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Current Perspective

A snapshot of current genetic testing practice in Lynch syndrome: The results of a representative survey of 33 Latin American existing centres/registries

Adriana Della Valle [a], Benedito Mauro Rossi [b], Edenir Inêz Palmero [c], Marina Antelo [d], Carlos Alberto Vaccaro [e], Francisco López-Kostner [f], Karin Alvarez [f], Marcia Cruz-Correa [g], Luisina Inés Bruno [h], Nora Manoukian Forones [i], Jorge Andres Rugeles Mindiola [j], José Buleje [k], Florencia Spirandelli [l], Mabel Bohorquez [m], Alicia Maria Cock-Rada [n], Yasser Sullcahuaman [o,p], Ivana Nascimento [q], Kiyoko Abe-Sandes [q], Leonardo S. Lino-Silva [r], Florencia Petracchi [s], Alejandra Mampel [t], Yeni Rodriguez [u], Norma Teresa Rossi [v], Claudio Benavides Yañez [w], Cladelis Rubio [x], Tirzah Braz Petta-Lajus [y], Elizabeth Lemos Silveira-Lucas [z], Geiner Jiménez [aa], Carlos Mario Muñeton Peña [ab], Carlos Reyes-Silva [ac], María de la Luz Ayala-Madrigal [ad], Julio Sánchez del Monte [ae], Richard Quispe [af], Alcides Recalde [ag], Florencia Neffa [a], Carlos Sarroca [a], Henrique de Campos Reis Galvão [b], Mariano Golubicki [d], Tamara A. Piñero [e], Pablo G. Kalfayan [e], Fabiana Alejandra Ferro [e], Maria Laura Gonzalez [e], Julyann Pérez-Mayoral [g], Celia Aparecida Marques Pimenta [i], Sandra Patricia Bello Uyaban [j], Ana Protzel [k,ah], Guiliana Chávez [k,ah], Milagros Dueñas [k,ah], María Luisa Guevara Gil [k], Enrique Spirandelli [l], Sergio Chialina [l], Magdalena Echeverry [m], Luis José Palacios Fuenmayor [n], Mariela Torres [o,p], Thais F.Bonfim Palma [q], Nadia Cambados Héritas [s], Claudia Martin [v], Alfonso Suárez [x], Michael Vallejo [x], Ana Rafaela de Souza Timoteo [y], Carlos Afanador Ayala [ab], Gabriela Jaramillo-Koupermann [ac], Jesús Arturo Hernández-Sandoval [ad],

* *Corresponding author*: Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Norway.
E-mail address: Mev.Dominguez.Valentin@rr-research.no (M. Dominguez-Valentin).

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Angélica Hernandez Guerrero [ae], Constantino Dominguez-Barrera [ai], Juan Carlos Bazo-Alvarez [aj,ak], Patrik Wernhoff [al], John-Paul Plazzer [am], Yesilda Balavarca [an], Eivind Hovig [al,ao], Pål Møller [al,ap], Mev Dominguez-Valentin [al,*], in collaboration with LA-GETH

