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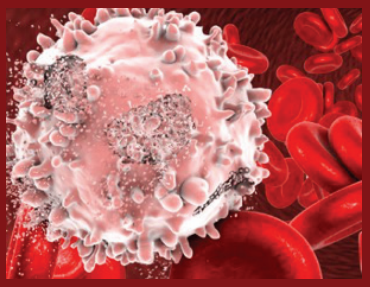

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Review Article : Adopting Molecular Testing for Solid Tumors in Latin America: Challenges and Opportunities

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Abstract:
Introduction: The advent of precision medicine, including molecular testing (MT), has revolutionized the cancer care landscape and may provide a path forward in the sustainability of cancer care.
Methods: Americas Health Foundation (AHF) identified a panel of seven experts in MT with backgrounds in clinical oncology, molecular pathology, and bioethics from Argentina, Brazil, and Colombia. They convened for a three-day virtual meeting on November 10-12, 2021, to discuss the need for widespread access and adoption of MT for solid tumors in Latin America (LA).
Results: The authors identified challenges in MT access in molecular medicine (MM) in LA and proposed suggestions to manage them. Development and implementation of human talent, infrastructure, and policy strategies are essential to provide MT in LA. This review outlines the substantial challenges faced by countries in LA to the widespread adoption of MT in oncology and provides recommendations on overcoming them.
Conclusions: Despite the many advantages of MT for solid tumors, the challenges for implementation in LA healthcare systems are sizable and multidimensional. These include regional deficiencies in trained teams, fragmented healthcare systems, and inefficiently distributed budget allocations.
Keywords: solid tumor, molecular testing, precision medicine, Latin America.

Introduction :

Latin America (LA) contains 8.5% of the world's population and is characterized by ethnic, social, economic, and political heterogeneity. Cancer is the second leading cause of death (1.4 million new cases and over 670,000 deaths annually) and represents a financial burden of over US$4 billion.[1] Although cancer incidence in the area is generally lower than in high-income countries (HICs), mortality is significantly higher. Sociodemographic changes, like population aging, urbanization, and economic growth, have led to a rapid upward shift in the region's cancer burden, with almost 10 million cases expected by 2040.[2,3]

The advent of precision medicine (PM), including MT, has revolutionized the cancer care landscape.[4] Oncology practice in most HICs has evolved in line with these advanced diagnostic platforms that establish disease and host factors and better characterize each cancer for a targeted approach. PM has proven more effective, less toxic, and produced improved outcomes compared to conventional chemotherapy. Although these diagnostic methods and associated targeted treatments (TT) carry high costs that have stifled PM uptake in limited-resource countries (LRC), MT is the cornerstone of precision oncology (PO). LA must consider access to high-value MT for moving toward modern oncology practice. This review assesses the substantial challenges LA faces to the widespread MT adoption in oncology and provides recommendations on overcoming them.

Methods

The AHF identified seven experts in pathology, hematology, oncology, genetics, and molecular biology from Argentina, Brazil, and Colombia. They were convened for a three-day virtual meeting on November 8-10, 2021, to develop recommendations for increasing the implementation of MT for solid tumors in LA. To identify the panel, AHF conducted a literature review using PubMed, MEDLINE, and EMBASE

to identify scientists and clinicians from LA who have published in the field of oncology and MT since 2016. Augmenting this search, AHF contacted opinion leaders from LA's medical field to corroborate that the list of individuals adequately represented the necessary fields of study. All the experts who attended the meeting are named authors of this manuscript. An AHF staff member moderated the discussion. The authors retain complete control over the content of the paper.

Search strategy AHF conducted a literature review using PubMed, MEDLINE, and EMBASE for any publications on MT. The following search terms were used: "solid tumor," "oncology," "molecular testing," and "screening" in combination with "Latin America," "Argentina," "Brazil," "Colombia," and "Mexico" from 01/01/2016 until 04/10/2021. The articles identified were in English, Portuguese, and Spanish. Particular attention was paid to identifying literature and research from LA.

AHF developed specific questions to address barriers limiting MT in LA and assigned one to each panel member. A written response to each question was drafted by individual panel members based on the literature review and personal expertise. The panel reviewed and edited each narrative during the three-day conference through numerous rounds of discussion until a total agreement was reached. The recommendations developed were based on the evidence gathered, expert opinion, and personal experience and were approved by the entire panel. After the conference, the final manuscript was distributed by email to the panel for review and approval.

