City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

APPENDICEAL CANCERS

Molecular and Histologic Classification of Appendiceal Neoplasms

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- I do not have any relevant financial relationships to disclose.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Epidemiology of appendiceal tumors.
- Limits to genetic availability.

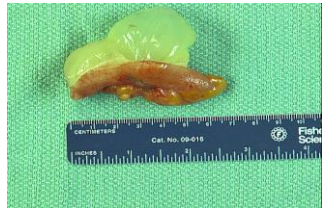
City of Hope

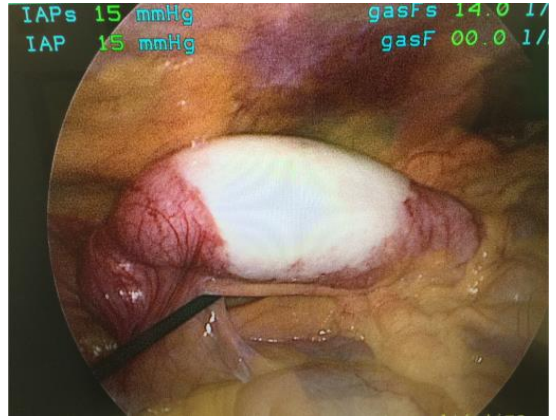
ISSPP

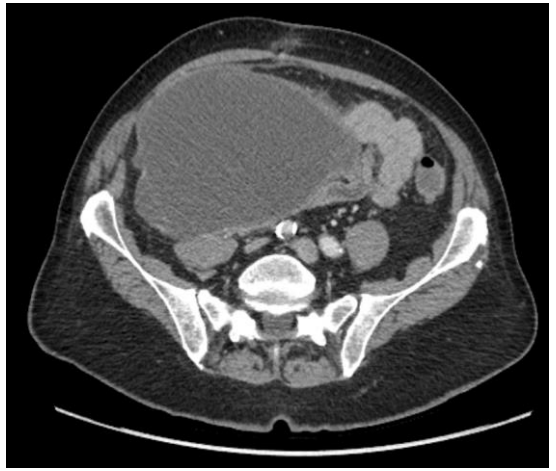
Appendiceal Tumors: Benign

- ~10,000/year U.S.
- Slightly more common than malignant
- Most incidental to appendicitis
- Adenoma: LAMN/HAMN benign?
- Leiomyoma, Lipoma, Neuroma, Mucocele*
- Simple Appendectomy Curative (if unruptured and margins negative)
- Elective appendectomy for tumor benign lesion;

  – unusual, most incidental finding on CT…







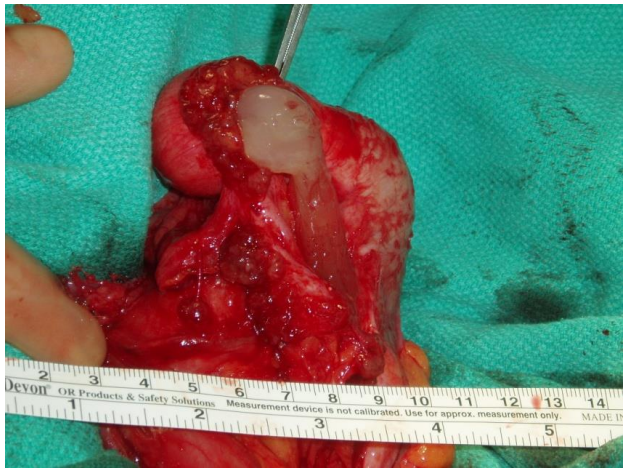
*Benign or malignant lesion - Dan Quayle's appendix (1995)

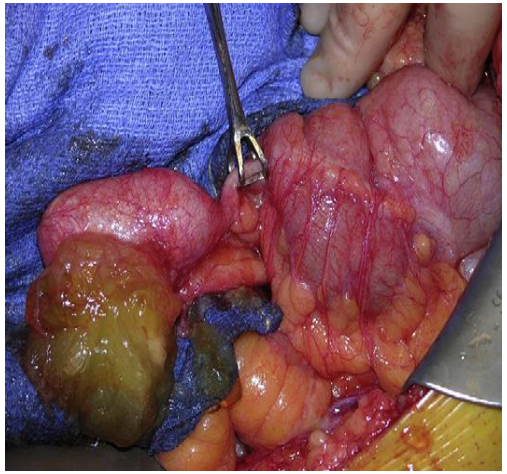
Appendiceal Tumors: Malignant

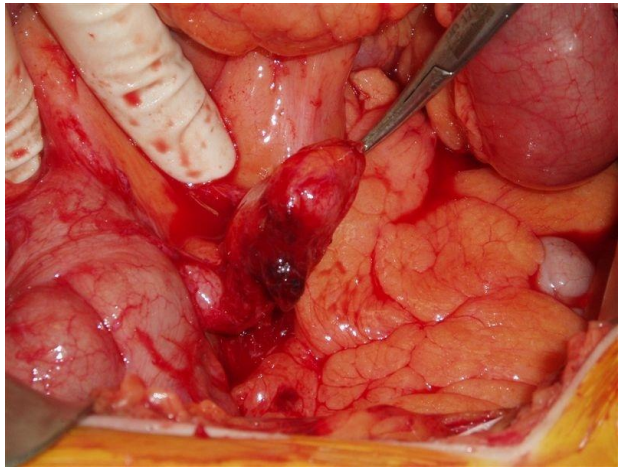
Pathologic Subtypes*:

- Carcinoid ~40%
- Adenocarcinoma ~55%
  - Mucinous
  - Adenocarcinoid (MANEC)
  - Well to poorly differentiated
  - Goblet cell,
  - Signet ring…
- Lymphoma
- GIST
- Sarcoma
- Secondary

*Confusing, varied and changing







Appendiceal Tumors: Malignant

Incidence is Increasing

↑ 250% 1970-2010

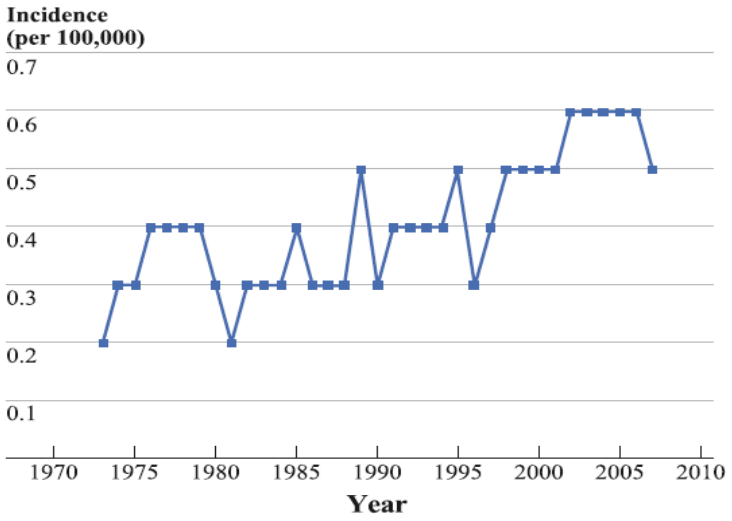
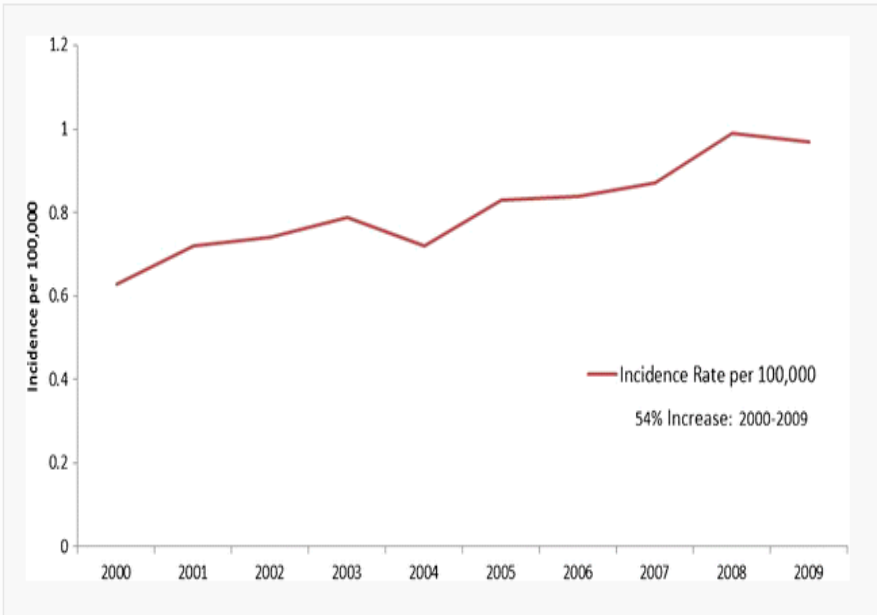


