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Multiple Myeloma in Latin America

Supporting early and equitable
access to care to improve
patient outcomes

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About this report

Multiple Myeloma in Latin America: Supporting early and equitable access to care to improve patient outcomes is an Economist Impact white paper, commissioned by Janssen. The report provides an independent analysis of Multiple Myeloma and its growing burden in the Latin American region. The report evaluates the current care pathways for myeloma in five countries in the region (Argentina, Brazil, Colombia, Mexico and Panama), the chasm between the public and private sector, barriers for access to care, and the opportunities for improving patient outcomes. The insights in this report are based on an extensive literature review and desk research, expert panel discussions, and in-depth interviews with relevant clinical experts, scientific leaders, policy stakeholders and patient advocates. The editorial team at Economist Impact would like to thank the following individuals (listed alphabetically) for generously contributing their time and insights, which have been critical to the creation of this report:

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Executive summary

Myeloma – a growing burden in Latin America

Multiple myeloma, a disease of the elderly, is a cancer that arises in the bone marrow from plasma cells that make antibodies. The cancerous plasma cells make excessive amounts of abnormal antibodies, suppress the normal cells in the bone marrow and cause anemia, bone damage and kidney failure. The manifestations of multiple myeloma are summarized by the mnemonic CRAB, which stands for hyper Calcaemia, Renal failure, Anemia and Bone disease. Frequent infections are also common due to suppression of the normal immune system.

Multiple myeloma accounts for 10% of all blood cancers and is the 2nd most common blood cancer globally. The past three decades have seen a doubling of the global incidence and mortality of myeloma with the rise being most pronounced in lower and middle-income countries (LMICs).¹ Countries in Latin America (LATAM), including Brazil, Colombia and Mexico, have documented rising incidence and mortality due to multiple myeloma. An aging population, increased awareness of myeloma and better case identification are contributing to the increasing incidence, while lack of timely

diagnosis and inadequate access to appropriate therapies appear to be fueling the rising mortality. Projections suggest that over the next two decades, the combined number of new cases of and deaths from multiple myeloma will increase by about 1.7 to 1.8 fold, respectively in the countries of focus for this research, namely Brazil, Colombia, Argentina, Mexico and Panama.²

Gaps in myeloma care in LATAM

Lack of robust data to accurately quantify the burden of myeloma

Research studies and anecdotal evidence from experts in these countries attest to the increasing disease burden of myeloma, diagnostic delays, impaired access to treatment and resultant suboptimal outcomes. However, there is a shortage of registries and systematic data collection to corroborate this. Overburdened healthcare professionals, inadequate financial resources, decreased emphasis on research as compared to clinical care, and a lack of policy-level focus on clinical registries are the main impediments to development in this area. Harmonization of data collection across various centers is a challenge, especially in federal countries like Argentina where the practice varies across different provinces.

Delayed diagnosis, referral bottlenecks and the burden of myeloma-related complications

Despite the rising incidence of the disease, lack of awareness of myeloma and delayed presentation of patients have been consistently documented across the LATAM region. Even after patients present to primary care physicians, diagnosis of the disease is usually delayed. Myeloma, with symptoms of anemia, bone pain and kidney failure, is a great mimicker of other benign conditions and patients are often treated symptomatically for a significant period of time before multiple myeloma is suspected. Furthermore, access to simple laboratory tests to confirm the diagnosis of myeloma is lacking in peripheral centers. Experts suggest that in some cases diagnosis could take as long as six months after initial symptoms occur. Then, the lack of adequate

specialists and geographical barriers lead to long wait times for evaluation by a hematologist.

Patients with myeloma, therefore, often present to a hematologist with advanced disease, including fractures, neurological complications such as compression of the spinal cord associated with limb weakness, kidney failure and severe anemia. Such complications necessitate hospitalization, expensive therapies and prolonged rehabilitation, resulting in significant morbidity to patients and huge costs to the healthcare system. There is limited data on the economic burden of myeloma in LATAM, but the available literature suggests that about 50% of the costs are related to hospitalization for a disease that could typically be managed in the outpatient setting in the absence of complications.





The public-private divide in access to myeloma care

Treatment for myeloma has progressed manifold in the past two decades with an extensive array of novel agents now available to patients. Early treatment of symptomatic myeloma with novel therapies has shown to reduce complications and improve the overall chances of survival. While most of these novel agents have regulatory approval in the five countries of study, access is variable with huge disparities between the private and the public sector. The private sector, funded by health insurance and out-of-pocket (OOP) payments, has nearly unrestricted access to approved novel agents, while the public sector has a limited repertoire of novel therapies that are funded. Even those that are funded often require complex administrative procedures before they can be prescribed; these complexities, together with inadequate inventory management lead to significant delays

in therapy. This differential access to treatment results in disparate outcomes between the two settings with survival rates in the private sector mirroring those of high-income countries, and those in the public sector lagging far behind. Autologous stem cell transplant (use of high doses of chemotherapy and infusion of the patient's own stem cells) in young and fit patients is crucial to consolidate the response to initial novel agent therapies. Data suggest that a majority of patients in our countries of study that are seen by hematologists for myeloma treatment are transplant eligible.³ However, the capacity for transplants is limited in these countries with only a few centers being equipped to perform them. In Brazil and Argentina, transplant is more accessible to patients treated in the private sector, whereas in Colombia and Mexico, access to transplants is poor, regardless of the healthcare sector. Wait lists are long across the board; only about half of eligible patients get transplanted, significantly impacting outcomes.³

Opportunities for improvement of myeloma care in LATAM

Improving estimates of the disease burden

For successful policymaking, a good understanding of the disease burden is essential. Depending solely on population-based cancer registries is insufficient in this regard; developing robust clinical registries is key to having a holistic understanding of the gaps in the care pathway, as well as to project the future disease burden and healthcare system needs. Making myeloma a notifiable disease will be a positive step towards a more accurate estimation of the disease burden. Efforts must be taken to encourage collaborations across different institutions in various provinces within countries, and eventually at a regional level, to develop integrated clinical registries. The establishment of organizations such as the International Agency for Research on Cancer (IARC) to support regional exchanges are a definitive step in this direction. Appropriate resource allocation to secure adequate research staff to maintain these databases is also essential to ensuring sustainability.

Facilitating early diagnosis and specialist evaluations

Supporting patient organizations in their efforts to improve awareness of myeloma among the public is imperative to ensuring that early medical care is sought. Furthermore, primary care physicians need more education and training to identify the signs and symptoms of myeloma. Developing diagnostic algorithms and clinical decision-making aids would facilitate speedier evaluations and early diagnosis.

Improving laboratory services in peripheral centers should go hand-in-hand with education efforts to improve the diagnostic process. In addition, public-private partnerships could mitigate bottlenecks in specialist care in the public sector. Capacity building in primary and secondary centers to offer simple systemic myeloma therapies would also free up more resources for transplantation in the referral centers. Innovative approaches such as outpatient transplants may be considered for appropriate patients and settings.

Improving access to novel agents and closing the public-private treatment gap

Financial, administrative and logistical challenges are impediments to accessing novel agents in the public sector. Experts, interviewed as part of this research programme, suggested that disease-specific financing, value-based pricing, and establishing national cancer funds are mechanisms for mitigating financial risk and guaranteeing access. Developing models to understand the economic burden of myeloma-related complications due to delayed and inadequate access to appropriate therapies will provide a more comprehensive and accurate assessment of the value of these agents, and lead to more informed decisions about their inclusion in national formularies. Administrative and bureaucratic processes in the public healthcare system for drug approvals on a case-by-case basis should be minimized. Inventory management and procurement protocols need to be streamlined to ensure timely treatment. Equitable access to therapies should be prioritized to ensure favorable disease outcomes, regardless of care setting.

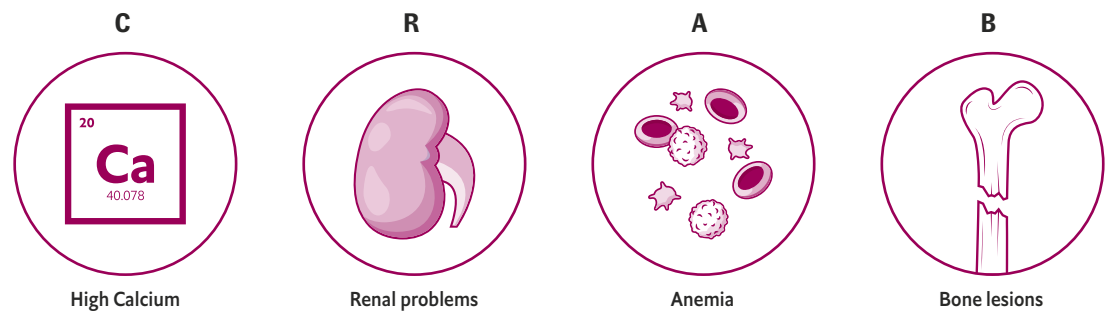
Multiple myeloma: a case of plasma cells gone rogue

Multiple myeloma is an incurable blood cancer that typically originates in the bone marrow. Myeloma accounts for 10% of all blood cancers and is the 2nd most common blood cancer globally. It is a disease of the elderly with a median age of 70 years at presentation and is more common in men. The disease originates in plasma cells in the bone marrow, some of which start multiplying excessively, often due to the acquisition of genetic mutations.⁴ Eventually, a group of cancerous plasma cells appear, which suppress the production of other normal cells in the marrow such as red blood cells, platelets and other subsets of white blood cells.

