to health systems.[70] Nephropathy alone has been shown to increase costs of treating Type 2 diabetes patients by 75%.[71] The numbers associated with retinopathy are also staggering, particularly where studies account for the economic impact of visual impairment beyond individuals and their families.[72] The loss of productivity and earning capacity coupled with the need for increased social support heavily impacts communities and governments. Without access to medications to maintain control over diabetes, patients are likely to suffer from disease progression and complications.[73]

As the mix of co-morbidities among diabetes patients increases, so does the economic impact of poorly controlled diabetes. Patients with diabetes complications are at greater risk of catastrophic out-of-pocket expenditure (defined as payments exceeding 40% of a household's disposable income).[74] A recent study of patients in China reported that patients with Type 2 diabetes who are obese and hypertensive have twice as many physician visits, and five times as many hospitalizations and ER visits compared to patients with Type 2 diabetes who do not have these co-morbidities.[75]

Impact of Access Barriers to Innovative Diabetes Therapies. Significant delays in listing medications on national formularies, restrictions on reimbursement, and low levels of reimbursement for listed medications ultimately result in limited access and reduced treatment benefits for patients with Type 2 diabetes in all of the studied countries. This is particularly true for innovative diabetes therapies and novel insulins. Unreimbursed or inadequately reimbursed therapies also increase out-of-pocket costs and financial burden for patients and their families, which contributes to non-adherence to well-established, effective medications.[76] Researchers reported that doubling out-of-pocket costs reduced adherence to prescribed diabetes medications by 25% in a U.S. population.[77] High out-of-pocket costs have been shown to cause patients to intentionally avoid necessary care, leading to worse outcomes and higher total costs.[78] Non-adherence to medications can pose a significant societal and economic burden on economies through increased disease-related morbidity and associated healthcare spending, reduced productivity, and increased diabetes-related mortality. [79] For example, a study conducted in 2012 using data from a large U.S. managed care company reported that improved adherence to diabetes medication was associated with 13% lower odds of subsequent hospitalizations or emergency department visits.[80] The authors of the study project that improved adherence to diabetes medications could result in 699,000 emergency department visits and 341,000 hospitalizations annually in the U.S.[81] Given the high prevalence of Type 2 diabetes in the studied countries, a similar clinical and economic impact of medication adherence would be significant.

Public-Private Partnerships to Improve Access to Therapies

As discussed above, providing meaningful and appropriate patient access to high quality care for Type 2 diabetes in middle-income countries requires cooperation between government and private payers, providers, and patients. Governments have also recognized that non-governmental organizations and

biopharmaceutical companies can be effective partners in the design and execution of patient-centered clinical pathways. These organizations leverage international experience to help countries develop primary care and prevention solutions, improve linkage to care, and optimize use of innovative therapies through adherence promotion and data solutions. Below are case studies from the studied countries in which public-private partnerships are improving appropriate patient access to high quality care for Type 2 diabetes throughout the continuum of care.

China – Together on Diabetes[82]

Since 2011, this Bristol-Myers Squibb has partnered with the Chinese CDC, Chinese NGOs including the Beijing Diabetes Prevention and Treatment Association, and multinational private insurers to build capacity through patient and physician training at the primary care levels to aid the daily management of Type 2 diabetes for patients in rural and underserved areas. The initiative's focus on developing capacity at the community and primary care levels has involved the dissemination of international best practices for prevention and primary care as well as the dissemination of technologies such as self-monitoring blood glucose devices to aid in-home patient monitoring.

South Africa - HOPE Centre[83]

Located in Johannesburg, the HOPE Centre is a partnership between Project HOPE and Eli Lilly that focuses on addressing non-communicable diseases, including Type 2 diabetes, in impoverished communities. The HOPE Centre uses an innovative approach to make diabetes prevention, screening, education, and care accessible within the community. This model combines a) health promotion and screenings, b) delivery of quality primary health care, and c) support programs that promote patient self-care and prevention. The HOPE Centre utilizes community outreach, whereby teams of healthcare workers go out into the community to educate patients about diabetes as a disease, screen patients for diabetes, and refer patients to the appropriate care. Additionally, patients receive point-of-care testing for diabetes at the local clinic. Finally, support groups further educate patients about diabetes and appropriate care, including health promotion and wellness programs (cooking, exercise classes).

