

Review

The Genomic Topography of Appendiceal Cancers: Our Current Understanding, Clinical Perspectives, and Future Directions

Daniel J. Girona ^{1,2} , Richard A. Erali ^{2,3} , Steven D. Forsythe ^{2,4} , Ashok K. Pullikuth ^{1,2} ,
Rui Zheng-Pywell ³ , Kathleen A. Cummins ³, Shay Soker ^{2,5,6}, Xianying Gui ^{6,7}, Edward A. Levine ^{2,3,6} ,
Konstantinos I. Votanopoulos ^{2,3,5,6} and Lance D. Miller ^{1,2,6,*} 

- ¹ Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA; daniel.girona@wfusm.edu (D.J.G.); ashok.pullikuth@advocatehealth.org (A.K.P.)
 - ² Wake Forest Organoid Research Center, Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27101, USA
 - ³ Department of Surgery, Section of Surgical Oncology, Atrium Health Wake Forest Baptist, Winston-Salem, NC 27157, USA; rui.zhengpywell@advocatehealth.org (R.Z.-P.)
 - ⁴ Neuroendocrine Cancer Therapy Section, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
 - ⁵ Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27101, USA
 - ⁶ Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC 27157, USA
 - ⁷ Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA
- * Correspondence: lance.miller@wfusm.edu

Simple Summary

Appendiceal cancer (AC) is a rare and often fatal malignancy with poorly understood pathogenesis and limited treatment options. Although recent genomic studies have begun to shed light on the more prominent genetic drivers of AC, the rarity of the disease has impeded the comprehensive genomic characterization of its diverse histologic subtypes. In this review, we synthesize the current literature on the genomic landscape of AC, highlighting subtype-specific mutational profiles, their prognostic implications, and the emerging role of molecular profiling in guiding future research and shaping prospective therapeutic strategies.

Abstract

Background/Objectives: Appendiceal cancer (AC) is a rare and understudied malignancy with limited genomic data available to guide clinical interventions. Historically treated as a subtype of colorectal cancer, AC is now recognized as a distinct disease with unique histologic subtypes and molecular features. This review aims to consolidate current genomic data across AC subtypes and explore the clinical relevance of recurrent mutations. **Methods:** A systematic literature review was performed in accordance with general Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines. Using search engines such as PubMed and Web of Science, we selected studies based on relevance to AC genomics using search terms such as “appendix cancer”, “appendiceal cancer”, “pseudomyxoma peritonei”, “sequencing”, “mutation”, and “genotype”. **Results:** AC comprises five major histologic subtypes—appendiceal neuroendocrine neoplasms (ANENs), mucinous appendiceal neoplasms (MANs), goblet cell adenocarcinomas (GCAs), colonic-type adenocarcinomas (CTAs) and signet ring cell adenocarcinomas (SRCs)—each with unique clinical behaviors and mutational profiles. Low-grade tumors, such as ANENs and MANs, frequently harbor *KRAS* and *GNAS* mutations, while high-grade subtypes, such as CTAs and SRCs, are enriched for *TP53*, *APC*, and *SMAD* gene alterations. GCA tumors exhibit a distinct mutational spectrum involving chromatin remodeling genes such as



Academic Editor: Jason Roszik

Received: 18 September 2025

Revised: 4 October 2025

Accepted: 7 October 2025

Published: 9 October 2025

Citation: Girona, D.J.; Erali, R.A.; Forsythe, S.D.; Pullikuth, A.K.; Zheng-Pywell, R.; Cummins, K.A.; Soker, S.; Gui, X.; Levine, E.A.; Votanopoulos, K.I.; et al. The Genomic Topography of Appendiceal Cancers: Our Current Understanding, Clinical Perspectives, and Future Directions. *Cancers* **2025**, *17*, 3275. <https://doi.org/10.3390/cancers17193275>

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

ARID1A and *KMT2D*. Compared to colorectal cancer, AC demonstrates lower frequencies of *APC* and *TP53* mutations and a higher prevalence of *GNAS* mutations, consistent with a pathological divergence from CRC. **Conclusions:** The genomic heterogeneity of AC is commensurate with its histological complexity and has important implications for diagnosis, prognosis and treatment. While certain actionable mutations are present in a subset of tumors, large-scale genomic characterization efforts and development of subtype-specific models will be essential for advancing precision medicine in AC.

Keywords: appendix cancer; colon cancer; bowel malignancy; molecular profiling; next-generation sequencing; mutational landscape; precision medicine

1. Introduction

Appendiceal cancer (AC) is a rare malignancy of the gastrointestinal tract associated with variable patterns of malignant spread and patient survival [1,2]. The estimated incidence of AC in the United States is approximately 6 cases per 1,000,000 individuals annually, with an increasing trend observed over the past two decades [3–6]. Clinical outcomes are largely influenced by tumor grade, tumor burden at diagnosis, histologic type, medical comorbidities, performance status (i.e., Eastern Cooperative Oncology Group and Karnofsky), and completeness of surgical cytoreduction, with AC 5-year survival ranging from 18% in advanced disease to 97% in well-differentiated neuroendocrine tumors [6–12].

To date, no screening programs are used clinically for the early detection of AC. AC is incidentally diagnosed in roughly 1% of appendectomies, with most tumors being detected after clinical presentation of acute appendicitis secondary to tumoral obstruction of the appendiceal lumen [13–17]. Given that the appendix embryonically arises from the cecum [18] and remains as an anatomical constituent of the colon throughout development, AC has historically been categorized and treated as a variant of colorectal cancer (CRC). However, AC remains histologically distinct from CRC and is resistant to most standard CRC treatment regimens [4,19]. At present, the therapeutic management of AC depends largely on tumor grade and surgical resectability. Non-resectable cases are treated with palliative chemotherapy [13,20], whereas resectable tumors are often managed with cytoreductive surgery (CRS), followed by hyperthermic intraperitoneal chemotherapy (HIPEC) and, in some cases, adjuvant chemotherapy [10,13,20,21].

Histological classification of AC has evolved over the past few decades, with the American Joint Committee on Cancer (AJCC) 8th Edition now recognizing five major subtypes: appendiceal neuroendocrine neoplasms (ANENs), mucinous appendiceal neoplasms (MANs—which includes non-infiltrating low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs), and invasive mucinous adenocarcinomas (MAAs), goblet cell adenocarcinomas (GCAs), colonic-type adenocarcinomas (CTAs), and signet ring cell adenocarcinomas (SRCs) [3,22–24] (Figures 1 and 2a). These subtypes differ significantly in their clinical behavior. For instance, poorly differentiated tumors and those with signet ring morphology portend a worse prognosis, while ANENs and well-differentiated MANs often follow a more indolent disease course (Figure 2b).

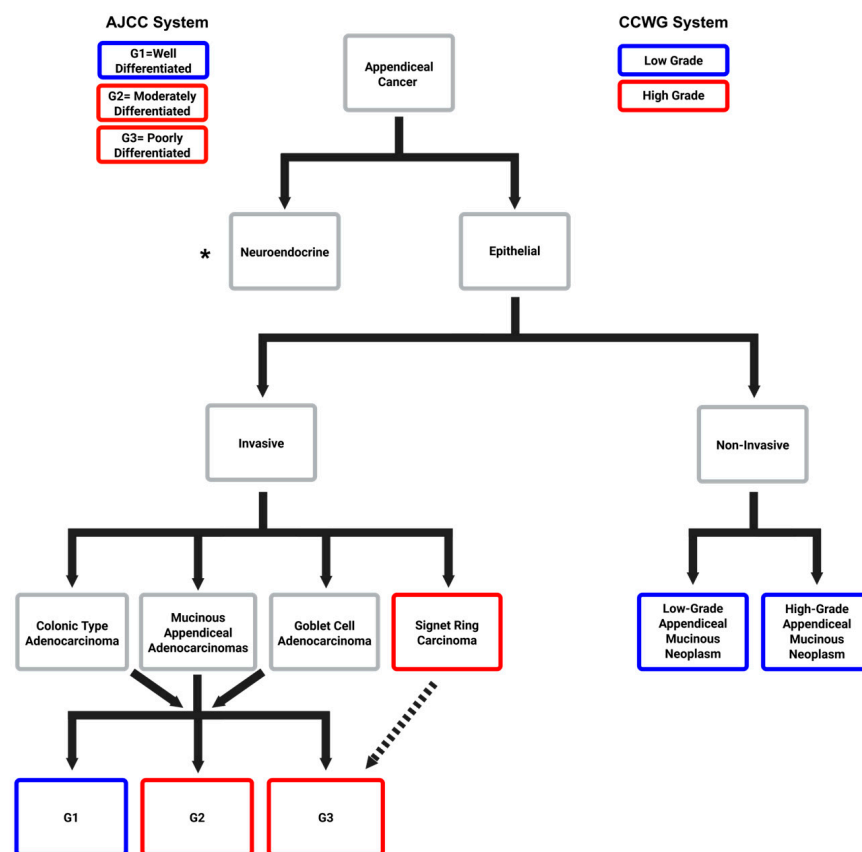
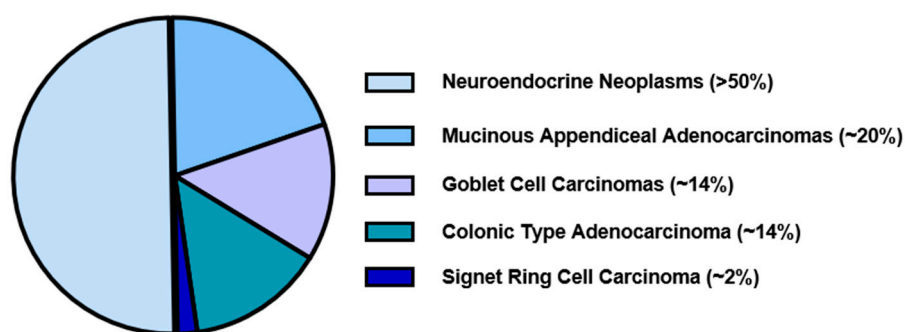


Figure 1. Consolidation of appendiceal cancer grading schemas between the 8th Edition AJCC Guidelines and Chicago Consensus Working Group (CCWG). Solid arrows indicate primary pathological subclassifications. Invasive histologic variants (i.e., Neuroendocrine, Colonic Type, Goblet Cell Adenocarcinoma) can be further classified into grades G1–G3. The dashed arrow indicates a secondary subclassification with regard to grade: any histologic variant with a signet ring component is clinically assessed as high-grade or G3 disease. * Appendiceal neuroendocrine neoplasms (ANENs) are typically non-aggressive and associate with favorable survival; however, poorly differentiated ANENs are considered malignant and high-grade (Made with bioRender).

In AC, two main grading systems are used clinically: the three-tiered AJCC system (G1–G3) based on cellular differentiation, and the dichotomous Chicago Consensus system that categorizes tumors into low- and high-grade disease [24–26]. Grading involves the pathologic assessment of cellular features that include nuclear architecture, tumor cellularity, mitotic frequency, and the presence of signet ring morphology [24]. Low-grade appendiceal tumors can present as LAMNs and HAMNs, or invasive low-grade MAAs that present as well-differentiated cells with dysmorphic cellularity of the superficial epithelia [27]. High-grade AC is characterized by moderate to poor cellular differentiation and tissue invasion. These tumors are clinically more aggressive and include moderately to poorly differentiated ANENs, MANs, CTAs, GCAs, as well as SRCs [26]. A detailed schema of the relationship between histologic subtype and grade is shown in Figure 1.

