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Evaluation of barriers to referral for cancer predisposition syndromes in pediatric oncology patients

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Abstract

Background: Cancer predisposition syndromes (CPS) are underdiagnosed in the pediatric population, though the diagnosis of a CPS has important implications for the child and their family. CPS are often diagnosed by geneticists or oncologists with expertise in CPS following a malignancy. This requires a member of the care team, most commonly, the treating oncologist to suspect a CPS and refer the patient for assessment. Procedure: An online survey was distributed to members of the Children's Oncology Group to elucidate current referral practices and barriers to referral for patients suspected to have a CPS. Results: Of the 189 respondents, 80.4% were pediatric oncologists and most (69%) used formal guidelines to aid in referral assessment. Most respondents indicated they would rarely refer patients with tumors highly associated with CPS. Participants were more likely to refer patients with malignancy and additional features of a CPS than for a specific type of cancer, despite the use of guidelines. Parent knowledge of family history was considered the most challenging barrier to obtaining a family history, though a thorough pedigree was not consistently elicited. Providers indicated the most significant barrier to referral was priority given the patient's more immediate care needs. Conclusions: Provider education about CPS and creation of clear referral guidelines should increase appropriate referrals. Utilization of a genetic counselor within the pediatric oncology clinic may encourage CPS assessment and enable oncologists to focus on the patient's immediate care needs.

INTRODUCTION

Cancer predisposition syndromes (CPS) are caused by pathogenic germline mutations in tumor suppressor genes, or more rarely oncogenes, which confer an increased lifetime risk for cancer. Historical data estimated 10% of all pediatric cancers were due to a CPS.[1,2]Data now suggest 7.6-35.5% of childhood cancers are due to an underlying CPS.[3-10] While the proportion of individuals with a CPS varies based on tumor type, study population, and classification of mutations, these data illustrate that overall, CPS are underdiagnosed in the pediatric population.

Individuals with a CPS are at an increased risk to develop treatment toxicity and secondary cancers, and thus benefit from early diagnosis, which may inform management and surveillance.[1,11-13]To facilitate the identification of patients with a suspected CPS, referral guidelines have been established.[14-17]

Numerous barriers to genetics referrals have been identified in the primary care and adult oncology literature and can be broadly categorized as knowledge, clinical validity, and system barriers. Some healthcare providers (HCP) perceive genetic services lack clinical utility and are not integral to their practice.[18-20]Unsurprisingly, this perception has been linked to lack of genetics knowledge and poor adherence to guidelines.[20,21] In adult oncology, further distance from a genetic counselor or genetics clinic has been correlated with decreased referral likelihood for CPS evaluation.[18,22] In addition, some research suggests that the referral process itself may be a hinderance, as primary care providers (PCP) are unaware which clinic to refer to, or how to initiate

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the process.[18,23,24] Cost has also been considered a barrier to genetics referral by the HCP and uptake by the patient.[18,25-27]

Given that most research on the topic of barriers to genetics referrals focuses on data from primary care and adult oncology, this study investigates current referral practices of HCP involved in the care of pediatric oncology patients with a suspected CPS.

METHODS

An electronic survey link was emailed to 3,219 active COG members located in the United States who indicated their specialty was hematology/oncology, surgery, pathology, cellular therapy, or cytogenetics. Responses were recorded February 5, 2020 – March 2, 2020. A reminder was sent one week prior to closure of the survey. In total, 230 responses were returned. Forty-one incomplete responses were excluded. The total number of complete responses was 189. The response rate was 5.8%. This study was approved by the University of Pittsburgh Institutional Review Board as an exempt protocol (STUDY19090002).

Data were analyzed by descriptive statistics. Totals vary by question as some questions allowed respondents to select all choices that apply. Proportion of response was calculated based on the number of total responses for each individual question. Pearson's χ^2test was used to assess relationships between guideline use and demographic factors. Z-test for proportions was used to compare guideline use and Likert scale questions. Analyses were performed with Stata (v.16).

RESULTS

Demographics

Participant demographic data are summarized in Table 1. The majority of respondents were staff physicians (80.4%, 152/189), other respondents were fellows (15.3%, 29/189), PhDs (7.4%,14/189), or a genetic counselor (0.5%, 1/189). Of those participants who possessed a PhD, 13/14 were also MDs.