[a] *Hospital Fuerzas Armadas, Grupo Colaborativo Uruguayo. Investigación de Afecciones Oncológicas Hereditarias (GCU), Montevideo, Uruguay*
[b] *Hospital Sirio Libanes, São Paulo, Brazil*
[c] *Molecular Oncology Research Center, Barretos Cancer Hospital, Brazil and Barretos School of Health Sciences, Dr. Paulo Prata - FACISB, Barretos, Brazil*
[d] *Oncology Section of the Public Hospital of Gastroenterology "Dr. C. B. Udaondo", Buenos Aires, Argentina*
[e] *Hereditary Cancer Program (PROCANHE), Hospital Italiano, Buenos Aires, Argentina and Instituto de Medicina Traslacional e Ingeniería Biomédica (IMTIB), CONICET, Instituto Universitario (IUHI), Hospital Italiano de Buenos Aires (HIBA), Argentina*
[f] *Laboratorio de Oncología y Genética Molecular, Clínica Los Condes, Santiago, Chile*
[g] *University of Puerto Rico Medical Sciences Campus Department of Medicine, San Juan, Puerto Rico*
[h] *Instituto Alexander Fleming, Buenos Aires, Argentina*
[i] *Gastroenterology Division, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil*
[j] *Instituto Medico de Alta Tecnologia Oncomedica, Monteria, Colombia*
[k] *Centro de Genética y Biología Molecular, Instituto de Investigación, Facultad de Medicina Humana, Universidad de San Martín de Porres, Lima, Peru*
[l] *Asesoría Genética Oncologica Sanatorio Parque, GO, Rosario, Argentina*
[m] *Grupo de Investigación Citogenética, Filogenia y Evolución de Poblaciones, Facultades de Ciencias y de Ciencias de Salud, Universidad Del Tolima, Ibagué, Colombia*
[n] *Instituto de Cancerología Las Americas, Medellin, Colombia*
[o] *Universidad Peruana de Ciencias Aplicadas, Lima, Peru*
[p] *Instituto de Investigación Genomica, Lima Peru*
[q] *Instituto de Ciências da Saúde/Universidade Federal da Bahia, Salvador, Brazil*
[r] *Departamento de Patologia, Instituto Nacional de Cancerologia, Mexico City, Mexico*
[s] *Centro de Educacion Medica e Investigaciones Clinicas (CEMIC), Buenos Aires, Argentina*
[t] *Hospital Universitario, Instituto de Genética, Area Genética UNde Cuyo, COIR Centro Oncológico de Integración Regional, Mendoza, Argentina*
[u] *Clinica Del Country, Bogota, Colombia*
[v] *Hospital Privado Universitario de Cordoba, Cordoba, Argentina*
[w] *Hospital Regional de Concepción, Concepcion, Chile*
[x] *Sociedad de Cirugía de Bogotá - Hospital de San José, Colombia*
[y] *Liga Norte-Riograndense Contra o Cancer, Natal, Brazil*
[z] *Consultorio Genetica Clinica, Porto Alegre, Brazil*
[aa] *Hospital Dr. Rafael Ángel Calderón Guardia, San José, Costa Rica*
[ab] *Unidad de Genética Médica, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia*
[ac] *Hospital de Especialidades Eugenio Espejo, Subproceso de Anatomía Patológica, Área de Genética Clínica, Quito, Ecuador*
[ad] *Instituto de Genética Humana "Dr. Enrique Corona Rivera" y Doctorado en Genética Humana, Centro Universitario de Ciencias de La Salud, Universidad de Guadalajara, Jalisco, Mexico*
[ae] *Departamento de Gastroenterologia, Instituto Nacional de Cancerologia de México, México City, Mexico*
[af] *Laboratorio de Genética Molecular Del Instituto de Servicios de Laboratorio de Diagnóstico e Investigación en Salud (SELADIS), La Paz, Bolivia*
[ag] *Facultad de Ciencias Medicas Médicas, Universidad Nacional de Asunción, Asuncion, Paraguay*
[ah] *Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima, Peru*
[ai] *Facultad de Enfermería, Universidad Particular Ricardo Palma, Lima, Peru*
[aj] *Research Department of Primary Care and Population Health, University College London, UK*
[ak] *Instituto de Investigación, Universidad Católica Los Ángeles de Chimbote (ULADECH-Católica), Chimbote, Peru*
[al] *Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway*
[am] *Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, Australia*
[an] *Independent Researcher, Heidelberg, Germany*
[ao] *Institute for Informatics, University of Oslo, Oslo, Norway*
[ap] *Department of Human Medicine, Universität Witten/Herdecke, Germany*

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Abstract We aimed to assess the current genetics practice to manage patients with Lynch syndrome (LS) across Latin America. A Latin American LS survey was sent out to 52 centres/registries, comprising a total of 12 countries from the region. Overall, 33 centres completed the survey, of which the oldest LS registry was established in 1992 in Sao Paulo (Brazil), and the youngest this year in San Jose (Costa Rica). In total, 87% (26/30) of the participating centres/registries belonging to the nine countries are performing genetic testing. Overall, 1352 suspected families were sequenced. Pathogenic variants were identified in 34% of the families, with slightly differing distribution of variants between females and males. *Path_MLH1* variants were identified in 39% of females and 50% of males ($p = 0.023$), while *path_MSH2* were identified in 37% of females and males, followed by *path_PMS2* in 11% of females and 8% of males, *path_MSH6* in 13% of females and 3% of males ($p < 0.001$) and *path_EPCAM* in 0.3% of females and 2% of males. In Latin America, 9 of 12 (75%) participating countries had implemented healthcare for LS. LS screening is inconsistently applied within Latin America healthcare systems because of structural differences in the healthcare systems between the countries.