Peritoneal carcinomatosis (PC) frequently arises in AC as a result of appendix rupture and the subsequent dissemination of tumor cells throughout the peritoneum [28]. In this metastatic state, the clinical aggressiveness of AC is largely dependent on tumor grade—patients with low-grade disease exhibit a 5-year survival of 84%, compared to just 48% in those with high-grade tumors [29].

a. Appendiceal Cancer Incidence by Pathological Subtype



b. Associated 1-, 2-, and 5-Year Survival Ranges by AC Pathological Subtype

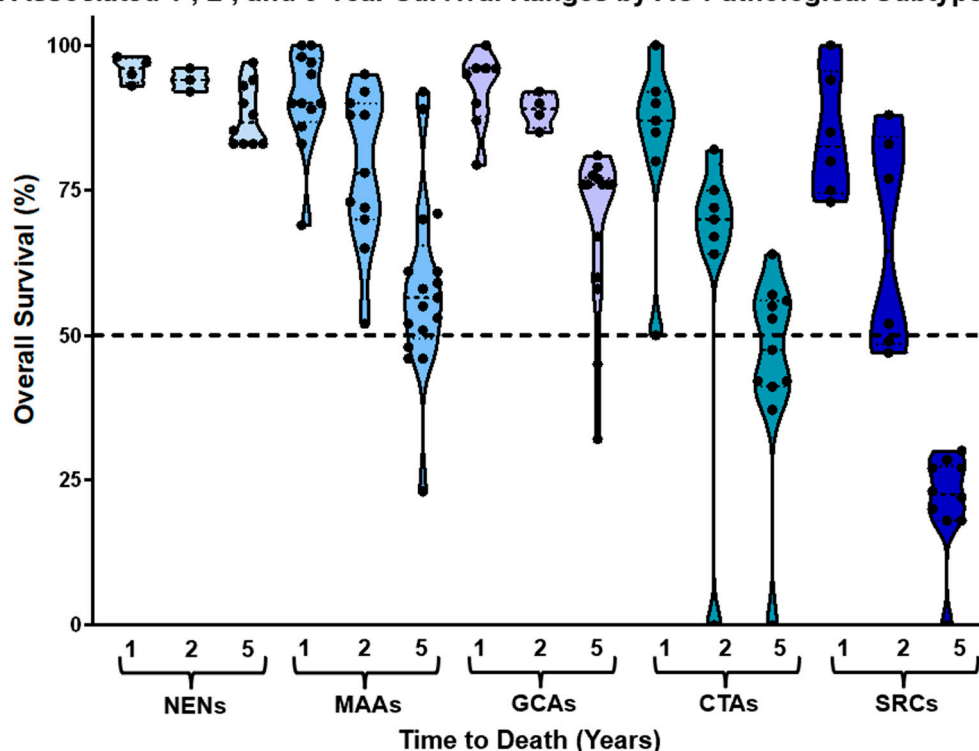


Figure 2. (a), Incidence of appendiceal cancer subtypes and (b), mortality by pathological subtype. NEN = Neuroendocrine Neoplasm. GCA = Goblet Cell Adenocarcinoma. MAN = Mucinous Appendiceal Neoplasms. CTA = Colonic Type Adenocarcinoma. SRC = Signet Ring Cell Adenocarcinoma. Reference data for (a,b) can be found in Supplementary Data S1. Each data point in (b) represents a reported survival rate as listed from an individual study.

Although our understanding of the mutational drivers of AC is still emerging, genomic studies have begun to identify patterns of somatic mutations linked to specific histologic subtypes (Figure 2b; Table 1). Most studies to date have been derived from small cohorts and targeted sequencing efforts using a variety of diverse gene panels including the MSK-IMPACT, Ion Ampliseq Cancer Panel, Oncomine Comprehensive Cancer Panel, and Ion AmpliSeq Comprehensive Cancer panel, which vary widely with respect to the breadth and type of genes represented. Despite preliminary successes in the targeted sequencing era, the need for broader characterization approaches like whole-exome and whole-genome sequencing remains for AC patients. This review consolidates recent genomic findings, compares mutational frequencies and their clinical implications across AC subtypes, and highlights opportunities for translational research.

Table 1. Additional gene alterations observed in AC subtypes.

Altered Gene	AC Subtype	Percent of Cases per Study (No Pts) in Reference Order	Reference(s)
EGFR	NEN	40% (5)	[30]
RN43	MAA	44% (9), 7% (44), 33% (9)	[31–33]
SMAD2	MAA	26% (29)	[34]
SMAD3	MAA	10% (10)	[34]
TGFBR1	MAA	10% (10)	[34]
TGFBR2	MAA	10% (10)	[34]
ARID1A	GCA	15% (84), 15.4% (13), 33% (9), 11% (18)	[12,35–37]
FAT3	GCA	17% (84)	[12]
MSH2	GCA	17% (18)	[37]
SOX9	GCA	22% (9), 10% (72), 9.2% (141), 11% (18)	[36–39]
ARID1A	CTA	11% (208)	[12]
ARID1A	SRC	7% (37), 11% (27)	[12,32]
CDH1	SRC	7.1% (14)	[40]
LRP1B	SRC	16.7% (24)	[39]
PRKDC	SRC	12.0% (50)	[39]

2. Appendiceal Neuroendocrine Neoplasms

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) arise from neuroendocrine cell types including enterochromaffin cells, L-cells, as well as tubular epithelial cells, and are histologically defined by well-differentiated growth patterns. Among these tumors, the appendix is the fifth most common site of origin [41,42]. Appendiceal NENs (ANENs) are the most frequently occurring appendiceal cancer histologic subtype [43] (Figure 2a).

ANENs are generally associated with favorable clinical outcomes. Surveillance, Epidemiology, and End Results (SEER) data indicate a 5-year overall survival (OS) of approximately 90%, with some studies reporting rates as high as 97% [44–50] (Figure 2b). Grading of appendiceal NENs is typically based on the World Health Organization (WHO) and AJCC classification schemes, which stratify tumors as well-differentiated (NEN-G1; KI-67 expression < 3%), moderately differentiated (NEN-G2; KI-67 = 3–20%), and poorly differentiated (NEN-G3; KI-67 > 20%), with a separate category for mixed adenoneuroendocrine carcinomas (MANECs) [50–53]. Unlike other appendiceal malignancies, ANENs generally exhibit a low overall burden of somatic mutations and chromosomal aberrations. This has led to the hypothesis that ANEN pathogenesis is more dependent on tumor grade and differentiation status rather than widespread genomic instability [8,54].

The most frequently mutated genes in ANENs are *TP53* (average 23.1%, range: 10.7–44%), *APC* (11.4%, 3.3–28.6%), *SMAD4* (11.5%, 0–40%), and *KRAS* (11.4%, 0–28.6%), as extrapolated from multiple reports [30,35,36,40,55] (Figure 3a; Supplementary Table S1). While these alterations are commonly seen in colorectal and other appendiceal cancer subtypes, their presence in ANENs may reflect tumor heterogeneity or sampling from mixed phenotypes. A broader analysis of 84 primary GEP-NENs, including only five appendiceal NENs, identified *TP53* (13.1%), *PTEN* (7.1%), *SMAD4* (6%), *EGFR* (6%), *ATM* (4.8%), *CDKN2A* (6%), and *KIT* (4.8%) as the most commonly altered genes [30]. These data suggest that *TP53* and *SMAD4* mutations may be shared among NENs across the GI tract, whereas *KRAS* and *APC* mutations may be more specific to the appendiceal subtype.

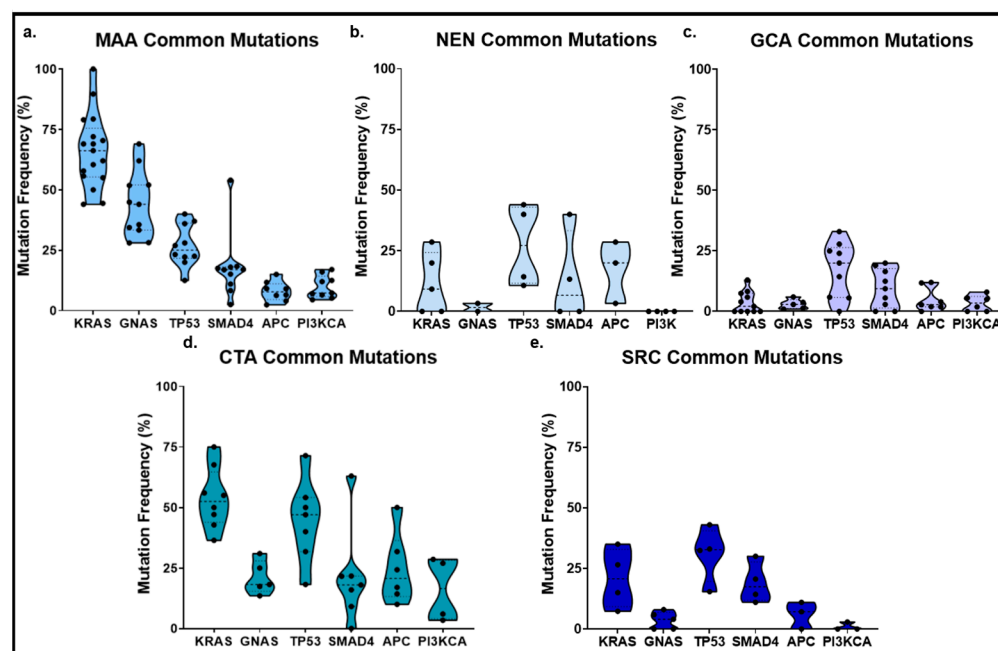


Figure 3. Frequencies of common oncogenic mutations by histologic subtype. Shown are mutation frequencies extrapolated from multiple reports. (a), Neuroendocrine Neoplasms (NEN). (b), Mucinous Appendiceal Neoplasms (MAN). (c), Goblet Cell Adenocarcinoma (GCA). (d), Colonic Type Adenocarcinoma (CTA). (e), Signet Ring Cell Adenocarcinoma (SRC). Reference data for (a–e) can be found in Supplementary Data S1. Each data point in (a–e) represents a reported gene mutation rate as listed from an individual study.

Germline and somatic mutations in several genes have been implicated in GEP-NEN development [8,54]. For instance, *CDKN1B*, which encodes a cyclin-dependent kinase inhibitor, has been identified as a tumor suppressor gene whose inactivation promotes unchecked cell cycle progression [56]. In addition, genes such as *IPMK*, *MEN1*, *VHL*, *TSC2* and *NF* have been identified as potential germline drivers of intestinal NEN [7,57,58], although their precise roles in appendiceal NEN remain unclear.

Among ileal carcinoids, hemizygous deletion of chromosome 18q is the most frequent chromosomal aberration and is present in 61–74% of cases [8,59]. While similar deletions have been observed in appendiceal NENs, robust evidence is lacking. Genomic susceptibility to pancreatic NENs has been linked to inherited mutations in *MEN1*, *DAXX*, *ATRX*, *VHL*, *NF1*, *EPAS1*, *TSC1*, and *CDKN1B*, with potential relevance to duodenal and gastric NENs as well [8,54]. However, the frequency and impact of these mutations in appendiceal NENs remain largely unknown.

3. Mucinous Neoplasms of the Appendix

Mucinous appendiceal neoplasms (MANs) are known to cause malignant pseudomyxoma peritonei (PMP)—a condition characterized by the excessive production of mucin by neoplastic epithelial cells, resulting in mucin accumulation within the peritoneal cavity [60,61]. In these tumors, mucin may account for over 50% of the acellular tumor volume [4,62,63]. Mucinous appendiceal adenocarcinoma (MAA) is the predominant invasive form of MAN, and a recent analysis of the SEER database encompassing 13,456 patients with pathologically confirmed MAA reported a 5-year mortality rate of 55% [44]. One- and two-year survival rates were 90.5% and 78.5%, respectively [6,31,45,64–70] (Figure 2b).

The most prevalent genetic alterations observed in MAAs are missense mutations in *KRAS*, *GNAS* and *TP53*, with estimated frequencies of 67% (range: 44–100%), 44% (28–69%), and 28% (10–40%), respectively [9,12,32–36,38–40,71–74] (Figure 3b). Notably,

the mutational frequencies of *KRAS* and *GNAS* appear to correlate with tumor grade. In a study analyzing MAA tumors stratified by the AJCC grading system, *KRAS* mutations were present in 61% of G1, 72% of G2, and only 19% of G3 tumors [25]. Analysis of open-source data on 164 MAA tumors generated by an MSK-Impact Trial that followed the WHO classification system [38] showed a similar grade-dependent trend with *KRAS* mutations rates of 88% (G1), 83% (G2), and 53% (G3)—the higher overall frequencies possibly owing to variation in grade classification system or sequencing method. When classified using the Chicago Consensus' grading system, *KRAS* alterations were found in 60% of low-grade and 56% of high-grade PMP cases [74]. In a similar vein, *GNAS* mutations are more prevalent in low-grade MAAs (~70%) as compared to high-grade MAAs (~17%) [3,12,34,75], suggesting a potential role in early tumorigenesis. Furthermore, early-onset MAAs (<50 years) were found to have significantly lower odds of harboring *GNAS* mutations as compared to late-onset cases (19% vs. 29%) [76]. These observations suggest that *RAS* and *GNAS* pathway activation are key oncogenic events in the development of low-grade MAAs in older patients, whereas alternative pathways may predominantly drive early onset and high-grade disease [25,77,78].

