

# From colorectal cancer pattern to the characterization of individuals at risk: Picture for genetic research in Latin America

Carlos Alberto Vaccaro<sup>1</sup>, Francisco López-Kostner<sup>2</sup>, Della Valle Adriana<sup>3</sup>, Edenir Inez Palmero<sup>4</sup>, Benedito Mauro Rossi<sup>5</sup>, Marina Antelo<sup>6,7</sup>, Angela Solano<sup>8</sup>, Dirce Maria Carraro<sup>9</sup>, Nora Manoukian Forones<sup>10</sup>, Mabel Bohorquez<sup>11</sup>, Leonardo S. Lino-Silva<sup>12</sup>, Jose Buleje<sup>13</sup>, Florencia Spirandelli<sup>14</sup>, Kiyoko Abe-Sandes<sup>15</sup>, Ivana Nascimento<sup>16</sup>, Yasser Sulcahuaman<sup>17,18</sup>, Carlos Sarroca<sup>3</sup>, Maria Laura Gonzalez<sup>1</sup>, Alberto Ignacio Herrando<sup>1</sup>, Karín Alvarez<sup>2</sup>, Florencia Neffa<sup>3</sup>, Henrique Camposreis Galvão<sup>4</sup>, Patricia Esperon<sup>3</sup>, Mariano Golubicki<sup>19</sup>, Daniel Cisterna<sup>19</sup>, Florencia C. Cardoso<sup>8</sup>, Giovana Tardin Torrezan<sup>9</sup>, Samuel Aguiar Junior<sup>9</sup>, Célia Aparecida Marques Pimenta<sup>10</sup>, Maria Nirvana da Cruz Formiga<sup>9</sup>, Erika Santos<sup>5</sup>, Caroline U. Sá<sup>5</sup>, Edite P. Oliveira<sup>5</sup>, Ricardo Fujita<sup>13</sup>, Enrique Spirandelli<sup>14</sup>, Geiner Jimenez<sup>20</sup>, Rodrigo Santa Cruz Guindalini<sup>21</sup>, Renata Gondim Meira Velame de Azevedo<sup>22</sup>, Larissa Souza Mario Bueno<sup>23</sup>, Sonia Tereza dos Santos Nogueira<sup>24</sup>, Mariela Torres Loarte<sup>17,18</sup>, Jorge Padron<sup>25</sup>, Maria del Carmen Castro-Mujica<sup>26</sup>, Julio Sanchez del Monte<sup>27</sup>, Carmelo Caballero<sup>28</sup>, Carlos Mario Muñeton Peña<sup>29</sup>, Joseph Pinto<sup>30</sup>, Claudia Barletta-Carrillo<sup>26</sup>, Gutiérrez Angulo Melva<sup>31</sup>, Tamara Piñero<sup>1,32</sup>, Paola Montenegro Beltran<sup>26</sup>, Patricia Ashton-Prola<sup>33</sup>, Yenni Rodriguez<sup>34</sup>, Richard Quispe<sup>35</sup>, Norma Teresa Rossi<sup>36</sup>, Claudia Martin<sup>36</sup>, Sergio Chialina<sup>14</sup>, Pablo German Kalfayan<sup>1</sup>, Juan Carlos Bazo-Alvarez<sup>37,38</sup>, Alcides Recalde Cañete<sup>39</sup>, Constantino Dominguez-Barrera<sup>40</sup>, Lina Nuñez<sup>41</sup>, Sabrina Daniela Da Silva<sup>42,43</sup>, Yesilda Balavarca<sup>44</sup>, Patrik Wernhoff<sup>45</sup>, John-Paul Plazzer<sup>46,47</sup>, Pål Møller<sup>45,48,49†</sup>, Eivind Hovig<sup>45,50,51†</sup>, and Mev Dominguez-Valentin<sup>45†</sup>, in collaboration with GETH

<sup>1</sup>PROCANHE- Instituto de Medicina Traslacional e Ingeniería Biomédica (IMTIB)-CONICET, Instituto Universitario del Hospital Italiano (IUHI), Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

<sup>2</sup>Laboratorio de Oncología y Genética Molecular, Clínica Los Condes, Santiago, Chile

<sup>3</sup>Hospital Fuerzas Armadas, Grupo Colaborativo Uruguayo, Investigación de Afecciones Oncológicas Hereditarias (GCU), Montevideo, Uruguay

<sup>4</sup>Molecular Oncology Research Center, Barretos Cancer Hospital, Brazil & Barretos School of Health Sciences – FACISB, Barretos, SP, Brazil

<sup>5</sup>Hospital Sirio Libanes, São Paulo, Brazil

<sup>6</sup>Oncology Section of the Public Hospital of Gastroenterology “Dr. C. B. Udaondo”, Buenos Aires, Argentina

<sup>7</sup>Instituto de Salud Colectiva, Universidad Nacional de Lanús, Buenos Aires, Argentina

<sup>8</sup>Sección de Genotipificación, Departamento de Análisis Clínicos, Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina

<sup>9</sup>AC Camargo Cancer Center, Sao Paulo, Brazil

<sup>10</sup>Gastroenterology Division, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil

<sup>11</sup>Grupo de Investigación Citogenética, Filogenia y Evolución de Poblaciones, Facultades de Ciencias y de Ciencias de Salud, Universidad del Tolima, Ibagué, Colombia

<sup>12</sup>Departamento de Patología, Instituto Nacional de Cancerología, Mexico City, Mexico

<sup>13</sup>Centro de Genética y Biología Molecular, Instituto de Investigación, Facultad de Medicina Humana, Universidad de San Martín de Porres, Lima, Perú

<sup>14</sup>Servicio de Coloproctología y Asesoría Genética en Cáncer, Hospital Español de Rosario, Rosario, Argentina

<sup>15</sup>Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, Brazil

<sup>16</sup>Instituto de Ciência da Saúde e Núcleo de Oncologia da Bahia, Salvador, Brazil

<sup>17</sup>Universidad Peruana de Ciencias Aplicadas, Lima, Peru

<sup>18</sup>Instituto de Investigación Genómica, Lima, Peru

<sup>19</sup>Molecular Laboratory, Hospital of Gastroenterology “Dr. C. B. Udaondo”, Buenos Aires, Argentina

<sup>20</sup>Hospital Dr. Rafael Angel Calderón Guardia, Caja Costarricense de Seguro Social, San Jose, Costa Rica

**Key words:** colorectal cancer, hereditary, lynch syndrome, Latin America

†Joint authorship: GETH: Hereditary Tumors Study Group.

