Phenotypic Differences in Juvenile Polyposis Syndrome With or Without a Disease-causing *SMAD4/BMPR1A* Variant

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ABSTRACT

Juvenile polyposis syndrome (JPS) is a clinically diagnosed hamartomatous polyposis syndrome that increases the risk of gastrointestinal cancer. Approximately 40%–50% of JPS is caused by a germline disease-causing variant (DCV) in the *SMAD4* or *BMPR1A* genes. The aim of this study was to characterize the phenotype of DCV-negative JPS and compare it with DCV-positive JPS. Herein, we analyzed a cohort of 145 individuals with JPS from nine institutions, including both pediatric and adult centers. Data analyzed included age at diagnosis, family history, cancer history, need for colectomy/gastrectomy, and polyp number and location. Compared with DCV-positive JPS, DCV-negative JPS was associated with younger age at diagnosis ($P < 0.001$), lower likelihood of having a family history of JPS ($P < 0.001$), and a lower risk of colectomy ($P = 0.032$). None of the DCV-negative individuals had gastric or duodenal polyps, and polyp burden decreased after the first decade compared with DCV-positive JPS. Subgroup analysis between *SMAD4* and *BMPR1A* carriers showed that *SMAD4* carriers were more likely to have a family history of JPS and required gastrectomy. Taken together, these data provide the largest phenotypic characterization of individuals with DCV-negative JPS to date, showing that this group has distinct differences compared with JPS due to a *SMAD4* or *BMPR1A* variant. Better understanding of phenotype and cancer risk associated with JPS both with and without a DCV may ultimately allow for individualized management of polyposis and cancer risk.

Prevention Relevance: Juvenile Polyposis Syndrome (JPS) is a gastrointestinal cancer predisposition syndrome requiring lifelong surveillance, however there is limited data comparing individuals with and without a germline disease-causing variant in *SMAD4* or *BMPR1A*. Herein we show that individuals with JPS without an underlying disease-causing variant have distinct phenotypic differences including lack of upper gastrointestinal polyps and lower rates of a family history of JPS, suggesting that a different approach to management may be appropriate in this population.

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Introduction

Juvenile polyposis syndrome (JPS) is a rare hereditary gastrointestinal (GI) polyposis syndrome with an increased risk of GI cancer. Clinical diagnostic criteria for JPS include having five or more cumulative pathologically defined juvenile polyps in the colon, at least one pathologically defined juvenile polyp from both the upper and lower intestinal tracts, or any number of juvenile polyps with a family history of JPS (1). In some cases, JPS is caused by a pathogenic or likely pathogenic (P/LP) germline variant in either *SMAD4* or *BMPR1A*, whose protein products are important components of the TGFβ–BMP signaling pathway (2). The frequency of a *SMAD4* or *BMPR1A* P/LP variant, henceforward collectively referred to as a disease-causing variant (DCV), in individuals who meet clinical criteria for JPS is reported to be between 40% and 50% (3).

Although several cohorts of patients with JPS have been described (**Table 1**), these studies have either focused largely on patients with a known *SMAD4* or *BMPR1A* DCV (4, 5) or have not differentiated between those with or without an identifiable

Table 1. Prior reported JPS cohorts.

	Total (*N*)	DCV positive	Age at diagnosis (average, range)	Family history of JPS	Required colectomy or gastrectomy	Cancer prevalence	Age of cancer diagnosis
Coburn and colleagues 1995 (9)	218	NR	19 y (9 mo–67 y)	50% ($n = 109$)	45% ($n = 99$)	17% ($n = 36$)	36 y (4 y–60 y)
Howe and colleagues 1998 (10)	29	NR	32 y (6 y–68 y)	100%	NR	55% ($n = 16$)	42 y colorectal (17 y–68 y) 58 y upper (20 y–72 y)
Brosens and colleagues 2007 (8)	84	NR	NR	NR	NR	18% ($n = 8$)	44 y
Latchford and colleagues 2012 (7)	44	64% ($n = 28$)	27 y (4 y–57 y)	NR	30% ($n = 13$)	14% ($n = 6$)	47 y
Aytac and colleagues 2015 (5)	35	100%	17 y (3 y–65 y)	83% ($n = 29$)	69% ($n = 24$)	11% ($n = 4$)	38 y (29 y–70 y)
Ishida and colleagues 2018 (6)	171	NR	28 y (1–80 y)	NR	NR	86% ($n = 147$)	NR

Abbreviations: mo, months; NR, not recorded; y, years.