Results

Clinical trials for PM

Traditionally, advances in oncology have been bolstered by large phase III clinical trials, on which health technology assessment (HTA) agencies in LA generally base evaluations. However, a "molecular-turn" has shifted the alignment between biology and treatment in the modern clinical trial era.[5] Identifying biomarkers that drive tumor proliferation, a new agent class targeting specific pathways replaces the traditional "one-size-fits-all" medicine. Instead of testing agents in a particular disease, researchers test a drug (or combination) in a molecularly defined disease subset. Such approaches required new trial designs because the patient number within each subtype is smaller. [6,7] New trial designs challenge regulatory agencies because HTA methodologies are not adapted for PM. Historically, HTA agencies have approved antineoplastic drugs exclusively for treating tumor types based on a histologic approach at single anatomic sites. In 2017, a basket trial that evaluated pembrolizumab in advanced solid tumors with microsatellite instability (MSI) or mismatch repair (MMR) deficiency led to the first FDA tissue-agnostic treatment approval.[8] This treatment works in tumors from different tissues because tumors from different organs may share the same molecular alterations and activated pathways, creating an opportunity to target the alteration.[2] This approval brought a paradigm shift in trial development, from conventional to biomarker-driven and tissue-agnostic trials.[3]

Basket trials are a modern design that assumes that the molecular markers foretell the response to TT, independently of tumor histology. They involve conducting several independent parallel phase II trials in distinct cancer types that share a unique molecular alteration.[9,10] Integrating PM into clinical trials drives research for infrequent molecular alterations, allowing patient allocation based on the genetic alterations of their tumors.[11] Adaptive trial design, another innovation, analyzes data at interim time points and allows changing participants' treatments.[12,13]

Following pembrolizumab approval, larotrectinib and entrectinib received agnostic approval for *NTRK*-fused neoplasms.[5] While it may not be effective for all tumors and molecular alterations, it introduces a new and exciting chapter in PM.[6]

Depending on the specific case and resources available, many MT methods are employed for solid tumors. Each method has both advantages and disadvantages (Table 1).

Table 1. Regulatory and access landscape of MT for solid tumors in LA

Molecular Test	Description	Advantages	Disadvantages
Immuno histochemistry	Labeled monoclonal antibodies identify specific proteins in normal and tumor tissues	- Relatively low cost - Fast turnaround - Can be directly interpreted using a conventional optical microscope - Can classify difficult to recognize tumors based only on morphology - Can determine the primary tumor - Can investigate markers associated with biological behavior and genetic alterations - Can predict response to target therapy	- May need confirmatory testing with NGS or a second assay - Variability in interpretation
In-situ hybridization	Uses molecular probes with a complementary sequence to a segment of DNA or RNA. Probes bind to targets that can be identified under a conventional or fluorescence microscope	- Can identify gene amplifications, deletions, and fusions. - Can identify ERBB2 gene amplification in breast cancer in cases where the IHC result was equivocal - Can identify ALK rearrangements in NSCLC and NTRK fusions - Objective or quantitative results reduces interpretation variability	- Time-consuming - High-cost - Genes or sequences being investigated must be known, making it impossible to identify a new fusion partner

Molecular Test	Description	Advantages	Disadvantages
Real-time PCR	Extraction of genetic material where sequences complementary to the gene or gene segment to be identified are used. The target sequence is amplified and thus, detected and quantified by fluorescence at each amplification cycle	- Allows rapid and quantitative analysis of mutation and fusion identification and gene expression evaluation - Variations in tissue fixation and processing have little impact on results - Large dynamic range and accurate quantification - Less interobserver variability	- Because specific primers must be used, it is challenging to detect unknown fusion through this method
Sanger sequencing	Involves electrophoresis and is based on the random incorporation of chain-terminating dideoxynucleotides by DNA polymeraseduring in vitro DNA replication	- Allows the identification of several molecular alterations, such as single-nucleotide variants	- Single gene-reaction evaluation method, which may restrict its application when a more comprehensive evaluation is needed - Sequencing for low number of targets (1-20) - Low sensitivity (limit of detection ~15-20)
Next-generation sequencing	Uses electrophoresis to massive parallel sequencing of DNA	- Ability to sequence hundreds or thousands of genes simultaneously - May be cost-effective - Fast turnaround - Comprehensive genomic coverage - High capacity with sample multiplexing - Evaluation of the main classes of genetic alterations (base substitutions, indels, copy number variations, and gene fusions/rearrangements). - Lower limit of detection - Permits analysis of tumor mutational burden (TMB) and MSI - Higher sample throughput	- Demands significant resources in terms of bioinformatics systems, data processing, and large data storage capabilities, which can be costly - Requires highly trained personnel

