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Challenges in the care of patients with RET-altered thyroid cancer: a multicountry mixed-methods study

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Abstract

Background The discovery of driver oncogenes for thyroid carcinomas and the identification of genomically targeted therapies to inhibit those oncogenes have altered the treatment algorithm in thyroid cancer (TC), while germline testing for RET mutations has become indicated for patients with a family history of RET gene mutations or hereditary medullary TC (MTC). In the context of an increasing number of selective RET inhibitors approved for use, this paper aims to describe challenges and barriers affecting providers' ability to deliver optimal care for patients with RET-altered TC across the patient healthcare journey.

Methods A mixed-method educational and behavioral needs assessment was conducted in Germany (GER), Japan (JPN), the United Kingdom (UK), and the United States (US) prior to RET-selective inhibitor approval. Participants included medical oncologists (MO), endocrinologists (EN) and clinical pathologists (CP) caring for patients affected with TC. Data collection tools were implemented in three languages (English, German, Japanese). Qualitative data were coded and thematically analyzed in NVivo. Quantitative data were analyzed via frequency and crosstabulations in SPSS. The findings presented here were part of a broader study that also investigated lung cancer challenges and included pulmonologists.

Results A total of 44 interviews and 378 surveys were completed. Suboptimal knowledge and skills were self-identified among providers, affecting (1) assessment of genetic risk factors (56%, 159/285 of MOs and ENs), (2) selection of appropriate genetic biomarkers (59%, 53/90 of CPs), (3) treatment plan initiation (65%, 173/275 of MOs and ENs), (4) management of side effects associated with multitargeted tyrosine kinase inhibitors (78%, 116/149 of MOs and ENs), and (5) transfer of patients into palliative care services (58%, 160/274 of MOs and ENs). Interviews underscored the presence of systemic barriers affecting the use of RET molecular tests and selective inhibitors, in addition to suboptimal knowledge and skills necessary to manage the safety and efficacy of targeted therapies.

Conclusion This study describes concrete educational needs for providers involved in the care of patients with RET-altered thyroid carcinomas. Findings can be used to inform the design of evidence-based education and performance

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improvement interventions in the field and support integration into practice of newly approved RET-selective inhibitors.

Keywords RET Gene Mutation, Thyroid Cancer, Delivery of Health Care, Medical oncology, Endocrinology, Pathology

Background

A number of genetic and epigenetic studies have been completed in the last three decades to understand the pathogenesis of thyroid carcinomas [1]. The discovery of driver oncogenes and the identification of genomically targeted therapies to inhibit those oncogenes have altered the treatment algorithm for TC. One of the most important regulators of the mitogen active kinase (MAPK) signaling pathway in both medullary and papillary TCs is a receptor-tyrosine kinase encoded by the 'rearranged during transfection' (RET) gene [2]. Activation of this receptor triggers a cascade of events involved in cell growth, proliferation, and survival [3]. Approximately 50% of sporadic medullary TC (MTC) cases, and virtually all hereditary MTC cases, are associated with mutations in the RET gene [4]. Chimeric products resulting from fusion of RET kinase with other genes have also been identified and can vary by country depending on multiple factors, including ethnicity and exposure to radiation [5]. For example, RET/PTC fusions have been identified in 8% of PTC cases in Germany [6], compared with 30% in Japan [7], and may increase to up to 60–80% in areas exposed to radiation [8, 9].

The European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) suggest that germline testing for RET mutations is indicated for patients with a family history of RET gene mutations or hereditary MTC, patients with clinical features suspicious for multiple endocrine neoplasia type II, and newly diagnosed patients with clinically apparent sporadic MTC. ESMO recommends detecting RET rearrangements in nonmedullary thyroid carcinomas through next generation sequencing techniques or fluorescent in situ hybridization (FISH) when sufficient tissue is provided and the risk of RET abnormality is high [10]. Analysis of RET mutations and fusion can be accomplished via commercially available DNA or RNA next generation sequencing (NGS) assays, including multianalyte assays that also assess other targetable alterations [10].

Understanding the molecular pathologies associated with TC has greatly impacted the development of new targeted therapies, with an increasing number of selective RET inhibitors demonstrating promising results compared with multikinase inhibitors (MKIs) [11, 12]. Recently, selpercatinib and prasletinib were granted approval from the Food and Drug Administration (FDA), and selpercatinib was granted approval from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for the treatment of patients with advanced or metastatic RET-mutant MTC or radioactive iodine-refractory RET fusion-positive TC patients [13–15].

As the field of precision medicine in TC continues to grow, healthcare professionals (HCPs) are expected to stay abreast of evolving scientific advancements regarding new targeted therapies and associated genomic tests. A crucial step in bridging the gap between current and best practice is to assess the educational needs of HCPs across this expanding continuum of patient care [16].

The study objectives were (1) to report on the healthcare journey of patients with RET-altered TC (HCPs involved, services received, and transfer in care between providers) and (2) to identify challenges and barriers experienced by HCPs in the care of patients with RET-driven TC. Similar objectives were established in relation to the care of RET-altered lung cancer (LC) patients, which is being reported separately.

Methods

This study employed a parallel mixed-methods design with qualitative semi-structured interviews and a quantitative online survey. Interviews documented the current practices, challenges, and barriers to optimal care. The survey assessed the magnitude and frequency of these practices, barriers, and challenges [17]. Both interview and survey questions assessed self-reported knowledge, skills, attitude, confidence, and systemic or contextual barriers (e.g., access to resources) [18, 19]. Triangulation of data sources, methods, and perspectives was performed [20].

