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Characterization of Screening Strategies for Lynch Syndrome in Latin America

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Abbreviations used in this paper: **CRC, colorectal cancer; dMMR, deficient MMR; GC, cancer genetic counseling; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; TS, traditional screening; UTS, universal tumor screening.**

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BACKGROUND & AIMS: **In Latin America, genetic testing for Lynch syndrome (LS) has been partially implemented. Traditionally, LS diagnosis relied on the Amsterdam criteria and Bethesda guidelines, collectively known as traditional screening (TS). However, TS may miss up to 68% of LS cases. To improve detection rates, universal tumor screening (UTS) has been introduced. UTS involves screening all newly diagnosed patients with colorectal cancer for molecular markers to more effectively identify LS cases.**

METHODS: **Clinical and molecular data on 1684 patients with colorectal cancer, collected between 1999 and 2020, were provided by 24 Latin American genetic cancer registries and centers. Germline genetic testing was not consistently performed across all cases.**

RESULTS: **LS screening strategies were available for 72% (1209/1684) of cases, with germline testing conducted in one-quarter (304/1209) of these. Most cases (78%; n = 943) underwent UTS, primarily in Argentina, Chile, and Uruguay, whereas 22% (266/1209) were screened through TS. UTS identified deficient mismatch repair tumors in 29% (272/943) of cases. The rate of LS confirmed by sequencing was higher with UTS (53.3%; 65/122) compared with TS (47.8%; 87/182), although the difference was not statistically significant ($P = .175$).**

CONCLUSIONS: **UTS is widely implemented in Latin America; however, the low detection rate of LS demonstrated in this study raises concerns about the routine use of germline genetic testing in our region. Our study provides real-world outcomes that highlight disparities in screening uptake and counseling referrals, illustrating the challenges that Latin American countries face in hereditary cancer syndrome screening. These results contribute to the rationale for designing effective screening strategies for LS, which may also be applicable to other hereditary cancer syndromes, ultimately.**

Keywords: Lynch Syndrome; Traditional Screening; Universal Tumor Screening; Latin America.

Genetic testing for Lynch syndrome (LS) is routinely used in Western populations. However, it has been partially implemented in Latin America.[1,2] Traditionally, cases of LS have been identified from personal and family histories using the Amsterdam criteria and Bethesda guidelines (herein termed as traditional screening [TS]). However, up to 68% of patients with LS may be missed when identified based on family history alone,[3] thus limiting the ability to identify and reduce the risk of colorectal cancer (CRC) and other types of cancer associated to LS.[4] Therefore, the use of universal tumor screening (UTS) was implemented as a molecular marker and involves the screening of all newly diagnosed patients with CRC, regardless of age and family history, by immunohistochemistry (IHC) or microsatellite instability (MSI) analysis[5,6]; and it has been shown to have >90% sensitivity of identifying cases with LS.[7] When complemented with tumor *MLH1* promoter methylation or *BRAF p.*V600E to exclude sporadic cancers, UTS has proven to be a cost-effective approach.[8]

Prospective and epidemiologic studies have shown that there are 4 different dominantly inherited MSI

cancer syndromes, caused by germline (likely) pathogenic variants in 1 of the 4 mismatch repair (MMR) genes (*path_MMR*): *MSH2*, *MLH1*, *MSH6*, and *PMS2* or by deletion of the 3′ end of *EPCAM (TACSTD1)*, which results in hypermethylation of the *MSH2* promoter.[9] Each syndrome has a differential penetrance and expressivity of CRC and non-CRC.[10] Therefore, the identification of LS is important for clinical management, such as for the decision for surgery, appropriate surveillance, and/or clinical trial eligibility. Additionally, it provides an opportunity for risk reduction and early cancer detection, with enhanced surveillance for at-risk family members.

In Latin America, there is an unbalanced distribution of resources and health care facilities in different geographic regions, not only when comparing high-income with low/middle-income countries, but also within countries (eg, rural vs urban areas).[11] Cancer genetic counseling (GC) services are scarce in some countries of Latin America but are growing despite limitations in infrastructure and qualified human resources. In a recent international collaborative study, we reported that 75% of participating centers have implemented GC for LS.[1] Because there are no regional guidelines or systematic screening for LS or other hereditary cancer syndromes in Latin America, this study aimed to characterize the current LS screening strategies, to explore the prevalence of LS, and to characterize the clinical and molecular profile of individuals with LS. We collected clinical, molecular, and genetic data of 1684 individuals with CRC from 24 existing cancer genetic registries/centers from 9 countries of Latin America.

What You Need to Know

Background

Lynch Syndrome (LS) diagnosis in Latin America traditionally relies on the Amsterdam criteria and Bethesda guidelines but may miss up to 68% of cases. Universal Tumor Screening (UTS) aims to improve detection by screening all newly diagnosed colorectal cancer (CRC) patients for molecular markers.

Findings

Data from 1,684 CRC patients revealed UTS is widely implemented, with 78% undergoing UTS. Although UTS identified more deficient mismatch repair tumors, the LS confirmation rate by sequencing was not significantly higher compared to Traditional Screening (TS).

