Mutational landscape of gastric adenocarcinoma in Latin America: A genetic approach for precision medicine

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Abstract Latin-America (LATAM) is the second region in gastric cancer incidence; gastric adenocarcinoma (GA) represents 95% of all cases. We provide a mutational landscape of GA highlighting a) germline pathogenic variants associated with hereditary GA, b) germline risk variants associated with sporadic GA, and c) somatic variants present in sporadic GA in LATAM, and analyze how this landscape can be applied for precision medicine. We found that Brazil, Chile, Colombia, Mexico, Peru, and Venezuela are the countries with more published studies from LATAM explicitly related to GA. Our analysis displayed that different germline pathogenic variants for the CDH1 gene have been identified for hereditary GA in Brazilian, Chilean,
Colombian, and Mexican populations. An increased risk of developing somatic GA is associated with the following germline risk variants: IL-4, IL-8, TNF-α, PTGS2, NFKB1, RAF1, KRAS and MAPK1 in Brazilian; IL-10 in Chilean; IL-10 in Colombian; EGFR and ERRB2 in Mexican, TCF7L2 and Chr8q24 in Venezuelan population. The path from mutational landscape to precision medicine requires four development levels: 1) Data compilation, 2) Data analysis and integration, 3) Development and approval of clinical approaches, and 4) Population benefits. Generating local genomic information is the initial padlock to overcome to generate and apply precision medicine.

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Introduction

Gastric cancer ranks fifth in cancer-related death, with a 5-year survival rate of less than 30% in Western countries.\(^1,2\) Asia is the region with the highest gastric cancer incidence, followed by Latin America (LATAM) and Europe.\(^3\) In LATAM, gastric cancer is in the sixth position in cancer incidence with Chile, Peru, Guatemala, Ecuador, and Costa Rica as the top five countries with the highest gastric cancer incidence and mortality rates.\(^5\) Up to 95% of all cases of gastric cancer are diagnosed as gastric adenocarcinoma (GA), and poor dietary habits,\(^5,6\) tobacco usage,\(^6,7\) Epstein Barr virus infection,\(^8,9\) and occupational exposure such as farming are the main risk factors\(^10-12\) (Fig. 1A). GA is classified into diffuse, intestinal, and mixed type (Fig. 1B) including sporadic and hereditary cases (Fig. 1C).\(^13\) Helicobacter pylori (H. pylori) infections\(^14\) have been considered one of the leading causes of the high GA incidence in LATAM,\(^15,16\) and 80% of GA cases are sporadic; the remaining cases are attributed to germline variants; however, the known germline pathogenic variants only explain 3% of these cases.\(^17\) Clinical peculiarities of LATAM GA patients could result in unknown interactions between the environment and either germline risk or somatic variants. GA Ecuadorian patients living in high altitude conditions that have higher prevalence and mortality odds than those residing at low-lying regions\(^18\); Peruvians with strong Native American ancestry that have a higher risk of developing GA\(^19\); or Hispanics that have more likelihood to be diagnosed with non-cardia GA at a younger age and with diffuse histology than non-Hispanics Caucasians from the United States\(^20\) are examples of the peculiarities which could be explained and probably prevented by elucidating genomic variants in LATAM populations. We aimed to analyze published studies highlighting germline pathogenic variants associated with hereditary GA, germline risk variants associated with sporadic GA, and somatic variants present in sporadic GA to
provide a GA mutational landscape from LATAM populations and an organizational level of the path from landscape to precision medicine achievement.

**Comprehensive literature search**

The present analysis was performed based on a comprehensive literature search from peer-reviewed studies published until January 2021 in PubMed, Europe PMC, Springerlink, SciELO, and Redalyc. We included articles from LATAM, Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Mexico, Peru, Uruguay, and Venezuela identifying germline pathogenic variants associated with hereditary GA, germline risk variants associated with sporadic GA, or somatic variants present in sporadic GA identified either by protein chain reaction, targeted sequencing, microarray, or whole exome/genome sequencing.

**Germline pathogenic variants associated with hereditary GA in LATAM**

Less than 3% of all GA cases are linked to germline pathogenic variants. Different hereditary GA syndromes have been described, including familial adenomatous polyposis (FAP), juvenile polyposis, Li-Fraumeni syndrome, Lynch syndrome, MUTYH-associated polyposis (MAP), hereditary diffuse gastric cancer (HDGC), familial intestinal gastric cancer (FIGC), and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). This review is focused on the three last mentioned syndromes: HDGC, FIGC, and GAPPS.

HDGC is the most common hereditary GA syndrome, and is associated with diffuse histology and pathogenic variations in CDH and CTNNA1. At least 122 CDH1 germline pathogenic variants have been identified worldwide. However, about 30% are missense alterations found in middle to high GA incidence regions like East Asia or LATAM.