DCV (6). These prior JPS cohorts have demonstrated variable cancer risk associated with JPS, ranging from 11% to 86%, in part, due to changes in screening recommendations over time, the heterogeneous populations included in each study, as well as likely selection bias (4–10). Although some studies support that *SMAD4* DCV carriers have a more severe upper GI polyposis and malignancy phenotype (4, 5, 7, 11), it remains difficult to determine the precise risk of GI cancer and optimal risk-reducing strategies for patients with JPS with and without a DCV given small sample sizes and cohort heterogeneity. For this reason, patients are recommended to undergo lifelong surveillance with endoscopy and colonoscopy starting in childhood (12–15).

Quantifying cancer risk in individuals with JPS without a DCV remains particularly challenging given the paucity of data on clinical characteristics and cancer risks in this population. This multi-institutional study is the largest study to date comparing patients with DCV-positive and DCV-negative JPS. The aim of this study was to characterize the differences between these two groups to understand the associated clinical phenotypes and cancer risks, and to help better inform risk management strategies for JPS.

Materials and Methods

Individuals were identified at nine different institutions, including the Children's Hospital of Philadelphia (Philadelphia, PA), Hospital of the University of Pennsylvania (Philadelphia, PA), Ann & Robert H. Lurie Children's Hospital of Chicago (Chicago, IL), Texas Children's Hospital (Houston, TX), Dana-Farber Cancer Institute (Boston, MA), University of Wisconsin (Madison, WI), University of Pittsburgh Medical Center (Pittsburgh, PA), Memorial Sloan Kettering Cancer Center (New York, NY), and Yale University (New Haven, CT). Each institution collected data for this study in accordance with an institution-specific institutional review board (IRB) protocol and the U.S. Common Rule, and patients were included per the individual institution recruitment period and exclusion/inclusion criteria. Where required by the IRB protocol and U.S. Common Rule regulations, written consent was obtained from participants. Deidentified data were transferred to the Children's Hospital of Philadelphia (Philadelphia, PA) and University of Pennsylvania (Philadelphia, PA) group within established data use agreements.

Individuals with a diagnosis of JPS were identified from each institution; for consistency, a uniform data collection template and data dictionary were used by all centers to standardize measures and ensure consistency of data, and the resulting quality of the data was checked by the Children's Hospital of Philadelphia (Philadelphia, PA) investigators. Patients were included if they met clinical diagnostic criteria for JPS, including one of the following: (i) having five or more cumulative pathologically defined juvenile polyps in the colon, (ii) at least one pathologically defined juvenile polyp from both the upper and lower intestinal tract, or (iii) any number of juvenile polyps with a family history of JPS (1). Complete genetic testing was defined as sequencing, deletion, and duplication analysis for the *BMPR1A* and *SMAD4* genes; those without complete genetic testing were excluded from the analysis.

Data collected included gender, age at last follow-up, age at time of JPS diagnosis, genetic testing results, family history of a JPS diagnosis (defined as having a family member meeting clinical criteria for a JPS diagnosis), personal history of cancer, personal history of colectomy, and personal history of gastrectomy. All cancer types were included in the dataset, but only GI cancers were included in the analysis. The pediatric age group was defined as age of last follow-up under 20 years. Information on GI polyp burden was also obtained, and was defined per decade as none, low (1–10 polyps), and high (>10 polyps); these numbers included both upper and lower GI polyps. Polyps were classified as upper gastrointestinal if they were gastric or duodenal, and classified as lower gastrointestinal if they were located in the colon or rectum; other small intestinal polyps were not tracked. The cutoff of 10 polyps was used for data consistency, as each institution recorded and obtained data

from different clinical reporting materials (e.g., colonoscopy reports, pathology reports, and clinical notes) and, therefore, in some circumstances the exact polyp number could not be determined. In addition, data on location of polyps and the presence of adenomas were collected; a distinction was not made between adenomas arising independently versus those arising from juvenile polyps.