The majority of respondents identified their specialty as pediatric hematology/oncology (70.4%, 131/186). Additional specialties included surgery (7.5%, 14/186), pediatrics (3.8%, 7/186), pathology (1.6%, 3/186), genetics (0.5%, 1/186), or other (3.8%, 7/186). Those participants who chose other indicated specialties in ophthalmology, pediatric urology, subspecialties of oncology or multiple specialties such as genetics and oncology.

The most common practice settings were children's hospitals within an academic center (55.7%, 108/194), or freestanding children's hospitals (40.2%, 78/194). Most participants indicated a clinical volume of less than 100 patients/year (42.8%, 80/187) or 100-250 patients/year (36.9%, 69/187). Respondents estimated their patient population was comparable to the known CPS population prevalence of approximately 10%. Those respondents who indicated more than 10% of their patients had a diagnosed CPS (6.5%, 12/186) practiced within a cancer predisposition clinic.

Access to Genetics Services

Greater than half (59.7%, 108/181) of respondents indicated their institution had a cancer predisposition clinic, with 70.8% (75/108) situated within the pediatric hematology/oncology division (Table 2). Furthermore, 97.3% (182/187) indicated they had access to a genetics specialist including a geneticist or genetic counselor. A large majority (87%, 160/184) of participants reported they consult with genetics or CPS specialists if they suspect a patient has a CPS. Feedback from the genetics clinic regarding referral appropriateness was common for 62.6% (114/182) of respondents. Some participants received feedback before referral at tumor board meetings or during consultations. Respondents also obtained genetics information from the scientific literature (95.2%, 177/186) and personal communication with genetics professionals (82.3%, 153).

Referral Practices

The majority of respondents believed a hematologist/oncologist was the most appropriate provider to initiate a CPS referral (83.9%, 151/180), whereas 5.6% (10/180) thought a medical geneticist was most appropri-

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ate (Table 3). Conversely, participants felt medical geneticists (62%, 111/179) were the most appropriate provider to diagnose a patient with a CPS, whereas 19.6% (35/179) thought hematologists/oncologists were most appropriate to make the diagnosis.

Respondents indicated that they rarely (42.6%, 78/183) or sometimes (30.1%, 55/183) referred patients for a CPS evaluation. Frequency was not correlated with use of referral guidelines. Formal referral guidelines were used always (34.2%, 63/184) or sometimes (34.8%, 64/184) and most respondents were somewhat (44.4%, 56/126) or extremely (15.9%, 20/126) satisfied with the guidelines they use, while 32.5% (41/126) were indifferent. A quarter of participants (45/180) did not use the same guidelines as their colleagues, and 58.9% (106/180) were unsure of which, if any, guidelines their colleagues used. Use of guidelines was dependent on clinical volume of CPS patients (Pearson's χ^2, $p = 0.01$).

The main reason for not using guidelines was the lack of guideline availability (34.4%, 45/131), with an additional 8.4% (11/131) who were unaware guidelines existed. About a quarter (32/131) of participants felt confident referring without guidelines, and 15.3% (20/131) indicated conflicting guidelines from different sources discouraged their use.

Of the cancer types recommended to result in referral regardless of family history, pheochromocytoma/paraganglioma (PPGL) and choroid plexus carcinoma (CPC) were the most likely to always result in referral, however, this was only indicated by 31.3% (51/163) and 29.4% (47/160) of respondents, respectively (Figure 1A). Participants who used guidelines were significantly more likely to always refer a patient with PPGL (one tailed z-test, $p<0.05$).

The majority of respondents indicated they rarely refer patients with medulloblastoma, osteosarcoma, rhabdomyosarcoma, glioma, neuroblastoma, Wilms tumor, acute myeloid leukemia, or Ewing sarcoma, many of which are linked to a CPS.[1,14,15] Most respondents also specified they rarely referred patients with Hodgkin lymphoma, a cancer that is often sporadic, for genetics referral. Hodgkin lymphoma was included to ensure the internal validity of the question.