In LATAM, only Brazil, Chile, Colombia, and Mexico have reported germline CDH1 variants. Also, Brazil is the country with the highest number of germline variants reported (Table 1).

Less than 40% of the patients meet the clinical criteria for HDGC carries a germline CDH1 variant. A thoughtful clinical scrutiny and high-throughput sequencing techniques should be used to identify the incidence and penetrance of clinically relevant CDH1 variants because of 1) most of the germline variants present by GA patients are non-missense or variables of uncertain significance and 2) not all the individuals presenting CDH1 missense variants met the criteria for HDGC.

A total of 7 germline pathogenic variants in PALB2 (c.1240C>T, c.3201+1G>T, c.1882_1890delAAAGTCCTGC, c.2753C>G) RAD51C (c.709C>T) and BRCA1 (c.3331_3334delCAAG, c.1674delA) were identified as germline pathogenic variants in CDH1 negative HDGC patients from Chile, Colombia, and Mexico. According to the genetic testing registry of the United States, only CDH1 and CTNNA1 genes are included in the Hereditary gastric cancer gene panel (GTR000525305.4). Because an increasing body of evidence suggest that germline pathogenic variants in PALB2 might play an important role in HDGC predisposition, they could be considered in gastric cancer genetic testing, but more information is needed to identify the incidence and penetrance of PALB2 and RAD51C germline variants in LATAM and world population.

For FIGC patients, no germline pathogenic variant is known yet. The diagnosis is performed by familial clustering of intestinal GA cases without polyposis.

**Germline risk variants associated to sporadic GA in LATAM**

IL-8 c.-251A>T, IL-10 c.-592C>A, and IL-10 c.-1082A>G are the most studied germline risk variants, with GA susceptibility studies reported in countries such as Brazil, Chile, Colombia, and Peru. Increased GA susceptibility with the IL-10 c.-1082A>G and the IL-10 c.-592C>A germline risk variants were associated to increased GA susceptibility in Brazil and Colombia, respectively. None of the studied inflammatory response-related germline risk variants were associated with GA susceptibility in the Mexican population. ILRIN VNTR was the only risk variant associated to LATAM population found in a meta-analysis including reports from Brazilian, Costa Rican, Honduran, Mexican, Peruvian and Venezuelan populations. No significant associations were found with IL-1β, TP53, TNFA or GSTM1 variants, heterogeneity among studies was a big limitation.

No associations were found with mutations in cytochrome P450 enzymes such as CYP2E1, CYP19A1, TCT Ins/Del, and uridine glucuronosyltransferase (UGT) UGT1A1 TATA box VNTR in the Brazilian population. However, the authors claimed limitations in terms of sample size and control to risk factors exposure could affect the results.

A reduction of GA susceptibility was associated to the germline risk variant c.-1518 Ins/Del on the MDM2 gene, whereas the presence of TP53 16bp deletion in Brazilian patients shown no association. Moreover, MAPK1 (c.857-3854A>C and c.119+2164G>A), RAF1 (c.1669-363C>T) and HRAS (c.1115T>C) intronic variants increased GA susceptibility on the Chilean population, even when they were initially reported as variables of uncertain significance in ClinVar. Similar disparities between studies were found in Mexican population, where an increased GA susceptibility was associated with the EGFR.
promoter region variants c.-216G > T, c.-191C > A \(^49\) (related to augmented expression of EGFR protein), the \(ERBB2\) intronic variants c.-18 + 1614C > T, c.-18 + 3073G > T and the missense variant c.3418C > G,\(^50\) classified as variables of uncertain significance in ClinVar. Also, a decreased susceptibility was associated with the TGF-\(\beta\) promoter variant c.-509C > T which is associated with higher TGF-\(\beta\) plasmatic concentration.

\(TCF7L2\) transcription factor variant IVS3 C > T and IVS4 G > T variant\(^51\) and to chromosome 8q24 position variation was associated with an increased GA susceptibility in Venezuelan patients.\(^52\) Germline risk variants related to oxidative damage and DNA repair genes, \(MTHFR, XRCC1\) and \(TYMS\) were studied in Brazilian population but association with GA susceptibility was not found.\(^40,53\) In addition, an analysis of epithelial-to-mesenchymal transition (EMT)-related genes (\(CDH1, TWIST1, SNAIL2, ZEB1, ZEB2\)) in Chilean population found that only TWIST (rs2526614 and rs6953766) and ZEB1 (rs431073) germline risk variants were associated with poor prognosis.\(^54\) A similar association was found in inflammatory response related to the germline risk variant IL-8 c.-251T > A, also in Chilean population.\(^55\)