Multiple myeloma accounts for 10% of all blood cancers and ranks 2nd among blood cancers in terms of new cases per year globally.

Plasma cells produce antibodies which help fight infections. When the plasma cells become cancerous, they produce an excess of one type of abnormal antibody (monoclonal protein or

M-protein). They also release abnormal free light chains from the antibody molecules into the blood. Patients become susceptible to repeated infections due inadequate amounts of normal antibodies in their blood. The manifestations of myeloma are well summarized by the mnemonic CRAB (hyperCalcaemia, Renal failure, Anemia and Bone disease).⁵ Patients with multiple myeloma are diagnosed based on the presence of 10% or more cancerous plasma cells in the bone marrow or a plasmacytoma (abnormal collection of cancerous plasma cells outside the bone marrow) and the coexistence of one or more end-organ damage as described by the CRAB criteria. Myeloma-defining events include the presence of over 60% cancerous plasma cells in the marrow, a ratio of abnormal to normal free light chains in the blood of over 100 and the presence of at least 1 bone lesion on magnetic resonance imaging (MRI). In the absence of CRAB criteria, the presence of any myeloma-defining event, along with the appropriate bone marrow or plasmacytoma findings, is considered diagnostic. Once myeloma is diagnosed based on blood, bone marrow and imaging findings, the disease is further staged and risk-stratified using the Durie Salmon Staging (DSS) or International Staging System (ISS).⁶

Figure 1: Typical clinical manifestations of multiple myeloma summarized by the acronym ‘CRAB’

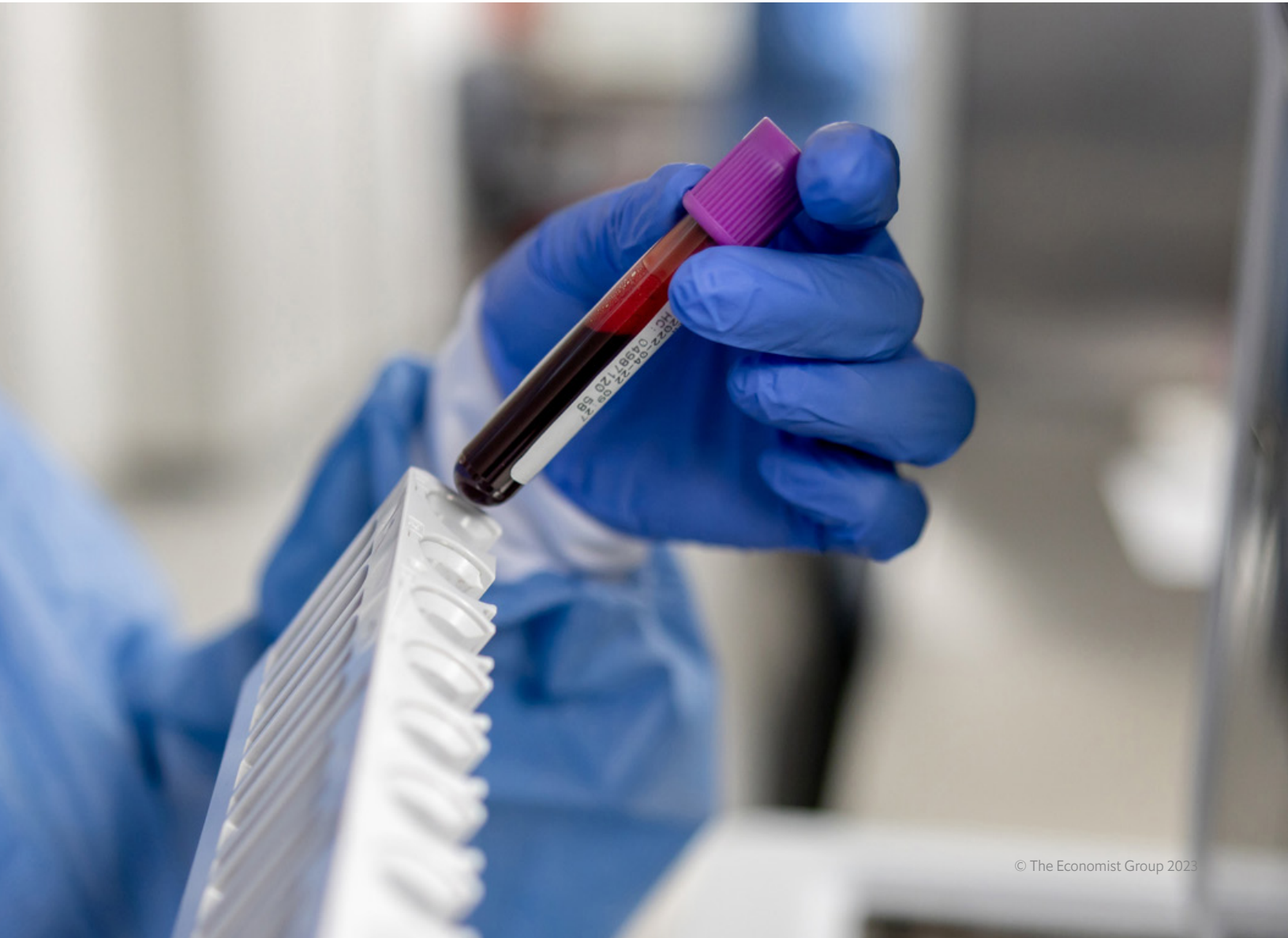
The treatment landscape of myeloma, which initially comprised of only steroids and chemotherapy such as melphalan and cyclophosphamide, has been revolutionized over the past two decades with the advent of novel agents. These include immunomodulators (Imids: thalidomide, lenalidomide and pomalidomide), proteasome inhibitors (PI: bortezomib, carfilzomib and ixazomib), and monoclonal antibodies (daratumumab, isatuximab and elotuzumab), Chimeric Antigen Receptor - T cell (CAR-T cell) therapy (idecabtagene vicleucel and ciltacabtagene autoleucel) and bispecific antibodies (teclistamab-cqyv). The care management pathway for patients with myeloma is primarily determined by the patient's ability to tolerate an autologous stem cell transplant (ASCT), which is a transplant performed by giving high doses of chemotherapy followed by reinfusion of the patient's own stem cells to regenerate the bone marrow. Eligibility for ASCT is usually determined by age, physical condition/status and comorbidities. Patients assessed as fit to undergo transplantation receive induction treatment to downstage the disease, followed by combination with high-dose chemotherapy and transplant to deepen the response, and then maintenance

treatment to keep the disease in remission for longer periods. Those who are elderly and/or unfit to tolerate a transplant receive systemic therapies without transplantation.^{7,8}

Using combinations of novel agents with different mechanisms of action in various phases of myeloma treatment clearly shown to improve outcomes.⁹ Therapy during induction usually comprises triplets or quadruplets containing various novel agents as well as steroids. For specific clinical scenarios, novel agents are combined with chemotherapy. In the maintenance setting, a single novel agent or doublets of novel agents are used in a risk-adapted fashion. Treatment in the relapsed setting also includes triplets or quadruplets of novel agents, the choice of which depends on previously used therapies and response. Multiply relapsed patients are eligible for treatments targeting the B Cell Maturation Antigen (BCMA), CAR-T cell therapy and bispecific antibodies.⁸ Bone-strengthening agents are given to all symptomatic myeloma patients. If treated appropriately, certain patients with high-risk disease can even have a median overall survival rate similar to that of patients with standard-risk disease.¹⁰

Great advances have been made in myeloma therapy in the last two decades, with significant improvements in overall survival rates, especially in high-income countries with better access to care. However, these gains have not consistently been reached in many LMICs due to lack of disease awareness, delayed diagnosis, and challenges in access to care, including barriers to receiving novel agent therapy. The private sector, which is funded through private insurance and out-of-pocket (OOP) payments in many LMICs, often offers better access to novel therapies

than the public sector. Studies across Latin America (LATAM) have shown major disparities in myeloma survival between the public and private sectors, with the private sector mirroring outcomes in high-income countries and the public sector lagging behind significantly.¹¹ Our research looks at five countries in LATAM, namely Argentina, Brazil, Colombia, Mexico, and Panama, evaluating the current care pathways for myeloma, the chasm between the public and private sector, barriers for access to care, and the opportunities for improving patient outcomes.



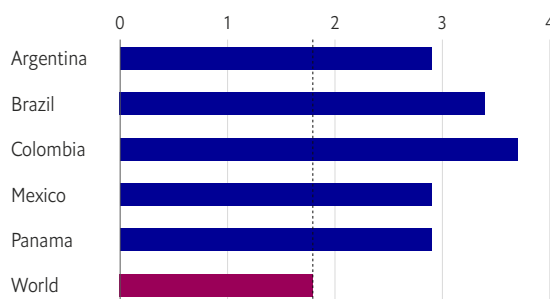
Burden of multiple myeloma in LATAM – Just the tip of the iceberg?

Rising human costs

In 2020, about 176,000 new cases of myeloma were diagnosed worldwide, and there were 117,000 deaths. The global standardized incidence rate (ASIR) in 2020 was 2.2 per 100,000 for men and 1.5 per 100,000 for women; the standardized mortality rate (ASMR) was 1.8 per 100,000 in men and 1.1 per 100,000 in women.¹² As myeloma is a disease of the elderly, ASIR and ASMR are much higher in people over 60 years of age, standing at 11 and 7.4 per 100,000, respectively.¹² All LATAM countries in our study have a higher ASIR and ASMR than the global average; amongst them, Colombia has the highest ASIR and ASMR (see Figure 2 and Table 1).