While the majority of respondents were likely to refer patients with concerning features of a CPS, the certainty with which they did so varied. Well understood indications were extremely likely to be referred, such as a patient with a malignancy and genetic test results indicating a germline mutation in a cancer predisposition gene (89.1%, 164/184) or multiple malignancies (85.9%, 158/184) (Figure 1B). In contrast, a patient presenting with a malignancy and developmental delay/intellectual disability was extremely likely to be referred by only 12.5% (23/184) of respondents, with most somewhat likely (45.1%, 83/184) or neither likely nor unlikely (34.2%, 63/184) to refer for genetic evaluation indicating physician uncertainty despite published guidelines that recommend referral for these indications.[11,14,17]

When familiarity with published guidelines for referral/evaluation of a CPS was used to stratify responses, those who did not use guidelines were significantly less likely to refer patients with a malignancy and immunodeficiency (one tailed z-test, $p<0.05$). Overall likelihood to refer patients with other features were not associated with guideline use, however tendency was significantly associated for some features. Patients with features of abnormal growth such as macrocephaly, or hemihyperplasia were extremely likely to be referred by 41.2% (52/126) of respondents who used referral guidelines compared to 23.6% (13/55) of respondents who did not use referral guidelines (one tailed z-test, $p<0.05$). Those participants who did not use guidelines still indicated they were somewhat likely to refer patients with abnormal growth (60%, 33/55). A similar trend was observed for the patients with excessive toxicity to cancer therapy; 23.8% (30/126) of respondents who use guidelines were extremely likely to refer compared to 10.9% (6/55) of those who do not use guidelines (z-test, $p<0.05$). These data suggest that guideline use increases confidence in appropriate referrals.

Family History Elicitation

Family history was considered essential to assessment of new pediatric oncology patients by greater than 90% of respondents regardless of whether or not a CPS was suspected. We asked respondents to indicate the frequency with which they ask about particular family members when eliciting family history for a routine

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pediatric oncology patient or a pediatric oncology patient with a suspected CPS (Table 4). Regardless of evaluation type, almost all respondents always collect information about the patient's mother, father, and full siblings (routine pediatric oncology patient 96%, or suspected CPS 98%). However, aunts/uncles and half siblings were asked about less often than grandparents despite the same degree of relationship to the patient. Grandparents were always included by 82.9% (150/181) of participants taking a family history for a routine patient whereas aunts/uncles were included by 56.7% (101/178). For most routine patients, family history was reviewed only if the patient mentioned an update (58.1%, 108/186) but if the patient was suspected to have a CPS, family history was reviewed most of the time (40.9%, 74/181).

Barriers to Complete Family History

Overall, respondents felt the patient/parent's lack of knowledge of the family history interfered a lot (43.2%, 79/183) or a great deal (16.4%, 30/183) with obtaining a family history. Eighty percent (46/183) felt this was the most challenging aspect. Patient or parent's anxiety (70.5%, 129/183), timing of family history elicitation in relation to diagnosis (53.6%, 98/183), and allocation of the provider's time (55.2%, 101/183) interfered a little or not at all (Figure 2A).

Barriers to Genetics Referrals

Respondents indicated that hematologists/oncologists are the most appropriate provider to refer a child for assessment for a CPS, yet the majority of participants rarely refer patients. Patient knowledge of family history was probably (59.4%, 107/180) or definitely (12.8%, 23/180) a barrier for most respondents (Figure 2B). Other barriers identified by at least half of respondents included priority given other immediate care needs (63.1%, 113/180), and patient understanding of genetic risk (52.2%, 93/178).

Lack of available genetics services, and insufficient institutional resources were definitely not barriers for 51.1% (92/180) and 55% (99/180) of respondents. In addition, 41.1% (74/180) and 30% (54/180) of participants indicated patient eligibility for genetics services was probably not or definitely not a barrier to referrals for their patients. Other issues including familiarity with genetic conditions, limited time at appointments, cost and/or insurance coverage, and lack of referral guidelines were less likely to be considered barriers.

When asked about the most challenging barrier to referral, 24% (44/183) of respondents indicated priority of the referral compared to other patient needs was the most challenging barrier. Patient knowledge of family history was not only considered a barrier to collection of family history information but also to genetics referral (21.3%, 39/183), as was cost/insurance coverage (12%, 22/183). Other issues were acknowledged by less than 10% of the respondents as the most significant barrier to referral.