Implications for patient care

UTS can enhance LS detection rates in Latin America, but the low overall detection rate highlights the need for improving and standardizing germline genetic testing across the region. Effective screening strategies for LS are crucial for better hereditary cancer syndrome management.

Material and Methods

Study Population

The Latin American Network on LS, established in 2011, was founded after the first characterization of germline *path_ MLH1* and *path_MSH2* variants in unrelated South American individuals suspected of having LS. This network is primarily composed of the membership directories of the Latin-America Study Group on Hereditary Tumors (LA-GETH), and research and clinical collaborators who are actively involved in the assessment and treatment of patients affected by LS.[1,2] The network's creation aimed to enhance the understanding of LS within the Latin American population by studying genetic mutations and providing clinical care. It serves as a platform for the exchange of research findings, clinical expertise, and advancements in genetic testing, with a focus on improving patient outcomes in hereditary cancer syndromes.

Twenty-four representative Latin American genetic cancer registries/centers were included in the study. Information on clinical history, personal/family history of cancer, and molecular and genetic testing data was collected between 1999 and 2020. The use of multigene panel testing began in the early 2010s at research and academic institutions in larger countries, such as Brazil, Argentina, Mexico, and Chile. Currently, multigene panel testing is accessible in many countries across Latin America, and most of these panels include genes associated with hereditary cancer predisposition, incorporating the analysis of large deletions and duplications as part of their genetic assessment protocols. Provider data were collected using an Excel format sheet and then curated and imported into PostgreSQL. In addition, a survey was performed to characterize the structure of the Latin American centers and their screening practice. The MMR variants were classified according to the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) database (http://insight-database.org/).

Lynch Syndrome Screening Strategies

UTS involved screening of all patients with CRC regardless of age at diagnosis or fulfillment of existing clinical criteria for LS, using MSI or IHC, with or without testing of *BRAF p.*V600E and/or *MLH1* promoter hypermethylation.

TS was applied if the patient met 1 or several of the following criteria: Amsterdam criteria (I or II)[12,13]; Bethesda guidelines[14]; and "Others" that included an isolated case of a patient tested for IHC, MSI, or *BRAF p.*V600E, and/or *MLH1* promoter hypermethylation.

Statistical Analysis

Descriptive statistics (frequencies and percentages) were obtained to describe the type of LS screening strategy and corresponding diagnostic methods applied to detect LS cases. The rate of LS cases confirmed by MMR sequencing (ie, true positives) was compared between the UTS and TS strategies using the Z-test. Cases having an unknown screening strategy were not considered in this analysis.

Descriptive statistics (mean, standard deviation, frequencies, and percentages) were applied to report clinical and molecular characteristics of the CRC cases by the screening strategy (UTS and TS), and genetic confirmation of LS (LS and non-LS cases). The differences of patients' characteristics between screening strategies or between LS outcomes were evaluated using the Fisher exact test. The respective differences of patients' age were evaluated using the T-test. These differences were evaluated only for characteristics with more than 20% of data available.

All reported $P < .05$ were considered statistically significant. Statistical analyses and figures of the study were performed using R software version 4.4.0.

Ethics Statement

The study has been approved by the Institutional Human Ethics Committees, institutional review boards, or national central authorities of the participating centers. Patients were informed of their inclusion in the study. Written informed consent was obtained from all participants during GC sessions. All reporting centers exported deidentified data.

Results

Demographics and Characteristics of the Latin American Genetic Cancer Registries/Centers

Out of the 24 representative Latin American genetic cancer registries/centers, 6 centers were located in 5 cities of Argentina: Buenos Aires (2), Rosario (1), Neuquén (1), Mendoza (1), and Córdoba (1). Five centers were located in 5 cities of Brazil: Salvador, Porto Alegre, Recife, São Paulo, and Vitoria. Four centers were located in 3 cities of Colombia: Medellin (2), Monteria (1), and Ibague (1). Three centers were located in 2 cities of Chile: Santiago (2) and Concepcion (1). Two centers were located in the city of Lima (Peru). In addition, 1 registry/center was also included from each of the following cities: Quito (Ecuador), Mexico DF (Mexico), San Juan (Puerto Rico), and Montevideo (Uruguay).

Available information about the infrastructure and screening strategy was obtained from 21/24 of the genetic cancer registries/centers. Almost half (42.9%; 9/21) of the cancer registries/centers were reported as private clinics, 23.8% (5/21) as academic or public entities, followed by public/university hospitals (9.5%; 2/21). A hereditary gastrointestinal service/program has been established by most of the participating centers (76.2%; 16/21). Interestingly, only 14.3% (3/21) of the centers (located in Argentina and Uruguay) have reported to have a national hereditary cancer program. The first CRC Family registry in Latin America started in 1992 (São Paulo, Brazil),[15,16] whereas the youngest one was recently implemented in the Northeastern of Brazil (Recife) in 2019. The average number of patients seen per month for initial gastrointestinal cancer risk assessment has been represented as follows: 0 (5%), 1–5 (47%), 6–10 (29%), 11–20 (14%), and 21–39 (5%) patients.