### Table 1

| Population   | Variants  | Exon/Intron | Mutation         | Significance       | Reference |
|--------------|-----------|-------------|------------------|--------------------|-----------|
| Brazil       | c.48-6C>T | Intron 1    | Intrinsic variant | Non-coding         | 23        |
|              | c.49-9G>T | Intron 1    | Intrinsic variant | Non-coding         | 23        |
|              | c.163-57G>A| Intron 1    | Intrinsic variant | Non-coding         | 23        |
|              | c.163-59G>C| Intron 2    | Intrinsic variant | Non-coding         | 23        |
|              | c.313T>A  | Exon 3      | Missense         | p.S105T            | 23        |
|              | c.324A>G  | Exon 3      | Synonymous        | p.R108R            | 23        |
|              | c.345G>A  | Exon 3      | Synonymous        | p.T115T            | 23        |
|              | c.387G>T  | Exon 3      | Missense         | p.Q129H            | 23        |
|              | c.387+27C>T| Intron 3    | Intrinsic variant | Non-coding         | 23        |
|              | c.388-44G>A| Intron 3    | Intrinsic variant | Non-coding         | 23        |
|              | c.531-10G>C| Intron 4    | Intrinsic variant | Non-coding         | 23        |
|              | c.532-18C>T| Intron 4    | Intrinsic variant | Non-coding         | 23        |
|              | c.833-16C>G| Intron 6    | Intrinsic variant | Non-coding         | 23        |
|              | c.1676G>A | Exon 11     | Missense         | p.S555N            | 23        |
|              | c.1806C>A | Exon 12     | Missense         | p.F602L            | 23        |
|              | c.1849G>A | Exon 12     | Missense         | p.A617T            | 23,27     |
|              | c.1937-13T>C| Intron 12  | Intrinsic variant | Non-coding         | 23        |
|              | c.2076T>C | Exon 13     | Synonymous        | p.A692A            | 23,27     |
|              | c.2164+16insA| Intron13   | Intrinsic variant | Non-coding         | 23        |
|              | c.2253C>T | Exon 14     | Synonymous        | p.N751N            | 23        |
|              | c.2439+10C>T| Intron 15   | Intrinsic variant | Non-coding         | 23        |
|              | c.2439+56T>G| Intron 15  | Intrinsic variant | Non-coding         | 23        |
|              | c.2634C>T | Exon 16     | Synonymous        | p.G878G            | 23,27     |
|              | c.160C>A  | Promoter    | —                | Decreased transcription | 24       |
|              | c.347GinsGA| Promoter    | —                | —                  | 24        |
|              | c.1763-176DelTG| —       | —                | Frameshift         | 25        |
|              | c.185G>T  | Exon 3      | Missense         | p.G62V             | 26        |
|              | c.1018A>G | Exon 8      | Missense         | p.T340A            | 26        |
|              | c.1023T>G | Exon 8      | Nonsense         | p.Y341*            | 27        |
| Chile        | c.285C>A  | Promoter    | —                | Non-coding         | 28        |
|              | c.197A>C  | Promoter    | —                | Non-coding         | 28        |
|              | c.48-6C>T | Intron1     | Splice site      | —                  | 28        |
|              | c.88C>A  | Exon 2      | Missense         | p.P30T             | 28        |
|              | c.531+10G>C| Intron 4    | Splice site      | —                  | 28        |
|              | c.1272A>T | Exon 9      | Synonymous        | p.T424T            | 28        |
|              | c.1531C>T | Exon 10     | Nonsense         | p.Q511*            | 28        |
|              | c.1893A>T | Exon 12     | Synonymous        | p.T631T            | 28        |
|              | c.2052C>T | Exon 13     | Synonymous        | p.S684S            | 28        |
|              | c.2076T>C | Exon 13     | Synonymous        | p.A692A            | 28        |
|              | c.2253C>T | Exon 14     | Synonymous        | p.N751N            | 28        |
| Colombia     | c.2245C>T | Exon 14     | Missense         | p.R749W            | 29        |
| Mexico       | c.160C>A  | Promoter    | —                | Decreased transcription | 30–32    |
|              | c.347GinsGA| Promoter    | —                | —                  | 31        |