DISCUSSION

This study assessed current referral practices of American pediatric hematologists/oncologists for patients with a suspected CPS. Nearly 84% of respondents indicated that hematologists/oncologists were the most appropriate provider to refer a patient with a suspected CPS for genetics evaluation. Of these participants, 72.7% were hematologists/oncologists themselves, yet close to three quarters of all participants indicated they only sometimes or rarely refer such patients. Recent data suggest the prevalence of CPS in the pediatric cancer population ranges from 7.6-35.5%.[3-10] Thus respondents may have indicated they rarely refer patients because they rarely encounter appropriate patients for referral, or because other barriers prevent it.

The majority of respondents indicated they used guidelines to assess patients for referral and more than half were satisfied with the guidelines they use. Guideline use was associated with CPS clinical volume over 5%. Overall, participants were more likely to refer patients with malignancy and additional features of a CPS than they were for a specific type of cancer. PPGL was the only type of cancer the largest proportion of participants indicated they were likely to always refer for evaluation of a CPS, although guidelines recommend all index cases of PPGL be assessed for a CPS. These guidelines also recommend referral for cases of CPC, medulloblastoma, and sarcoma regardless of family history yet most respondents indicated they rarely refer patients with such malignancies for genetics evaluation despite their strong association with CPS.[11,15,17] Regardless of guideline usage, these data suggest further education and guidance is required for providers.

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Indeed, tumor and germline sequencing in pediatric oncology has already discovered new candidate cancer predisposition genes, which may become relevant to patient care.[7,28]

For CPS-associated features, likelihood to refer varied by the specific feature, and was generally not associated with guideline use except for immunodeficiencies. Most respondents were likely to refer patients with malignancy and abnormal growth or excessive toxicity to cancer therapy, however, unfamiliarity with guidelines led to significantly decreased tendency to refer. The features described in this section of the survey were based on criteria described by European groups and thus may not be familiar to our American cohort.[11,14] Nonetheless, inconsistency to refer for each CPS feature suggests participants may consider additional factors and/or be using different guidelines to assess whether to refer a patient for a suspected CPS.

In addition to guidelines, family history is often utilized to assess for a CPS.[24,29-33] In this study, the most challenging aspect of obtaining a family history identified by participants was the patient/parent's lack of knowledge about the family, which influenced their ability to refer the patient. Nonetheless, survey respondents reported they do not always collect a full three-generation pedigree, the gold standard in genetics, or a two-generation pedigree as recommended by the American Society of Clinical Oncology.[34] These data suggest both physician and patient factors contribute to incomplete family history documentation and suggest respondents rely on complete, positive family histories to determine referral for a CPS.[35] Patient knowledge may limit family history elicitation, but should not prevent referral of patients with high-risk tumors for evaluation.[15]

Patient needs are prioritized during oncology visits and family history elicitation may initially be deferred, but research in the pediatric cancer survivor setting has illustrated the importance of frequent family history review.[2,36,37] As expected, respondents indicated they reviewed family history more often for patients with a suspected CPS, yet only 14.9% reviewed family history at every appointment. Instead, the most common answers were most of the time or if the patient mentioned an update. Some respondents may see their patients more often than the family history would be expected to change thus decreasing the proportion of physicians who would review history at every appointment, however, patients are less likely to mention updates unprompted and thus these responses may represent missed referral opportunities.[24]

In addition to family history review, CPS evaluation may be considered low priority given other patient needs.[2,15] Nearly two thirds of respondents indicated priority was a barrier to genetics referral and it was considered the most significant barrier by 24%. Indeed, the majority of participants surveyed were hematologists/oncologists and pediatric surgeons whose main concerns are focused on the acute needs of their patients. Of note, limited time was not identified as a barrier by most respondents.

Evidence suggests that HCP who deem genetics integral to their practice are more likely to refer.[20] While referral to another specialist at an overwhelming and busy time for the family may not be a top priority for the treating physician, identification of a CPS can have immediate effects on the patient's siblings, parents, and other family members and should be addressed in a timely manner.[2] Delegating family history elicitation to a genetic counselor or establishing specific timepoints by which to review family history within the clinic may ensure the patient's immediate care needs are met without forgoing family history assessment. Patients with an underlying CPS have been identified by family history review in survivorship clinics which may provide a reasonable option for some practitioners.[36,37]

This survey focused on barriers to physician-initiated referrals. Interestingly, patient understanding of genetic risk, a patient-centered issue, was considered a barrier by over half of respondents. This issue is often considered in the context of referral uptake rather than the initiation of the referral itself.[38] Other groups have addressed this problem successfully by embedding genetic counseling services into adult oncology clinics.[39,40]