**Conflicts of interest:** Rodrigo Santa Cruz Guindalini has declared as a consultant and speaker at Astrazeneca (Brazil) and Honorarium in mendelics Analise Genomica.

**Grant sponsor:** Helse Sor-Øst RHF; **Grant sponsor:** Helse Sor-Øst; **Grant sponsor:** Radium Hospital Foundation; **Grant sponsor:** The Norwegian Breast Cancer Society; **Grant numbers:** 194751-2017; **Grant sponsor:** Kreftforeningen

**DOI:** 10.1002/ijc.31920

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**History:** Received 17 Jul 2018; Accepted 19 Sep 2018; Online 10 Oct 2018

**Correspondence to:** Mev Dominguez-Valentin, Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway, Tel.: +4-740-381-634, E-mail: mev.dominguez.valentin@rr-research.no

- <sup>21</sup>Faculdade de Medicina-Universidade de São Paulo and Clínica de Oncologia/grupo (CLION), Clínica de Assistência à Mulher (CAM), Bahia, Brazil
- <sup>22</sup>CLION and CAM, Bahia, Brazil
- <sup>23</sup>Complexo Hospital Universitário Professor Edgar Santos, Universidade Federal da Bahia, Bahia, Brazil
- <sup>24</sup>ONCOCLIN (Clínica Oncológica), Manaus, Brazil
- <sup>25</sup>Fundación Santa Fé de Bogotá, Bogota, Colombia
- <sup>26</sup>Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru
- <sup>27</sup>Instituto Nacional de Cancerología de México, México City, México
- <sup>28</sup>Genpath, Asunción, Paraguay
- <sup>29</sup>Unidad de Genética Médica, Departamento de Pediatría, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia
- <sup>30</sup>Unidad de Investigación Básica y Traslacional, Oncosalud-AUNA, Lima, Peru
- <sup>31</sup>Centro Universitario de los Altos, Universidad de Guadalajara, Jalisco, México
- <sup>32</sup>INTIB-Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
- <sup>33</sup>Departamento de Genética da Universidade Federal do Rio Grande do Sul (UFRGS) e Serviço de Genética Médica do Hospital de Clinicas de Porto Alegre (HCPA) & Rede Brasileira de Câncer Hereditário, Porto Alegre, Brazil
- <sup>34</sup>Clinica del Country, Bogota, Colombia
- <sup>35</sup>Laboratorio de Genética Molecular del Instituto de Servicios de Laboratorio de Diagnóstico e Investigación en Salud (SELADIS), La Paz, Bolivia
- <sup>36</sup>Hospital Privado Universitario de Cordoba, Cordoba, Argentina
- <sup>37</sup>Research Department of Primary Care and Population Health, University College London, London, United Kingdom
- <sup>38</sup>Centro de Estudios de Población, Universidad Católica los Ángeles de Chimbote (ULADECH-Católica), Chimbote, Perú
- <sup>39</sup>Facultad de Ciencias Medicas Médicas, Universidad Nacional de Asunción, Asuncion, Paraguay
- <sup>40</sup>Facultad de Enfermería, Universidad Particular Ricardo Palma, Lima, Peru
- <sup>41</sup>National Institute of Cancer, Buenos Aires, Argentina
- <sup>42</sup>Lady Davis Institute for Medical Research and Segal Cancer Center, Jewish General Hospital, Montreal, QC, Canada
- <sup>43</sup>Department of Otolaryngology-Head and Neck Surgery, McGill University, Montreal, QC, Canada
- <sup>44</sup>Division of Preventive Oncology, German Cancer Research Center and National Center for Tumor Diseases, Heidelberg, Germany
- <sup>45</sup>Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway
- <sup>46</sup>Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, Australia
- <sup>47</sup>Department of Medicine, Melbourne University, Melbourne, Australia
- <sup>48</sup>Department of Medical Genetics, Oslo University Hospital, Oslo, Norway
- <sup>49</sup>Department of Human Medicine, Universität Witten/Herdecke, Witten, Germany
- <sup>50</sup>Institute of Cancer Genetics and Informatics, Oslo University Hospital, Oslo, Norway
- <sup>51</sup>Department of Informatics, University of Oslo, Oslo, Norway

Colorectal cancer (CRC) is one of the most common cancers in Latin America and the Caribbean, with the highest rates reported for Uruguay, Brazil and Argentina. We provide a global snapshot of the CRC patterns, how screening is performed, and compared/contrasted to the genetic profile of Lynch syndrome (LS) in the region. From the literature, we find that only nine (20%) of the Latin America and the Caribbean countries have developed guidelines for early detection of CRC, and also with a low adherence. We describe a genetic profile of LS, including a total of 2,685 suspected families, where confirmed LS ranged from 8% in Uruguay and Argentina to 60% in Peru. Among confirmed LS, *path\_MLH1* variants were most commonly identified in Peru (82%), Mexico (80%), Chile (60%), and *path\_MSH2/EPCAM* variants were most frequently identified in Colombia (80%) and Argentina (47%). *Path\_MSH6* and *path\_PMS2* variants were less common, but they showed important presence in Brazil (15%) and Chile (10%), respectively. Important differences exist at identifying LS families in Latin American countries, where the spectrum of *path\_MLH1* and *path\_MSH2* variants are those most frequently identified. Our findings have an impact on the evaluation of the patients and their relatives at risk for LS, derived from the gene affected. Although the awareness of hereditary cancer and genetic testing has improved in the last decade, it remains deficient, with 39%–80% of the families not being identified for LS among those who actually met both the clinical criteria for LS and showed MMR deficiency.