Abbreviations: Ins: insertions, Del: deletion, fs: frameshift.
Figure 2  Mutational landscape of gastric adenocarcinoma from LATAM. Genes with described germline risk variants are reported from Mexico, Colombia, Perú, Chile, Venezuela, and Brazil, while data from Guatemala, El Salvador, Puerto Rico, Costa Rica, and Panamá are not available. Clinical trials conducted for targeted therapies in LATAM are available for all mentioned countries. The higher prevalence in mutations could be grouped into five categories of cellular significance: a) apoptosis and oncogenes (SOS1, MSMB, MDM2, KRAS, HRAS, ERBB2, FGFR, CDH1, EGFR, MAPK1, PDGFRB, RAF1, MAP2K1, TCF7L2, CASP8, TGF-β, GRB2, TP53); b) inflammatory response (IL-8, IL-4Ra, IL-10, IL-17, IL-1b, TNF-α, IFN-γ, IL-32, IL-1α, IL-1β, IL-6, IL-17F, IL-10, IL-6, IL-1b, TLR9, IL-1RN, PTGS2, NFkB1 and IL-8R); c) oxidative damage and DNA repair (XRCC, MTHFR, TYMS); d) detoxifying mechanisms (CYP19A1, CYP2E1 and UGT1A1) and e) unknown function (Chr8q24). Currently, EGFR/HER 2 and PD-1/PD-L1 inhibitors are the most common targeted therapies used in clinical trials conducted in LATAM.
| Pathway               | Genes                      | Germline risk variants | dbSNP       | Population | Risk   | Reference |
|----------------------|----------------------------|------------------------|-------------|------------|--------|-----------|
| **Inflammatory response** | IL-1β                      | c.-511C>T              | rs16944     | Brazil     | Not-aff | 39        |
|                      |                            | c.-31C>T               | rs1143627   | Chile      | Not-aff | 44        |
|                      |                            | c.-3954C>T             | rs1143634   | Chile      | Not-aff | 44        |
|                      | IL-1α                      | 4-bp Ins/Del           | rs3783553   | Brazil     | Not-aff | 40        |
|                      | IL-1RN                     | Intron 2, VNTR         | rs380092    | Chile      | Not-aff | 44        |
|                      | IL-4                       | c.-590C>T              | rs1800629   | Mexico     | Not-aff | 47        |
|                      |                            | Intron 3, 70 bp VNTR   | rs79071878  | Brazil     | Inc    | 40        |
|                      | IL-4Rα                     | p.Q576R                | —           | Columbia   | Not-aff | 46        |
|                      |                            | p.150V                 | —           | Columbia   | Not-aff | 46        |
|                      | IL-6                       | c.-573G>C              | rs1800796   | Mexico     | Not-aff | 47        |
|                      | IL-8                       | c.-251A>T              | rs4073      | Brazil     | Red    | 39        |
|                      |                            | c.-845T>C              | rs2227532   | Brazil     | Inc    | 43        |
|                      | IL-8Rβ                     | —                      | rs4674258   | Peru       | Not-aff | 48        |
|                      | IL-10                      | c.-1082A>G             | rs1800896   | Mexico     | Not-aff | 47        |
|                      |                            | c.-819C>T              | rs1800871   | Mexico     | Red    | 47        |
|                      |                            | c.-592C>A              | rs1800872   | Mexico     | Inc    | 44        |
|                      | IL-17                      | c.-197G>A              | rs2275913   | Chile      | Not-aff | 44        |
|                      | IL-17F                     | c.482A>G (p.H161R)     | rs763780    | Chile      | Not-aff | 44        |
|                      | IL-32                      | —                      | rs28372698  | Chile      | Not-aff | 44        |
|                      | TNF-α                      | c.-308G>A              | rs1800629   | Chile      | Not-aff | 44        |
|                      |                            | c.-857C>T              | rs1799724   | Brazil     | Inc    | 43        |
|                      | IFN-γ                      | c.-1615C>T             | rs2069705   | Mexico     | Not-aff | 47        |
|                      | TLR9                       | c.-1237T>C             | rs5743836   | Brazil     | Inc    | 41        |
|                      |                            | c.-1486C>T             | rs187084    | Brazil     | Inc    | 41        |
|                      | PTGS2                      | c.-1195G>A             | rs689466    | Perú       | Not-aff | 48        |
|                      |                            | c.-1290A>G             | rs689465    | Perú       | Not-aff | 48        |
|                      |                            | c.-765G>C              | rs20417     | Brazil     | Inc    | 42        |
|                      | NFKB1                      | promoter, -94 ATTAG Ins/Del | rs28362491 | Brazil     | Inc    | 40        |
|                      | CYP2E1                     | 96 bp Deletion         | —           | Brazil     | Not-aff | 40        |
|                      | CYP19A1                    | Intro 4, TCT Ins/Del   | rs11575899  | Brazil     | Not-aff | 40        |
|                      | UGT1A1                     | TATA box, VNTR         | rs8175347   | Brazil     | Not-aff | 40        |
|                      | MTHFR                      | c.677C>T (p.A222V)     | rs1801133   | Brazil     | Not-aff | 40        |
|                      | XRCC1                      | Gene deletion          | rs3213239   | Brazil     | Not-aff | 40        |
|                      | TYMS                       | 6bp Ins/Del            | rs16430     | Brazil     | Not-aff | 40        |
|                      |                            | —                      | —           | Brazil     | Not-aff | 40        |
|                      | Apoptosis and Oncogenesis  | CASP8                  | rs45445694  | Brazil     | Not-aff | 53        |
|                      |                            | TP53                   | rs34743033  | Brazil     | Not-aff | 40        |
|                      |                            | MDM2                   | rs3834129   | Brazil     | Not-aff | 40        |
|                      |                            | EGFR                   | rs712829    | Mexico     | Inc    | 49        |
|                      |                            | —                      | —           | Chile      | Not-diff | 45        |
|                      |                            | c.-191C>A              | rs712830    | Mexico     | Inc    | 49        |
|                      |                            | IVS1                   | —           | Mexico     | Not-aff | 49        |

