GI06
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Methylated *EVL* is a potential risk biomarker for colorectal cancer

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Early Detection Research Network

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Colorectal Cancer Overview

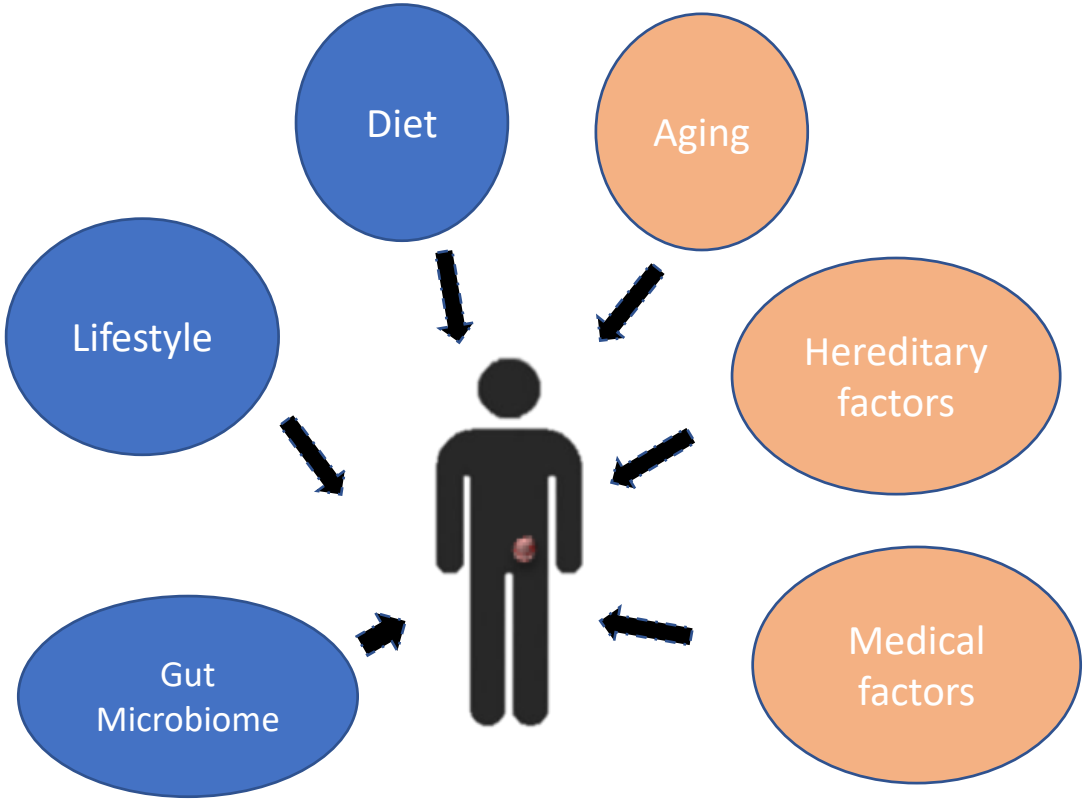
Prevalent: One of the most common cancers in U.S.

Deadly: 2nd leading cause of cancer-related death in U.S.