Benefits of MT

MT assists in diagnosis, prognosis, and treatment.[14] For example, cervical cancer screening can be complemented with human papillomavirus detection.[15] Circulating tumor DNA, or liquid biopsy (LB), is being studied as a biomarker for detecting lung cancer and other neoplasms.[16] In clinical practice, LB is used to genotype single genes such as *EGFR* or multiple genes using next-generation sequencing (NGS) to establish resistance mechanisms.[17]

In uncertain cytopathological or histopathological diagnosis, molecular biomarkers can refine or define etiology and management. For example, fine-needle aspiration of undetermined thyroid nodules can be submitted to genomic classifiers to aid in malignancy diagnosis.[18,19] For brain tumor diagnosis, where there is a natural biopsy size limitation and different tumors displaying overlapping morphological and immunohistochemical features, several molecular approaches have been used, including gene sequencing, methylation profiling, and copy number variation analysis.[20,21] This reduces interpretation variability and provides a more refined tumor classification, enabling accurate treatment, prognosis, and enrollment in appropriate clinical trials.[22] RNA-based sequencing is a powerful diagnostic tool for bone and soft tissue pathology, identifying gene fusions in common sarcoma subtypes and revealing new fusions and fusion partners.[23] For prognostic and predictive purposes, MT is commonplace to determine antineoplastic treatment in different clinical scenarios, often through complementary diagnostic tests. For patients, better treatment selection translates into less treatment toxicity. Additionally, treatment costs are lower since expensive interventions are avoided where biomarker results suggest no benefit.

Targeted treatment (TT) for solid tumors

Imatinib mesylate, used for *BCR-ABL1* positive chronic myeloid leukemia as the first targeted oncologic therapy, has revolutionized medicine.[24,25] Recently, non-small cell lung cancer (NSCLC) has become a prototype for PM. Several driver mutations that define tumor subsets with specific therapy sensitivity are known.[26] Following TT discovery for *EGFR*-mutant lung adenocarcinoma, many other driver genes and respective therapies have become available, and there is a growing list of potential new candidate genes.[27] Survival is improved in patients with tumors with altered driver genes and access to TT than in those without access.[28] For example, mortality from metastatic driver-positive NSCLC decreased by 6.3% annually from 2013 to 2016, corresponding to the approval of several TTs.[29] Brazilian guidelines recommend a molecular panel including at least *EGFR, ALK, ROS, BRAF,* and *NTRK* for advanced non-squamous NSCLC.[30] However, recommendations are lacking in other countries.

In colorectal cancer, *KRAS, NRAS,* and *HRAS* are frequently

altered by somatic mutations.[30] *RAS* and *BRAF* V600E are negative benefit predictors of anti-EGFR therapy.[31] The *BRAF* V600E mutation may occur in 4-10% of metastatic colorectal adenocarcinomas in LA. It guides TT such as BRAF inhibitor combinations, chemotherapy, anti-EFGR antibodies,[32] and MEK inhibitors. However, access in most of LA is lacking. [33,34] *NTRK* is a less frequent molecular alteration but is important due to the potential for treating with larotrectinib, which was recently approved in Brazil.[35]

In breast cancer, *ERBB2* amplification determines the HER2 enriched subtype and is widely validated as a response predictor to anti-HER2 therapies with improved outcomes.[36] About 40% of hormone-positive metastatic breast cancers have an activating *PIK3CA* mutation.[37]

Homologous recombination (HR) deficiency has been used for decades to predict response to poly adenosine diphosphate-ribose polymerase (PARP) inhibitors, specifically in ovarian, breast, prostate, and pancreatic cancers. Pathogenic variants, including germline and somatic events, in one of the BRCA genes are found in about 20% of patients with ovarian cancer. Overall, defects in DNA repair secondary to deficiency of HR pathways are detected in up to 50% of patients and have been associated with response to PARP inhibitor therapy.[38] Findings from four randomized studies supported the use of this drug class in the first line in patients with epithelial ovarian cancer. They contributed to its approval in some LA countries. [39] In breast cancer, despite the robust evidence that BRCA germline mutations predict benefits in using PARP inhibitors [40,41] or platinum agents,[42] data on somatic mutations are still preliminary.[43]