(continued on next page)
Somatic variants present in sporadic GA in LATAM

Single gene approaches report an alteration in different TP53 exons, frequently exon 5 and 9 in individuals with G > A transitions as the most common nucleotide substitution in Chilean population.56 A high frequency of TP53 somatic variation in tumoral samples but failed finding associations between this somatic variant and clinical outcomes such as tumor localization, histological type, and presence of lymph node metastasis were found in the Chilean population.57 Comparable results were found in MYC, FBXW7, and TP53 copy number variation in Brazilian patients, and only high expression of MYC detected by immunohistochemistry was associated with intestinal-type GA patients.58 In other populations TP53, MYC, and PIK3CA are also among the most frequently mutated genes.59,60

Table 2 (continued)

| Pathway | Genes | Germline risk variants | dbSNP | Population | Risk | Reference |
|---------|-------|------------------------|-------|------------|------|----------|
|         |       | c.1881-600G >A         | rs10228436 | Chile | Not-aff | 45 |
|         |       | c.2283+1296C>T         | rs11514996 | Chile | Not-aff | 45 |
|         |       | c.88+3321T>C           | rs11770506 | Chile | Not-aff | 45 |
|         |       | c.89–58442T>C          | rs17172438 | Chile | Not-aff | 45 |
|         |       | c.2470–3426C>T         | rs2740761  | Chile | Not-aff | 45 |
|         |       | c.88–37628A>G          | rs6593201  | Chile | Not-aff | 45 |
|         |       | c.2469–959G>A          | rs7795743  | Chile | Not-aff | 45 |
|         |       | ERBB2                  |       |       |      |          |
|         |       | c.-18+1614C>T          | rs2643194  | Mexico | Inc | 50 |
|         |       | c.-18+1663C>T          | rs2517951  | Mexico | Not-aff | 50 |
|         |       | c.-18+1684A>G          | rs2643195  | Mexico | Not-aff | 50 |
|         |       | c.-18+3073G>T          | rs2934971  | Mexico | Inc | 50 |
|         |       | c.3418C>G              | rs1058808  | Mexico | Inc | 50 |
|         |       | SOS1                   |       |       |      |          |
|         |       | c.1859–1142T>C         | rs10184015 | Chile | Not-aff | 45 |
|         |       | RAF1                   |       |       |      |          |
|         |       | c.1417+170C>G          | rs2290159  | Chile | Not-aff | 45 |
|         |       | c.1669-36C>T           | rs3729391  | Chile | Inc | 45 |
|         |       | c.-26-2203C>T          | rs73812837 | Chile | Not-aff | 45 |
|         |       | HRAS                   |       |       |      |          |
|         |       | c.-1115T>C             | rs45604736 | Chile | Not-aff | 45 |
|         |       | KRA5                   |       |       |      |          |
|         |       | c.*633T>C              | rs9266    | Chile | Inc | 45 |
|         |       | MAPK1                  |       |       |      |          |
|         |       | c.857–3854A>C          | rs2283792  | Chile | Inc | 45 |
|         |       | c.119–7040A>G          | rs4821401  | Chile | Not-aff | 45 |
|         |       | c.857–1944T>C          | rs743409   | Chile | Not-aff | 45 |
|         |       | c.*3186C>T             | rs9340    | Chile | Not-aff | 45 |
|         |       | MAP2K1                 |       |       |      |          |
|         |       | c.81–996C>T            | rs1347069  | Chile | Not-aff | 45 |
|         |       | MAP2K2                 |       |       |      |          |
|         |       | c.919+423T>C           | rs350912   | Chile | Not-aff | 45 |
|         |       | c.303+1424C>T          | rs1823059  | Chile | Not-aff | 45 |
|         |       | GRB2                   |       |       |      |          |
|         |       | c.78+20210G>A          | rs959260   | Chile | Not-aff | 45 |
|         |       | TGF-β                  |       |       |      |          |
|         |       | c.509C>T               | rs1800469  | Mexico | Red | 47 |
|         |       | PAR1                   |       |       |      |          |
|         |       | c.506 Ins/Del          | rs11267092 | Brazil | Not-aff | 40 |
|         |       | MSMB                   |       |       |      |          |
|         |       | c.57C>T                | rs10993994 | Peru | Not-aff | 48 |
|         |       | FGFR2                  |       |       |      |          |
|         |       | c.*805C>T              | rs1017375  | Chile | Not-aff | 45 |
|         |       | c.-152-8335A>G         | rs10066011 | Chile | Not-aff | 45 |
|         |       | c.-153+4691A>G         | rs58746386 | Chile | Not-aff | 45 |
|         |       | TCF7L2                 |       |       |      |          |
|         |       | IVS3 +T                | rs7903146  | Venezuela | Inc | 51 |
|         |       | c.483-9017G>T (IVS4 +T) | rs12255372 | Venezuela | Not-aff | 52 |
|         |       | Unknown function       |       |       |      |          |
|         |       | Chr8q24                |       |       |      |          |
|         |       | Chr8q24                |       |       |      |          |
|         |       | Chr8q24                |       |       |      |          |

