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Therapy-associated polyposis in survivors of childhood and young adulthood cancers – a multi-institutional analysis

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- Dr. Yurgelun has no financial disclosures/conflicts of interest

Background

- Survivors of childhood/young adulthood cancers (CYAC) are at increased risk of developing colorectal cancer (CRC)
  - Abdominopelvic radiotherapy (RT): Odds ratio (OR) >8
  - Alkylating chemotherapy: OR >8

- Children's Oncology Group (COG) guidelines

  → For CYAC survivors treated with ≥30 Gy abdominopelvic RT, begin colonoscopic screening at age 30 **or** 5 years after RT, whichever occurs **LATER**

- We previously described a phenomenon of therapy-associated polyposis (TAP) in a small series of 5 CYAC survivors (4 Hodgkin lymphoma, 1 neuroblastoma)
  - All received alkylating chemotherapy and abdominopelvic RT
  - GI polyposis developed median of 24 years after initial cancer treatment
  - Negative germline *APC* and *MUTYH* testing; no family history of polyposis

Yurgelun MB, et al. *Clin Gastroenterol Hepatol* 2014;12:1046-50.
Nottage K, et al. *J Clin Oncol* 2012;30:2552-8.
Henderson TO, et al. *Ann Intern Med* 2012;156:757-66.
https://childrensoncologygroup.org/index.php/survivorshipguidelines

Study Aim & Methodology

- Aim: Further describe the phenotypic spectrum of TAP in a multi-institutional analysis

- Descriptive case series – ascertainment through cancer genetics/high-risk clinics at 7 different institutions
  - Dana-Farber Cancer Institute
  - Columbia University Medical Center
  - Memorial Sloan Kettering Cancer Center
  - University of Wisconsin
  - Cleveland Clinic
  - Fox Chase Cancer Center
  - University of Southern California

- Data extracted from chart review

- TAP case definition:
  - Survivor of childhood/young adulthood cancer
    - Age ≤30 at initial cancer diagnosis **OR** Age ≤45 if polyps developed >10 years after initial cancer treatment
  - Lifetime aggregate of ≥10 upper and/or lower GI polyps
  - No known pathogenic/likely pathogenic germline variant in a hereditary cancer predisposition gene

Study Cohort – Initial CYAC Diagnosis

	N=33 (%)
Type of Cancer	
Hodgkin lymphoma	27 (82)
Neuroblastoma	3 (9)
Acute myeloid leukemia	1 (3)
Non-Hodgkin lymphoma	1 (3)
Wilms' tumor (nephroblastoma)	1 (3)
Sex	
Male	21 (64)
Female	12 (36)
Median Age at CYAC Diagnosis (range)	18 years (0.7-44)
Treatment for CYAC	
Chemotherapy	25 (76)
RT (any)	27 (82)
Abdominopelvic RT	20 (61)
Unknown	3 (9)
Any 1st/2nd degree relative with CRC age <50 years	1 (3)
Any family history of colorectal polyposis (≥20 polyps)	0 (0)