Ethical approval

The study was approved by an independent ethics review board (VERITAS IRB, Quebec, Canada).

Selection and description of participants

Two physician databases operating in compliance with the guidelines of the European Society for Opinion and Marketing Research were used to recruit potential participants [21]. Email invitations included a secured URL to an online screener. Inclusion criteria were: practicing in Germany (GER), Japan (JPN), the UK, or the US; either (a) medical/clinical oncologist with a minimum of 20 TC and 20 LC patients per year, (b) endocrinologist with a minimum of 10 TC patients per year, or (c) pathologist analyzing a minimum of 10 TC and 10 LC samples per year; and three years of practice or more; minimum

of 50% time spent caring for patients. Data were monitored to ensure that a diverse sample of participants was obtained (e.g., mix of regions within each country) via purposive sampling [22].

Data collection

Interview guides and surveys were developed in English based on a literature review and discussion with subject matter experts (SMEs; i.e., co-authors VS, SIS, KN, AS, and CG) [23]. Data collection tools were adapted for each specialty's scope of practice. Semi-structured interviews (45 min) included 18–22 open-ended questions with suggested probes to elicit comprehensive responses [24]. The 31-item survey (20 min) asked participants to rate their perceived level of knowledge and skill (5-point rating scale), confidence (100-point visual analogue rating scale), or agreement (5-point Likert scale) with various items [25, 26]. The option of selecting "not relevant to my current role" was provided to ensure ratings accounted for the perceived roles and responsibilities of participants. In addition, participants were asked to select one or more response that best described their approach to RET-altered TC patients [27]. Data collection tools were translated into German and Japanese.

A briefing session was held between researchers and interviewers to ensure alignment with the intent of the interview questions and probes [28]. Interviews were conducted in the participants' language of choice over a secure call. Upon participant consent, audio was recorded, transcribed, and translated to English when required. Surveys were programmed on a secured webpage and tested for accuracy and navigation experience.

Analysis & statistics

Qualitative analysis

A coding tree was developed *a priori* in NVivo 12 (QSR International Pty Ltd.) to categorize relevant transcript information by key area of exploration [29–31]. Researchers coded transcripts and regularly discussed required modifications to the coding tree based on emerging themes. Thematic analysis was performed to identify trends in reported experiences and perspectives by country and specialty [31]. Visual maps were created through an iterative process to depict patients' healthcare journey.

Quantitative analysis

Values representing knowledge and skill ratings were dichotomized as follows: 1 (none), 2 (basic), and 3 (intermediate) were grouped as 'suboptimal'; 4 (advanced) and 5 (expert) were grouped as 'optimal'. Values representing agreement ratings were regrouped as follows: 1 (strongly disagree) with 2 (disagree); 3 (neither agree nor disagree) unchanged; 4 (agree) with 5 (strongly agree). Frequency tables were run for demographic variables. Differences by country and specialty were analyzed via crosstabulations with chi-square statistics. Non-parametric Kruskal H Wallis tests were performed on confidence rating variables to assess differences in mean rankings between country and specialty [32]. Missing values and data from participants who selected "not relevant to my current role" were excluded from the analysis for each specific question. All statistical analyses were performed using IBM SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp.)

Triangulation

Findings from both qualitative and quantitative phases were compared to identify areas of convergence [20, 33]. The findings were interpreted with the expertise of clinical SMEs and adult education specialists (co-authors SM, SP, PL) to provide context on the reported patient healthcare journey in each country and identify the most pressing educational needs for each specialty [16, 20].

Results

A total of 422 participants completed the study (44 interviews and 378 surveys). A similar demographic representation was obtained for both phases (Table 1), and a lot of variation was reported by participants in terms of thyroid cancer caseload (Table 1). Triangulated findings pertaining to the healthcare journey of patients with RET-altered TC (Fig. 1) alongside challenges and barriers across the continuum of care include (1) screening, (2) diagnosis, (3) treatment, (4) monitoring and management, and (5) palliative care.

Screening

Interviewees reported that the healthcare journey of patients with RET-altered TC begins when patients present to an endocrinologist, medical oncologist, thyroid surgeon, or general practitioner (in GER), with symptoms (e.g., neck lumps) or high risk of TC (e.g., family history of multiple endocrine neoplasia type 2 or MEN2). Patients then undergo preliminary imaging, neck ultrasound or CT scans. Alternatively, asymptomatic patients are identified through incidental imaging.

> *… if you have a known gene mutation which is related, let's say, to a condition called Cowden syndrome, then you have an increased risk of thyroid cancer, and those patients would have screening. So, it would only be for select groups.*
> *-Endocrinologist, UK.*

Barriers to optimal care at this stage include suboptimal knowledge of screening tools (40%, 113/282) and genetic risk factors of TC (56%, 159/285) found among

Table 1 Descriptive statistics by study phase.