India – IDF Life for a Child[84]

The International Diabetes Federation (IDF) established the Life for a Child Programme in 2000 with Diabetes New South Wales and HOPE Worldwide, and is currently partnered with Boehringer Ingelheim, Eli Lilly, Johnson & Johnson, Roche, and Sanofi. With support from donors, Life for a Child provides screening, treatment, and diabetes education to children and youth across India. Contributions from donors are distributed to established diabetes centers so that they can provide ongoing clinical care and diabetes education. Specifically, the Programme aims to provide insulin and syringes, blood glucose monitoring equipment, appropriate clinical care, HbA1c testing, diabetes education, and technical support for health professionals. In 2002, Life for a Child partnered with the DREAM (Diabetes Research Education and Management) Trust in Nagpur, India to provide quality medical care, insulin and syringes, monitoring, and diabetes education to children.

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Mexico – CASALUD[85]

In partnership with the Carlos Slim Foundation – a non-profit organization founded in 2007 to create solutions impacting Mexico's most vulnerable populations – the Lilly NCD partnership has worked to standardize, monitor, and evaluate a pilot of the CASALUD model, which focuses on primary care facilities in the treatment and monitoring of chronic diseases including diabetes. CASALUD leveraged Eli Lilly's global experience to develop a strategic approach to Type 2 diabetes management, which was incorporated into Mexico's national strategy against obesity and diabetes in 2013. The program has provided valuable insight into supply chain issues for diabetes therapies, and Lilly has contributed to the development of a Six-Sigma based implementation manual supporting the scale up from two initial pilots to programs in 12 states covering nearly 800,000 Mexican patients.

Indonesia – Blueprint for Change Program[86]

Beginning in 2006, Novo Nordisk's partnership with the Indonesian government and NGOs, Indonesian clinicians and scientific centers of excellence, and the World Diabetes Foundation takes a multi-stakeholder approach to eliminating the primary barriers to high quality patient-centered diabetes care in Indonesia. The Blueprint for Change tackles five categories of barriers: Awareness, Accessibility, Availability, Affordability, and Quality of Care by bringing together international expertise and resources to promote best practices in diabetes care and management, while also developing the financing, clinical expertise, and patient and provider education necessary to ensure patient access and adherence to high quality diabetes treatment. The program has driven the development of clinical practice guidelines by the Indonesian Society of Endocrinology (PERKENI) to ensure consistent and high quality care. It has organized patient groups locally to raise awareness and provide education to patients about diabetes, its risks, prevention, and proper management. It has also supported a diabetes research center of excellence (STENO) in the development of a system of quality measures and physician monitoring tool to help physicians track their patients' progress and make appropriate treatment modifications.

Brazil -- Starbem[87]

In 2012, Sanofi consolidated several programs to improve education and access to Type 2 diabetes in Brazil into a single program, Starbem, which supports patient access through activities founded on information, education, support, access, and solutions. The program works with clinicians, patients, and accredited pharmacies to provide education about appropriate disease management and treatment, which are coordinated to ensure appropriate patient access to its innovative diabetes products through its partner pharmacies. The program is estimated to have benefited 40,000 patients.

Conclusion

Diabetes and its comorbidities have a significant clinical and economic burden not only globally, but in particular in middle-income countries. This is in part due to a lack of patient access to rapidly emerging care paradigms, including structural challenges (e.g., limited primary care) and limited availability of

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emerging treatments due to both regulatory approval and reimbursement listing barriers. Improvements in the overall healthcare infrastructure across the markets (described earlier in this paper) will address some of these issues if implemented, both promoting regular access to care and adherence to appropriate therapeutic interventions. Recent conversations with leading clinicians and government officials in China support the conclusion that improvements to primary care infrastructure and availability of high-quality treatment options through physician adherence to guidelines would significantly improve the clinical and economic burden of diabetes for millions of patients. The factors cited by these Chinese key opinion leaders are applicable in all of the studied countries.