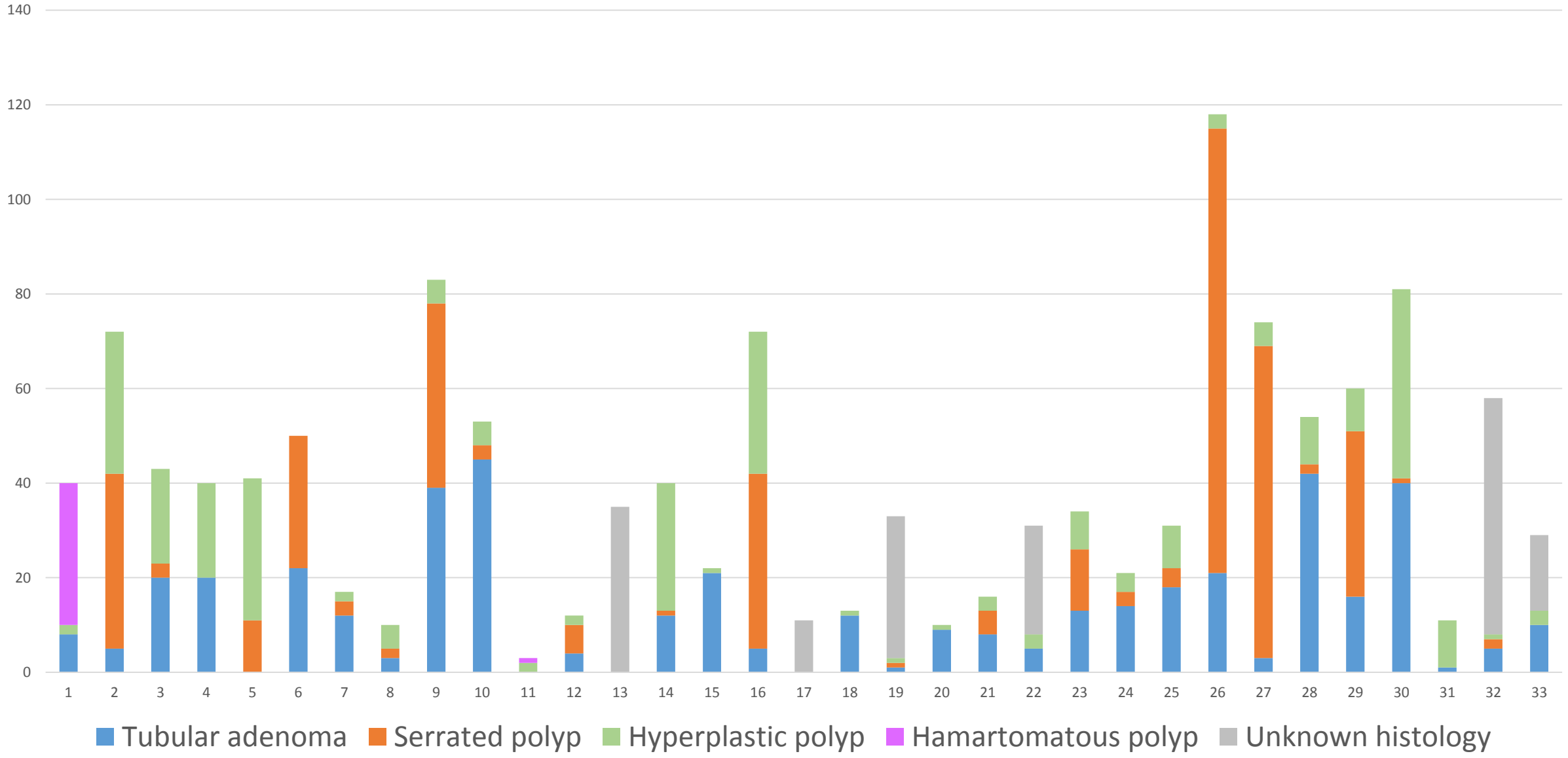
Study Cohort – TAP Manifestations

	N=33 (%)
Median Duration from CYAC Treatment Until 1st Polyp (range)	27 years (10-43)
TAP developed before COG-recommended screening start	7 (21)
Aggregate # Colorectal Polyps	
Median # (IQR)	31 polyps (14-50)
>50	10 (30)
21-50	14 (42)
10-20	8 (24)
Any Upper GI Polyps	21 (64)
Colorectal cancer (CRC)*	7 (21)
CRC developed before COG-recommended screening start*	3 of 7 (43)
Germline testing history	
Negative panel testing (including *APC/MUTYH*)	27 (82)
Negative *APC* and *MUTYH* testing only	3 (9)
No germline testing**	3 (9)