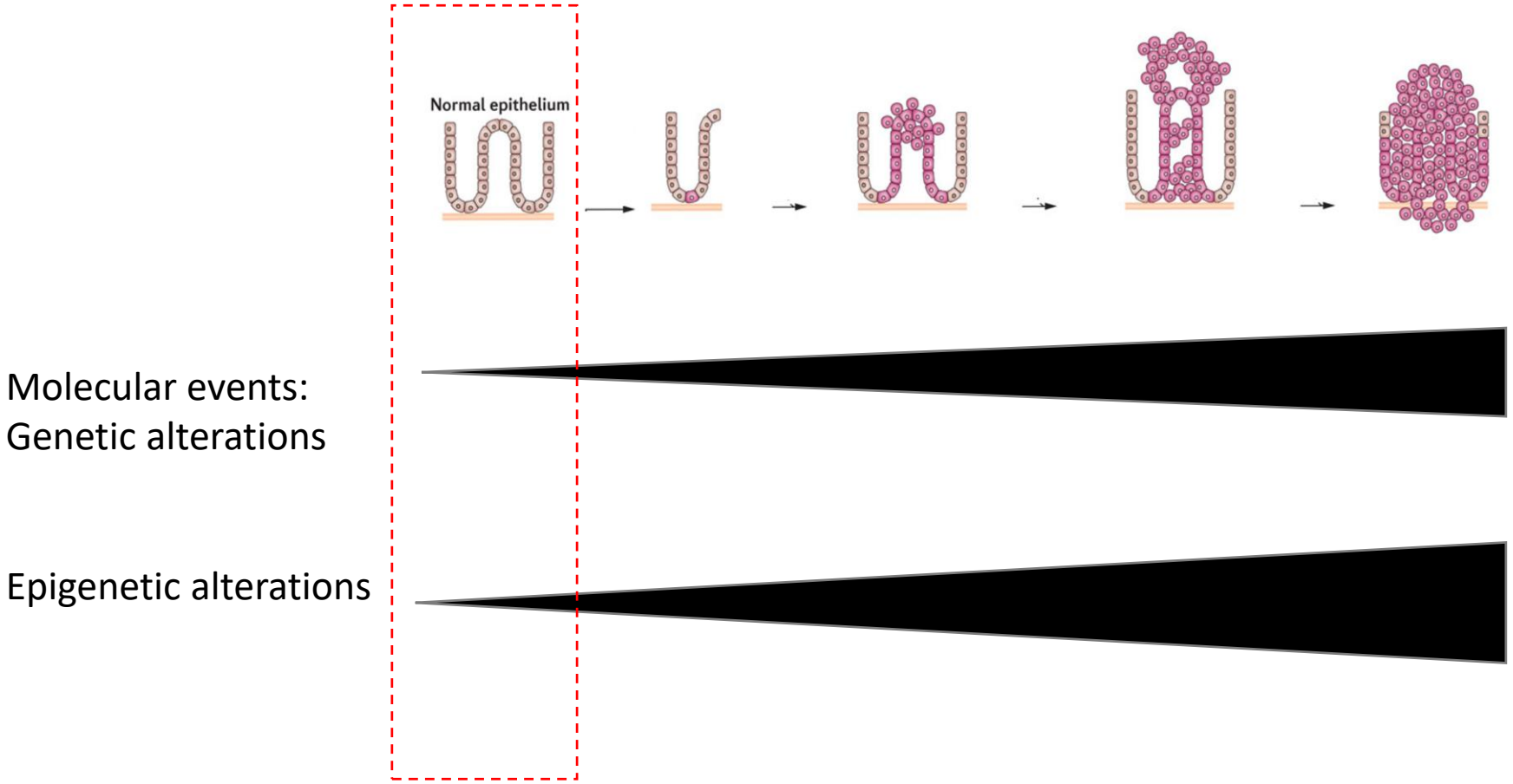
Preventable: By removing precursor lesions

Treatable: When detected early

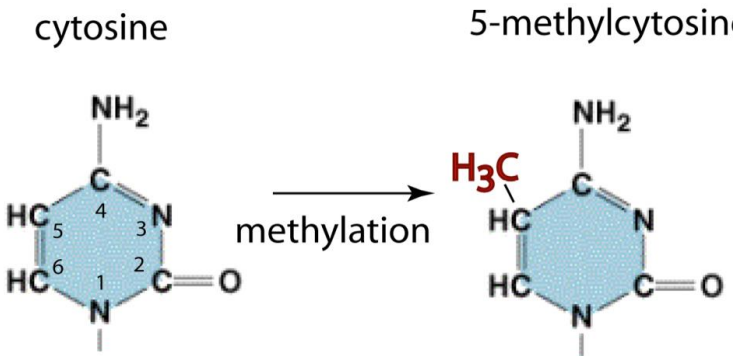
Colorectal Cancer Risk Factors = increased or high risk



Normal—polyp—cancer sequence:



DNA Methylation



- The most well characterized epigenetic mechanism.
- In humans, DNA methylation occurs in cytosines that precede guanines (dinucleotide CpGs).
- One of the most robust classes of biomarkers for CRC risk determination.