Patients were only included in the final analysis if a P/LP variant was identified in either *SMAD4* or *BMPR1A*, or if there was documented negative genetic testing for both *SMAD4* and *BMPR1A*, with no P/LP or variant of uncertain significance (VUS) identified in either gene. Patients with a VUS in *SMAD4* or *BMPR1A* were excluded from analysis. No patients were known to have a P/LP variant in any other polyposis gene, however, comprehensive polyposis genetic testing outside of *SMAD4* and *BMPR1A* was not required for inclusion. Data were analyzed in Stata statistical analysis software (v.16) using Wilcoxon rank-sum and χ^2 analyses, where appropriate. For variables whose outcome might be biased by age (personal history of cancer, gastrectomy, and colectomy), analysis was completed through logistic regression controlling for age at last follow-up.

Results

A total of 145 individuals with JPS from 137 families were collected from nine institutions (**Fig. 1**). Twenty-five patients were excluded given incomplete genetic testing and two individuals were excluded for VUSs in *BMPR1A* (c.1433G>A and c.1559_1560insTT). After exclusions, 118 individuals remained for analysis. Of the included individuals, 64 (54%) had no P/LP variant identified in *SMAD4* or *BMPR1A*, hereafter referred to as DCV-negative JPS, and 54 (46%) had a P/LP variant identified in either *SMAD4* ($n = 27$) or *BMPR1A* ($n = 27$), hereafter referred to as DCV-positive JPS. Of the *BMPR1A* P/LP variants identified, three individuals had a 10q23 deletion involving both *PTEN* and *BMPR1A*. When the pediatric JPS group ($n = 71$) was analyzed separately, 22% had a DCV identified, whereas in the adults ($n = 47$), 83% had a DCV identified ($P < 0.001$).

There were no statistically significant differences in gender between DCV-positive and DCV-negative individuals (**Table 2**). Patients with DCV-negative JPS were on average younger at diagnosis (median 5 vs. 18 years; $P < 0.001$) and were less likely to have a family history of JPS compared with DCV-positive individuals ($P < 0.001$; **Table 2**). Individuals with DCV-negative JPS were also on average younger at last follow-up (median, 11 years; range, 3–57 years) than those with a DCV (median, 33.5 years; range, 2–73 years; $P < 0.001$), however, the overall years of follow-up were similar (median, 4.5 vs. 5 years; $P = 0.350$). In assessing polyp location, none of the DCV-negative group individuals had upper GI (gastric/duodenal) polyps, whereas all had polyps in the lower GI tract (**Table 2**; $P < 0.001$ for lower GI polyps in DCV-negative vs. DCV-positive individuals). In addition, no individuals in the DCV-negative JPS group developed adenomas, as compared with almost half (45%) of those in the DCV-positive group ($P < 0.001$). For individuals with a DCV, DCV-specific subgroup analysis was also performed (**Table 2**). When *SMAD4* carriers were compared with *BMPR1A* carriers, there were no statistically significant differences between