1. Introduction

Massively parallel sequencing technologies have transformed testing practices for hereditary cancers by the use of multigene panels in most of the countries of Europe, North America, Australia and Asia [1]. However, cancer genetic services in some countries of Latin America are scarce, but growing, despite limitations in infrastructure and qualified human resources [2].

Genetic testing for Lynch syndrome (LS) is being routinely used only in a few of these countries [3]. There is still a challenge in the identification of LS carriers in Latin America because of the limited availability of cancer risk evaluation programs and genetic testing services *per se* [4].

The detection of germline pathogenic variants in mismatch repair (MMR) genes (*path_MMR*) is essential to assess the risk, management and surveillance of patients with LS and their family members. In Latin America, the genetic profile of LS has been recently characterised such that *path_MLH1* variants are most commonly identified in Perú (82%), Mexico (80%) and Chile (60%), while *path_MSH2/EPCAM* variants in Colombia (80%) and Argentina (47%) [3]. *Path_MSH6* and *path_PMS2* display an important presence in Brazil (15%) and Chile (10%) [3].

In the Latin American countries, training in human genetics and medical genetics is scarce. Genetic counselling is mainly offered by medical geneticists and other specialists with training in genetics. In addition, national and international collaborations in LS have been crucial, especially in generating knowledge about MMR gene variant classification and sharing of genetic practices within the region [5–10]. Collaborative efforts aim to ensure that all Latin Americans have access to genetic services and to bring additional awareness to medical professionals and public health leaders.

We here present an assessment of the current genetic practice and management of patients with LS across the Latin American countries and a description of the existing LS registries/centres, genetic testing and research initiatives in the region.

2. Material and methods

The Latin American LS network [3], the membership directories of the Latin America – Study Group on Hereditary Tumors (LA-GETH), as well as the scientific hereditary cancer network in Latin America were used to reach 52 genetic service centres/registries that assess and treat patients with LS in 12 of 26 countries of Latin America.

The survey questions focused on four different areas: current conditions in the genetic practice of LS management, status of the scientific research and collaborations within Latin America and abroad, an assessment of unmet needs and an assessment on recommendations for components of future regional resource centres.

2.1. Summary statistics

Provider data were collected using an Excel format document. Descriptive statistics, such as frequencies and percentages describing the characteristics of the participating centres, were calculated. To estimate the distribution of MMR variants over all centres, weighted frequencies and percentages were obtained, with weights assigned to each centre according to the following expression: (the number of affected families in the centre)/(the number of affected families over all centres). Distributions were calculated overall and stratified by sex. Proportions of MMR variants carried by males and females were compared using the Z-

test at 0.05 significant level. All quantitative analyses were performed using R software, version 3.5.2.

3. Results

3.1. Characteristics and structure of the LS centres/registries

Of the 52 invited centres/registries from 12 countries, 33 (63%) agreed to participate, where more than half (58%, 19/33) are located in Argentina (n = 7), Brazil and Colombia (n = 6 each) (Table 1 and Fig. 1). Of the 19 non-responding centres/registries, 12 of 19 (63%) do currently not have practitioners performing LS genetic testing. Seven centres/registries perform genetic testing in LS (n = 5), while not providing any feedback, and 2 of 19 performed genetic testing only for hereditary breast cancer.

In total, 33 centres/registries agreed to participate, while 3 of them reported to perform only research and 1 is no longer active (Table 1, Fig. 1). The oldest LS registry was established in 1992 in Sao Paulo (Brazil) [11], followed by Buenos Aires (Argentina) in 1996, while the youngest one was established in San Jose (Costa Rica) this year. The centres/registries (n = 33) have been supported by public university/hospitals (55%, 18/33) or private hospitals/clinics (45%, 15/33), which are mainly located in the respective capitals or large urban areas.