DNA methylation as markers for epigenetic field cancerization:

- Hypermethylation of *MGMT* gene promoter and the $p14^{ARF}$ locus in the normal mucosa adjacent to CRC.
- Hypomethylation of LINE-1, SAT-alpha, and SINE elements as possible field cancerization markers.
- These markers can be used to identify individuals at increased risk for CRC.

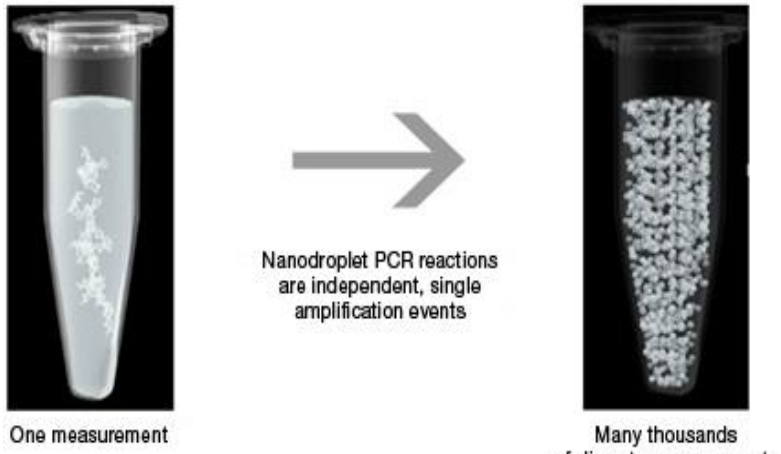
Shen 2005; Braakhuis BJ, Cancer Res 2003; Park SK Gut liver 2006; Hawthorn L Genomics 2013

EVL methylation in CRC

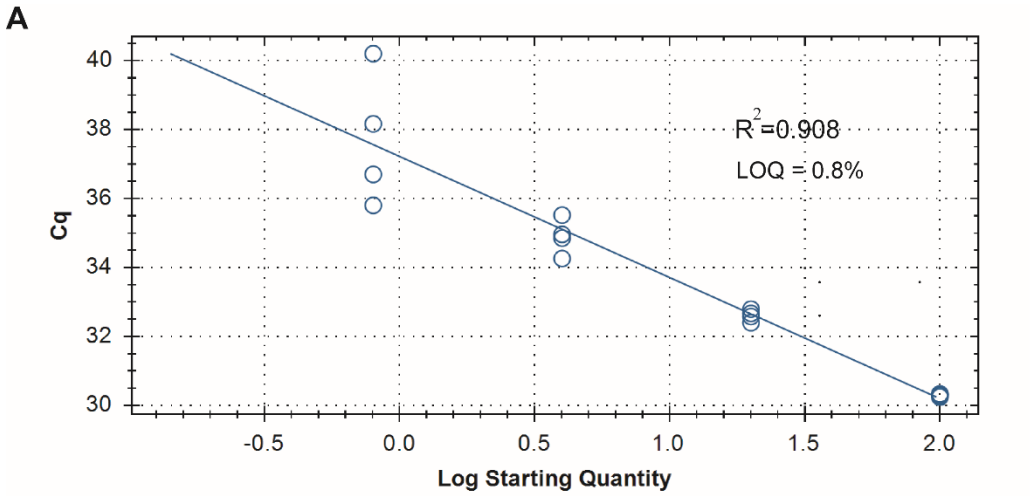
- Methylation of the microRNA *has-miR-342* and its host gene Ena/Vasp-like (EVL) was frequently methylated in adenoma and CRC.
- EVL methylation was present at higher frequency in the normal colon of people with CRC compared to average risk individuals.

(Grady WM et al., 2008)