TP53 mutations, which are common (~70%) in colorectal cancer (CRC), occur in only ~28% of MAAs overall but are more frequent in high-grade tumors (47%) than low-grade tumors (32%) [72,74]. Inactivating mutations in *SMAD4*, a critical mediator of TGF- β signaling, was found in 24% of high-grade MAAs (G2/G3), and in 0% of low-grade (G1) tumors, further implicating TGF- β pathway deregulation in high-grade disease [79].

Additional genomic alterations have been reported in MAAs including *COX2* expression (61%) and mutations in *PIK3CA* (17%), *SMAD2* (20%), *SMAD3* (20%), *RNF43* (15%), *TGFBR1* (10%) and *TGFBR2* (10%) [3,9,32,35,38–40,70]. High-grade MAAs are more likely to harbor alterations in *RNF43*, *APC*, *TP53*, *SMAD2*, and *SMAD3*, thus highlighting potential molecular distinctions between low- and high-grade disease.

Loss of heterozygosity (LOH)—the loss of one or more functional copies of a particular gene—was found to be a relatively rare phenomenon in MAAs as 76% of cases demonstrated a low fractional mutation rate [79]. However, a high fractional mutation rate, i.e., the occurrence of $\geq 25\%$ mutations at a particular chromosomal locus, was found to occur at chromosomes 18q and 17p in MAAs and with greater frequency in G2 (31%) and G3 (38%) disease as compared to G1 (14%). No grade-related LOH differences were observed at chromosomes 1p, 3p, 5q, 7q, 9q, 9p, 10q [79]. Microsatellite instability (MSI) is a measure of DNA mutation frequency owing to loss of DNA damage repair mechanisms. While associated with pathogenicity in 15% of CRCs, MSI appears to be an infrequent phenomenon (0.9%) among MAAs [5,9,80].

4. Appendiceal Goblet Cell Adenocarcinoma

Goblet cell adenocarcinomas (GCAs) represent approximately 14–19% of primary appendiceal cancers [6,81] (Figure 2a). These tumors exhibit pleiomorphic histologic features, with elements of both epithelial and neuroendocrine differentiation, often arising from goblet cells and infrequently incorporating Paneth cells [74,82,83]. Historically, GCAs have been referred to by several terms, including “mucinous carcinoid,” “mixed crypt cell carcinoma,” and “adenocarcinoid”, which underscores their histologic complexity [52,84–86]. Clinically, GCAs exhibit an intermediate behavior between neuroendocrine neoplasms (NENs) and conventional adenocarcinomas. Average 5-year survival has been reported at approximately 72%, with one- and two-year survival estimates of 92.4% and 88.8%, respectively [43,68,87–93] (Figure 2b).

Genomic studies suggest that GCA harbors a mutational profile distinct from other appendiceal neoplasms. Specifically, *KRAS* (6.9%, range: 0–8.3%), *GNAS* (2.9%, 1–3.8%),

and *APC* (3.8%, 0–11.8%) mutations are far less frequent in GCAs than in MAAs or CTAs [12,35–39,52,55,94–96] (Figure 3c). Instead, recurrent mutations have been observed in *ARID1A* (11.8%), *ARID2* (11.8%), *CDH1* (11.8%), *RHPN2* (11.8%), and *MLL2/KMT2D* (8.8%) [37] (Table 1). Interestingly, the *RHPN2* gene, which encodes a Rho GTPase-binding protein, has been implicated in promoting epithelial-to-mesenchymal transition (EMT) in gliomas through activation of RhoA signaling [97,98], suggesting a similar functional consequence of *RHPN2* mutation in GCAs.

Chromatin remodeling has also emerged as a potential pathogenic mechanism in GCAs. In one study, 4 of 9 cases harbored truncating or splice site mutations in *ARID1A*, *KDM6A*, or *KMT2D*—all major regulators of chromatin structure and gene expression [36]. Additional alterations in *SOX9* (frameshift), *ERBB3* (missense), and *EDNRB* (nonsense) were also reported in the same cohort. Loss of heterozygosity in chromosomes 11q, 16q, and 18q have been reported in up to 25%, 38%, and 56% of GCAs, suggesting that the loss of these chromosomes may drive GCA pathogenesis [99].

Clonality studies comparing “pure” goblet cell carcinoids and adenocarcinoma ex-goblet cell carcinoids (GCAs that are morphologically distorted or present disbursed goblet cell clusters) revealed shared *TCF7L2* mutations, implicating Wnt signaling and confirming a common origin [37,100]. Of note, *BRAF* mutations, which are frequently observed in colorectal and other gastrointestinal cancers, appear to be absent in GCAs [12,92], consistent with a divergence from canonical *RAS/RAF*-driven tumorigenesis.

5. Appendiceal Colonic-Type Adenocarcinoma

Colonic-type adenocarcinomas (CTAs), also known as intestinal-type adenocarcinomas, are non-mucinous adenocarcinomas that share mutational and clinical features with colorectal adenocarcinomas [66]. CTAs frequently arise at the base of the appendix and are often diagnosed incidentally during surgical treatment for acute appendicitis [65]. SEER survival data suggest that CTAs have a 1-year survival rate of 83%, a 2-year survival rate of 61%, and a 5-year survival rate of approximately 61% [3,6,12,25,44,67–69,77,101,102] (Figure 2b). Historically, CTAs were thought to represent a more aggressive subtype compared to mucinous adenocarcinomas (MAAs). However, a retrospective SEER analysis from 1973 to 1988 reported no statistically significant difference in survival between mucinous and non-mucinous appendiceal adenocarcinomas [68,69].

The mutational spectrum of CTAs largely overlaps with that of MAAs, particularly in genes involved in *RAS*/MAPK signaling and tumor suppressor pathways. Common mutations include *KRAS* (average: 54.8%, range: 36.4–75%), *TP53* (43.8%, 18.2–71.4%), and *GNAS* (26%, 13.5–31%) [12,32,38–40,66,103] (Figure 3d). *GNAS* mutations appear more frequently in late-onset than in early-onset disease [76], though the clinical implications of this distinction remain to be elucidated.

Mutations in the *RAS*/*RAF* signaling pathway, including *BRAF*, *HRAS*, *KRAS*, and *NRAS*, are observed in up to 60% of CTAs [12]. These findings highlight the central role of MAPK/ERK signaling in CTA tumorigenesis. By contrast, alterations in the *PI3K/AKT* pathway are comparatively rare in CTAs and MAAs (~9% and 8%, respectively), suggesting a relatively minor contribution of this pathway to CTA pathobiology [3,9,32,35,38–40,70,95]. Other commonly mutated genes in CTAs include *SMAD4* and *APC*, indicating potential involvement of the TGF- β and Wnt signaling pathways, respectively [12,39].

CTA microsatellite instability rates have been reported to more closely match that of CRC, with up to 18% of CTAs presenting with high MSI. MSI-high status may be dependent on CTA differentiation, as half of poorly differentiated CTAs, and no well- or moderately differentiated CTAs, were MSI-high [80]. Similar to CRC, the loss of chromosome 18q—a region harboring tumor suppressors *SMAD2*, *SMAD4*, and *DCC*—is frequently observed

in CTAs and has been associated with poor prognosis in colorectal cancers [104,105]. In one study, 5 of 8 CTAs and 7 of 13 MAAs exhibited 18q deletions, implicating this event in the pathogenesis of both subtypes [104].

6. Appendiceal Signet Ring Cell Adenocarcinoma

Signet ring cell adenocarcinoma (SRC) is the rarest and most lethal histologic subtype of appendiceal cancer, which comprises approximately 2% of all AC cases [5,68,89] (Figure 2a). SRC is characterized by its distinctive cell morphology: poorly cohesive malignant cells with intracellular mucin displacing the nucleus, yielding a “signet ring” appearance [106]. True SRCs exhibit a diffuse cord-like infiltrative growth pattern with minimal gland formation and often overlap histologically with poorly differentiated mucinous adenocarcinomas [6,19,107]. SRCs carry the worst prognosis among appendiceal cancers. SEER-based survival analyses have demonstrated a 1-year survival rate of 85%, a 2-year rate of 66%, and markedly diminished 5-year survival rate of 21% [3,6,12,24,67–69,77,101,102] (Figure 2b).

Given the rare and deadly nature of SRC, molecular and genomic characterization studies have remained limited [7,107]. As extrapolated from multiple reports, the most frequently mutated genes are *TP53* (average: 34.2%, range = 15.4–43%) and *SMAD4* (20.5%, range = 11–30%), both with mutation rates similar to that observed in CTAs [12,32,39,40,108] (Figure 3e). Unlike MAAs or CTAs, SRCs exhibit lower frequencies of *KRAS* mutation (average: 19%, range = 7–35%) [12,32,39,40]. This low occurrence of RAS pathway activation may reflect a divergent oncogenic mechanism in SRC as compared to other adenocarcinomas of the appendix. Other mutations frequently observed in high-grade appendiceal tumors, such as those affecting *APC* or *PIK3CA*, have not been consistently reported in SRCs, which may owe to the low incidence of this subtype and limited genomic sampling. In a small study of twenty-three appendiceal SRC cases, none presented high MSI [80].

7. Molecular Divergence Between Appendiceal and Colorectal Cancers

While AC and CRC share anatomic origins within the gastrointestinal tract, accumulating evidence suggests that they are molecularly distinct entities. This distinction can be observed in the differential mutational profiles of several canonical oncogenic driver genes, particularly those within the *TP53*, *APC*, *KRAS*, *GNAS*, *SMAD4*, *BRAF*, and *PIK3CA* signaling axes [109,110]. A 2020 report comparing 193 appendiceal adenocarcinoma (AA) patients to 2860 CRC patients [9] identified comparable rates of mutation in *SMAD4* (16.9% vs. 13.6%), with AA presenting higher rates of *GNAS* (28% vs. 2%) mutation and lower rates of *TP53* (27% vs. 68%) and *APC* (9% vs. 55%) compared to CRC. Notably, the authors reported that AA ctDNA sensitivity was significantly lower in AA (particularly low grade AA) relative to CRC (e.g., reduced detection of *TP53* variants), suggesting ctDNA’s clinical utility may be limited to only high-grade AA patients.

In CRC, mutations in *TP53* and *APC* are hallmark features of the disease that occur at frequencies approaching 70% for both genes [107,111,112]. However, these genes are mutated at significantly lower frequencies across most subtypes of AC. In mucinous adenocarcinomas (MAAs), *TP53* mutations are detected in approximately 28% of cases overall, with enrichment in high-grade tumors (47%) relative to low-grade tumors (32%) [72,74]. Similarly, *APC* mutations are relatively infrequent across AC subtypes, with reported rates of 12.2% in ANENs [30,35,40], 3.8% in goblet cell adenocarcinoma (GCA) [12,35,37–39,52,77], 8.0% in MAAs [9,12,32,34,35,38–40,71], and 6.4% of SRCs [12,32,40]. CTAs demonstrate moderately higher *APC* mutation rates with an average mutational frequency of 15.5% [12,32,36,38,40,95]. In sum, these rates fall short of the rates

observed in CRC, consistent with a fundamental divergence in oncogenic Wnt signaling between the two tumor types [9,113].

Another point of divergence lies in the *GNAS* gene, which is rarely mutated in CRC [111] but is among the most frequently altered genes in appendiceal mucinous tumors. Mutations in *GNAS* occur in ~44% of MAAs overall [72] and are particularly prevalent in low-grade disease (up to 70%) [3,12,34,75]. Known oncogenic driving mutations of *GNAS* include R201C/H gain-of-function mutations, which have been implicated in the oncogenesis of gastrointestinal and pancreatic tumors [113,114]. This contrast suggests a prominent role for the Gs α -cAMP-PKA and mucin signaling pathways in appendiceal tumorigenesis that is not shared with CRC.