FIG. 1 Age-adjusted incidence rates for appendiceal tumors from 1973 to 2007 from 9 SEER registries (per 100,000 population)

Annals Surg Onc 2012;19:1379-1386

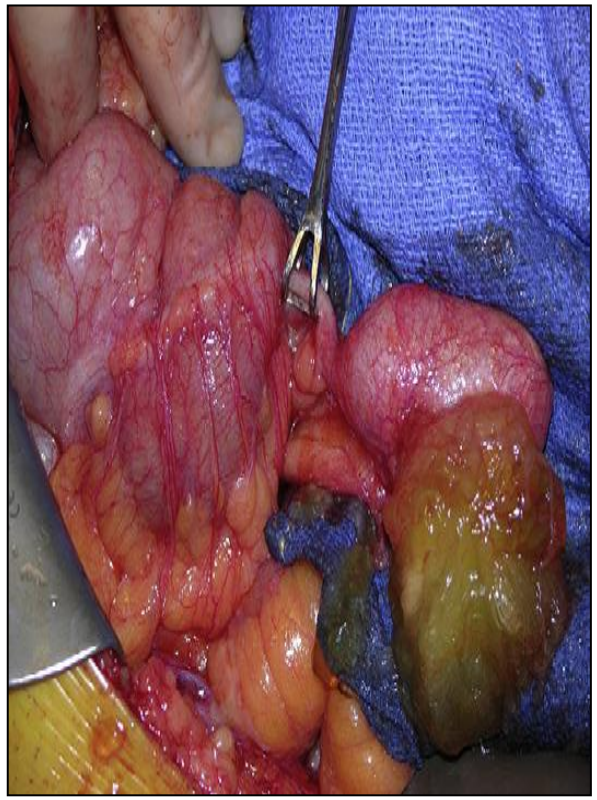
↑ 54% in 2000-2009

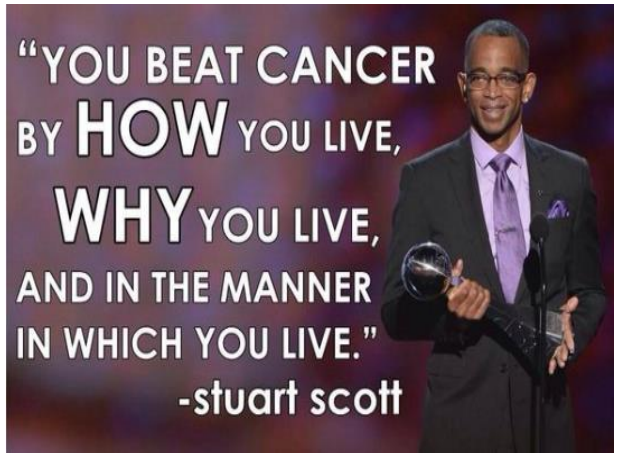


Journal of GI Surgery 2015;19: 743-750

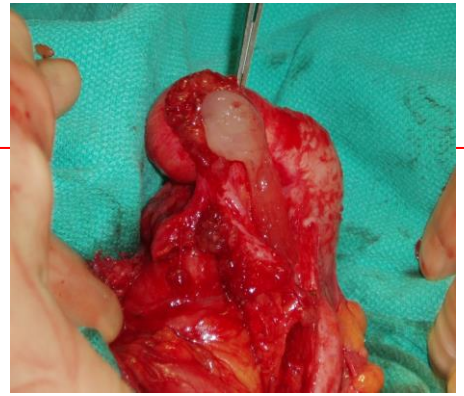
Appendiceal Tumors – Adenocarcinoma

- ~ 2,500 cases/year in the U.S.
- Rarely found unruptured
- Beware Second Primary!
- Tumor markers useful (CEA, CA 19-9, CA-125)
- Prognosis closely related to grade
- Risk of nodal disease closely related to grade
- Several pathologic descriptions (beware!)
- High grade R Colectomy, Low grade Appendix only for M0





PATHOLOGY



- 3 Tier System (Ronnett WHC/Hopkins)

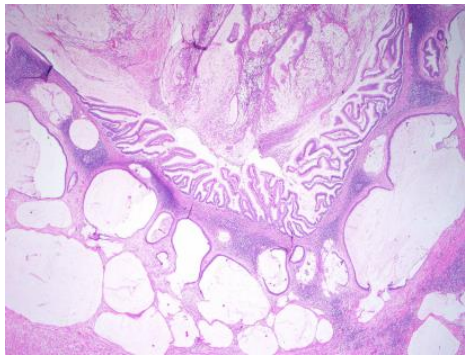
  Am J Surg Pathol. 1995 Dec;19(12):1390-408.

- 2 Tier System (Bradley Wake Forest & MSK)

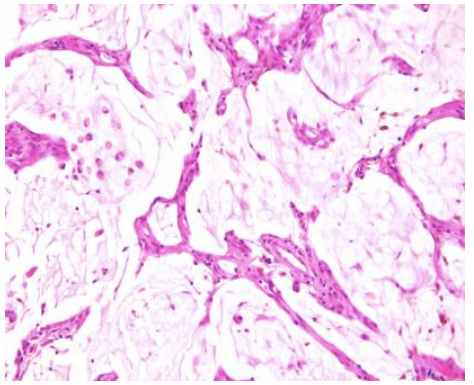
  Am J Surg Pathol. 2006 May;30(5):551-9.

- Beware signet rings…
- WHO fascicles
- Confusing descriptors
- Older systems worse!
- Variable pathologist confidence in diagnosis

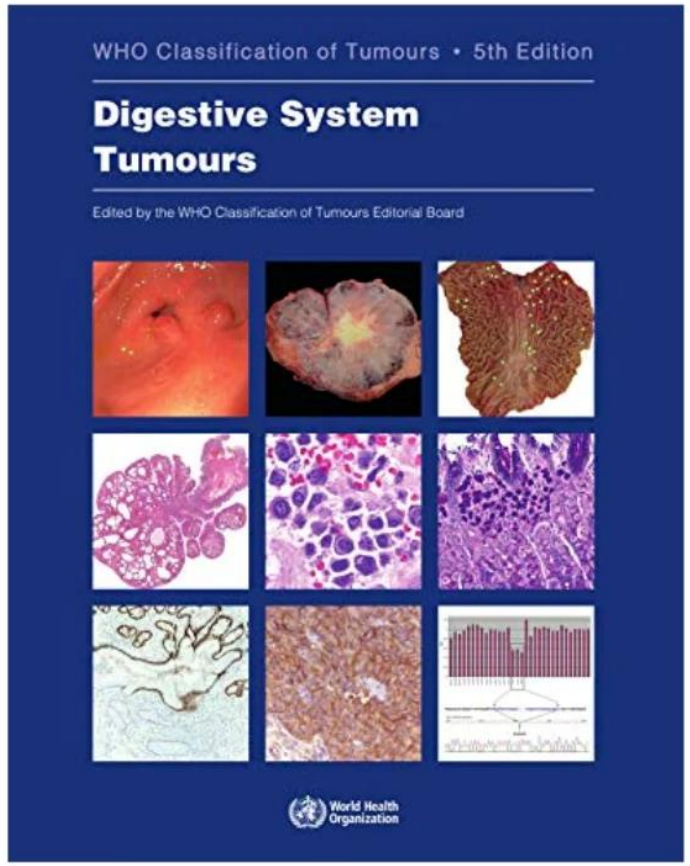
Low Grade



High Grade



World Health Organization – 2019
APPENDICEAL NEOPLASMS



	In the peritoneal metastasis
LOW Grade1	Hypocellular mucinous deposits Neoplastic epithelial elements have low-grade cytology No infiltrative-type invasion
HIGH Grade 2 Grade 3	Hypercellular mucinous deposits as judged at 20× magnification High-grade cytological features Infiltrative-type invasion characterized by jagged or angulated glands in a desmoplastic stroma, or a small mucin pool pattern with numerous mucin pools containing clusters of tumour cells
	Mucinous tumour deposits with signet-ring cells[b]