### Colorectal Cancer Pattern in Latin America

Based on the 2012 GLOBOCAN database, the most common cancers in Latin America and the Caribbean were prostate, breast, cervix uteri and colorectal cancer (CRC), followed by lung and gastric cancer (combined for both

sexes). A representative marker of economic development and extent of westernization in Latin American and the Caribbean States is that of the increasing incidence of CRC, which now ranks as a top five cancer in approximately 80% of its countries.<sup>1</sup>

The global burden of CRC is rising, with 2.2 million predicted new cases (and 1.1 million deaths) by 2030.<sup>2</sup> Within Latin America and the Caribbean, the highest mortality of CRC was found in Trinidad and Tobago, Uruguay, Barbados and Argentina, while the highest increasing trends in mortality were found in Brazil, Chile and Mexico.<sup>3</sup> The high rates of CRC could be associated with lifestyle behaviors, including diet, physical inactivity, overweight and obesity, but may also reflect the limited availability of screening programmes, early diagnosis and curative treatment programmes in these countries. This is the result of suboptimal organization of national health systems, as well as social, cultural and economic inequalities in these countries.<sup>3–6</sup>

CRC also represents a major health challenge in Europe. While most countries in Europe have established guidelines for the management of CRC, in which population screening plays a vital role, there are still knowledge gaps regarding improved prevention and treatment of CRC. Compared to Europe, the Latin America and Caribbean population still has a lower cumulative risk of CRC (1.6 vs. 3.5 for incidence and 0.8 vs. 1.4 for mortality, for Latin America and Caribbean vs. Europe, respectively), but the numbers for Latin America and Caribbean are expected to increase.<sup>1,3,7</sup> Some of the differences may be related to lower levels of reporting of CRC cases in Latin America and the Caribbean, and insufficient organization and funding of cancer registries compared to Europe and United States. Only 6% of the Latin America and the Caribbean population is covered by population-based cancer registries, compared to 96% of the United States and 32% of the European populations.<sup>5,8</sup>

### CRC Screening and Early Detection

CRC primarily affects men and women above 50 years of age. However, recent data show that younger adults are becoming more affected in the Latin America and the Caribbean countries.<sup>4,8</sup> Effective CRC screening programs may reduce its incidence by detection and removal of precursor lesions and its mortality by early diagnosis of localized disease, when accompanied by effective diagnostic follow-up procedures and treatment.<sup>9,10</sup> While representing a highly preventable disease, and perhaps the most preventable of cancers,<sup>11–14</sup> the majority of the Latin American countries lacks adequate systematic screening or prevention programmes. It is widely accepted that general screening of people above 50 years is a cost-effective and efficacious way of reducing CRC.<sup>9,10</sup> From our literature research, only nine (20%) of the Latin America and the Caribbean countries have developed guidelines for early detection of CRC (Argentina, Brazil, Chile, Colombia, Cuba, Ecuador, Mexico, Puerto Rico and Uruguay), based on fecal immunochemical testing (FIT), sigmoidoscopy, or colonoscopy. Even in these countries, low adherence to the CRC guidelines remains a challenge – as does the fact that the screening programmes are mainly covering urban areas. In contrast, 24 out of 28 European Union countries had

established or were preparing to establish nationwide screening programmes in 2015.<sup>15</sup>

### Genetic Profile for Hereditary CRC: Lynch Syndrome

There is currently an incomplete picture of the risk attributable to inherited, environmental or lifestyle factors for CRC. Understanding the hereditary risk will refine the clinical management and genetic counseling of these patients and their families.

Lynch syndrome (LS) is caused by a defective mismatch repair (MMR) system due to the presence of pathogenic variants in at least one of the MMR genes (*path\_MLH1*, *path\_MSH2*, *path\_MSH6* and *path\_PMS2*) or due to deletions of the 3' portion of the *EPCAM* gene.<sup>16</sup> However, the presence of *PMS2* pseudogenes complicates the analysis of pathogenic variants in a clinical settings, where diagnostic laboratories should apply strategies, e.g. DNA-based or RNA-based long-range PCR with a forward primer in the unique *PMS2* exon 10, to detect pathogenic point variants in exons 11–15, and/or multiplex ligation-dependent amplification (MLPA) to detect large deletions and duplications in the gene conversion region and, and/or using PCR primers based on paralogous sequence variants (PSV) to avoid sequences homologous to exons 1–5 of *PMS2*.<sup>17</sup>

Currently, patients with CRC are referred to germline MMR testing based on the identification of high-risk phenotypic features (i.e. early age of onset, family history, clinical criteria).<sup>18–20</sup> Systematic screening for LS by MMR immunohistochemistry (IHC) was first included in the National Comprehensive Cancer Networking (NCCN) guidelines in 2017.<sup>21</sup> Until regional guidelines consider and adopt this systematic screening, patients with CRC in Latin America are after NCCN recommendations. This points out the awareness and capacity of physicians to identify potential LS candidates. Genetic testing for hereditary CRC patients has not been routinely used in all countries from Latin America and the Caribbean. Even in the developed world, genetic screening has not yet been fully deployed.

The diagnosis of LS has been aided by the advent of next-generation sequencing (NGS). This technology allows clinicians to simultaneously test multiple genes with massive parallel sequencing in a cost-effective manner. The number of genes in a panel range from two to >100 and the use of gene panels to test for hereditary cancer syndromes became integrated into standard clinical practice starting in 2012 in developed countries,<sup>22</sup> and in some countries from Latin America, e.g. Argentina, Brazil, Uruguay and Peru. However, NGS studies have reported that as much as ~18% of patients diagnosed with CRC < age of 50 years have pathogenic variants in genes that are not traditionally associated with CRC (*ATM*, *CHEK2*, *BRCA1*, *BRCA2*, *CDKN2A* and *PALB2*).<sup>18,23</sup> Notably, there is a need to determine whether these variants contribute to hereditary CRC risk *via* the combination of low- and moderate-penetrance susceptibility alleles.<sup>18,20,23–25</sup>

### Cancer risks in LS

The Prospective Lynch Syndrome Database (PLSD) ([www.PLSD.eu](http://www.PLSD.eu)) described that the cumulative incidence of any cancer at 70 years of age is 72% for *path\_MLH1* and *path\_MSH2* carriers, but lower in *path\_MSH6* (52%) and *path\_PMS2* (18%) carriers. *Path\_MSH6* and *path\_PMS2* carriers do not have an increased risk for cancer before 40 years and 50 years of age, respectively.<sup>26–28</sup>

The cumulative risk for cancer in specific organs or group of organs at 75 years was: CRC: 46%, 43% and 15% in *path\_MLH1*, *path\_MSH2* and *path\_MSH6* carriers; for endometrial cancer 43%, 57% and 46%; for ovarian cancer 10%, 17% and 13%; for upper gastrointestinal (gastric, duodenal, bile duct or pancreatic) cancers 21%, 10% and 7%; for urinary tract cancers 8%, 25% and 11%; for prostate cancer 17%, 32% and 18%; and for brain tumors 1%, 5% and 1%, respectively. Ovarian cancer occurred mainly premenopausally. By contrast, upper gastrointestinal, urinary tract and prostate cancers occurred predominantly at older ages. Overall 5-year survival for prostate cancer was 100%, urinary bladder 93%, ureter 85%, duodenum 67%, stomach 61%, bile duct 29%, brain 22% and pancreas 0%.<sup>28</sup>

There is a significant variation in lifetime cancer risks and mean age at diagnosis in LS patients who harbor *path\_MMR* variants. Therefore, genetic cancer risk assessment and counseling should be based on the affected gene, gender and age of the patient.<sup>26</sup> These studies lend support to the need to establish the genetic testing in most of the countries from Latin America in order to assess the cancer risk in these not yet studied populations. Importantly, the cancer risk is influenced by environmental factors, and one may expect different risks in different countries due to epidemiological factors.