KRAS mutations, on the other hand, are observed in both appendiceal and colorectal tumors, but with a more nuanced profile. In CRC, *KRAS* mutations are present in 40–50% of cases [111,115], while in appendiceal tumors, *KRAS* mutation rates are comparable or even higher in some subtypes. *KRAS* mutation rates have been observed in up to 67% of MAAs [9,12] and 55% of CTAs [12,32] but are notably infrequent in GCAs (~7%) [12] and SRCs (~19%) [12]. While oncogenic *KRAS* signaling has a role in the pathobiology of both cancer types, subtype-specific differences underscore the molecular heterogeneity of AC.

SMAD4, a tumor suppressor in the TGF- β pathway, is altered in approximately 14% of CRCs [111,115]. In AC, *SMAD4* mutations are reported at similar or higher frequencies in certain high-grade subtypes, including 20.5% in SRC [12,32,39,40] and 24% in high-grade MAAs [79]. However, this mutation is rarely observed in low-grade AC, suggesting a functional association with more aggressive cancers.

Mutations in *PIK3CA*, which occur in 18–20% of CRCs [13] are comparatively infrequent in AC, with reported rates of 17% in MAAs [3,32] and even lower in CTAs and other subtypes [38,39]. Similarly, *BRAF* mutations, which are present in approximately 10% of CRCs and associated with poor prognosis, are rarely observed in AC tumors at rates as low as 3% [116]. Despite the rarity of *BRAF* mutations in AC, *BRAF* V600E-targeted inhibition has demonstrated disease control rates of 80% [116]. Microsatellite instability (MSI) is observed in approximately 15% of CRCs [107,112,117] and is often used as a biomarker for immunotherapy response. However, MSI is exceedingly rare in AC and has been documented in less than 1% of MAAs [80,96], suggesting fundamental differences in DNA repair activity between the two cancer types.

Transcriptomic variation between AA and CRC has also been observed. In a microarray profiling study of AC ($n = 26$) and CRC ($n = 15$), unsupervised hierarchical cluster analysis demonstrated that global gene expression could significantly differentiate AA and CRC cases [118]. Three principal tumor clusters were identified, two of which were comprised predominantly of AA cases (with several CRC tumors co-clustering with AA), and the other comprised mostly of CRC cases (with one AA tumor co-clustering with CRC). The co-clustering samples were not studied further, but could reflect rare convergent transcription events related to tumor heterogeneity. In addition, the three tumor clusters were shown to vary by survival, with the CRC-predominant cluster exhibiting the worst prognosis.

Together, these data reinforce the notion that AC, despite sharing a gross anatomical origin with CRC, arises from distinct molecular pathways of tumorigenesis. The low prevalence of *APC* and *TP53* mutations, the rarity of *BRAF* alterations, and the predominance of *GNAS* mutations together argue against the classification of AC as an anatomical variant of CRC. Rather, AC should be viewed as a biologically distinct cancer with subtype-specific genomic alterations that require further investigation to help inform the development of tailored therapeutic strategies.

8. Mutated Genes with Potential Clinical Actionability in AC

Identifying clinically actionable mutations in AC remains a challenge given its rarity and histologic heterogeneity, plus the limited availability of genome-wide sequencing data [118–123]. However, a number of genetic alterations have emerged as potential therapeutic targets in AC.

KRAS mutations are among the most common across AC subtypes and represent a promising yet difficult target. *KRAS* is a well-established oncogene in many solid tumors, but the development of inhibitors has been hampered by the protein's structure, mainly due to a lack of accessible binding sites on RAS-associated proteins [124]. Drugs specifically designed to target the *KRAS* G12C mutation, such as Sotorasib and Adagrasib, inhibit oncogenic *KRAS* signaling and have demonstrated response rates of 33–43% in metastatic CRC [125]. Analysis of the Foote et al. data set (via cBioPortal: https://www.cbioportal.org/study/summary?id=appendiceal_msk_2022 accessed on 9 September 2025) identified *KRAS* G12C mutations in 6.1% of MAAs ($n = 10/164$), suggesting a small but potentially targetable patient population [38]. *KRAS* G12C mutations are of clinical interest because this mutation is targeted by clinically efficacious inhibitors such as Sotorasib, which holds promise for this minority of AC patients. No G12C mutations were found in GCAs ($n = 0/72$) or CTAs ($n = 0/37$). For tumors harboring these and other *KRAS* mutations, multiple targeted approaches are in development, including *KRAS* G12D inhibitors (e.g., Zoldonrasib) and pan-*KRAS* inhibitors (e.g., Daraxonrasib), which have shown promising results in pre-clinical models and early clinical trials [126,127].

Currently, for other *KRAS* variants, targeting downstream of *KRAS* in the MEK-ERK or PI3K/AKT pathways may prove more efficacious [34,78]. An analysis of 78 appendiceal colonic type adenocarcinomas found that ~5% of cases exhibited one or more potentially druggable targetable mutations in *ALK*, *EGFR*, *MET*, *IDH1* and *ERBB2*—all of which intersect the RAS/RAF signaling cascade [71].

Another emerging target is *PIK3CA*, which encodes the catalytic subunit of PI3K. Although *PIK3CA* mutations are relatively infrequent in AC, FDA-approved inhibitors such as alpelisib, which has been used successfully in *PIK3CA*-mutated breast cancer, may be an effective treatment approach for a subset of AC patients, such as MAAs [128,129].

9. New Technologies for Understanding AC Pathophysiology and Therapeutic Response

Recent advances in single-cell profiling are beginning to illuminate the biology of appendiceal cancer (AC), though relevant models remain limited [12,25]. In a recent study comparing low- and high-grade mucinous neoplasms (MANs) with matched normal tissue, defining goblet cell-like features predominated adenocarcinomas not otherwise pathologically defined as GCAs, suggesting a pervasive goblet cell, or goblet cell-precursor lineage among MANs [130]. Prospective analyses of the intersection between AC histology and cellular-genomic architecture using modern spatial single-cell transcriptomics and epigenomic technologies will further clarify cell-of-origin, and link cellular organization and pathobiology to patient outcomes.

Modeling AC remains challenging due to the low cellularity of mucin-rich tumors and the absence of a defined precancerous lesion [12,24]. Patient-derived tumor organoids (PTOs) have emerged as promising pre-clinical models that are robust to low cellularity and the mucinous phenotype, enabling ex vivo modeling of AC pathophysiology and drug responsiveness, and demonstrating prognostic power for predicting patient clinical benefit [129,131]. Notably, comparable predictive accuracy has also been reported in colorectal cancer PTOs [132,133], underscoring their utility across gastrointestinal tumor types. Through integration of PTO models with genomic and transcriptomic profiling,

researchers may be able to identify patient subsets predictive of a range of therapeutic and surgical outcomes, including those most likely to benefit from cytoreductive surgery and/or HIPEC [21,122,123,129,131]. The establishment of advanced pre-clinical models represents a critical step toward precision oncology in AC, offering functional evidence to guide treatment selection in a setting where therapeutic options remain empiric and outcomes variable.

10. Discussion

A comprehensive understanding of the genetic underpinnings of appendiceal cancer across its histological subtypes is essential for improving diagnostic precision, prognostication, and therapeutic decision-making. This review highlights key mutational differences across the five major histologic subtypes of AC, which provides new insights into their heterogeneity, relevance in disease progression, and potential clinical actionability.

KRAS and *GNAS* mutations are characteristic of low-grade appendiceal cancers and are generally associated with more indolent clinical behavior [12,25,77,78]. By contrast, high-grade subtypes such as CTAs, SRCs and high-grade MAAs exhibit frequent mutations in *TP53*, *APC*, and *SMAD* gene family members, reflecting their involvement in more aggressive AC tumor phenotypes.

Among AC subtypes, *TP53* mutations are most prevalent in CTAs (~44%) and SRCs (~34%), followed by MAAs (~28%), with the lowest frequency observed in neuroendocrine neoplasms (NENs, ~23%) and goblet cell adenocarcinomas (GCAs, ~21%). Similarly, *APC* mutations are enriched in high-grade CTAs, SRCs, and MAAs—reminiscent of the mutational spectrum of colorectal cancer and indicative of a shared dependency on Wnt pathway activation in these more lethal subtypes [25,134]. Components of the TGF- β signaling pathway, *SMAD2*, *SMAD3* and *SMAD4*, are also frequently altered in high-grade MAAs thereby linking this pathway to MAA disease progression and metastatic potential.

At present, the strongest independent predictors of survival outcome in AC remain the traditional clinicopathologic factors: histologic subtype, tumor grade, extent of disease at diagnosis, performance status, and completeness of surgical cytoreduction. The attendant comorbidity associated with CRS/HIPEC for the management of disseminated AC tumors emphasizes the value of prognostic genetic signatures in the diagnostic setting, particularly for the delineation of HIPEC eligibility [122,123]. An example where genomic insights can provide practice-guiding information is in AC patients that would be traditionally excluded from receiving post-operative HIPEC due to overwhelming tumor burden in the peritoneal cavity prior to cytoreductive surgery. Despite clinical experience associating tumor burden with refractory disease, pre-operative genomic profiling can shed insight on the molecular programming associated with favorable HIPEC response independent of pre-operative tumor burden, in turn increasing the eligibility pool to receive curative CRS/HIPEC rather than palliative systemic chemotherapy.

Building on these molecular insights, recent work by Foote et al. [38] showed that co-occurring mutations in *RAS*, *GNAS*, and *TP53* could be used to classify appendiceal adenocarcinomas into molecular subtypes with distinct clinical trajectories. Specifically, *RAS*-mutant/*GNAS*-wildtype/*TP53*-wildtype tumors defined a genomically quiet, clinically indolent subtype with minimal stromal invasion and exceptional survival outcomes that persisted in the metastatic setting. Tumor clonality analyses revealed that *RAS* mutations tend to occur early in tumor evolution, preceding the acquisition of *TP53* or *GNAS* mutations. This temporal ordering suggests that *RAS*-mutant tumors are molecularly young, a feature that may underlie their favorable prognosis. In contrast, *TP53*-mutant tumors exhibited high aneuploidy, destructive stromal invasion and poor survival, while *GNAS*-mutant tumors showed chemoresistance and elevated peritoneal tumor burden. No-

tably, these molecular subtypes retained prognostic significance independent of histologic grade and subtype, thus demonstrating the clinical utility of integrated genomic profiling in AC.

In current practice, diagnostic targeted gene sequencing panels offer the convenience of cheap cost production at scale, and have enabled the relatively quick turnaround on AC genomic assessment. However, the comprehensive molecular characterization of appendiceal cancers, at the level needed to reveal meaningful new insights, will require greater oncogenic granularity such as that afforded by whole-exome and full-genome sequencing strategies. Another limitation, and one that no doubt impacts the accuracy of the data synthesized in this review, is study-to-study variation in sample collection procedures, quality control practices, sequencing methods used, and cohort size—all factors that contribute to inherent study bias. For the effective characterization of AC and its histologic variants, standard clinical and analytical protocols must be developed and implemented.

As molecular insights into appendiceal cancer continue to evolve, these findings collectively support a shift beyond histopathologic classification and toward a molecularly informed framework for appendiceal cancer—one that enhances our understanding of AC biology and directs mechanistic studies to elucidate how recurrent mutations shape tumor evolution, clinical behavior, and therapeutic vulnerability.

11. Conclusions

Preliminary efforts to implement gene-panel profiling in AC have yielded promising results [118,123,135], but large-scale, subtype-specific genomic studies remain critically needed. The prioritization of deep sequencing technologies, such as whole-exome sequencing, whole-genome sequencing and single-cell analysis, will be paramount for prospective AC research. Such approaches will shed light not only on the full mutational spectrum, but also on the chromosomal and copy number changes that underlie the etiology of AC and allow new insight into the AC tumor microenvironment. Equally important will be the development of physiologically relevant models, including patient-derived organoids [136] and xenografts [137] that can recapitulate AC biology and support mechanistic studies. Ultimately, through the delineation of subtype-specific molecular drivers, the field is poised to usher in a new era of precision oncology for appendiceal cancer, where therapeutic interventions are tailored to the unique genetic profiles of individual tumors.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cancers17193275/s1>, Table S1: Associated gene mutation frequency data and corresponding references by subtype. Data S1: Excel file containing pertinent survival and mutation data for Figures 2b and 3a–e.