Evidence-based guidelines, such as those published by IDF, should be reflected in treatment options made available in middle-income countries so that patients can realize the benefits of new medications. As the overall healthcare available to patients improves with proposed structural changes in care delivery, simultaneous efforts should continue to increase access to innovative diabetes medications. Improved access can be accomplished through regular review and updating of regulatory and reimbursement pathways to ensure consistency with established international treatment guidelines.

References

[1] World Bank, *Health Financing Revisited*, 250 (Pablo Gottrett & George Scheiber, eds.) (2006). Available at: http://siteresources.worldbank.org/INTHSD/Resources/topics/Health-Financing/HFRFull.pdf.

[2] World Health Organization & World Bank, *Tracking Universal Health Coverage: First Global Monitoring Report*, 46-48 (2015). Available at: http://apps.who.int/iris/bitstream/10665/174536/1/9789241564977_eng.pdf?ua=1.

[3] World Health Organization, Fact Sheet: Noncommunicable Diseases (updated January, 2015). Available at: http://www.who.int/mediacentre/factsheets/fs355/en/.

[4] Id.

[5] Id*.*

[6] International Diabetes Federation. Diabetes Atlas. 7th Edition (2015).

[7] Id.

[8] World Health Organization. Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000-2012. Geneva, WHO, 2014.

[9] International Diabetes Federation. Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes, 2012. http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf.

[10] Diabetes Myths. American Diabetes Association. http://www.diabetes.org/diabetes-basics/diabetes-myths

[11] Chao, E. C. "SGLT-2 Inhibitors: A New Mechanism for Glycemic Control." Clinical Diabetes 32.1 (2014): 4-11. Http://clinical.diabetesjournals.org. American Diabetes Association, Jan. 2014. Web. Jan. 2015.

[12] Garber AJ. Long-acting glucagen-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care*. 2011;34(S2):S279-S284.

[13] Albert Wertheimer, Richard Levy and Thomas O'Connor. Too Many Drugs? The Clinical and Economic Value of Incremental Innovations. http://www.who.int/intellectualproperty/topics/ip/Toomanydrugs2001.pdf.

[14] Brock. CM. DPP-4 Inhibitors: What Is Their Place in Therapy? US Pharm. 2010;35(5)(Diabetes suppl):8-13.

[15] Kim, Y.G. *et. al.* Differences in the Glucose-Lowering Efficacy of Dipeptidyl Peptidase-4 Inhibitors between Asians and non-Asians: A Systematic Review and Meta-Analysis. *Diabetlogia* 56 (2013): 696-708.

[16] Mu, Yu-Ming, *et. al.* Managing Diabetes in Asia: Overcoming Obstacles and the Role of DPP-IV Inhibitors. *Diabetes Research and Clinical Practice* 95:2 (2012): 179-188.

[17] Mohan, Viswanathan, *et. al.* Efficacy and Safety of Sitagliptin in the Treatment of Patients with Type 2 Diabetes in China, India, and Korea. *Diabetes Research and Clinical Practice* 83 (2009): 106-116.

[18] Barquera, Simone *et. al.* Diabetes in Mexico: cost and management of diabetes and its complications and challenges for health policy. *Globalization and Health* 9(3) (2013); Ketevan Rtveladze. Health and Economic Burden of Obesity in Brazil (2013).

[19] Guo, XH. The Value of Short- and Long-acting Glucagon-like Peptide-1 Agonists in the Management of Type 2 Diabetes Mellitus: Experience with Exenatide. 11 *Current Medical Research and Opinion*, 1-16 (2015).