In castration-resistant prostate cancer, patients with HR pathway alteration are candidates for PARP inhibitor therapy, while germline BRCA mutation has been linked to PARP inhibitor benefit.[45-47] In advanced pancreatic cancer, a PARP inhibitor improved progression-free survival (PFS) as maintenance therapy in patients with *BRCA* germline mutations.[47]

NTRK gene fusions cause overexpression of activated tropomyosin kinase receptor proteins, resulting in persistent signaling, increasing tumor cell survival and proliferation.[48] NTRK tyrosine kinase inhibitors are active in several cancer types and histologies.[49] This alteration is one of the most important used to guide tumor-agnostic therapy and the first agnostic marker to be approved in LA (Brazil). *NTRK* fusions are described in 90-100% of infantile fibrosarcomas and secretory salivary gland carcinomas.[51,52] They may also be present in 2-15% of papillary thyroid carcinomas[53-55] and to a lesser extent in other tumors such as CRC and HER-2, drastically improving the survival of patients with this alteration.[55,56]

HER2 expression and amplification in gastrointestinal tumors and cholangiocarcinomas,[57-59] FGFR mutations or fusions in the bladder and biliary cancers [61-63] and *BRAF* mutations in melanoma and anaplastic thyroid cancers are examples of biomarker applications.[63-67]

Immunotherapy

Immune checkpoint blockade represents a breakthrough in cancer treatment by activating the immune system to attack tumor cells. Several biomarkers have arisen in clinical practice, such as *PD-L1* expression, microsatellite instability (MSI), and tumor mutational burden (TMB) assessment.[68] Both MSI and TMB are recommended as agnostic markers for anti-PD1 inhibitors, although clear guidance is lacking in LA. Microsatellites are simple nucleotide sequences in the genome. MSI is a marker of MMR deficiency, a system comprising four enzymes encoded by the *MLH1, MSH2, MSH6,* and *PMS2* genes, whose dysfunction can be germline (Lynch syndrome) or somatic, more often associated with epigenetic changes (*MLH1* methylation).[69] Detecting this alteration in somatic panels is associated with a potential response to immune checkpoint inhibitors in several histologic types.[70] This approach was the first agnostic cancer therapy approved in many HICs after failing at least one treatment line. After that, the FDA approved TMB as a second biomarker for anti-PD1 blockade for solid tumors, determined by NGS.[71] This treatment approval was based on a retrospective multi-arm basket trial.[72]

MT and associated treatments will gradually become a new standard of care. While many cancer-specific regional and national clinical practice guidelines exist throughout LA, they only limitedly consider molecular-guided therapy.[1] However, international guidelines (i.e., NCCN, ESMO, among others) recommend MT, especially regarding NSCLC.[73] Furthermore, molecular tumor boards may be an effective strategy to overcome diagnostic and management barriers in LA, where specialist availability is limited. To support comprehensive care in remote and rural areas, healthcare facilities could partner with regional or private academic centers to implement tumor boards remotely. Thus, molecular tumor boards will become as essential as disease-specific ones.[74]

The current knowledge of cancer biology and the variety of TT available render incorporating molecular methods in oncology and pathology critical. Expanding access to these methods could be cost-effective and should be considered to allow more precise diagnosis, early detection of cancer, and an effective PM approach.[75]

Access to MT in LA and cost considerations

MT is essential for diagnostics, treatment planning, and disease regression and progression monitoring. However, the benefits of PM have not permeated homogenously and are seen chiefly where sufficient access exists. The more PM advances, the greater disparities grow, underpinning the global variations in MT uptake. Despite efforts to improve coverage and reimbursement, molecular-based PM remains inaccessible to most of LA.[76]

MT in the region depends on healthcare budgets, pharmaceutical industry support, and out-of-pocket expenses. The introduction of MT in LA continues to occur under the aegis of pharmaceutical companies. However, this situation is unsustainable as it increases dependency on industry and limits the ability to negotiate drug prices due to the lack of MT coverage. Sponsored vouchers are an immediate solution for the widespread use of MT and overcoming the access gap momentarily.