Author Contributions: Conceptualization, D.J.G. and L.D.M.; methodology and data curation, D.J.G.; writing—original draft preparation, D.J.G.; writing—review and editing, L.D.M., R.A.E., S.D.F., A.K.P., R.Z.-P., K.A.C., S.S., X.G., E.A.L. and K.I.V.; figure generation, D.J.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Cancer Institute (NCI), National Institutes of Health (NIH), USA, grant numbers R01CA258692 (to L.D.M.) and R01CA249087 (to K.I.V.).

Data Availability Statement: This is a systematic review; no new data were created.

Acknowledgments: The authors would like to thank William H. Gmeiner for his feedback on the manuscript during the drafting process.

Conflicts of Interest: The authors declare no conflicts of interest regarding the information contained within this manuscript.

Abbreviations

The following abbreviations are used in this manuscript:

AC	Appendix Cancer
CRC	Colorectal Cancer
WES	Whole-Exome Sequencing
NGS	Next-Generation Sequencing
KRAS	Kirsten Rat Sarcoma viral oncogene homolog
GNAS	Guanine Nucleotide-binding protein, Alpha Stimulating
TP53	Tumor Protein 53

References

1. Carr, N.J.; McCarthy, W.F.; Sobin, L.H. Epithelial Noncarcinoid Tumors and Tumor-Like Lesions of the Appendix: A Clinicopathologic Study of 184 Patients with a Multivariate Analysis of Prognostic Factors. *Cancer* **1995**, *75*, 757–768. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Polydorides, A.D.; Wen, X. Clinicopathologic parameters and outcomes of mucinous neoplasms confined to the appendix: A benign entity with excellent prognosis. *Mod. Pathol.* **2022**, *35*, 1732–1739. [\[CrossRef\]](#)
3. Raghav, K.P.S.; Shetty, A.V.; Kazmi, S.M.A.; Zhang, N.; Morris, J.; Taggart, M.; Fournier, K.; Royal, R.; Mansfield, P.; Eng, C.; et al. Impact of Molecular Alterations and Targeted Therapy in Appendiceal Adenocarcinomas. *Oncologist* **2013**, *18*, 1270–1277. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Hoehn, R.; Rieser, C.; Choudry, M.; Melnitchouk, N.; Hechtman, J.; Bahary, N. Current Management of Appendiceal Neoplasms. *Am. Soc. Clin. Oncol. Educ. Book* **2021**, *41*, 118–132. [\[CrossRef\]](#)
5. Shaib, W.L.; Goodman, M.; Chen, Z.; Kim, S.; Brucher, E.; Bekaii-Saab, T.; El-Rayes, B.F. Incidence and Survival of Appendiceal Mucinous Neoplasms: A SEER Analysis. *Am. J. Clin. Oncol.* **2017**, *40*, 569–573. [\[CrossRef\]](#)
6. Turaga, K.K.; Pappas, S.G.; Gamblin, T.C. Importance of Histologic Subtype in the Staging of Appendiceal Tumors. *Ann. Surg. Oncol.* **2012**, *19*, 1379–1385. [\[CrossRef\]](#)
7. Carr, N.J. Updates in Appendix Pathology. *Surg. Pathol. Clin.* **2020**, *13*, 469–484. [\[CrossRef\]](#)
8. Crona, J.; Skogseid, B. GEP-NETS Update: Genetics of Neuroendocrine Tumors. *Eur. Soc. Endocrinol.* **2016**, *174*, 275–290. [\[CrossRef\]](#)
9. Raghav, K.P.S.; Shen, J.; Jácome, A.A.; Guerra, J.L.; Scally, C.P.; Taggart, M.W.; Foo, W.C.; Matamoros, A.; Shaw, K.R.; Fournier, K. Integrated Clinico-Molecular Profiling of Appendiceal Adenocarcinoma Reveals a Unique Grade-Driven Entity Distinct from Colorectal Cancer. *Br. J. Cancer* **2020**, *123*, 1262–1270. [\[CrossRef\]](#)
10. Levine, E.A.; Votonopolous, K.I.; Shen, P.; Russell, G.; Fenstermaker, J.; Mansfield, P.; Bartlett, D.; Stewart, J.H. A Multicenter Randomized Trial to Evaluate Toxicities After Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin or Mitomycin in Patients with Appendiceal Tumors. *J. Am. Coll. Surg.* **2018**, *226*, 434–443. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Nitecki, S.S.; Wolff, B.G.; Schlinkert, R.; Sarr, M.G. The Natural History of Treated Primary Adenocarcinoma of the Appendix. *Ann. Surg.* **1994**, *219*, 51–57. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Ang, C.; Shen, J.; Hardy-Abeloos, C.; Huang, J.; Ross, J.; Miller, V.; Jacobs, M.; Chen, I.; Xu, D.; Ali, S.; et al. Genomic Landscape of Appendiceal Neoplasms. *JCO Precis. Oncol.* **2018**, *8*, 1–18. [\[CrossRef\]](#)
13. Sugarbaker, P.H. New Standard of Care for Appendiceal Epithelial Neoplasms and Pseudomyxoma Peritonei Syndrome? *Lancet Oncol.* **2006**, *7*, 69–76. [\[CrossRef\]](#)
14. Gupta, S.; Parsa, V.; Adsay, V.; Heilbrun, L.K.; Smith, D.; Shields, A.F.; Weaver, D.; Phillip, P.A.; El-Rayes, B.F. Clinicopathological Analysis of Primary Epithelial Appendiceal Neoplasms. *Med. Oncol.* **2009**, *27*, 1073–1078. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Ruoff, C.; Hanna, L.; Zhi, W.; Shahzad, G.; Gotlieb, V.; Saif, M. Cancers of the Appendix: Review of the Literatures. *ISRN Oncol.* **2011**, *2011*, 728579. [\[CrossRef\]](#)
16. Xie, X.; Zhou, Z.; Song, Y.; Li, W.; Diao, D.; Dang, C.; Zhang, H. The Management and Prognostic Prediction of Adenocarcinoma of Appendix. *Sci. Rep.* **2016**, *6*, 39027. [\[CrossRef\]](#)
17. Connor, S.J.; Hanna, G.B.; Frizelle, F.A. Appendiceal Tumors: Retrospective Clinicopathologic Analysis of Appendiceal Tumors from 7,970 appendectomies. *Dis. Colon Rectum* **1998**, *41*, 75–80. [\[CrossRef\]](#)
18. Schumpelick, V.; Dreuw, B.; Ophoff, K.; Prescher, A. Appendix and cecum. Embryology, anatomy, and surgical applications. *Surg. Clin. N. Am.* **2000**, *80*, 295–318. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Leonards, L.; Pahwa, A.; Patel, M.; Petersen, J.; Nguyen, M.; Jude, C. Neoplasms of the Appendix: Pictorial Review with Clinical and Pathological Correlation. *Radiographics* **2017**, *37*, 1059–1083. [\[CrossRef\]](#)

20. Kusamura, S.; Barretta, F.; Yonemura, Y.; Sugarbaker, P.H.; Moran, B.J.; Levine, E.A.; Goere, D.; Baratti, D.; Nizri, E.; Morris, D.L.; et al. The Role of Hyperthermic Intraperitoneal Chemotherapy in Pseudomyxoma Peritonei After Cytoreductive Surgery. *JAMA Surg.* **2021**, *156*, e206363. [\[CrossRef\]](#)
21. Cashin, P.; Sugarbaker, P.H. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Colorectal and Appendiceal Peritoneal Metastases: Lessons Learned from PRODIGE 7. *J. Gastrointest. Oncol.* **2021**, *12* (Suppl. 1), S120–S128. [\[CrossRef\]](#)
22. Valasek, M.A.; Pai, R.K. An Update on the Diagnosis, Grading, and Staging of Appendiceal Mucinous Neoplasms. *Adv. Anat. Pathol.* **2018**, *25*, 38–60. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Gündoğar, Ö.; Kınıloğlu, E.; Komut, N.; Cin, M.; Bektaş, S.; Gönüllü, D.; İlgün, A.S.; Erdoğan, N. Evaluation of Appendiceal Mucinous Neoplasms with a New Classification System and Literature Review. *Turk. J. Gastroenterol.* **2018**, *29*, 533–542. [\[CrossRef\]](#)
24. Bradley, R.F.; Stewart, J.H., IV; Russel, G.B.; Levine, E.A.; Geisinger, K.R. Pseudomyxoma Peritonei of Appendiceal Origin: A Clinicopathologic Analysis of 101 Patients Uniformly Treated at a Single Institution, with Literature Review. *Am. J. Surg. Pathol.* **2006**, *30*, 551–559. [\[CrossRef\]](#)
25. Davison, J.M.; Choudry, H.A.; Pingpank, J.F.; Ahrendt, S.A.; Holtzman, M.P.; Zureikat, A.H.; Zeh, H.J.; Ramalingam, L.; Zhu, B.; Nikiforova, M.; et al. Clinicopathologic and Molecular Analysis of Disseminated Appendiceal Mucinous Neoplasms: Identification of Factors Predicting Survival and Proposed Criteria for a Three-Tiered Assessment of Tumor Grade. *Mod. Pathol.* **2014**, *27*, 1521–1539. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Chicago Consensus Working Group. The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms. *Cancer* **2020**, *126*, 2525–2533. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Misdraji, J. Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. *Mod. Pathol.* **2014**, *28* (Suppl. 1), S67–S79. [\[CrossRef\]](#)
28. Cortés-Guiral, D.; Hübner, M.; Alyami, M.; Bhatt, A.; Ceelen, W.; Glehen, O.; Lordick, F.; Ramsay, R.; Sgarbura, O.; Van Der Speeten, K.; et al. Primary and Metastatic Peritoneal Surface Malignancies. *Nat. Rev. Dis. Primers* **2021**, *7*, 91. [\[CrossRef\]](#)
29. Legué, L.M.; Creemers, G.-J.; de Hingh, I.H.J.T.; Lemmens, V.E.P.P.; Huysentruyt, C.J. Review: Pathology and Its Clinical Relevance of Mucinous Appendiceal Neoplasms and Pseudomyxoma Peritonei. *Clin. Color. Cancer* **2019**, *18*, 1–7. [\[CrossRef\]](#)
30. Park, H.Y.; Kwon, M.J.-K.; Ho, S.K.; Kim, Y.J.; Kim, N.Y.; Kim, M.J.; Min, K.-W.; Choi, K.C.; Nam, E.S.; Cho, S.J.; et al. Targeted Next-Generation Sequencing of Well-Differentiated Rectal, Gastric, and Appendiceal Neuroendocrine Tumors to Identify Potential Targets. *Hum. Pathol.* **2019**, *87*, 83–94. [\[CrossRef\]](#)
31. Yanai, Y.; Saito, T.; Hayashi, T.; Akazawa, Y.; Yatagai, N.; Tsuyama, S.; Tomita, S.; Hirai, S.; Ogura, K.; Matsumoto, T.; et al. Molecular and clinicopathological features of appendiceal mucinous neoplasms. *Virchows Arch. Int. J. Pathol.* **2021**, *478*, 413–426. [\[CrossRef\]](#)
32. Tokunaga, R.; Xiu, J.; Johnston, C.; Goldberg, R.M.; Philip, P.A.; Seeber, A.; Naseem, M.; Lo, J.H.; Arai, H.; Battaglin, F.; et al. Molecular Profiling of Appendiceal Adenocarcinoma and Comparison with Right-Sided and Left-Sided Colorectal Cancer. *Transl. Cancer Mech. Ther.* **2019**, *25*, 3096–3103. [\[CrossRef\]](#)
33. Munari, G.; Businello, G.; Mattiolo, P.; Pennelli, G.; Sbaraglia, M.; Borga, C.; Pucciarelli, S.; Spolverato, G.; Mescoli, C.; Galuppini, F.; et al. Molecular Profiling of Appendiceal Serrated Lesions, Polyps and Mucinous Neoplasms: A Single-Centre Experience. *J. Cancer Res. Clin. Oncol.* **2021**, *147*, 1897–1904. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Alakus, H.; Babicky, M.L.; Ghosh, P.; Yost, S.; Jepsen, K.; Dai, Y.; Arias, A.; Samuels, M.L.; Mose, E.S.; Schwab, R.B.; et al. Genome-Wide Mutational Landscape of Mucinous Carcinomatosis Peritonei of Appendiceal Origin. *Genome Med.* **2014**, *6*, 43. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Arai, H.; Baca, Y.; Battaglin, F.; Kawanishi, N.; Wang, J.; Soni, S.; Zhang, W.; Millsteain, J.; Johnston, C.; Goldberg, R.M.; et al. Molecular Characterization of Appendiceal Goblet Cell Carcinoid. *Mol. Cancer Ther.* **2020**, *19*, 2634–2640. [\[CrossRef\]](#)
36. Wen, K.W.; Grenert, J.P.; Joseph, N.M.; Shafizadeh, N.; Huang, A.; Hosseini, M.; Kakar, S. Genomic Profile of Appendiceal Goblet Cell Carcinoid is Distinct Compared to Appendiceal Neuroendocrine Tumor and Conventional Adenocarcinoma. *Hum. Pathol.* **2017**, *77*, 164–174. [\[CrossRef\]](#)
37. Johncilla, M.; Stachler, M.; Misdraji, J.; Lisovsky, M.; Yozu, M.; Lindeman, N.; Lauwers, G.Y.; Odze, R.D.; Srivastava, A. Mutational Landscape of Goblet Cell Carcinoids and Adenocarcinoma Ex Goblet Cell Carcinoids of the Appendix is Distinct from Typical Carcinoids and Colorectal Adenocarcinomas. *Mod. Pathol.* **2018**, *31*, 989–996. [\[CrossRef\]](#)
38. Foote, M.B.; Walch, H.; Chatila, W.; Vakiani, E.; Chandler, C.; Steinrucke, F.; Nash, G.M.; Stadler, Z.; Chung, S.; Yaeger, R.; et al. Molecular Classification of Appendiceal Adenocarcinoma. *J. Clin. Oncol.* **2023**, *41*, 1553–1564. [\[CrossRef\]](#) [\[PubMed\]](#)
39. The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine through an International Consortium. *Cancer Discov.* **2017**, *7*, 818–831. [\[CrossRef\]](#)
40. Borazanci, E.; Millis, S.Z.; Kimbrough, J.; Doll Von Hoff, D.; Ramanathan, R.K. Potential Actionable Targets in Appendiceal Cancer Detected by Immunohistochemistry, Fluorescent In Situ Hybridization, and Mutational Analysis. *J. Gastrointest. Oncol.* **2017**, *8*, 164–172. [\[CrossRef\]](#)

