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

Carlos Alberto Vaccaro1, Francisco López-Kostner2, Della Valle Adriana3, Edenir Inez Palermo4, Benedito Mauro Rossi5, Marina Antelo6,7, Angela Solano8, Dirce Maria Carraro9, Nora Manoukian Forones10, Mabel Bohorquez11, Leonardo S. Lino-Silva12, Jose Buleje13, Florencia Spirandelli14, Kiyoko Abe-Sandes15, Ivana Nascimento16, Yasser Sullcahuaman17,18, Carlos Sarroca3, Maria Laura Gonzalez1, Alberto Ignacio Herrando1, Karin Alvarez2, Florencia Neffa3, Henrique Camposreis Galvão1, Patricia Esperon13, Mariano Golubicki19, Daniel Cisterna19, Florencia C. Cardoso8, Giovana Tardin Torrezan6, Samuel Aguiar Junior9, Célia Aparecida Marques Pimenta10, Maria Nirvana da Cruz Formiga9, Erika Santos5, Caroline U. Sá5, Edite P. Oliveira5, Ricardo Fujita13, Enrique Spirandelli14, Geiner Jimenez20, Rodrigo Santa Cruz Guindalini21, Renata Gondim Meira Velame de Azevedo22, Larissa Souza Mario Bueno23, Sonia Tereza dos Santos Nogueira24, Mariela Torres Loarte17,18, Jorge Padron25, Maria del Carmen Castro-Mujica26, Julio Sanchez del Monte27, Carmelo Caballero28, Carlos Mario Muñeton Peña29, Joseph Pinto30, Claudia Barletta-Carrillo26, Gutiérrez Angulo Melva31, Tamara Piñero1,32, Paola Montenegro Beltran26, Patricia Ashton-Prolla33, Yenni Rodriguez34, Richard Quispe35, Norma Teresa Rossi26, Claudia Martin36, Sergio Chialina14, Pablo German Kalfayan3, Juan Carlos Bazo-Alvarez37,38, Alcides Recalde Cañete39, Constantino Dominguez-Barrera40, Lina Nuñez11, Sabrina Daniela Da Silva42,43, Yesilda Balavarca44, Patrik Wernhoff45, John-Paul Plazzer46,47, Pål Meller8,48,49, Eivind Hovig45,50,51, and Mev Dominguez-Valentin45, in collaboration with GETH

1PROCANHE- Instituto de Medicina Traslacional e Ingeniería Biomédica (IMTIB)-CONICET, Instituto Universitario del Hospital Italiano (IUHI), Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
2Laboratorio de Oncología y Genética Molecular, Clínica Los Condes, Santiago, Chile
3Hospital Fuerzas Armadas, Grupo Colaborativo Uruguayo, Investigación de Afecciones Oncológicas Hereditarias (GCU), Montevideo, Uruguay
4Molecular Oncology Research Center, Barretos Cancer Hospital, Brazil & Barretos School of Health Sciences – FACISB, Barretos, SP, Brazil
5Hospital Sírio Libanes, São Paulo, Brazil
6Oncology Section of the Public Hospital of Gastroenterology “Dr. C. B. Udaondo”, Buenos Aires, Argentina
7Instituto de Salud Colectiva, Universidad Nacional de Lanús, Buenos Aires, Argentina
8Centro de Genética y Biología Molecular, Instituto de Investigación, Facultad de Medicina Humana, Universidad de San Martín de Porres, Lima, Perú
9Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, Brazil
10Instituto de Ciências da Saúde e Núcleo de Oncologia da Bahia, Salvador, Brazil
11Universidad Peruana de Ciencias Aplicadas, Lima, Peru
12Instituto de Investigación Genomica, Lima, Peru
13Molecular Laboratory, Hospital of Gastroenterology “Dr. C. B. Udaondo”, Buenos Aires, Argentina
14Hospital Dr. Rafael Angel Calderón Guardia, Caja Costarricense de Seguro Social, San Jose, Costa Rica

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Correspondence to: Mev Dominguez-Valentin, Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway, E-mail: mev.dominguez-valentin@rr-research.no. Tel.: +4-740-381-634.
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 is 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.1
The global burden of CRC is rising, with 2.2 million predicted new cases (and 1.1 million deaths) by 2030. 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. 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.

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 the Latin America and Caribbean population, the European populations still have 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. 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.

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. 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. While representing a highly preventable disease, and perhaps the most preventable of cancers, 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. 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.

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. 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.

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). Systematic screening for LS by MMR immunohistochemistry (IHC) was first included in the National Comprehensive Cancer Networking (NCCN) guidelines in 2017. Until regional guidelines consider and adopt this systematic screening, patients with CRC in Latin America are after NCNN 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, 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, CDKNA2 and PALB2). 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.
Cancer risks in LS
The Prospective Lynch Syndrome Database (PLSD) (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.26–28

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%.28

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.26 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_MSH2 variants in up to 54% of the cases, path_MSH6 variants in up to 43%, path_PMS2 variants in up to 10%, path_EPCAM variants in up to 3%, and path_MML variants in up to 0.8%.29 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.19,29,30

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 centers), 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.31 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.31–33 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.34

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.28

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.35,36

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>
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<tr>
<th>Country</th>
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<th>Center type</th>
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<th>Clinical criteria</th>
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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_MSK2, pathogenic variant of the MSH2 gene; path_MSK6, pathogenic variant of the MSH6 gene; path_PMS2, pathogenic variant of the PMS2 gene; na, not available; CIION, Clínica de Oncologia/grupo; ONCOCLIN, Clínica Oncológica; UNIFESP, Universidade Federal de São Paulo; AMS, Amsterdam criteria; IHC, immunohistochemistry; MSI, microsatellite instability analysis.

¹Tumor screening applied to select suspected families for the germline MMR genetic test.
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.

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. We recently identified 16 internationally well-known founder MMR variants in Brazil, Colombia, Argentina, Uruguay and Chile. 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. 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. Founder mutations provide a cost-effective molecular diagnostic approach with the benefit of unambiguous results, and thereby do not demand highly skilled professional training.
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). 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.\(^3\) 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.\(^4\) 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

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

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 country as big and heterogeneous as Argentina is a challenging process 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.

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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
cancer de Peru. Rev Gastroenterol Peru 2016;36:35–42.