LA has been acquiring modern technology for MT; however, access inequities to these technologies are pervasive. Because MT and TT are not standard of care in most public health systems in LA, very few cancer centers and laboratories offer them, as these are not routinely reimbursed.[77]Few LA centers

have the specialized equipment and trained personnel to perform MT, which is costly due to the reagents and platforms used. [78] Therefore, access is restricted mainly to reference centers, primarily concentrated in large cities.[73,79] Consequently, patients in remote areas are less likely to have access to MT.

Some strategies have increased patient access to molecular oncology in LA, including developing in-house NGS panels to reduce costs and improve availability.[80] However, the region must still improve to reach a value-based model for PM.

Cost-effectiveness

MT in oncology poses unique challenges to generating comparative clinical and economic evidence that proves clinical benefits and efficient use of limited healthcare resources. The economic impact of gene sequencing in low-and-middle-income countries has not been adequately studied. There are issues related to the feasibility, timeliness, and cost of conducting traditional randomized trials with adequate power to test whether PM truly provides clinically meaningful benefits and improves overall survival and quality of life (QoL).[81] Furthermore, the genetic admixture in LA could generate differences in treatment responses from one population to another, which should be evaluated before establishing TT.[82] The regulatory and access landscape is summarized in Table 2.

Table 2. Regulatory and access landscape of MT for solid tumors in LA

Genomic Alteration	Alteration and testing method	Most common Therapeutic Indications in Solid Tumors	Approval of targeted therapy		
			ARGENTINA	BRAZIL	COLOMBIA
ALK	Rearrangements and specific mutations: sequencing*, RT-PCR, IHC, ISH	Lung	crizotinib, alectinib	crizotinib, alectinib, brigatenib, lorlatinib- the private system only	crizotinib, alectinib
BRAF	Specific mutations: sequencing, RT-PCR, ddPCR, IHC	Melanoma, colorectal, NSCLC, biliary, neuroendocrine, anaplastic thyroid, glioma	dabrafenib + trametinib	dabrafenib + trametinib- Melanoma and NSCLC, vemurefinib + cobimetinib- melanoma private system only	Approved for melanoma
BRCA1 and BRCA2	Specific mutations, copy number variation: sequencing, RT-PCR, MLPA	Breast, prostate, ovarian, pancreatic	olaparib	olaparib (prostate, ovarian, pancreatic) niraparib (ovarian) private system only	Olaparib (breast and ovarian)
EGFR	Specific mutations: sequencing, RT-PCR, IHC, ddPCR	NSCLC	erlotinib, gefitinib, afatinib, osimertinib	erlotinib, gefitinib, afatinib, osimertinib, amivantamab- private system, public system- only first-generation agents (erlotinib, gefitinib)	erlotinib, gefitinib, afatinib, osimertinib
ER and PR	Protein expression: IHC	Breast	tamoxifeno, letrozol, anastrozol, fulvestrant	tamoxifeno, letrozol, anastrozol, fulvestrant, abemaciclib, ribociclib, palbociclib - Private and public system	tamoxifeno, letrozol, anastrozol, fulvestrant
FGFR2 *FGFR3*	Specific mutation/ rearrangement: sequencing, RT-PCR	Biliary, urothelial Urothelial	N/A	erdafitinib- Private care (urothelial)	N/A
ERBB2	Protein expression, gene amplification or mutation: sequencing, IHC, ISH	Breast, lung, colorectal, biliary, stomach, endometrial	trastuzumab, lapatinib, pertuzumab	trastuzumab, lapatinib, pertuzumab, T-DM1, trastuzumab deruxtecan- Private trastuzumab- public care (Breast only)	trastuzumab, lapatinib, pertuzumab breast
IDH1/IDH2	Specific mutations: sequencing, RT-PCR	Biliary	N/A	N/A	N/A
KIT	Specific mutations: sequencing, RT-PCR	GIST, melanoma	imatinib, nilotinib, regorafenib, sunitinib, pazopanib	imatinib- Private and public care (GIST) nilotinib, regorafenib, sunitinib - private (GIST)	Approved
MET	Specific mutation/ amplification: sequencing, RT-PCR, ISH	NSCLC	N/A	capmatinib, tepotinib- Private care	N/A