Regarding management of suspected patients with LS, 67% (20/30) centers assessing and treating patients with LS) described a general structure, including genetic counsellors, while only 63% (19/30) reported to provide psychological support. Insurance coverage (mainly partial) for genetic testing was described by 43% (13/30) of the participating registries, including Argentina (n = 5/7), Brazil (n = 2/6), Colombia (n = 2/6), Puerto Rico (n = 1/1) and Costa Rica (n = 1/1).

3.2. Current genetic practice to identify LS carriers

Of the 30 centres/registries, systematic microsatellite instability (MSI) testing was described for 4 of 30 (13.3%) centres, while immunohistochemistry (IHC) existed in 9 of 30 (30%) centers, and both types of analyses were undertaken in 5 of 30 (16.7%) of the participating centers/registries. Table 1 describes the profile of each participating country/center/registry by MSI and/or IHC analysis.

The most common clinical criteria used to select individuals to perform genetic testing were Amsterdam I or II criteria, followed by Bethesda guidelines, family history or early-onset colorectal cancer (CRC) diagnosis, in addition to the IHC or MSI results (Table 1).

In total, 87% (26/30) of the participating registries belonging to 9 countries are currently performing genetic testing using a panel of LS cancer–associated genes (>50% of the centers) (Table 1, Fig. 1). However, in 4 of 30 centers/registries where genetic testing is not yet implemented, only tumour (IHC or MSI) or family history analyses are already being performed for identifying patients most likely to carry a *path_MMR* variant (Table 1).

Genetic testing for the MMR genes was performed in 1.352 families. Class 4 or 5 MMR gene variants were identified in only 34% (including 681 affected cases belonging to 459 families). Variants were identified in *Path_MLH1* in 39% of females and 50% of males (43% overall), with significant higher presence in males than in females (p = 0.023); *path_MSH2* in 37% of females and males (37% overall); *path_MSH6* in 13% of females and 3% of males (9% overall), with significantly higher presence in females than in males (p = 0.0001); *path_PMS2* in 11% of females and 8% of males (10% overall) and *path_EPCAM* in 0.3% of females and 2% of males (1% overall) (Fig. 2A and B). The reported range for the mean age at diagnosis for *path_MMR* carriers was 23–51 years.

Some recurring *path_MMR* variants have been described frequently and exclusively in certain countries, suggesting founder effects. Nineteen percent (56/295) of the reported class 4/5 MMR gene variants in our survey have not been previously described in Europe, USA, Africa or Asia, which is probably because of the genetic background of the admixed Latin American populations (data not shown) [3,9].

The world reference database for MMR gene variants (InSiGHT) recommends submission of all MMR variants, irrespective of variants being benign, uncertain or pathogenic, to provide classifications of pathogenicity for MMR variants with evidential basis [12]. However, 65% (17/26) of the informing centers/registries do not report MMR variants to national or international databases. Regarding the non-MMR variant databases, only 23% (7/30) of the informing centers reported submission to Sistema de Información de tumores hereditarios (SITHER), Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) or Invitae.

3.3. Research and collaborations

More than half of the centres/registries reported performing research studies (58%, 19/33). The number of publications generated from hereditary CRC or LS research has been described to be up to 345 articles, with Brazil (49%) and Argentina (18%) having the highest number of publications.

Regarding national or international research collaborations, 55% (18/33) reported collaborations within Latin America, Europe, USA or Australia. One of the main topics of these collaborations is the interpretation and classification of the MMR variants to provide appropriate genetic counselling and clinical management for individuals and their relatives carrying these

Table 1
Overview of the participating LS centres/registries in Latin America.