Lynch Syndrome Screening Diagnostic Practice in Latin America

In total, data were collected from 1684 patients with CRC: 1209 cases having and 475 not having information on the practice of the screening strategy (UTS or TS). Of the 1209 cases, 943 (78%) were found using the UTS strategy, mainly in Argentina, Chile, and Uruguay, whereas 266 met the clinical criteria (TS strategy) (Figure 1 and Table 1).

When UTS was used (n = 943), IHC was more frequently applied (85.5%; 808/943), either alone or in combination with another method. IHC plus MSI (44.2%; 418/943) was the most frequently combined method. Out of UTS-evaluated patients, 28.8% (272/943) showed abnormal results (deficient MMR [dMMR]) based on either 1 or more combined methods described in Table 2. Out of these UTS-evaluated patients, 12.9% (122/943) were submitted to germline sequencing, identifying 65 LS-confirmed cases (Table 2).

However, 266 CRC cases were enrolled by TS: 51.5% were based on the Amsterdam criteria (137/266) and 45.9% on Bethesda guidelines (122/266). Seven cases (3%) did not fully meet the Amsterdam or Bethesda criteria but were assessed by an isolated IHC or MSI or *BRAF p.*V600E testing. Out of these TS-evaluated patients, 68.4% (182/266) were submitted to germline sequencing, identifying 87 LS-confirmed cases (Figure 1).

When analyzing the screening strategy by country, UTS was mainly applied by Argentina (n = 21; 32.31%), followed by Uruguay (n = 15; 23.08%), Chile (n = 12; 18.46%), and Puerto Rico (n = 11; 16.92%) (Figure 2*A*). TS was mainly used in Colombia, (n = 61; 70.11%), followed by Brazil (n = 15; 17.24%) and Mexico (n = 7; 8.05%) (Figure 2*B*).

Rate of the path_MMR Variants by Screening Strategy

Overall, LS screening strategy and germline testing was available for 72% (1209/1684) and one-quarter

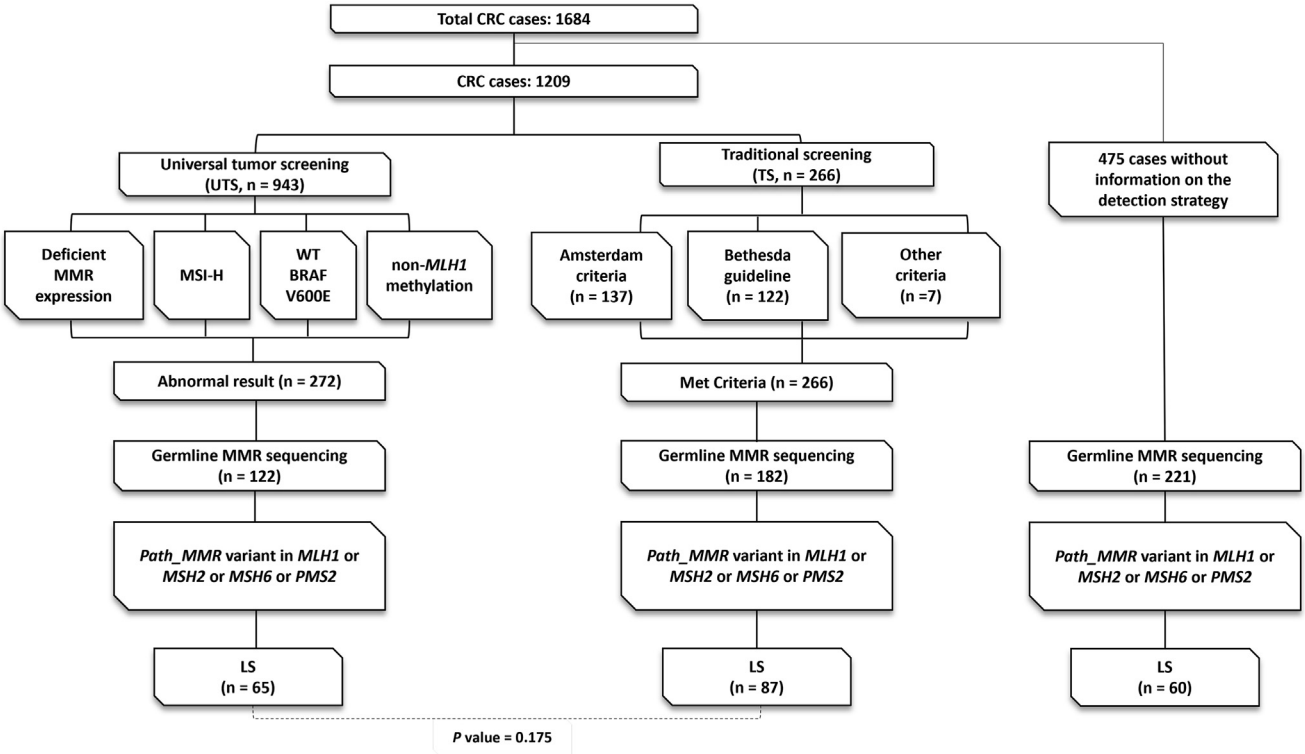

Figure 1. Flow diagram of the screening strategies for LS cases in Latin America. WT, wild type.

