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ORIGINAL ARTICLE

Access to accurate genetic diagnoses impacts the clinical management of neuroendocrine neoplasms

El acceso a los diagnósticos genéticos de precisión impacta el manejo clínico de las neoplasias neuroendocrinas

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ABSTRACT

Background: Genetic tests are a fundamental part of the approach to patients with neuroendocrine neoplasms (NENs), but their availability and the experience with their use greatly vary among clinical centers. **Objective:** To analyze the knowledge and perceptions of medical professionals from Mexico and other countries regarding the role of diagnostic genetic tests in the clinical management of patients with NENs. **Method:** Between 2023 and 2024, physicians from Mexico and other countries completed an electronic survey based on six clinical cases regarding the use of diagnostic genetic tests in patients with NENs. **Results:** Eighty-two physicians from eleven countries (68% from Mexico) completed the survey. More unanswered questions were observed among participants from Mexico compared with those from other countries (3[1-6] vs. 0 [0-1.3], p = 0.0001) and among those with no access to routine genetic testing compared with the rest (3 [1-6] vs. 1 [0-4], p = 0.0041). Out of all participants, 21.6 ± 7.7% expressed a lack of knowledge regarding the impact of genetic data in clinical management. **Conclusion:** The inclusion of genetic data on precision medicine strategies for patients with NENs requires a wide availability of routine tests and adequate training of the healthcare staff.

Keywords: Genetic counseling. Genetic tests. Multiple endocrine neoplasia. Neuroendocrine neoplasm. Next-generation sequencing. Precision medicine.

RESUMEN

Antecedentes: Las pruebas genéticas son fundamentales en el abordaje de pacientes con neoplasias neuroendocrinas (NENs), pero su disponibilidad y la experiencia con su aplicación varían considerablemente entre centros clínicos. **Objetivo:** Analizar el conocimiento y la percepción de profesionales médicos de México y otros países con respecto al papel de las pruebas de diagnóstico genético en el tratamiento clínico de los pacientes con NENs. **Método:** Entre 2023 y 2024, médicos de México y otros países respondieron una encuesta electrónica basada en seis casos clínicos sobre el empleo de pruebas de diagnóstico genético en pacientes con NEN. **Resultados:** Ochenta y dos médicos de 11 países (68% de México) respondieron a la encuesta. Se observaron más preguntas no respondidas entre los participantes de México, en comparación con los de otros países (3 [1-6] vs. 0 [0-1.3]; p = 0.0001) y entre aquellos sin acceso a puebas genéticas de rutina, comparados con el resto (3 [1-6] vs. 1 [0-4]; p = 0.0041). Del total de participantes, el 21.6 ± 7.7% expresaron desconocimiento sobre el impacto de los datos genéticos en el manejo clínico. **Conclusión:** La inclusión de los datos genéticos en estrategias de medicina de precisión para pacientes con NENs precisa la amplia disponibilidad de pruebas de rutina y la adecuada capacitación del personal médico.

Palabras clave: Consejería genética. Estudios genéticos. Medicina de precisión. Neoplasia endocrina múltiple. Neoplasia neuroendocrina. Secuenciación de nueva generación.

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INTRODUCTION

Most neuroendocrine neoplasms (NENs) are sporadic lesions, but 5-40% of them are due to germline defects and may arise in the setting of various hereditary syndromes (Table 1)[1,2]. Features that could raise suspicion of a hereditary neoplasm include younger age at presentation, additional neoplasms occurring in the same patient or the same family, and multiple NENs of the same type occurring in a single individual[3]. NENs are often underdiagnosed due to their variable and nonspecific clinical presentation[4]. Their incidence, however, has significantly increased in recent years, most likely thanks to greater clinical suspicion and improved diagnostic methods, including biochemical, imaging-based, and molecular studies[5]. Although characteristic clinical presentations are associated with several genetic defects in NENs, these phenotypes can overlap, complicating the establishment of diagnoses based solely on the clinical pictures[6-8].

Our understanding of the molecular bases of NENs has boosted in the last two decades, mainly thanks to research based on high-throughput technologies for genetic analyses[9]. The translation of these data onto diagnostic tests has led to earlier and more accurate diagnoses, better clinical outcomes, and improved genetic counseling[10-12]. Nevertheless, the routine use of these tools in many medical fields means that nowadays decisions regarding genetic testing are not limited to geneticists. This poses a challenging scenario, since most physicians have not received specific training on the indications, ethical and technical aspects, and interpretation of genetic data[13]. On the other hand, the limited availability of state-of-the-art genetic tests in many clinical settings precludes the advancement of precision medicine strategies into the "real world" medical practice. These caveats in the modern clinical care of individuals with NENs have not been assessed before. Therefore, we sought to analyze the knowledge and perception of medical professionals from Mexico and other countries regarding the role of diagnostic genetic tests in the clinical management of patients with NENs, using a clinical case-based electronic survey.

MATERIALS AND METHODS

Survey design

An electronic survey was designed using the Google Forms platform. The first part of the survey collected anonymized demographic data (place of origin, educational status, primary specialty, types of professional activities, and availability of genetic tests at their workplaces) using preset responses in a drop-down menu format. Brief clinical cases of patients with NENs were then presented, which were extracted from an ongoing study on the genetic bases of NENs (ClinicalTrials.gov: NCT06523582), based at two reference hospitals in Mexico City (Hospital de Especialidades de Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán). The internal review boards of both centers approved the project (protocols R-2022-785-011 and 4090, respectively), and all participants provided written informed consent upon inclusion. These individuals underwent peripheral blood panel-based next-generation sequencing (pNGS) for 53 NEN-associated genes; results have been reported elsewhere[14]. After each clinical summary, three questions (the same for all cases) aimed to determine diagnostic considerations, whether the participants would request a genetic test, and, if so, what type of test they would select. These questions also had preset answers, but for diagnostic considerations and type of genetic tests, the option "other" with space for free text was also included. The pNGS results for each case were then presented, followed by two questions interrogating whether the test results would alter the clinical management and how. The former question had "yes," "no," and "I do not know" as possible answers, while the latter was open-ended.