Figure 2: Multiple myeloma ASIR and ASMR are higher in the five countries studied compared to the global average (per 100,000 population)

Standardized Incidence Rates



Standardized Mortality Rates

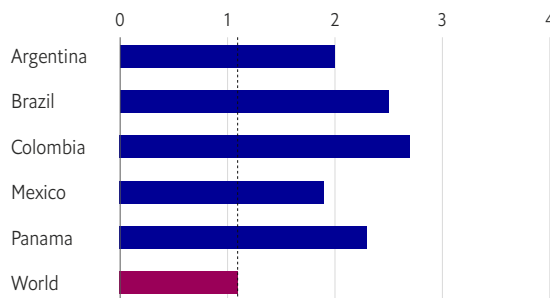


Table 1: ASIR, ASMR and prevalence rates for multiple myeloma in 2020 in countries of interest

Country	Population in 2020	Incident cases in 2020 (% of total cancers)	Estimated ASIR per 100,000 population	Deaths in 2020 (% of total cancer deaths)	Estimated ASMR per 100,000 population	5-year prevalence
Argentina	45m	1,102 (0.84%)	2.9	780 (1.1%)	2.0	2,835 (6.27/100,000)
Brazil	213m	5,655 (0.95%)	3.4	4,293 (1.7%)	2.5	13,568 (6.38/100,000)
Mexico	126m	2,390 (1.2%)	2.9	1,538 (1.7%)	1.9	5,914 (4.59/100,000)
Colombia	51m	1,376 (1.2%)	3.7	1,035 (1.9%)	2.7	3,340 (6.56/100,000)
Panama	4m	88 (1.1%)	2.9	71 (1.9%)	2.3	221 (5.12/100,000)

A study comparing the mortality to incidence ratio of multiple myeloma as a proxy for survival among 50 countries across the globe identified a range of values between 9% and 64%, with lower values denoting poorer outcomes.⁹ Among our countries of focus, Mexico had the lowest value at ~15%, followed by Argentina at ~32% and Brazil at ~35%. Colombia had the best outcomes, with a mortality to incidence ratio of ~40%. Data from Panama was not available at the time of writing this report. The best outcomes globally were observed in New Zealand (64%), Iceland (62%), the United Kingdom (60%), Belgium (59%), and Australia (57%), significantly higher than the outcomes observed in LATAM. Survival was found to be closely correlated with myeloma incidence, patient empowerment, healthcare access and quality index, access to cancer treatments, and overall healthcare expenditure.

An aging population has resulted in progressive increases in crude incidence of the disease globally and across the LATAM region. The global number of incident cases of myeloma

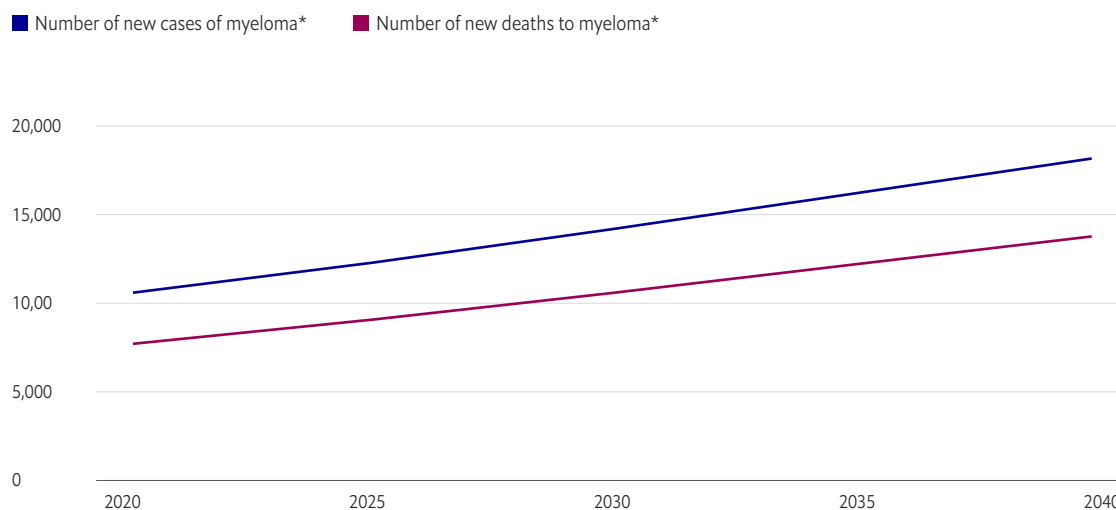
and the number of deaths have more than doubled over the past three decades. The ASIR and ASMR have remained relatively stable in high-income countries due to the high rates of case identification and access to better treatments. In contrast, some regions have seen steeper rises in ASIR and ASMR, despite lower incidence of the disease. Central Latin America and Tropical Latin America are among the top three regions that experienced the highest rise in ASIR between 1990 and 2019. They are also among the regions that showed the highest increase in ASMR in the same time-period.¹

The rising burden of myeloma across our countries of interest is evident. In a retrospective study based on data obtained from the public healthcare system in Brazil, 27,100 patients with multiple myeloma were treated between 2008 and 2017. Regional variations were seen in the number of patients with multiple myeloma seeking care; the states with the highest numbers of patients with multiple myeloma were located in the more affluent south-eastern region of

the country, and incidence was higher in urban areas and among Caucasians. These findings likely reflect the social determinants of health and access to care, with wealthier and more educated patients being more likely to seek medical attention. The number of patients with multiple myeloma treated in the healthcare system has increased year-on-year, reflecting both an aging population with rising incidence as well as better survival rates due to improved therapies. Over nine years, the number of patients seen with multiple myeloma annually in Brazil increased by 1.7 times.¹³ Crude and age-adjusted mortality rates for myeloma have also been rising in Brazil. An evaluation of patients with multiple myeloma treated in the Brazilian public healthcare system, called the Sistema Único de Saúde (SUS), between 1996 and 2015, showed an annual increase of 2.5% for age-adjusted mortality rates for patients over the age of 20, and a more dramatic increase of 3.4% for patients over 60 years of age. Higher

mortality rates were observed among patients living in the north, north-east and mid-west compared to those living in the more wealthy southern regions. The rising mortality, despite the introduction of novel agents, suggests that there are significant barriers in access to care and therapeutics in the public healthcare system and potentially that older patients, the typical demographic for myeloma, are being treated less aggressively.¹⁴ Another epidemiological study evaluating myeloma incidence between 1990 and 2007, and mortality between 1995 and 2013, in 17 LATAM countries showed a rising trend in incidence in Colombia (2% in men and 2.8% in women). Increasing mortality was noted for patients over 60 years of age in Brazil and Colombia, and for women over 60 years of age in Mexico.¹⁵ Future projections suggest that the combined number of new cases in all five countries is expected to increase by about 1.7 times and the number of deaths by almost 1.8 times in the next two decades (see Figure 3).¹⁵

Figure 3: Projections of crude incidence and mortality due to myeloma, in our five study countries, 2020-2040



*Number of new cases of myeloma and immunoproliferative disorders

Rising healthcare costs

Delayed diagnosis of multiple myeloma often results in hospitalization for inpatient therapy and management of complications. Organ damage may become irreversible when therapy is delayed. “The complications of myeloma, fractures and other surgeries usually generate huge expenses. We have to thank institutions that make this more visible so that people who can make decisions, make the right decisions, such that we can prioritize this pathology”, says Dr. Humberto Martínez-Cordero, Head of Hematology and bone marrow transplantation program, Colombian Military Hospital.

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In a 2015 study from Mexico, almost 80% of patients seen with myeloma that year required hospitalization. Advanced-stage disease was identified in about 80% of patients at presentation, 50% presented with bone fractures, and one-third with kidney failure, likely contributing to the increased need for inpatient therapy.¹⁶ Data from Brazil shows that about 20-30% of patients present with renal failure at the time of diagnosis, almost 50% develop this during the course of disease, and about 12% of patients eventually need dialysis.¹⁷ The estimated annual cost per patient with multiple myeloma in the private sector in Brazil is US\$49,508ⁱ with about 40% of the costs accounted for by hospitalization and 54% of costs related to medications.¹⁸

Hospitalization rates in Brazil are higher in the public (15-25%) compared to the private sector (10%), likely due to patients in the public sector presenting with more advanced disease.¹⁹ A study of the Colombian healthcare system costs due to multiple myeloma in 2018 showed that the total direct costs for 2,132 patients was US\$188m of which 75% were attributed to expenses not covered by the Health Benefit Package.²⁰ A 2015 study using hospital databases conducted in Argentina, Colombia and three other countries in LATAM to study the hospitalization rates for patients with multiple myeloma found that patients over 60 years of age accounted for 57% of admissions in Argentina and 73% of admissions in Colombia.²¹

Skeletal-related events (SRE) due to lytic bone lesions caused by myeloma result in significantly high healthcare costs due to expensive diagnostic tests, such as MRIs, utilization of radiotherapy for management, and the long-term consequences of conditions such as compression of the spinal cord, which could result in paralysis, the need for rehabilitation, and work absenteeism. In a modeling study based on literature reviewed from Argentina, Brazil, Colombia, and Mexico, the yearly economic burden due to SRE in multiple myeloma was estimated to be US\$7.19m in Argentina, US \$48.3m in Brazil, US\$14.8m in Colombia and US\$13.2m in Mexico.²² A study of the private healthcare system in Brazil estimated the annual costs of SRE in patients with multiple myeloma to be about US\$28,805 per 100 patients.²³ Novel myeloma therapies, including proteasome inhibitors, immunomodulators and monoclonal antibodies, as well as chemotherapy with ASCT, have all been shown to reduce bone resorption by inhibiting osteoclast activity. In addition, bisphosphonates and RANK-ligand inhibitors are used for reducing SRE in myeloma.²⁴ Early treatment with these agents could reduce the risk of SRE and the associated morbidity and costs.²³

ⁱ Converted from a cost of Brazilian Real \$124,144. The cost reported was based on data collected between 2013 and 2015. Brazilian Real to US Dollar conversion rate applied was 0.3988. Value was converted based on the average exchange rate between 2013 and 2015.