### The spectrum of *path\_MMR* variants

A recent description of the spectrum of the *path\_MMR* variants in Latin America LS families included the identification of *path\_MLH1* variants in up to 54% of the cases, *path\_MSH2* variants in up to 43%, *path\_MSH6* variants in up to 10%, *path\_PMS2* variants in up to 3%, and *path\_EPCAM* variants in up to 0.8%.<sup>19</sup> A slightly higher contribution for *path\_MLH1* variants and *path\_MSH2* variants and lower for *path\_MSH6* variants and *path\_PMS2* variants was described when comparing to international reports.<sup>19,29,30</sup>

With the aim to describe a more complete *path\_MMR* spectrum from Latin America, we invited 35 institutions from 14 countries to participate in a survey of MMR variants. Of these, 25 institutions from ten different countries accepted to participate and provided information about *path\_MMR* variants or tumor MMR analysis. Briefly, 2,685 suspected LS families from Argentina (five centers), Brazil (six centers), Chile (one center), Colombia (two centers), Costa Rica (one center), Mexico (one center), Peru (two centers) and Uruguay (one center) were selected to perform germline MMR genetic testing (Table 1). The Amsterdam criteria (AMS) or Bethesda guidelines were mostly used to select cases for screening by IHC and/or

microsatellite instability (MSI) analysis or *BRAF* sequencing. MMR deficiency was identified in 30% (774/2,552) of the cases who underwent screening analysis (Table 1).

In total, 1,052 families were sequenced, and on average 39% (406/1052) carried a *path\_MMR* variant, albeit with large variation between countries, ranging from 8% families in Uruguay and Argentina to 60% in Peru (Table 1, Fig. 1). The mean age of cancer diagnosis of 41 years (range 30–51) was described for *path\_MMR* carriers (data not shown). Interestingly, 39%–80% of the families not being identified for the presence of a *path\_MMR* variant actually met both the clinical criteria for LS and had an MMR deficiency. This point highlights the challenge associated with using family history for detecting families with *path\_MMR* variant.<sup>31</sup> Our data support the recommendation on the application of population-based screening protocols for all CRC and endometrial cancers diagnosed below age 70 using IHC of the MMR proteins.<sup>31–33</sup> Nonetheless, patients with a young age of onset and/or a positive family history of LS-associated cancers without an identified *path\_MMR* variant, may suggest the involvement of pathogenic variants in as yet undiscovered genes.<sup>34</sup>

Based on this large cohort, the spectrum of *path\_MLH1* include variants from Argentina (41%), Brazil (42%), Chile (60%), Colombia (12%), Mexico (80%), Peru (82%) and Uruguay (51%), while *path\_MSH2/EPCAM* include Argentina (47%), Brazil (34%), Chile (30%), Colombia (81%), Mexico (20%), Peru (5%) and Uruguay (31%). So far, Costa Rica has described only one case harboring a widely known *path\_MSH2* located on intron 5 (c.942 + 3A > T). Importantly, the spectrum of *path\_MSH6* were most frequently described in Brazil (15%) followed by Uruguay (9%), Peru (6%) and Argentina (3%), while the *path\_PMS2* variants were found in Chile (10%), Brazil and Uruguay (9%, each), Argentina (8%), Colombia (7%) and Peru (6%) (Fig. 2). The high prevalence of the *path\_MSH6* in Brazilian population (15%) may be taken as an argument for the surveillance and follow-up for the patients and their families. In this regard, PLSD describes a cumulative risk at 75 years for CRC of 15%; for endometrial cancer of 46%; for ovarian cancer of 13% and for prostate cancer of 18% in *path\_MSH6* carriers.<sup>28</sup>

When we analyzed data from tumor MMR analysis of 547 suspected LS cases for which further genetic testing was not available, MMR deficiency was present in 54% (296/547) of the cases (Table 2). Keeping in line with the above estimates, we could expect approximately 100 cases with a *path\_MMR* variant. Unfortunately, genetic services are still underdeveloped across Latin America, and access to genetic testing and counseling is very limited in the region.<sup>35,36</sup>

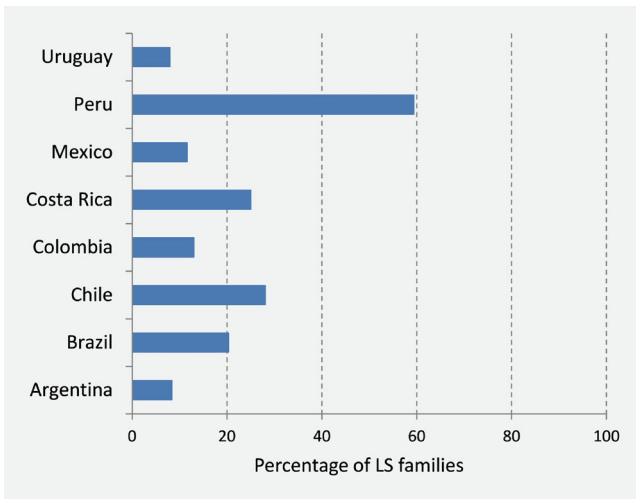
Some of the barriers that most of these countries are facing include a limited number of adequately trained health care professionals to perform cancer risk assessment (i.e. genetic counseling *per se* is not recognized as a profession), a high cost of genetic tests and lack of insurance coverage for such genetic tests. Furthermore, the lack of supportive healthcare policies, limited awareness about hereditary cancer and its risk

Table 1. Summary of genetic testing results from LS cancer registries in Latin America