A preliminary version of the survey, including nine clinical cases, was assessed in a pilot study with nine participants. Based on their feedback, and following review by a panel of clinical experts to ensure face and content validity, as recommended in previously published methodological guidelines, the wording and clarity of items were improved, and the number of clinical cases was reduced to six

Table 1. Main genetic syndromes associated with neuroendocrine neoplasms*

Syndromes	Genes (causative defects)	MOI	Associated features
Carney complex	*PRKAR1A* (LOF), *PRKACB* (GOF)	AD	Blue nevi, large cell calcifying Sertoli cell tumors, lentiginosis, liver cancer, myxomas in multiple organs, ovarian cancer, pancreatic cancer, PitNETs (somatotropinomas, rarely corticotropinomas), PPNAD, schwannomas, testicular cancer, thyroid nodules
Carney-Stratakis syndrome	*SDHB*, *SDHC*, *SDHD* (LOF)	AD	GISTs, PPGLs
Carney triad	Unknown	Not inherited	GISTs, pulmonary chondromas, PPGLs
Cowden syndrome	*PTEN* (LOF)	AD	Breast, thyroid (follicular carcinoma), and endometrial cancers
DICER1 syndrome	*DICER1* (LOF)	AD	Genitourinary sarcoma, pituitary blastoma, pleuropulmonary blastoma, rhabdomyosarcoma, others
Familial PPGLs syndromes	*MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, other genes (LOF), *RET* (GOF)	AD	GISTs, PitNETs (rarely), PPGLs, renal cell carcinoma
FIPA	*AIP* (LOF)	AD	PitNETs (usually somatotropinomas, somatomammotropinomas or prolactinomas)
Li-Fraumeni syndrome	*TP53* (LOF)	AD	Adrenocortical carcinomas, breast cancer, brain tumors, leukemias, sarcomas
Lynch syndrome	*MSH2*, *MSH6*, *MLH1*, *PMS2* (LOF)	AD	Biliary carcinoma, colorectal carcinoma, endometrial carcinoma, gastric carcinoma, glioblastoma, ovarian carcinoma, pancreatic carcinoma, PitNETs (rarely), small intestine carcinoma, urothelial carcinoma
McCune-Albright syndrome	*GNAS* (GOF)	Not inherited (mosaic)	*Café au lait* spots, MNG, multinodular adrenal hyperplasia, PitNETs (somatotropinomas or somatomammotropinomas), polyostotic fibrous dysplasia, precocious puberty
MEN1	*MEN1* (LOF)	AD or mosaic	Adrenocortical tumors, angiofibromas, BP-NENs, breast cancer, collagenomas, ependymomas, GI-NENs, hibernomas, leiomyomas, lipomas, meningiomas, panNENs, PHPT, PitNETs, PPGLs (rarely), thymomas
MEN1-like syndrome	*CDKN1A*, *CDKN2B*, *CDKN2C* (LOF)	Unknown	Similar to MEN1
MEN type 2A, 2B, and familial medullary thyroid carcinoma	*RET* (GOF)	AD	MTC, PHPT, PitNETs, PPGLs
MEN4	*CDKN1B* (LOF)	AD	Similar to MEN1
MEN5	*MAX* (LOF)	AD	Chondrosarcoma, ganglioneuromas, lung adenocarcinomas, neuroblastomas, PHPT, PitNETs (PIT1 lineage), PPGLs, renal cell, oncocytomas, breast adenocarcinomas
Neurofibromatosis type 1	*NF1* (LOF)	AD	*Café au lait* spots, gliomas, Lisch nodules, neurofibromas, panNENs, PHPT, PitNETs, PPGLs
Pacak-Zhuang syndrome	*EPAS1* (LOF)	Likely AD	PPGLs polycythemia, and somatostatinoma

(Continues)

Table 1. Main genetic syndromes associated with neuroendocrine neoplasms* *(continuation)*

Syndromes	Genes (causative defects)	MOI	Associated features
Tuberous sclerosis complex	*TSC1*, *TSC2* (LOF)	AD	Cardiac rhabdomyomas, renal angiomyolipomas, subependymal giant cell astrocytomas
Von Hippel-Lindau disease	*VHL* (LOF)	AD	Brain, cerebellar, spinal cord and retinal hemangioblastomas, clear cell renal cell carcinoma, ELSTs, epididymal (in men) and broad ligament (in women) cystadenomas, panNENs, PPGLs, renal and pancreatic cysts
X-LAG	*GPR101* (GOF)	Mosaic or X-linked dominant	Pituitary hyperplasia or PitNETs (somatotropinomas or somatomammotropinomas)

**Adapted from references* [1,26,47,48].
AD: autosomal dominant; CNS: central nervous system; ELST: endolymphatic sac tumors; FIPA: familial isolated pituitary adenomas; GIST: gastrointestinal stromal tumor; GOF: gain-of-function; LOF: loss-of-function; MEN1: multiple endocrine neoplasia type 1; MOI: mode of inheritance, MNG: multinodular goiter; panNEN: pancreatic neuroendocrine neoplasm; PHPT: primary hyperparathyroidism (due to parathyroid tumors and/or hyperplasia); PPGLs: pheochromocytomas and paragangliomas; PPNAD: primary pigmented nodular adrenocortical disease; X-LAG: X-linked acrogigantism.

Table 2. Clinical cases presented in the survey

Case no.	Clinical summary
Case 1	Sixty-three-year-old man. His father died suddenly at age 79, his mother suffered from breast cancer, one brother has ischemic heart disease and three other brothers have T2DM. He has three children, the youngest with history of recurrent episodes of epistaxis. He has a history of HBP, obesity, and T2DM. Twenty years ago, he was diagnosed with kidney cancer and treated with nephrectomy and left adrenalectomy. He is currently in remission. Seven years ago, multiple vascular ectasias and arteriovenous malformations involving multiple organs were found. A CT scan of the chest and abdomen performed for follow-up of renal cancer revealed diffuse bilateral pulmonary fibrosis, bilateral pulmonary nodules (< 4 mm) and four hyperdense, rounded lesions with ill-defined margins in the pancreas, two located in the head (6-8 mm) and two in the tail (10 mm). CgA 4.5xULN was documented, with plasma gastrin, metanephrines, and catecholamines within normal ranges. A 99mTc-HYNIC-TOC SPECT-CT scan confirmed the presence of lesions with overexpression of somatostatin receptors in the head and tail of the pancreas and on the posterior wall of the stomach, suggestive of NENs. In subsequent 99mTc-HYNIC-TOC SPECT-CT, a lesion compatible with a paraaortic abdominal PGL was found, which, based on available laboratory studies, was non-functioning. He is currently stable, awaiting surgical resection of the pancreatic lesions.
Case 2	Forty-two-year-old man. His father suffered from bladder cancer, his mother had a kidney cyst, and an uncle had probable renal hypoplasia. One year prior to his evaluation, he developed difficult-to-treat HBP, headaches, dizziness, nausea, and palpitations. Due to clinical suspicion of intracranial hypertension, MRI was performed, finding hydrocephalus and diffuse cerebral edema secondary to a 45x33x31 mm lesion in the cerebellar vermis with mass effect, and another 19 × 21 mm lesion posterior to the right hemicerebellum. A craniotomy with resection of a Vermian cerebellar hemangioblastoma and radiosurgery with 18 Gy for residual lesions in the posterior fossa were performed. A CT-scan of the thorax and abdomen showed a 2.5 mm subpleural pulmonary nodular lesion in the right anterobasal segment, multiple ovoid lesions in the pancreas with defined and lobulated edges, from 19 to 72 HU, the largest of them hyperdense, with homogeneous enhancement of 27 × 33 × 24 mm, suggestive of a NEN. There were also multiple renal cysts, and an interpolar, endophytic, heterogeneous, and hyperdense left renal lesion of 30 × 27 × 30 mm and 189 HU. PET-CT showed an increase in somatostatin receptors in the uncinate process of the pancreas, bilateral renal lesions, pancreatic lesions, and a calcified pulmonary granuloma. Tumor markers (carcinoembryonic antigen and α-fetoprotein) were negative. Treatment was started with lanreotide 120 mg monthly and a 24 × 21 mm lesion was resected, which was reported as an ISUP grade 1 ccRCC. Disease was stable at the last assessment.