Contrary to other studies, access to genetics services, professionals, and resources generally and within the respondent's institution were not perceived as barriers to referral.[18,19,22,23] In fact, almost 60% of participants reported their institution has a cancer predisposition clinic and most participants receive helpful feedback on referrals. While most participants also indicated access to a genetic counselor, geneticist, or other colleague with expertise in CPS for formal or informal consultations, further implementation of genetics into the pe-

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diatric oncology clinic may be beneficial to the identification of patients with an underlying CPS, especially since over a quarter of respondents do not receive feedback following referral.[41] While nearly half of respondents indicated they participate in molecular/genetics tumor boards, 31.9% of respondents indicated their institution conducts tumor boards but they do not attend. This may represent an opportunity for genetic counselors and others with expertise in CPS to educate colleagues and increase referrals, and participation from multiple departments should be encouraged. This may also ensure consistent referral practices within an institution, as our data suggests only 16% of respondents use common institutional referral guidelines.

Although most participants surveyed use referral guidelines, almost half of those who do not indicated a lack of guideline availability or unawareness of guidelines as the reason. One respondent commented that guidelines would be more useful if risk for a CPS was defined relative to family history, whereas others indicated their institutions refer all pediatric oncology patients. These comments demonstrate a lack of consensus on which patients should be referred for CPS evaluation and how strictly guidelines are followed by the pediatric oncology community. This is a problem others have documented.[42,43] While it may not be feasible for each cancer predisposition clinic to accept referrals of all pediatric oncology patients, guidelines aim to ensure a balance between the benefit of diagnosing children with an underlying CPS and the risks of over-referring patients to genetics/cancer predisposition clinics. This must also be balanced with the availability of genetics professionals to prevent overwhelming the genetics workforce, of which there is a documented shortage.[44,45] Therefore, efforts should be made to develop and distribute sensitive, specific, easy-to-use guidelines for CPS evaluation and to encourage consultation between specialties to increase appropriate referrals.

Evidence suggests lack of adherence to guidelines is closely related to genetics knowledge and perceived clinical utility.[21,46] The majority of respondents reported they received adequate genetics education during their training and stated scientific literature, personal communications with genetics professionals, and multidisciplinary tumor board meetings as the major channels through which they continue to obtain information. Over half of respondents also indicated familiarity with genetic conditions was not a barrier to genetics referral. This study was not designed to measure genetics knowledge, but it does suggest that further education may be helpful to aid survey respondents in identification of patients who may benefit from genetics evaluation for a CPS.

Limitations to this study include the low response rate which may have been due to the short data collection phase, and availability of respondents. Participants were not asked to specify which guidelines they use or how closely they are followed, preventing further association of responses with specific guideline recommendations. Referral behavior questions addressed likelihood or frequency of referral and wording was not consistent between these questions which may have changed respondents' interpretations. This survey focused on behaviors and attitudes and did not quantify referral rates. Although the survey was piloted, it was not formally validated with content validity or reliability measures.[47]

Future studies may quantify pediatric oncology HCP knowledge to elucidate the relationship between CPS knowledge and guideline adherence, or genetics referral. Lastly, survey respondents represent a small proportion of all pediatric oncology HCP; future work will aim to collect data from a more representative sample of hematology/oncology practitioners and other pediatric providers to understand the perspectives of the care team as a whole.

Identification of individuals with a CPS is important for proper management and surveillance of the patient and their family.[13,48] The results of this study are comparable to findings in adult oncology, but to our knowledge, this is the first study in pediatric oncology that investigates these issues. Overall, these data demonstrate physician, patient, and system level barriers to genetics evaluation for children with a suspected CPS. Both patient and physician factors prevent the collection of in-depth family history information but this should not preclude referral. Education about features and high-risk cancers associated with CPS, more widely distributed referral recommendations, and further implementation of genetics experts into pediatric oncology practices may contribute to increased genetics referrals and ultimately improve recognition of at-risk patients.

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Conflict of Interest

The authors have no conflicts of interest to declare.

References

1. Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J Clin Oncol.* 2005;23(2):276-292.