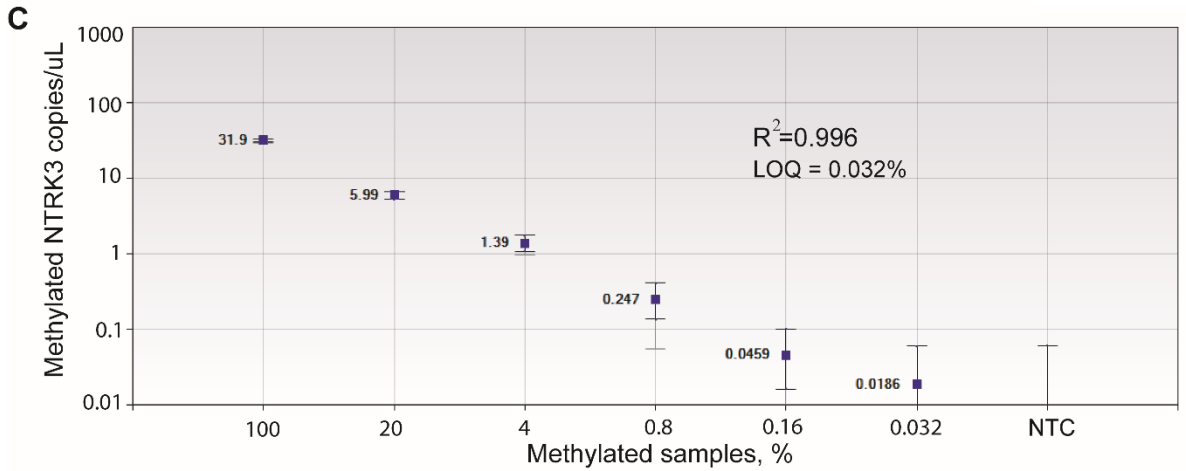
Assessment of EVL methylation using methylation-specific droplet digital (MS-ddPCR)