Country	City	Latin American Institution	Center type	Suspected N Families	Clinical criteria	Screening	Sequenced N Families	Germline MMR Genetic Testing				
								Path_MLH1	Path_MSH2/EPCAM	Path_MSH6	Path_PMS2	LS families
Argentina	Buenos Aires	Hospital of Gastroenterology "Dr. C. B. Udaondo"	Public Hospital	850	AMS, Bethesda, universal screening	IHC and/or MSI, BRAF sequencing <sup>1</sup>	70	17	18	1	4	40
Argentina	Buenos Aires	Hospital Italiano	Hereditary Cancer Reference University Hospital	244	AMS, Bethesda	Mainly IHC <sup>1</sup>	82	13	13	1	1	28
Argentina	Buenos Aires	Centro de Educación Médica e Investigaciones Clínicas (CEMIC)	University Hospital	104	AMS, Bethesda	IHC and/or MSI <sup>1</sup>	26	9	10	3	1	23
Argentina	Rosario	Hospital Español	Private Hospital	61	AMS, Bethesda	IHC and/or MSI <sup>1</sup>	17	3	10	0	1	14
Argentina	Cordoba	Hospital Privado Universitario de Cordoba	Private Hospital	18	AMS, Bethesda	IHC and BRAF sequencing <sup>1</sup>	3	0	2	0	0	2
Brazil	Barretos	Barretos Cancer Hospital	Cancer Register Hospital	510	AMS, Bethesda, universal screening	IHC and/or MSI, BRAF sequencing and methylation <sup>1</sup>	165	29	25	10	7	71
Brazil	Bahia, Amazonas	Universidade Federal da Bahia, CLION, ONCOCLIN	Public University, Private Hospital	28	AMS, Bethesda	IHC <sup>1</sup>	14	2	2	2	0	6
Brazil	Porto Alegre	Hospital das Clinicas	Public Hospital	18	AMS, Bethesda	na	na	8	3	0	na	11
Brazil	Sao Paulo	Sirio Libanes Hospital	Private Hospital	63	AMS	IHC <sup>1</sup>	51	12	13	2	8	35
Brazil	Sao Paulo	A.C. Camargo Cancer Center	Private Hospital	na	AMS, Bethesda	IHC and/or MSI	173	28	20	6	1	55
Brazil	Sao Paulo	Hospital São Paulo of the UNIFESP	University Hospital	95	Bethesda	IHC	95	11	6	5	0	22
Chile	Santiago	Clinica Las Condes	Private Hospital	107	AMS, Bethesda, universal screening	Mainly IHC <sup>1</sup>	80	18	9	0	3	30
Colombia	Ibague	Universidad de Tolima	Public University	59	AMS, Bethesda	Mainly IHC <sup>1</sup>	48	1	6	0	0	7
Colombia	Bogota	Clinica del Country	Private Hospital	10	AMS	Not	4	0	1	0	1	2
Costa Rica	San Jose	Hospital Dr. Rafael Angel Calderón Guardia	Public Hospital	4	AMS, Bethesda	Not	na	0	1	0	0	1
Mexico	Mexico City	National Cancer Institute	Public National Reference	43	AMS	IHC <sup>1</sup>	10	4	1	0	0	5
Peru	Lima	Universidad de San Martín de Porres	Private University	26	AMS, Bethesda	IHC and/or MSI <sup>1</sup>	25	15	1	0	0	16
Peru	Lima	Instituto de Investigación Genómica	Private Hospital	6	Family history	Not	6	1	0	1	1	3
Uruguay	Montevideo	Grupo Colaborativo Uruguayo - Investigación de afecciones oncológicas hereditarias	Hereditary Cancer Reference	439	AMS, Bethesda	MSI <sup>1</sup>	183	18	11	3	3	35
Total (n)				2,685			1,052	189	152	34	31	406

Abbreviations: LS, Lynch syndrome; MMR, mismatch repair; Path\_MMR, Pathogenic (disease-causing) variant of an MMR gene; path\_MLH1, pathogenic variant of the MLH1 gene; path\_MSH2, pathogenic variant of the MSH2 gene; path\_MSH6, pathogenic variant of the MSH6 gene; path\_PMS2, pathogenic variant of the PMS2 gene; na, not available; CLION, Clínica de Oncología/grupo; ONCOCLIN, Clínica Oncológica; UNIFESP, Universidade Federal de São Paulo; AMS, Amsterdam criteria; IHC, immunohistochemistry; MSI, microsatellite instability analysis.  
<sup>1</sup>Tumor screening applied to select suspected families for the germline MMR genetic test.





**Figure 1.** Percentage of LS families from the total LS suspected families in Latin American countries. The percentage for each country was obtained by a weighted sum of percentages over all its participating centers. The weight for a center was:  $\text{weight} = (\text{number of LS suspected families in the center}) / (\text{total number of LS suspected families in the respective country})$ . [Color figure can be viewed at [wileyonlinelibrary.com](#)]

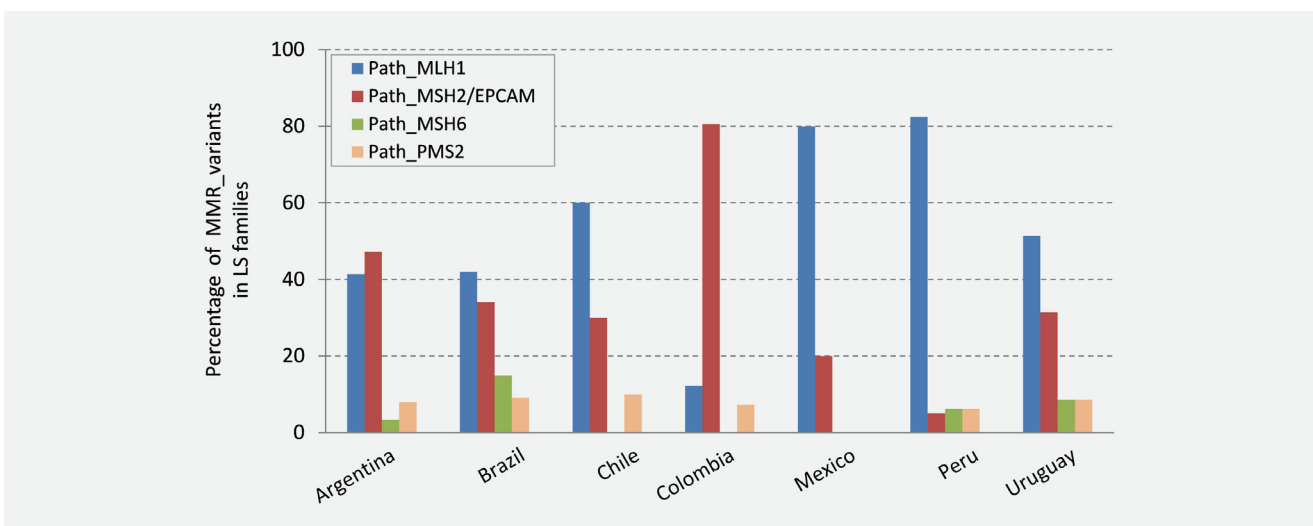
by patients and physicians, few educational opportunities in cancer genetics, and the lack of infrastructure constitute some of the challenges for Latin America. Aside from these, most of the existing programs from public or private hospitals are located in large urban areas, making them practically inaccessible to people living in rural regions.<sup>36</sup>

#### Founder path\_MMR variants

Founder pathogenic variants in CRC predisposition genes appear to be less well studied when compared to breast

cancer in several Latin American populations.<sup>37</sup> We recently identified 16 internationally well-known founder MMR variants in Brazil, Colombia, Argentina, Uruguay and Chile.<sup>19</sup> The *MLH1* *c.1039-8T\_1558 + 896Tdup* and the *MSH2* *c.2185\_2192del7insCCCT* variants have been suggested to have their origin in Colombia and Amerindian populations, respectively. No reports on founder pathogenic variants in individuals from Peru, Paraguay, Bolivia and other Latin America countries have been identified.