[20] Gaziano, Thomas *et. al.* Increasing Prescription Length Could Cut Cardiovascular Disease Burden And Produce Savings In South Africa. *Health Affairs* 34(9) (2015): 1578-1585; Amod, Aslam *et. al.* Diabetes Guidelines and Clinical Practice: Is There a Gap? The South African cohort of the International Diabetes Management Practices Study. *Journal of Endocrinology, Metabolism and Diabetes of South Africa* 17(2) (2012): 85-90; IMS Health. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies across G20 Countries.

[21] Chao. EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control Clinical Diabetes January 2014 vol. 32 no. 1 4-11. http://clinical.diabetesjournals.org/content/32/1/4.full.

[22] Hermansen K et al. A 26-Week, Randomized, Parallel, Treat-to-Target Trial Comparing Insulin Detemir With NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin-Naïve People With Type 2 Diabetes. Diabetes Care. 2006;29(6)1269-1274.

[23] International Diabetes Federation. Global Diabetes Plan 2011-2021 (2011). Available at: https://www.idf.org/sites/default/files/Global_Diabetes_Plan_Final.pdf.

[24] International Diabetes Federation. Global Diabetes Plan 2011-2021 (2011). Available at: https://www.idf.org/sites/default/files/Global_Diabetes_Plan_Final.pdf.

[25] IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015).

[26] Beaglehole, Robert et. al. Improving the Prevention and Management of Chronic Disease in Low- and Middle-income Countries: A Priority for Primary Health Care. 372 *The Lancet*, 940-49 (2008).

[27] Pfizer. 2014. The value of drug adherence. Available at: http://www.pfizer.com/files/health/VOM_DrugAdherence.pdf

[28] http://www.chinacdc.cn/en/ne/201207/t20120725_64430.html

[29] http://pib.nic.in/newsite/efeatures.aspx?relid=76249

[30] Indonesian Ministry of Health Directorate of Non-Communicable Diseases Control, National Action Plan for Prevention and Control of Non-communicable Diseases in Indonesia 2015-2019.

[31] http://bvsms.saude.gov.br/bvs/publicacoes/plano_acoes_enfrent_dcnt_2011.pdf

[32] de Almeida-Pititto, Bianca *et. al.* Type 2 Diabetes in Brazil: Epidemiology and Management. Diabetes, Metabolic Syndrome, and Obesity: Targets and Therapy 2015: 8 (2015): 25.

[33] Gobierno de la República. Plan Nacional de Desarrollo 2013–2018. Mexico, D. F., Mexico: Presidencia de la República, 2013. Available at: http://www.diputados.gob.mx/LeyesBiblio/compila/pnd/PND_2013-2018_20may13.doc

[34] http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf

[35] International Diabetes Federation.

[36] http://www.chinacdc.cn/en/ne/201207/t20120725_64430.html

[37] http://www.searo.who.int/india/topics/cardiovascular_diseases/National_Action_Plan_and_Monitoring_Framework_Prevention_NCDs.pdf

[38] Indonesian Ministry of Health Directorate of Non-Communicable Diseases Control, National Action Plan for Prevention and Control of Non-communicable Diseases in Indonesia 2015-2019.

[39] http://bvsms.saude.gov.br/bvs/publicacoes/plano_acoes_enfrent_dcnt_2011.pdf

[40] Gobierno de la República. Plan Nacional de Desarrollo 2013–2018. Mexico, D. F., Mexico: Presidencia de la República, 2013. Available at: http://www.diputados.gob.mx/LeyesBiblio/compila/pnd/PND_2013-2018_20may13.doc

[41] http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf

[42] International Diabetes Federation. Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes, 2012. http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf.

[43] Indonesian Endocrinology Society, Konsensus Pengendalian dan Pencegahan Diabetes Mellitus Tipe2 di Indonesia (2011).

[44] http://www.semdsa.org.za/About/AboutUs.

[45] Gil-Velázquez, Luisa Estela et. al. Guía de Práctica Clínica: Diagnóstico y Tratamiento de la Diabetes Mellitus Tipo 2. 51 Rev. Med. Inst. Mex. Seguro Soc. (2013): 104-119.

[46] Kaveeshwar, S.A. & Jon Cornwall. The Current State of Diabetes Mellitus in India. Australasian Medical Journal 7(1) (2014): 45-48.