(304/1209) of the cases, respectively (Figure 1). Therefore, the rate of *path_MMR* variants and its comparison between UTS and TS strategies could be evaluated using only a reduced number of cases (ie, 304 cases with available germline testing). Despite no statistical difference ($P = .175$), the overall rate of positive LS cases confirmed by sequencing was higher for the UTS (53.3%; 65/122) than for the TS strategy (47.8%; 87/182) (Figure 1).

Profile and Frequency of the path_MMR Variants in Latin America

Regarding the profile and frequency of *path_MMR* variants, UTS identified 65 *path_MMR* carriers: 28 (43.08%) in *MLH1*, followed by 24 (36.92%) in *MSH2*, 6 (9.23%) in *MSH6*, 4 (6.15%) in *PMS2*, and 3 (4.62%) large deletions that involving *EPCAM* or *EPCAM-MSH2*. Of the 87 *path_MMR* carriers identified by TS, 47 (54.02%) had *path_MMR* variant in *MLH1*, 38 (43.68%) in *MSH2*, 1 (1.15%) in *MSH6*, and 1 (1.15%) in *PMS2* (Figure 3).

Clinical and Molecular Characterization of Lynch Syndrome and Non–Lynch Syndrome from Latin America

In total, 31.2% (525/1684) of CRC cases were sequenced; of these, 40.4% (212/525) were LS and 59.6% (313/525) were non-LS. The mean age at CRC diagnosis was 41 years (standard deviation, 11.5) and 47 years (standard deviation, 12.5), respectively ($P < .001$) (Table 3).

An overall profile of LS compared with non-LS cases from Latin America included a significant association between the location of the tumor ($P < .001$), with a predominance of right-sided tumors in the LS group. The personal history of multiple tumors and family history of CRC showed significant differences in the LS group ($P = .012$ and $P < .001$, respectively). However, non-LS patients presented more advanced disease at the diagnosis in comparison with LS (stage III and IV; $P = .039$). dMMR proteins were mostly reported for the LS group ($P < .001$). However, a similar MSI-high rate was observed for both groups. Regarding *BRAF p.*V600E, a mutation rate of 5.1% was observed in the non-LS group (Table 3).

Discussion

In Latin America, there are some challenges that low-resource setting cities are facing, including a lack of global implementation of cancer screening programs, accurate data and statistics that may aid the health authorities to guide future public health activities, and reorient strategies, interventions, and budgets to promote lifestyles that help prevent disease. Current cancer care does not fully reflect ethnic, cultural, environmental, and resource differences.[17]

In an effort to characterize hereditary cancer syndromes in Latin America, we have previously reported the genetic and clinical profile of individuals with LS, but there is limited information about the screening

Table 1. Overview of the Clinical, Molecular, and Family History Characteristics of 1684 Patients with CRC from Latin America, and by Use of LS Screening Strategy

	Total cohort	UTS	TS	
	n (%)	n (%)	n (%)	*P* value[a]
Total CRC cases	1684[b]	943	266	
Participating countries				—
Argentina	513 (30.5)	210 (22.3)	26 (9.8)	
Brazil	80 (4.7)	17 (1.8)	46 (17.3)	
Chile	504 (30.0)	456 (48.4)	3 (1.1)	
Colombia	126 (7.5)	3 (0.3)	122 (45.9)	
Ecuador	18 (1.1)	0 (0.0)	18 (6.8)	
Mexico	51 (3.0)	7 (0.7)	44 (16.5)	
Peru	23 (1.3)	0 (0.0)	7 (2.6)	
Puerto Rico	122 (7.2)	122 (12.9)	0 (0.0)	
Uruguay	247 (14.7)	128 (13.6)	0 (0.0)	
Age of CRC diagnosis				< .001
Mean ± STD	55 ± 17.3	56 ± 16.4	44 ± 13.9	
Median; 25th–75th percentile	55; 41–68	57; 44–68	44; 34–55	
Gender				.1452
Female	862 (51.2)	455 (48.3)	142 (53.4)	
Male	821 (48.7)	488 (51.7)	124 (46.6)	
Missing	1 (0.1)	0 (0.0)	0 (0.0)	
Tumor location				.0019[c]
Right colon	673 (40.0)	382 (40.5)	106 (39.8)	
Transverse colon	23 (1.3)	6 (0.6)	5 (1.9)	
Left colon	804 (47.8)	463 (49.1)	115 (43.2)	
Rectum	84 (5.0)	76 (8.2)	6 (2.3)	
Cecum	1 (0.1)	1 (0.1)	0 (0.0)	
Left and right	10 (0.5)	6 (0.6)	2 (0.8)	
Left and transverse	1 (0.1)	1 (0.1)	0 (0.0)	
Right, left, and transverse	1 (0.1)	1 (0.1)	0 (0.0)	
Missing	87 (5.1)	7 (0.7)	32 (12.0)	
Stage				< .001
I	218 (13.0)	132 (14.0)	20 (7.5)	
II	589 (35.0)	309 (32.8)	96 (36.1)	
III	513 (30.5)	324 (34.3)	59 (22.2)	
IV	235 (14.0)	136 (14.4)	54 (20.3)	
Missing	129 (7.5)	42 (4.5)	37 (13.9)	
Presence of multiple tumors				.5270
Yes	323 (19.2)	165 (17.5)	51 (19.2)	
No	1358 (80.6)	777 (82.4)	215 (80.8)	
Missing	3 (0.2)	1 (0.1)	0 (0.0)	
MMR expression				< .001
Normal	775 (46.0)	544 (57.7)	51 (19.2)	
Absent	387 (23.0)	259 (27.5)	76 (28.5)	
Missing	522 (31.0)	140 (14.8)	139 (52.3)	
MSI status				.0167
MSI-H	258 (15.3)	202 (21.4)	48 (18.0)	
MSS/MSI-L	408 (24.2)	352 (37.3)	48 (18)	
Missing	1018 (60.5)	389 (41.3)	170 (64.0)	
BRAF V600E				—
Yes	81 (4.8)	65 (6.9)	1 (0.5)	
No	300 (18.0)	251 (26.6)	39 (14.5)	
Missing	1303 (77.2)	627 (66.5)	226 (85.0)	
MLH1 methylation				—
Yes	22 (1.3)	19 (2.0)	3 (1.1)	
No	150 (9.0)	146 (15.5)	4 (1.5)	
Missing	1512 (89.7)	778 (82.5)	259 (97.4)	