MSI/MMR	Multiple gene alterations/protein expression: Sequencing, RT-PCR, IHC	Agnostic use	pembrolizumab	N/A	N/A
NTRK	Rearrangements: sequencing, RT-PCR, IHC, ISH	Agnostic use	N/A	larotrectinib-Private care	N/A
PD-L1	Protein expression: IHC	head and neck, NSCLC, breast gastroesophageal, cervix, urothelial	Pembrolizumab, Nivolumab	Pembrolizumab, Nivolumab, ipilimumab, atezolizumab, durvalumab- Private	Approved for lung, head and neck, and urothelial (2nd line)
PGFRA	Specific mutations: sequencing, RT-PCR	GIST	Imatinib, Sunitinib, Regorafenib	Imatinib – public imatinib, Sunitinib, Regorafenib-Private care	Approved
PIK3CA	Specific mutations: sequencing, RT-PCR, ddPCR	Breast	Alpelisib	Alpelisib- Private care	N/A
RAS (KRAS/NRAS)	Specific mutations: sequencing, RT-PCR, ddPCR	Colorectal, NSCLC	N/A	N/A	N/A
RET	Rearrangement: sequencing, RT-PCR	NSCLC, thyroid	N/A	N/A	N/A
ROS1	Rearrangements: sequencing, RT-PCR, IHC, ISH	NSCLC	Crizotinib, Ceritinib	crizotinib - Private care	crizotinib

Discussion/Conclusion

Challenges

Despite the many advantages of MT for solid tumors, the challenges for implementation in LA are large and multidimensional. These include regional deficiencies in trained teams, fragmented healthcare systems, and inefficiently distributed budget allocations,as in Figure 1.

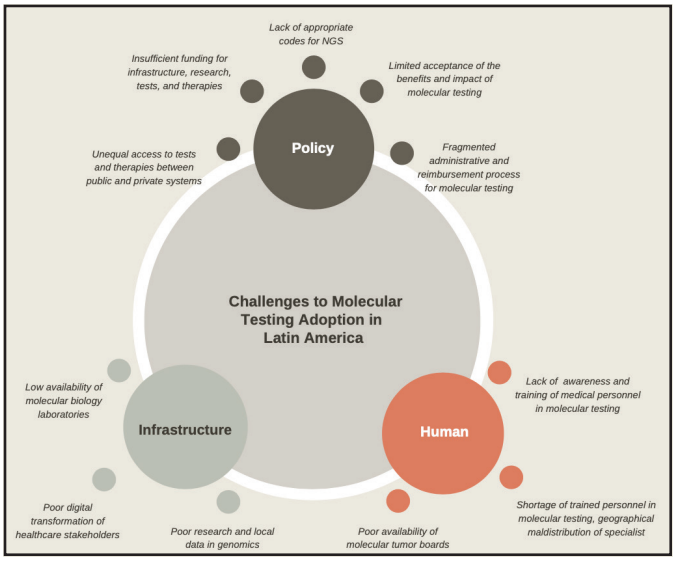

Fig. 1. Main gaps for the implementation of molecular oncology in Latin America

Cost

Despite the high up-front costs, this technology poses sizable potential savings by eliminating payments for ineffective drugs where biomarker results suggest no benefit. MT facilities require increased up-front investment in equipment and training. MT and TT's cost is considered a significant obstacle to widespread use in LA, [76] where limited resources are a chief concern. Methods such as NGS can cost up to 4-5 times higher in LA than in other regions because of taxes, analysis, and shipping expenses. Furthermore, there is a lack of optimized procurement strategies for high-cost TT, such as managed entry agreements, risk-sharing strategies, and pooled purchases that may help mitigate costs. For example, of 25 patients with advanced thyroid cancer from an Argentinian database, only 32% could afford to pay for genetic testing or had coverage through health insurance.[83]

Disconnects in coverage and reimbursement

There is limited acceptance of MT's value among policymakers. Few reimbursement decisions in LA are based on the test or therapy's value. Reimbursement is generally based on lump sums for healthcare institutions, laboratories, and systems, with cost and price considered the main criteria. The introduction of novel TT is not routinely linked to the regulatory approval of MT in LA, creating a lack of reimbursement for numerous clinically relevant tests in oncology. Conversely, some tests may be reimbursed without the availability of the appropriate TT. This fragmented approval system leads clinicians to conduct tests that might yield results they cannot act upon. For example, multiplex testing such as comprehensive NGS may offer multiple gene results that may respond to numerous clinical questions, leading to social, legal, ethical, and economic consequences. Furthermore, vast inequities exist between LA's public and private healthcare systems regarding access to MT and available therapies.