* All CRCs diagnosed on patients' first ever colonoscopy

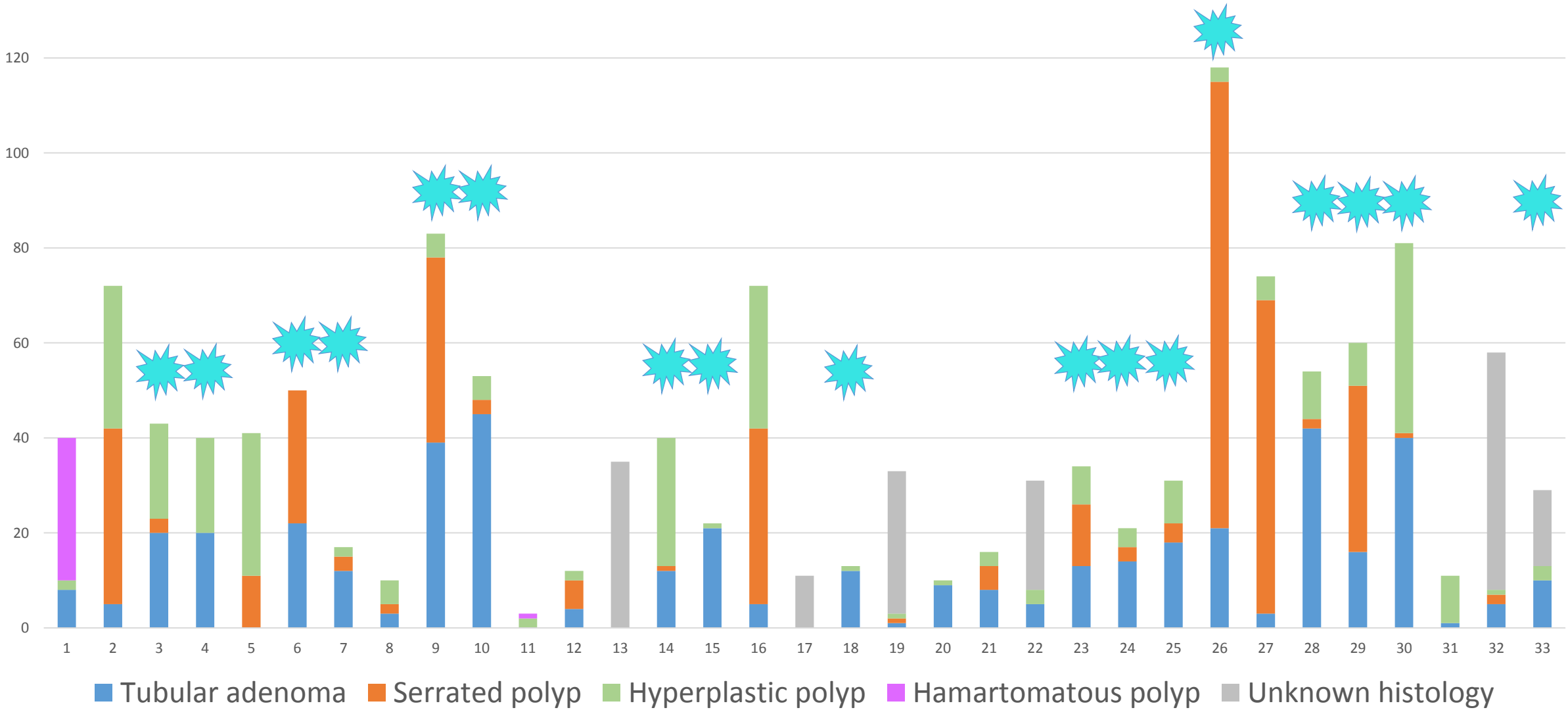
** Includes one patient who underwent blood-based germline testing after allogeneic stem cell transplant