[47] For a full definition of the concept of "Clinical Inertia," *see* Shah, Baiju *et. al.*, Clinical Inertia in Response to Inadequate Glycemic Control. 28 Diabetes Care 600-606 (2005).

[48] Widyahening *et al.* Awareness, Agreement, Adoption, and Adherence to Type 2 Diabetes Mellitus Guidelines: A Survey of Indonesian Primary Care Physicians. Available at: http://www.biomedcentral.com/content/pdf/1471-2296-15-72.pdf.

[49] Bertoldi, Andrea *et al.* Epidemiology, Management, Complications and Costs Associated with Type 2 Diabetes in Brazil: A Comprehensive Literature Review. Globalization and Health 9:62 (2013).

[50] de Almeida-Pititto, Bianca *et. al.* Type 2 Diabetes in Brazil: Epidemiology and Management. Diabetes, Metabolic Syndrome, and Obesity: Targets and Therapy 2015: 8 (2015): 25.

[51] Steyn, Krisela *et. al.* Implementation of National Guidelines, Incorporated with Structured Diabetes and Hypertension Records at Primary Level Care in Cape Town, South Africa: A Randomized Controlled Trial. *Global Health Action*. 2013; 6. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3784670/pdf/GHA-6-20796.pdf.

[52] Liberti, Lawrence et. al. Characterising the Influencers of Submission Lag Time for Medicines in the Emerging Markets: Analysis of Short and Long Lag Time Factors. Centre for Innovation in Regulatory Science R&D Briefing 51 (2012).

[53] IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015).

[54] IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015).

[55] IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015).

[56] Gross, Ames. Gaining Market Access in China: The Complex Process of Drug Listing, Bidding, Pricing and Reimbursement. Regulatory Affairs Professionals Society: Regulatory Focus Features (June 11, 2014). Available at: http://www.raps.org/regulatory-focus/features/2014/06/19457/Pharmaceutical-Reimbursement-in-China/.

[57] Gross, Ames. Gaining Market Access in China: The Complex Process of Drug Listing, Bidding, Pricing and Reimbursement. Regulatory Affairs Professionals Society: Regulatory Focus Features (June 11, 2014). Available at: http://www.raps.org/regulatory-focus/features/2014/06/19457/Pharmaceutical-Reimbursement-in-China/.

[58] IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015).

[59] Gross, Ames. Gaining Market Access in China: The Complex Process of Drug Listing, Bidding, Pricing and Reimbursement. Regulatory Affairs Professionals Society: Regulatory Focus Features (June 11, 2014). Available at: http://www.raps.org/regulatory-focus/features/2014/06/19457/Pharmaceutical-Reimbursement-in-China/.

[60] IMS. Evaluating Patient Access to Type 2 Diabetes and Renal Cell Carcinoma Therapies Across G20 Countries (2015).

[61] International Diabetes Federation. Diabetes Atlas. 7th Edition (2015)

[62] Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *Am J Med.* 2010;123(3 Suppl):S3-11.

[63] Liu L, Wu X, Liu L, Geng J, Yuan Z, et al. (2012) Prevalence of Diabetic Retinopathy in Mainland China: A Meta-Analysis. PLoS ONE 7(9): e45264. doi:10.1371/journal.pone.0045264.

[64] Kaveeshwar, S.A. & Jon Cornwall. The Current State of Diabetes Mellitus in India. Australasian Medical Journal 7(1) (2014): 45-48.

[65] Kaveeshwar, S.A. & Jon Cornwall. The Current State of Diabetes Mellitus in India. Australasian Medical Journal 7(1) (2014): 45-48.

[66] Soewondo, Pradana *et al.* Challenges in diabetes management in Indonesia: A literature review. *Globalization and Health* 9 (2013): 63.

[67] Kalk, W.J. *et. al.* The prevalence and incidence of and risk factors for, micro-albuminuria among urban Africans with type 1 diabetes in South Africa: An inter-ethnic study. *International Journal of Diabetes Mellitus* 2(3) (2010): 148-153.