Off-label use

In most LA countries, there is a chasm between FDA/EMA and local regulatory approvals. As a result, local authorities consider many indications approved by these agencies as off-label. Because of the limited access to TT, physicians frequently prioritize the use of therapies that deviate from the standard of care, or patients must pursue lengthy and costly legal action to obtain reimbursement for off-label indications. This situation presents the ethical quandary of prescribing off-label drugs or

failing to act on test results. Off-label indications are sometimes available through compassionate-use programs, which provide a temporary solution.

Coding for MT

In Colombia, genetic testing is ordered through several nonspecific codes. Brazil and Argentina share a similar situation in that the codes in the public healthcare system for some MTs are inadequate. For example, there are no specific codes for NGS or methylation arrays in Brazil, and the indications approved for this testing are limited. The issue with nonspecific codes for a given biomarker is that actual coverage may be limited to a different, often less accurate testing modality.[84] Several efforts are underway to address these issues within each regulatory agency mentioned.

Lack of local genomic data

An essential challenge to implementing widespread MT is establishing the frequency of genetic alterations in different tumors to correctly characterize the cancer landscape in LA, which includes heterogeneous genetics derived from several ethnic groups and various lifestyle factors.[85] However, conducting high-quality cancer trials is challenging in resource-limited settings. Furthermore, clinicians trained in alternative design trials are scarce throughout the region.[89] The absence of regional or national genomic databases hinders platform development customized to the genomic characteristics of the population they serve. Such platforms may reduce costs and improve access.[80]

Training and awareness

MT in oncology requires an informed medical community and a collaborative environment between the relevant disciplines. Adequate quality is often cited as a barrier in resource-limited settings; thus, highly trained surgical and clinical oncology personnel, bioinformatics, pathology, genetic counseling, and molecular biology must avoid pre-analytical issues.[78] While physicians are more likely to order molecular tests for cancers such as lung and breast, training on adequate testing for cancers such as sarcomas and central nervous system is limited due to a lack of TT access. Consequently, in LA, reagents sometimes expire because MT is not ordered, further dissuading hospital administrations from acquiring the tests in the first place. Regionally, there is a general lack of awareness and education on MT's indications, benefits, and implications for solid tumors for all stakeholders, including the medical community, policymakers, and patients.[76]

Human and Technologic resources

MT requires a robust human, technological, financial, and bioinformatics resource infrastructure that most LA institutions lack. To execute reliable and accurate testing, experienced and trained personnel are crucial. Specialization programs, certifications, and education in molecular oncology are scarce; thus, a shortage of specialists pervades the region. Furthermore, as pathology departments and laboratories often receive insufficient funding, acquiring, and maintaining equipment represents a massive barrier to making MT available.[78]

Future of molecular oncology in Latin America

Molecular oncology is one of the five axes on which the future of cancer care moves in terms of prevention, diagnosis, and treatment. Digital health, interoperable databases, artificial intelligence (AI), and advanced analytics are the other four. The PM market in LA and the Caribbean was worth US$5.66 billion in 2021 and is projected to reach US$10-11 billion by 2026.[94] This projection is due to the expected demand for customized medical solutions, growth in healthcare technologies, favorable government regulations, and MT in clinical practice.[95] One of the broadest horizons for PM will be integrating AI. AI assists in several areas, including analysis of complex and heterogeneous data sets (multi-omics, inter-omics), data integration to provide a holistic disease molecular mechanism, identifying diagnostic and prognostic markers, and monitoring patient response to drugs/treatments and recovery. Digital pathology is another rapidly growing field. When incorporated with AI, digital pathology enhances workflows by allowing physicians to analyze images accurately and reduce subjectivity and human error. It also has the potential to broaden access by bridging the geographic disparities created by the concentration of specialists in major cities.

Despite these promising advances, the discussed barriers must be addressed to transform the healthcare systems, infrastructure, and human resources.[88] LA is still a long way from having the necessary capabilities and local genomic data required to migrate to in-house testing or include technologies such as LB in screening programs or follow-up. Moving forward, limited-resource countries must generate unique schemes to implement MT.