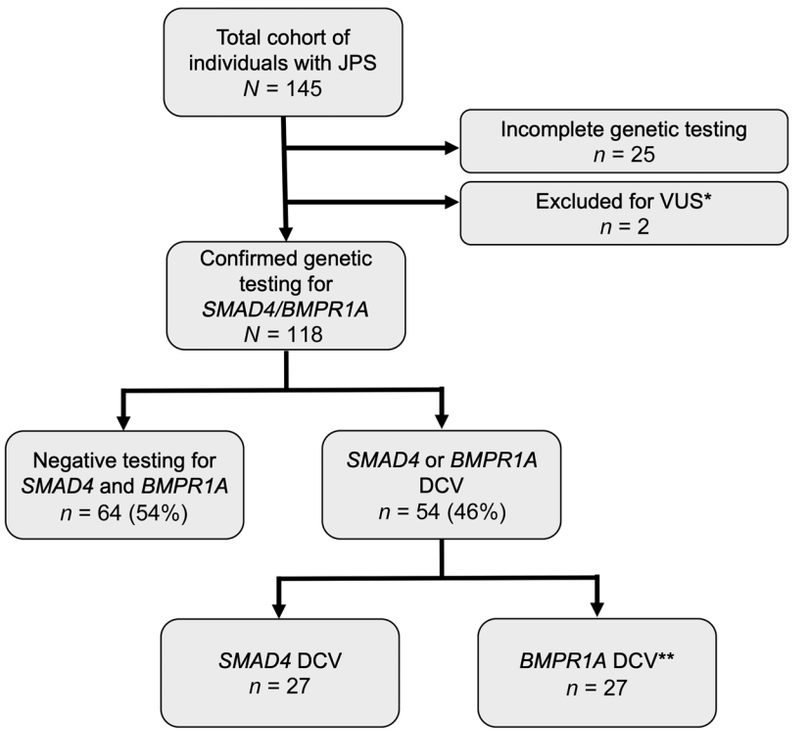

Figure 1.
JPS inclusion cohort. Schematic representation of individuals included in the JPS cohort for final analysis. **BMPR1A* VUS in 2 patients, excluded from analysis. **Includes three individuals with *BMPR1A*/*PTEN* inclusive 10q23 deletion.

Table 2. JPS demographic data and clinical history.

	DCV-negative JPS ($n = 64$)	DCV-positive JPS ($n = 54$)		P
		SMAD4 ($n = 27$)	*BMPR1A* ($n = 27$)	
Female (%)	42	56		0.123
		61	*52*	*0.511*
Age at diagnosis, median (range, years)	5 (2–55)	18 (1–72)		**<0.001**
		19 (2–54)	*18 (1–72)*	*0.996*
Age at last follow-up, median (range, years)	11 (3–57)	33.5 (2–73)		**<0.001**
		37 (13–65)	*27 (2–73)*	*0.394*
Years of follow-up, median (range, years)	4.5 (0–30)	5 (0–48)		0.350
		8 (0–48)	*2 (0–44)*	***<0.001***
Family history of JPS (%)	6	52		**<0.001**
		56	*48*	***0.016***
Presence of adenomas (%)[a]	0	45		**<0.001**
		52	*38*	*0.635*
Upper GI polyps (%)[a]	0	57		**<0.001**
		60	*55*	*0.839*
Lower GI polyps (%)[a]	100	87		**0.003**
		88	*86*	*0.548*

Note: Demographic data, clinical history, polyp location, and adenoma frequency in individuals with JPS, subdivided by no DCV and *SMAD4/BMPR1A* DCV. Bold values are statistically significant.
[a]Polyp and adenoma burden as measured by lifetime presence of upper (gastric/duodenal) polyps, lower (colonic/rectal) polyps, and adenomas (upper or lower).

gender, age at diagnosis, age at last follow-up, location of polyps, and presence of adenomas. However, *SMAD4* carriers were more likely to have a family history of JPS ($P = 0.016$).

Only two individuals (3%) in the DCV-negative group developed cancer, as compared with 14 individuals (26%) in the DCV-positive group; of the latter group, 10 individuals developed 11 incidences of GI cancer (19%; **Tables 3** and **4**). In logistic regression, controlling for age at last follow-up, the difference in incidence of GI cancer was not statistically significant [**Table 3**; 95% confidence interval (CI), 0.4–45.5; $P = 0.208$]; non-GI cancers were not included in this analysis. Two individuals (3%) in the DCV-negative group required a colectomy, one for polyp burden and one for cancer (ages, 44 and 55), and none required gastrectomy. In the DCV-positive group, 18 individuals (33%; median age, 24 years; range, 5–72) required colectomy, one for cancer, 16 for polyp burden (including three with severe anemia), and one for diverticulitis, and eight (15%; median age, 38.5 years; range, 15–58) required gastrectomy, five for polyp burden and three for cancer (**Table 3**). The difference in colectomy requirement was statistically significant (95% CI, 1.2–34.2; $P = 0.03$), whereas the need for gastrectomy was not statistically significant when analysis was controlled for age at last follow-up. In subgroup analysis, *SMAD4* carriers were more likely to require gastrectomy ($P = 0.02$), but the incidence of GI cancer and need for colectomy were not significantly different.

To quantify differences in polyp burden in the JPS cohort, cumulative upper and lower GI polyp burden was defined as absent, low (1–10 polyps), or high (>10 polyps) over each decade of life. The data on polyp burden are included in **Fig. 2**, which delineates polyp burden over each decade of life, as available. Similar polyp burden was noted in the first decade of life. However, DCV-negative individuals had a lower polyp burden in the second and third decades of life. After the age of 40 years, the DCV-negative group was not large enough to track polyp burden.