(Continues)

Table 2. Clinical cases presented in the survey *(continued)*

Case no.	Clinical summary
Case 3	Forty-nine-year-old woman. Her father died of unspecified lymphoma, one maternal cousin has multiple lipomas, another maternal cousin was diagnosed with acromegaly, and the daughter of one more maternal cousin presented clinical data compatible with acromegaly. The patient was diagnosed with acromegaly at age 15 years in the context of secondary amenorrhea, headaches, acral growth, and elevated GH and IGF1 levels for her age and sex. She was treated with bromocriptine for 5 years. Due to persistently active acromegaly, she underwent transsphenoidal resection of a 10 × 10 × 3 mm pituitary macroadenoma and later received radiotherapy with linear accelerator (54 Gy) directed at a remnant in the right cavernous sinus, subsequently developing panhypopituitarism.
Case 4	An 18-year-old man with 2 years history of accelerated linear growth, developed decreased visual acuity and bitemporal hemianopsia. Biochemical tests revealed excess of GH and PRL production, central hypogonadism, hypothyroidism, and hypocortisolism. An MRI showed a 32 × 26 × 27 mm pituitary tumor lesion with infra, supra, and parasellar extension (predominantly left), heterogeneous due to hemorrhage, with compression of the pituitary stalk, optic chiasm, floor of the third ventricle, and adjacent brain parenchyma (Knosp II). Hormone replacement treatment and octreotide LAR 20 mg monthly were started. The pathology report after transsphenoidal surgery confirmed positive immunohistochemistry for GH and PRL. Due to persistently active disease, treatment with octreotide LAR was restarted and cabergoline was added.
Case 5	Thirty-five-year-old woman. Her father suffered from an unspecified thyroid disease, six half-siblings required total thyroidectomy, one of them due to unspecified thyroid cancer and the rest for unknown causes. Five years before her first clinical evaluation, she developed progressive growth of the right anterior region of the neck, which caused dysphagia to solids and orthopnea. A thyroid US showed multinodular goiter that required biopsy, reporting a Bethesda IV follicular neoplasia. A CT-scan showed bilateral ovoid lymph nodes with loss of their fatty hilum in levels IIA, IIB and III and left VB, as well as a 15 × 16 × 18 mm conglomerate. Total thyroidectomy and bilateral modified radical dissection were performed with histopathological result of MTC with lymphatic, perineural, and extrathyroidal invasion of cervical muscles. Immunohistochemistry was positive for calcitonin and carcinoembryonic antigen, negative for thyroglobulin and Ki-67 +++. The disease stage was IVA (T2 N1b M0) and the patient is currently under surveillance.
Case 6	Fifty-four-year-old man with a family history of consanguinity. His paternal grandmother died of unspecified cancer and his mother died at age 48 due to an unknown cause. He mentioned the presence of *café-au-lait* spots in his father (who died at age 85), eight of his ten siblings (three died before age 65), and his 29-year-old daughter (alive). A brother also developed primary biliary cirrhosis and a nephew died at age 28 from complications of epilepsy. The patient has a history of HBP, prediabetes, dyslipidemia, pernicious anemia, and corneal transplantation in the right eye, with amaurosis of the same eye due to retinal detachment 20 years ago. Four months prior to his evaluation, he developed short-term memory impairment, holocranial headache, and seizures, for which an MRI was performed. The study reported an incidental 15 × 16 mm left parasagittal pituitary lesion, contacting the wall of the cavernous sinus, with homogeneous enhancement and displacement of the pituitary stalk to the left and the optic chiasm anteriorly. Laboratory studies demonstrated hyposomatotropinemia, while the rest of the pituitary hormones were normal. He is currently awaiting transsphenoidal surgery.

99mTc-HYNIC-TOC SPECT-CT: technetium-99m-hydrazinonicotinamide-Tyr3-octreotide single-photon emission computed tomography-CT; ccRCC, clear cell renal cell carcinoma; CgA: chromogranin A; CT: computed tomography; GH: growth hormone; HBP: high blood pressure; HU: Hounsfield units; IGF1: insulin-like growth factor 1; ISUP: International society of urological pathology; LAR: long-acting release; MRI: magnetic resonance imaging; MTC: medullary thyroid carcinoma; NENs: neuroendocrine neoplasms; PET-CT: positron emission tomography; PGL: paraganglioma; PRL: prolactin; T2DM: type 2 diabetes mellitus; ULN: upper limit of normal; US: ultrasound.

(Table 2)[15,16]. A link to the survey was distributed through private WhatsApp chat groups of medical specialists, residents, and fellows, as well as through direct e-mail and text messages, and personal social media accounts (Facebook and X) in Mexico and other countries. No official channels of medical societies were used. Spanish and English versions of the survey were used for Spanish speakers and the rest of the participants, respectively. The primary goal was to apply the survey to endocrinologists, although invitations were also extended to physicians from other specialties caring for patients with NENs. Data collection was conducted from July 15, 2023, to October 8, 2024. Participants were given

the option to contact the researchers for feedback if they wished to learn more about the survey, the research, or its results. Responses were stored anonymously, and no personal identifiable data were collected from participants.

STATISTICAL ANALYSES

Since there are no available data on similar studies, the sample size calculation could not be performed. Therefore, a non-probabilistic sampling method was selected, including nine surveys in the pilot study and at least 40 additional complete surveys for validation and analysis. Data were analyzed using the Prism 10.3.1 (GraphPad) software. Quantitative variables are reported as mean ± standard deviation or median and interquartile range, according to their distribution as per the Shapiro-Wilk test. Comparisons were established using the Mann-Whitney U test. Qualitative variables are presented using frequencies and percentages and were compared using the X^2 or Fisher's exact test, as appropriate. A $p < 0.05$ was considered statistically significant.

Modified natural semantic network techniques were used to analyze the open-ended responses from the survey[17]. This method involves presenting stimuli (phrases, words, or definitions, among others) to participants, who are then asked to write at least five words that come to their minds in response. In our study, six clinical cases involving the use of genetic diagnostic tests in patients with NENs were used as stimuli. Subsequently, participants are instructed to rank the words by assigning a "1" to the word that they feel closest to their experience, followed by "2," and so on. Based on the frequencies and percentages of the terms provided, semantic proximity was statistically analyzed, following the methodology described by Rodríguez-Pérez et al.[18]. Answers were classified as whether physicians considered the tests useful for diagnosing the patient, changing the proposed treatment, or establishing a prognosis. We also quantified the number of questions where physicians did not consider the test to be useful or did not know the answer.