Peritoneal metastases

(from appendiceal mucinous neoplams/adenocarcinoma)

G1 – LOW GRADE Intermediate? G2-G3 HIGH GRADE

UNIFIED FIELD THEORY OF APPENDICEAL NEOPLASMS

Histopathology

Histopathology 2017, 71, 847–858. DOI: 10.1111/his.13324

REVIEW

The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei

Norman J Carr,[1] Frederic Bibeau,[2] Robert F Bradley,[3] Peggy Dartigues,[4] Roger M Feakins,[5] Kim R Geisinger,[6] Xianyong Gui,[7] Sylvie Isaac,[8] Massimo Milione,[9] Joseph Misdraji,[10] Reetesh K Pai,[11] Manuel Rodriguez-Justo,[12] Leslie H Sobin,[13] Marie-Louise F van Velthuysen[14] & Rhonda K Yantiss[15]

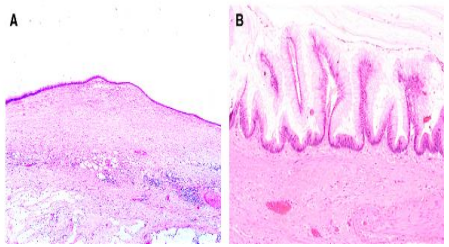
My “go to” reference on histopathology for appendiceal neoplasms

Pathologic Classification Criteria for Epithelial Neoplastic Appendiceal Lesions

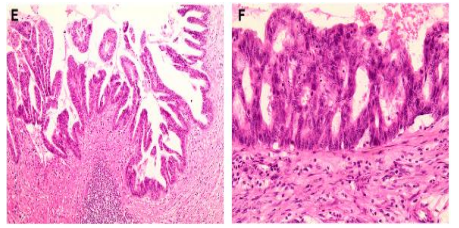
Table 1. Classification of epithelial neoplasia of the appendix, excluding goblet cell tumours (adapted from Carr *et al.*15)

Terminology	Histological features
Low-grade appendiceal mucinous neoplasm (LAMN) if atypia is low-grade. High-grade appendiceal mucinous neoplasm (HAMN) if atypia is high-grade	Mucinous neoplasm without infiltrative invasion but with any of the following: • loss of muscularis mucosae • fibrosis of submucosa • 'pushing invasion' (expansile or diverticulum-like growth) • dissection of acellular mucin in wall • undulating or flattened epithelial growth • rupture of appendix • mucin and/or cells outside appendix
Serrated polyp with or without dysplasia (low- or high-grade)	Tumour with serrated features confined to the mucosa, muscularis mucosae intact
Tubular, tubulovillous or villous adenoma, low- or high-grade dysplasia	Adenoma resembling usual colorectal type, confined to mucosa, muscularis mucosae intact
Mucinous adenocarcinoma – well, moderately or poorly differentiated	Mucinous neoplasm with infiltrative invasion
Adenocarcinoma – well, moderately or poorly differentiated	Non-mucinous adenocarcinoma resembling usual colorectal type

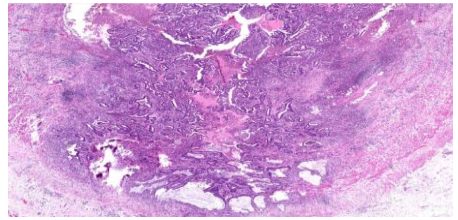
LAMN



HAMN



CANCER



AJCC STAGING FOR APPENDIX NEOPLASMS

Table 3. Summary of TNM8 classification of appendiceal adenocarcinomas, low-grade appendiceal mucinous neoplasms (LAMNs) and goblet cell carcinoids.44

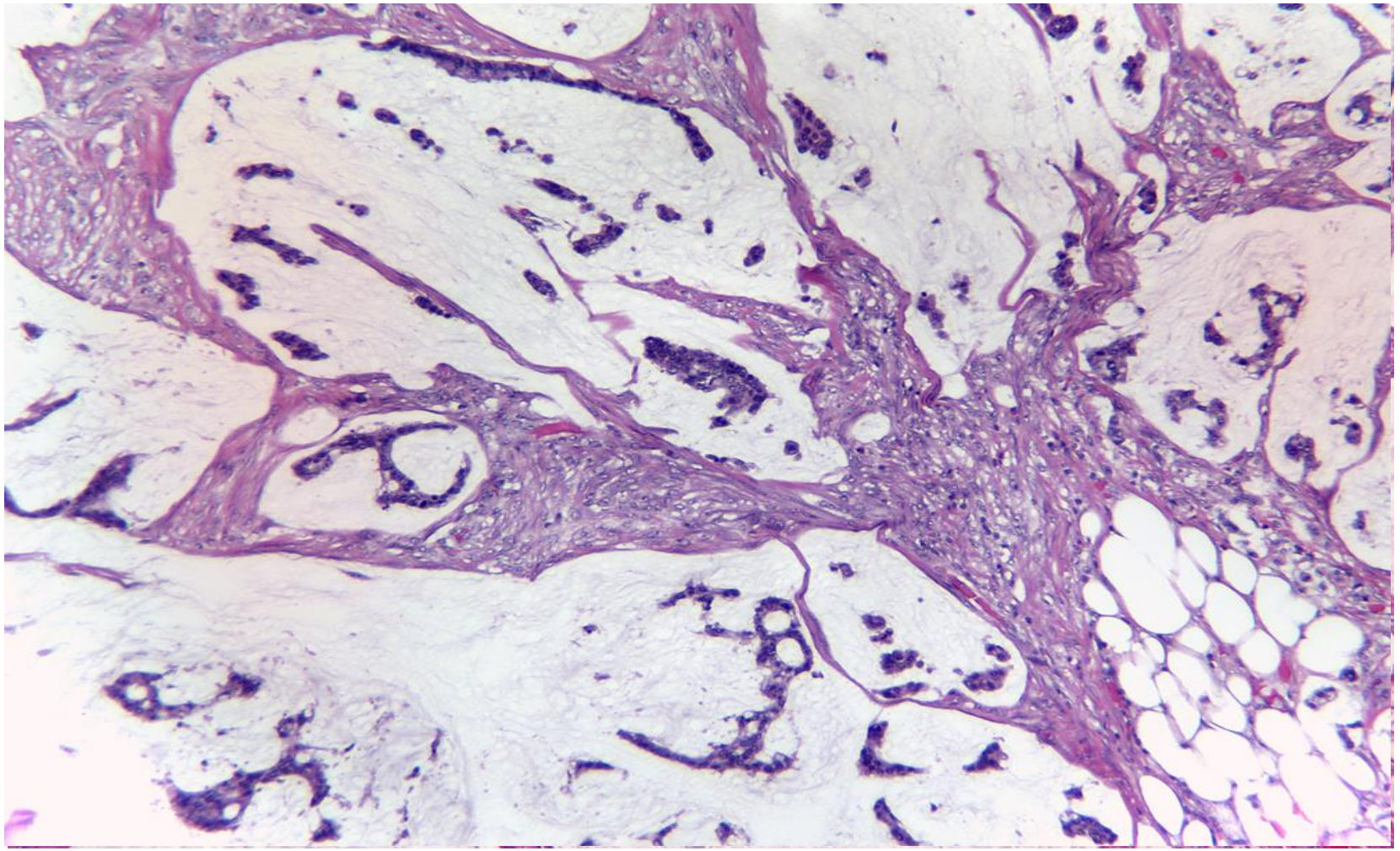
Primary tumour	LAMN confined to appendix (acellular mucin or mucinous epithelium may extend into muscularis propria)	Tis (LAMN)
	Tumour invades submucosa (does not apply to LAMN)	T1
	Tumour invades muscularis propria (does not apply to LAMN)	T2
	Tumour invades subserosa or mesoappendix (including LAMN)	T3
	Tumour perforates visceral peritoneum, including mucinous peritoneal tumour or acellular mucin on the serosa of the appendix or mesoappendix (including LAMN)	T4a
	Tumour directly invades other organs or structures	T4b
Regional nodes	No regional nodal metastasis	N0
	Metastasis in one regional node	N1a
	Metastases in 2–3 regional nodes	N1b
	Satellite deposits[a] without regional lymph node metastasis	N1c
	Metastasis in 4 or more regional nodes	N2
Distant metastasis	No distant metastasis	M0
	Intraperitoneal acellular mucin only	M1a
	Intraperitoneal metastasis only, including mucinous epithelium	M1b
	Non-peritoneal metastasis	M1c

[a] Satellite deposits are discrete nodules in adipose tissue in the lymph drainage area of a primary carcinoma showing no evidence of residual lymph node or identifiable vascular or neural structures.