		Semi-structured interviews (n = 44)		Online survey (n = 378)		Total (n = 422)	
		%	*n*	%	*n*	%	*n*
Country	Germany	**27**	*12*	**24**	*90*	**24**	*102*
	United Kingdom	**18**	*8*	**25**	*96*	**25**	*104*
	Japan	**27**	*12*	**19**	*73*	**20**	*85*
	United States	**27**	*12*	**32**	*119*	**31**	*131*
Specialty	Medical oncologists	**36**	*12*	**35**	*133*	**34**	*145*
	Endocrinologists	**27**	*16*	**41**	*154*	**40**	*170*
	Pathologists	**36**	*16*	**24**	*91*	**25**	*107*
Years of practice	3–10 years	**56**	*7*	**25**	*96*	**24**	*103*
	11–20 years	**27**	*25*	**51**	*191*	**51**	*216*
	21 years or more	**16**	*12*	**21**	*91*	**24**	*103*
Practice setting	NCCN-affiliated / NCI-designated cancer center	**0**	*0*	**1**	*3*	**1**	*3*
	Specialized cancer center	**23**	*10*	**6**	*21*	**7**	*31*
	Academic hospital	**39**	*17*	**47**	*178*	**46**	*195*
	Community hospital	**16**	*7*	**14**	*52*	**14**	*59*
	Community clinic	**5**	*2*	**1**	*4*	**1**	*6*
	Multi-specialty physician group practice	**7**	*3*	**18**	*66*	**16**	*69*
	Single-specialty physician group practice	**5**	*2*	**9**	*33*	**8**	*35*
	Solo practice	**7**	*3*	**5**	*18*	**5**	*21*
	Government medicine (e.g. Veterans Affairs)	**0**	*0*	**0.3**	*1*	**0.2**	*1*
	Other	**0**	*0*	**0.5**	*2*	**0.5**	*2*
Academic affiliation	Yes (practice setting is academic affiliated)	**61**	*17*	**54**	*202*	**52**	*219*
	No (practice setting is community based)	**39**	*27*	**46**	*174*	**48**	*201*

Table shows sample demographics obtained from the qualitative phase (semistructured interviews) and quantitative phase (online survey). Significant differences were found in years of practice and academic affiliation depending on country in the quantitative phase sample ($p < 0.05$): 3–10 years (13% in Germany, 24% in the United Kingdom, 26% in Japan, 35% in the United States), 11–20 years (70% in Germany, 45% in the United Kingdom, 44% in Japan, 46% in the United States), 21 years or more (17% in Germany, 31% in the United Kingdom, 30% in Japan, 20% in the United States), and academic affiliation (56% in Germany, 83% in the United Kingdom, 55% in Japan and 28% in the United States).

Bold for % and italics for n were used to increase legibility of the table.

Table 2 Participants' reported caseload for thyroid cancer.

		Semi-structured interviews (n = 44)			Online survey (n = 378)		
		Mean	*Median*	Range	Mean	*Median*	Range
Specialty	Medical oncologists* (n = 12, 133)	**48**	*30*	20–180	**177**	*78*	*20-1800*
	Endocrinologists* (n = 16, 154)	**191**	*100*	12–600	**69**	*50*	*10–500*
	Pathologists** (n-16, 91)	**275**	*50*	10-2000	**159**	*80*	*10-2000*

* Medical oncologists and Endocrinologists were asked "What is your caseload of thyroid cancer patients per year?"

** Pathologists were asked "How many samples per year do you analyze (from biopsy/surgery) to inform the diagnostic or treatment of thyroid cancer?".

Bold for means and italics for medians were used to increase legibility of the table.

both medical oncologists and endocrinologists with statistically significant differences ($p < 0.05$) by country (Table 3).

Diagnosis

During interviews, participants described how patients with thyroid nodules are diagnosed by an endocrinologist, medical oncologist, or thyroid surgeon with the help of pathologists. Diagnostic modalities include ultrasound, PET CT scan, X-ray, thyroid scintigraphy, isotope imaging with radioactive iodine (UK), followed by fine needle aspiration (FNA) or surgical resection, as well as blood tests of calcitonin (GER, UK), thyroid stimulating hormone (TSH) or thyroglobulin (Tg) levels. If accessible, RET testing is performed via FISH (specifically for fusions) or NGS (for fusions and/or mutations). Access to these tests depends on laboratory resources, patient insurance, and physicians' understanding of the diagnostic and prognostic significance of available biomarkers for various forms of TC.

> *Since they thought that the patient had papillary cancer, they didn't think that a genetic test was necessary, and after the surgery was done, they realized*