Polyp Number and Histology by Patient

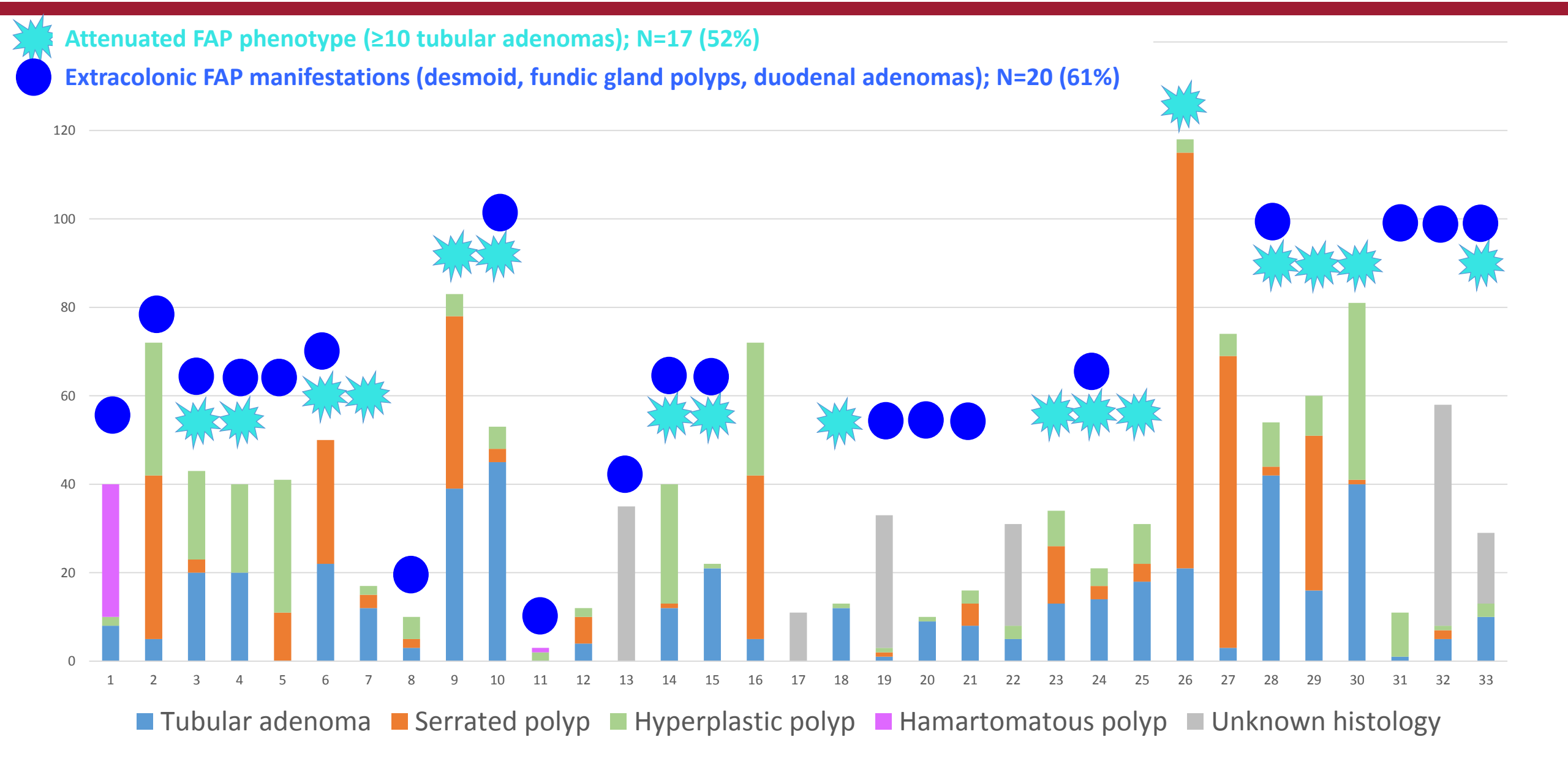


Polyp Number and Histology by Patient