Institution name	City	Country	Only MSI	Only IHC	Genetic Testing	Both	Number of affected families with cancer	Number of sequenced families	Criteria used to sequence	Number of affected cases with class 5/4 variants	Number of affected families with class 5/4 variants*	*path_MLH1*		*path_MSH2*		*path_MSH6*		*path_PMS2*		*path_EPCAM*	
												Female carriers	Male carriers	Female carriers	Male carriers	Female carriers	Male carriers	Female carriers	Male carriers	Female carriers	Male carriers
Hospital Italiano	Buenos Aires	Argentina	N	Y	N	Y	85	85	AMSI, AMSII, Bethesda, others	44	28	8	4	9	4	0	1	1	1	0	0
Instituto Alexander Fleming	Buenos Aires	Argentina	N	Y	N	Y	527	90	AMSI, AMSII, Bethesda, deficient IHC	27	21	5	3	5	2	6	0	0	0	0	0
Hospital of Gastroenterology "Dr. C. B. Udaondo"	Buenos Aires	Argentina	N	N	Y	Y	846	130	Deficient IHC, MSI-H, others	107	61	15	13	11	14	1	1	3	2	0	1
Centro de Educacion Medica e investigaciones Clinicas (CEMIC)	Buenos Aires	Argentina	N	N	N	Y	5	5	na	5	4	2	1	0	1	0	0	0	0	0	0
Hospital Privado Universitario de Cordoba	Cordoba	Argentina	N	Y	N	Y	13	4	Deficient IHC and others	3	2	0	0	1	1	0	0	0	0	0	0
COIR Centro Oncológico de Integración Regional	Mendoza	Argentina	N	N	Y	Y	5	5	Deficient IHC, MSI-H	7	3	2	1	0	0	0	0	0	0	0	0
Asesoría Genética Oncologica Sanatorio Parque	Rosario	Argentina	N	Y	N	Y	67	30	AMSI, AMSII, Bethesda	23	16	4	1	3	7	0	0	1	0	0	0
Instituto de Servicios de Laboratorio de Diagnóstico e Investigación en Salud (SELADIS)[a]	La Paz	Bolivia	na	na	Na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Barretos Cancer Hospital	Barretos	Brazil	N	N	Y	Y	510	134	na	151	58	9	14	17	4	9	1	3	1	0	0
Instituto de Ciências da Saúde/Universidade Federal da Bahia	Salvador	Brazil	N	Y	N	Y	23	12	AMSI, AMSII, Bethesda, deficient IHC, others	na	6	3	1	1	0	0	0	0	0	1	0
Sirio Libanes Hospital	Sao Paulo	Brazil	N	Y	N	Y	248	248	AMSI, AMSII, deficient IHC	na	58	12	7	12	8	0	0	12	7	0	0
Universidade Federal de Sao Paulo (UNIFESP)	Sao Paulo	Brazil	N	N	N	Y	101	95	Bethesda	na	22	5	6	3	3	4	1	0	0	0	0
Liga Norte-Riograndense contra o Cancer	Natal	Brazil	N	N	N	Y	10	10	AMSI, AMSII, Bethesda	1	1	1	0	0	0	0	0	0	0	0	0
Consultorio Genetica Clinica	Porto Alegre	Brazil	N	N	N	Y	1	1	Others	1	1	0	0	0	0	0	1	0	0	0	0
Hospital Regional de Concepción	Concepcion	Chile	N	Y	N	Y	16	4	AMSI, AMSII, Bethesda, deficient IHC, others, prediction models	na	2	1	1	0	0	0	0	0	0	0	0
Clínica Los Condes	Santiago	Chile	N	Y	N	Y	105	80	AMSI, AMSII, Bethesda, deficient IHC	54	31	13	7	5	1	0	0	3	0	2	0
Hospital de San José	Bogota	Colombia	N	N	N	Y	20	14	AMSI, AMSII, Bethesda	3	2	1	0	0	1	0	0	0	0	0	0
Clinica del Country	Bogota	Colombia	Y	N	N	Y	26	20	AMSI, AMSII, Bethesda	na	5	1	0	2	0	0	0	2	0	0	0
Universidad de Antioquiaa	Medellin	Colombia	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Instituto de Cancerología Las Americas	Medellin	Colombia	N	N	N	Y	na	55	AMSI, AMSII, Bethesda, deficient IHC, others	na	12	1	2	5	0	0	0	4	0	0	0