RESULTS

Sociodemographic data

Eighty-two physicians from eleven different countries participated in the survey. Two-thirds of participants (n = 56) were from Mexico, of which over one-half (n = 30) were from Mexico City (Fig. 1A and B). Almost two-thirds (n = 50) worked in specialty hospitals that are referral centers for NENs (Fig. 1C). Their main area of specialization was endocrinology (79.3%, n = 65), followed by internal medicine and endocrine surgery (Fig. 1D). According to their roles, most participants were attending physicians (65.9%, n = 54), followed by residents or fellows, while researchers comprised the smallest group (Fig. 1E); their primary occupation was outpatient care (74.4%, n = 61) (Fig. 1F). Nearly half of the participants (n = 37), including 53.6% (n = 30) of the total physicians from Mexico, reported that genetic tests are not performed at their centers. Conversely, 34.1% (n = 28) confirmed that these tests are routinely conducted in their centers, 18.3% (n = 15) had tests available, but only within research protocols, and 2.4% (n = 2) were unaware of the availability of genetic testing at their centers (Fig. 2).

ANALYSIS OF CLINICAL CASES

Table 3 summarizes the answers for all cases. In case 1, the most frequently suspected clinical diagnoses were familial pheochromocytoma/paraganglioma (FPPGLs) and Von Hippel–Lindau disease (VHL). The clinical picture was complex, due to the overlap of features of hereditary hemorrhagic telangiectasia with renal cancer and two types of NENs. The three neoplasms detected could occur in the setting of VHL, while pancreatic NENs (panNENs) are not a known association of FPPGLs[19]. Almost all participants (96.3%, n = 79) would request genetic testing for this patient; pNGS was the most frequent selection (48.8%, n = 40), and 24.4% (n = 20) did not know what test to perform. A genetic study was indeed indicated for this individual, with the most cost-efficient initial test being pNGS for FPPGLs-causative genes.

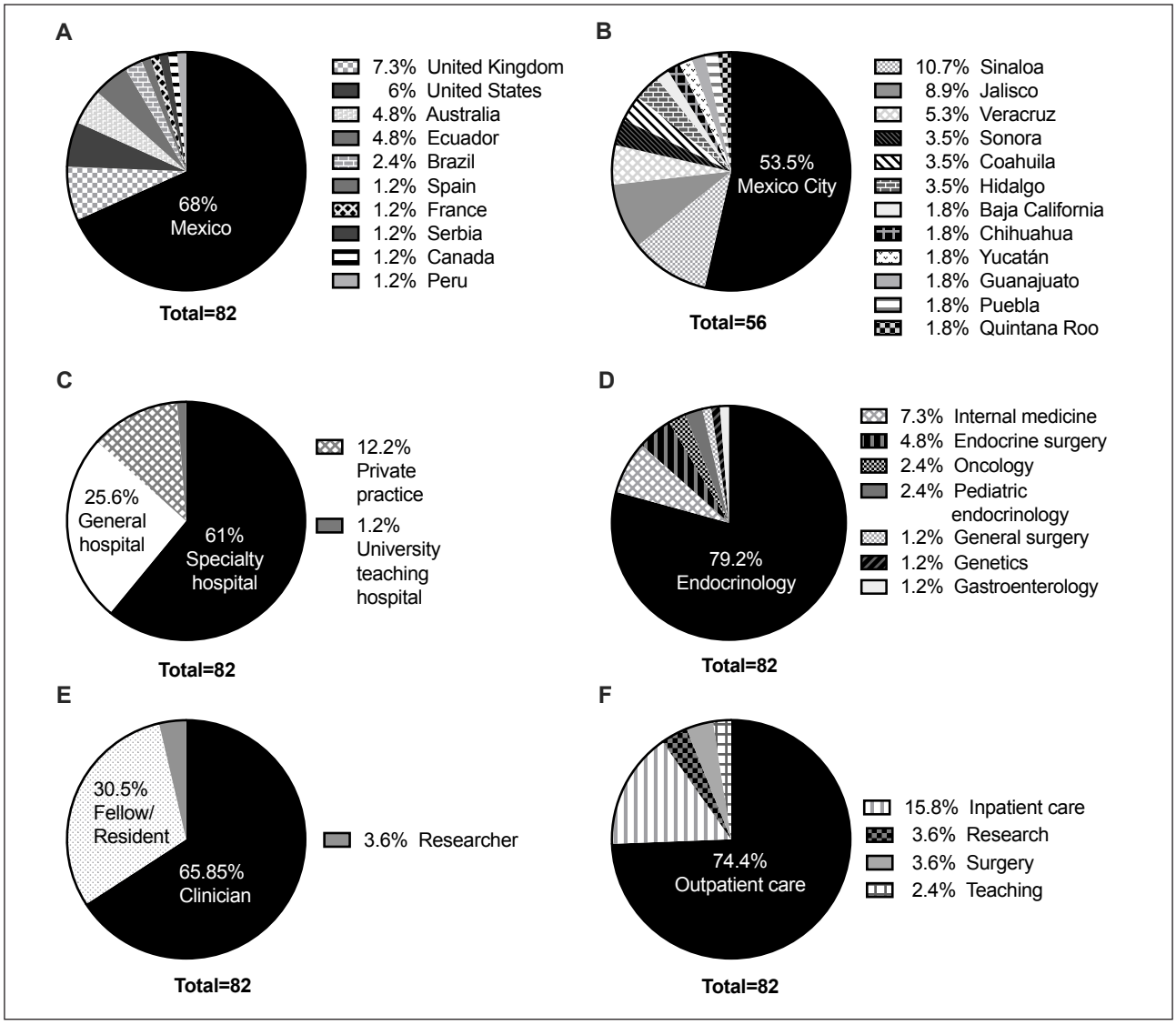

Figure 1. Sociodemographic characteristics of the participants. **A:** countries of residence. **B:** states of residence of participants from Mexico. **C:** type of centers of affiliation. **D:** areas of specialization. **E:** current position. **F:** primary professional activities.

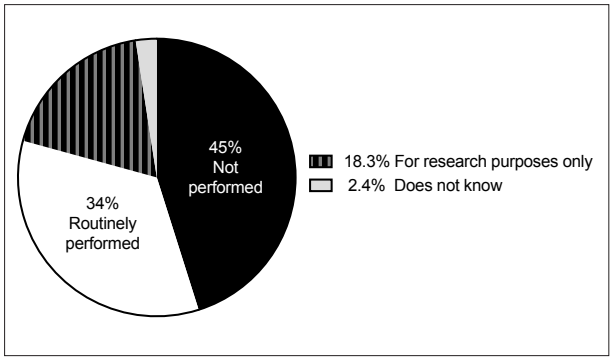

Figure 2. Availability of genetic tests in the centers of affiliation of the participants.