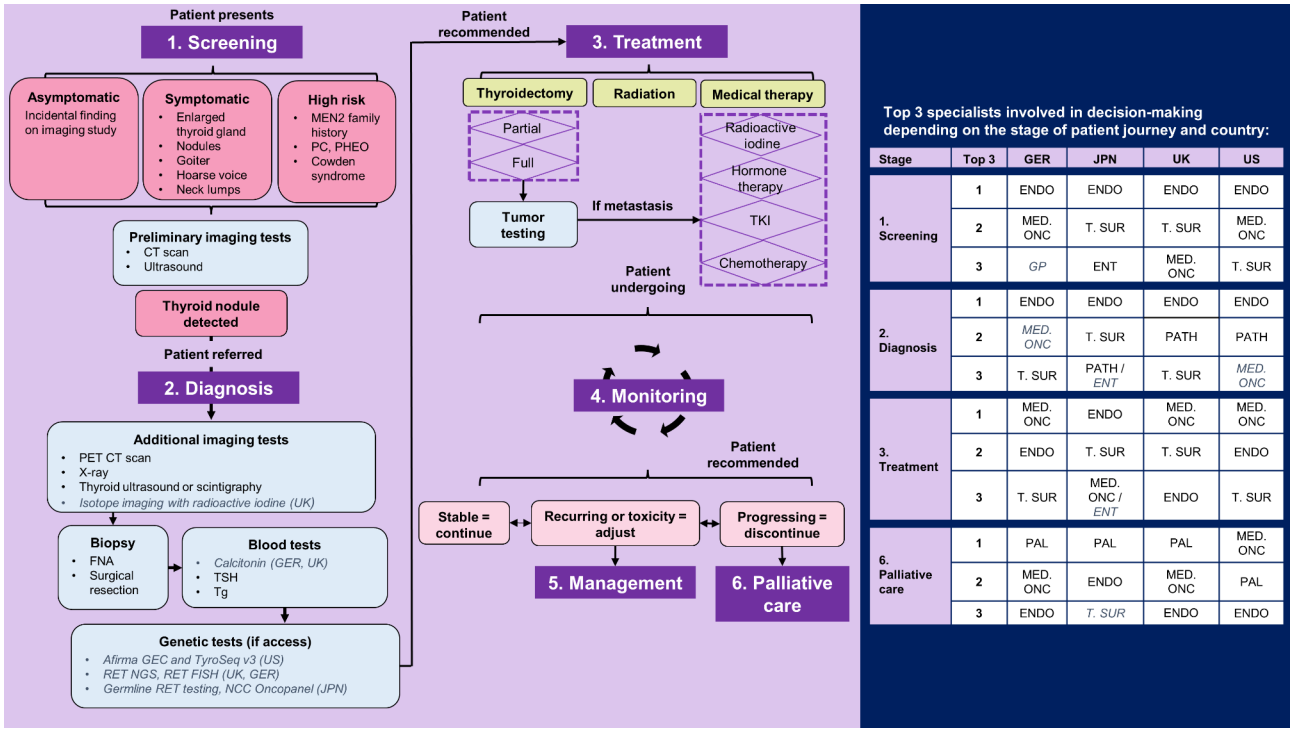

Fig. 1 Overview of the healthcare journey of patients with RET-altered thyroid cancer

Details: Services provided during screening, diagnosis, treatment, monitoring, management and palliative care. Differences by country are demonstrated in italics. The top 3 specialists involved at each stage of the patient journey are reported on the right

Legend: MEN2 = Multiple endocrine neoplasia type 2, PC = parathyroid carcinoma, PHEO = phleochromocytoma, FNA = fine needle aspiration, TSH = thyroid stimulating hormone, Tg = thyroglobulin, NGS = next generation sequencing, FISH = fluorescence in situ hybridization, DTC = differentiated thyroid carcinoma such as papillary or follicular thyroid carcinoma, TKI = tyrosine kinase inhibitor, ENDO = endocrinologist, MED. ONC = medical oncologist, T. SUR = thyroid surgeon, GP = general practitioner or primary care physician, ENT = otorhinolaryngologist or ear-nose-throat specialist, PATH = pathologist, PAL = palliative care physician, GER = Germany, UK = United Kingdom, JPN = Japan, US = United States.

that the patient had medullary cancer—that was scary …
-Pathologist, Japan.

Sub-optimal knowledge of genetic biomarker tests for TC was reported by 50% of medical oncologists (66/133), 62% of endocrinologists (95/154) and 59% of pathologists (53/90) (Table 3). In addition, over three-fifths of endocrinologists (63%, 96/153) reported sub-optimal skills determining if a genetic biomarker test is necessary to inform the diagnosis, and 59% of pathologists (53/90) reported sub-optimal skills selecting the appropriate genetic biomarker(s) to diagnose TC (Table 4).

Treatment

Barriers to assessing the molecular profile of RET-altered TC patients include suboptimal skills among medical oncologists and endocrinologists (55%, 157/287) in deciding which genetic biomarker test to order and suboptimal skills among pathologists (59%, 53/90) in selecting appropriate genetic biomarkers with statistically significant differences ($p<0.05$) by country (Table 3).

Interviewees described how patients with operable TC undergo thyroidectomy. If the disease progresses, radiation therapy and/or systemic therapy (i.e., radioactive iodine, hormone therapy, immunotherapy, MKIs) is administered. Selective RET inhibitors were reported as only administered in the scope of clinical trials. Treatment decisions are based on tumor histology and stage. Patient age, comorbidities, existing medications, health status, and insurance coverage are also considered. Experienced medical oncologists may discuss off-label treatments with their patients.

A challenge in planning and determining treatment was identified. According to survey data, 65% (173/275) of endocrinologists and medical oncologists reported suboptimal skills determining the initial treatment plan after staging of RET-altered TC. The mean confidence score for determining the treatment plan in a patient with RET-altered TC was 51%.

Statistically significant differences were found among countries in providers' perspectives regarding patient access to RET-selective inhibitors and multikinase inhibitors (Fig. 2).

Table 3 Percent of providers reporting suboptimal knowledge in the care of patients with RET-altered thyroid cancer.