Instituto Medico de Alta Tecnologia Oncomedica	Monteria	Colombia	N	N	Y	Y	42	na	Cascade Testing	na	20	3	6	3	5	0	0	1	2	0	0
Universidad del Tolima	Ibague	Colombia	N	N	N	Y	69	69	AMSI, AMSII, Bethesda, others	na	13	3	0	5	5	0	0	0	0	0	0
Hospital Dr. Rafael Ángel Calderón Guardia	San Jose	Costa Rica	N	N	N	Y	8	3	Cascade Testing	1	1	1	0	0	0	0	0	0	0	0	0
Hospital de Especialidades Eugenio Espejo	Quito	Ecuador	Y	N	N	N	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Universidad de Guadalajara	Jalisco	Mexico	Y	N	N	N	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Departamento de Patologia, Instituto Nacional de Cancerologia (INC)	Mexico City	Mexico	N	Y	N	Y	10	10	AMSI, AMSII, Bethesda, deficient IHC	5	5	3	1	0	1	0	0	0	0	0	0
Departamento de Gastroenterologia, INC	Mexico City	Mexico	N	N	Y	N	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Universidad Nacional de Asunción[b]	Asuncion	Paraguay	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Instituto de Investigación Genomica	Lima	Peru	N	N	N	Y	8	8	AMSI, AMSII	11	8	2	1	1	1	1	0	1	1	0	0
Universidad de San Martín de Porres	Lima	Peru	N	N	N	Y	35	35	Bethesda	25	20	13	5	1	0	1	0	0	0	0	0
Hospital Nacional Edgardo Rebagliati Martins	Lima	Peru	N	N	N	C	na	na	Bethesda	na	na	na	na	na	na	na	na	na	na	na	na
University of Puerto Rico Medical Sciences Campus	San Juan	Puerto Rico	N	N	N	Y	27	27	AMSI, AMSII, Bethesda, others	23	20	1	3	7	6	1	1	1	0	0	0
Grupo Colaborativo Uruguayo (GCU)	Montevideo	Uruguay	Y	N	N	Y	na	178	AMSI, AMSII, Bethesda, deficient IHC	190	39	12	11	4	3	5	0	2	1	0	1
							2807	1352		681	459	121	88	95	67	28	6	34	15	3	2

IHC: immunohistochemistry; MSI: microsatellite instability; N: No; Y: Yes; na: not applied/not available; C: in collaboration; * Class 5/4 variants are identified in probands in families; AMSI: Amsterdam criteria I; AMSII: Amsterdam criteria II; MSI-H: microsatellite instability analysis-high.

[a] Only research.

[b] Not active; others: family history or early-onset CRC diagnosis.

Fig. 1. Overview of the participant centres/countries and the profile of the current use of IHC and MSI analysis in Latin America. IHC: immunohistochemistry; MSI: microsatellite instability.

variants. The Prospective Lynch Syndrome Database (PLSD) (www.plsd.eu) is an international, multicentre database recording prospective observational data on *path_MMR* carriers to provide age- and organ-specific cancer risks according to gene and gender and to determine survival after these cancers. Three countries (Argentina, Chile and Uruguay) have contributed data to this worldwide effort.

In addition, a low participation rate to international scientific societies, such as the International Society of Gastrointestinal Hereditary Tumors (InSiGHT) (18%) followed by the Collaborative Group of the Americas (CGA) (12%) and the European Hereditary Tumor Group (EHTG) (6%), has been reported. Interestingly, 24% (8/33) of the participating centres/registries are members of the Study Group of Hereditary Tumors (LA-GETH), while 58% (15/26) described having access to an international expert opinion (mainly European).

With the aim to strengthen capacity by stimulating research, developing networks, and to deliver training and education in our region, we initiated these activities in 2005 in some countries of South America, and, from 2016, we invited other countries than South America, including Costa Rica, Mexico and Puerto Rico. Thus, we have been established as a LA-GETH. Since its inception, more than ten reports have been published, with enhanced participation in international multicentre collaborations, including the PLSD [13–17] (Dominguez-Valentin *et al. in press*). Funding applications to national and European agencies are ongoing. In this scenario, and with the aim of