MS-ddPCR:
Sensitive, Precise, Quantitative



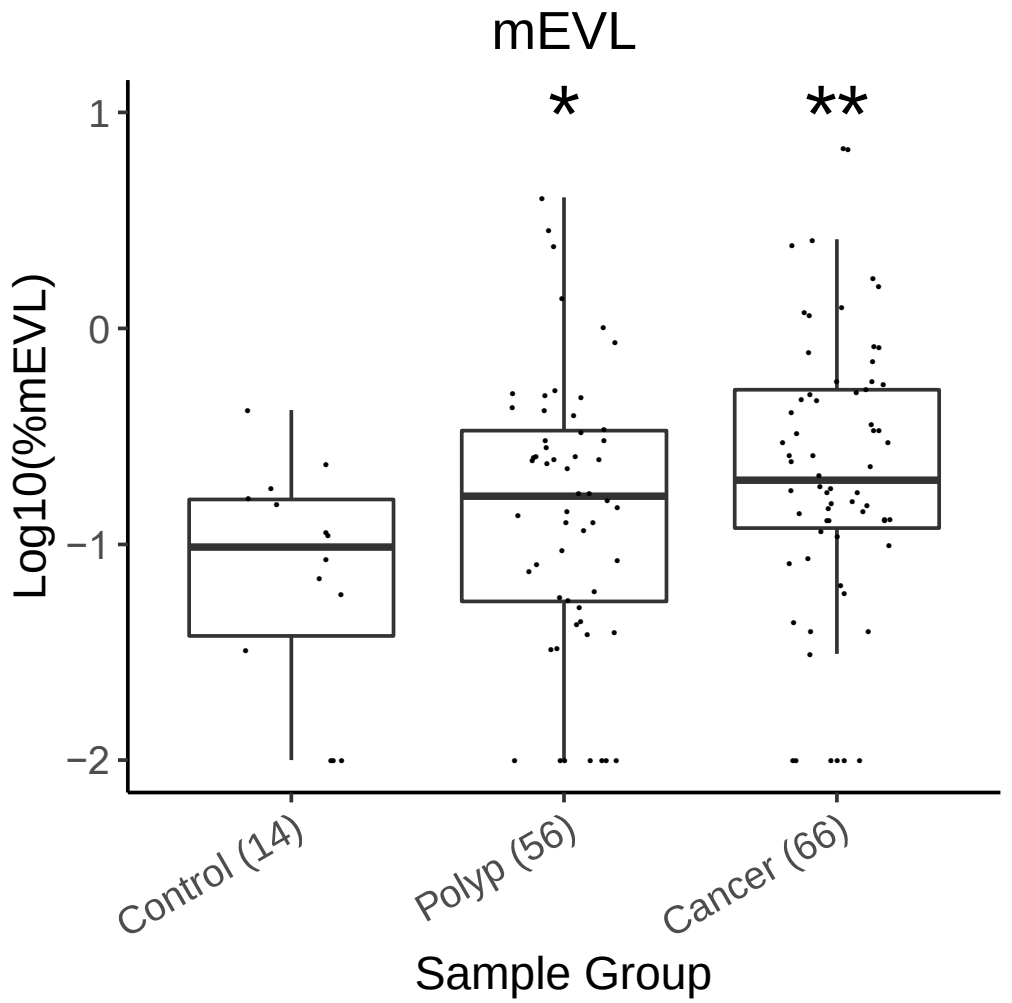
mEVL



Seattle cohort for CRC risk marker development

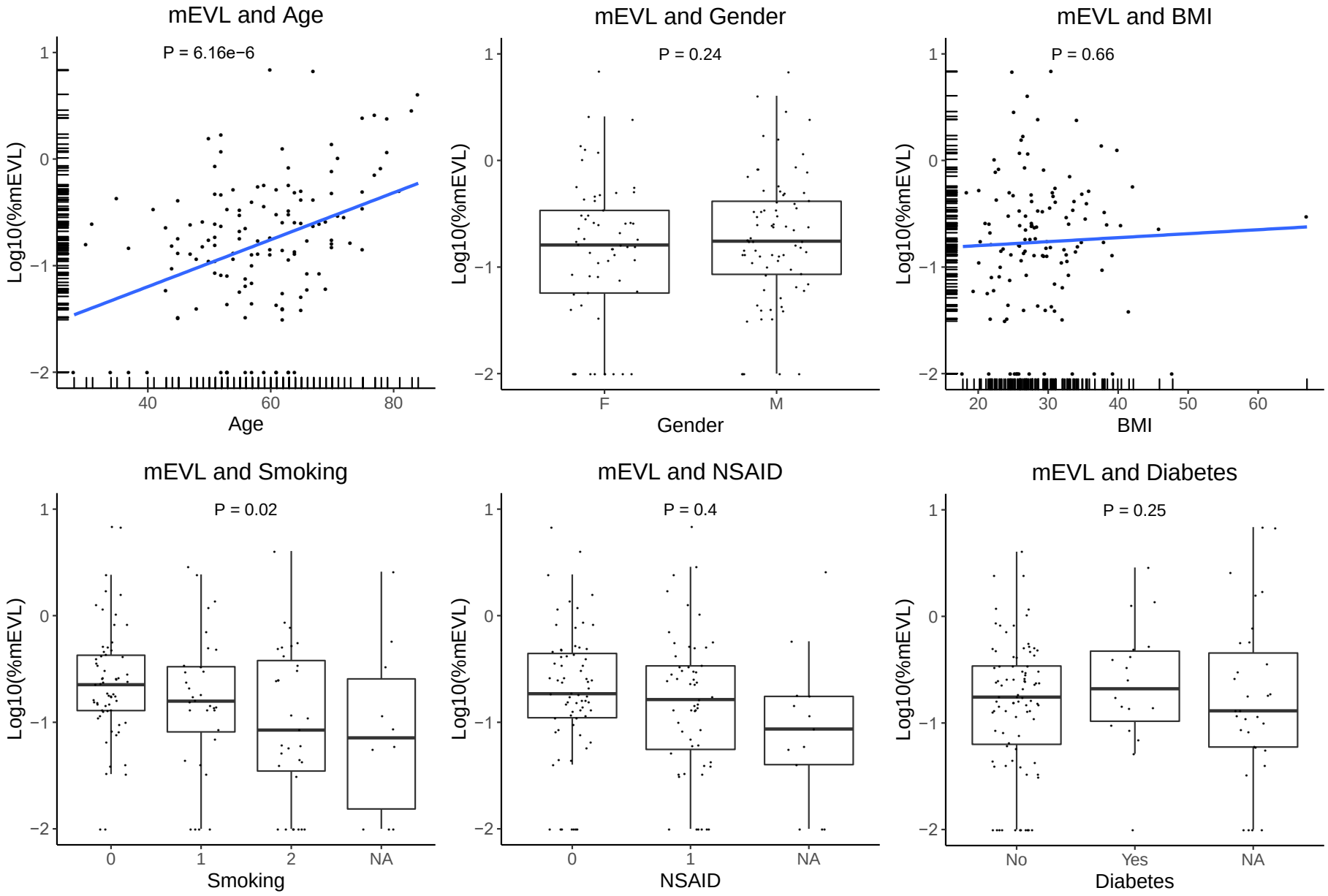
	All Patients (n = 136)	
	N	**%**
Age at First Colonoscopy		
Median (Range)	54.3	(28.5 , 85.0)
Age at Biopsy		
Median (Range)	58.3	(28.5 , 85.0)
Gender		
F	61	45%
M	75	55%
Total # of Colonoscopy Visits		
1	25	18%
2	46	34%
3	37	27%
4	8	6%
5	8	6%
6	5	4%
7	3	2%
8	3	2%
9	1	1%
Total	**136**	**100%**