		GER		UK		JPN		US		Total		
Sub-optimal knowledge of:	**Profession**	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**Sig.**
Screening tools for TC	MED. ONC	**57**	*44*	**37**	*41*	**-**	-	**36**	*44*	**43**	*129*	0.087
	ENDO	**35**	*26*	**27**	*41*	**67**	*43*	**19**	*43*	**37**	*153*	>0.001*
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Genetic risk factors of TC	MED. ONC	**68**	*44*	**56**	*43*	**-**	-	**39**	*44*	**54**	*131*	0.020*
	ENDO	**54**	*26*	**51**	*41*	**78**	*43*	**46**	*44*	**57**	*154*	0.019*
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Genetic biomarker tests for TC	MED. ONC	**52**	*44*	**52**	*44*	**-**	-	**44**	*45*	**50**	*133*	0.694
	ENDO	**50**	*26*	**48**	*41*	**77**	*43*	**39**	*44*	**62**	*154*	>0.001*
	PATH	**30**	*20*	**73**	*11*	**79**	*29*	**53**	*30*	**59**	*90*	0.004*
Tests required in order to initiate treatment for TC	MED. ONC	**55**	*44*	**40**	*43*	**-**	-	**42**	*45*	**46**	*132*	0.322
	ENDO	**54**	*26*	**42**	*41*	**62**	*42*	**25**	*44*	**44**	*153*	0.005*
	PATH	**30**	*20*	**73**	*11*	**76**	*29*	**70**	*30*	**63**	*90*	0.006*
Specific mechanisms of action of multi-kinase inhibitors for TC	MED. ONC	**50**	*44*	**41**	*44*	**-**	-	**42**	*45*	**44**	*133*	0.650
	ENDO	**58**	*26*	**73**	*40*	**69**	*42*	**76**	*41*	**70**	*149*	0.455
	PATH	**40**	*20*	**82**	*11*	**83**	*29*	**72**	*29*	**70**	*89*	0.009*
Specific mechanisms of action of selective RET inhibitors for TC	MED. ONC	**61**	*44*	**47**	*44*	**-**	-	**44**	*45*	**54**	*133*	0.252
	ENDO	**68**	*25*	**83**	*40*	**46**	*41*	**77**	*39*	**77**	*145*	0.608
	PATH	**50**	*20*	**75**	*8*	**78**	*27*	**83**	*29*	**73**	*84*	0.071
National guidelines for the management of TC	MED. ONC	**41**	*44*	**32**	*44*	**-**	-	**38**	*45*	**37**	*133*	0.668
	ENDO	**42**	*26*	**37**	*41*	**56**	*43*	**33**	*43*	**42**	*153*	0.142
	PATH	**35**	*20*	**82**	*11*	**84**	*30*	**72**	*29*	**69**	*90*	0.002*
International guidelines for the management of TC	MED. ONC	**39**	*44*	**50**	*44*	**-**	-	**49**	*45*	**46**	*133*	0.498
	ENDO	**46**	*26*	**44**	*41*	**69**	*43*	**58**	*43*	**56**	*153*	0.078
	PATH	**55**	*20*	**91**	*11*	**97**	*30*	**83**	*29*	**82**	*18*	0.002*
Side effects of multi-kinase inhibitors	MED. ONC	**46**	*44*	**34**	*44*	**-**	-	**39**	*44*	**39**	*132*	0.547
	ENDO	**77**	*26*	**80**	*40*	**79**	*42*	**76**	*41*	**78**	*149*	0.969
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Side-effects of selective RET inhibitors	MED. ONC	**64**	*44*	**52**	*44*	**-**	-	**41**	*44*	**52**	*132*	0.103
	ENDO	**80**	*25*	**88**	*40*	**85**	*41*	**77**	*39*	**83**	*145*	0.596
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Ongoing clinical trials on selective RET inhibitors	MED. ONC	**67**	*43*	**73**	*44*	**-**	-	**61**	*44*	**67**	*131*	0.525
	ENDO	**87**	*23*	**90**	*40*	**90**	*40*	**85**	*39*	**88**	*142*	0.861
	PATH	**45**	*20*	**86**	*7*	**86**	*27*	**90**	*29*	**77**	*82*	0.002*

GER = Germany, UK = United Kingdom, JPN = Japan, US = United States.

* significant difference between countries ($p<0.05$) bold for % and italics for n were used to increase legibility of the table.

Monitoring and management

Based on interview data, treatment adjustments are made for patients on an ongoing basis (e.g., when disease recurs or an adverse event is reported). In this process, many providers associated a high rate of side effects with new medications for RET fusion mutations and were concerned about their ability to manage these side effects, especially in an outpatient setting. On average, surveyed endocrinologists reported suboptimal knowledge of side effects associated with MKIs (78% (116/149)) and selective RET inhibitors (83% (120/145)), compared to 40% (52/132) and 52% (69/132), respectively, for medical oncologists. Interviewees erroneously perceived that patients on selective RET inhibitors would likely require more dose adjustment due to side effects.

> *… the RET specific TKIs have a really high-level toxicity so that approximately half the patients need at least a dose reduction because of the side effects.*
> *-Endocrinologist, Germany*

Over two-thirds (70%; 192/275) of endocrinologists and medical oncologists reported suboptimal skills determining when the initial treatment plan should be changed due to RET-altered TC progression.

Palliative Care

Interviewees described that some RET-altered TC patients experience critical disease progression causing severe declines in quality of life. For these patients, palliative care may be suggested, resulting in referral to palliative care specialists. A suboptimal level of skill was reported by 58% (160/274) of endocrinologists and medical oncologists in determining when this service is appropriate, with a statistically significant difference by country among medical oncologists (Table 3).

Discussion

This study provides a clearer picture of the healthcare journey of patients with RET-altered TC and a better understanding of the HCPs involved, services received, and how care transfers between providers. The findings suggest the need to improve medical oncologists', endocrinologists', and clinical pathologists' knowledge of the predictive value of RET testing in TC. The need to improve all specialists' skill and confidence when selecting germline or somatic RET testing for patients with inherited or sporadic MTC, respectively, was identified. Although selpercatinib and prasletinib were not approved by any national regulatory bodies for the treatment of TC patients at the time of data collection, these findings suggest suboptimal knowledge among medical oncologists regarding ongoing clinical trials on selective RET inhibitors. Furthermore, medical oncologists and endocrinologists experience challenges managing the side effects of selective RET inhibitors (especially in an outpatient setting), likely due to suboptimal knowledge of potential side effects and toxicity management skills.