41. Mafficini, A.; Scarpa, A. Genetics and Epigenetics of Gastroenteropancreatic Neuroendocrine Neoplasms. *Endocr. Rev.* **2019**, *40*, 506–536. [\[CrossRef\]](#)
42. Das, S.; Dasari, A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? *Curr. Oncol. Rep.* **2021**, *23*, 43. [\[CrossRef\]](#)
43. Van de Moorele, M.; De Hertogh, M.; Sagaert, X.; Van Cutsem, E. Appendiceal Cancer: A Review of the Literature. *Acta Gastro-Enterologica Belg.* **2020**, *83*, 441–448.
44. Wang, D.; Ge, H.; Lu, Y.; Gong, X. Incidence trends and survival analysis of appendiceal tumors in the United States: Primarily changes in appendiceal neuroendocrine tumors. *PLoS ONE* **2023**, *18*, e0294153. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Onyempka Davis, A.; McLeod, M.; Oysaiji, T. Typical carcinoids, goblet cell carcinoids, mixed adenoneuroendocrine carcinomas, neuroendocrine carcinomas and adenocarcinomas of the appendix: A comparative analysis of survival profile and predictors. *J. Gastrointest. Oncol.* **2019**, *10*, 300–306. [\[CrossRef\]](#)
46. Griniatsos, J.; Michail, O. Appendiceal Neuroendocrine Tumors: Recent Insights and Clinical Implications. *World J. Gastrointest. Oncol.* **2010**, *2*, 192–196. [\[CrossRef\]](#)
47. Deschamps, L.; Couvelard, A. Endocrine Tumors of the Appendix: A Pathologic Review. *Arch. Pathol. Lab. Med.* **2010**, *134*, 871–875. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Volante, M.; Grillo, F.; Massa, F.; Maletta, F.; Mastracci, L.; Campora, M.; Ferro, J.; Vanoli, A.; Papotti, M. Neuroendocrine Neoplasms of the Appendix, Colon and Rectum. *Pathologica* **2021**, *113*, 19–27. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Twito, O.; Paran, H.; Avital, S.; Kravtsov, V.; Rosenblum, R.C.; Rotman-Pikielny, P.; Klein, N. Temporal Trends in Incidence, Evaluation and Management of Neuroendocrine Neoplasms of the Appendix: 14 Years' Experience. *Am. J. Surg.* **2021**, *221*, 1000–1004. [\[CrossRef\]](#)
50. Moris, D.; Tsilimigras, D.I.; Vagios, S.; Ntanasis-Stathopoulos, I.; Karachaliou, G.-S.; Papalampros, A.; Alexandrou, A.; Blazer, D.G., III; Felekouras, E. Neuroendocrine Neoplasms of the Appendix: A Review of the Literature. *Anticancer Res.* **2018**, *38*, 601–611.
51. Nadler, A.; Cukier, M.; Rowsell, C.; Kamali, S.; Feinberg, Y.; Singh, S.; Lawm, C.H.L. Ki-67 is a reliable pathological grading marker for neuroendocrine tumors. *Virchows Arch. Int. J. Pathol.* **2013**, *462*, 501–505. [\[CrossRef\]](#)
52. Taggart, M.W.; Abraham, S.C.; Overman, M.J.; Mansfield, P.F.; Rashid, A. Goblet Cell Carcinoid Tumor, Mixed Goblet Cell Carcinoid-Adenocarcinoma, and Adenocarcinoma of the Appendix: Comparison of Clinicopathologic Features and Prognosis. *Arch. Pathol. Lab. Med.* **2015**, *139*, 782–790. [\[CrossRef\]](#)
53. Popa, O.; Taban, S.M.; Pantea, S.; Ploeanu, A.D.; Barna, R.A.; Cornianu, M.; Pascu, A.-A.; Dema, A.L.C. The New WHO Classification of Gastrointestinal Neuroendocrine Tumors and Immunohistochemical Expression of Somatostatin Receptor 2 and 5. *Exp. Ther. Med.* **2021**, *22*, 1179. [\[CrossRef\]](#)
54. van Riet, J.; van de Werken, A.J.G.; Cuppen, E.; Eskens, F.A.L.M.; Tesselaar, M.; van Veenendaal, L.M.; Klümper, H.-J.; Dercksen, M.W.; Valk, G.D.; Lolkema, M.P.; et al. The genomic landscape of 85 advanced neuroendocrine neoplasms reveals subtype-heterogeneity and potential therapeutic targets. *Nat. Commun.* **2021**, *12*, 4612. [\[CrossRef\]](#)
55. Ramnani, D.M.; Wistuba, I.I.; Behrens, C.; Gazdar, A.F.; Sobin, L.H.; Albores-Saavedra, J. K-Ras and p53 Mutations in the Pathogenesis of Classical and Goblet Cell Carcinoids of the Appendix. *Cancer* **2000**, *86*, 14–21. [\[CrossRef\]](#)
56. Polyak, K.; Lee, M.H.; Erdjument-Bromage, H.; Koff, A.; Roberts, J.M.; Tempst, P.; Massagué, J. Cloning of p27Kip1, a Cyclin-Dependent Kinase Inhibitor and a Potential Mediator of Extracellular Antimitogenic Signals. *Cell* **1994**, *78*, 59–66. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Carpizo, D.R.; Harris, C.R. Genetic Drivers of Ileal Neuroendocrine Tumors. *Cancers* **2021**, *13*, 5070. [\[CrossRef\]](#) [\[PubMed\]](#)
58. Öberg, K. The Genetics of Neuroendocrine Tumors. *Semin. Oncol.* **2013**, *40*, 37–44. [\[CrossRef\]](#)
59. Cunningham, J.L.; de Ståhl, T.D.; Sjöblom, T.; Westin, G.; Dumanski, J.P.; Janson, E.T. Common pathogenetic mechanism involving human chromosome 18 in familial and sporadic ileal carcinoid tumors. *Genes Chromosomes Cancer* **2010**, *50*, 82–94. [\[CrossRef\]](#)
60. Carr, N.J.; Emory, T.S.; Sobin, L.H. Epithelial Neoplasms of the Appendix and Colorectum: An Analysis of Cell Proliferation, Apoptosis, and Expression of p53, CD44, and bcl-2. *Arch. Pathol. Lab. Med.* **2002**, *126*, 837–841. [\[CrossRef\]](#) [\[PubMed\]](#)
61. Smeenk, R.M.; van Velthuisen, M.L.F.; Verwaal, V.J.; Zoetmulder, F.A.N. Appendiceal Neoplasms and Pseudomyxoma Peritonei: A Population Based Study. *Eur. J. Surg. Oncol. (EJSO)* **2008**, *34*, 196–201. [\[CrossRef\]](#)
62. Szych, C.; Steabler, A.; Connolly, D.C.; Wu, R.; Cho, K.R.; Ronnett, B.M. Molecular Genetic Evidence Supporting the Clonality and Appendiceal Origin of Pseudomyxoma Peritonei in Women. *Am. J. Pathol.* **1999**, *154*, 1848–1855. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Amini, A.; Masoumi-Moghaddam, S.; Ehteda, A.; Morris, D.L. Secreted mucins in pseudomyxoma peritonei: Pathophysiological significance and potential therapeutic prospects. *Orphanet J. Rare Dis.* **2014**, *9*, 71. [\[CrossRef\]](#)
64. Benedix, F.; Reimer, A.; Gastinger, I.; Mroczkowski, P.; Lippert, H.; Kube, R. Primary appendiceal carcinoma- Epidemiology, surgery, and survival: Results of a German multi-center study. *Eur. J. Surg. Oncol.* **2010**, *36*, 763–771. [\[CrossRef\]](#)
65. Bradley, R.F.; Carr, N.J. Pseudomyxoma Peritonei: Pathology, a Historical Overview, and Proposal for Unified Nomenclature and Updated Grading. *Am. J. Surg. Pathol. Rev. Rep.* **2019**, *24*, 88–93. [\[CrossRef\]](#)