2. Schiffman JD. Hereditary cancer syndromes: if you look, you will find them. *Pediatr Blood Cancer.* 2012;58(1):5-6.

3. Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. *N Engl J Med.* 2015;373(24):2336-2346.

4. Grobner SN, Worst BC, Weischenfeldt J, et al. The landscape of genomic alterations across childhood cancers. *Nature.*2018;555(7696):321-327.

5. Mody RJ, Wu YM, Lonigro RJ, et al. Integrative Clinical Sequencing in the Management of Refractory or Relapsed Cancer in Youth. *JAMA.*2015;314(9):913-925.

6. Oberg JA, Glade Bender JL, Sulis ML, et al. Implementation of next generation sequencing into pediatric hematology-oncology practice: moving beyond actionable alterations. *Genome Med.* 2016;8(1):133.

7. Chang W, Brohl AS, Patidar R, et al. MultiDimensional ClinOmics for Precision Therapy of Children and Adolescent Young Adults with Relapsed and Refractory Cancer: A Report from the Center for Cancer Research. *Clin Cancer Res.* 2016;22(15):3810-3820.

8. Kline CN, Joseph NM, Grenert JP, et al. Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. *Neuro Oncol.* 2017;19(5):699-709.

9. Diets IJ, Waanders E, Ligtenberg MJ, et al. High Yield of Pathogenic Germline Mutations Causative or Likely Causative of the Cancer Phenotype in Selected Children with Cancer. *Clin Cancer Res.*2018;24(7):1594-1603.

10. Parsons DW, Roy A, Yang Y, et al. Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. *JAMA Oncol.* 2016;2(5):616-624.

11. Jongmans MC, Loeffen JL, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. *Eur J Med Genet.* 2016;59(3):116-125.

12. Malkin D, Nichols KE, Schiffman JD, Plon SE, Brodeur GM. The Future of Surveillance in the Context of Cancer Predisposition: Through the Murky Looking Glass. *Clin Cancer Res.* 2017;23(21):e133-e137.

13. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol.* 2016;17(9):1295-1305.

14. Ripperger T, Bielack SS, Borkhardt A, et al. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet A.* 2017;173(4):1017-1037.

15. Druker H, Zelley K, McGee RB, et al. Genetic Counselor Recommendations for Cancer Predisposition Evaluation and Surveillance in the Pediatric Oncology Patient. *Clin Cancer Res.*2017;23(13):e91-e97.

16. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2018;68(4):297-316.

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17. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med.* 2015;17(1):70-87.

18. Vig HS, Armstrong J, Egleston BL, et al. Cancer genetic risk assessment and referral patterns in primary care. *Genet Test Mol Biomarkers.* 2009;13(6):735-741.

19. Chen MJ, Holt CL, Lose EJ, Robin NH. The use by Alabama pediatricians of genetics consultation in the evaluation of developmental delay. *Am J Med Genet A.* 2008;146A(4):421-425.

20. Diamonstein C, Stevens B, Shahrukh Hashmi S, Refuerzo J, Sullivan C, Hoskovec J. Physicians' Awareness and Utilization of Genetic Services in Texas. *J Genet Couns.* 2018;27(4):968-977.

21. Batra S, Valdimarsdottir H, McGovern M, Itzkowitz S, Brown K. Awareness of genetic testing for colorectal cancer predisposition among specialists in gastroenterology. *Am J Gastroenterol.*2002;97(3):729-733.

22. Garcia C, Harrison K, Ring KL, Sullivan MW, Rauh LA, Modesitt SC. Genetic counseling referral for ovarian cancer patients: a call to action. *Fam Cancer.* 2019;18(3):303-309.

23. Carroll JC, Cappelli M, Miller F, et al. Genetic services for hereditary breast/ovarian and colorectal cancers - physicians' awareness, use and satisfaction. *Community Genet.*2008;11(1):43-51.

24. Al-Habsi H, Lim JN, Chu CE, Hewison J. Factors influencing the referrals in primary care of asymptomatic patients with a family history of cancer. *Genet Med.* 2008;10(10):751-757.

25. Acheson LS, Stange KC, Zyzanski S. Clinical genetics issues encountered by family physicians. *Genet Med.* 2005;7(7):501-508.

26. Brandt R, Ali Z, Sabel A, McHugh T, Gilman P. Cancer genetics evaluation: barriers to and improvements for referral. *Genet Test.* 2008;12(1):9-12.