Gaps in data: true estimates are likely much higher

While epidemiological data are quoted by various studies, it is very likely that these figures are simply the tip of the iceberg and not a true representation of the actual number of cases and deaths related to multiple myeloma in these countries. In Colombia, the population-based cancer registry (PBCR) of Cali is the oldest in the country and has been expanded to four regional registries, including Cali, Bucaramanga, Manizales and Pasto. Overall, there is approximately 22% population coverage by PBCRs, with 10% coverage by high-quality PBCRs in Colombia.²⁵ These data are used to determine disease burden by the World Health Organization (WHO) Global Cancer Observatory (GCO). “We need better data to know the actual prevalence of myeloma in the country; it should be higher I believe. There must be regions of the country where there are many more cases of myeloma than we are identifying,” says Dr. Martínez-Cordero. Myeloma is only registered when the patient seeks care in a hematology unit in Colombia as it is not a reportable disease. “We have data, we have updated information but not as much as we want,” reflects Dr. Virginia Abello Polo, Hematologist & Head of Leukaemia, Lymphoma and Myeloma Functional Unit at The Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center (CTIC), Bogotá, Colombia. “We are making great effort”, she says, “but it is a fact that we have problems related to the number of hematologists, we don’t have that many hematologists in LATAM. Most of us are focused on clinical work rather than research.”

The national budget for research is minimal and this is a huge challenge.” Despite these challenges, the Colombian Association of Hematology and Oncology (ACHO) developed the Colombian Registry of Hematological Neoplasms (RENEHOC), an observational registry, in 2018. Patients diagnosed with blood cancers from the prior decade and all prospective newly diagnosed patients are entered into this registry. Fourteen centers across the cities of Bogotá, Medellín, Cali and Bucaramanga participate in RENEHOC, and as of July 2020, 890 patients with multiple myeloma had been entered into the registry. MiMENTe (Mieloma Múltiple Epidemiología Nacional y territorial) is a collaborative effort across Colombia where patients with multiple myeloma are identified based on International Classification of Diseases (ICD10) codes included in the Individual Registry of Health Services Delivery (RIPS). This study identified 26,356 patients with multiple myeloma between 2009 and 2018. The highest incidence of the disease was found in the Andean region, the highest prevalence in Bogotá and Antioquia, and the highest mortality in the region of Orinoco. ASIR and ASMR estimated by MiMENTe were higher than the 2018 Globocan estimates, produced by IARC.²⁶ Dr. Luis Pino, CEO at OxLER; Founder of Alpocrates; Hematologist, Bogotá Santa Fe Foundation, Colombia, refers us to the Cuenta de Alto Costo (CAC), or the High Cost Account, a non-governmental technical body established in Colombia to improve data collection, management of and financial allocation for high-cost diseases. The organization has developed an excellent registry for high-cost diseases, including myeloma, and the outcomes of included illnesses are measured and reported annually.²⁷

Argentina has several regional PBCRs covering about 41% of the population and about 18.6% population is covered with high-quality PBCRs.²⁸ The Institutional Registry of Tumors in Argentina (RITA) is a hospital-based electronic registry implemented in 2012. Across 15 jurisdictions of the country, 29 hospitals that treat patients with cancer contribute to RITA. This is intended to be a complete, easily accessible, up-to-date and high-quality registry that covers all aspects of the diagnosis and treatment pathway of patients with cancer.²⁹ So far, there is no myeloma-specific registry in the country and myeloma is not a reportable disease. "At the national level in our country, Argentina, it is very complex to be able to generate data. Being a federal country, different provinces have different working methods and it is difficult to achieve national coordination. The entire population ends up suffering because there is no political or economic interest in this area", observes Ms Mariana Auad, Vice-President, Argentine Myeloma Foundation.

The regional cancer registries in Brazil cover about 22% of the population, with 10% covered by high-quality PBCRs.²⁸ The Brazilian multiple myeloma study group (GBRAM) has developed an electronic database to prospectively register patients diagnosed with multiple myeloma in the Brazilian healthcare system. Since January 2018, 1,113 patients with newly diagnosed multiple myeloma from 44 reference centers have been registered in this database.³⁰ "This is investigator-initiated work," describes Professor Angelo Maiolino, Professor of Medicine, The Federal University of Rio de Janeiro, Brazil, when he discusses the work of GBRAM. "As myeloma is not a reportable disease, it's likely that the PBCRs of Brazil do not accurately reflect the number of cases," he adds.

The National Cancer Registry of Panama was established in 1964 and converted to an electronic database in 2012.³¹ The entire population is covered by this database, but the quality of data is suboptimal. Ms.

Faustina Diaz, President of the Panamanian Association of Patients and Relatives with Hematological Diseases, notes that this database only contains basic information about the site and type of cancer and very limited information about multiple myeloma.

Mexico has faced wide-ranging challenges to the development of cancer registries. The Merida PBCR was the first PBCR to be established in Mexico in 2016 and covers a population of about 1 million.³² In 2018, an ordinance was passed to develop a national PBCR and nine cities have been included in the initial stages of development.³³ "We don't have data managers. This is a major limitation to data collection and development of registries as physicians are often overburdened and do not have the time. In some countries, there are people to help with filling in forms on patients' information. Doctors need more hands to help in this regard," notes Dr. David Gomez-Almaguer, Director of the Hematology Center, Gómez Almaguer Clinica de Hematología, Mexico.

IARC Latin America hub is working with its member countries to offer technical support for the development of high-quality PBCRs, data management, data analysis and quality control. The hub coordinating center is located in Buenos Aires at the National Cancer Institute of Argentina. The National Cancer Institute of Colombia and the National Cancer Institute of Brazil (INCA) are collaborating centers. Mexico and Panama are two of the 20 member countries that receive direction and support from the hub.³⁴ MYLACRE is a clinical registry of patients with myeloma that is being developed with the collaboration of 22 centers across the 5 countries of our study.³⁵ These concerted efforts to develop stronger PBCRs and more detailed myeloma-specific cancer registries will help further understand the disease burden in these countries, make more accurate projections about future needs, and facilitate capacity-building of health systems.

Barriers to care for multiple myeloma and the public-private divide

Delayed diagnosis and lack of streamlined referral pathways

"Myeloma is a rare and fairly unknown disease, and late diagnosis is often a fairly common problem," says Ms. Auad when asked about barriers to care. Symptoms of myeloma, such as back pain, anemia or kidney failure, mimic other non-cancerous problems adding another layer of complexity. "Patients with myeloma are being assessed at several different levels of the healthcare system", says Dr. Martínez-Cordero. "Often, they stay at the first level for a long time without a diagnosis, being treated with painkillers for back pain. Then they get transferred to the second level where an internist makes a diagnosis in about 40% of cases. Once successfully diagnosed, they are referred to a hematology center but usually this is quite late in the disease course," he explains. Delayed diagnosis is also a pervasive issue in Brazil.

In a survey of 200 patients with multiple myeloma in Brazil, 98% stated that they had never heard of the disease before diagnosis, 37% saw multiple doctors before a diagnosis was made, and 29% took over a year to receive the diagnosis.

In a survey of 200 patients with multiple myeloma in Brazil, 98% stated that they had never heard of the disease before diagnosis, 37% saw multiple doctors before a diagnosis was made, and 29% took over a year to receive the diagnosis.¹³ Ms. Alma Ortiz, consultant and external advisor to the Mexican Association for the Fight against Cancer, describes that in Mexico, there are low levels of awareness among primary care physicians about blood cancers in general and specifically about myeloma.

Besides lack of awareness among physicians and delayed presentation by patients, limited access to laboratory tests in peripheral centers and public hospitals further delay diagnosis. A survey of hematologists from LATAM countries, including Argentina and Colombia, showed poor availability of tests for diagnosis and risk stratification of multiple myeloma in the public system. About 30% of physicians in the public sector could not access the serum protein electrophoresis (SPEP) test to make a diagnosis of myeloma, 60-70% of physicians could not obtain genetic tests on the bone marrow sample for risk stratification, 60% could not obtain serum free light chain (SFLC) tests for diagnosis/ risk stratification, and MRIs to diagnose SRE were only accessible to half of the physicians.³⁶

In the Hemato-oncology Latin America (HOLA) study, 83% of patients from the public sector and 76% of patients in the private sector did not receive genetic tests for risk stratification.³ “When we do not have basic tests like SPEP for diagnosis of myeloma in many centers, risk stratification is almost a dream,” says Prof Maiolino.