EVL methylation is elevated in normal colon from patients with cancer or polyps.

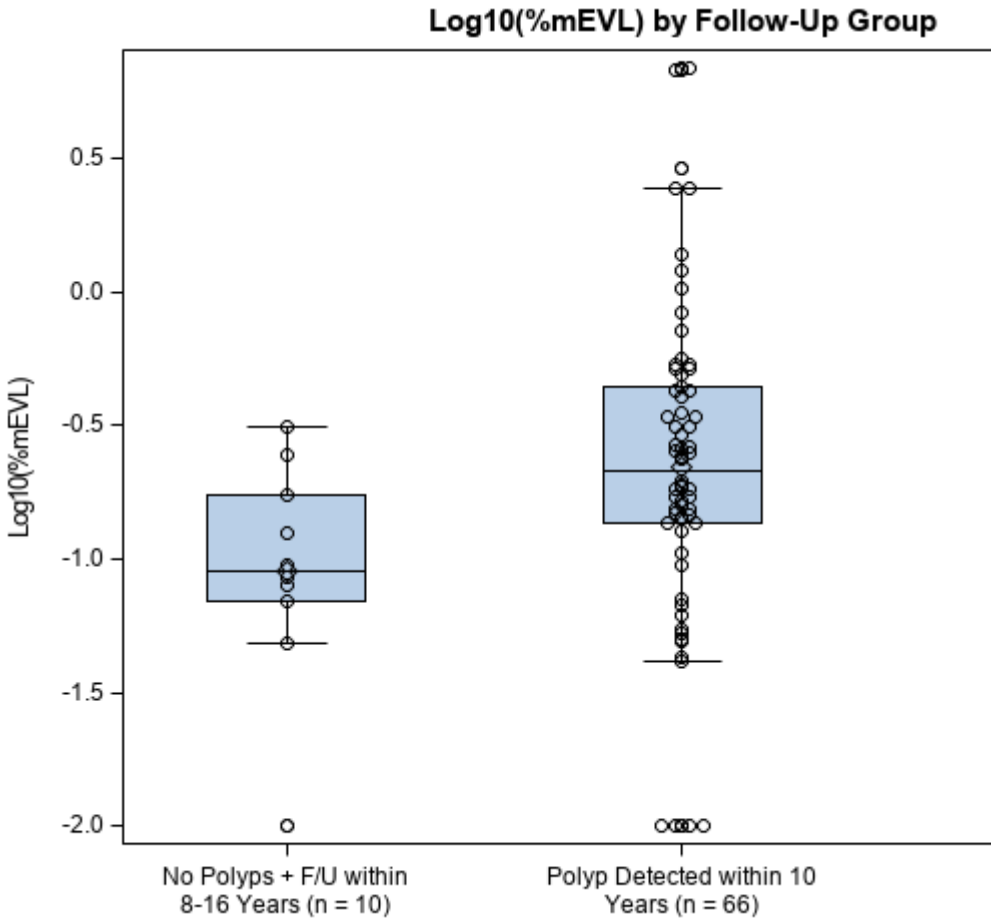


Mann-Whitney test, * for $p < 0.05$, ** for $p < 0.01$

Methylated EVL is significantly associated with age.