Discussion

JPS is a GI cancer risk syndrome whose diagnosis and risk management are important for both pediatric and adult practitioners. Although prior studies have focused on the cancer risks associated with JPS (6, 7), there still remains limited data on the cancer risks of individuals with DCV-negative JPS, a subpopulation that accounts for at least half the JPS population. In this study, we present the findings from a large, multi-institutional evaluation of individuals with JPS, which is the largest cohort to date to compare affected individuals with or without a DCV in *SMAD4* or *BMPR1A*. As such, this cohort provides important insight into the undercharacterized group of individuals with JPS who lack an identifiable *SMAD4* or *BMPR1A* DCV.

The percentage of our study population with a DCV is similar to the prevalence of DCVs previously reported in JPS

Table 3. GI cancer and colectomy/gastrectomy incidence.

	DCV-negative JPS (%; $n = 64$)	DCV-positive JPS (%; $n = 54$)	OR (95% CI)	P
History of GI cancer (%)	1.6 ($n = 1$)	18.5 ($n = 10$)	4.45 (0.4–45.5)	0.208
Colectomy (%)	3.1 ($n = 2$)	33.3 ($n = 18$)	6.40 (1.2–34.3)	**0.030**
Gastrectomy (%)	0 ($n = 0$)	14.8 ($n = 8$)	3.80 (0.4–41.2)	0.272

History of GI cancer, need for colectomy, and need for gastrectomy in those with and without a DCV. Bold value is statistically significant.

Table 4. Cancers reported in the JPS cohort.

Gene	P/LP variant	Age of cancer diagnosis (years)	Type of cancer
BMPR1A	c.1433G>A	26	**Colon**
	c.44_47delTGTT	68	Pancreas
	c.182G>A	44	**Rectosigmoid**
SMAD4	c.372_373dupTA	45;64	**Gastric; colon**
	c.692dupG	29	**Gastric**
	c.692dupG	39	Cervical
	c.692dupG	46	**Esophageal**
	c.1507_1508insATCC	44	Breast cancer
	c.1206dupT	24	**Colon**
	c.1447+2T>C	48	Papillary thyroid cancer
	c.403C>T	39	**Colon**
	c.1308+2T>G	47	**Colon**
	c.1231_1232delAG	28	**Colon**
	c.1245_1248delGACA	15	**Gastric**
No DCV	NA	55	**Colon**
	NA	34	Bladder

Note: Bolded cancers were considered within the JPS spectrum.

studies (7, 15). However, when divided into the pediatric and adult JPS groups, based on age at last follow-up, the pediatric group had a strikingly lower rate of DCVs identified (22%), compared with the adult group, in which a large majority (83%) had a DCV. This difference was borne out in the polyposis data in adults, as few of the individuals followed at adult institutions were DCV negative, which was accounted for in the statistical analysis of adult-onset outcomes, such as cancer and need for gastrectomy or colectomy. This age difference could be explained by increasing diagnosis of DCV-negative JPS in pediatric populations, or decreased follow-up of these individuals with adult providers. It is also possible that in DCV-negative individuals the long-term cancer risk is lower or their polyp burden decreases after adolescence. Conversely, this could be a population that requires, but does not always receive, more intensive surveillance.

Our data also demonstrate that individuals with DCV-negative JPS were less likely to have a family history of JPS and were diagnosed at a younger age; a smaller study from 1998 also supported these findings (10). However, given the small sample size, other differences between the groups in this prior study did not reach statistical significance (10). We further demonstrate that individuals with DCV-negative JPS were significantly less likely to undergo colectomy compared with individuals with a DCV-positive JPS. However, given the younger age at last follow-up of the DCV-negative group, this study was underpowered to show a difference in cancer incidence or need for gastrectomy. More extensive study of disease burden and cancer incidence of the DCV-negative group into adulthood will be necessary to better elucidate this population's risk.