Abbreviations: dbSNP: National Center for Biotechnology Information single nucleotide polymorphism database, Inc: Increased risk, Red: Reduced risk, Not-aff: Not Affected, VNTR: variable number tandem repeat, IVS: intervening sequence.

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Colombian patients. TP53 c.782 + 72C > T and c.782 + 92T > G were also frequent in Colombian GA patients. KRAS coding variants, c.35G > A (p.G12D) and c.38G > A (p.G13D), were found in 6.9% of Colombian GA patients and the intronic variants, c.111 + 190A > T and c.111 + 116_111 + 120delAGTTA, in 27.6% and 3.5% of the patients, respectively. Sotorasib (formerly AMG 510) and Adagrasib (formerly MRTX849) are two novel drugs with targeted activity to KRAS p.G12D variant in non-small cell lung cancer (NSCLC) and other solid tumors like colorectal cancer, that could be an asset to GA precision medicine. The NSCLC group treated with sotorasib show a 32.2% of objective response rate and a median progression-free survival of 6.3 months.

Another Colombian study identified that some KRAS somatic variations could be determinant to precancerous lesion progression to cancerous lesions, especially G>A transitions in position 1 of codon 12. Contrasting results were found in Venezuelan patients with *H. pylori* infection, where KRAS somatic variations in codon 12 were common in precancerous lesions but uncommon in cancerous lesions.

DNA copy number alterations affect both protein-coding and non-coding genes present in the affected region. Amplification involving 8q, 20q, and 17q; deletions involving 3p, 6p, and 2q as well as loss of heterogeneity in 16p were present in 50% or more intestinal type GA Brazilian patients. TP53TG3B, TP53TG3 and ZNF267 were the most frequently affected genes by the previous genetic alterations and were not frequent in genomic sequencing studies from other populations and they could be distinctive for Brazilian population, but more information is needed. Gains in Xq26 (cancer/testis antigen family 4, subfamily N, member 5 - OR52N5) and Xp22.31 (microsomal steroid sulfatase, member A4) and Xp22.31 (microsomal steroid sulfatase, isozyme S) and loss in 11p15.4 (olfactory receptor, family 52, subfamily N, member 5 - OR52N5 and OR52N1) were associated with early-onset intestinal type GA. Further copy number analysis of 17q21 located prohibitin gene in Brazilian patients and found amplification in 34.2% of patients but no association to disease clinicopathological features.

The comparative genomic hybridization in Brazilian patients highlighted the high frequency of chromosomal gains in GA intestinal type, specially 8q chromosomal gains with 8q24 amplification in metastasized intestinal-type GA and a high-frequency chromosomal losses in chromosome regions 11q and 18q were found in Brazilian patients with diffuse type GA, and similar alterations were found in Asian and European populations.

Tumoral tissue had significantly higher heteroplasmy than paired healthy tissues and gastric tissue of healthy zilian patients. Tumoral tissue had significantly higher heteroplasmy than paired healthy tissues and gastric tissue of healthy zilian patients.

**From GA mutational landscape to precision medicine in LATAM**

Precision medicine is based on two main pillars. First, determining cancer predisposition through germline pathogenic or risk variants identification to provide a prompt diagnose and genetic counseling. Second, to test the tumor itself to decide the best treatment option through somatic variants evaluation. The starting point for precision medicine is the design of epidemiological studies that include sequencing strategies to obtain the mutational landscape of the tumor (Level 1: Data compilation). The subsequent bioinformatic analysis plays a key role in finding functional and clinically relevant mutations and the non-actionable mutation are re-analyzed, providing novel information later (Level 2: Data analysis and integration). Then, the data can be used for early diagnosis and the development of clinical approaches of specific therapeutic targets, which normally is expensive in terms of economic resources and time (Level 3: Development and approval of clinical approaches). If a specific therapy for a novel detected mutation does not exist, conventional therapy is used, but simultaneously
Figure 3  From mutational landscape to precision medicine for gastric adenocarcinoma (GA) in LATAM. The achievement of precision medicine requires several levels. The first level is the design of a proper cohort selection in which patients without previous treatment for GA are included properly for mutational landscape detection through available sequencing strategies (exome/transcriptomic/proteomic). Level 2 requires the data analysis derived from sequencing methods and for this purpose bioinformatic tools delivers functional and clinically relevant data or non-actionable mutations, which can be re-analyzed and deliver information that correlates with epidemiological data and turns into clinically relevant information. Level 3 is reached when the mutational landscape is applied for diagnosis/prognosis and therapeutic development for precision medicine. Finally, level 4 is successfully achieved by significantly decreasing the incidence and/or mortality of the cancer.