Importantly, further studies analyzing large series of these families in different geographic regions will be necessary to accurately estimate the prevalence and the relevance of these variants in these populations. The Latin America and Caribbean population is the result of interethnic crossing between European ancestry, African slaves and the autochthonous Amerindians, but the proportions may vary between countries. For instance, European ancestry predominates in Uruguay and Argentina, whereas Brazil includes a more heterogeneous population, which is the result of interethnic crosses between the European colonizers (mainly Portuguese), African slaves and the autochthonous Amerindians.<sup>38</sup> The Peruvian population is a multi-ethnic population with Amerindian (45%), Mestizo (37%) and white Spanish influence (15%), along with the presence of other minority ethnic groups, such as African American, Japanese and Chinese (3%). In Colombia, Chile and Bolivia, Spanish colonists and American Indian ancestry influence the populations. Typically, Caribbean Hispanics have higher percentages of African ancestry than Argentinians and Uruguay nationals, who are predominantly of European descent.<sup>19</sup> Founder mutations provide a cost-effective molecular diagnostic approach with the benefit of unambiguous results, and thereby do not demand highly skilled professional training.<sup>19</sup>



**Figure 2.** Spectrum of *path\_MMR* in Latin American countries. The percentage for each country was obtained by a weighted sum of percentages over all its participating centers. The weight for a center was:  $\text{weight} = (\text{number of LS suspected families in the center}) / (\text{total number of LS suspected families in the respective country})$ . [Color figure can be viewed at [wileyonlinelibrary.com](#)]

**Table 2.** Summary of tumor MMR screening from the participating centers where germline genetic MMR testing is not available yet

Country	City	Center	Suspected LS cases	Clinical criteria	Tumor screening	MMR deficient	MMR nondeficient
Bolivia	La Paz	Centro de Enfermedades Neoplásicas Oncovida	61	AMS	MSI	3	58
Colombia	Bogota	Fundacion Santa Fe	209	AMS, younger <60 years	MSI	160	49
Colombia	Medellin	Universidad de Antioquia	43	AMS, Bethesda, <45 years	MSI	14	29
Paraguay	Asuncion	GenPat	46	na	IHC	11	35
Peru	Lima	Instituto Nacional de Enfermedades Neoplásicas	132	AMS, Bethesda	IHC and/or MSI	61	71
Peru	Lima	Oncosalud	3	AMS	IHC	1	2
Mexico	Mexico City	Instituto Nacional de Cancerología de México	53	AMS, Bethesda	IHC	46	7

Abbreviations: LS, Lynch syndrome; MMR, mismatch repair; AMS, Amsterdam criteria; IHC, immunohistochemistry; MSI, microsatellite instability analysis.

### Latin American Hereditary CRC Collaborative Research Network and Educational Programs

Several CRC initiatives are ongoing in Latin America and Caribbean, regarding multidisciplinary research, innovation and networking. With the mission of improving teaching and research into hereditary cancer and encouraging national and international collaboration, the Brazilian Hereditary Tumors Study Group (GBETH) was set up in 2003. In 2005 and 2007, the group published two books with updates on hereditary cancer. After this, professionals from other Latin American countries began to show interest in joining the group. As a result, in 2006 GBETH changed its name to Hereditary Tumors Study Group (GETH) ([www.geth.org.br](http://www.geth.org.br)). This initiative led to the inclusion of professionals from throughout the South and Latin American continent. In 2004, the Regional Collaborative Group of the Americas (CGA) meeting was held in Argentina; two years later, the Annual CGA and the First International Symposium was organized in Brazil with the aim to set up a collaborative hereditary cancer register (the South

American Hereditary Cancer Register) and to consolidate the research all over the continent.<sup>39</sup> Subsequent scientific international meetings were undertaken, of which one served as a base for the 6th Biennial Meeting of the International Society for Gastrointestinal Hereditary in Tumors (InSIGHT) in São Paulo.<sup>40</sup> This work remains being developed, and this year, the fifth annual Latin-American Symposium in endoscopy, ENDOSUR, will be held in Santiago. For the first time, a Latin American Symposium on CRC screening will accompany it (Table 3).

Likewise, in 2013, a multidisciplinary group of professionals with expertise in hereditary cancer syndromes developed a pioneering initiative in Latin America, which consisted of the creation of an e-learning course in cancer genetic counseling. This work was developed by the joint efforts of different professionals belonging to Clínica Las Condes, Universidad del Desarrollo, Pontificia Universidad Católica de Chile and Kaiser Permanente (USA). The goal was to provide specialized training to oncology professionals, and improve the care of high-risk patients in this region of the world. To date, the 39 students who completed this

**Table 3.** Scientific International meetings in Latin America

Meeting	Year	Institution/Society	City	Country
Regional CGA Meeting	2004	CGA	Buenos Aires	Argentina
Annual CGA Meeting	2006	CGA	Sao Paulo	Brazil
First International Symposium	2006	AC Camargo/GETH	Sao Paulo	Brazil
Regional CGA Meeting	2008	CGA	Santiago	Chile
I Latin American Congress of Human Genetics and IX Colombian Congress of Genetics	2008	ACGH	Cartagena de Indias	Colombia
Regional CGA Meeting	2010	CGA	Buenos Aires	Argentina
Regional CGA Meeting	2012	CGA	Santiago	Chile
I International Congress of Molecular Biology in Breast and Colon Cancer: Diagnosis and Treatment	2012	UNMSM	Lima	Peru
Regional CGA Meeting	2014	CGA	Sao Paulo	Brazil
South American Workshop of Hereditary Cancer	2014	Sirio Libanes/GETH	Sao Paulo	Brazil
InSIGHT	2015	InSIGHT	Sao Paulo	Brazil
V Latin American Symposium on Hereditary Syndromes in conjunction with CGA	2018	ENDOSUR	Santiago	Chile

Abbreviations: CGA, Collaborative Group of the Americas; GETH, Hereditary Tumors Study Group; ACGH, Colombian Association of Human Genetics; UNMSM, Universidad Nacional Mayor de San Marcos; ENDOSUR, Latin-American Symposium in endoscopy.

e-learning course in cancer genetic counseling have already been applying their knowledge in order to improve the care of high-risk patients and families in Latin America.