When it comes to referral pathways, geographical constraints are a major barrier. “Treatment centers for myeloma are concentrated in large cities, and small cities do not have enough access in Colombia,” observes Dr. Abello. “Wait times to see a hematologist after an initial diagnosis of myeloma can be as long as five to six months in the Brazilian SUS,” informs Prof Maiolino. Delayed access to both diagnosis as well as specialist care is a major cause of poor outcomes for multiple myeloma, especially in the public sector.

So close and yet so far: barriers to accessing novel agents and transplant for myeloma treatment

The past two decades have seen an explosion in the armamentarium of novel agents for myeloma therapy resulting in dramatic improvements in the overall survival rates of patients.^{8,37} In addition to conventional treatments, such as alkylators and steroids, several classes of novel therapeutics are now available, including immunomodulators, proteasome inhibitors, monoclonal antibodies, bispecific antibodies and CAR-T cells. Survival of patients with relapsed disease has almost doubled, and that of newly diagnosed patients increased by about 50%, following the introduction of novel agents.

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However, countries in LATAM have faced challenges in introducing novel agents due to great variability in regulatory processes between different countries, economic constraints, and different healthcare financing models.³⁸ The introduction of bortezomib and lenalidomide lagged behind US Food and Drug Authority (FDA) approval by up to seven years in some LATAM countries. Often, drugs that are approved are not funded in the public healthcare system. Even when drugs are approved and funded, various administrative and bureaucratic processes can delay patients’ access to novel therapies.³⁹

In addition, there is great heterogeneity in access to novel agents and transplant between the public and private healthcare systems. “Autologous transplant is in fact the least expensive of the highly effective treatments for myeloma but the wait lists are very long in the Brazilian SUS. They can be as long as six to eight months in states like Rio de Janeiro and São Paulo. In contrast, access to transplant is very easy in the private sector,” explains Prof Maiolino. This chasm between the public and private sector has been demonstrated in different studies across the region.

The HOLA observational study was conducted between 2008 and 2015 in seven LATAM countries including Argentina, Brazil, Columbia, Mexico and Panama. Among the 1,103 patients included, thalidomide was the most common first-line therapy and was used in over half the patients, and bortezomib, used in about one-third of patients, was the second most common. When patients were disaggregated into those receiving therapy in the private versus public sector, bortezomib alone or bortezomib and thalidomide was used as first-line therapy in about 54% of patients treated in the private sector, versus only in 15% of those treated in the public sector. There has been progressive increase in bortezomib utilization year-on-year, but the increase has been much higher in the private sector as compared to the public sector.³ Most patients in Argentina



and Colombia were treated in the private sector with higher utilization of bortezomib, as compared to Mexico and Brazil, where most patients were treated in the public sector.

Another retrospective multicenter study, by the Latin American Study Group on Multiple Myeloma, also known as GELAMM, which was performed across six countries, included 395 transplant-eligible patients from Argentina, 209 from Colombia and 151 from Mexico. In Argentina, 82% of patients were treated in the private sector, 97% received bortezomib-based induction and 87% of patients (the highest proportion among the countries in the study) eventually received ASCT. In Colombia, 100% of patients were treated in private, 96% received bortezomib-based induction, but only 42% had ASCT performed. In contrast, over half the patients (56%) in Mexico were treated in the public sector, only 41% received bortezomib-based induction, and 44% had a transplant performed. Maintenance therapy was given to 62% of patients, with 57% of them receiving lenalidomide-based maintenance and 33% thalidomide-based maintenance. Patients treated in the public sector had more advanced disease at diagnosis, were less likely to receive bortezomib induction, and less likely to receive ASCT and lenalidomide maintenance. At a median follow-up of 32 months, the 5-year overall survival rate of the entire cohort

was 64% with patients treated in the private setting having almost double the 5-year overall survival rate compared to those treated in the public setting (80% v 46%). Subgroups analyses showed that overall survival was superior in patients treated in private in both patients that underwent or did not undergo ASCT.¹¹

A retrospective study of 43 patients in Brazil, who received either bortezomib-based or thalidomide-based induction, showed that about 46% of patients in the bortezomib arm had a complete remission of their disease before transplant, whereas only 7% had a complete remission in the thalidomide arm.⁴⁰ Achievement of complete remission before ASCT has been associated with better post-transplant outcomes, including overall survival, underscoring the importance of optimal induction therapy.⁴¹

Patients in LATAM countries sometimes resort to lawsuits to facilitate access to drugs. Acquiring therapies through legal action may further exacerbate inequities in care given that all patients do not have similar access to the judicial system, and all diseases and therapies may not be viewed similarly.⁴²

In the following sections, we will review the regulatory processes for drug approval in our countries of focus, the access to novel agents and ASCT in the public versus private system and its impact on outcomes.



Brazil

The introduction of new therapies in Brazil requires review by the Brazilian Health Regulatory Agency (ANVISA), which is responsible for drug registration, licensure and price regulation.⁴³ In the past, ANVISA was plagued by several administrative barriers, language requirements, delays and backlogs. Following the inclusion of ANVISA in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2016, the regulatory process has been revamped and streamlined. The maximum timeframe for approval of prioritized agents is now 120 days, while that for drugs in the ordinary category is 365 days. Some leeway is given, and the timeframes can be extended by a third in both cases.⁴⁴ With these interventions, the backlog in approvals has steadily decreased over time. As Dr. Fabiana Higashi, Hematologist at the Santa Casa da Misericórdia de São

Paulo, Brazil, notes, however, the path to approval, for instance, with lenalidomide, can sometimes be a challenging one.⁴⁵ Nonetheless, many novel drugs for multiple myeloma have recently been approved by ANVISA.⁴⁶

Brazil has had SUS, a universal healthcare system, since 1988, which has consistently worked towards reducing health inequalities and improving care. The majority of Brazil's population seeks care in the public sector. Roughly one-quarter of the population can afford health insurance and receives care in the private system.⁴⁷ Despite improvements in the public healthcare system over the past decades, considerable challenges related to overcrowding, workforce constraints, long wait times and decreased access to sophisticated diagnostic and treatment modalities in SUS remain.¹⁹ Not all treatments approved by ANVISA are funded by the SUS. In a survey of seven hemato-oncologists from three regions of Brazil, the median time from diagnosis to start of therapy was 7.5 months in the public sector and 2.5 months in the private sector. The availability of specific drugs in the institution was a factor in determining the type of therapy offered in public hospitals in 17% of responses, but this was not raised as a determinant in the private sector.¹⁹

The National Committee for Health Technology Incorporation (CONITEC) is the apex body that determines the inclusion of therapies in SUS, while ANS is the National regulatory agency for private health insurance and plans.^{17,48} Both agencies engage in public consultations for the approval process. The Brazilian Health Technology Assessment Network (REBRATS) is a network of collaborating teaching and research institutions that enables the discussion and dissemination of priority Health Technology Assessment (HTA) studies to the regulatory agencies, contributing to continuing education and decision-making in this area.⁴⁹ While bortezomib was approved for first-line treatment in the diagnostic and therapeutic guidelines for

myeloma in Brazil 2015, it has only been approved by CONITEC for use in the public sector for first-line and relapsed refractory patients since September 2020.⁵⁰ Lenalidomide, carfilzomib and daratumumab are yet to be approved for use by the SUS in newly diagnosed or relapsed refractory disease.^{17,51} Despite approval in the SUS, actual access to novel agents in the public system is still a challenge since a monthly limit for reimbursement for each line of therapy is set by the Authorization for High Complexity Procedures (APAC), which may not cover the cost of the drug.⁵¹ A high discrepancy between drug price and APAC reimbursement rate can act as barrier impacting patients access to newer treatments. As the APAC system has not changed in years, there have been calls to update the system, with payment rates that reflect both the increased cost and improved outcomes that more innovative treatments offer.^{52,53} In contrast, all the novel agents that are approved by ANVISA are easily accessible in the private sector. Several centers for ASCT exist in different parts of Brazil, including Rio De Janeiro, São Paulo, Minas Gerais, Bahia, Pernambuco, Paraná, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina, Goiás and Distrito Federal.⁵⁴ While transplantation in the public sector is fraught with long wait lists and delays, ASCT is more easily accomplished in a timely fashion in the private sector, according to Prof Maiolino.

The gap between the public and private sector in Brazil has been elucidated clearly in different studies. A study comparing patients with various cancer diagnoses treated in the public and private sector in São Paulo showed that patients with myeloma had the greatest disparity in outcomes, with those treated in the public sector having about 2.4 times higher risk of death compared to those in the private sector.⁵⁵ In the HOLA study that enrolled patients with multiple myeloma treated between 2008 and 2015, 287 patients from eight public hospitals and one private hospital in Brazil were included. Thalidomide was used in about 68% of patients

for induction therapy, while bortezomib was only used in 15% of patients. Chemotherapy was used for induction in 13% of patients. Only 30% of patients underwent ASCT.³ More recent data is available from the electronic database developed by GBRAM, which has enrolled 1,113 newly diagnosed myeloma patients from 44 centers since January 2018.³⁰ Of the 919 patients that were enrolled with an intent to perform a transplant, 81% were from the public sector. Bortezomib-based induction was administered to 76% of patients in the private sector, compared to only 37% of the patients in the public sector. While 89 of 178 patients (66%) in the private sector eventually received a transplant, only 154 of 737 patients (33%) were recipients in the public sector. The complete remission rate to transplant was significantly higher for patients in the private compared to the public system (29% vs 14%), likely reflecting better access to novel agents for induction and better supportive care during the transplant.⁵⁶

“The gap between public and private is only going to widen further”

Prof Angelo Maiolino, Professor of Medicine, The Federal University of Rio de Janeiro, Brazil

With bispecific antibodies and CAR-T cell therapies on the horizon to be incorporated into the treatment pathway in the private sector, “the gap between public and private is only going to widen further”, says Prof Maiolino. There is, therefore, an urgent need to improve access to novel agents and ASCT in SUS so as to improve myeloma-related outcomes. “We must at least work towards having lenalidomide for maintenance therapy and carfilzomib and daratumumab in the relapsed refractory setting to improve outcomes in the public sector,” he adds.