Table 3  Clinical trials for targeted therapies for gastric cancer in LATAM.

| Agent                      | Trial name  | LATAM participating countries                        | NCT Identifier (Status) |
|----------------------------|-------------|------------------------------------------------------|-------------------------|
| EGFR/HER 2 inhibitors      | GATSBY      | Argentina, Brazil, Guatemala, Mexico, Panama, Peru   | NCT01641939 (Terminated) |
| Trastuzumab-emtansine      | TRAXHER2    | Argentina, Brazil                                    | NCT01702558 (Terminated) |
| Trastuzumab-emtansine      | GATHERHER2  | Brazil                                               | NCT04168931 (Not yet recruiting) |
| Trastuzumab-emtansine      | EXPAND      | Argentina, Brazil, Chile                            | NCT00678535 (Completed) |
| Trastuzumab-emtansine      | DESTINY-Gastric03 | Brazil                                           | NCT04379596 (Recruiting) |
| Pertuzumab                 | JACOB       | Brazil, El Salvador, Guatemala, Mexico, Panama, Peru | NCT01774786 (Completed) |
| Trastuzumab                | ToGA Study  | Brazil, Costa Rica, Guatemala, Mexico, Panama, Peru  | NCT01041404 (Completed) |
| Trastuzumab                | HELOISE     | Brazil, Chile, Mexico, Panama, Peru                 | NCT01450696 (Terminated) |
| RTK Inhibitors             | LOGIC       | Argentina, Brazil, Chile, Mexico, Peru              | NCT00680901 (Active)    |
| Lapatinib                  |             | Argentina, Brazil, Colombia                          | NCT00428220 (Completed) |
| Sunitinib                  |             | Argentina, Brazil, Colombia                          | NCT00526669 (Completed) |
| Gefetinib                  |             | Puerto Rico                                          | NCT00215995 (Completed) |
| PI3K/AKT/mTOR Inhibitors   | GRANITE-1   | Argentina, Mexico, Peru                             | NCT00879333 (Completed) |

*MET Inhibitors*
specific therapy is developed, and clinical trials succeed, followed by the approval of health authorities (Level 3: Development and approval of clinical approaches). The cost for sequencing large cohorts and the high costs of treatments targeting specific mutations are the main padlocks. We consider that precision medicine will succeed until the personalized treatments achieve a significant decrease in the incidence or mortality in the population (Level 4: Population benefits) (Fig. 3).

The United States and Puerto Rico are conducting MATCH (molecular analysis for therapy choice) clinical trial, which falls within the level 3 of the proposed pathway from mutational landscape to precision medicine. This trial is based on genomic screening where patients are allocated to experimental aims depending on the genetic changes found in the tumor, regardless the cancer type.86,87 Several clinical studies have been conducted in LATAM to prove the efficacy and security of targeted therapies (Table 3) but