This study identified gaps in knowledge of screening tools and in the skills to determine which genetic biomarker tests to order, selecting appropriate genetic biomarkers and determining treatment plans. Current guidelines detail recommendations for HCPs in this area, suggesting that additional CME is needed to support the integration of available knowledge into practice [10, 34].

There were gaps in the skills and knowledge needed to support optimal decision-making at key points in patient care. HCPs reported a misplaced perception that frequent treatment changes are needed due to adverse events associated with selective RET inhibitors. This suggests that HCPs may not be aware of current studies that show an improved safety profile among emerging treatments and may therefore base consequential treatment decisions on outdated information. Similarly, challenges were reported when making changes to the treatment plan due to RET-altered TC progression and determining when to suggest palliative care. Considering new studies on treatment for patients with advanced TC and the widespread gaps in TC quality of life considerations [35], these gaps may have an impact on the patient's health outcomes and experience of care [36]. To improve in this area, HCPs could benefit from education designed to improve practical decision-making skills with a consideration of current and emerging treatment options [37]. The impact of these initiatives may be widespread: studies show that patients are more satisfied with their care when provided with education from informed caregivers [38].

Implications for Clinicians and Policy-makers

The present findings can be used to develop continuous educational programs for HCPs involved in the diagnosis, treatment, and management of advanced TC patients. The behavioral change wheel may be used as a framework in linking the most appropriate intervention design to the educational needs identified in this study [39, 40]. For instance, online lectures could be delivered by experts in precision medicine to build and reinforce the knowledge base of medical oncologists and endocrinologists in relation to available biomarker tests and targeted therapies for patients with MTC or PTC [41]. A suggested emphasis may be placed on the relevance of RET testing (e.g., FISH or fusion testing, germline for mutations, tumor NGS for mutations or fusions) and ongoing clinical trials for selective RET inhibitors in addition to registry data providing real-word evidence on the safety and efficacy of available TKIs [42]. A decision-making tool to assist clinicians in the identification and referral of

Table 4 Percent of providers reporting suboptimal skill in the care of patients with RET-altered thyroid cancer.

		GER		UK		JPN		US		Total		
Sub-optimal skill in:	**Profession**	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**Sig.**
Deciding which genetic biomarker test(s) to order when TC is suspected	MED. ONC	**55**	*44*	**48**	*44*	**-**	-	**33**	*45*	**45**	*133*	0.121
	ENDO	**62**	*26*	**73**	*41*	**77**	*43*	**41**	*44*	**63**	*154*	0.002*
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Determining if a genetic biomarker test is necessary to inform the diagnosis	MED. ONC	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
	ENDO	**58**	*26*	**73**	*41*	**74**	*43*	**44**	*43*	**63**	*153*	0.012*
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Selecting the appropriate genetic biomarker(s) to diagnose TC	MED. ONC	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
	ENDO	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
	PATH	**25**	*20*	**73**	*11*	**23**	*29*	**57**	*30*	**59**	*90*	0.001*
Determining the initial treatment plan after staging RET-altered TC	MED. ONC	**52**	*44*	**52**	*44*	**-**	-	**36**	*45*	**47**	*133*	0.188
	ENDO	**75**	*24*	**85**	*39*	**85**	*41*	**82**	*38*	**82**	*142*	0.728
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Managing side effects of multi-kinase inhibitors	MED. ONC	**41**	*44*	**27**	*44*	**-**	-	**36**	*44*	**35**	*132*	0.393
	ENDO	**80**	*25*	**85**	*39*	**81**	*42*	**84**	*38*	**83**	*144*	0.945
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Managing side effects of selective RET inhibitors	MED. ONC	**64**	*44*	**57**	*44*	**-**	-	**39**	*44*	**53**	*132*	0.052
	ENDO	**79**	*24*	**85**	*39*	**85**	*41*	**84**	*37*	**84**	*141*	0.926
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Identifying eligible patients for clinical trials of selective RET inhibitors	MED. ONC	**60**	*42*	**46**	*44*	**-**	-	**34**	*44*	**46**	*130*	0.061
	ENDO	**79**	*24*	**87**	*39*	**88**	*40*	**79**	*39*	**84**	*141*	0.624
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Identifying the signs of TC progression	MED. ONC	**46**	*44*	**21**	*44*	**-**	-	**31**	*45*	**32**	*133*	0.042
	ENDO	**84**	*26*	**37**	*41*	**69**	*42*	**35**	*43*	**48**	*152*	0.005*
	PATH	**35**	*20*	**90**	*10*	**87**	*29*	**74**	*27*	**71**	*86*	0.001*
Identifying the relevant genetic biomarker(s) to inform the progression of TC	MED. ONC	**52**	*44*	**55**	*44*	**-**	-	**37**	*45*	**47**	*133*	0.146
	ENDO	**69**	*26*	**69**	*39*	**81**	*42*	**48**	*44*	**66**	*151*	0.011*
	PATH	**40**	*20*	**73**	*11*	**83**	*29*	**63**	*30*	**66**	*90*	0.019*
Determining when the initial treatment plan should be changed due to RET-altered TC progression	MED. ONC	**64**	*44*	**52**	*44*	**-**	-	**42**	*45*	**53**	*133*	0.129
	ENDO	**75**	*24*	**92**	*38*	**85**	*41*	**87**	*39*	**86**	*142*	0.305
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-
Determining when palliative care is appropriate for a patient with thyroid RET cancer	MED. ONC	**57**	*44*	**30**	*43*	**-**	-	**33**	*45*	**40**	*132*	0.021*
	ENDO	**75**	*24*	**67**	*40*	**85**	*40*	**74**	*38*	**75**	*142*	0.335
	PATH	**-**	-	**-**	-	**-**	-	**-**	-	**-**	-	-

MED. ONC = Medical Oncologist, ENDO = Endocrinologist, PATH = Pathologist

GER = Germany, UK = United Kingdom, JPN = Japan, US = United States.