[68] Barquera, Simone *et. al.* Diabetes in Mexico: cost and management of diabetes and its complications and challenges for health policy. *Globalization and Health* 9(3) (2013).

[69] International Diabetes Federation. Diabetes Atlas. 7th Edition (2015)

[70] Bloom, D.E. et. al. The Global Economic Burden of Noncommunicable Diseases, 24-25 (2011).

[71] Barquera, Simone *et. al.* Diabetes in Mexico: cost and management of diabetes and its complications and challenges for health policy. *Globalization and Health* 9(3) (2013).

[72] Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *Am J Med.* 2010;123(3 Suppl):S3-11; Liu L, Wu X, Liu L, Geng J, Yuan Z, et al. (2012) Prevalence of Diabetic Retinopathy in Mainland China: A Meta-Analysis. PLoS ONE 7(9): e45264. doi:10.1371/journal.pone.0045264; Ruta LM, et al. Prevalence of diabetic retinopathy in Type 2 diabetes in developing and developed countries. Diabet Med 2013; 30: 387-398.

[73] Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *Am J Med.* 2010;123(3 Suppl):S3-11.

[74] Smith-Spangler CM, Bhattacharya J, and Goldhaber-Fiebert JD. Diabetes, its treatment, and catastrophic medical spending in 35 developing countries. *Diabetes Care*. 2012;35(2):319-326.

[75] Marco DiBonaventura. Kantar Health. (2012). The Burden of the Complicated Type 2 Diabetes Patient in China. http://www.kantarhealth.com/docs/white-papers/burden-complicated-type-2-diabetes-china.pdf?sfvrsn=12.

[76] Goldman, DP, et al. Pharmacy Benefits and the Use of Drugs by the Chronically Ill. JAMA, May 19, 2004—Vol 291, No. 19. http://www.researchcore.org/publications/docs/solomon_JAMA_chronically_ill.pdf.

[77] Goldman, DP, et al. Pharmacy Benefits and the Use of Drugs by the Chronically Ill. JAMA, May 19, 2004—Vol 291, No. 19. http://www.researchcore.org/publications/docs/solomon_JAMA_chronically_ill.pdf.

[78] de Almeida-Pititto, Bianca *et. al.* Type 2 Diabetes in Brazil: Epidemiology and Management. Diabetes, Metabolic Syndrome, and Obesity: Targets and Therapy 2015: 8 (2015): 25; Widyahening *et al.* Awareness, Agreement, Adoption, and Adherence to Type 2 Diabetes Mellitus Guidelines: A Survey of Indonesian Primary Care Physicians. Available at: http://www.biomedcentral.com/content/pdf/1471-2296-15-72.pdf.

[79] Pfizer. 2014. The value of drug adherence. Available at: http://www.pfizer.com/files/health/VOM_DrugAdherence.pdf

[80] Ashish K. Jha et al. Greater Adherence to Diabetes Drugs is linked to Less Hospital Use and Could Save Nearly $5 Billion Annually. Health Affairs, 31, No.8 (2012): 1836-1846.

[81] Ashish K. Jha et al. Greater Adherence to Diabetes Drugs is linked to Less Hospital Use and Could Save Nearly $5 Billion Annually. Health Affairs, 31, No.8 (2012): 1836-1846; Pfizer. 2014. The value of drug adherence. Available at: http://www.pfizer.com/files/health/VOM_DrugAdherence.pdf

[82] http://www.bms.com/togetherondiabetes/china-india/Pages/home.aspx.

[83] http://www.thehopecentresouthafrica.blogspot.com/p/about-us.html.

[84] http://www.idf.org/lifeforachild/countries/india

[85] Tapia-Conyer et. al. CASALUD: An Innovative Health-Care System to Control and Prevent Non-Communicable Diseases in Mexico (2014)

[86] Novo Nordisk, The Blueprint for Change Programme (March, 2013).

[87] http://gpah.bsr.org/en/case-studies/view/starbem