Differences in polyp burden over time between DCV-positive and DCV-negative groups were another notable phenotypic difference in our data. Although both the DCV-positive and DCV-negative JPS groups had significant polyp burden in the first decade of life, the DCV-negative JPS group had decreased polyp burden in the second and third decades, whereas the DCV-positive group maintained a persistently elevated polyp burden. Furthermore, DCV-negative individuals did not have upper GI polyposis, a difference in polyp presentation that has not previously been noted. To further understand the lifetime polyposis risk, individuals with DCV-negative JPS need longer term follow-up in research registries with close documentation and tracking of polyp histology, location, and number. While upper and lower GI polyps can often be managed endoscopically, some individuals in this JPS cohort also underwent gastrectomy or colectomy for polyp control. A higher percentage of those undergoing colectomy did so for polyp control compared with those undergoing gastrectomy, where a higher percentage did so for cancer. Although the severity of disease at time of gastrectomy/colectomy was not captured in this study, these differing rates may be attributed to the different morbidities, or perceived morbidities, of these procedures, or may be due to differing effectiveness of endoscopic surveillance in the upper versus lower GI tract, as well as differing thresholds for recommending surgery among different centers.

It has long been suspected that there may be additional disease-causing germline variants that have yet to be identified in patients with a clinical diagnosis of DCV-negative JPS. However, the lack of family history and younger age of

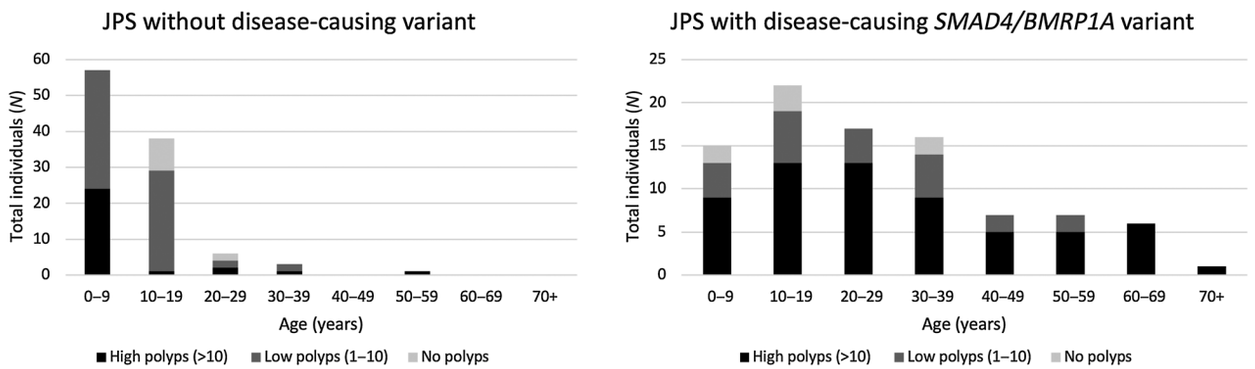

Figure 2.
JPS polyp burden by age. Representation of high (>10), low (1–10), and no (zero) polyps present (both upper and lower) in the 10-year age range.

diagnosis also suggest that there may be a low penetrance autosomal dominant variant, an autosomal recessive variant, mosaicism, or epigenetic change that is responsible for driving the phenotype. Additional genomic studies of this DCV-negative population, in particular, are required to better understand the underlying risk for JPS. Furthermore, this suggests that pediatric providers should consider underlying JPS in the setting of juvenile polyps, regardless of whether a family history of JPS exists. Should an individual have DCV-negative JPS, testing for other pathogenic germline variants, in genes such as *ENG* and *PTEN*, should also be considered, especially in the setting of physical features, such as macrocephaly. It is also possible that DCV-negative JPS is a distinct clinical phenotype and should be treated as such; these individuals could have an acquired phenotype rather than a syndromic phenotype, as isolated juvenile polyps in children are common. Should this be the case, it would imply that there is a population of patients with juvenile polyps that are not at high risk of cancer and do not require close longitudinal follow-up throughout adulthood. This underscores the importance of designation and close longitudinal follow-up of DCV-negative JPS individuals in research registries to help better clarify their follow-up patterns in adulthood, as well as their long-term outcomes and cancer risks.

Although the main focus of our study was comparison of JPS with and without a DCV in *SMAD4* or *BMPR1A*, subset analysis of individuals with a *SMAD4* P/LP variant compared with those with a *BMPR1A* variant suggested that patients with a *SMAD4* P/LP variant have a higher rate of malignancy, although this difference did not quite reach statistical significance ($P = 0.051$). The overall cancer risk in the study population (13.4% of total patients, 8.4% when restricted to GI cancers) was similar to risk estimates previously reported in other studies (7). Of note, patients with 10q23 deletions involving both *PTEN* and *BMPR1A* are known to have a more severe JPS phenotype, with onset often in infancy and requiring early colectomy (16, 17). None of the three individuals with 10q23 deletions included in this study developed cancer, and their removal from the analysis led to no change in statistical significance of other measures, and thus, they were included in the final analysis presented.