* significant difference between countries ($p<0.05$) bold for % and italics for n were used to increase legibility of the table.

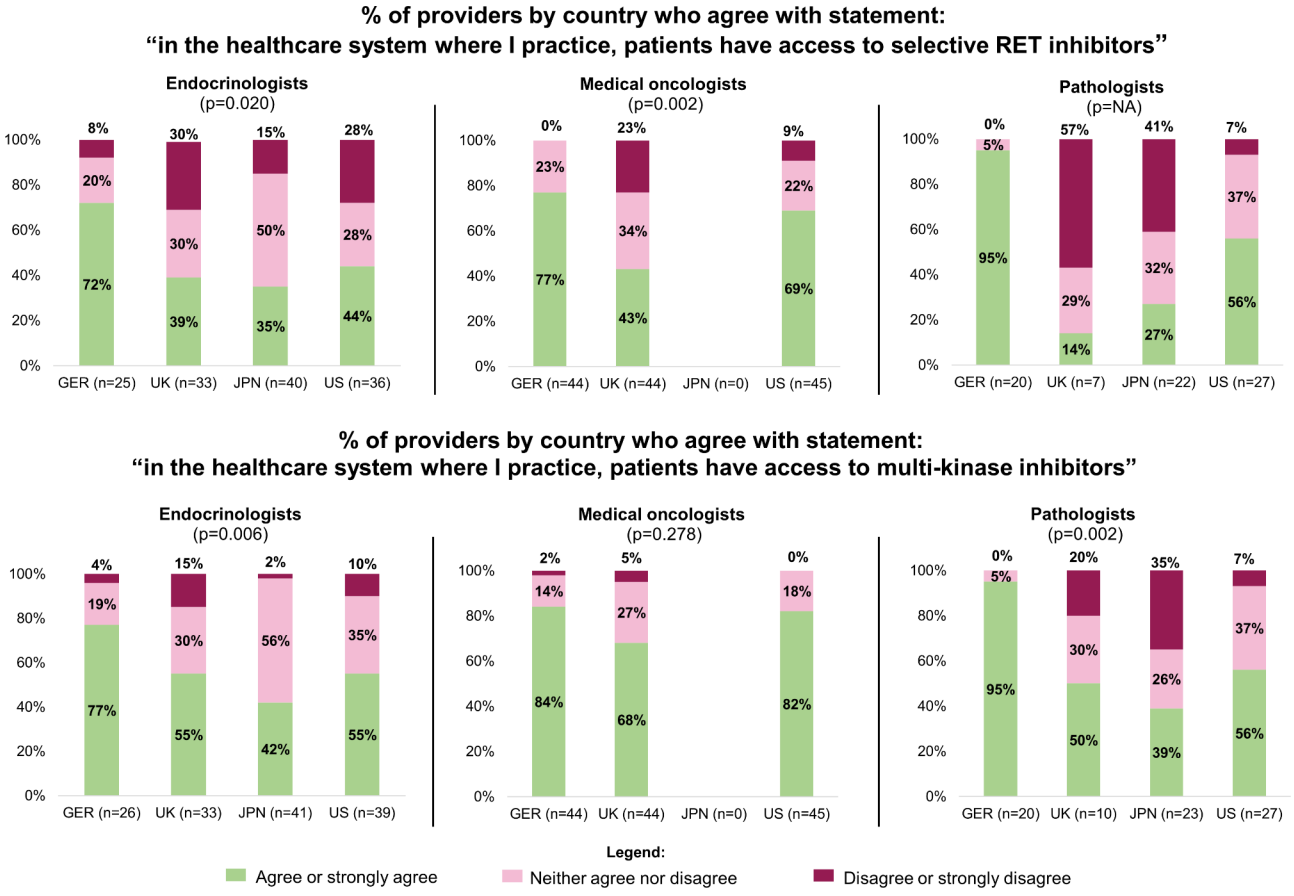

Fig. 2 Percent of providers by country who agree with statement regarding access to treatment

Details: Significance of differences by country of each profession (endocrinologist, medical oncologist, or pathologist) indicated by p-value in parentheses below title

Legend: Dark pink indicates % who responded "disagree or strongly disagree", light pink "neither agree nor disagree", green "agree or strongly agree"

GER = Germany, UK = United Kingdom, JPN = Japan, US = United States.

eligible TC patients with RET alterations to existing clinical trials could prove useful [43]. A patient-friendly tool could be developed to inform patients of available clinical trials for which they may be eligible [44]. Case-based learning opportunities may support skill and confidence acquisition among medical oncologists and allied HCPs in managing side-effects associated with selective RET inhibitors and other types of TKIs [45, 46].

Policymakers should consider optimizing reimbursement and payment models to encourage adherence to guidelines for the screening, diagnosis, treatment, and management of RET-altered TC patients. There is an opportunity for guidelines to be updated regularly to capture the rapid pace of testing and treatment advancements for patients with RET-altered TC.