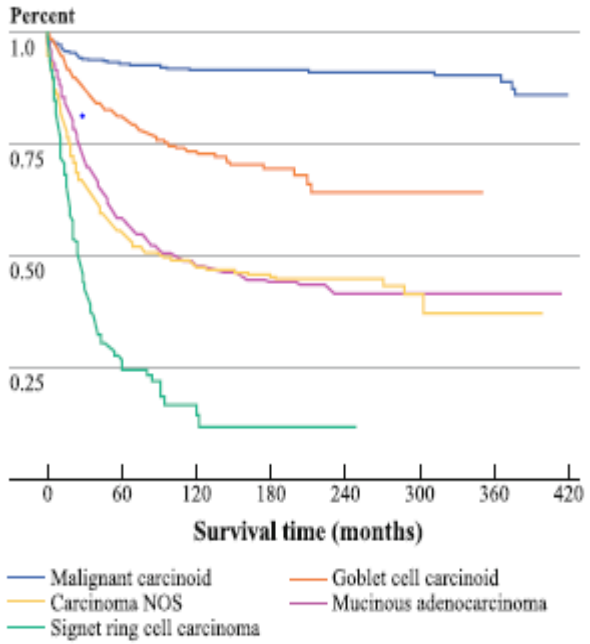
When T Is...	and N Is...	and M Is...	and the Grade Is...	Then the Stage Group I
Tis	N0	M0		0
Tis(LAMN)	N0	M0		0
T1	N0	M0		I
T2	N0	M0		I
T3	N0	M0		IIA
T4a	N0	M0		IIB
T4b	N0	M0		IIC
T1	N1	M0		IIIA
T2	N1	M0		IIIA
T3	N1	M0		IIIB
T4	N1	M0		IIIB
Any T	N2	M0		IIIC
Any T	Any N	M1a		IVA
Any T	Any N	M1b	G1	IVA
Any T	Any N	M1b	G2, G3, or GX	IVB
Any T	Any N	M1c	Any G	IVC

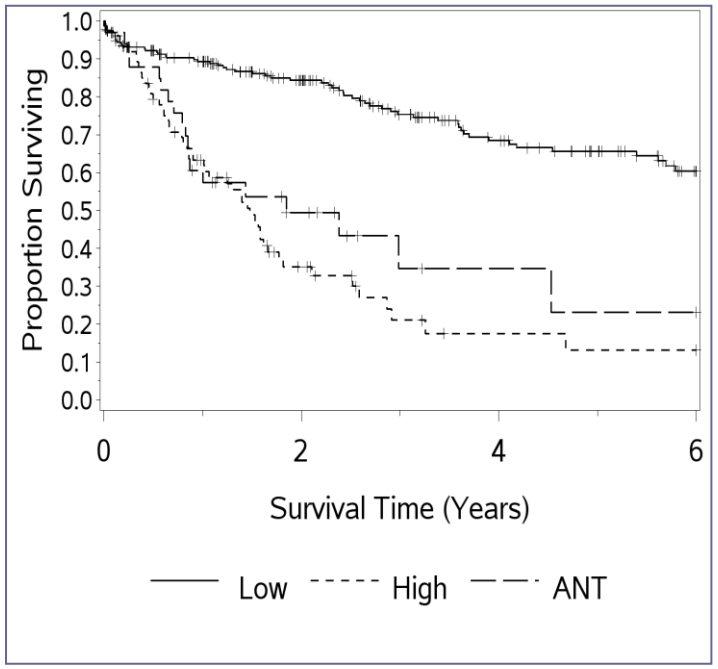
Brierley JD, Gospodarowicz MK, Wittekind C. UICC (Union for International Cancer Control) TNM classification of malignant tumours. 8th ed.

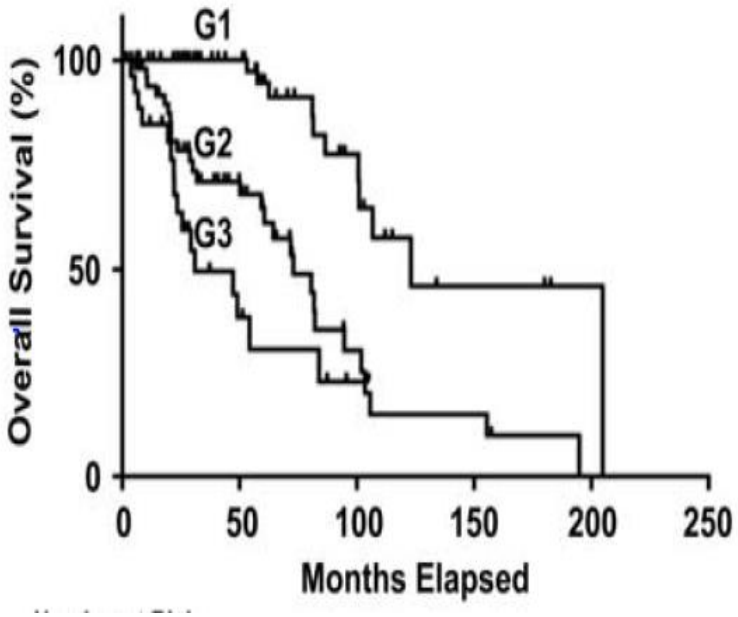
Peritoneal Tumor Histology



Grade/Type of Appendiceal Lesion Overall Survival







ASO 2012;19:1379-1385. MCW SEER database

JSR 2015; 196: 229-234. WFU

Modern Pathology 2014:27;1521-1539 UPMC

Expert pathologic opinion critical!

Mucinous Carcinoma Peritonei Survival and Resection Status

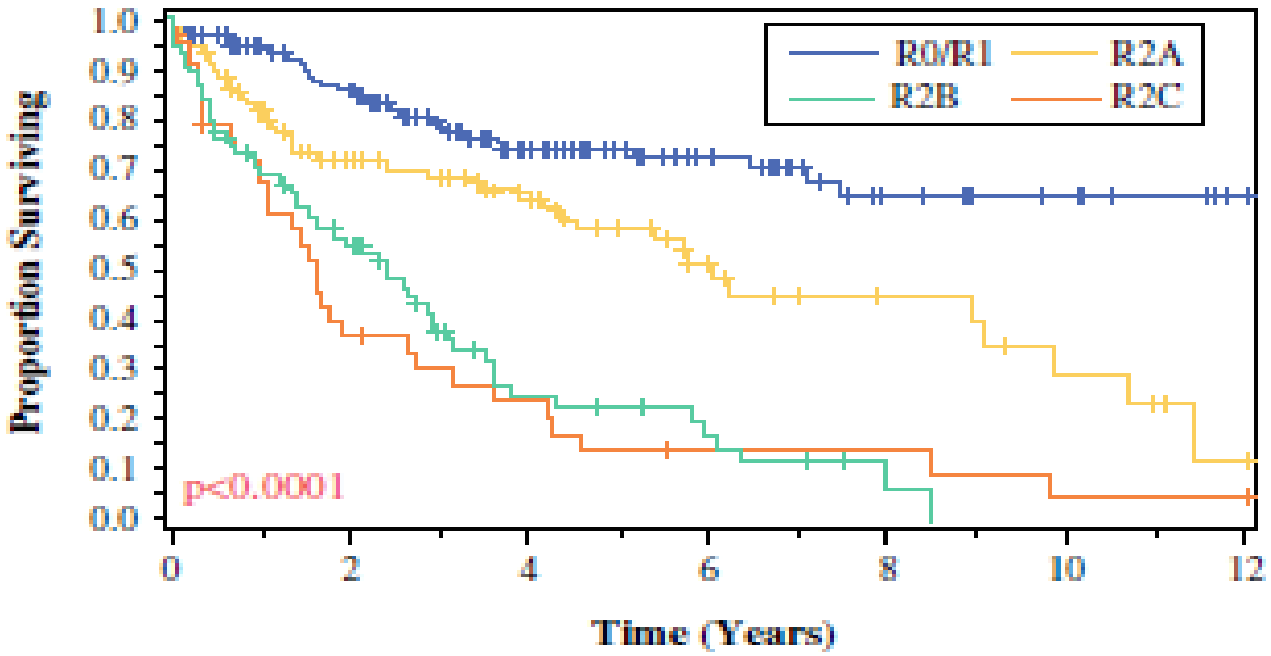
ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Peritoneal Surface Disease (PSD) from Appendiceal Cancer Treated with Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Overview of 481 Cases