Regarding hereditary cancer registries in Latin America and Caribbean, there remains no national hereditary or familial cancer registers in these countries. With the mission to implement a national registry of families and the coverage of every jurisdiction of Argentina, an Argentinian Hereditary and Familial Cancer Program (PROCAFA) was created under the coordination of the National Cancer Institute of Argentina in 2011 (<https://bit.ly/2r4eeD6>). The main goals are improving detection, prevention and management of high risk cancer population in the country. The existence of a governmental hereditary cancer program in a country as big and heterogeneous as Argentina is a challenging pioneering initiative in Latin America.

This whole process of network construction and research development on hereditary cancer in Latin America prepares the ground for global Latin American collaborations on increasing the knowledge of MMR variants in different populations and to bring additional awareness of this condition to medical professionals and public health leaders in this region. Since its inception, more than ten international scientific publications have been generated in hereditary CRC by our network.<sup>19,39–48</sup> Furthermore, Argentina, Uruguay and Chile have initiated their participation on the PLSD,<sup>26–28</sup> providing information of a total of 128 prospective *path\_MMR* carriers to enrich the global database of variation. Importantly, international multicenter collaborations are needed to enhance representation from all the countries of Latin America. We welcome other parties to join us to contribute in future studies.

## Conclusion

CRC is the third most common cancer in Latin America and Caribbean and the most frequent cancer affecting both genders. The geographic variations rates observed within the region are probably due to differences in the prevalence of obesity, physical inactivity, diet, as well as early detection program and health care infrastructure. Limitations on genetic testing have an impact in the evaluation of the patients at risk of hereditary CRC and their relatives, and ultimately increases the burden of cancer for this minority population. Still, existing countries where germline genetic testing is not available. However, in an effort to strengthen capacity by stimulating research, developing networks, delivering training and education, we have provided a broader genetic profile characterizing 406 LS families coming from 2,685 suspected LS. Our data provides an estimation and sensitivity of the current clinical criteria and screening methods used to

analyze suspected LS cases in Latin America and Caribbean. For the first time, we described the spectrum of *path\_MMR* across the countries, e.g. *path\_MLH1* variants were most commonly identified in Peru (82%) and Mexico (80%), *path\_MSH2/EPCAM* variants in Colombia (83%) and Argentina (47%). *Path\_MSH6* and *path\_PMS2* variants were the less common variants, but they showed important presence in Brazil (15%) and Chile (10%), respectively. We aim to strengthen this work further, through collaborative projects for research, the organization and upkeep of new hereditary cancer registries, arranging regional meetings and other regional efforts in this continent. Thus, the main challenges for Latin American countries are: (a) increase awareness of the population and health care professionals about hereditary cancer; (b) enhance training both for MDs and non-MDs in genetic cancer risk assessment; (c) develop guidelines for risk assessment, cancer screening and genetic testing for these conditions; (d) implement genetic testing for patients from both private and public health care systems.

## Acknowledgements

We thank the families for their participation and contribution to our study. This work was supported by the Radium Hospital Foundation (Oslo, Norway) in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript, Helse Sør-Øst (Norway) in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. This work was supported by the The Norwegian Cancer Society, contract 194751-2017.

## Authors' contributions

All authors have read and approved the final version of our study.

## Declarations

Ethics approval and consent to participate: All patients provided an informed consent for inclusion into the Latin America registers during genetic counseling sessions and is in compliance with the Helsinki Declaration. Written informed consent was obtained from all participants during genetic counseling sessions.

## Consent for publication

Not Applicable.

## Availability of data and material

Data from the Latin America hereditary cancer registers, this is indeed available for researchers after direct contact with the register (thus not freely available online).

## References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136: E359–86.
2. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–91.
3. Bray F, Pineros M. Cancer patterns, trends and projections in Latin America and the Caribbean: a global context. *Salud Publica Mex* 2016;58: 104–17.
4. Ruiz R, Taxa L, Ruiz EF, et al. Cancer colorrectal en los jóvenes: factores pronosticos y características clinico patologicas en un instituto del