Argentina

Argentina has one of the most efficient regulatory systems for the approval of pharmaceutical products in LATAM. New drugs entering the market in Argentina can acquire regulatory approval from Argentina's National Administration of Drugs, Food and Medical Technology (ANMAT) through two mechanisms. If the drug has already been approved by any of the 15 countries recognised by Argentina to have high-level surveillance, presenting that certificate of approval to the regulatory agency is sufficient. Otherwise, the application has to undergo a full safety and efficacy assessment by the agency.⁵⁷

The Argentinian health system has three wings. The government-funded public healthcare system is accessed by about one-third of the population, mostly comprising the poor and uninsured. The social security sector known as Obras Sociales (OS), funded primarily through payroll contributions, covers all individuals employed in the formal workforce. The private sector provides care for those covered by OS through contracting mechanisms, as well as people with private health insurance (Prepaid Medical Enterprises: EMP).⁵⁸ While theoretically, all approved agents can be accessed equally in the public and private sector, in reality, there are major hurdles, especially in the public system. "Most of the patients in the public, social security or private health systems have insurance and prior approval is required from the insurance company before using high-cost drugs," notes Dr. Miguel Pavlovsky, Hematologist and Medical & Scientific Director, FUNDALEU, Buenos Aires, Argentina. "Securing reimbursement approvals are more challenging in the public sector; wait times for approvals have also been progressively increasing and can be as long as 3 to 6 weeks in the social security or private health systems from the time of application," he adds. "Sometimes the drugs are not in stock in the public system. Two or three months may pass before the patient receives the medication, and sometimes it is not the

original medication recommended by the treating physician," explains Professor Dorotea Fantl, Internal Medicine Consultant of the Hematology Department of the Italian Hospital, Buenos Aires and vice-president of the Latin American Multiple Myeloma Study Group. Dr. Pavlovsky describes attempts to circumvent these challenges. "We often save a stock of crucial medications and lend them to patients in dire need for early therapy," he says. In the HOLA study, four private hospitals and one public hospital contributed 198 patients from Argentina and only 46% of patients received bortezomib-based induction, reflecting the challenges in access.³ There is a need to focus on administrative processes, procurement and the supply chain to ensure consistent availability in the public sector. Dr. Claudia Shanley, Hematologist, Hospital Británico, Buenos Aires, Argentina, notes that there are very few centers performing ASCT in the public sector, adding further barriers. "Once the patient finishes induction therapy, a request for approval of transplantation is sent to the governing body and then it's in their hands," she explains.



Another challenge in Argentina is the high cost of novel agents.^{36,57} Programa de Atención Médica Integral (PAMI), the OS that serves the retired population, elderly and war veterans, covers up to 80% of the costs of outpatient drugs and 100% of the costs of special treatments. While PAMI negotiates its share of the cost of drugs with the pharmaceutical industry, there is no control over the end-user costs at the pharmacy. Since 2018, changes have been introduced to the system of procurement by PAMI to facilitate lower end-user costs, especially for cancer drugs.⁵⁹ Plans are underway in Argentina to establish an official national HTA agency to further streamline the funding for and costs of therapies.

In the interim, the Institute of Clinical Effectiveness and Health Policy (IECS) issues HTA reports that facilitate the decision-making of the National Commission for the Evaluation of Health Technologies (CONETEC).⁶⁰ There is scope for generics to be introduced at the same time as the original product in Argentina. “Generics are widely used in Argentina towards reducing costs,” mentions Prof Fantl. However, the recent changes to the approval process for generics, in that there will no longer be a mandate for bioequivalence studies, is being viewed with a certain degree of caution.⁶¹

“Looking forward, Argentina should work towards incorporating newer myeloma therapies such as bispecific antibodies and CAR-T cells in the armamentarium. Capacity-building for clinical trials will be crucial,” says Prof Fantl. “Most of all, I hope that all patients have access to standardized high-quality treatment in the country”, adds Dr. Christian Seehaus, Hematologist in the Italian Hospital, Buenos Aires, Argentina.

Mexico

Mexico’s Health Authority, the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), is responsible for the approval and registration of new drugs. During the pandemic, to facilitate the purchase of vaccines and medications, the regulatory process was modified such that drugs that had received approval from the Swiss or US FDA, or had received prequalification by the WHO, could be purchased without registration by COFEPRIS.⁶² The General Health Council, Consejo de Salubridad General (CSG), determines which of the approved drugs can be included in the National Compendium called Libro de Medicamentos del Compendio Nacional de Insumos para la Salud. Public institutions in the country can only use therapies which are included in this compendium.⁶³ Between 2018 and 2022, there have been repeated overhauls to the drug procurement system of Mexico, which have impacted access. In 2019, the responsibility of public procurement of drugs was transferred to the administrative office of the MoF (Oficialia Mayor), but due to its lack of experience in drug procurement, shortages of various drugs occurred throughout the country. Following this, the president transferred the procurement responsibility from the MoF to the United Nations Office for Project Services (UNOPS) in 2020. However, the calls for procurement by UNOPS were delayed resulting in about 35% of the drug codes not being filled. Three private companies which were responsible for about 70% of the distribution of medical equipment and supplies



in Mexico were also banned, resulting in further widespread shortages, especially in cancer drugs.⁶² “Even though doctors are projecting requirements and requesting the purchase of drugs, about 40% of patients have not been receiving their therapies due to challenges in drug procurement,” according to Ms. Ortiz.

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Ms Alma Ortiz – Consultant and External Advisor, Mexican Association for the Fight against Cancer, Mexico

Healthcare in Mexico is delivered through three systems: 1) social security institutions that offer health services and a majority of treatments for about 60% of the population comprised of formally employed people and their families, 2) government-funded services, known as the Instituto de Salud para el Bienestar (INSABI), provide a limited treatment package for uninsured patients accounting for 30% of the population, and 3) private healthcare, financed through OOP payments and insurance, that covers 10% of the population.⁶⁴ “In the private healthcare system, we can prescribe almost every novel agent freely. However, in the public sector we typically use bortezomib, thalidomide and dexamethasone. Access to lenalidomide and monoclonal antibodies is limited and if prescribed, requires proof of refractory status and prior approvals through bureaucratic processes. Patients cannot get them in a timely manner,” observes Dr. Gómez-Almaguer. “Besides, there is inter-institutional variability in treatment protocols and drug

procurement which further affects outcomes,” he says. The capacity for transplant in the public sector is inadequate. While 60-70% of the patients with myeloma should be transplanted, only 20-30% of patients actually receive a transplant due to logistical constraints and long wait lists, according to Dr Gómez-Almaguer.

In a retrospective study with multiple myeloma patients, stark differences were noted between the 77 patients without health insurance, treated as public patients, compared to the 71 patients with health insurance, treated as private patients in the University Hospital in Monterrey, Mexico. Uninsured patients were more likely to present with advanced and high-risk disease, 91% of the uninsured received thalidomide-based induction compared to 75% of the insured receiving bortezomib-based induction. Only 38% of patients deemed fit for ASCT of the uninsured group proceeded to transplant versus 84% in the insured group. Early mortality within 12 months of diagnosis was more common in the uninsured (12.9%) as compared to the insured (4.2%), and most cases of early mortality were directly attributable to disease progression. While patients with relapsed disease in the insured group were treated with different agents such as bortezomib, lenalidomide and carfilzomib or pomalidomide, those in the uninsured group exclusively received thalidomide-based regimens. Median overall survival in the insured group of patients was significantly longer than in the uninsured (79 v 51 months).⁶⁴ Another study, evaluating 2,569 patients treated in the National Health System in 2015, showed that all patients treated in the private sector in 2015 received bortezomib-based induction with 18% receiving the triplet combination of bortezomib, lenalidomide and dexamethasone (VRD). In contrast, only 50% of patients in the public sector received bortezomib-based induction, with none receiving the VRd combination.¹⁶

There is a need to augment the workforce and resources for data collection, unify existing health registries, standardize treatment protocols between different healthcare institutions, improve transplant capacity and develop funding mechanisms for uninsured patients in order to improve myeloma outcomes in Mexico.³³



Colombia

The healthcare system in Colombia was reformed in 1993 when the national health system called the Sistema General de Seguridad Social en Salud (SGSSS) was created. Individuals can become affiliated with the SGSSS through a contributory regime for those in formal employment, a subsidized regime for those without formal employment, or a special benefits scheme for teachers, armed forces and employees of a state-owned petroleum company.⁶⁵ A mandatory health insurance model is used to finance the system with a vast majority having access to healthcare, and approximately 1% of the population being uninsured.⁶⁶ Roughly 6% of the population has additional voluntary private health insurance.⁶⁷

The National Institute of Drug and Food Surveillance, known as the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), is responsible for the regulatory approval of pharmaceutical products.⁶⁸ While regulations have set a review timeframe of 6 months for a new drug application, in reality, the approval process can take 12 months or longer. Dr. Pino recommends that “Transparency around drug approvals by INVIMA could be enhanced. Given that understanding myeloma therapies requires deep knowledge and technical skills, assessments by INVIMA could be further improved by greater communication with experts in the field”, he says. HTAs are conducted by the Instituto de Evaluación Tecnológica en Salud (IETS) to advise which technologies should be financed using public funds.^{69,70} “We are fortunate”, mentions Dr. Martínez-Cordero, “in that we have very good access to novel agents for myeloma therapy across the board. The majority of patients receive triple induction with a PI, Imid and steroids and now we are faced with the challenge of triplet refractory disease.” Bone-strengthening agents such as bisphosphonates and denosumab are also funded

“Moving ahead, we must improve health system capabilities to manage novel therapies, such as CAR-T cells, and their side effects. It would be important to work with various stakeholders to expedite the ethics review process, expand clinical trials in Colombia, and improve access to newer agents, including investigational therapies”

Dr Humberto Martínez-Cordero, Head of Hematology and bone marrow transplantation program, Colombian Military Hospital

and easily accessible. While the situation in Colombia is enviable in terms of access to novel agents, significant challenges still exist. “With specialists working across different hospitals, developing a multidisciplinary care team that provides a one-stop shop for patients with myeloma is almost impossible,” says Dr. Pino.