Strengths

The mixed-methods approach leveraged the strengths of qualitative (collecting rich, contextual information) and quantitative (assessing frequency and magnitude, comparison by demographics) research methods [17, 47]. Purposive sampling minimized the risk of selection bias by including a diverse representation of medical oncologists, endocrinologists, and clinical pathologists. A mix of years of practice, genders, regions within each country, thyroid cancer caseload and access to genomic testing was considered in the generation of findings. Data sources, methods, and perspectives were triangulated with current published evidence and guidelines during the interpretation and generation of final findings, thereby minimizing biases associated with single-observed and single-method studies.

Limitations

The patient perspective was not included in the collection and analysis of data. The practices and competencies of providers were self-reported, which increases subjective reporting. Survey items were not validated for internal consistency reliability, short-term retest correlations, and convergent validity. However, they were critically reviewed by clinical SMEs and educational experts to optimize face validity, readability, comprehension, and

relevancy within the clinical context. When interpreting findings, caution should be used when considering the applicability to countries, practice settings, and specialties excluded from this study.

Recommendations for Future Research

Future studies may develop and evaluate interventions addressing the challenges identified by this study [16, 48, 49]. Implementation research should determine the best interventions to optimize care for patients with TC and/or validate the presence of suboptimal practices in RET-altered TC patient care via observational studies, assessment of patient registry data, or inclusion of patients in data collection and analysis [50–52]. Similar studies may investigate clinical practice gaps, challenges, and barriers experienced by stakeholders excluded from this study (e.g., thyroid surgeons).

Conclusions

This mixed-methods study revealed the current healthcare journey of patients with RET-altered TC in Germany, Japan, the UK, and the US and the challenges and barriers experienced by medical oncologists, endocrinologists, and pathologists along the way. Educational needs were identified, including the needs to improve: knowledge of MTC and PTC risk and the value of RET molecular tests; skills assessing the efficacy versus toxicity profile of emerging targeted therapies in RET-altered tumors; and transitioning RET-altered TC patients into palliative care. Future interventions may provide needed support by addressing advancements in RET-altered TC care via online lecture-based and case-based learning.

Abbreviations

CHMP	Committee for Medicinal Products for Human Use
CP	Clinical pathologist
EMA	European Medicines Agency
EN	endocrinologist
ESMO	The European Society of Medical Oncology
FISH	Fluorescent in situ hybridization
FNA	Fine needle aspiration
GER	Germany
HCP	Healthcare professional
JPN	Japan
LC	Lung cancer
MAPK	Mitogen-activated protein kinase
MEN2	Multiple endocrine neoplasia type 2
MKI	Multikinase inhibitor
MO	Medical oncologist
MTC	Medullary thyroid cancer
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
PTC	Papillary thyroid cancer
RET	Rearranged during transfection
TC	Thyroid cancer
Tg	Thyroglobulin
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
UK	United Kingdom
US	United States

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Authors' contributions

SM: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration, Resources; Supervision; Writing - review & editing. VS: Methodology; Validation; Writing - review & editing. SS: Methodology; Validation; Writing - review & editing. SP: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration, Supervision; Validation; Writing - review & editing. AS: Methodology; Validation; Writing - review & editing. CG: Methodology; Validation; Writing - review & editing. PB: Conceptualization; Funding acquisition; Writing - review & editing. PL: Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing - review & editing. All co-authors contributed to the interpretation of data and have contributed sufficiently to this article to be considered as authors, as per the ICMJE authorship requirements.

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Data Availability

The full datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The authors confirm that all research meets ethics guidelines and legal requirements of the countries where the study took place. The study was approved by VERITAS IRB (Quebec, Canada), an independent ethics review board.

Consent for publication

Not applicable.

Competing interests

SM is CEO and Founder of AXDEV Group Inc., AXDEV Global Inc., and AXDEV Europe GmbH. SP and PL are employees of AXDEV Group Inc. VS is an Andrew Sabin Family Foundation Fellow at The University of Texas MD Anderson Cancer Center. VS acknowledges support of The Jacquelyn A. Brady Fund. VS is supported by NIH grant R01CA242845. MD Anderson Cancer Center Department of Investigational Cancer Therapeutics is supported by the Cancer Prevention and Research Institute of Texas (RP1100584), the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy (1U01 CA180964), NCATS Grant UL1 TR000371 (Center for Clinical and Translational Sciences), and the MD Anderson Cancer Center Support Grant (P30 CA016672), all outside the submitted work. VS reports grants from Eli Lilly/LOXO Oncology, Blueprint Medicines Corporation, Turning Point Therapeutics, Boston Pharmaceuticals; and grants from Helsinn Pharmaceuticals during the conduct of the study; in addition, VS reports a grant and advisory board/consultant position with Eli Lilly/Loxo Oncology during the conduct of the study; research grants from Roche/Genentech, Bayer, GlaxoSmithKline, Nanocarrier, Vegenics, Celgene, Northwest Biotherapeutics, Berghealth, Incyte, Fujifilm, D3, Pfizer, Multivir, Amgen, Abbvie, Alfa-sigma, Agensys, Boston Biomedical, Idera Pharma, Inhibrx, Exelixis, Blueprint Medicines, Altum, Dragonfly Therapeutics, Takeda, National Comprehensive Cancer Network, NCI-CTEP, University of Texas MD Anderson Cancer Center, Turning Point Therapeutics, Boston Pharmaceuticals, Novartis, Pharmamar, Medimmune; an advisory board/consultant position with Helsinn, Incyte, QED Pharma, Daiichi-Sankyo, Signant Health, Novartis, Relay therapeutics, Roche, Medimmune; travel funds from Pharmamar, Incyte, ASCO, ESMO; other support from Medscape. Outside submitted work, SS reports a grant from Exelixis and advisory board membership with Exelixis and Eisai during the course of this

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