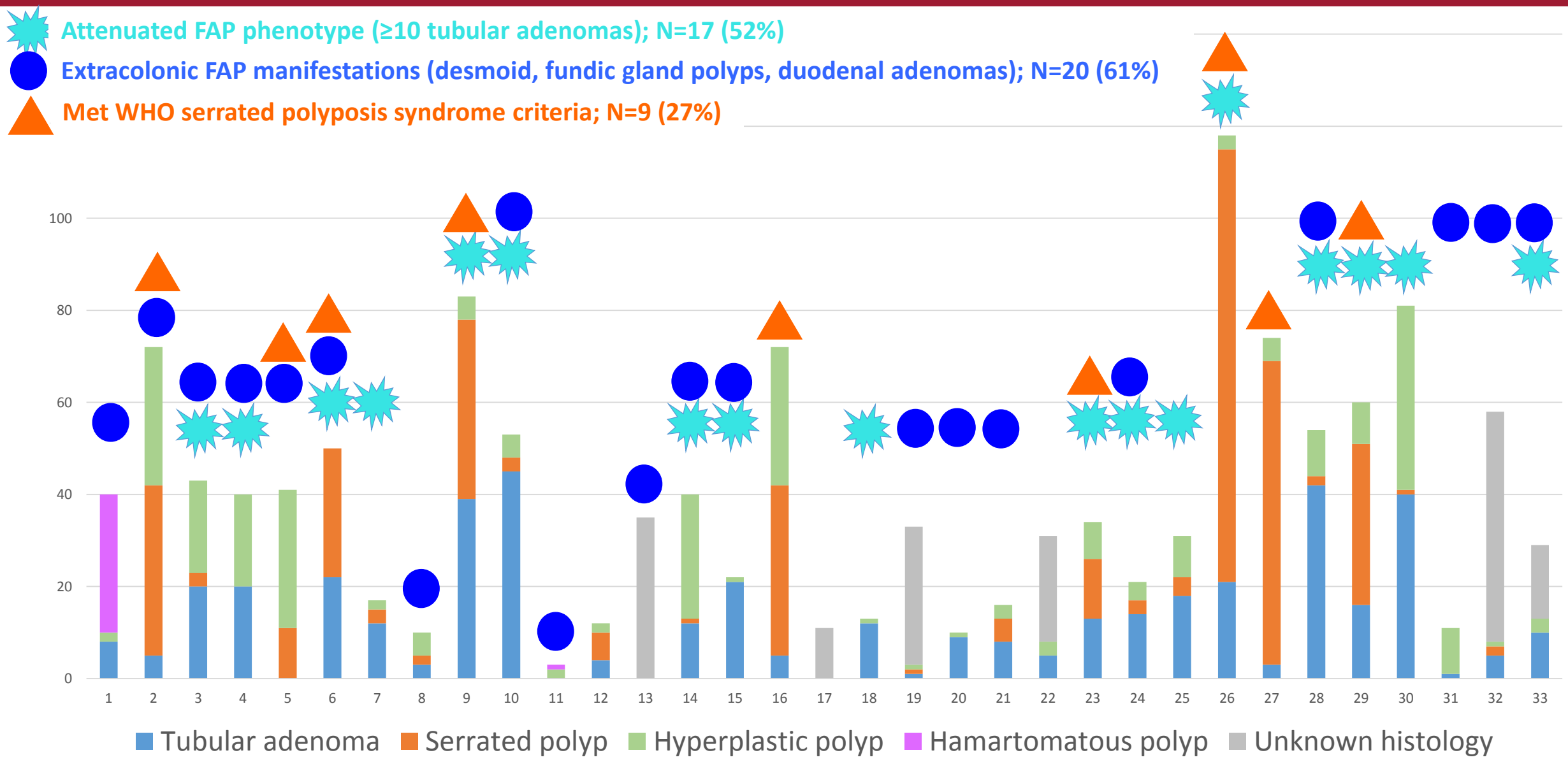
Attenuated FAP phenotype (≥10 tubular adenomas); N=17 (52%)