Table 1. Continued

	Total cohort	UTS	TS	
	n (%)	n (%)	n (%)	*P* value[a]
Family history of CRC				.004
Yes	263 (15.6)	115 (12.2)	50 (18.8)	
No	1212 (72.0)	817 (86.6)	206 (77.4)	
Missing	209 (12.4)	11 (1.2)	10 (3.8)	
Affected MMR gene				—
MLH1	144 (8.6)	34 (3.6)	47 (17.7)	
MSH2/EPCAM	105 (6.2)	30 (3.2)	40 (15.0)	
MSH6	14 (0.8)	6 (0.6)	1 (0.4)	
PMS2	12 (0.7)	4 (0.5)	1 (0.4)	
Other	20 (1.2)	10 (1.0)	0 (0.0)	
Missing	1389 (82.5)	859 (91.1)	177 (66.5)	
Type of genetic variant in MMR genes (only class 4/5)				—
Nonsense	89 (5.3)	12 (1.3)	47 (17.7)	
Frameshift_Indel	55 (3.3)	14 (1.5)	12 (4.5)	
Missense	61 (3.6)	17 (1.8)	15 (5.6)	
Exon deletion	24 (1.4)	11 (1.2)	3 (1.1)	
Intronic	18 (1.0)	8 (0.8)	4 (1.5)	
Other	15 (0.9)	6 (0.6)	1 (0.4)	
Missing	1422 (84.5)	875 (92.8)	184 (69.2)	

NOTE. 25th–75th percentile refers to the interquartile range statistics. Em dash refers to test was not performed because of >80% missing data.
CRC, colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; STD, standard deviation; TS, traditional screening; UTS, universal tumor screening.
[a]Fisher exact test was used for the association of cases' categorical characteristics and detection of LS (missing category was not included in the evaluation). T-test was used to compare age of diagnosis between LS screening strategies.
[b]Total CRC cases, including cases with unknown LS screening strategy; 475 did not present a defined screening method.
[c]Evaluated only for tumor locations: right colon, transverse colon, left colon, rectum.

strategies across all countries. Limited access to genetic care and counselling tailor the need to design a systematic screening approach for cancer risk genetic assessment to reduce cancer burden in this region. This study reported the current LS screening strategies in a large cohort of 1684 individuals with CRC from 9 countries in Latin America (Argentina, Brazil, Colombia, Chile, Peru, Ecuador, Mexico, Puerto Rico, and Uruguay) collected between 1999 and 2020. We aim to contribute with some rationale for designing screening strategies for LS and highlight ongoing research and the need for inclusive data to better serve diverse populations in Latin America.

UTS is widely used in Latin America, particularly in Argentina, Chile, and Uruguay. These countries have been at the forefront of implementing molecular analysis and genetic testing protocols for LS since 2010. With the advent of new targeted treatments and a focus on personalized medicine in CRC, tumor molecular testing has rapidly evolved in Colombia in recent years. Following the introduction of immunotherapy for CRC, patients with stage II disease can now be selected for adjuvant 5-FU treatment based on their MMR results. Consequently, most pathology laboratories now routinely screen newly diagnosed patients with CRC for dMMR using IHC. Patients identified with dMMR are increasingly referred for genetic consultations to evaluate the need for germline testing and to receive GC.