### Table 3 (continued)

| Agent                        | Trial name       | LATAM participating countries | NCT Identifier (Status)     |
|------------------------------|------------------|------------------------------|----------------------------|
| Rilotumumab                  | RILOMET-1        | Brazil, Mexico               | NCT01697072 (Terminated)   |
| AMG 337                      |                  | Chile, Peru                  | NCT02016534 (Terminated)   |
| Omitzumab                    | METGastric       | Guatemala, Mexico, Panama    | NCT01662869 (Completed)    |
| JAK/STAT Inhibitors          | Napabucasin (BB1608) | BRIGHTER                    | Brazil                     | NCT02178956 (Completed) |
| PD-1/PD-L1 Inhibitors        |                  |                              |                            |
| Relatlimab/Nivolhumab        |                  |                              |                            |
| Nivolhumab                   | CheckMate649     | Argentina, Brazil, Chile,    | NCT03704077 (Withdrawn)    |
| Relatlimab/Nivolhumab        |                  | Colombia, Mexico, Puerto Rico|                            |
| Pembrolizumab                | MK-3475-859/     | Argentina, Brazil, Chile,    | NCT03662659 (Active)       |
|                               | KEYNOTE-859      | Colombia, Costa Rica,        |                            |
|                               |                  | Guatemala, Mexico, Peru      |                            |
| Durvalumab                   |                  | Argentine, Peru              |                            |
| Pembrolizumab                | MK-3475-811/     | Brazil, Chile, Guatemala     | NCT03615326 (Recruiting)   |
|                               | KEYNOTE-811      |                              |                            |
| Pembrolizumab                | MK-3475-585/     | Brazil, Chile, Guatemala     | NCT03221426 (Recruiting)   |
|                               | KEYNOTE-585      |                              |                            |
| Avelumab                     | JAVELIN Gastric 100 | Brazil                      | NCT02625610 (Active)       |
| Pembrolizumab                | MK-7902-005/     | Chile                        | NCT03797326 (Recruiting)   |
|                               | E7080-G000-224/LEAP-005 |                              |                            |
| Pembrolizumab                | MK-3475-062/     | Argentina, Brazil, Chile,    | NCT02494583 (Active)       |
|                               | KEYNOTE-062      | Colombia, Guatemala, Mexico, |                            |
|                               |                  | Puerto Rico                  |                            |
| Angiogenesis inhibitor       | Ramucirumab      | Argentine, Brazil, Chile,    | NCT00917384 (Completed)    |
|                              | REGARD           | Colombia, Guatemala, Mexico  |                            |
| Ramucirumab                  | RAINBOW          | Argentine, Brazil, Chile,    | NCT01170063 (Completed)    |
|                               | RAINFALL         | Mexico                       | NCT02314117 (Completed)    |
| Ramucirumab                  |                  | Argentine, Mexico, Puerto Rico| NCT02443883 (Completed)    |
| CLDN18.2 directed antibody   | Zolbetuximab     | Argentina                    | NCT03653507 (Recruiting)   |
| MMP9 Inhibitors              | Zolbetuximab     | Brazil, Chile, Colombia,     | NCT03504397 (Recruiting)   |
|                              |                  | Mexico, Peru                 |                            |
| Antisense non-coding         | Andecaliximab    | Colombia, Chile, Peru        | NCT02545504 (Completed)    |
| mitochondrial RNA Inhibitors | GAMMA-1          |                              |                            |
| Andes-1537                   |                  | Chile                        | NCT03985072 (Recruiting)   |

Abbreviations: LATAM: Latin America, BSC, best supportive care; XELOX, Oxaliplatin and capecitabine; FOLFOX, Oxaliplatin, leucovorin and fluorouracil; SOX, Oxaliplatin and tegafur/gimeracil/oteracil potassium; FP, 5-Fluorouracil and cisplatin; FLOT, Fluorouracil, leucovorin, oxaliplatin and docetaxel; ECX, Epirubicin, cisplatin and capecitabine; SOC, Cisplatin, 5-Fluorouracil, capecitabine.

8 Pharmacokinetic studies.
non involving genomic screening and a design like the MATCH clinical trial. To date, only HER-2 and PD-1/PD-L1 inhibitors are only targeted therapies available to treat GA patients in LATAM. GA patients with KRAS, PIK3CA, ERBB2, EGFR, CD247, CLDN18, MET and FGFR pathogenic variants could be benefit from precision medicine clinical trials.

Brazil and Chile are the countries with more tangible scientific efforts done to generate local genetic data and elucidate the GA mutational landscape, this would ease the implementation of precision medicine and gene counseling programs to provide better care to GA patients. Even though the direct impact of this care options has not been measured, a decrease of GA incidence and mortality in these countries has been reported, with up to a 15% reduction in gastric cancer mortality in Brazilian cohorts and a 3.5% annual percentage reduction of mortality from 2012 to 2015 in Chilean cohorts. On the other hand, in most of LATAM countries the shortage on genetic data and founding opportunities hampers the implementation of short-term precision medicine and genetic counseling programs.

Conclusions

Despite LATAM population shares vast ethnic and cultural background, the mutational landscape is dissimilar. Brazilians show increased GA risk associated with variants in interleukins; Mexicans display also increased GA risk associated with growth factor receptors. Chileans and Mexicans present discrepancies in all the top 5 frequently mutated somatic variants. Though some difficulties should be overcome, Brazil, Chile, and Mexico may become the first LATAM countries providing precision medicine fighting GA based on its regional mutational landscape.

Author contributions

Dennis Cerrato-Izaguirre: Conceptualization, Writing-Original draft preparation, Writing-Reviewing and Editing. Yolanda I. Chirino: Writing-Original draft preparation, Writing-Reviewing and Editing. Claudia M Garcia-Cuellar: Writing-Reviewing and Editing. Miguel Santibáñez-Andrade: Conceptualization, Writing-Original draft preparation, Writing-Reviewing and Editing. Didder Prada: Writing-Reviewing Angélica Hernández-Guerrero: Writing-Reviewing. Octavio Alonso Larraza: Writing-Reviewing. Javier Camacho: Writing-Reviewing and Editing. Yesenia Sánchez-Pérez: Conceptualization, Writing-Reviewing and Editing.

Conflict of interests

Authors declare that they have no conflicts of interest.

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