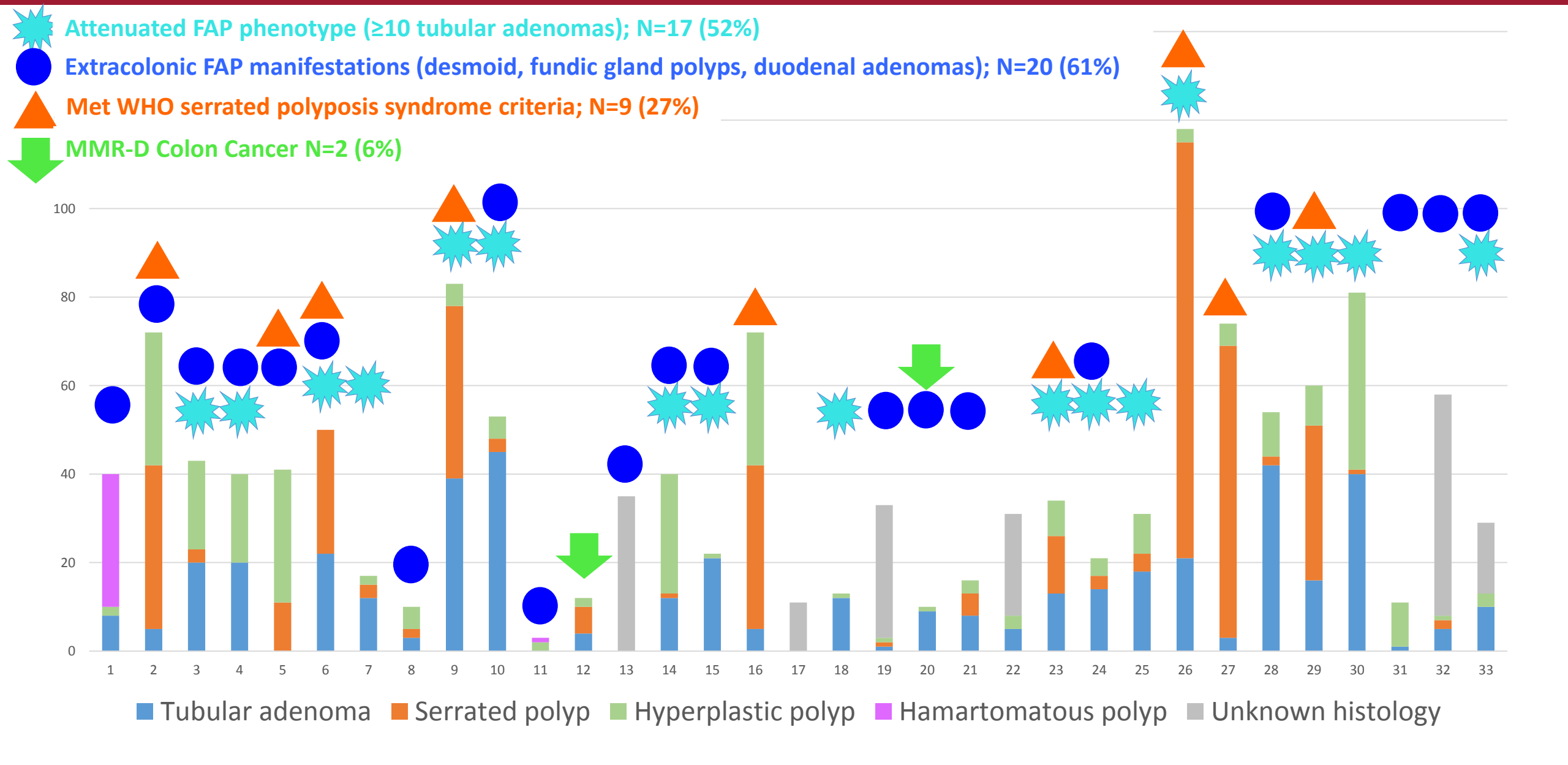
Polyp Number and Histology by Patient



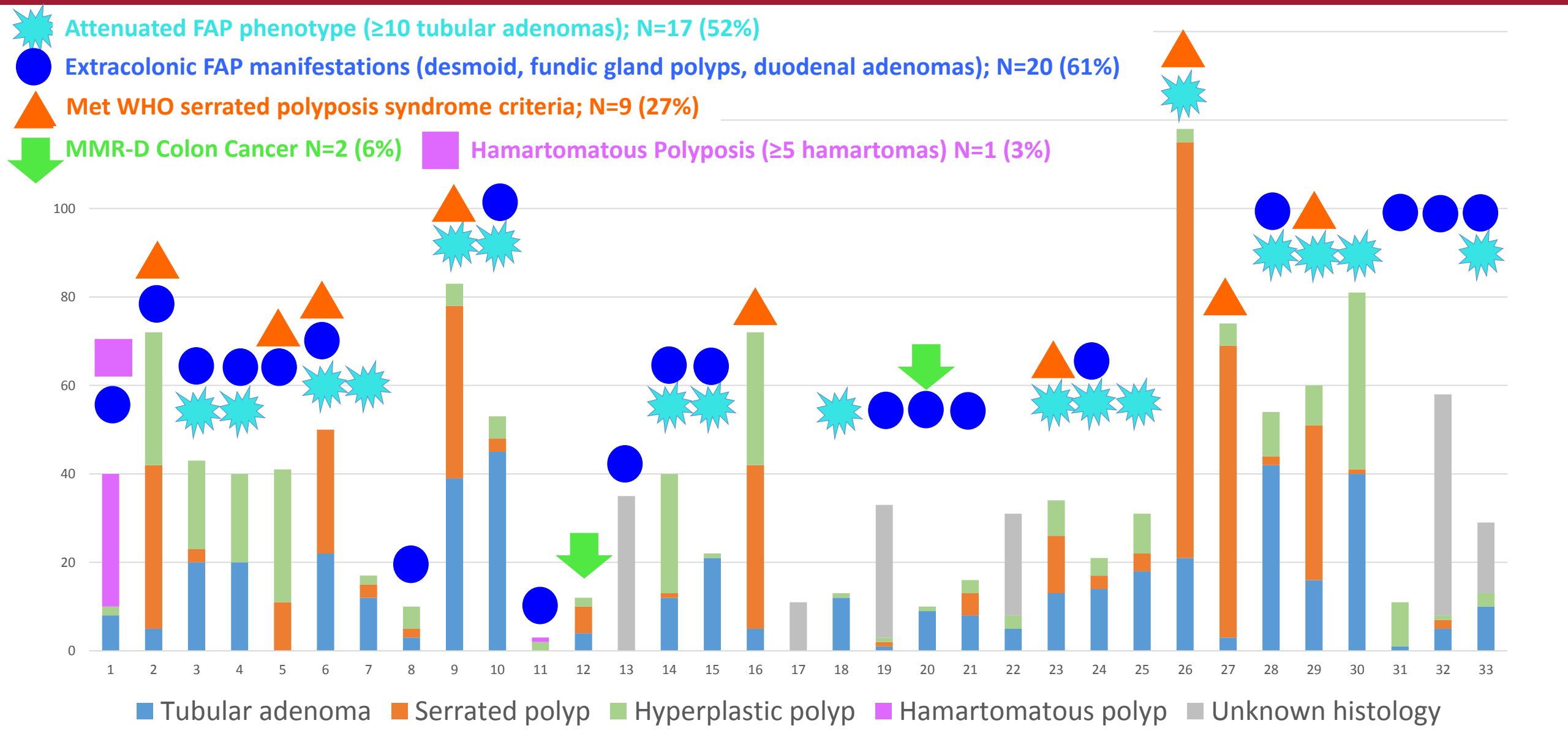
Polyp Number and Histology by Patient



Polyp Number and Histology by Patient



Polyp Number and Histology by Patient



Results Summary

- As an apparently acquired phenotype, TAP may mimic various hereditary CRC syndromes
  - 94% of cohort had phenotypic manifestations of at least one syndrome
  - 42% had manifestations of multiple syndromes
  - 94% of individuals had multiple polyp histologies

- Median duration of 27 years (range 10-43 years) from initial CYAC treatment until identification of polyposis

- TAP was not just limited to CYAC survivors treated with abdominopelvic RT

Limitations

- Descriptive case series
- Inherent ascertainment bias
- Incomplete records on some patients (some with missing polyp histology, details of prior chemo/RT)
- No molecular testing on polyp tissue to further assess pathophysiology/causation

Conclusions and Future Directions

- TAP should be considered in CYAC survivors who present with polyps/GI neoplasia

- Likely under-recognized phenomenon (nearly 1/3 developed polyposis or CRC prior to COG recommended initiation of colonoscopies)

- Hope to further assess the molecular biology of tissue from TAP patients to better understand pathophysiology
  - Heterogeneous phenotype suggests multiple neoplastic pathways

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- Michael Hall

- Erin Salo-Mullen
- Rania Sheikh
- Zsofia Stadler

- Elana Levinson
- Fay Kastrinos

Join us at the 23rd Annual Meeting of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer at the Hilton Salt Lake City Center in Salt Lake City, UT.