Dr. Abello describes the situation with ASCT in the country. “The number of patients undergoing ASCT is steadily increasing in Colombia from about 150 per year in 2010 to 500 per year in 2020. However, transplantation for consolidation only reaches about 30% of patients, and there are often long wait times due to resource and infrastructure constraints. This is a significant bottleneck impacting outcomes,” she says. “There are only five to six transplant centers for all of Colombia,” adds Dr. Pino. Whether you are referred from the public healthcare system or from the private sector with voluntary insurance, there is no difference in access to transplants in Colombia. Paying OOP for a transplant could expedite the process but this rarely happens given the formidable costs. “You could arrive at the park by the highway or the trailway but often, when you arrive, you will find that the park is closed to both,” he opines. According to Dr. Pino, not only is access to ASCT a challenge, but there is also fragmentation of care referring to “a lack of communication between the referring centers and the transplant centers, lack of harmonization of treatment protocols between different transplant centers, and high variability of costs between transplant centers.”

Analysis of treatment patterns for multiple myeloma across 14 centers participating in the RENEHOC registry yielded important insights.⁷¹ As of July 2020, 890 patients with multiple myeloma were entered into the registry. From these data, at the time of diagnosis, over 50% of patients had advanced disease, with about 42% presenting with a fracture, 37% with anemia, 16% with kidney failure and 12% with hypercalcaemia. Patients under 65 years of age were more likely to have fractures. About 90% of transplant-eligible patients and 70% of transplant-ineligible patients received bortezomib-based induction. The combination of cyclophosphamide, bortezomib and dexamethasone was the most common induction therapy. Only about 40% of patients who were considered transplant-eligible received an ASCT. For maintenance, lenalidomide was used most often, followed by thalidomide and then bortezomib. The median overall survival for the whole cohort was 88 months. “These are academic registries”, notes Dr. Abello, “so, patients in these registries are likely to have received better treatments.” In the HOLA study, which was conducted in an earlier time period, although all 259 patients from Colombia were treated in the private setting, only about 64% of patients received bortezomib-based induction and 40% underwent an ASCT suggesting that treatment patterns have changed over time and vary between academic and private settings.³

“Moving ahead, we must improve health system capabilities to manage novel therapies, such as CAR-T cells, and their side effects. It would be important to work with various stakeholders to expedite the ethics review process, expand clinical trials in Colombia, and improve access to newer agents, including investigational therapies”, opines Dr. Martínez-Cordero. Dr. Abello emphasizes that timely and assured access to ASCTs is key to improving outcomes overall.

Panama

The National Directorate of Pharmacy and Drugs in Panama is responsible for the regulation of pharmaceutical products. In August 2002, a decree was signed that allows the importation of medicinal products from other countries provided import certification has been given by the Sanitary Registry. This move was made to reduce drug oligopoly in the country and make medications more affordable.⁷² Panama has a public healthcare system that offers universal coverage. The Social Security Fund (SSF) finances care for people in the formal workforce. The Ministry of Health finances care for people who have limited financial resources or are outside of the formal workforce.⁷³ The country also has private hospitals providing care for patients through OOP payments or private insurance.

“In Panama, there is inadequate inventory management for novel agents in myeloma,” describes Ms. Faustina Diaz. “Physicians project the needs fairly accurately, but often there is inadequate supply, predominantly due to budgeting constraints for procurement. Sometimes the supplier is unhappy with the tender and the whole purchase is suspended,”

she explains. Besides procurement and financing, administrative procedures pose barriers to accessing these agents. According to Ms. Diaz, if a novel therapy is prescribed, the path to access is very bureaucratic. The physician prescribes the medicine, then it goes to the medical director for authorisation, following which a specific committee decides whether the therapy can be changed. If a new drug needs to be approved, typically, a pre-existing drug that the patient is receiving will need to be dropped. Together, these factors result in increased wait times for patients to receive novel therapies.

In the HOLA study, two public hospitals and one private hospital from Panama contributed patients. Combined with one center each from Chile and Guatemala, a total of 87 patients were enrolled by the three countries. Among these patients, about 44% received first-line therapy with thalidomide, while about 24% received bortezomib. About 21% of the patients still received chemotherapy-based induction rather than novel agents. Only 16% of the patients proceeded to ASCT. These data reiterate the challenges of accessing myeloma treatment in Panama.³



Towards improving outcomes in myeloma: bridging the gap

The advent of novel therapies and ASCT has transformed myeloma from a lethal disease into a chronic illness. A subset of younger patients treated aggressively with novel agent-based triplet induction, ASCT and maintenance therapy remain in remission for over 10 years. The possibility of an “operational cure” is becoming increasingly likely in such a group of patients, especially with the further addition of daratumumab to the induction regime.⁷⁴ While we advance towards this goal, unfortunately, great inequities remain in terms of access to appropriate treatment and improved survival. In our countries of study, the disparity between the private and public sector in terms of clinical presentation, diagnosis, access to novel agents and transplant is striking, with the public sector lagging far behind in outcomes. In the private sector, while treatments and outcomes are comparable to high-income countries, challenges still remain for patients who depend on OOP payments rather than insurance to finance their care. There is an urgent need to offer equitable care for myeloma and reduce the financial consequences of therapy for patients.

Improving awareness of multiple myeloma among the public and policymakers

Patients with myeloma in LATAM often present late to a physician. Furthermore, once the diagnosis is made, patients are usually unaware of their treatment options. The Panamanian Association of Patients and Relatives with Hematological Diseases engages with communities to celebrate events, and organize activities and workshops to improve awareness of hematological disorders including myeloma. “In Argentina, all patients have the same rights of access to health in cancer treatments, but there are often many obstacles in the way, mainly in the public sector. If patients do not have the appropriate information, they will not attempt to access the appropriate treatment. Therefore, it is essential that the patient be well educated regarding their health rights, and treatment options,” emphasizes Ms. Auad.

“The CAC (referring to the Cuenta de Alto Costo, or the High Cost Account) has done a very good job with multiple myeloma and has put the disease in the view of policymakers in Colombia,” says Dr. Pino. Efforts are ongoing to improve visibility of myeloma in Mexico, mentions Dr. Gómez-Almaguer. “Physicians and patient organizations, especially in Mexico City, are trying to connect with policymakers to improve awareness of the disease and increase funding in this area.

However, the outcome of these efforts often depends on the economic status of the country," he notes.

Facilitating early diagnosis and referral for specialist care

"One word – education", says Dr. Fantl, when asked about how to improve myeloma care. Ms. Auad shares a similar sentiment, stating that "Myeloma education and awareness must start at the undergraduate level of the medical school to have a significant impact especially in achieving earlier diagnoses and optimising myeloma treatment outcomes." Her optimizing, Fundación Argentina de Mieloma, has worked with hematologists to develop short videos about myeloma that have been shared with primary care physicians and orthopedic surgeons. The organization continues to collaborate with medical societies and universities with the intent of eventually reaching healthcare workers in training. The Panamanian Association of Patients and Relatives with Hematological Diseases is also developing a program for continuing education and support where primary care physicians receive ongoing training from hematologists with regard to various blood disorders including myeloma. The project has been approved for launch in Colón, but implementation has been delayed by the pandemic.

"All patients have the same rights but there are many hurdles along the way, such as resource limitations in the public sector. If patients don't have the proper information, they will not attempt to access the right treatment. So, it is crucial that the patient is well educated with regard to their treatment options."

Ms Mariana Auad, Vice-President, Argentine Myeloma Foundation, Argentina

Our experts emphasize the importance of developing diagnostic and clinical decision-making aids for frontline physicians to facilitate early diagnosis and appropriate management. "The Mexican Society of Hematology (AMEH) along with the National Foundation of Health in Mexico are working together to improve diagnosis and management of myeloma in Mexico," mentions Ms. Ortiz. She describes the efforts of an inter-institutional group of hematologists who have developed an algorithm from diagnosis all the way to tertiary management of myeloma. Efforts are being made to bring this algorithm to policymakers for introduction into the healthcare system. In collaboration with different organizations, the Mexican Association for the Fight against Cancer has developed educational platforms and clinical case reviews for frontline physicians to facilitate early diagnosis of the disease. An app is also being developed for primary care physicians. This app provides information on myeloma diagnosis using simple and accessible tests, acts as a platform for primary care physicians to connect with specialists to clarify any aspects of myeloma care, and facilitates early referrals for management. "Our goal is to reach around 84,000 primary care physicians in Mexico using this app," declares Ms. Ortiz.