Almost three-quarters of participants (n = 59) stated that the test result would influence their treatment and follow-up strategies. Penetrance is low for *SDHA* loss-of-function (LOF)-associated disease, but clinical guidelines for individuals with *SDHA* LOF variants recommend annual clinical and biochemical (plasma metanephrines and catecholamines) assessments, as well as magnetic resonance imaging (MRI) or computerized tomography of the neck, chest, abdomen, and pelvis every 3-5 years[20,21]. Although orthogonal verification did not confirm the variant, this case analysis remains valid for the survey.

Table 3. Summary of responses to questions 1-4 of the survey

Questions and answers	No. of respondents (%)					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
1. What clinical syndrome do you suspect?						
Familial isolated pituitary adenoma	1 (1.2)	1 (1.2)	68 (82.9)	36 (43.9)	-	2 (2.4)
Familial medullary thyroid carcinoma	-	-	1 (1.2)	-	53 (64.6)	-
Familial pheochromocytoma/paraganglioma	34 (41.5)	1 (1.2)	-	1 (1.2)	-	-
Multiple endocrine neoplasia type 1	7 (8.5)	2 (2.4)	11 (13.4)	15 (18.3)	2 (2.4)	1 (1.2)
Multiple endocrine neoplasia type 2	1 (1.2)	4 (4.9)	-	1 (1.2)	27 (32.9)	2 (2.4)
Multiple endocrine neoplasia type 4	4 (4.9)	1 (1.2)	2 (2.4)	10 (12.2)	-	1 (1.2)
Neurofibromatosis type 1	2 (2.4)	2 (2.4)	-	1 (1.2)	-	74 (90.2)
Von Hippel-Lindau disease	33 (40.2)	70 (85.4)	-	2 (2.4)	-	1 (1.2)
Other: Beckwith-Wiedemann syndrome	-	-	-	1 (1.2)	-	-
Other: isolated acromegaly	-	-	-	13 (15.9)	-	-
Other: kidney cancer syndrome	-	1 (1.2)	-	-	-	-
Other: McCune-Albright syndrome	-	-	-	-	-	1 (1.2)
Other: X-linked acrogigantism	-	-	-	1 (1.2)	-	-
Does not know	-	-	-	1 (1.2)	-	-
2. Would you indicate a genetic test for this patient?						
Yes	79 (96.3)	78 (95.1)	72 (87.8)	54 (65.9)	79 (95.3)	75 (91.5)
No	-	1 (1.2)	6 (7.3)	18 (22.0)	1 (1.2)	3 (3.7)
Does not know	3 (3.7)	3 (3.7)	4 (4.9)	10 (12.2)	2 (2.4)	4 (4.9)
3. If you requested a genetic study, what type of test would you consider most useful?						
Targeted next generation sequencing (panel)	40 (48.8)	44 (53.7)	33 (40.2)	33 (40.2)	39 (47.6)	32 (39)
Does not know	20 (24.4)	5 (6.1)	30 (36.6)	33 (40.2)	19 (23.2)	27 (32.9)
Exome sequencing	12 (14.6)	11 (13.4)	8 (9.8)	6 (7.3)	8 (9.8)	7 (8.5)
Genome sequencing	6 (7.3)	11 (13.4)	6 (7.3)	3 (3.7)	3 (3.7)	7 (8.5)
Sanger sequencing	3 (3.7)	9 (11)	4 (4.9)	3 (3.7)	12 (14.6)	8 (9.8)
Other: seek advice from geneticist	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Other: all of the above	-	1 (1.2)	-	-	-	-
Other: It is not necessary	-	-	-	1 (1.2)	-	-
4. Case-specific questions						
Case 1: the genetic test reported a deletion of one exon in the *SDHA* gene at the germline level. Would this result change your treatment and follow-up strategy in this patient?						
Case 2: the genetic test reported a pathogenic germline missense variant in the *VHL* gene. Would this result change your treatment and follow-up strategy in this patient?						
Case 3: the genetic study reported a likely pathogenic germline missense variant in the *AIP* gene. Would this result change your treatment and follow-up strategy in this patient?						
Case 4: the genetic test reported a germline missense variant of uncertain significance in the *CDKN1B* gene. Would this result change your treatment and follow-up strategy in this patient?						

(Continues)

Table 3. Summary of responses to questions 1-4 of the survey *(continued)*

Questions and answers	No. of respondents (%)					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Case 5: the genetic test reported a pathogenic germline variant in the *RET* gene. Would this result change your treatment and follow-up strategy in this patient?						
Case 6: the genetic study reported a nonsense pathogenic germline variant in the *NF1* gene. Would this result change your treatment and follow-up strategy in this patient?						
Yes	59 (72)	48 (58.5)	48 (58.5)	38 (46.3)	65 (79.3)	53 (64.6)
No	13 (15.9)	20 (24.4)	21 (25.6)	19 (23.2)	11 (13.4)	17 (20.7)
Does not know	10 (12.2)	14 (17.1)	13 (15.9)	25 (30.5)	6 (7.3)	12 (14.6)

The patient described in case 2 exhibited a classic clinical presentation of VHL, which matched the diagnostic impressions of most participants (85.4%, n = 70). Nearly all respondents (95.1%, n = 78) would request genetic testing, with pNGS being the most commonly selected technique, followed by exome sequencing (ES) and genome sequencing (GS). More than half indicated that the genetic test result would alter their clinical strategies, while 24.4% (n = 20) stated that it would not change their approach, and 17.1% (n = 14) were unsure. For this clearly defined phenotype, either Sanger sequencing (SS) of *VHL* followed by multiplex ligation-dependent probe amplification (MLPA) if required, or pNGS including *VHL* would be appropriate[22]. The well-established surveillance protocol for individuals with VHL and *VHL* defect carriers involves annual clinical and biochemical evaluations, beginning at the first decade of life. Retinal hemangioblastoma screening through fundoscopic examinations is recommended every 6-12 months, starting at age 1 year. Neurological and sensory assessments should be done annually, starting in early childhood. Central nervous system MRI should be performed every 2 years starting at the age of 11 years to screen for lesions such as hemangioblastomas. Abdominal MRI is done every 2 years from age 15 years for early detection of renal cell carcinoma, panNENs, and PPGLs. Audiograms are recommended at least once in a lifetime or every 2-3 years starting at age 11, with increased frequency in symptomatic cases. MRI of the internal auditory canals is advised for asymptomatic individuals aged 15-20 years. Psychosocial assessments should be conducted during each visit to address the psychological impact of living with a hereditary cancer syndrome[22-25].