66. Kabbani, W.; Houlihan, P.S.; Rajayalaksh, L.; Hamilton, S.R.; Rashid, A. Mucinous and Nonmucinous Appendiceal Adenocarcinomas: Different Clinicopathological Features but Similar Genetic Alterations. *Mod. Pathol.* **2002**, *15*, 599–605. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Grotz, T.E.; Royal, R.E.; Mansfield, P.F.; Overman, M.J.; Mann, G.N.; Robinson, K.A.; Beaty, K.A.; Rafeeq, S.; Matamoros, A.; Taggart, M.W.; et al. Stratification of Outcomes for Mucinous Appendiceal Adenocarcinoma with Peritoneal Metastasis by Histological Grade. *World J. Gastrointest. Oncol.* **2017**, *9*, 354–362. [\[CrossRef\]](#)
68. McCusker, M.E.; Coté, T.R.; Clegg, L.X.; Sobin, L.H. Primary Malignant Neoplasms of the Appendix: A Population-Based Study from the Surveillance, Epidemiology, and End-Results Program, 1973–1998. *Cancer* **2002**, *94*, 3307–3312. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Overman, M.J.; Fournier, K.; Hu, C.-Y.; Eng, C.; Taggart, M.; Royal, R.; Mansfield, P.; Chang, G.J. Improving the AJCC/TNM Staging for Adenocarcinomas of the Appendix The Prognostic Impact of Histological Grade. *Ann. Surg.* **2013**, *257*, 1072–1078. [\[CrossRef\]](#)
70. Pietrantonio, F.; Perrone, F.; Mennitto, A.; Gleeson, E.M.; Milione, M.; Tamborini, E.; Busico, A.; Settanni, G.; Berenato, R.; Caporale, M.; et al. Toward the Molecular Dissection of Peritoneal Pseudomyxoma. *Ann. Oncol.* **2016**, *27*, 2097–2103. [\[CrossRef\]](#)
71. Raghav, K.P.S.; Loree, J.M.; Fournier, K.F.; Shaw, K.R.; Taggart, M.W.; Foo, W.C.; Matamoros, A.; Mehdizadeh, A.; Ahmed, S.U.; Guerra, J.L.; et al. Comprehensive Genomic Profiling of Appendiceal Adenocarcinoma. *J. Clin. Oncol.* **2018**, *36*, S298. [\[CrossRef\]](#)
72. Hara, L.; Saito, T.; Hayashi, T.; Yimit, A.; Takahashi, M.; Keiko, M.; Takahashi, M.; Yao, T. A Mutation Spectrum that Includes GNAS, KRAS, and TP53 May be Shared by Mucinous Neoplasms of the Appendix. *Pathol. Res. Pract.* **2015**, *211*, 657–664. [\[CrossRef\]](#)
73. Matson, D.R.; Xu, J.; Huffman, L.; Barroilhet, L.; Accola, M.; Rehrauer, W.M.; Weisman, P. KRAS and GNAS Co-Mutation in Metastatic Low-Grade Appendiceal Mucinous Neoplasm (LAMN) to the Ovaries: A Practical Role for Next-Generation Sequencing. *Am. J. Case Rep.* **2017**, *18*, 558–562. [\[CrossRef\]](#)
74. Shetty, S.; Thomas, P.; Ramanan, B.; Sharma, P.; Govindarajan, V.; Loggie, B. KRAS mutations and p53 overexpression in pseudomyxoma peritonei: Association with phenotype and prognosis. *J. Surg. Res.* **2013**, *180*, 97–103. [\[CrossRef\]](#)
75. Nishikawa, G.; Sekine, S.; Ogawa, R.; Matsubara, A.; Mori, T.; Taniguchi, H.; Kushima, R.; Hiraoka, N.; Tsuta, K.; Tsuda, H.; et al. Frequent GNAS Mutations in Low-Grade Appendiceal Mucinous Neoplasms. *Br. J. Cancer* **2013**, *108*, 951–958. [\[CrossRef\]](#)
76. Holowatyj, A.; Eng, C.; Wen, W.; Idrees, K.; Guo, X. Spectrum of Somatic Cancer Gene Variations Among Adults with Appendiceal Cancer by Age. *JAMA Netw. Open* **2020**, *3*, e2028644. [\[CrossRef\]](#)
77. Liu, X.; Mody, K.; de Abreu, F.B.; Pipas, J.M.; Peterson, J.D.; Gallagher, T.L.; Suriawinata, A.A.; Ripple, G.H.; Hourdequin, K.C.; Smith, K.D.; et al. Molecular Profiling of Appendiceal Epithelial Tumors Using Massively Parallel Sequencing to Identify Somatic Mutations. *Clin. Chem.* **2014**, *60*, 1004–1011. [\[CrossRef\]](#)
78. Zhu, X.; Salhab, M.; Tomaszewicz, K.; Meng, X.; Mathew, C.; Bathini, V.; Switzer, B.; Walter, O.; Cosar, E.F.; Wang, X.; et al. Heterogenous Mutational Profile and Prognosis Conferred by TP53 Mutations in Appendiceal Mucinous Neoplasms. *Hum. Pathol.* **2019**, *85*, 260–269. [\[CrossRef\]](#)
79. Davison, J.M.; Hartman, D.A.; Singhi, A.D.; Choudry, H.A.; Ahrendt, S.A.; Zureikat, A.H.; Ramalingam, L.; Nikiforova, M.; Pai, R.K. Loss of SMAD4 Protein Expression is Associated with High Tumor Grade and Poor Prognosis in Disseminated Appendiceal Mucinous Neoplasms. *Am. J. Surg. Pathol.* **2014**, *38*, 583–592. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Taggart, M.W.; Galbincea, J.; Mansfield, P.J.; Fournier, K.F.; Royal, R.E.; Overman, M.J.; Rashid, A.; Abraham, S.C. High-Level Microsatellite Instability in Appendiceal Carcinomas. *Am. J. Surg. Pathol.* **2014**, *37*, 1192–2000. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Shenoy, S. Goblet cell carcinoids of the appendix: Tumor biology, mutations and management strategies. *World J. Gastrointest. Surg.* **2016**, *8*, 660–669. [\[CrossRef\]](#)
82. Isaacson, P. Crypt Cell Carcinoma of the Appendix (So-Called Adenocarcinoid Tumor). *Am. J. Surg. Pathol.* **1981**, *5*, 213–224. [\[CrossRef\]](#)
83. Carr, N.J.; Sobin, L.H. Neuroendocrine Tumors of the Appendix. *Semin. Diagn. Pathol.* **2004**, *21*, 108–119. [\[CrossRef\]](#)
84. Pham, T.H.; Wolff, B.; Abraham, S.C.; Drelichman, E. Surgical and Chemotherapy Treatment Outcomes of Goblet Cell Carcinoid: A Tertiary Cancer Center Experience. *Ann. Surg. Oncol.* **2006**, *13*, 370–376. [\[CrossRef\]](#)
85. Roy, P.; Chetty, R. Goblet Cell Carcinoid Tumors of the Appendix: An Overview. *World J. Gastrointest. Oncol.* **2010**, *2*, 251–258. [\[CrossRef\]](#) [\[PubMed\]](#)
86. National Cancer Institute. NCI Thesaurus Version 18.11d. 2018. Available online: <https://ncit.nci.nih.gov/ncitbrowser/> (accessed on 24 October 2022).
87. Tang, L.H.; Shi, J.; Soslow, R.A.; Dhall, D.; Wong, W.D.; O'Reilly, E.; Qin, J.; Paty, P.; Weiser, M.R.; Guillem, J.; et al. Pathologic Classification and Clinical Behavior of the Spectrum of Goblet Cell Carcinoid Tumors of the Appendix. *Am. J. Surg. Pathol.* **2008**, *32*, 1429–1443. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Sinno, S.A.J.; Jurdi, N.M.H. Goblet Cell Tumors of the Appendix: A Review. *Ann. Diagn. Pathol.* **2019**, *43*, 151401. [\[CrossRef\]](#)

89. Reid, M.D.; Basturk, O.; Shaib, W.L.; Xue, Y.; Balci, S.; Choi, H.-J.; Akkas, G.; Memis, B.; Robinson, B.S.; El-Rayes, B.F.; et al. Adenocarcinoma Ex-Goblet Carcinoid (Appendiceal-Type Crypt Cell Adenocarcinoma) is a Morphologically Distinct Entity with Highly Aggressive Behavior and Frequent Association with Peritoneal/Intra-Abdominal Dissemination: An Analysis of 77 Cases. *Mod. Pathol.* **2017**, *29*, 1243–1253. [[CrossRef](#)] [[PubMed](#)]
90. Hsu, C.; Rashid, A.; Xing, Y.; Chiang, Y.-J.; Chagbar, R.B.; Fournier, K.F.; Chang, G.J.; You, N.; Feig, B.W. Varying Malignant Potential of Appendiceal Neuroendocrine Tumors: Importance of Histologic Subtypes. *J. Surg. Oncol.* **2012**, *107*, 136–143. [[CrossRef](#)]
91. Clift, A.K.; Kornasiewicz, O.; Drymoussis, P.; Faiz, O.; Wasan, H.S.; Kinross, J.M.; Cecil, T.; Frilling, A. Goblet cell carcinomas of the appendix: Rare but aggressive neoplasms with challenging management. *Endocr. Connect.* **2018**, *7*, 268–277. [[CrossRef](#)]
92. Zambrano-Vera, K.; Sardi, A.; Munoz-Zuluaga, C.; Studeman, K.; Nieroda, C.; Sittig, M.; King, M.C.; Sipok, A.; Gushchin, V. Outcomes in Peritoneal Carcinomatosis from Appendiceal Goblet Cell Carcinoma Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC). *Ann. Surg. Oncol.* **2020**, *27*, 179–187. [[CrossRef](#)] [[PubMed](#)]
93. Olsen, I.H.; Holt, N.; Langer, S.W.; Hasselby, J.P.; Grønbaek, H.; Hillingsø, H.; Mahmoud, M.; Ladekarl, M.; Iversen, L.H.; Kjær, A.; et al. Goblet Cell Carcinoids: Characteristics of a Danish Cohort of 83 Patients. *PLoS ONE* **2015**, *10*, e0117627. [[CrossRef](#)]
94. Pai, R.K.; Hartman, D.J.; Gonzalo, D.H.; Lai, K.K.; Downs-Kelly, E.; Goldblum, J.R.; Liu, X.; Patil, D.T.; Bennett, A.E.; Plessec, T.P.; et al. Serrated Lesions of the Appendix Frequently Harbor KRAS Mutations and not BRAF Mutations Indicating a Distinctly Different Serrated Neoplastic Pathway in the Appendix. *Hum. Pathol.* **2014**, *45*, 227–235. [[CrossRef](#)]
95. Jesinghaus, M.; Konukiewitz, B.; Foersch, S.; Stenzinger, A.; Steiger, K.; Muckenhuber, A.; Groß, C.; Mollenhauer, M.; Roth, W.; Detlefsen, S.; et al. Appendiceal goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid are genetically distinct from primary colorectal-type adenocarcinoma of the appendix. *Mod. Pathol.* **2018**, *31*, 829–839. [[CrossRef](#)] [[PubMed](#)]
96. Dimmler, A.; Geddert, H.; Faller, G. EGFR, KRAS, BRAF-Mutations and Microsatellite Instability are Absent in Goblet Cell Carcinoids of the Appendix. *Pathol.-Res. Pract.* **2014**, *210*, 274–278. [[CrossRef](#)]
97. Danussi, C.; Akavia, U.D.; Niola, F.; Jovic, A.; Lasorella, A.; Pe'er, D.; Lavarone, A. RHPN2 Drives Mesenchymal Transformation in Malignant Glioma by Triggering RhoA Activation. *Cancer Res.* **2013**, *73*, 5140–5150. [[CrossRef](#)] [[PubMed](#)]
98. Yao, L.; Tak, Y.G.; Berman, B.P.; Farnham, P.J. Functional Annotation of Colon Cancer Risk SNPs. *Nat. Commun.* **2014**, *5*, 5114. [[CrossRef](#)]
99. Stancu, M.; Wu, T.-T.; Wallace, C.; Houlihan, P.S.; Hamilton, S.R.; Rashid, A. Genetic Alterations in Goblet Cell Carcinoids of the Veriform Appendix and Comparison with Gastrointestinal Carcinoid Tumors. *Mod. Pathol.* **2003**, *16*, 1189–1198. [[CrossRef](#)]
100. LaFramboise, W.A.; Pai, R.K.; Petrosko, P.; Belsky, M.A.; Dhir, A.; Howard, P.G.; Becich, M.J.; Holtzman, M.P.; Ahrendt, S.A.; Pingpank, J.F.; et al. Discrimination of Low- and High-Grade Appendiceal Mucinous Neoplasms by Targeted Sequencing of Cancer-Related Variants. *Mod. Pathol.* **2019**, *32*, 1197–1209. [[CrossRef](#)]
101. Chandana, S.R.; Shah, C. Appendiceal Adenocarcinoma: Analysis of SEER Database. *J. Clin. Oncol.* **2017**, *35*, e18097. [[CrossRef](#)]
102. McGory, M.L.; Maggard, M.A.; Kang, H.; O'Connell, J.B.; Ko, C.Y. Malignancies of the Appendix: Beyond Case Series Reports. *Dis. Colon Rectum* **2005**, *48*, 2264–2271. [[CrossRef](#)]
103. Yajima, N.; Wada, R.; Yamagishi, S.-I.; Mizumaki, H.; Itabashi, C.; Yagihashi, S. Immunohistochemical Expressions of Cytokeratins, Mucin Core Proteins, p53, and Neuroendocrine Cell Markers in Epithelial Neoplasm of Appendix. *Hum. Pathol.* **2005**, *36*, 1217–1225. [[CrossRef](#)]
104. Maru, D.; Wu, T.-T.; Canada, A.; Houlihan, P.S.; Hamilton, S.R.; Rashid, A. Loss of Chromosome 18q and DPC4 (Smad4) Mutations in Appendiceal Adenocarcinomas. *Oncogene* **2004**, *23*, 859–864. [[CrossRef](#)]
105. Font, A.; Abad, A.; Monzó, M.; Sanchez, J.J.; Guillot, M.; Manzano, J.L.; Piñol, M.; Ojanguren, I.; Rosell, R. Prognostic value of K-ras mutations and allelic imbalance on chromosome 18q in patients with resected colorectal cancer. *Dis. Colon Rectum* **2001**, *44*, 549–557. [[CrossRef](#)]
106. Andjelkovic, B.; Stojanovic, B.; Stojanovic, M.D.; Milosevic, B.; Cvetkovic, A.; Spasic, M.; Jakovljevic, S.; Cvetkovic, D.; Stojanovic, B.S.; Milosev, D.; et al. Appendiceal Signet Ring Cell Carcinoma: An Atypical Cause of Acute Appendicitis—A Case Study and Review of Current Knowledge. *Diagnostics* **2023**, *13*, 2359. [[CrossRef](#)]
107. Burke, A.P.; Sobin, L.H.; Federspiel, B.H.; Shekitka, K.M.; Helwig, E.B. Goblet Cell Carcinoids and Related Tumors of the Veriform Appendix. *Am. J. Clin. Pathol.* **1990**, *94*, 27–35. [[CrossRef](#)]
108. Singhi, A.D.; Davison, J.M.; Choudry, H.A.; Pingpank, J.F.; Ahrendt, S.A.; Holtzman, M.P.; Zureikat, A.H.; Zeh, H.J.; Ramalingam, L.; Mantha, G.; et al. GNAS is Frequently Mutated in Both Low-Grade and High-Grade Disseminated Appendiceal Mucinous Neoplasms by Does Not Affect Survival. *Hum. Pathol.* **2014**, *45*, 1737–1743. [[CrossRef](#)]
109. Liebl, M.C.; Hofmann, T.G. The Role of p53 Signaling in Colorectal Cancer. *Cancers* **2021**, *13*, 2125. [[CrossRef](#)] [[PubMed](#)]
110. Tan, X.; Chen, S.; Wu, J.; Lin, J.; Pan, C.; Ying, X.; Pan, Z.; Lin, Q.; Liu, R.; Geng, R.; et al. PI3K/AKT- Mediated Upregulation of WDR5 Promotes Colorectal Cancer Metastasis by Directly Targeting ZNF407. *Cell Death Dis.* **2017**, *8*, e2686. [[CrossRef](#)] [[PubMed](#)]
111. Chung, D.C. The Genetic Basis of Colorectal Cancer: Insights into Critical Pathways of Tumorigenesis. *Gastroenterology* **2000**, *119*, 854–865. [[CrossRef](#)] [[PubMed](#)]