"Proper laboratories are not available in most peripheral locations and this is a major limitation for diagnosis," observes Dr. Martínez-Cordero. "General physicians can request a total protein with relation to albumin. We can have this test probably," he says. Such a simple test could offer an early clue regarding a myeloma diagnosis and expedite further workup. Dr. Martínez-Cordero describes the efforts of his team, in collaboration with physicians in Argentina, Chile and Uruguay, to develop diagnostic aids for primary care physicians including case studies of various clinical presentations of myeloma like classic, complicated and infectious. "Thinking of this connection and having a proper laboratory can go a long way," he says.

Marrying innovation and access - policy-level action to facilitate access to care in myeloma

“Access, access, access”, states Prof Maiolino when asked about the most important factor in improving outcomes for patients with myeloma. He continues, “timing and access are critical for these patients. Access to early diagnosis, access to novel agents, and access to early transplant are imperative to improve outcomes.” The pathways to regulatory approval for novel agents are becoming more streamlined in our countries of interest; several drugs have already been approved and many others, such as bispecific antibodies and CAR-T therapies, are in the pipeline for approval. However, access remains a huge challenge, especially in the public sector.

“Timing and access are critical for these patients. Access to early diagnosis, access to novel agents, and access to early transplant are imperative to improve outcomes.”

Prof Angelo Maiolino, Professor of Medicine,
The Federal University of Rio de Janeiro, Brazil

Innovative models for financing therapies would be crucial to improving access in the public healthcare system. Prof Maiolino discusses the ongoing efforts of the Brazilian Myeloma Group in working with the Ministry of Health to establish a National Program for Cancer funding. The utilization of such funds should be transparent and accountable for the success of this endeavor. Ms. Ortiz says that having a specific budget for a specific disease could help improve financing for therapies. “Colombia was in the process of developing ‘value-based pricing’ for drugs,” says Dr. Pino. “However, the new government has put this process on hold and plans to introduce

a new healthcare system reform in the first quarter of 2023. It is unclear at the moment as to what change this will entail,” he explains.

Accurate projections of the health and economic burden of multiple myeloma is essential to earmark future funding for innovative therapies. For this purpose, the development of robust myeloma registries is essential. Bridging the private-public gap to enable more equitable access is the ultimate goal. Prof Maiolino mentions that the Brazilian Society of Hematology is working in collaboration with the American Society of Hematology on an equity program for drug access. In 2020, the Mexican Foundation for Health and Research Center in Politics, Population and Health of the Faculty of Medicine of the National Autonomous University of Mexico (UNAM) published a general framework for comprehensive public policy for equitable, timely and quality care for patients with myeloma. It is important to bring such work to the attention of policymakers to facilitate change.³³ Besides funding, administrative challenges such as poor inventory management and complex bureaucratic processes for approval of drugs for individual patients need to be addressed in the public system to reduce wait times to access critical therapies.

Capacity-building of the health system from primary to tertiary levels would be key to tackle the rising burden of myeloma. Improving laboratory facilities in peripheral centers will facilitate early diagnosis. Dr. Martínez-Cordero reiterates the importance of developing myeloma centers of excellence across the country to offer expedited, high-quality, multidisciplinary care for patients with the disease. He describes that physicians in Colombia are gradually getting organized to provide such care, and Ms. Ortiz echoes the development of similar physician groups in Mexico. However, given that tertiary centers are limited in number and localized to

specific areas, it is important for primary care centers to develop the capability to administer simple systemic therapeutic agents for myeloma, especially oral treatments or subcutaneous injections. These efforts will reduce wait times, lower the financial burden and indirect costs for patients, and improve follow-up rates. Developing doctor-to-doctor telemedicine support between primary care physicians and specialists will enable such efforts and ensure high-quality care.

“The number of transplant beds must be increased to offer timely transplant to patients with myeloma,” adds Dr. Abello. Innovative strategies like outpatient transplantation may be considered where the setting and resources are conducive. The evolution of health systems to facilitate easy access to clinical trials will help patients with multiply relapsed disease seek investigational therapies.



Conclusion and calls to action

The health and economic burden of myeloma is increasing in LATAM, yet the data we see is just the tip of the iceberg, given the inadequacy of existing disease registries. Despite the rising burden, awareness among the population is poor. Patients in our countries of interest frequently present late to the medical system, already having sustained kidney failure, fractures or damage to the spinal cord. Furthermore, frontline physicians have limited knowledge of myeloma, which mimics many benign conditions. Often patients with bone pain or anemia are treated symptomatically until late in the disease course. Once diagnosed with myeloma, referral to specialists is a challenge due to geographical and labor constraints; therefore, wait times for therapy initiation are often very long. A huge gap exists between novel therapies accessible in the public versus private healthcare systems. Access to ASCT is a challenge due to limited beds and specialist centers. This inequity results in poorer outcomes in the public sector. Cumulatively, these factors threaten the goal of improving survival for the vast majority of myeloma patients and moving towards an “operational cure” for a selected subsets of patients. Policy-level action is essential to bridge the gaps in myeloma care and improve survival rates.

Make myeloma a notifiable disease and develop robust clinical registries

The ability to accurately estimate the current disease burden and project future impact on health systems is key for efforts directed at capacity-building and financing. In this regard, making myeloma a notifiable disease would be a good first step by improving the recognition of the disease and enabling more accurate data collection.⁷⁵ Rather than depending solely on PBCRs, developing robust clinical registries through collaboration among physicians would help better understand the treatment landscape and identify inequities which require imminent attention. Lessons can be taken from the Colombian RENEHOC registry and the Brazilian registry developed by GBRAM for expansion into other countries in LATAM.

Improve education and infrastructure to facilitate early diagnosis and referral

Time is of the essence in myeloma therapy. Early treatment in symptomatic myeloma can mitigate organ damage, and significantly reduce morbidity and mortality. Being a great mimicker of other disorders, a high level of suspicion is



necessary to enable the diagnosis of myeloma in a patient and ensure timely management. Education of frontline physicians and equipping them with suitable job aids is key to achieving this goal. Such efforts should go hand-in-hand with infrastructure development. Availability of basic laboratory tests, such as a total protein and albumin level test, in peripheral centers is imperative to facilitate diagnosis. The public-private divide in terms of access to tests for diagnosis and evaluation of end-organ damage needs to be addressed urgently. Streamlined referral pathways and capacity-building across all levels of healthcare, from primary to tertiary care centers, is necessary to tackle the rising disease burden. Public-private partnerships could ease the burden on the public sector and expedite specialist evaluations.

Tackle the inequities in access to treatment between the public and private sector

Financial challenges, administrative barriers and bureaucracy are fundamental problems hampering access to novel agents in the public healthcare system in LATAM. To tackle these impediments, examples can be taken from Australia, where a National Strategic Action Plan

for Blood Cancers was proposed in 2020. The plan calls for the establishment of a multidisciplinary working group that will review existing therapies and gaps, prepare a list of important therapies which are currently inaccessible with public subsidy, and collaborate with the government to envision methods to improve access to these drugs including through investigator-initiated trials and participation in registries.⁷⁶ Innovative funding mechanisms need to be developed, and ring-fenced funding should be considered, to facilitate access while ensuring sustainable healthcare systems. Administrative processes, including inventory management, projections and procurement need to be streamlined, especially in Panama and Mexico, where these problems have been compounding lately.

Health system strengthening to support innovation

Patients with multiply relapsed or refractory myeloma have extremely limited access to therapies in our countries of interest. With CAR-T cells and bispecific antibodies on the horizon to be included in the armamentarium, there is a need for capacity-building in the health systems to administer these therapies, which have certain rare but serious and unique side effects. Such efforts would go hand-in-hand with expanding transplant access as transplant centers are necessary to perform CAR-T therapy.

Expanding availability of clinical trials will be key for patients with limited treatment options. In a systematic review of 18 pivotal clinical trials in myeloma between 2005 and 2019 that led to US FDA approvals, Brazil enrolled patients in four studies and Mexico in two studies while none of the other countries of study were listed as contributing to the trials.⁷⁷ Supporting clinical trials will require an overhaul of the administrative system, expedited ethics approvals, better research support and staffing along with training of healthcare professionals in this space.

Facilitate the growth of patient organizations to improve awareness among the public and policymakers

No amount of work towards improving data management, facilitating speedy diagnosis, or improving equitable access to therapies can be successful in enabling better myeloma outcomes without the participation of the patient. The work of patient organizations in improving awareness among the public regarding the symptoms of myeloma and the need to seek timely care cannot be overstated. Patients must be supported to navigate health systems and

advocate for themselves to be able to receive the best possible therapy and supportive care. As the Mexican Association for the Fight against Cancer is doing, important gaps in myeloma care and their consequences must be brought to the attention of policymakers. The work of patient groups to ensure the recent inclusion of myeloma among rare diseases in Argentina may be helpful in focusing the attention of policymakers on this illness and improving access to novel therapies.

With strong and concerted efforts in all these directions, we can move closer to early and equitable care for myeloma that will guarantee better outcomes for patients across the board.



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