Familial isolated pituitary adenoma (FIPA) was the most frequently reported clinical diagnosis in case 3 (82.9%, n = 68), including one survey with the answer "familial acromegaly with *AIP* mutation". The second most common answer was multiple endocrine neoplasia type 1 (MEN1), noted by 13.4% (n = 11) of respondents. While most respondents (87.8%, n = 72) would request genetic testing for this patient, 36.6% (n = 30) expressed uncertainty about which test to select. Among the genetic tests proposed, pNGS was the most frequently chosen (40.2%, n = 33), followed by the "I do not know" option. The genetic study of this individual described a likely pathogenic germline *AIP* variant, confirming the most popular diagnostic impression. Based on this report, more than half of the respondents would adjust their clinical management. The case summary clearly pointed toward FIPA, a phenotype caused by germline LOF *AIP* variants in 10-15% of cases, but with an unknown etiology in most families. Routine testing in FIPA can be achieved by means of *AIP* SS and MLPA, but given the high frequency of negative test results, pNGS for hereditary PitNETs is most frequently used nowadays[26]. Expert recommendations advocate for close surveillance, due to the frequent need for multimodal treatment in these individuals[27]. Early genetic testing is also strongly recommended in first-degree relatives, as the disease can manifest as early as age 4 years[28]. For asymptomatic individuals, annual growth assessments, hormonal measurements (insulin-like growth factor 1 and prolactin), and monitoring for clinical signs of PitNETs are advised. Baseline MRI should be performed at age 10 years (or earlier if symptomatic) with follow-up imaging every 5 years,

unless clinical symptoms arise. Surveillance can be relaxed after age 30 years, since *AIP*-associated PitNETs rarely develop beyond this age[26].

In case 4, the most frequently selected clinical diagnosis was FIPA (43.9%, n = 36), although there was no mention of additional PitNET cases in the family, a *sine qua non* condition for this entity. The clinical diagnosis for this patient was isolated gigantism, but acromegaly was also acceptable, and although these options were intentionally left out of the preset answers, "isolated acromegaly" was suggested by 15.9% (n = 13) of participants. More than half of the respondents would request genetic testing in this case, while 22% (n = 18) would not, and the remainder were unsure if testing should be done. Among those who selected a test, 40.2% (n = 33) chose pNGS, followed by ES at 7.3% (n = 6). In this case, genetic testing was indicated because gigantism has a known genetic etiology in up to 50% of cases[29]. Since this phenotype can be caused by defects in multiple genes, *AIP*, *MEN1*, *GNAS*, *CDKN1B*, and *GPR101* being the main ones, the recommended initial genetic test is pNGS. Almost half of the participants indicated that the report of a *CDKN1B* variant of uncertain significance (VUS) would change their clinical strategy, 30.5% (n = 25) were unsure if the result would alter their management, and the rest would not change their approach. Germline LOF *CDKN1B* variants cause multiple endocrine neoplasia type 4 (MEN4), but additional screening is not indicated for VUS carriers and their families, although they could be performed in the context of research protocols[30,31]. MEN4 remains an infrequent entity, and at present, there are no specific guidelines for the follow-up of individuals carrying *CDKN1B* defects[32].

In case 5, the most frequently suspected clinical diagnosis was familial medullary thyroid carcinoma (FMTC, 64.6%, n = 53), followed by multiple endocrine neoplasia type 2 (MEN2, 32.9%, n = 27). Nearly all participants would request genetic testing, with the most frequently chosen test being pNGS (47.6%, n = 39). A pathogenic germline *RET* variant was found and, based on the family history, the clinical diagnosis was FMTC[33]. MEN2 was also a reasonable differential diagnosis, as additional syndrome components such as PPGLs and PHPT could emerge later in the patient or her relatives. The genetic test recommended by the 2015 American Thyroid Association (ATA) guidelines in cases of FMTC is SS of selected *RET* exons, an approach that remains valid given the oligoexonic nature of this rare phenotype[34]. In rare cases with negative *RET* screening, pNGS in tumor samples can detect variants in other genes implicated in thyroid cancer (*HRAS*, *KRAS*, or *TP53*), which may influence prognosis and treatment[33,35]. Among the respondents, 79.3% were endocrinologists, most of whom are well-versed in ATA guidelines. This likely explains why this was the case, where most participants agreed that the genetic result would change their clinical strategies.

Finally, in case 6, 90.2% (n = 74) of participants selected neurofibromatosis type 1 (NF1) as the diagnosis, which was expected given the characteristic clinical picture described. Most participants would request genetic testing for this individual, with the majority selecting pNGS (39%, n = 32), followed by SS (9.8%, n = 8). In sharp contrast with the abovementioned for FMTC, clinically relevant *NF1* defects may arise in any region of this *57-exon* gene. Therefore, the recommended initial test is pNGS, although some cases require additional analyses for structural variants[36]. Even though the clinical presentation was typical for NF1, nearly two-thirds of participants (64.6%, n = 53) indicated that genetic confirmation would alter their subsequent clinical management. Indeed, this patient would definitely require screening for other potential NF1-associated manifestations. Interestingly, he developed a PitNET, which is not a typical component of NF1; whether this association is coincidental or causative, remains unclear[37]. In addition, since around 50% of patients with NF1 inherit the condition from an affected parent, detecting a pathogenic variant in the proband allows for targeted screening of at-risk family members, enabling early diagnosis and management[36].

PERCEPTIONS ON ROUTINE APPLICATIONS AND IMPACT OF GENETIC TESTS

A total of 30.5% of participants answered all survey questions, while only 1.2% left all unanswered or indicated "I do not know" (hereafter referred to as "unanswered questions") in every question. Participants