High mEVL level correlates with increased risk of having a polyp detected within 10 years



Inverse Probability Weighted (IPW) Model

Outcome = Polyp Detected within 10 Years (vs. No Polyps + F/U within 8-16 Years)

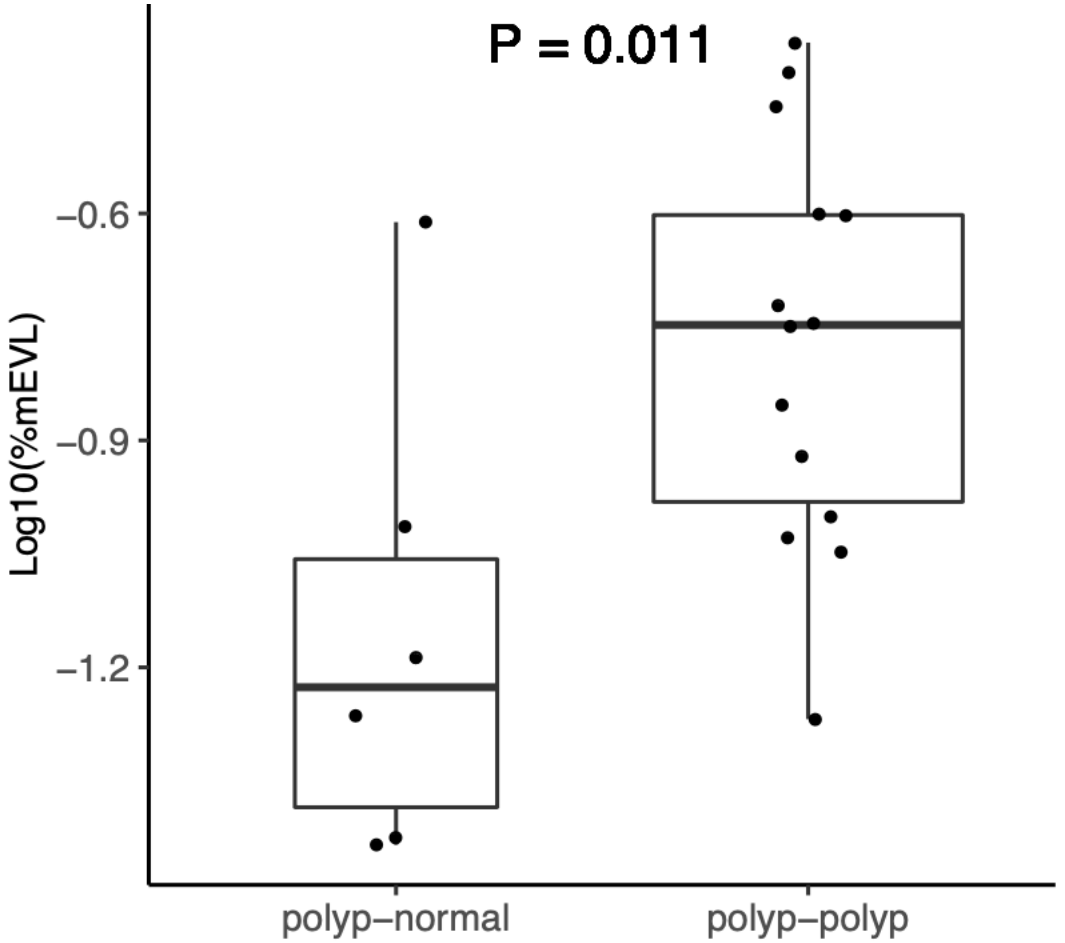
(Observations = 76; Events = 66)

Variable	Odds Ratio	95% Lower CL	95% Upper CL	P-Value
Log(%mEVL) - per 1 unit increase	4.08	1.24	13.46	**0.02**

High mEVL level is associated with risk for recurrent polyps

UPMC patients with follow-up information

	Follow-up Normal (n=6)	Follow-up Polyp (n=14)	*P*-value
Age			0.342
Median (Range)	58 (50, 76.5)	65 (48.5, 76)	
Gender			0.115
F	0	6	
M	6	8	
mEVL			0.049
Median (Range)	0.060 (0.037, 0.245)	0.179 (0.054, 0.423)	



Summary

- EVL methylation is elevated in normal colon from patients with cancer or polyps;
- Statistical analysis suggest that for higher levels of mEVL, there is increased risk of having a polyp detected within 10 years;
- EVL methylation level is associated with risk for recurrent polyps;
- Future validation study with prospective study design is needed to evaluate the potential of EVL methylation as CRC risk biomarker.

5 minute Q&A

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