112. Bogaert, J.; Prenen, H. Molecular Genetics of Colorectal Cancer. *Ann. Gastroenterol.* **2014**, *27*, 9–14.
113. Chowdhury, S.; Ito, I.; Patalachinti, V.K.; Shen, J.P. Abstract 880: Activation of the Wnt pathway is associated with GNASR201 mutant appendiceal cancer in the peritoneum. *Cancer Res.* **2023**, *83* (Suppl. 7), 880. [\[CrossRef\]](#)
114. More, A.; Ito, I.; Haridas, V.; Chowdhury, S.; Gu, Y.; Dickson, P.; Fowlkes, N.; Shen, J.-P. Oncogene Addiction to GNAS in GNASR201 Mutant Tumors. *Oncogene* **2022**, *41*, 4159–4168. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Ng, C.; Li, H.; Wu, W.K.K.; Wong, S.H.; Yu, J. Genomics and Metagenomics of Colorectal Cancer. *J. Gastrointest. Oncol.* **2019**, *6*, 1164–1170. [\[CrossRef\]](#)
116. Patalachinti, V.K.; Haque, E.; Yousef, M.; Yousef, A.; Chowdhury, S.; Overman, M.; Parseghian, C.M.; Morris, V.K.; Huey, R.W.; Raghav, K.; et al. BRAF Mutant Appendiceal Adenocarcinoma Differs from Colorectal Cancer but Responds to BRAF-Target Therapy. *npj Precis. Oncol.* **2025**, *9*, 38. [\[CrossRef\]](#)
117. The Cancer Genome Atlas Network. Comprehensive Molecular Characterization of Human Colon and Rectal Cancer. *Nature* **2012**, *487*, 330–337. [\[CrossRef\]](#)
118. Su, J.; Jin, G.; Votanopoulos, K.I.; Craddock, L.; Shen, P.; Chou, J.W.; Qasem, S.; O'Neill, S.S.; Perry, K.C.; Miller, L.D.; et al. Prognostic Molecular Classification of Appendiceal Mucinous Neoplasms Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. *Ann. Surg. Oncol.* **2020**, *27*, 1439–1447. [\[CrossRef\]](#)
119. Moaven, O.; Su, J.S.; Jin, G.; Votanopoulos, K.I.; Shen, P.; Mangieri, C.; O'Neill, S.S.; Perry, K.S.; Levine, E.A.; Miller, L.D. Clinical Implications of Genetic Signatures in Appendiceal Cancer Patients with Incomplete Cytoreduction/HIPEC. *Ann. Surg. Oncol.* **2020**, *27*, 5016–5023. [\[CrossRef\]](#) [\[PubMed\]](#)
120. Ihemelandu, C.; Mavros, M.N.; Sugarbaker, P. Adverse Events Postoperatively Had No Impact of Long-Term Survival of Patients Treated with Cytoreductive Surgery with Heated Intraperitoneal Chemotherapy for Appendiceal Cancer with Peritoneal Metastases. *Ann. Surg. Oncol.* **2016**, *23*, 4231–4237. [\[CrossRef\]](#) [\[PubMed\]](#)
121. Quénet, F.; Elias, D.; Roca, L.; Goere, D.; Ghouti, L.; Pocard, M.; Facy, O.; Arvieux, C.; Lorimier, G.; Pezet, D.; et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* **2021**, *22*, 256–266. [\[CrossRef\]](#)
122. Levine, E.A.; Blazer, D.G., III; Kim, M.K.; Shen, P.; Stewart, J.H., IV; Guy, C.; Hsu, D.S. Gene Expression Profiling of Peritoneal Metastases from Appendiceal and Colon Cancer Demonstrates Unique Biologic Signatures and Predicts Patient Outcomes. *J. Am. Coll. Surg.* **2012**, *214*, 599–606. [\[CrossRef\]](#)
123. Levine, E.A.; Votanopoulos, K.I.; Qasem, S.A.; Philip, J.; Cummins, K.A.; Chou, J.W.; Ruiz, J.; D'Agostino, R.; Shen, P.; Miller, L.D. Prognostic Molecular Subtypes of Low-Grade Cancer of the Appendix. *J. Am. Coll. Surg.* **2016**, *222*, 493–503. [\[CrossRef\]](#)
124. Indini, A.; Rijavec, E.; Ghidini, M.; Corellini, A.; Grossi, F. Targeting KRAS in Solid Tumors: Current Challenges and Future Opportunities of Novel KRAS Inhibitors. *Pharmaceutics* **2021**, *13*, 653. [\[CrossRef\]](#) [\[PubMed\]](#)
125. Pfeiffer, P.; Qvortrup, C. KRAS^{G12C} Inhibition in Colorectal Cancer. *Lancet Oncol.* **2022**, *23*, 10–11. [\[CrossRef\]](#)
126. Weller, C.; Burnett, G.L.; Jiang, L.; Chakraborty, S.; Zhang, D.; Vita, N.A.; Dilly, J.; Kim, E.; Maldonado, B.; Seamon, K.; et al. A Neomorphic Protein Interface Catalyzes Covalent Inhibition of RAS-G12D Aspartic Acid in Tumors. *Science* **2025**, *389*, eads029. [\[CrossRef\]](#)
127. Cregg, J.; Edwards, A.V.; Chang, S.; Lee, B.J.; Knox, J.E.; Tomlinson, A.C.A.; Marquez, A.; Liu, Y.; Aay, B.; Wang, Y.; et al. Discovery of Daraxonrasib (RMC-6236), a Potent and Orally Bioavailable RAS(ON) Multi-selective, Noncovalent Tri-complex Inhibitor for the Treatment of Patients with Multiple RAS-Addicted Cancers. *J. Med. Chem.* **2025**, *68*, 6064–6083. [\[CrossRef\]](#) [\[PubMed\]](#)
128. André, F.; Ciruelos, E.; Rubovszky, G.; Campone, M.; Loibl, S.; Rugo, H.S.; Iwata, H.; Conte, P.; Mayer, I.A.; Kaufman, B.; et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N. Engl. J. Med.* **2019**, *380*, 1929–1940. [\[CrossRef\]](#)
129. Janku, F.; Yap, T.A.; Meric-Bernstam, F. Targeting the PI3K Pathway in Cancer: Are We Making Headway? *Nat. Rev. Clin. Oncol.* **2018**, *15*, 273–291. [\[CrossRef\]](#)
130. Ayala, C.; Sathe, A.; Bai, X.; Grimes, S.M.; Shen, J.; Poultides, G.A.; Lee, B.; Ji, H.P. Distinct Gene Signatures Define the Epithelial Cell Features of Mucinous Appendiceal Neoplasms and Pseudomyxoma Metastases. *Front. Genet.* **2025**, *16*, 1536982. [\[CrossRef\]](#)
131. Forsythe, S.D.; Erali, R.A.; Sasikumar, S.; Laney, P.; Shelkey, E.; D'Agostino, R., Jr.; Miller, L.D.; Shen, P.; Levine, E.A.; Soker, S.; et al. Organoid Platform in Preclinical Investigation of Personalized Immunotherapy Efficacy in Appendiceal Cancer: Feasibility Study. *Clin. Cancer Res.* **2021**, *27*, 5141–5150. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Ganesh, K.; Wu, C.; O'Rourke, K.P.; Szeglin, B.C.; Zheng, Y.; Sauv  , C.-E.G.; Adileh, M.; Wasserman, I.; Marco, M.R.; Kim, A.S.; et al. A Rectal Cancer Organoid Platform to Study Individual Responses to Chemoradiation. *Nat. Med.* **2019**, *25*, 1607–1614. [\[CrossRef\]](#) [\[PubMed\]](#)
133. Yao, Y.; Xu, X.; Yang, L.; Zhu, J.; Wan, J.; Shen, L.; Xia, F.; Fu, G.; Deng, Y.; Pan, M.; et al. Patient-Derived Organoids Predict Chemoradiation Responses of Locally Advanced Rectal Cancer. *Cell Stem Cell* **2020**, *26*, 17–26. [\[CrossRef\]](#)

134. Wellenstein, M.D.; Coffelt, S.B.; Duits, D.E.; van Miltenburg, M.H.; Slagter, M.; de Rink, I.; Henneman, L.; Kas, S.M.; Prekovic, S.; Hau, C.-S.; et al. Loss of p53 Triggers Wnt-Dependent Systemic Inflammation to Drive Breast Cancer Metastasis. *Nature* **2019**, *572*, 538–542. [[CrossRef](#)] [[PubMed](#)]
135. Isella, C.; Vaira, M.; Robella Bellomo, S.E.; Picco, G.; Borsano, A.; Mignone, A.; Petti, C.; Porporato, R.; Ulla, A.A.; Pisacane, A.; et al. Improved Outcome Prediction for Appendiceal Pseudomyxoma Peritonei by Integration of Cancer Cell and Stromal Transcriptional Profiles. *Cancers* **2020**, *12*, 1495. [[CrossRef](#)]
136. Votanopoulos, K.; Mazzochi, A.; Sivakumar, H.; Forsythe, S.; Aleman, J.; Levine, E.; Skardal, A. Appendiceal Cancer Patient-Specific Tumor Organoid Model for Predicting Chemotherapy Efficacy Prior to Initiation of Treatment: A Feasibility Study. *Ann. Surg. Oncol.* **2019**, *26*, 139–147. [[CrossRef](#)]
137. Mavanur, A.A.; Parimi, V.; O'Malley, M.; Nikiforova, M.; Bartlett, D.L.; Davison, J.M. Establishment and characterization of a murine xenograft model of appendiceal mucinous adenocarcinoma. *Int. J. Exp. Pathol.* **2010**, *91*, 357–367. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.