Konstantinos I. Votanopoulos, MD, PhD, FACS[1], Greg Russell, MS[2], Reese W. Randle, MD[1], Perry Shen, MD[1], John H. Stewart, MD[1], and Edward A. Levine, MD[1]

[1]Section of Surgical Oncology, Department of General Surgery, Wake Forest Baptist Health, Winston-Salem, NC;
[2]Department of Biostatistical Sciences, Wake Forest Baptist Health, Winston-Salem, NC

N=481



ASO 2017

Clinical Prognostic Markers for Appendiceal Cancer

PCI	Ascites	Comorbidities
Grade	Extraperitoneal mets	Nodal Disease
Prior Surgery	Intrahepatic mets	Need for narcotics
CC/R score	Experience of Surgeon	Need for antidepressants
Performance status	Experience of Team	Systemic chemotherapy?
Histology	IP adjuvant therapy	Frailty/sarcopenia

Not all appendiceal lesions are created =
Even with the plethora of clinical markers some patients do poorly…

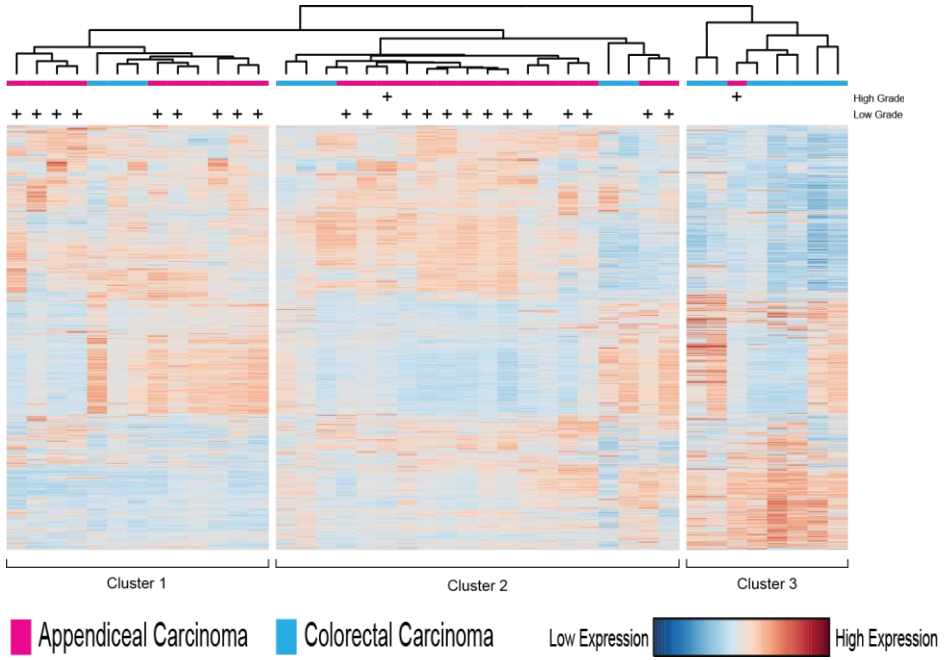
WHY?

Evaluate with Genomic profiling

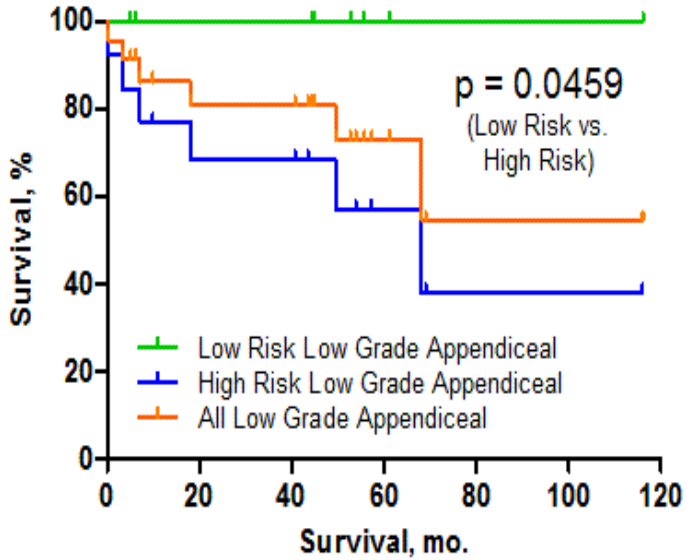
Gene expression profiling

Peritoneal Metastases - Appendiceal & Colon CA

Southern Surgical Association 2011



JACS 2012; 214: 599-607.



Small number(41) from single data set…

Gene profiling can improve prognostication

Appendiceal Cancer ≠ Colon Cancer

Outcomes stratified by 139 gene cluster

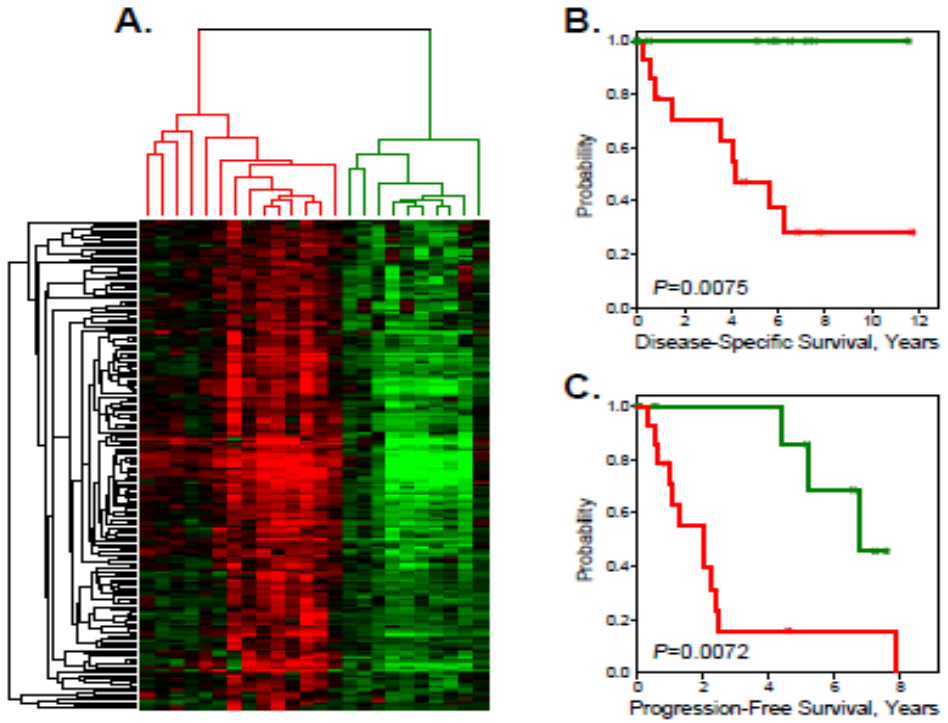
Initial series reanalyzed

Journal of the American College of Surgeons, 2016; 222; 493-504

- N = 39
- 25 low grade histology
- 14 high grade histology
- Dendrogram recapitulated
- Dendrogram &:

  Red: high expression

  Green: low expression
- ***Better signature…***

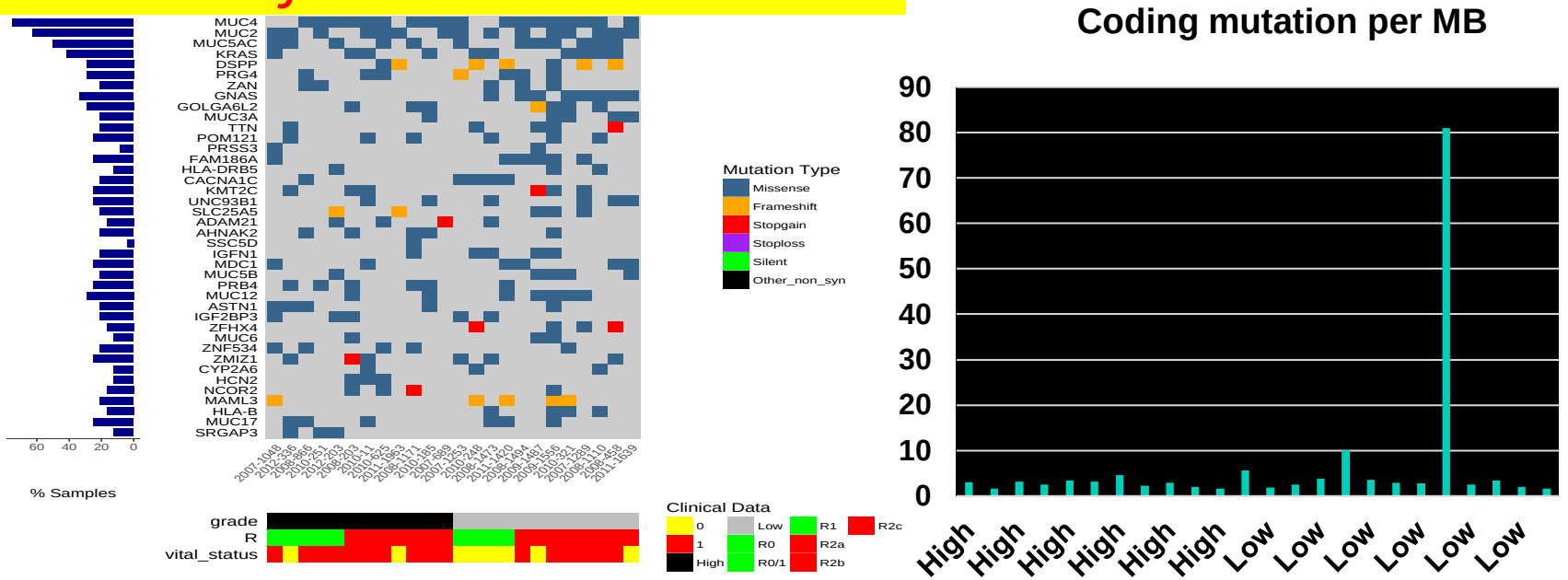


Genes comprising the 139-gene cassette cluster the tumors into two primary branches (subtypes) based on relative high and low gene expression. **B** and **C**, Kaplan-Meier survival curves corresponding by color to the tumor branches

Appendiceal Cancer Genomics

Journal of the American College of Surgeons, 2016; 222; 493-504 Wake Forest

- Mucinous Appendiceal Carcinoma N=39
- Whole Exome Sequencing
- KRAS & GNAS most frequently mutated
- Intact DNA mismatch repair
- Low mutational burden (TMB)
- *Genetics distinct from colorectal cancer*

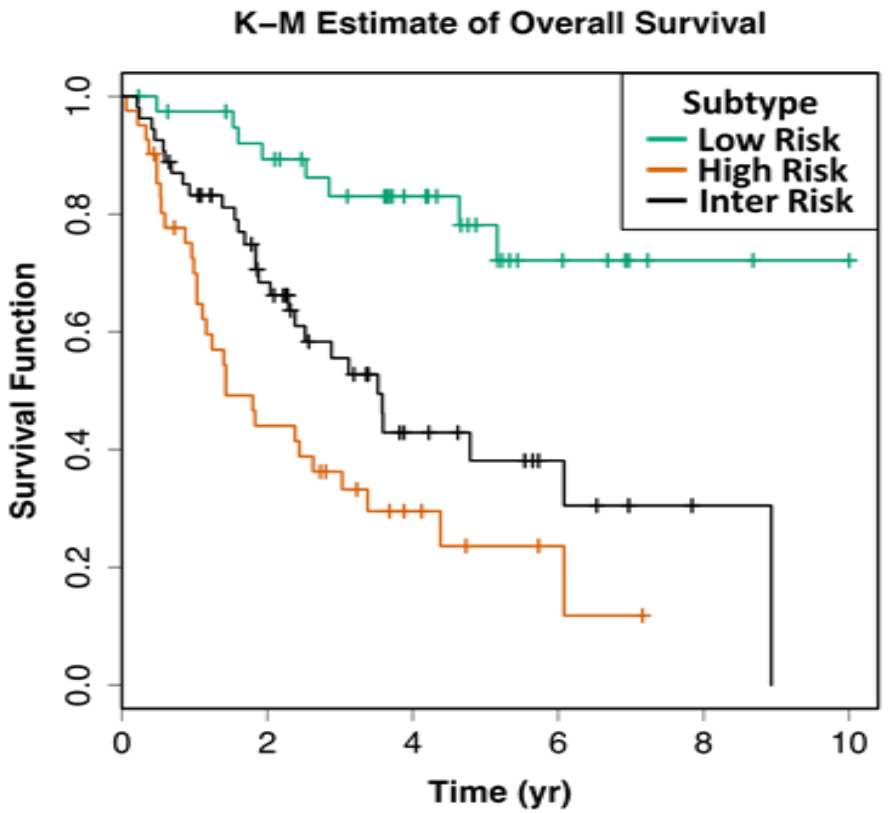


Discovered Subtypes are Independent to Known Clinical Prognostic Factors

Multivariable Overall Survival Analysis

	Hazard Ratio	95% Interval	p
Grade	**6.3**	2.7, 14.7	**1.7e-05**
ECOG Score	1.3	0.8, 2.1	0.23
R Score	**2.6**	1.2, 5.6	**0.014**
Adjuvant Chemo	1.41	0.6, 3.1	0.39
Age	0.99	0.97, 1.0	0.58
Sex (M)	1.0	0.54, 1.9	0.99
OE Subtype	**3.1**	1.2, 7.8	**0.017**
M Subtype	2.0	0.8, 5.0	0.14

n = 98, number of events = 45 Likelihood ratio test: **p=2e-10**



Regional therapies meeting 2018, @ ASO

Signature Confirmed - Turin, Italy group @ PSOGI September, 2018 Paris France

Ann Surg Oncol (2020) 27:5016–5023
https://doi.org/10.1245/s10434-020-08841-8

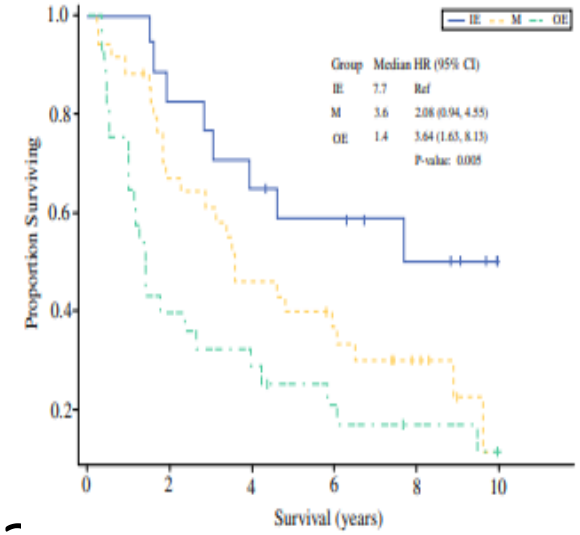
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

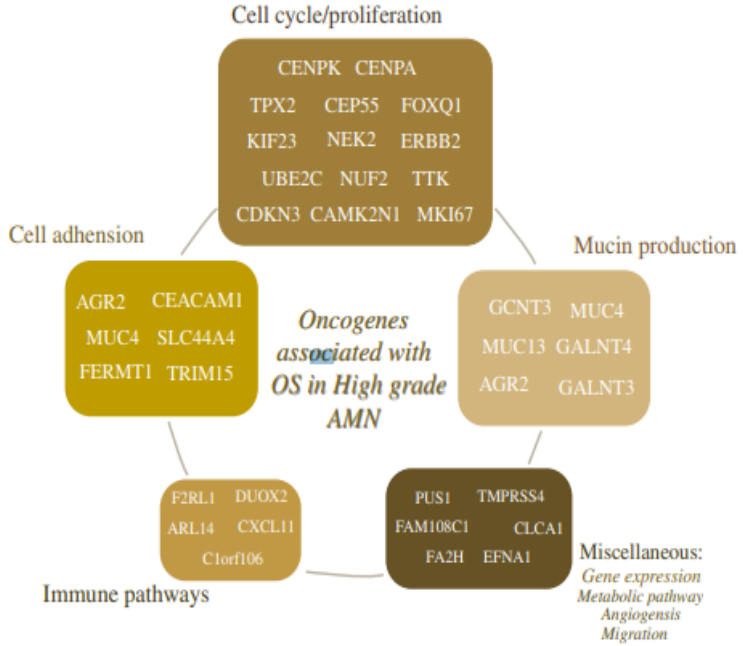
ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Clinical Implications of Genetic Signatures in Appendiceal Cancer Patients with Incomplete Cytoreduction/HIPEC