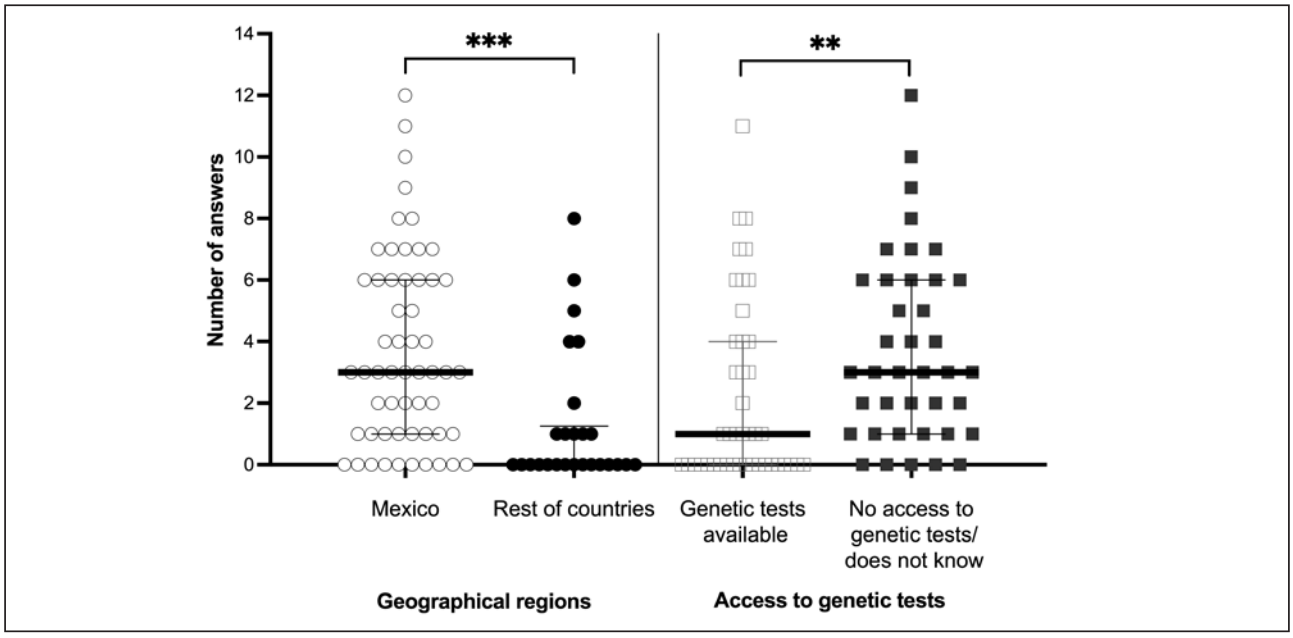

Figure 3. Number of answered questions according to the geographical regions of participants (left panel) or according to the availability of genetic tests in their center (right panel). **p > 0.001, ***p = 0.0001.

from Mexico had a significantly higher number of unanswered questions, compared with the rest (3 [1-6] vs. 0 [0-1.3], p = 0.0001, Fig. 3, left panel). The number of unanswered questions was apparently related to the availability of tests, as physicians working in centers with access to routine genetic testing had less unanswered questions, compared with the rest (1 [0-4] vs. 3 [1-6], p = 0.0041, Fig. 3, right panel). Notably, all participants from Europe and Australia had access to routine genetic tests, compared with 43.5% from other regions (p = 0.0001, Fig. 4).

In all cases, the majority of participants indicated that the genetic results provided would influence treatment or follow-up strategies: 72% (n = 59) in case 1, 58.5% (n = 48) in cases 2 and 3, 46.3% (n = 38) in case 4, 79.3% (n = 65) in case 5, and 64.6% (n = 53) in case 6. However, the specific ways in which the genetic results would influence decisions varied significantly among responders. To better understand these differences, we classified the reported considerations regarding the impact of genetic results for each case into six categories (Fig. 5). *Requires tailored follow-up* was the most prominent group of responses across all cases (43.3 ± 8.9%), particularly in case 5 (52.4%). The second most common

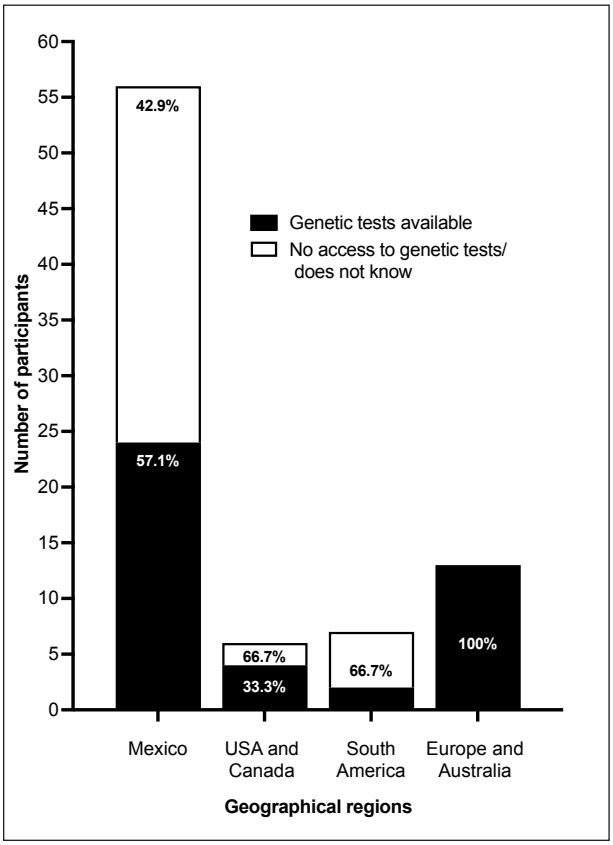

Figure 4. Availability of routine genetic tests across geographical regions of participants.