Limitations to this study include that data were collected from multiple different centers with differing levels of data granularity, which limits analysis of certain potential endpoints including: exact polyp number, origin of adenomas (isolated or arising from juvenile polyps), the severity of polyposis that led to decision to pursue gastrectomy or colectomy, other clinical features, including history of hereditary hemorrhagic telangiectasia, and the detailed family history of relatives with reported JPS. In addition, given the younger age of last follow-up of the DCV-negative JPS cohort, we had less data available on this cohort in older decades compared with the DCV-positive JPS cohort. Long-term follow-up of DCV-negative patients will be crucial to improved understanding of this cohort.

This study provides the largest characterization of a cohort of DCV-negative JPS to date. Our data provide evidence to suggest that given their different phenotype, DCV-negative JPS may be able to be surveyed and/or managed differently than those with JPS with an identifiable DCV, as has also been suggested by the most recent update to recommendations by the National Comprehensive Cancer Network (14). Additional research is needed to clinically distinguish those DCV-negative patients who may remain at risk for cancer throughout their lifetimes, and likely other germline changes remain to be identified in some DCV-negative individuals. At this time, we would still recommend following clinical guidelines for JPS as developed by expert consortia (12, 14). However, these data do suggest that there is a subset of individuals who meet clinical criteria for JPS, but have no identifiable DCV in *SMAD4* or *BMPR1A*, who may not have the same polyp distribution and long-term risks as individuals with DCV-positive JPS.

Authors' Disclosures

L.M. Bass reports personal fees from Mead Johnson Nutrition outside the submitted work. D.S. Fishman reports royalties from UpToDate (pediatric caustic ingestions). S. Plon reports membership (scientific advisory board) with Baylor Genetics Laboratories. Z.K. Stadler reports immediate family member serves as a consultant in the field of ophthalmology for Adverum Biotechnologies, Genentech/Roche, Novartis, Neurogene, Gyroscope Tx, Optos Plc, Regeneron, RegenexBio, and Spark Therapeutics. S. Syngal reports personal fees from Myriad Genetics outside the submitted work. M.B. Yurgelun reports personal fees from Janssen (one-time payment for consulting/scientific advisory board participation) and UpToDate (payment for peer-review services) outside the submitted work. B.W. Katona reports grants from NIH/NIDDK during the conduct of the study, other from Janssen (paid travel related to a clinical trial), and personal fees from Exact Sciences (consulting) outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

S.P. MacFarland: Conceptualization, resources, data curation, formal analysis, validation, writing-original draft, project administration, writing-review and editing. **J.E. Ebrahimzadeh:** Conceptualization, data curation, validation, writing-review and editing. **K. Zelley:** Conceptualization, data curation, writing-review and editing. **L. Begum:** Data curation, formal analysis. **L.M. Bass:** Data curation, writing-review and editing. **R.E. Brand:** Data curation, writing-review and editing. **B. Dudley:** Data curation, writing-review and editing. **D.S. Fishman:** Data curation, writing-review and editing. **A. Ganzak:** Data curation, writing-review and editing. **E. Karloski:** Data curation, writing-review and editing. **A. Latham:** Data curation, writing-review and editing. **X. Llor:** Data curation, writing-review and editing. **S. Plon:** Data curation, formal analysis, writing-review and editing. **M.K. Riordan:** Data curation, writing-review and editing. **S.R. Scollon:** Conceptualization, data curation, writing-review and editing. **Z.K. Stadler:** Data curation, writing-review and editing. **S. Syngal:** Data curation, writing-review and editing. **C. Ukaegbu:** Data curation, writing-review and editing. **J.M. Weiss:** Data curation, writing-review and editing. **M.B. Yurgelun:** Data curation, writing-review and editing. **G.M. Brodeur:** Data curation, writing-review and editing. **P. Mamula:** Conceptualization, data curation, methodology, writing-review and editing. **B.W. Katona:** Conceptualization, data curation, writing-original draft, project administration, writing-review and editing.

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