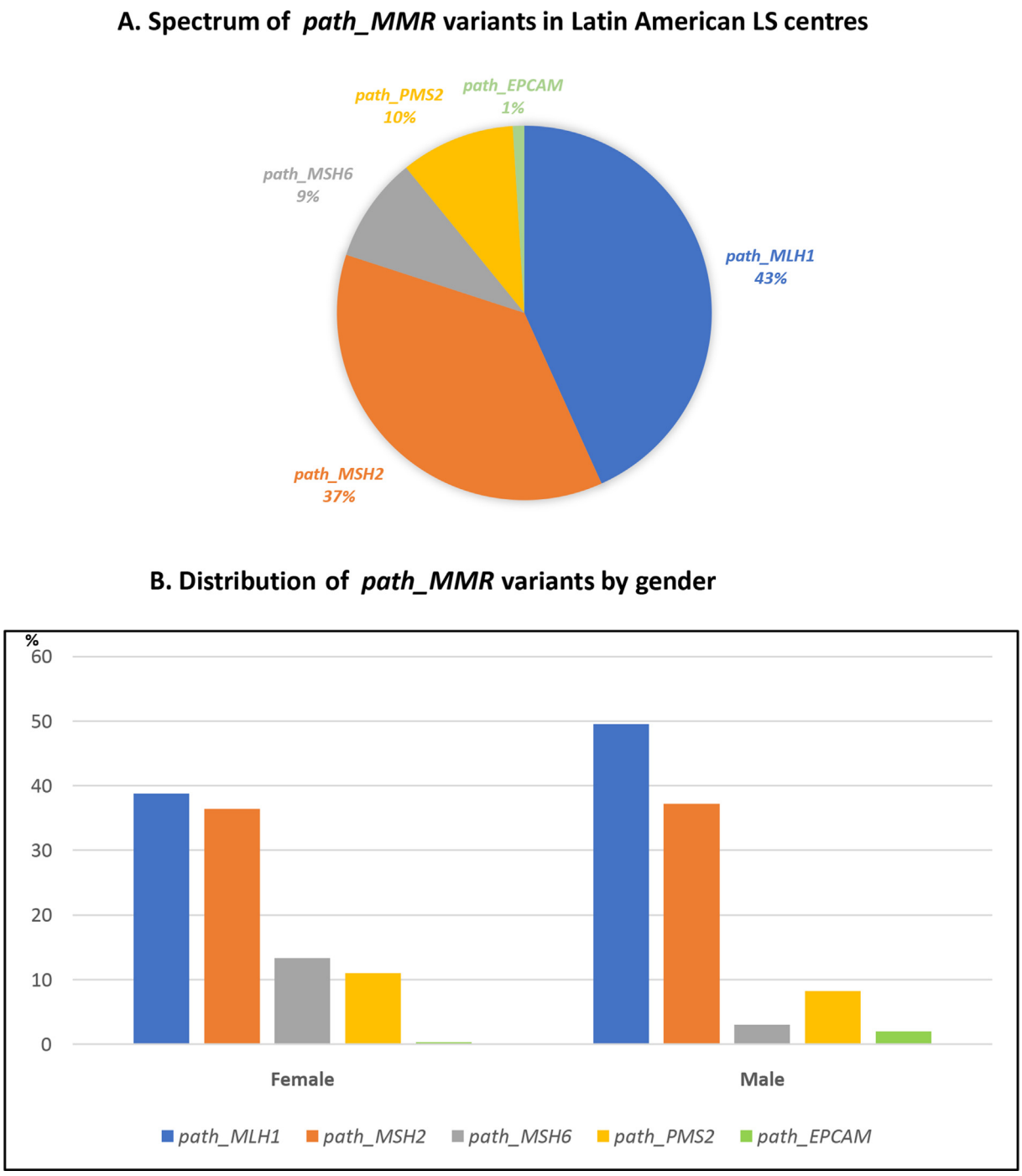

Fig. 2. (A) Spectrum of *path_MMR* in Latin American countries; (B) Distribution of *path_MMR* variants by gender. LS: Lynch syndrome.

providing specialised training in cancer genetic counselling to Latin America healthcare professionals, a pioneering initiative was started in Chile, consisting of an e-learning course in cancer genetic counselling. The study methodology includes an e-learning–based education platform (distance learning) and 40 h of an onsite workshop held at Clínica Las Condes (5 days). e-Learning methodology allows professionals located in distant areas to undergo this unique kind of academic training, thus having nearly 32% of international students participating from Colombia, Peru, Argentina and the Dominican Republic. A total of 39 students have graduated in the years from 2013 to 2015, including 27 medical doctors, 8 nurses and 4 MSc/PhD's. Five of these students became part of our Latin American collaborative studies on LS as they obtained the education and training to work in genetic counselling.

4. Discussion

Of the 26 countries from Latin America, our study described the current practice in LS clinical and genetic testing in 46% (12/26) of the countries. We here report the largest number of LS cases from Latin America (n = 459), including 12 new participating centres/registries from 7 countries, including Argentina (n = 3), Brazil (n = 2), Colombia (n = 3), Chile (n = 1), Mexico (n = 1), Puerto Rico (n = 1) and Ecuador (n = 1). Excepting Argentina, Brazil and Colombia, most of these centres/registries are located in the country capitals.