27. Liang MI, Wong DH, Walsh CS, Farias-Eisner R, Cohen JG. Cancer Genetic Counseling and Testing: Perspectives of Epithelial Ovarian Cancer Patients and Gynecologic Oncology Healthcare Providers. *J Genet Couns.* 2018;27(1):177-186.

28. Mirabello L, Zhu B, Koster R, et al. Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in Patients With Osteosarcoma. *JAMA Oncol.* 2020.

29. Bathurst L, Huang QR. A qualitative study of GPs' views on modern genetics. *Aust Fam Physician.* 2006;35(6):462-464.

30. Saul RA, Trotter T, Sease K, Tarini B. Survey of family history taking and genetic testing in pediatric practice. *J Community Genet.* 2017;8(2):109-115.

31. Rinke ML, Mikat-Stevens N, Saul R, Driscoll A, Healy J, Tarini BA. Genetic services and attitudes in primary care pediatrics. *Am J Med Genet A.* 2014;164A(2):449-455.

32. Acheson LS, Wiesner GL, Zyzanski SJ, Goodwin MA, Stange KC. Family history-taking in community family practice: implications for genetic screening. *Genet Med.* 2000;2(3):180-185.

33. Wood ME, Stockdale A, Flynn BS. Interviews with primary care physicians regarding taking and interpreting the cancer family history.*Fam Pract.* 2008;25(5):334-340.

34. Lu KH, Wood ME, Daniels M, et al. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. *J Clin Oncol.* 2014;32(8):833-840.

35. Febbraro T, Robison K, Wilbur JS, et al. Adherence patterns to National Comprehensive Cancer Network (NCCN) guidelines for referral to cancer genetic professionals. *Gynecol Oncol.* 2015;138(1):109-114.

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36. Knapke S, Nagarajan R, Correll J, Kent D, Burns K. Hereditary cancer risk assessment in a pediatric oncology follow-up clinic. *Pediatr Blood Cancer.* 2012;58(1):85-89.

37. Russo S, Warby M, Tucker KM, Wakefield CE, Cohn RJ. Importance of updating family cancer history in childhood cancer survivors. *Fam Cancer.* 2017;16(4):605-610.

38. Rolnick SJ, Rahm AK, Jackson JM, et al. Barriers in identification and referral to genetic counseling for familial cancer risk: the perspective of genetic service providers. *J Genet Couns.*2011;20(3):314-322.

39. Kentwell M, Dow E, Antill Y, et al. Mainstreaming cancer genetics: A model integrating germline BRCA testing into routine ovarian cancer clinics. *Gynecol Oncol.* 2017;145(1):130-136.

40. Senter L, O'Malley DM, Backes FJ, et al. Genetic consultation embedded in a gynecologic oncology clinic improves compliance with guideline-based care. *Gynecol Oncol.* 2017;147(1):110-114.

41. Kuhlen M, Wieczorek D, Siebert R, Fruhwald MC. How I approach hereditary cancer predisposition in a child with cancer. *Pediatr Blood Cancer.* 2019;66(11):e27916.

42. Prochniak CF, Martin LJ, Miller EM, Knapke SC. Barriers to and motivations for physician referral of patients to cancer genetics clinics. *J Genet Couns.* 2012;21(2):305-325.

43. Houwink EJ, van Luijk SJ, Henneman L, van der Vleuten C, Jan Dinant G, Cornel MC. Genetic educational needs and the role of genetics in primary care: a focus group study with multiple perspectives. *BMC Fam Pract.* 2011;12:5.

44. Cooksey JA, Forte G, Benkendorf J, Blitzer MG. The state of the medical geneticist workforce: findings of the 2003 survey of American Board of Medical Genetics certified geneticists. *Genet Med.*2005;7(6):439-443.

45. Hoskovec JM, Bennett RL, Carey ME, et al. Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. *J Genet Couns.* 2018;27(1):16-20.

46. Grover S, Stoffel EM, Bussone L, Tschoegl E, Syngal S. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. *Clin Gastroenterol Hepatol.*2004;2(9):813-819.

47. Tsang S, Royse CF, Terkawi AS. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. *Saudi J Anaesth.* 2017;11(Suppl 1):S80-S89.