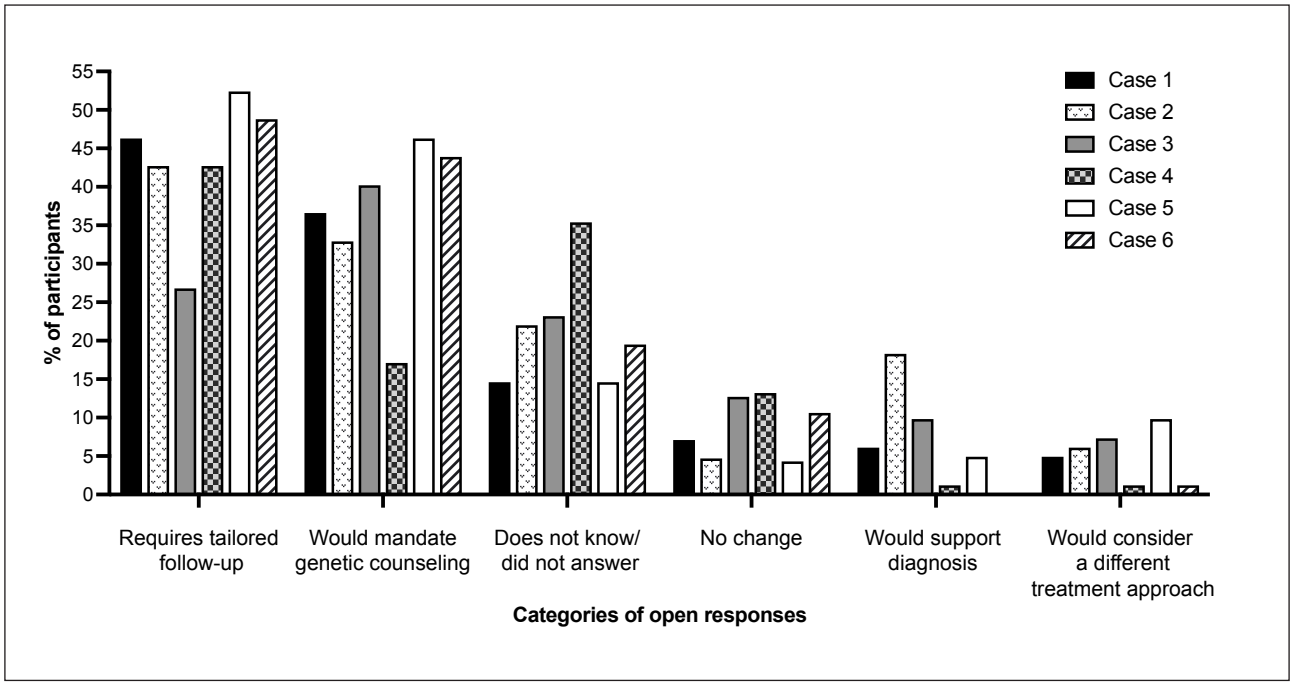

Figure 5. Considerations on the impact of genetic test results on the treatment and follow-up. *Requires tailored follow-up* included responses mentioning specific follow-up actions, such as screening for tumors, comorbidities, or other diseases, conducting specific studies, considering prognosis variations, or monitoring the risk of other neoplasms, tumors, or pathologies based on the genetic results. *Would mandate genetic counseling* grouped responses mentioning family evaluation, inheritance, and the involvement of family members or children. It also encompassed cases where additional genetic testing was suggested, the gene in question was not clearly associated with the disease, limitations of the results for management were noted, or a referral to a genetics specialist was recommended for further assessment. *Does not know/did not answer* included responses explicitly using terms such as "I do not know," or abbreviations such as "NA" or "IDK." It also included statements such as "it is not my area of specialty," "I am not sure," or "I am unaware," as well as blank responses, periods, ellipses, or the letter "N." *No change* encompassed responses explicitly stating that the genetic result would not alter treatment, follow-up, genetic counseling, or the existing management plan. Responses under *would support diagnosis* indicated that the genetic result confirmed the diagnosis, aligned with clinical suspicion, or was consistent with the case context, but did not specify whether the result would alter follow-up or management. *Would consider a different treatment approach* included responses suggesting specific changes in management, such as altering surgical plans, prescribing different medications, or prioritizing the treatment of one condition over another based on the genetic results. Some participants entered responses within more than one category.

category was *would mandate genetic counseling* (36.2 ± 10.5%), suggesting that assessing inheritance and family evaluation was a priority for participants. Strikingly, however, *does not know/did not answer* was the third most common group (21.6 ± 7.7%), reaching 35.4% in case 4. *No change* had a general frequency of 8.8 ± 3.9%, but accounted for 12.7 and 13.2% of responses in cases 3 and 4, indicating that genetic data was perceived to entail no practical implications for these scenarios. Responses labeled as *would support diagnosis* were less frequent overall (6.7 ± 6.7%), but accounted for 18.3% of responses in case 2 (18.3%), where the genetic results were seen as primarily confirmatory. Finally, *would consider a different treatment approach* was the less frequent category (5.1 ± 3.4%), but stood out in case 5 (9.8%), where genetic results were seen as directly influencing therapeutic decisions.

DISCUSSION

The rapid advancement of genomic medicine in recent years has outpaced the incorporation of genetic data in the standard clinical practices for most medical fields, including endocrinology. Even in cases with a single genetic cause and a typical clinical presentation, obtaining genetic confirmation allows

physicians to make patient management decisions with greater confidence. These data allow for tailored follow-up and treatment strategies, ultimately improving clinical outcomes. Genetic diagnoses are also important for genetic counseling and targeted screening of at-risk relatives. Early identification of additional variant carriers among family members allows for timely interventions, personalized monitoring, and prevention strategies. Genetic testing thus serves as a cornerstone in precision medicine in hereditary conditions[38].

Our study shows that, despite varying locations, types of practice, levels of training, and access to laboratory technologies, physicians consider genetic testing as an important tool for the study of patients with NENs. Nevertheless, specialized training is required to ensure the efficient selection of techniques within the vast toolkit of routine genetic tests. At present, pNGS represents the most cost-effective technique for genetic analyses in diseases caused by defects in a limited number of genes[39]. Accordingly, 44.9 ± 6% of participants chose pNGS as the suggested genetic test across the six clinical cases, making it the most popular option. Unexpectedly, an average of 10.6 ± 2.9% and 7.3 ± 3.6% of participants selected ES or GS, respectively, as the method of choice. The current clinical use of these techniques is restricted to cases without diagnosis after targeted sequencing, due to their comparatively higher cost, complex analysis, and risk of incidental findings[3,40]. Since short-read-based pNGS, ES, and GS entail the potential of missing structural variants, different tests are required in selected cases[41].

A large proportion of participants expressed a lack of knowledge or decided not to give an opinion on the use of genetic results as decisive factors for clinical management. Interestingly, substantially less unanswered questions were observed among physicians from Europe and Australia, compared with the rest of the participants. This apparent increased knowledge on the use of routine genetic tests seemed to be linked with the high availability of such resources within those regions. Participants from Mexico showed limited experience regarding the use of genetic data, perhaps explained by the very limited options for genetic testing offered by Mexican public hospitals. Only a few studies have focused on the use of genetic tests for the diagnosis and genetic counseling of individuals with NENs in Mexico[42-45]. In this country, health professionals responsible for genetic counseling are primarily medical geneticists, whose numbers are insufficient and whose geographical distribution is restricted[46]. Further efforts should be made to incorporate affordable genetic analyses into the routine care of patients with NENs worldwide, while improving the training of physicians on the role of genetic data in clinical decision-making.

We recognize the limitations of our study, including the relatively small number of completed surveys, the inclusion of a limited number of countries, and the small number of non-endocrinologists and non-Mexicans among participants. While the complexity of the cases might have biased participation toward more clinicians more familiar with NENs, the results seem to reflect the best possible scenarios regarding test availability and experience with their use. To the best of our knowledge, this is the first study analyzing how physicians from Mexico and other countries incorporate genetic testing in the clinical care of patients with NENs. Our results will hopefully contribute to highlight the urgent need for widely available and affordable genetic tests for patients with NENs in our region. An adequate education of physicians caring for patients with NEN is also required to ensure the efficient translation of genetic data into precision medicine strategies for our population.

CONCLUSION

We observed significant differences regarding the availability of genetic tests and the experience with the use of genetic data among physicians from centers caring for patients with NENs in Mexico and other countries. A wide availability of platforms for genetic analyses is key to make sure that patients with NENs will benefit from tailored clinical strategies, with potentially improved clinical outcomes. These technologies, however, will only be useful if they are implemented alongside training programs and informational resources for healthcare professionals from the various specialties involved in the management of these individuals.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL CONSIDERATIONS

Human and animal protection. The authors declare that the research procedures followed the ethical rules of the responsible human research committee and were conducted in accordance with the World Medical Association's Helsinki Declaration. The procedures were authorized by the Ethics Committee of the participating institution.

Confidentiality, informed consent, and ethical approval. The authors have followed the confidentiality protocols of their institution, have obtained the informed consent of the patients and have obtained the approval of the Ethics Committee. The recommendations from the SAGER guidelines have been followed, in accordance with the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

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