The mutation detection rate of UTS (53.3%) was comparable with TS (47.8%), although by crude percentages the UTS seemed to be slightly more effective in identifying individuals with LS. This detection rate reflects the limitations of genetic testing for LS, because it was applicable only to a subset of suspected cases (eg, 55% of patients having abnormal results in 1 of the UTS methods, did not undergo germline sequencing). The challenges in obtaining comprehensive genetic testing underscore the need for improved strategies in identifying individuals at risk in the region. In line with our study, Adar et al[18] reported that the UTS detection rate was very low (1.7%), because not all patients received GC, and consequently did not undergo germline genetic sequencing.

The superiority of UTS has been widely reported[3,19] and it is recommended by the National Comprehensive Cancer Network and other societies.[20,21] In this study, the UTS strategy is estimated to correctly detect approximately 5.5% more LS cases than the TS approach. To our knowledge, in Latin America there is no health system/insurance that provide germline testing to all patients with CRC regardless of age; therefore, UTS strategy could be a feasible option to be implemented.

Regarding the genetic and molecular profile, we identified that 24% (75 out of 313) of non-LS cases exhibited MSI-H or loss of expression of MMR proteins, without a germline *path_MMR* variant. This condition is

Table 2. Yield of Universal Tumor Screening in Individuals with LS from Latin America

UTS									Germline MMR sequencing			Confirmed LS positive	
IHC	MSI	*BRAF* V600E	*MLH1* promoter methylation	n	%	Results from UTS	n	%[a]	n	%[a]	%[b]	n	%[c]
Yes	Yes	Yes	Yes	133	14.1	Deficient MMR expression and wt *BRAF* V600E and MSI-H and non-*MLH1* promoter methylated	5	3.8	2	1.5	40.0	1	50.0
			NA	104	11.0	Deficient MMR expression, wt *BRAF V600E* and MSI-H	17	16.3	7	6.7	41.2	4	57.1
		NA	Yes	8	0.8	Deficient MMR expression, MSI-H and non-*MLH1* promoter methylated							
			NA	173	18.3	Deficient MMR expression and MSI-H	35	20.8	28	16.7	80.0	18	64.3
						Normal MMR expression or MSS	5	100.0	5	100.0	100.0	5	100.0
	NA	Yes	Yes	0									
			NA	54	5.7	Deficient MMR expression and wt *BRAF* V600E	17	31.5	8	14.8	47.1	6	75.0
		NA	Yes	0									
			NA	336	35.6	Deficient MMR expression	126	37.5	26	7.7	20.6	16	61.5
NA	Yes	Yes	Yes	24	2.5	MSI-H, wt *BRAF V600*E and non-*MLH1* promoter methylated	5	20.8	2	8.3	40.0	0	
			NA	7	0.7	MSI-H and wt *BRAF* V600E	2	28.6	2	28.6	100.0	1	50.0
		NA	Yes	0									
			NA	104	11.0	MSI-H	60	57.7	42	40.4	70.0	14	33.3
Total				943	100.0		272	28.9	122	12.9	44.9	65	53.3

IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability analysis; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NA, not applied, UTS, universal tumor screening; wt, wild type.
[a]Percent from the number of samples submitted to UTS.
[b]Percent from the number of samples with UTS result.
[c]Percent from the number of samples submitted to germline MMR sequencing.