48. Prete FP, Abdel-Aziz T, Morkane C, Brain C, Kurzawinski TR, Group MENiCUC. Prophylactic thyroidectomy in children with multiple endocrine neoplasia type 2. *Br J Surg.* 2018;105(10):1319-1327.

LEGENDS:

Figure 1 Likelihood to refer for CPS evaluation. (A) Likelihood of respondents to refer a patient for evaluation of a CPS based on disease type. (B) Likelihood of respondents to refer a patient for evaluation of a CPS based on features as described by Jongmans et al.[11] Abbreviations: CPC choroid plexus carcinoma, MB medulloblastoma, PPGL pheochromocytoma/paraganglioma, OS osteosarcoma, ERMS embryonal rhabdomyosarcoma, ARMS alveolar rhabdomyosarcoma, GLI glioma, NB neuroblastoma, WT Wilms tumor, ES Ewing sarcoma, HL Hodgkins lymphoma, DD/ID developmental delay/intellectual disability.

Figure 2 Barriers perceived by respondents to interfere with (A) obtaining a complete family history or (B) genetics referral.

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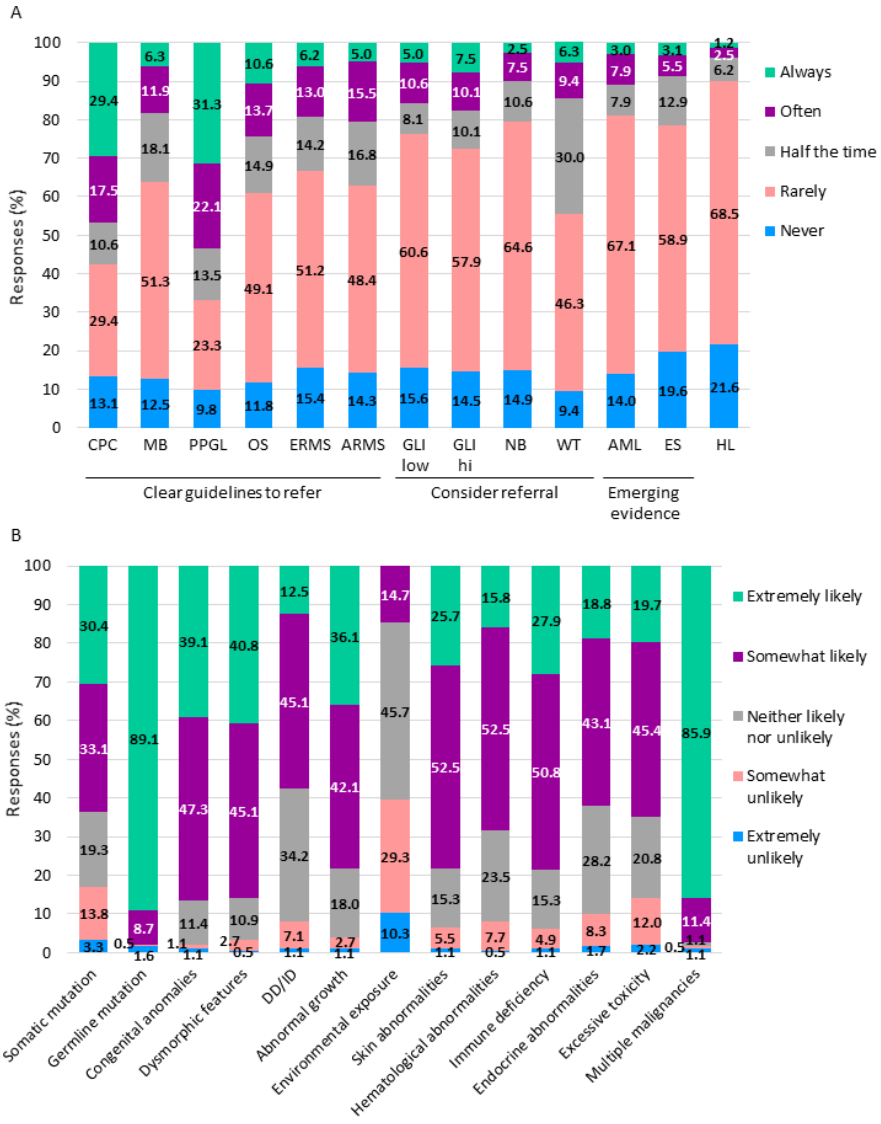

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