To our knowledge, there are no previous LS reports from Cuba, Dominican Republic, El Salvador, Nicaragua, Panama, Venezuela, Guatemala, Haiti and Honduras. Therefore, there is a need in our region to transfer the current practice used in clinical genetic risk assessment, which relies on family history and tumour phenotype to identify individuals who warrant germline MMR DNA sequencing. The limitation on genetic testing has an impact on the evaluation of the patients at risk of hereditary cancer and on their relatives. Current conditions and clinical management practices in medical genetics have recently been described in other populations [1,18].

The CRC profiles vary between the countries, thus providing a unique opportunity for diverse genetic studies in our populations. Nineteen percent (56/295) of the reported class 4/5 MMR gene variants in our survey have not been previously described in Europe, USA, Africa or Asia (data not shown). The Amerindian or mestizo origin from some populations of Latin America, or the genetic admixture background of Brazil, may explain the high frequency of novel variants in MMR genes. In addition, there may be some *de novo* mutations not present elsewhere. Importantly, we described a high frequency of *path_MSH6* and *path_PMS2* variants and their predominance in female carriers in our populations. However, larger studies are needed to validate this, and sample sizes may represent one of the limitations of the study.

Genetic testing for LS is not routinely available, and LS screening is inconsistently applied within the healthcare systems in Latin America. In countries where genetic testing for LS is available, some centres send abroad to commercial laboratories (mainly to the US because of the attractive costs), including some centres from Chile (n = 2), Argentina (n = 1) and Peru (n = 1), while other centres perform local testing, including centres mainly from Brazil, Uruguay and Argentina. In Brazil, 70–80% of the population relies on the public healthcare system, which does not provide genetic testing [19]. Interestingly, the 71%, 33% and 67% of the centers from Argentina, Brazil and Colombia, respectively, reported a partial insurance coverage. The only participating centre from Puerto Rico reported full insurance coverage for testing.

Some of the barriers that most of these countries are facing include a limited number of adequately trained healthcare professionals to perform LS risk assessment, a high cost of genetic tests and lack of insurance coverage for such genetic tests. Furthermore, the lack of supportive healthcare policies, limited awareness about hereditary cancer and its risks by patients and physicians, few educational opportunities in cancer genetics and the lack of infrastructure constitute some of the challenges for Latin America [3].

Our study has a number of significant strengths. One such strength is its focus on the prevalence of LS in the general population of Latin America, and for the first time, stratified by gender. We reported the profile of pathogenic MMR variants, *MLH1* or *MSH2* being the most affected genes followed by *PMS2*. *Path_MLH1* variants were significantly higher in males than in females ($p = 0.023$), while *path_MSH6* variants, in females than in males ($p = 0.0001$).

Another strength is the high number of LS centres/registries gathered in this study. Our approach is in line with the strength of collaborations within the region and the standardisation of genetic methods, analysis and sharing data to provide a precise diagnosis. We are currently developing strategies for reaching out and encouraging as many of the Latin America LS centres as possible to engage in international scientific societies and collaborations.

5. Conclusion

Our study brings knowledge on the genetic background of LS in Latin America and may enable the identification of multiple frequent founder variants, which subsequently may be subjected to testing in the areas where they occur. The local organisations of healthcare for LS may be used as models for healthcare of other inherited cancers, which may include effectively and efficiently collecting and collaborating with different areas of medicine, including surgeons, clinicians, biologists, nurses and oncologists.

We have highlighted differences across countries and have determined what additional information and infrastructure is still needed to move forward towards uniform international testing practices and management guidelines. Evidence about the importance of national and international collaborations that could impact and improve management of patients with LS is provided. There is an obvious need for increasing international collaboration.

We aim to translate our findings to the public health systems, which are instrumental in the implementation

of genetic testing for hereditary cancers. This implementation is expected to ultimately reduce the suffering of patients and their family members from preventable cancers, decrease waste in healthcare system costs and inform on strategies to facilitate the promise of precision medicine.

Conflict of interest statement

The authors declare no conflicts of interest.

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