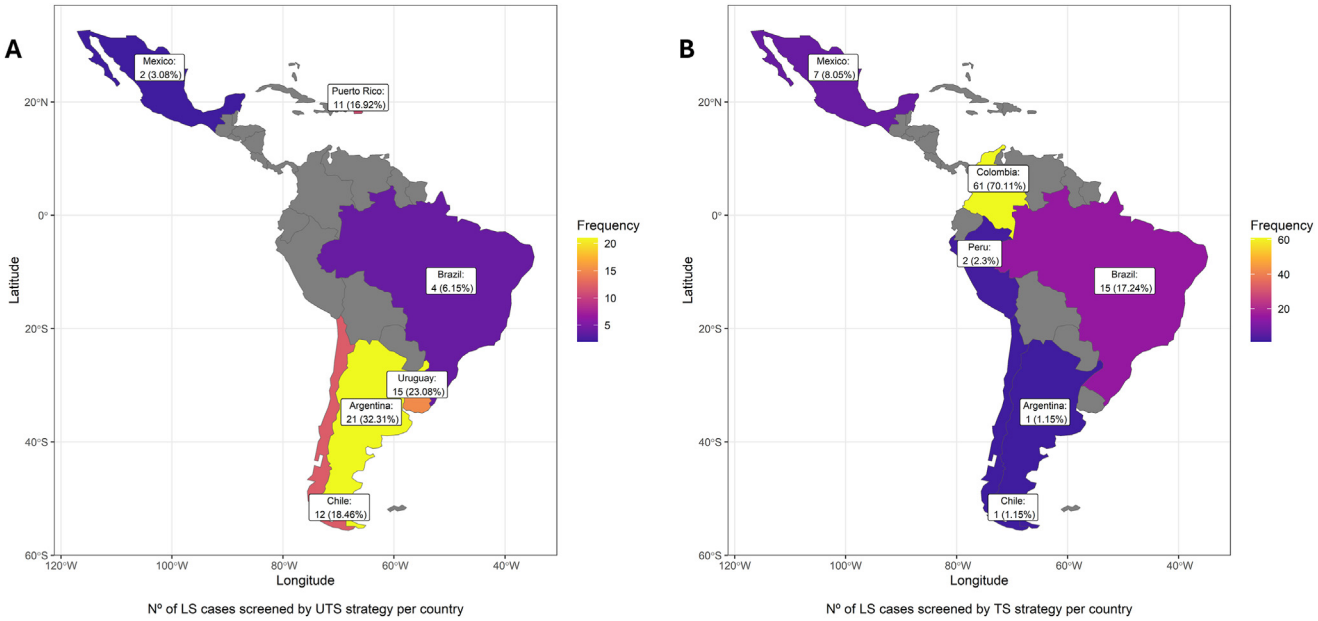

Figure 2. Frequency of LS individuals per country according to the screening strategies. (*A*) UTS (n = 65). (*B*) TS (n = 87).

commonly referred to as Lynch-like syndrome. These noninherited MSI CRC cases may also benefit from immunotherapy. This frequency (24%) is higher when compared with White populations (11.01%; 13/118).[22] Explanations for this include the occurrence of large rearrangements or false-positive screening results of MSI or IHC.[23] In addition, CRC cases were not investigated for the presence of biallelic somatic *path_MMR* variants, which have been reported to account for more than half of the CRC that could be classified as Lynch-like syndrome.[24] The inadequate classification of variants of uncertain significance in the MMR genes could also be a contributing factor. Additionally, pathogenic variants in other genes that may affect the MMR system, such *as MUTYH*, *POLE*, *POLD1*, and other candidate genes, cannot be ruled out. However, most participating cancer genetics centers are currently using panels that include several or even hundreds of cancer-associated genes.

In this study, we found that *path_MLH1* variants were more common than *path_MSH2* variants overall in our population, which contrasts with prospective studies[25] that reported a higher prevalence of *path_MSH2*

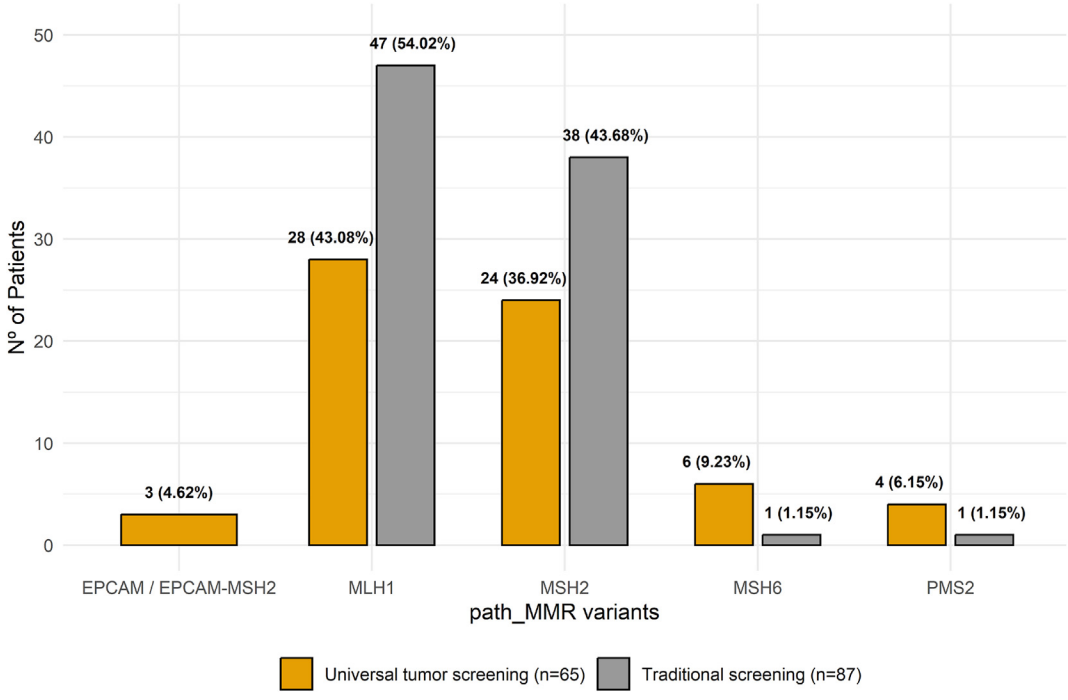

Figure 3. Frequency of the *path_MMR* variants identified by UTS and TS strategies per gene.