Omeed Moaven, MD[1], Jing Su, PhD[2], Guangxu Jin, PhD[3], Konstantinos I. Votanopoulos, MD, PhD[1], Perry Shen, MD[1], Christopher Mangieri, MD[1], Stacey S. O'Neill, MD, PhD[4], Kathleen C. Perry, MSc[1], Edward A. Levine, MD[1], and Lance D. Miller, PhD[3,5]

- N = 79
- Whole exome sequencing
- R2 resections
- Mean OS 7.2y
- Immune enhanced (IE) signature
- Oncogene enhanced (OE) signature
- Signature IE>OE → Better OS

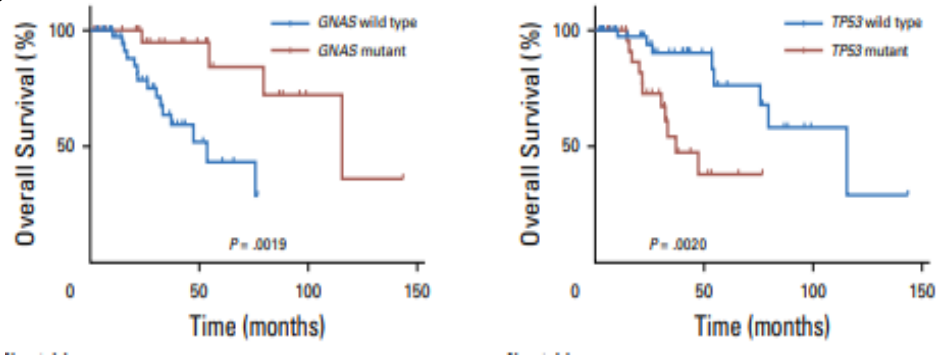




Annals of Surgical Oncology 2020; 27: 5016-5023

Appendiceal Cancer Genomics
NGS (Foundation1)

- Appendiceal Cancers N=703
- Outcome data N=76
- Stratified to 5 subtypes (mucinous & non-mucinous adenoca, GCC, "PMP", Signet ring)
- KRAS 35-81% GNAS 8-72%
- p53 and GNAS prognostic →

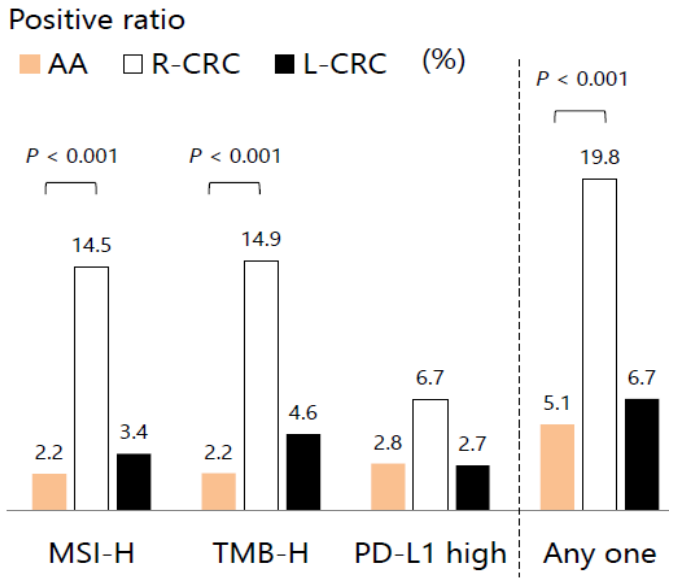


- Mutation profiles distinct from Colorectal Cancer

JCO Precision Oncology 2018;doi.org/10.1200/PO.17.00302
Genome Medicine 2014; 6(5): 43.

Appendiceal Cancer Genomics
NGS (CARIS)

- Appendiceal Cancers N=224 (183 evaluable 41 carcinoid/GCC excluded)
- Outcome data N = 0
- KRAS 55% GNAS 31% SMAD4 16%
- Low p53 and APC mutation rates
- MSI ↑ 2.2%
- TMB 1.4MB (<17MB) ↑ 2.2%
- PD-L1 high 2.8%



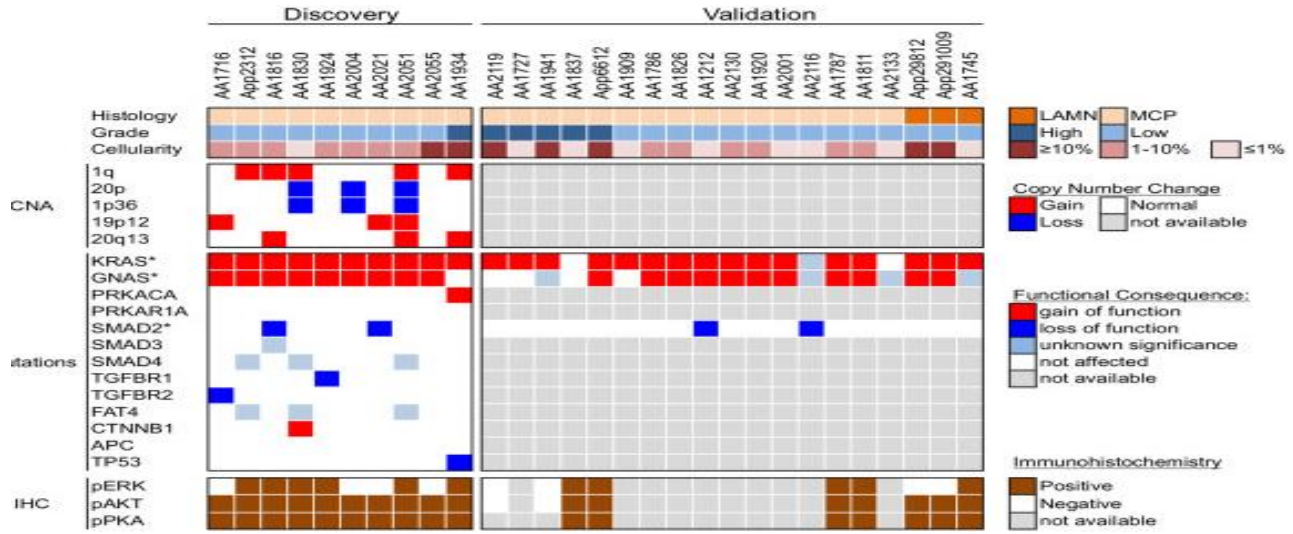
- Mutation profiles distinct from Colorectal Cancer

Clinical Cancer Research 2019. doi:10.1158/1078-4032.ccr-18-3388.

Appendiceal Cancer Genomics

Genome Medicine 2014; 6(5): 43. UCSD group

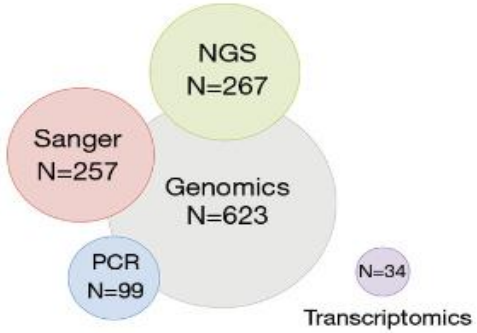
- Mucinous Appendiceal Carcinoma
- N=29 (10 discovery, 19 validation)
- Whole Exome Sequencing
- KRAS 90% and GNAS 69% most frequently mutated
- Low mutational burden (1.4-4.9x10^{-6} table S1)
- *Genetics distinct from colorectal cancer*



Appendiceal Cancer Genomics

Journal of Gastrointestinal Oncology 2021;12:doi:10.21037/jgo-20-136 Oslo, Norway

- Literature review (2020) for PMP and CRC with PM
- N=623 PMP, 1,779 CRC with peritoneal metastases
- Clinical outcome data available in only 19%
- *KRAS* & *GNAS* most frequently mutated
- *GNAS* much less common in CRC
- Frequency of reported mutations vary widely
- *KRAS* 38-100% depending upon series
- Low mutational burden
- Genetics *CRC-P ≠ PMP*