- cancer de Peru. *Rev Gastroenterol Peru* 2016;36:35–42.
5. Curado MP, de Souza DL. Cancer burden in Latin America and the Caribbean. *Ann Glob Health* 2014;80:370–7.
  6. Carioli G, La Vecchia C, Bertuccio P, et al. Cancer mortality predictions for 2017 in Latin America. *Ann Oncol* 2017;28:2286–97.
  7. Bray F, Soerjomataram I. The changing global burden of cancer: transitions in human development and implications for cancer prevention and control. In: Gelband H, Jha P, Sankaranarayanan R, et al., eds *Cancer: disease control priorities*, vol. 3, Third edn. Washington (DC), 2015. [https://doi.org/10.1596/978-1-4648-0349-9\\_ch2](https://doi.org/10.1596/978-1-4648-0349-9_ch2).
  8. Montenegro Y, Ramirez-Castro JL, Isaza LF, et al. Microsatellite instability among patients with colorectal cancer. *Rev Med Chile* 2006;134:1221–9.
  9. Goss PE, Lee BL, Badovinac-Crnjevic T, et al. Planning cancer control in Latin America and the Caribbean. *Lancet Oncol* 2013;14:391–436.
  10. Sankaranarayanan R. Screening for cancer in low- and middle-income countries. *Ann Glob Health* 2014;80:412–7.
  11. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US multi-society task force on colorectal cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570–95.
  12. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. multi-society task force on colorectal cancer. *Gastroenterology* 2017;153:307–23.
  13. Burt RW. Colorectal cancer screening. *Curr Opin Gastroenterol* 2010;26:466–70.
  14. Holme O, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. *BMJ* 2017;356:i6673.
  15. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015;64:1637–49.
  16. Kuiper RP, Vissers LE, Venkatchalam R, et al. Recurrence and variability of germline EPCAM deletions in lynch syndrome. *Hum Mutat* 2011;32:407–14.
  17. van der Klift HM, Mensenkamp AR, Drost M, et al. Comprehensive mutation analysis of PMS2 in a large cohort of Proband suspected of lynch syndrome or constitutional mismatch repair deficiency syndrome. *Hum Mutat* 2016;37:1162–79.
  18. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. *J Clin Oncol* 2017;35(10):JCO2016710012.
  19. Rossi BM, Palmero EI, Lopez-Kostner F, et al. A survey of the clinicopathological and molecular characteristics of patients with suspected lynch syndrome in Latin America. *Bmc Cancer* 2017;17:623.
  20. Dominguez-Valentin M, Nakken S, Tubeuf H, et al. Identification of genetic variants for clinical management of familial colorectal tumors. *BMC Med Genet* 2018;19:26.
  21. Gupta S, Provenzale D, Regenbogen SE, et al. NCCN guidelines insights: genetic/familial high-risk assessment: colorectal, version 3.2017. *J Natl Compr Canc Netw* 2017;15:1465–75.
  22. Blount J, Prakash A. The changing landscape of lynch syndrome due to PMS2 mutations. *Clin Genet* 2017;94:61–69. doi:10.1111/cge.13205.
  23. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and Spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol* 2016;3:464–471. doi:10.1001/jamaoncol.2016.5194.
  24. Picelli S, Lorenzo Bermejo J, Chang-Claude J, et al. Meta-analysis of mismatch repair polymorphisms within the cogent consortium for colorectal cancer susceptibility. *PLoS One* 2013;8:e72091.
  25. Boland PM, Yurgelun MB, Boland CR. Recent progress in lynch syndrome and other familial colorectal cancer syndromes. *CA Cancer J Clin* 2018;68:217–231. doi:10.3322/caac.21448.
  26. Moller P, Seppala T, Bernstein I, et al. Cancer incidence and survival in lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective lynch syndrome database. *Gut* 2015;1–9. doi:10.1136/gutjnl-2015-309675.
  27. Moller P, Seppala T, Bernstein I, et al. Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective lynch syndrome database. *Gut* 2016;1–8. doi:10.1136/gutjnl-2016-311403.
  28. Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path\_MMR carriers by gene and gender up to 75 years of age: a report from the prospective lynch syndrome database. *Gut* 2017;66:1657–64.
  29. Plazzer JP, Sijmons RH, Woods MO, et al. The InSIGHT database: utilizing 100 years of insights into lynch syndrome. *Fam Cancer* 2013;12:175–80.
  30. Gomez A, Salguero G, Garcia H, et al. Detection mutations in the DNA mismatch repair genes of hMLH1 and hMSH2 genes in Colombian families with suspicion of hereditary non-polyposis colorectal carcinoma (lynch syndrome). *Biomedica* 2005;25:315–24.
  31. Sjursen W, Haukanes BI, Grindedal EM, et al. Current clinical criteria for lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. *J Med Genet* 2010;47:579–85.
  32. Adar T, Rodgers LH, Shannon KM, et al. Universal screening of both endometrial and colon cancers increases the detection of lynch syndrome. *Cancer-Am Cancer Soc* 2018;124(15):3145–3153. doi: 10.1002/cncr.31534. Epub 2018 May 11.
  33. Vasen HF, Moslein G, Alonso A, et al. Recommendations to improve identification of hereditary and familial colorectal cancer in Europe. *Fam Cancer* 2010;9:109–15.
  34. Kayser K, Degenhardt F, Holzapfel S, et al. Copy number variation analysis and targeted NGS in 77 families with suspected lynch syndrome reveals novel potential causative genes. *Int J Cancer* 2018. doi: 10.1002/ijc.31725.
  35. Campacci N, de Lima JO, Carvalho AL, et al. Identification of hereditary cancer in the general population: development and validation of a screening questionnaire for obtaining the family history of cancer. *Cancer Med* 2017;6:3014–24.
  36. Chavarri-Guerra Y, Blazer KR, Weitzel JN. Genetic cancer risk assessment for breast cancer in Latin America. *Rev Invest Clin* 2017;69:94–102.
  37. Ashton-Prolla P, Vargas FR. Prevalence and impact of founder mutations in hereditary breast cancer in Latin America. *Genet Mol Biol* 2014;37:234–40.
  38. Clarizia AD, Bastos-Rodrigues L, Pena HB, et al. Relationship of the methylenetetrahydrofolate reductase C677T polymorphism with microsatellite instability and promoter hypermethylation in sporadic colorectal cancer. *Genet Mol Res* 2006;5:315–22.
  39. Rossi BM, Sarroca C, Vaccaro C, et al. The development of the study of hereditary cancer in South America. *Genet Mol Biol* 2016;39:166–7.
  40. Vaccaro CA, Sarroca C, Rossi B, et al. Lynch syndrome in South America: past, present and future. *Fam Cancer* 2016;15:437–45.
  41. Gonzalez ML, Causada-Calo N, Santino JP, et al. Universal determination of microsatellite instability using BAT26 as a single marker in an Argentine colorectal cancer cohort. *Familial Cancer* 2018;17:395–402.
  42. Dominguez-Valentin M, Nilbert M, Wernhoff P, et al. Mutation spectrum in south American lynch syndrome families. *Hereditary Cancer in Clinical Practice* 2013;11:18.
  43. Dominguez-Valentin M, Wernhoff P, Cajal AR, et al. MLH1 Ile219Val polymorphism in Argentinean families with suspected lynch syndrome. *Front Oncol* 2016;6:1–5.
  44. Valentin MD, da Silva FC, dos Santos EMM, et al. Characterization of germline mutations of MLH1 and MSH2 in unrelated south American suspected lynch syndrome individuals. *Fam Cancer* 2011;10:641–7.
  45. Valentin MD, Da Silva FC, Santos EM, et al. Evaluation of MLH1 I219V polymorphism in unrelated south American individuals suspected of having lynch syndrome. *Anticancer Res* 2012;32:4347–51.
  46. Santos EMM, Valentin MD, Carneiro F, et al. Predictive models for mutations in mismatch repair genes: implication for genetic counseling in developing countries. *BMC Cancer* 2012;12:1–9.
  47. Koger N, Paulsen L, Lopez-Kostner F, et al. Evaluation of MLH1 variants of unclear significance. *Genes Chromosomes Cancer* 2018;57:350–8.
  48. Karin Alvarez CA, Dominguez M, Carvalho P. Screening for hereditary cancer in Latin America. In: *Genomic medicine in emerging economies: genomics for every nation*. Academic Press, 2018, 204.