Table 3. Overview of the Clinical, Molecular, and Family History Characteristics Between LS and Non-LS Cases from Latin America

	LS	Non-LS	
	n (%)[b]	n (%)[c]	*P* value[a]
Total cases	212	313	
Participating countries			—
Argentina	27 (12.7)	52 (16.6)	
Brazil	24 (11.3)	40 (12.8)	
Chile	15 (7.1)	24 (7.6)	
Colombia	61 (28.8)	62 (19.8)	
Mexico	9 (4.2)	3 (1)	
Peru	2 (1.0)	0	
Puerto Rico	11 (5.2)	20 (6.4)	
Uruguay	63 (29.7)	112 (35.8)	
Age of CRC diagnosis			< .001
Mean ± STD	41 ± 11.5	47 ± 12.5	
Median; 25th–75th percentile	40; 34–48	47; 39–55	
Gender			.859
Female	111 (52.4)	161 (51.4)	
Male	101 (47.6)	152 (48.6)	
Tumor location			< .001
Right colon	106 (50.0)	129 (41.2)	
Transverse colon	9 (4.2)	9 (2.9)	
Left colon	61 (28.8)	162 (51.7)	
Rectum	2 (1.0)	9 (2.9)	
Missing	34 (16.0)	4 (1.3)	
Stage			.039
I	30 (14.2)	39 (12.5)	
II	85 (40.1)	123 (39.3)	
III	41 (19.3)	78 (25.0)	
IV	20 (9.4)	61 (19.4)	
Missing	36 (17.0)	12 (3.8)	
Presence of multiple tumors			.012
Yes	63 (29.7)	63 (20.1)	
No	148 (69.8)	250 (79.9)	
Missing	1 (0.5)	0 (0)	
MMR expression			< .001
Normal	9 (4.3)	70 (22.4)	
Absent	71 (33.5)	73 (23.3)	
Missing	132 (62.2)	170 (54.3)	
MSI status			< .001
MSI-H	48 (22.6)	75 (24.0)	
MSS/MSI-L	6 (2.8)	42 (13.4)	
Missing	158 (74.6)	196 (62.6)	
BRAF V600E			—
Yes	1 (0.5)	16 (5.1)	
No	24 (11.3)	35 (11.2)	
Missing	187 (88.2)	262 (83.7)	
MLH1 methylation			—
Yes	0	3 (1.0)	
No	1 (0.5)	16 (5.0)	
Missing	211 (99.5)	294 (94.0)	
Family history of CRC			< .001
Yes	153 (72.2)	91 (29.1)	
No	54 (25.5)	219 (69.9)	
Missing	5 (2.35)	3 (1.0)	

Table 3. Continued

	LS	Non-LS	
	n (%)[b]	n (%)[c]	*P* value[a]
Affected MMR gene			—
MLH1	116 (54.7)		
MSH2/EPCAM	80 (37.7)		
MSH6	10 (4.8)		
PMS2	6 (2.8)		
Type of genetic variant in MMR genes (only class 4/5)			
Nonsense	71 (33.5)		
Frameshift_Indel	50 (23.6)		
Missense	40 (18.9)		
Exon deletion	19 (9.0)		
Intronic	12 (5.6)		
Other	20 (9.4)		

NOTE. T-test was used to compare age of diagnosis between LS and non-LS cases. Em dash indicates test was not performed because of >80% missing data. 25th–75th percentile refers to the interquartile range statistics.
CRC, colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; STD, standard deviation.
[a]Fisher exact test was used for the association of cases' categorical characteristics and detection of LS (missing category was not included in the evaluation).
[b]The 212 LS cases includes 65 from UTS, 87 from TS, and 60 without a strategy available.
[c]The 313 non-LS cases includes 57 from UTS, 95 from TS, and 161 without a strategy available.

variants. Additionally, we observed a lower frequency of *path_PMS2* variants identified through TS. Identifying *path_PMS2* variants presents unique challenges because of its structure and the presence of pseudogenes.[26] This may also be because *path_PMS2* carriers predispose to develop CRC at a later age and may have less family history, making them less likely to be detected by the Amsterdam and Bethesda criteria. The same reasoning could apply to *path_MSH6* carriers.

The low detection rate of LS by the screening strategies demonstrated in this study does not indicate a limitation; rather, it raises concerns about the routine use of germline genetic testing in our region. Our study provides real-world outcomes that highlight disparities in screening uptake and counseling referrals, illustrating the challenges faced by Latin American countries in hereditary cancer syndrome screening. It also reflects the current state of genetic cancer care equity in Latin America, which is influenced by the structure and operation of each country's health care system, including access to genetic testing, population diversity, a shortage of genetic counselors and training, and limited financial resources

Conclusions

Our study reports that UTS has been implemented in Latin America, identifying a mutation rate similar to that of TS, with a slight improvement in diagnosing *path_MMR* variant carriers compared with the TS strategy. However, most dMMR CRC patients did not receive GC, even within cancer centers, because of either a lack of referral or personal choice. Additionally, not all patients who received GC opted for genetic testing.

Overall, our findings contribute to the rationale for designing effective screening strategies for LS, which may also be applicable to other hereditary cancer syndromes. This approach can facilitate appropriate surveillance for patients and their relatives, allowing them to benefit from medical management changes, including targeted therapies, eligibility for clinical trials, risk-reducing surgeries, surveillance and prevention of secondary malignancies, and GC and subsequent cascade testing for at-risk relatives.

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Conflicts of interest

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