Recommendations

PM is a substantial challenge for the region due to socioeconomic conditions, especially the region's healthcare systems' infrastructure. The scarcity of data related to cost-effectiveness and the regional genomic profile makes it difficult to assess the real value that these technologies can deliver. Regional discussions should focus on overcoming the capabilities, knowledge, and access gaps. Incrementally, this would allow for developing and implementing strategies that create the transition from classical to next-generation cancer care in LA. The recommendations below seek to comprehensively address the challenges of effectively implementing MT for solid tumors in LA and achieving the four primary goals summarized in Figure 2.

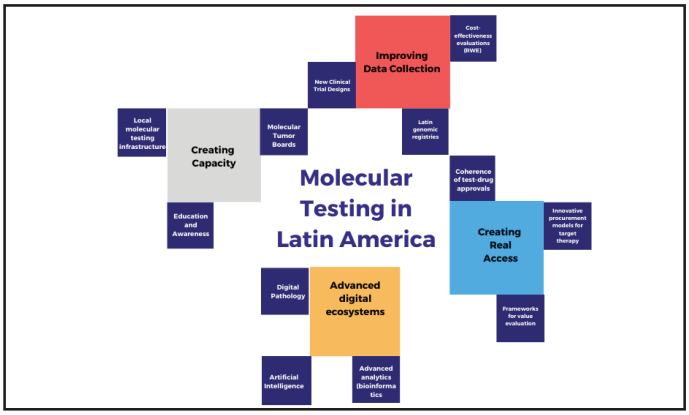

Fig. 2. Precision Oncology Implementation Blockers in Latin America

Human:

- Understand the clinical and economic value of PM strategies' benefits and opportunities for patients with solid tumors regarding health outcomes, QoL, and likely cost-effectiveness. (All Stakeholders)
- Prepare physicians and healthcare workers for genomic medicine by increasing education on PM for solid tumors, including when to order MT and act on results. (Medical Societies and Academic Institutions)
- Create molecular tumor boards that include clinical and surgical oncologists, pathologists, geneticists, bioinformatics experts, bioethicists, and other relevant specialists to ensure a multidisciplinary approach to diagnosis and management decisions in PO. (Health Institutions)

Infrastructure:

- Increase investments in pathology departments to reach the technological and human resources levels required for high-quality MT. (Government and Health Institutions)
- Address the PM specialist shortage by increasing training programs for bioinformatics, molecular biology, pathology, and oncology. (Academic Institutions, Ministry of Education, and Medical Societies)
- Prepare for the future of digital transformation of PM based on disruptive technologies that improve comprehensive cancer management, including AI, digital pathology, and advanced analytics. (All Stakeholders)
- Generate local data:

o Proponents of PO must continue to generate and disseminate evidence supporting MT's clinical and economic utility in LA. (Academic Institutions, Medical Community, and Medical Societies)

o Build country-specific or regional genetic databases to characterize the genomic landscape and lay the foundation for the future sustainability of in-house testing. (Government, Medical Societies, Academia, and Health Institutions)

o Design research to monitor the impact of PM and develop cost-effectiveness analyses with defined metrics to track outcomes, access, cost, and quality. (Government, Medical Societies, and Academia)

Policy:

- Foster policy that integrates innovative technology in oncology by optimizing dialogues between public and private sector stakeholders to develop sustainable funding mechanisms (i.e., MEA, risk-sharing agreements, pay-for-performance) that support the introduction of high-cost precision medicine in oncology (PO) interventions. (Government, Payers, and Medical Societies)
- Create a dedicated, value-based reimbursement pathway adapted to the requirements of MT and TT and implement it widely to streamline coherent approvals and improve equal access. (Governments and Regulatory Bodies)
- Concurrently evaluate molecular tests and the corresponding TT to enable comprehensive access to PO and ensure coherence between what is approved and reimbursed. (Governments and Regulatory Bodies)
- Create sufficient and specific molecular and genetic testing codes that support this technology's fair use, pricing, and reimbursement. (Government and Medical Societies)The

Statements

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature and the experience and opinion of an expert panel.

Conflict of Interest Statement

The authors have no conflicts of interest to declare

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FDAC. Writing-original draft, Investigation, formal analysis, validation.

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FP. Writing-original draft, Investigation, formal analysis, validation.

MRR. Writing-review and editing, visualization, conceptualization, methodology, project administration.

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