Gene	%/range	N
KRAS	78 [38–100]	18 [5–150]
GNAS	44 [17–100]	40 [5–66]
FAT4	35 [20–30]	8 [5–10]
TGFBR1	21 [20–22]	10 [9–10]
TP53	17 [5–38]	16 [5–75]
SMAD3/4	16 [3–60]	19 [5–66]
APC	11 [2–20]	19 [5–66]
ATM	11 [6–16]	19 [19–19]
FGFR2/3	7 [3–20]	15 [5–40]
PIK3CA	6 [2–10]	31 [19–66]
CTNNB1	6 [3–10]	25 [10–40]
HNF1A	5 [3–7]	28 [15–40]

Appendiceal Cancer Genomics & NGS (Typical Foundation1 Report)

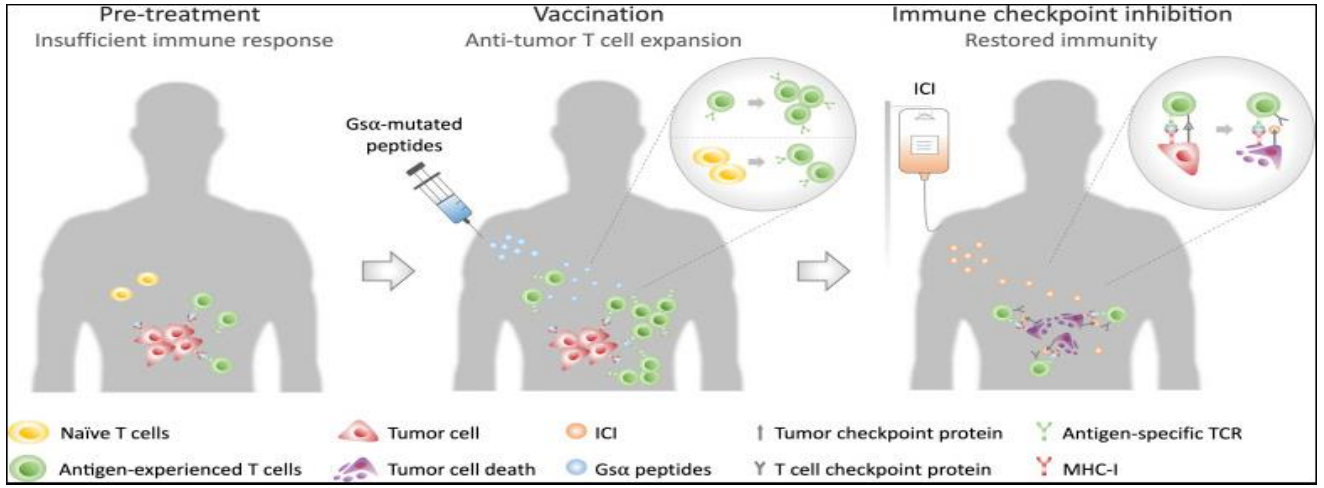
- Great excitement & potential
- Few actionable mutations
- Typically, MSI stable, Low Mutational burden, Low PD-L1 expression rates
- Rarely candidates for immunotherapy
- Little clinical impact

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - TMB-Low (1 Muts/Mb)	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
KRAS - G12D	none	Binimetinib
		Cobimetinib
7 Trials *see p. 7*		Trametinib
RNF43 - G4fs*4	none	none
2 Trials *see p. 9*		

Appendiceal Cancer Genomics & Potential Molecular Targets

- Great excitement & potential
- Few actionable mutations
- *KRAS* AMG510 (sotorasib) and MRTX849 (adagrasib) ??
- *GNAS* target via Gsα mutated Peptides (Flatmark) JITC 2021;9:e003109

= ?

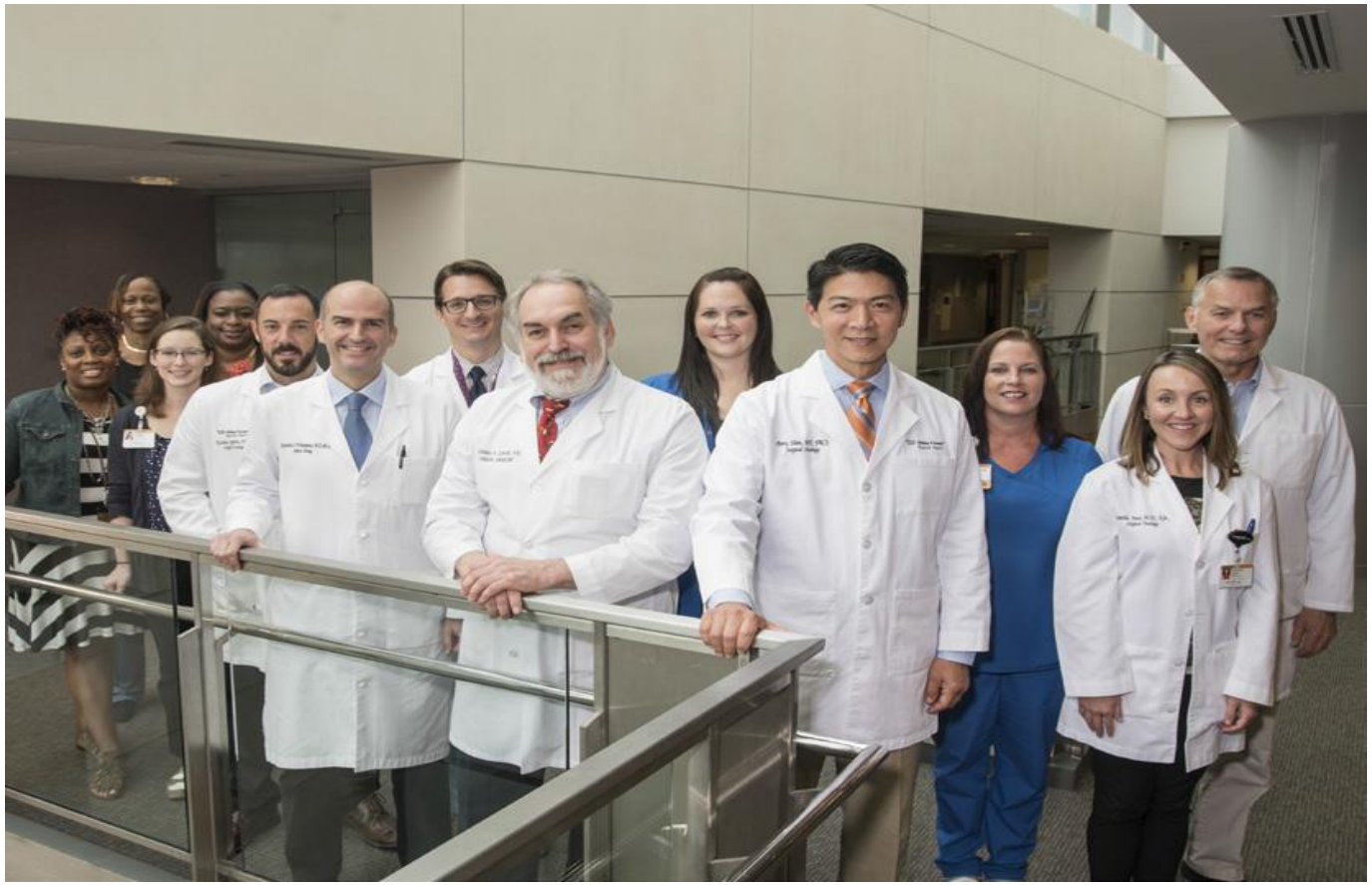


Sunset over Lanai’i from west Coast of Maui

Genomic data Appendiceal Cancer

- Genomics for Appendix Cancer here to stay…
- Appendiceal Cancer ≠ Colon Cancer
- Extrapolating systemic therapy from colon cancer regimens is unfounded.
- Genomics improve on pathologic grading
- Genomics may help identify targets for therapy
- Genomics rarely suggest better systemic therapy
- Signatures could define operative candidates

Thanks from our HIPEC Team
Celebrating 30 years of HIPEC!



Atrium Health Wake Forest Baptist

WAKE FOREST UNIVERSITY SCHOOL of MEDICINE

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute