Inflammatory Bowel Disease Neoplasia

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Neoplastic Progression in Chronic Inflammatory GI Dz

Inflammation

Dysplasia

Carcinoma

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Chronic Inflammatory GI Disease & Cancer

- Barrett's Esoph → Esoph CA
- HP Gastritis → Gastric CA
- Hepatitis B & C → HCC
- Ch Pancreatitis → Panc CA
- UC and Crohn's → Intestinal CA

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Ulcerative Colitis: A Paradigm

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Managing Cancer Risk in UC

- Ignore it
- "Prophylactic" colectomy
- Colonoscopic surveillance for dysplasia / early carcinoma

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Optimal Colonic Biomarker

- Pancolonic distribution
- Predate incurable cancer
- Objective
- Sensitive, Specific, ↑PPV, ↑NPV

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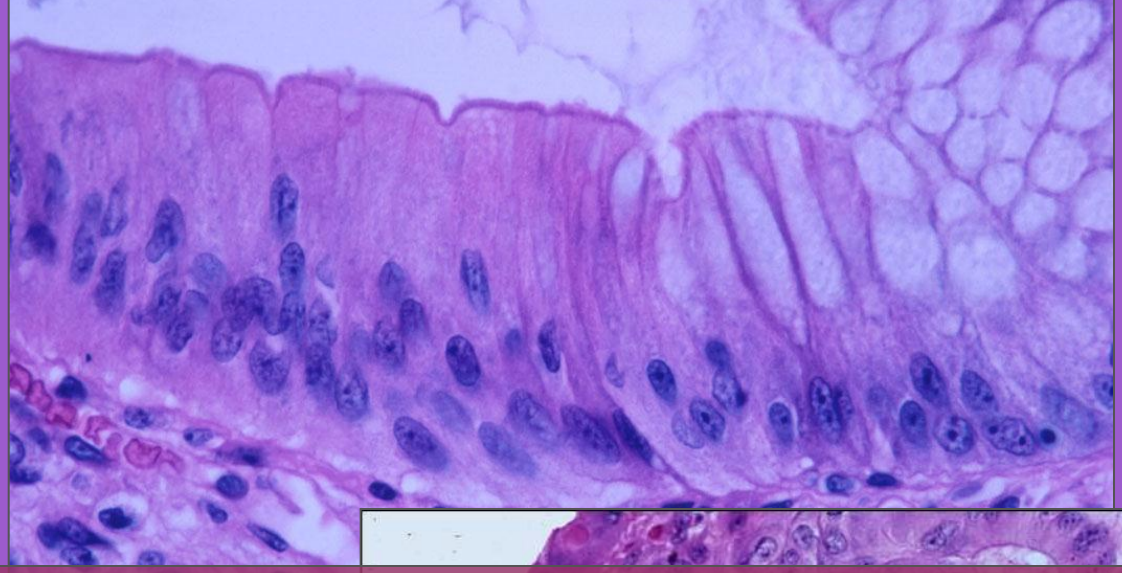
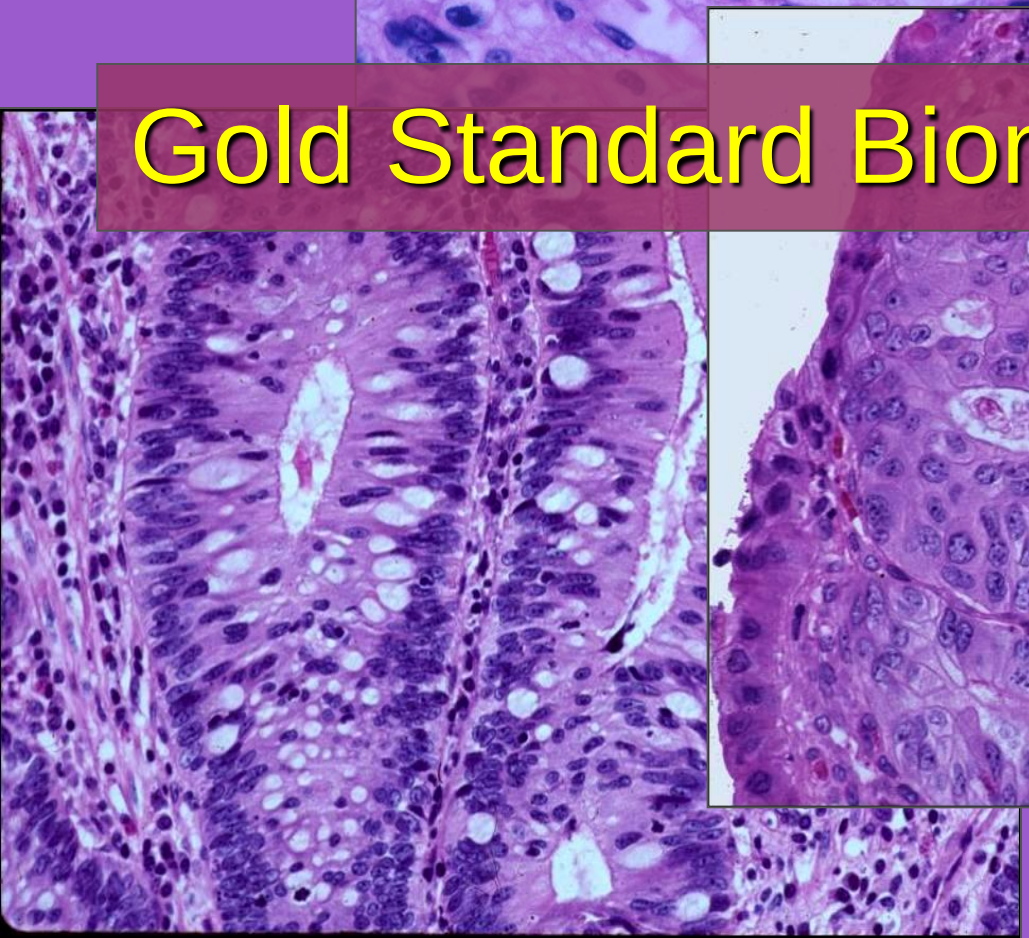
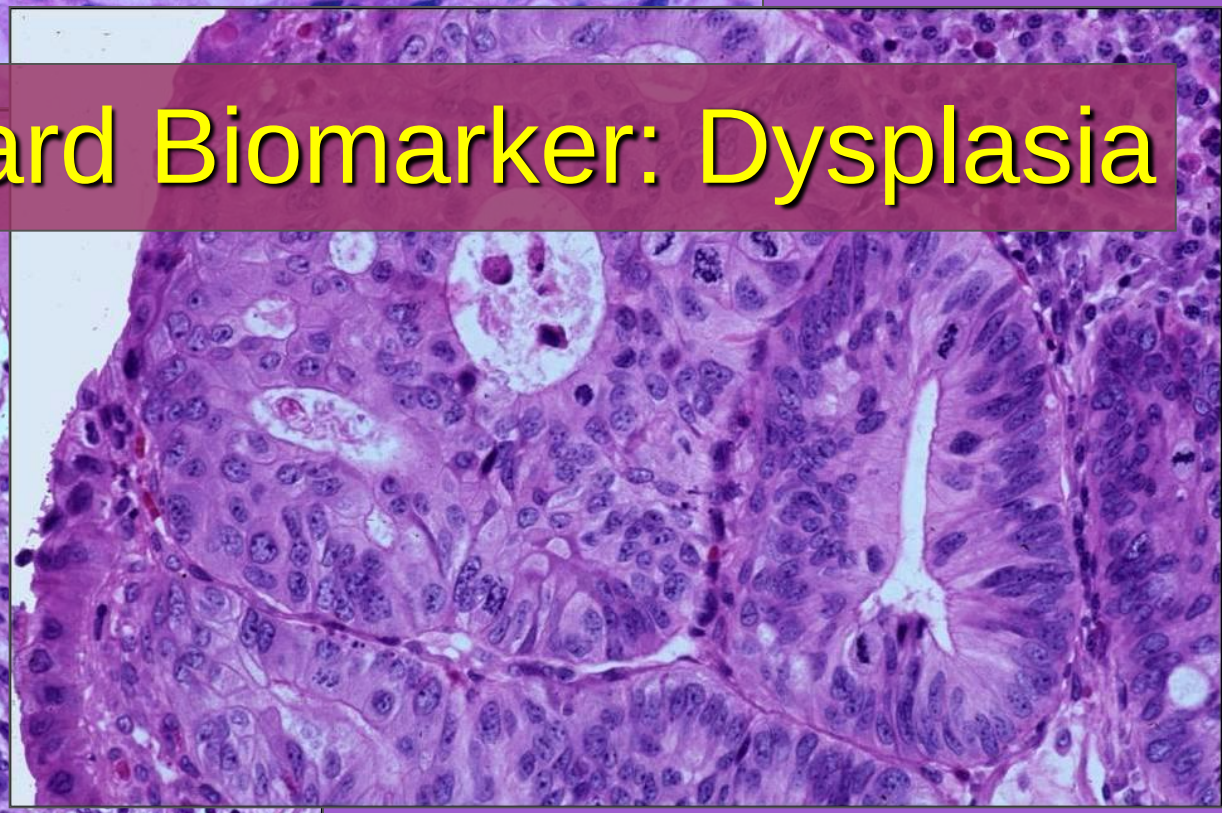
Gold Standard Biomarker: Dysplasia







Dysplasia: Problems

- Sampling
- Distinction from reactive change
- Observer variation
- Natural history incompletely understood

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Adequate Bx Sampling

	Histology	
	Dysplasia	Cancer
No. Bx's for 90% confidence	33	34
No. Bx's for 95% confidence	56	64

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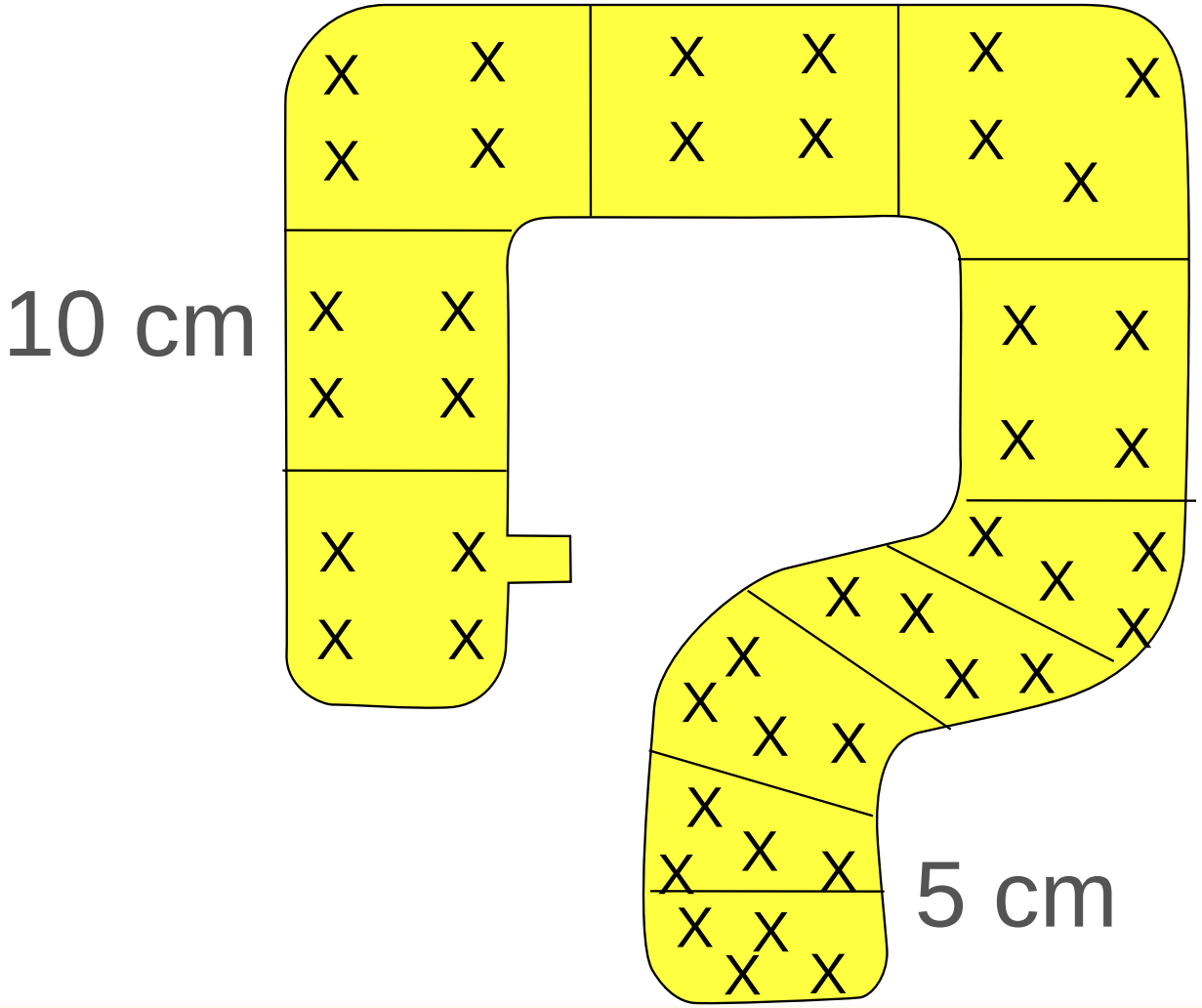
From: Rubin CE, et al. *Gastroenterology* 1992;103:1611

UC Surveillance Protocol



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Rectosigmoid Predominance of Ulcerative Colitis Cancer

Location of Colorectal Carcinoma

RS	D	T	A/C
52%	12%	21%	15%

Choi PM. *Gastroenterology* 1993;104:666 Summary of 5 Studies

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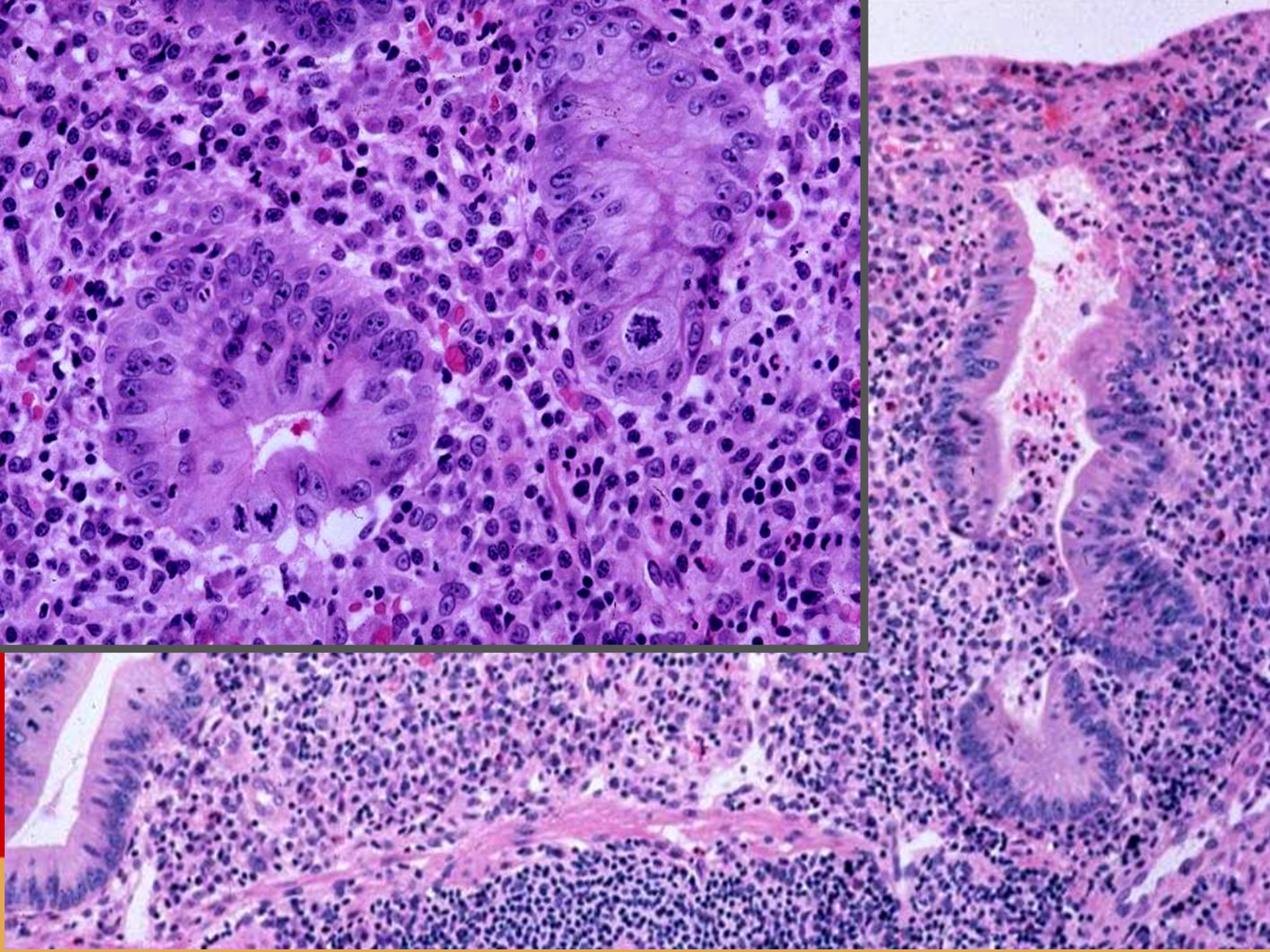

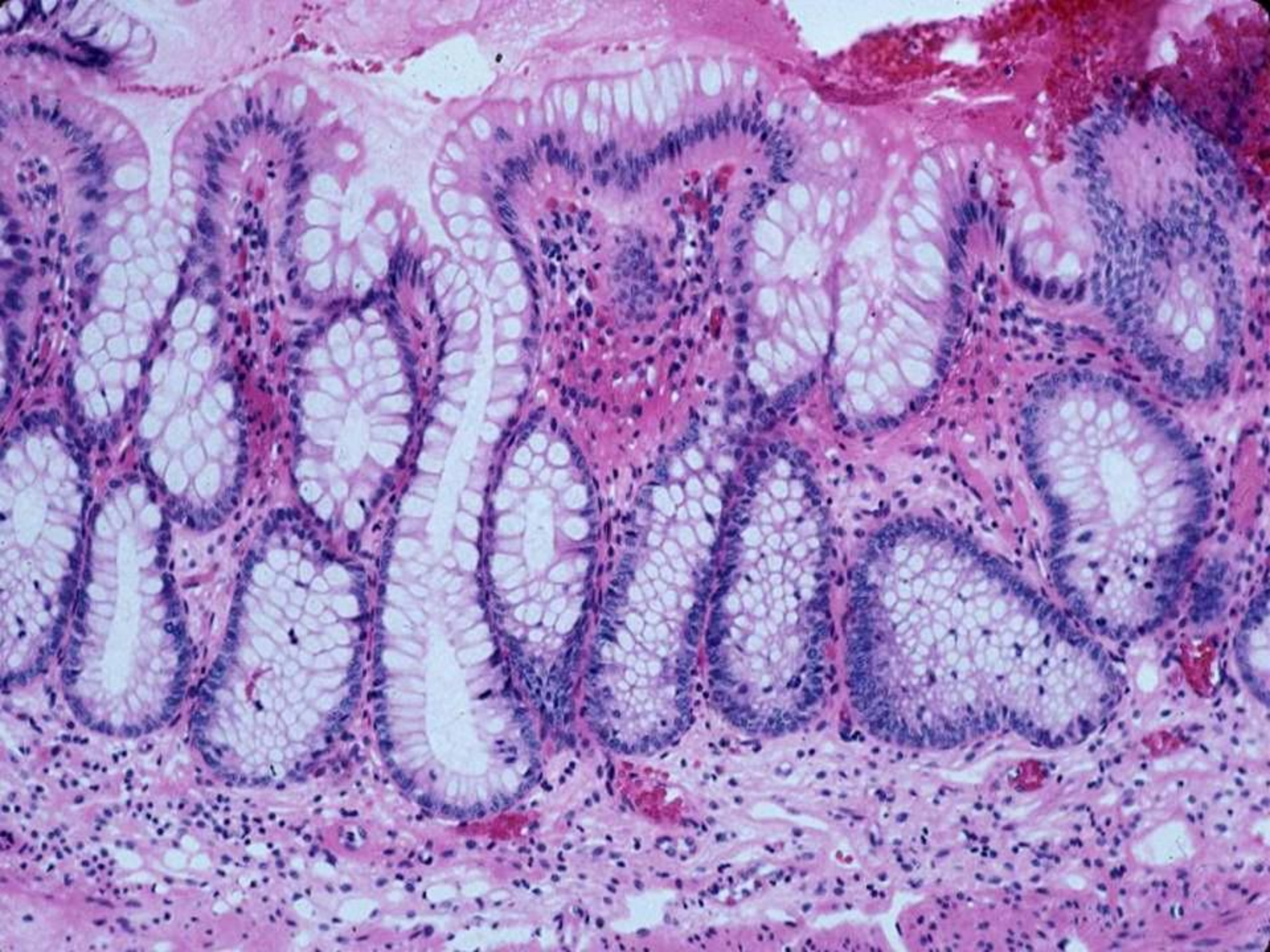

Dysplasia: Problems

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- Distinction from reactive change
- Observer variation
- Natural history incompletely understood

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Outcome of 40 UC LGD Patients

- 78% no progression, avg f/u 5y (1-13 y)
- 22% HGD, avg f/u 1.5 y (1-3 y)
- ≥3 LGD biopsies: 9x↑ progression risk
- 2 non-compliant patients developed Dukes' A cancer

Brentnall, Bronner, et al. Prospective study of progression of LGD in UC. *Inflamm Bowel Dis* 18:2240-6, 2012.

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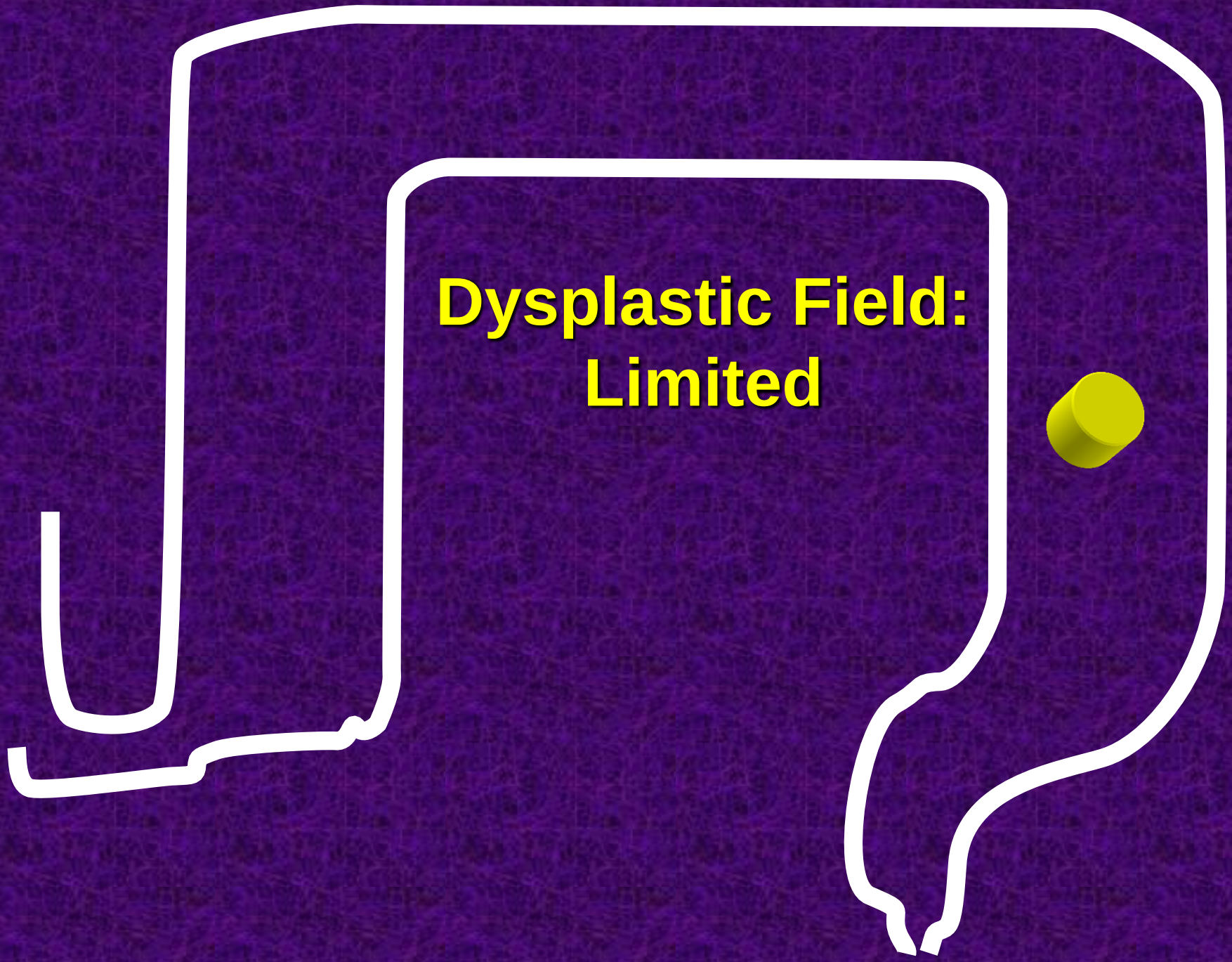
Dysplastic Field:
Limited

Better Biomarkers of Cancer Risk Greatly Needed!

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Chromosomal Instability?

- FCM Aneuploidy - Detects gross chromosomal instability
- CGH - Detects clonal gains and losses of chromosomal regions
- FISH - Detects clonal and *non-clonal* chromosomal abnormalities

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Biopsy Sampling: Flow Cytometry

	Dysplasia	Cancer
No. Bx for 90% confidence	20	8
No. Bx for 95% confidence	30	14

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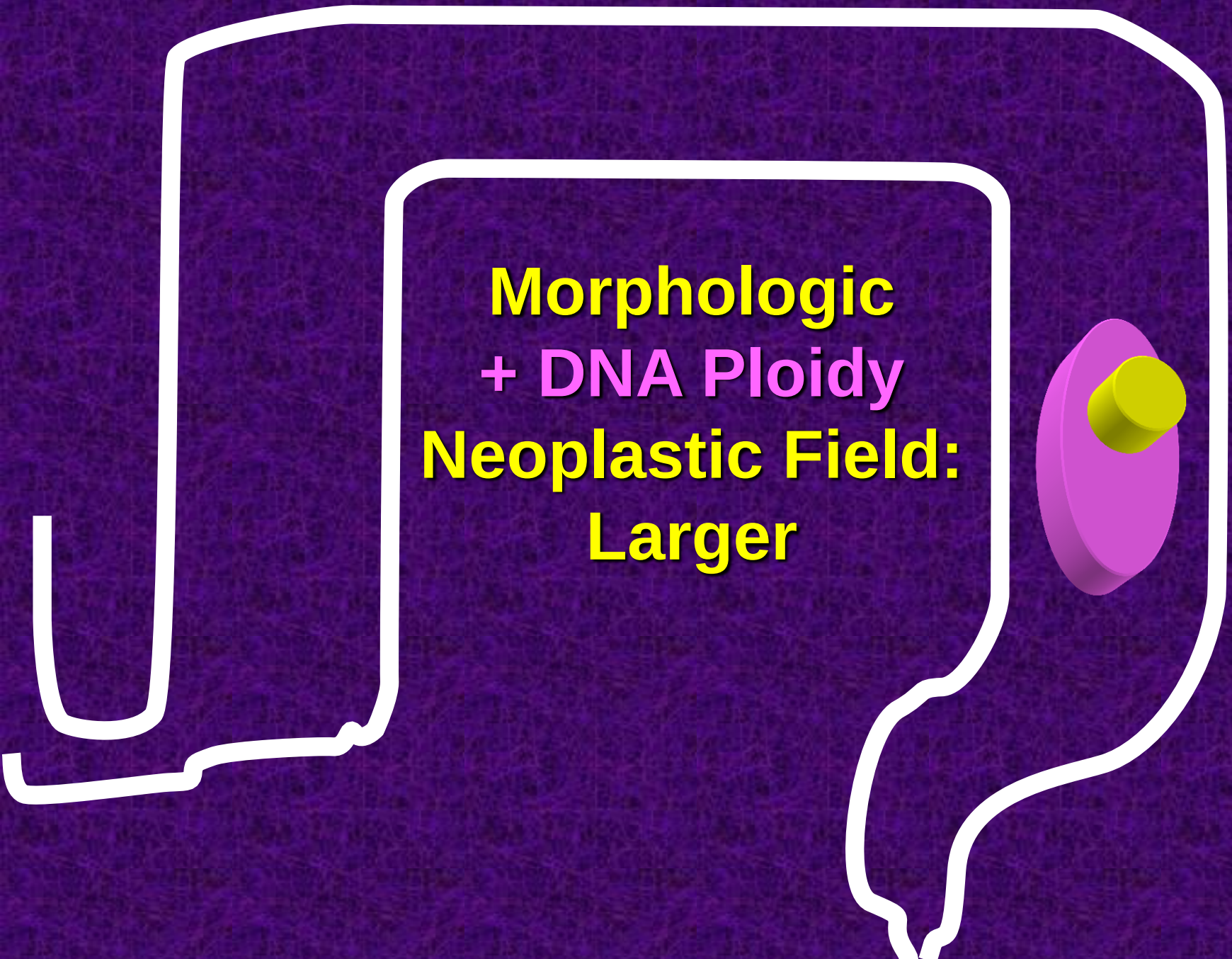
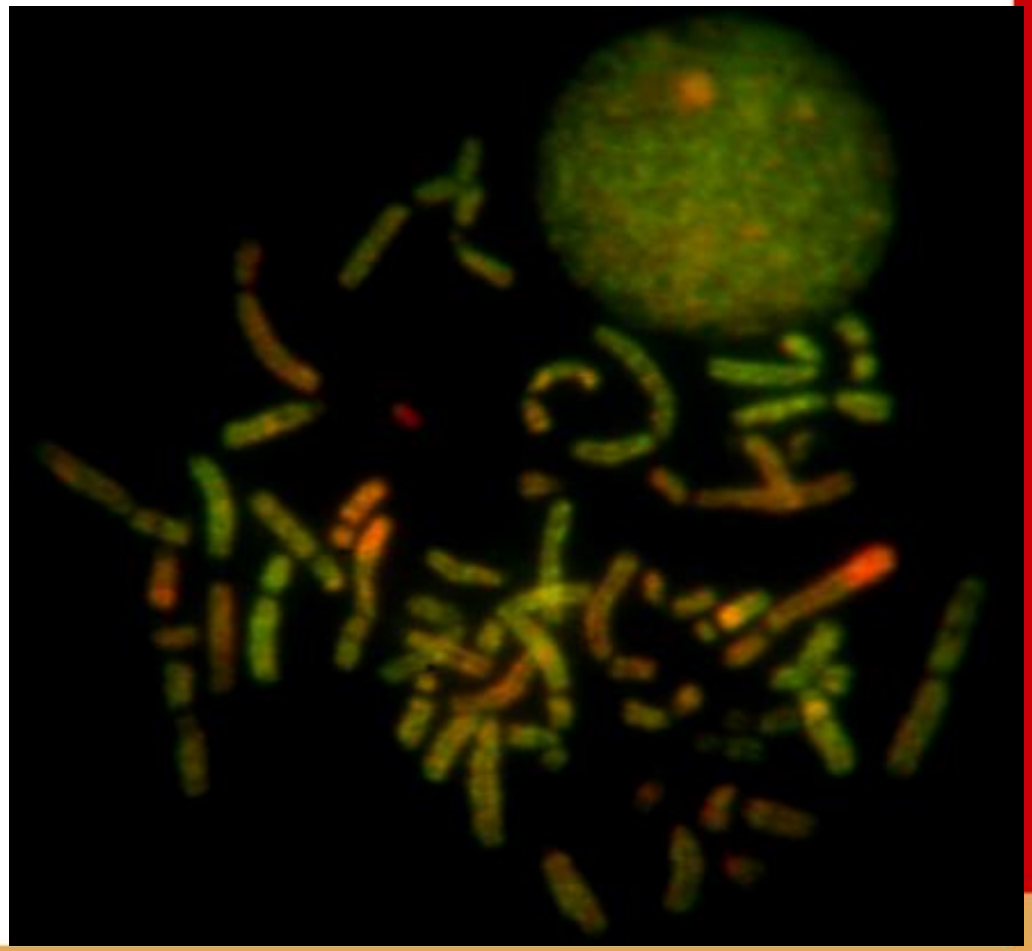
Rubin CE, et al. *Gastroenterology* 1992;103:1611


Morphologic
+ DNA Ploidy
Neoplastic Field:
Larger

Metaphase Comparative Genomic Hybridization in UC

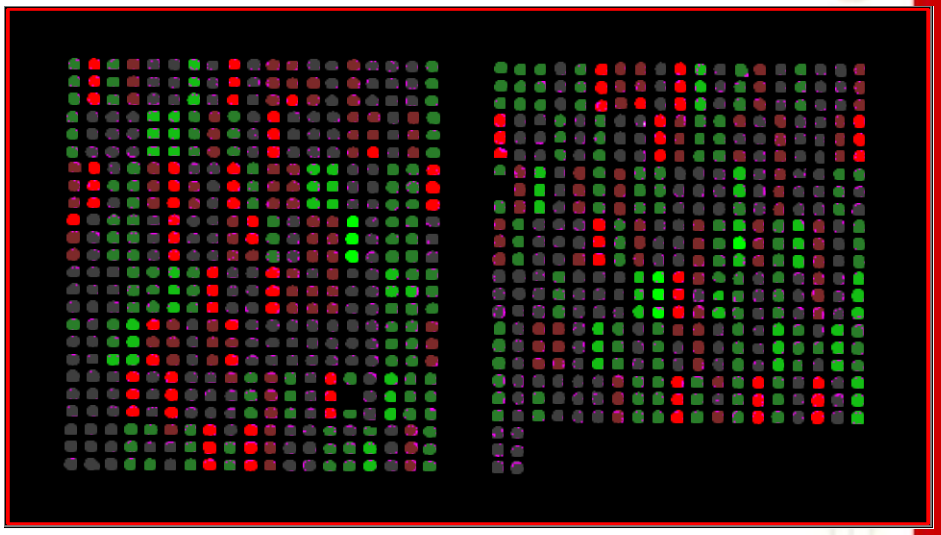
39% (15/38) of diploid bx's near dysplasia or cancer showed CGH detectable alterations

Performed in collaboration with F. Waldman, UCSF



Array-based Comparative Genomic Hybridization (CGH)

- Chromosomes replaced by ordered array of targets
- Karyotyping of metaphase spreads not necessary
- Greatly increased resolution



Array CGH in UC

- 100% (9/9) UC-progressors extensive chromosomal gains and losses
- FISH and PCR targets identified

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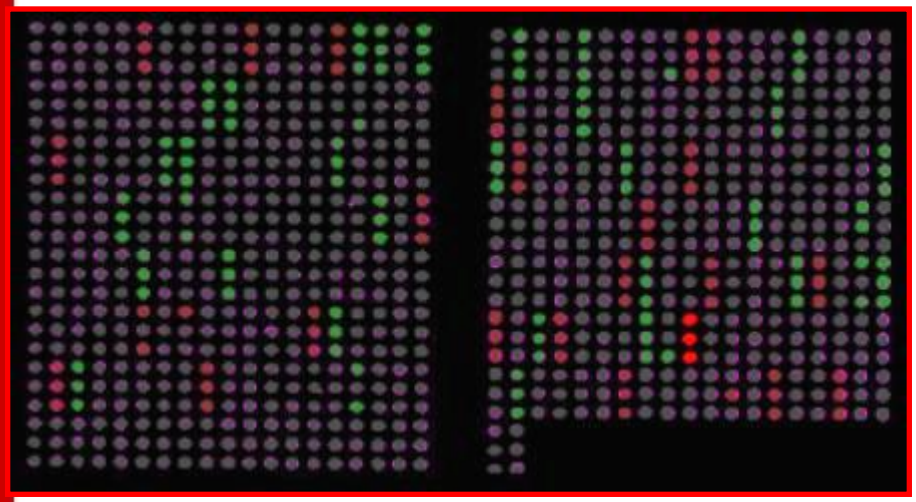
Bronner MP, *Mod Pathol* 2010;23:1624-33

Ulcerative Colitis A-CGH



- PROGRESSORS
- NON-PROGRESSORS

Gain
Loss

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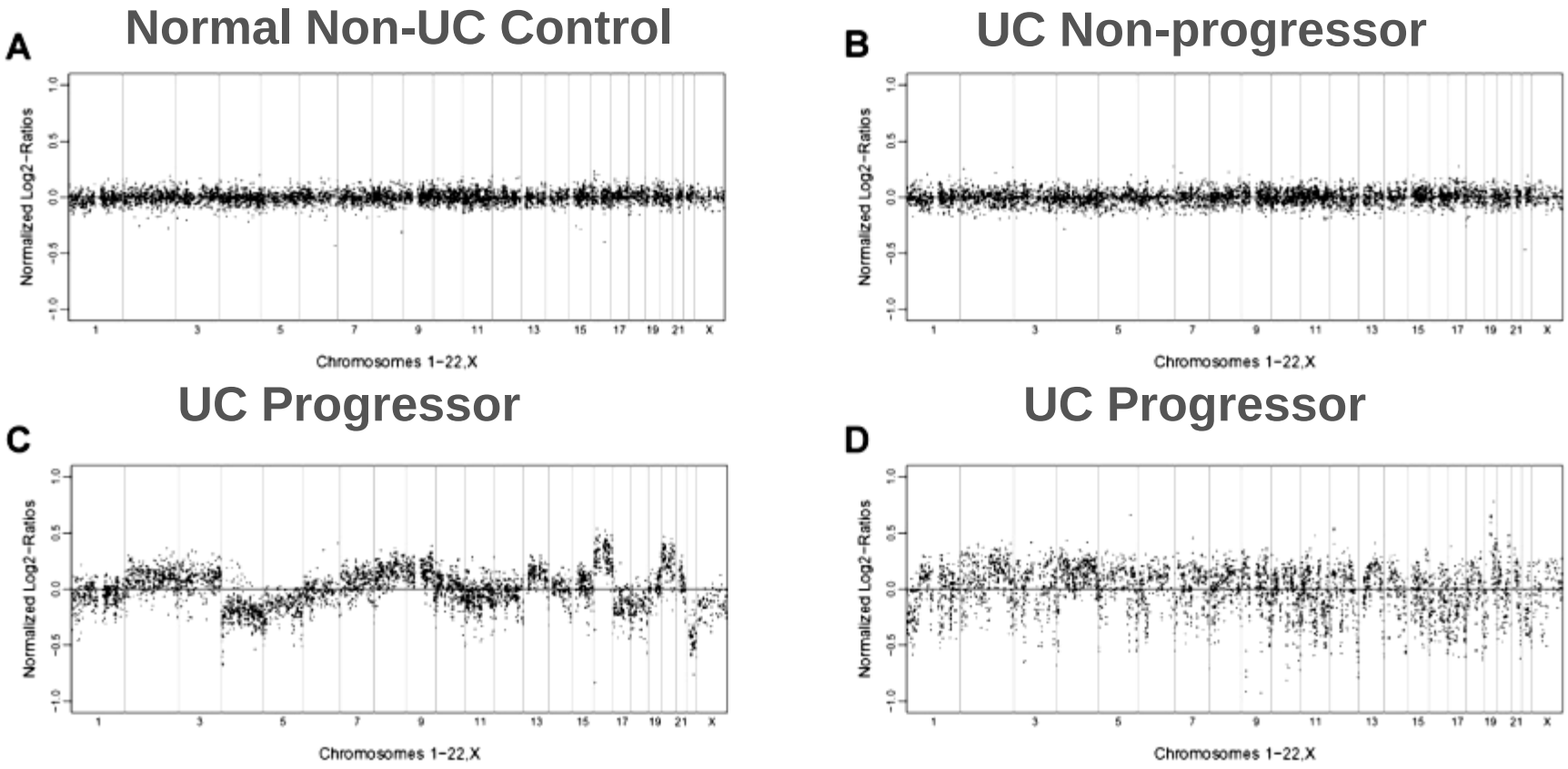
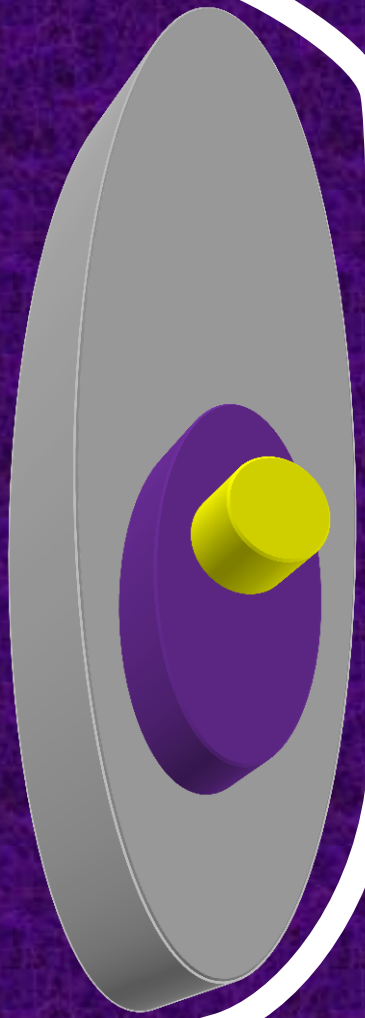
Bronner MP, *Mod Pathol* 2010;23:1624-33.

BAC CGH Whole Genome Log2-Ratio Plots of All Chromosomes



Bronner MP, *Mod Pathol* 2010;23:1624-33.

Morphology
+ DNA Ploidy
+ CGH
Neoplastic Field:
Larger Still



Non-Clonal Change in UC: Wider Field?

- DNA Flow & CGH detect clonally expanded abnormalities only
- Larger fields of *non-clonal* instability? Detectable in negative biopsies, even from rectum?
- Assessed by Fluorescence In Situ Hybridization (FISH)?

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UC FISH

Hypothesis:

UC progressors differ from UC non-progressors using non-clonal genomic instability biomarkers on *single negative rectal biopsies*

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FISH

- Interphase nuclear suspensions placed on glass slide
- Locus specific probes (Chrom 8, 11, 17, 18) & centromeres (green and red)
- Red and green FISH spots counted per 100 nuclei

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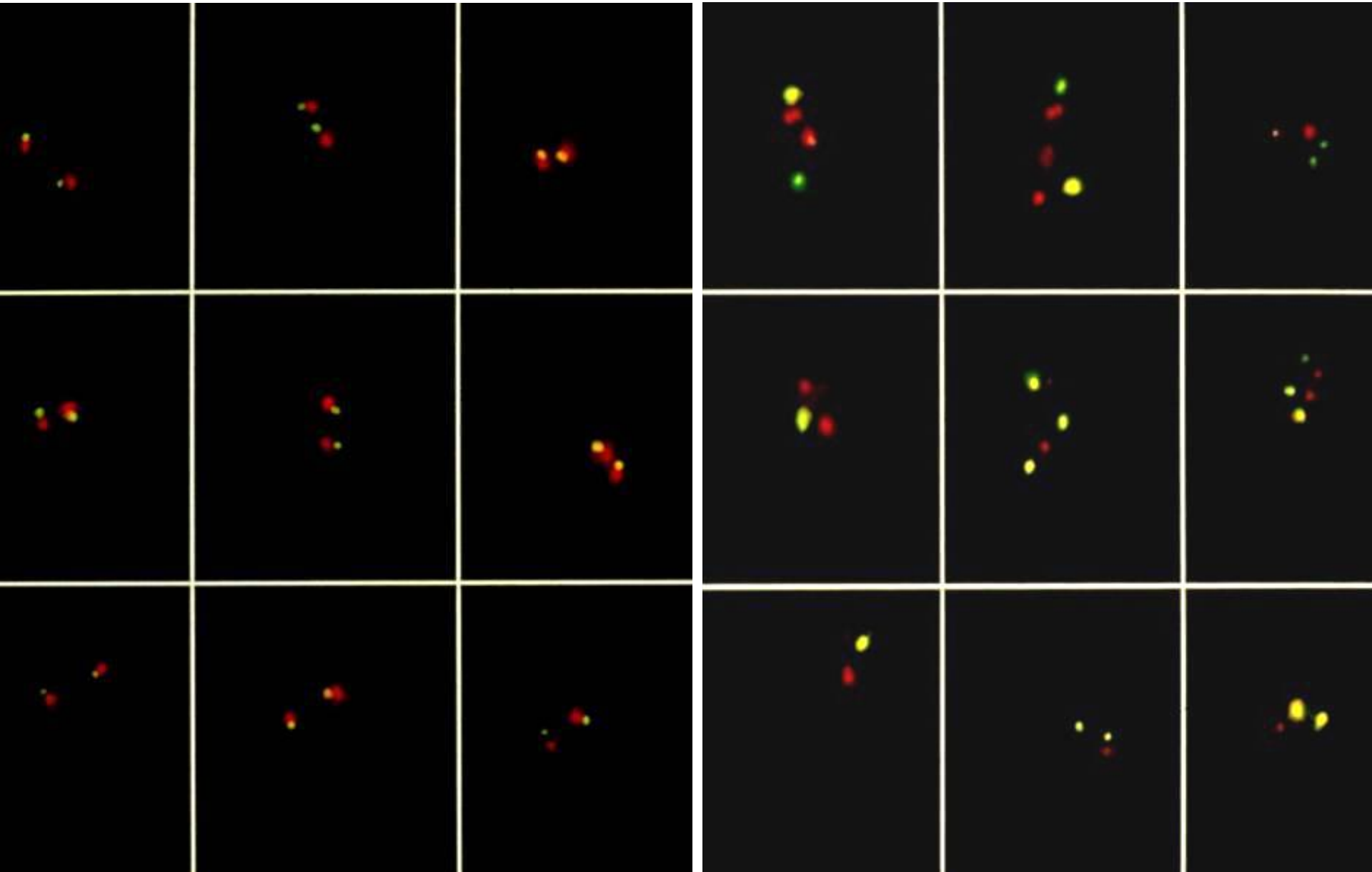
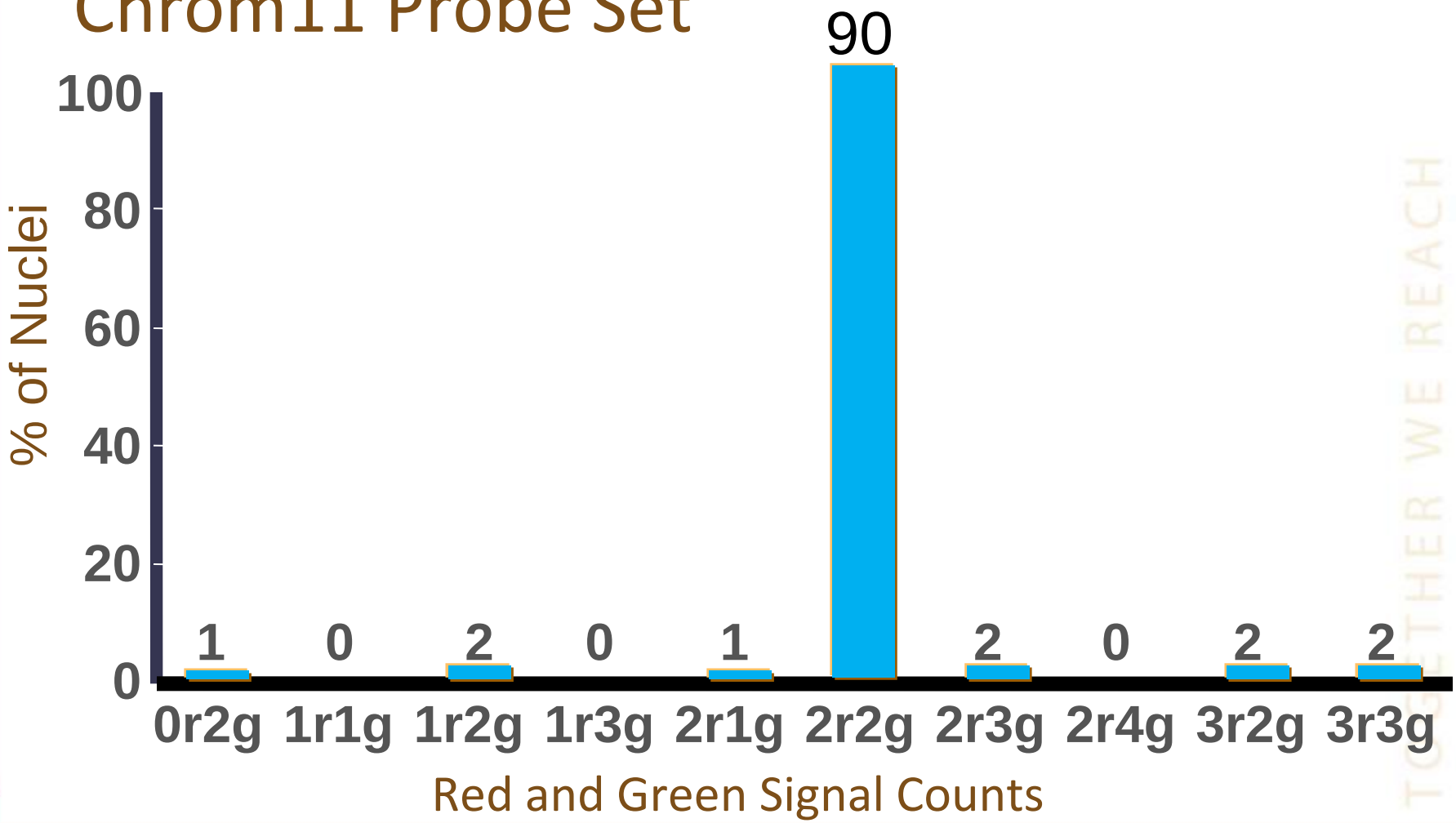
Normal Cells

Abnormal Cells



Control Normal Colon FISH Chrom11 Probe Set



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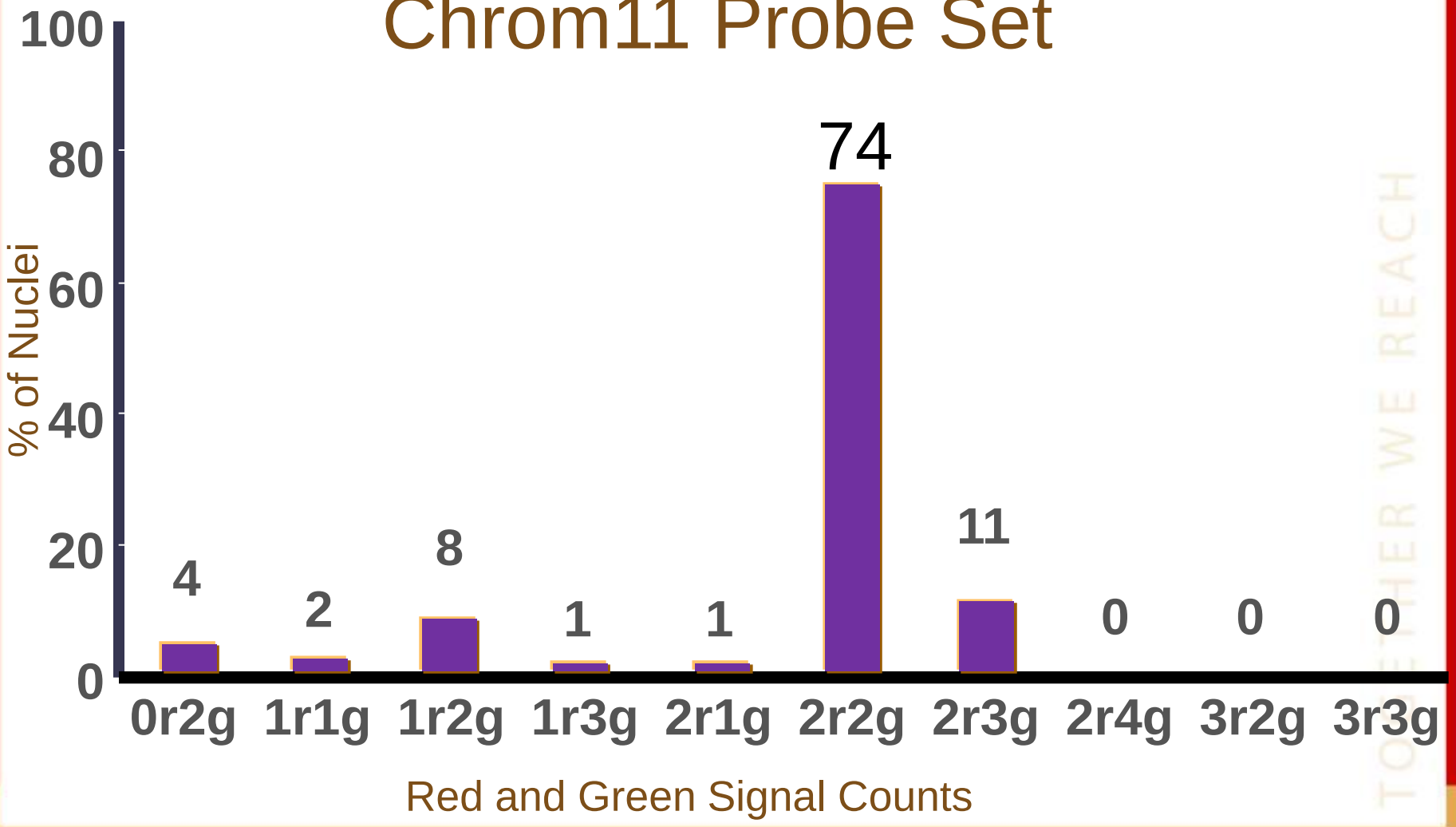
Diploid Neg Rectal Bx UC Progressor Chrom11 Probe Set



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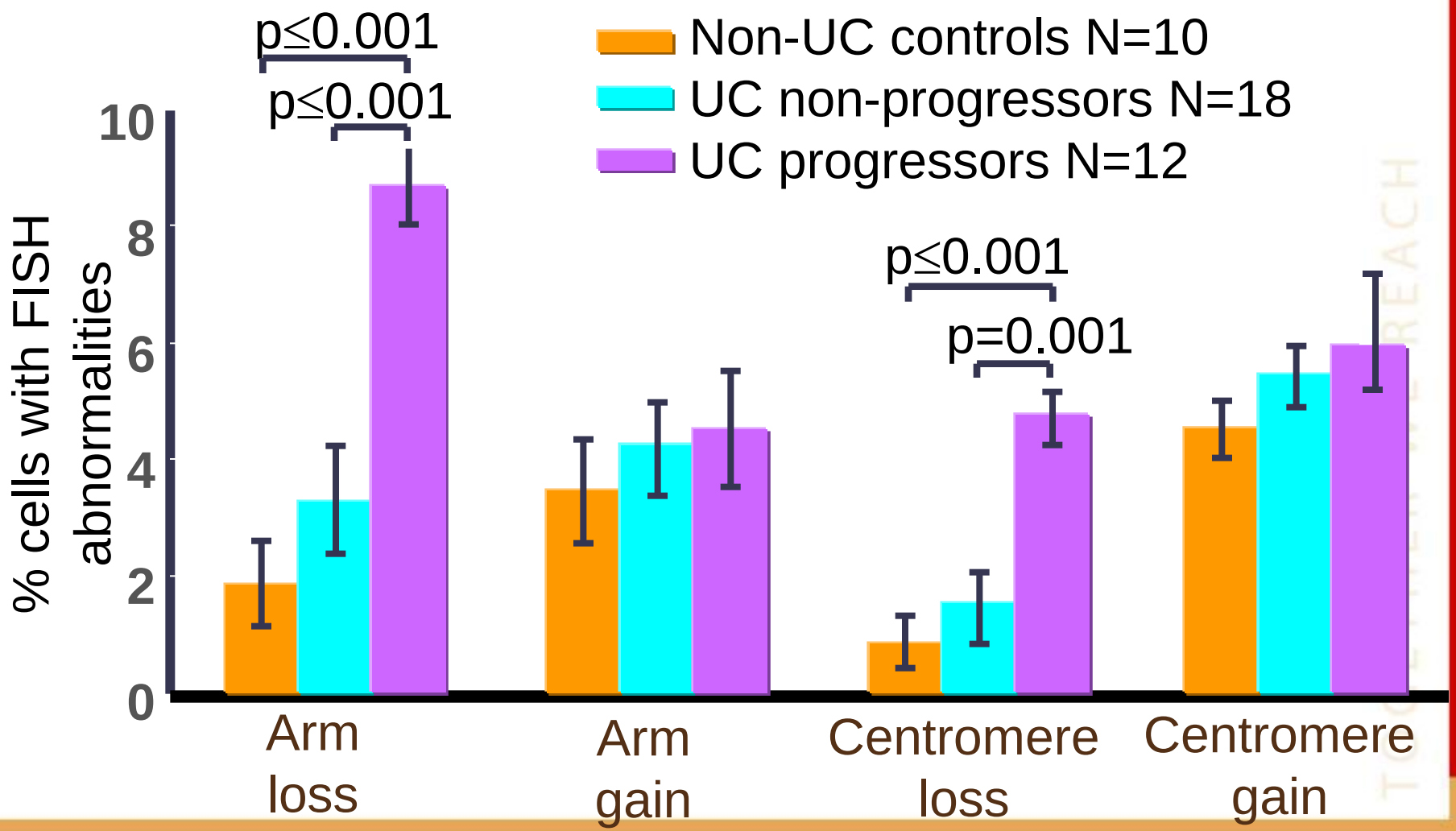
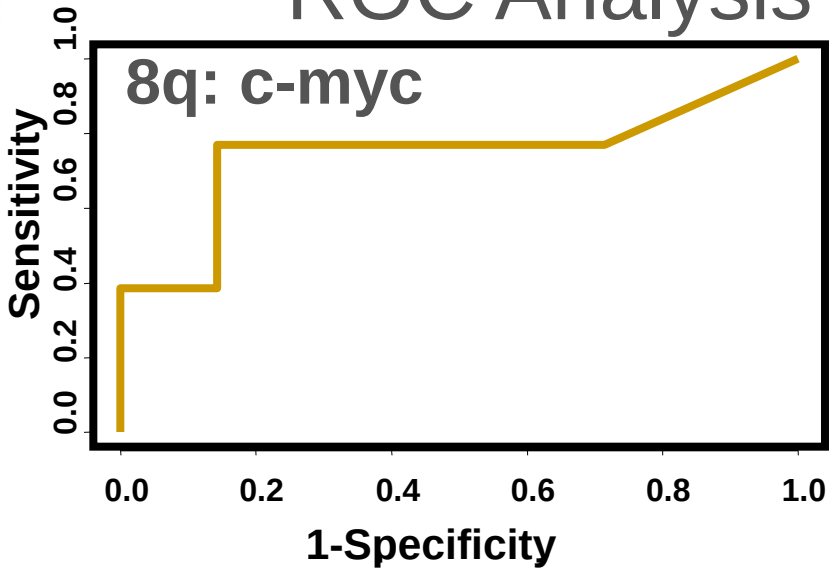
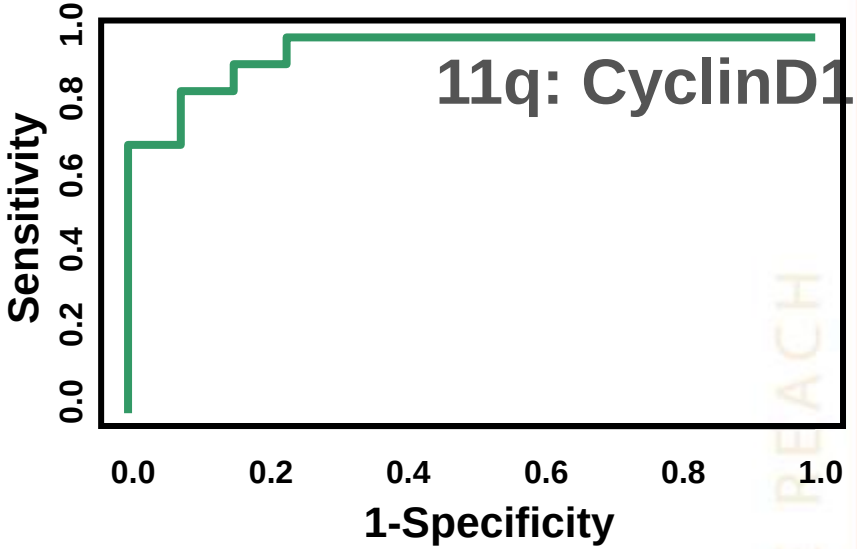
FISH in Ulcerative Colitis

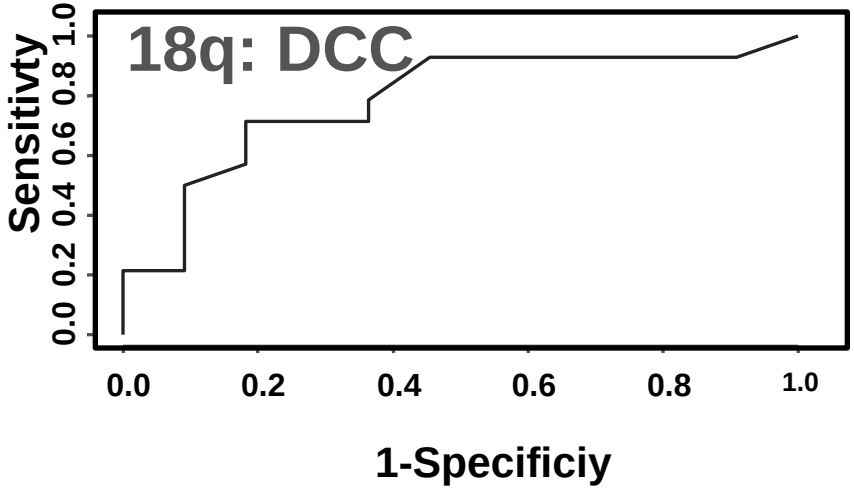


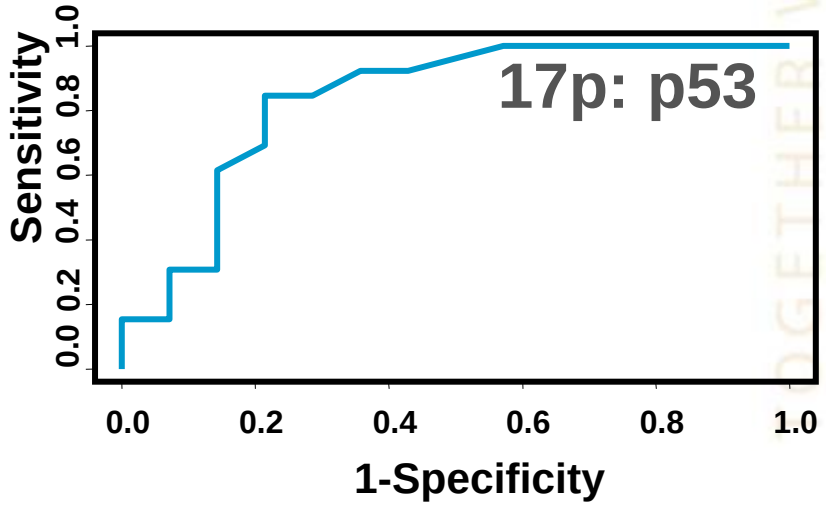
Bronner MP, et al. *Am J Pathol* 2008;173:1853.

ROC Analysis of FISH Biomarkers





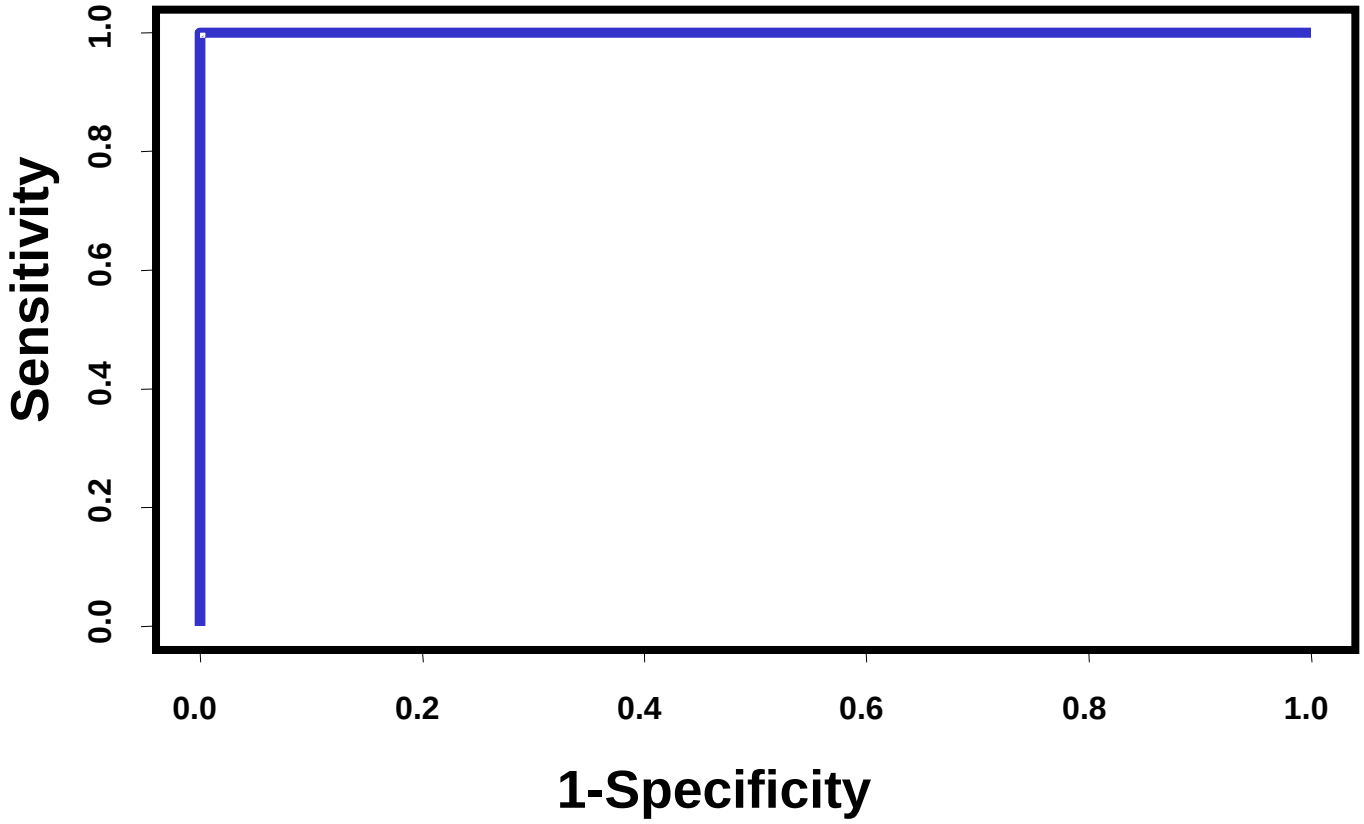




Bronner MP, et al. *Am J Pathol* 173:1853-1860, 2008

ROC Analysis of FISH Biomarkers

All 4 chromosomes combined



Bronner MP, et al. *Am J Pathol* 2008;173:1853.

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Consequences of Shortened Telomeres

- Sticky chromosomal ends
- Bridge-breakage-fusion cycles
- Chromosomal arm losses/gains and dicentrics

Studied by peptide nucleic acid (PNA) probe ISH or RT PCR

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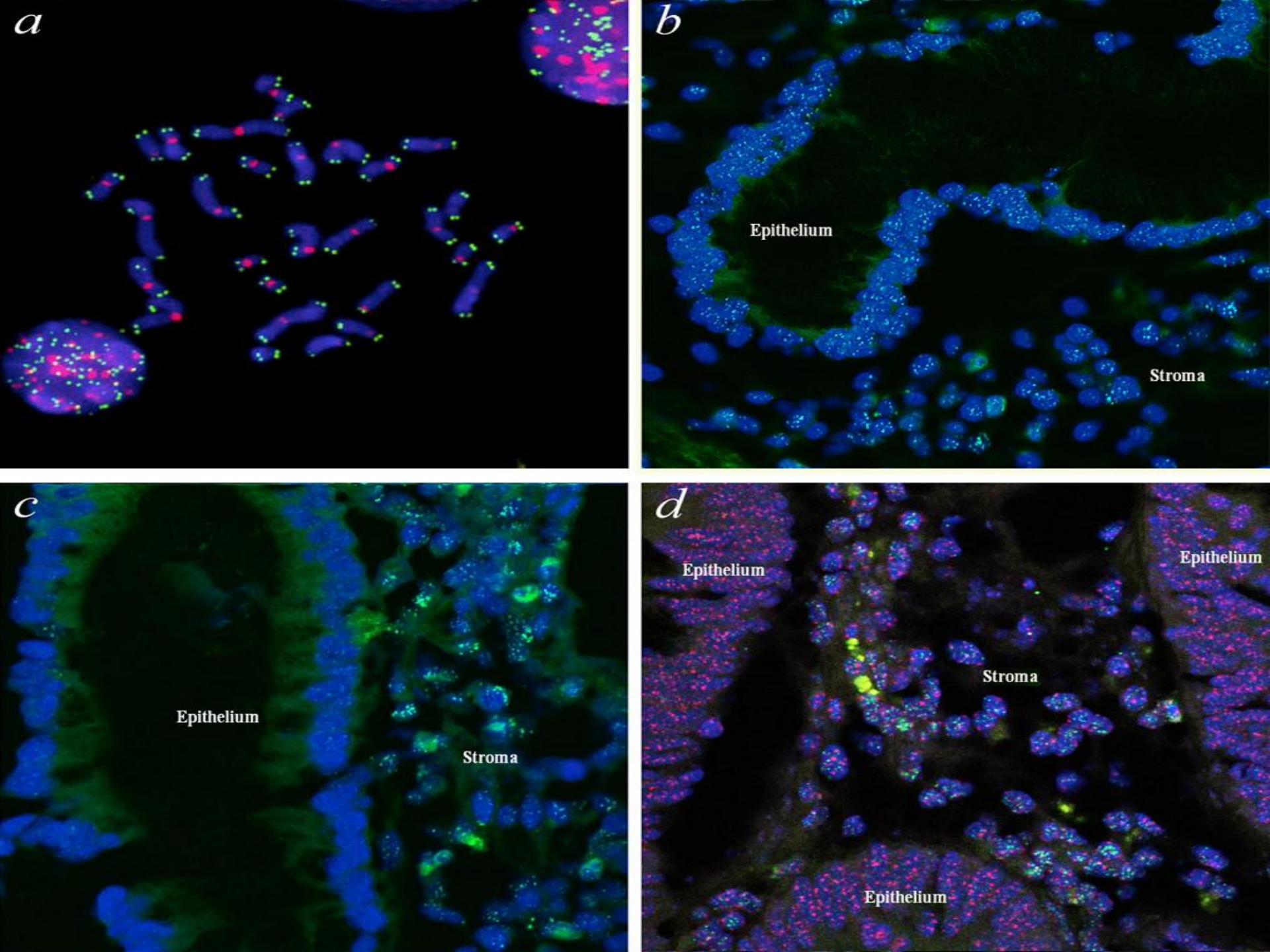
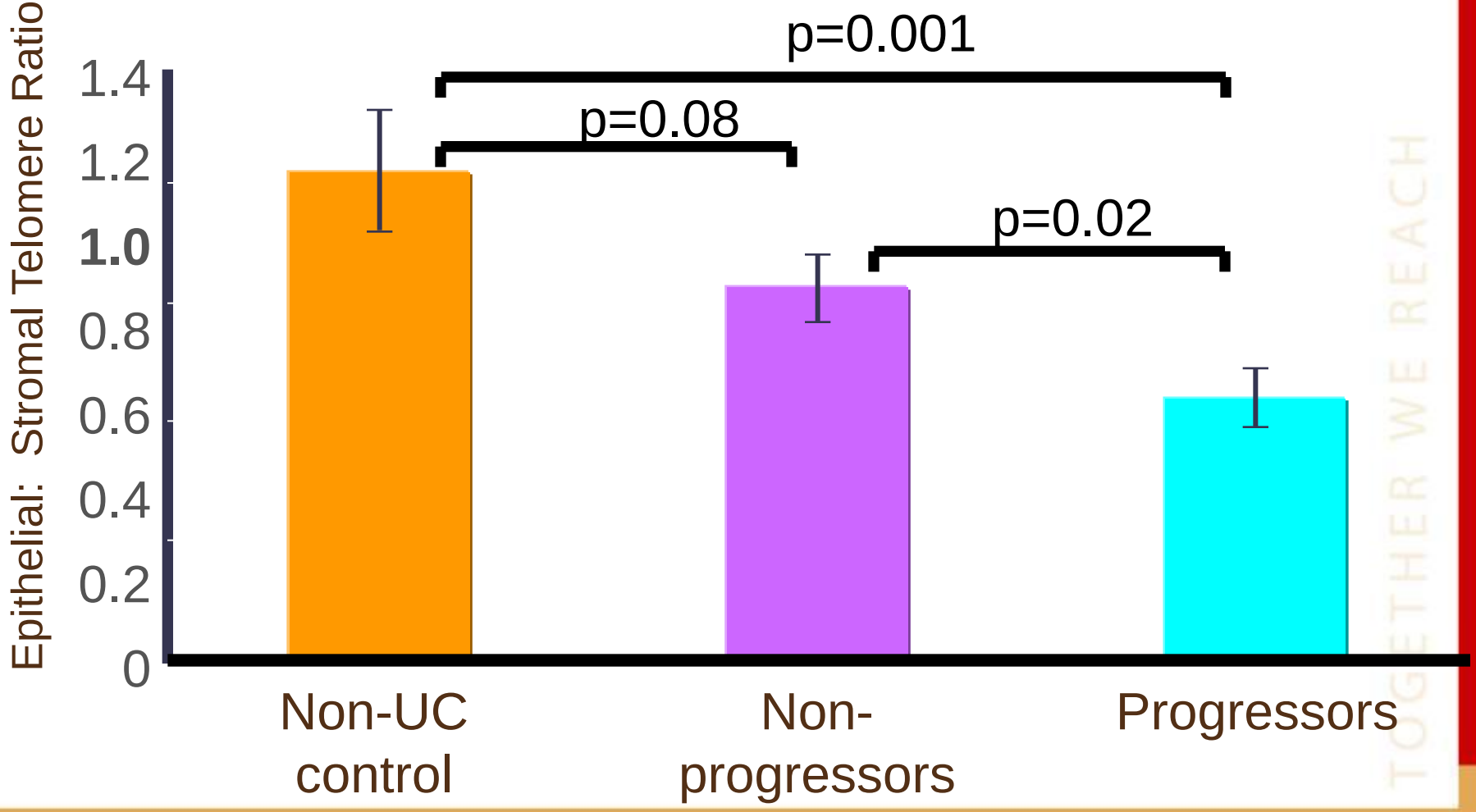

a
b
Epithelium
Stroma
c
Epithelium
Stroma
d
Epithelium
Epithelium
Stroma
Epithelium

Telomere Shortening in UC



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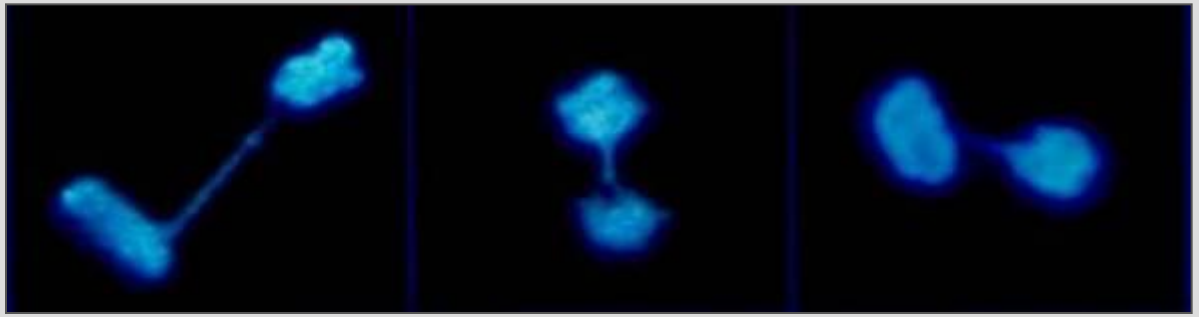
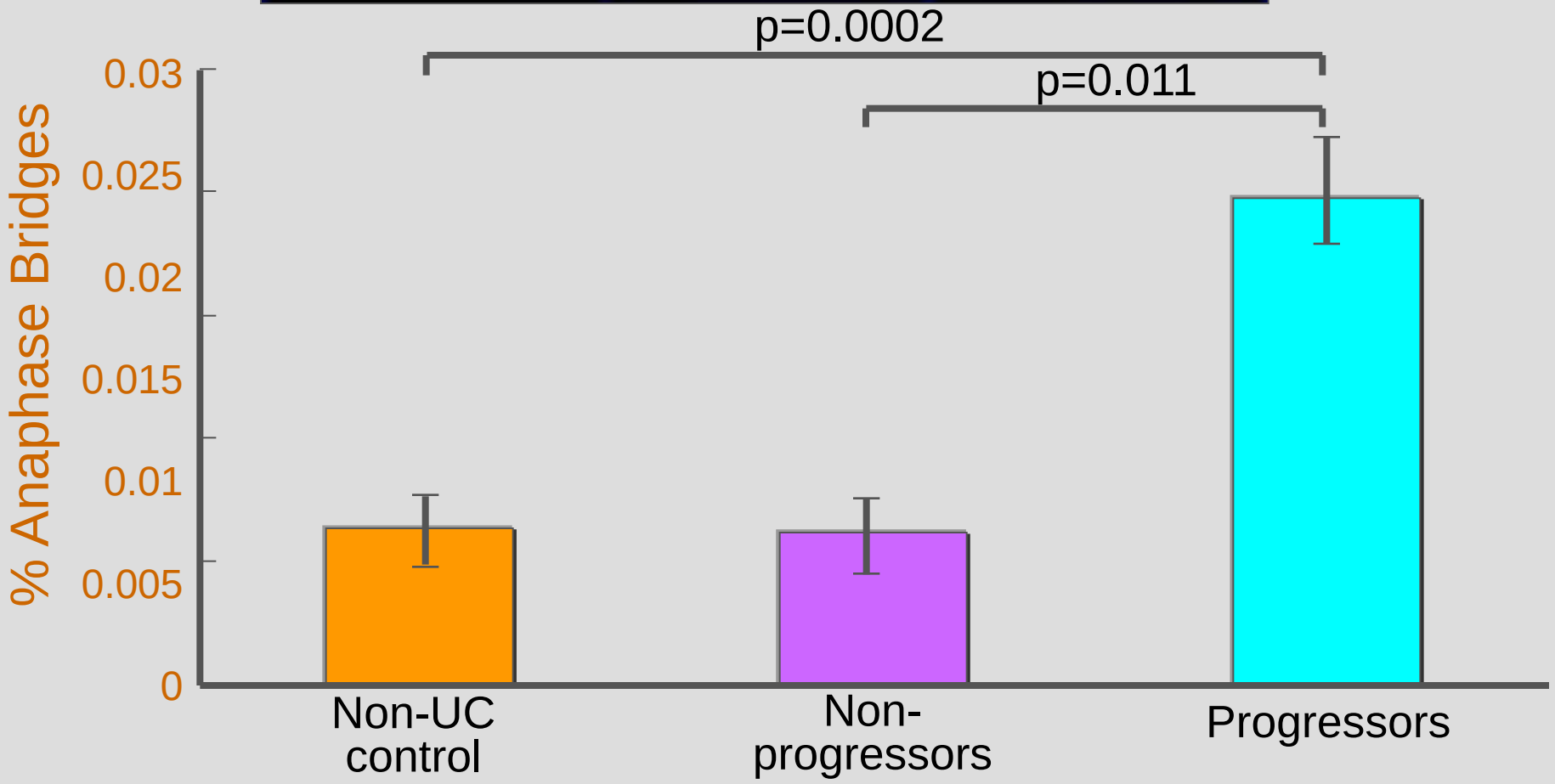
O'Sullivan J, et al. *Nat Genet* 2002;32:280-284.

Anaphase Bridges in UC



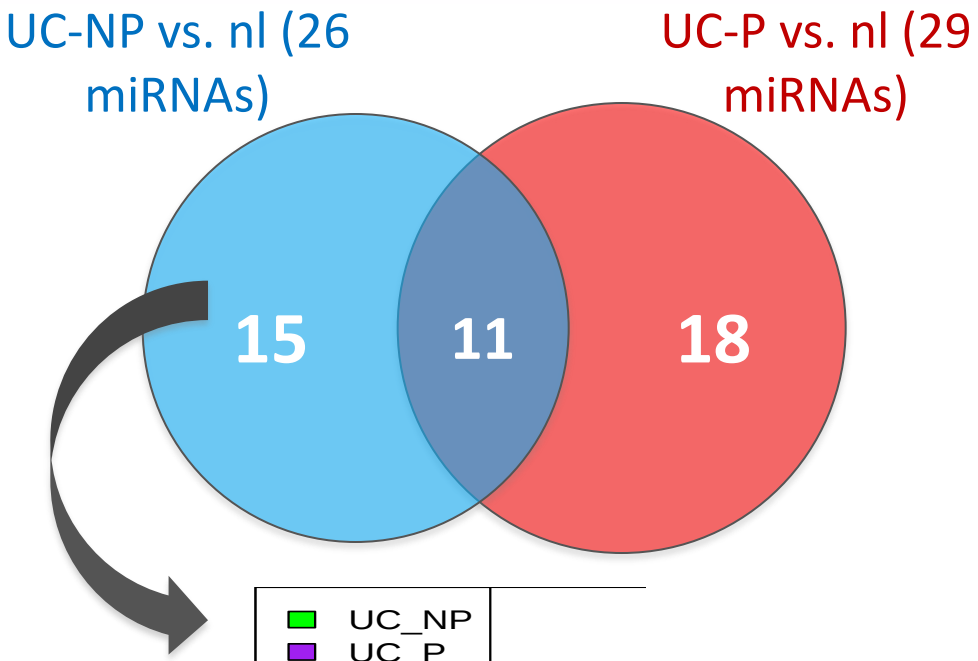


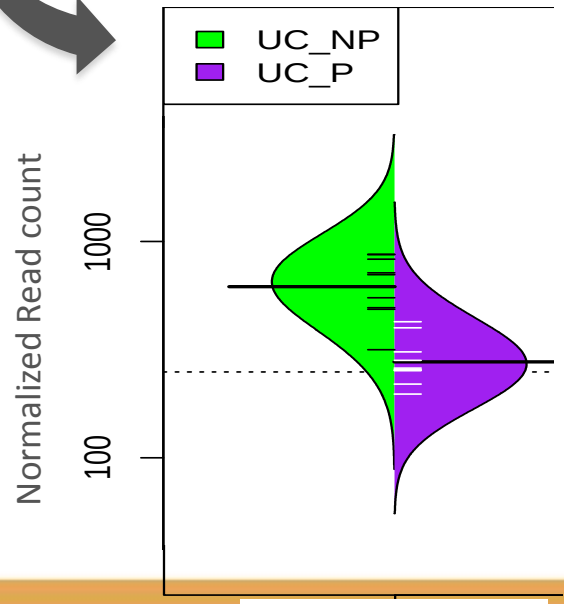
Bronner MP, et al. *Am J Pathol* 173:1853-1860, 2008

NGS miRNA bioclassifier of UC patients at increased risk of colon cancer

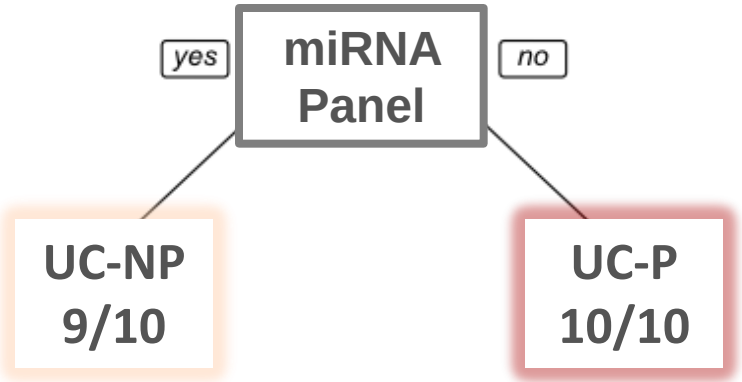
- Why miRNAs?
  - Small size (~21nt) more stable, less ribonuclease degradation
  - Readily detectable in FFPE and stained slides
  - Important roles in immune regulation

miRNAs misregulation in UC-P, UC-NP





- Linear discriminant analysis to predict UC-P vs. UC-NP
- Robust candidate panel selected for RT-PCR & additional cohort validation



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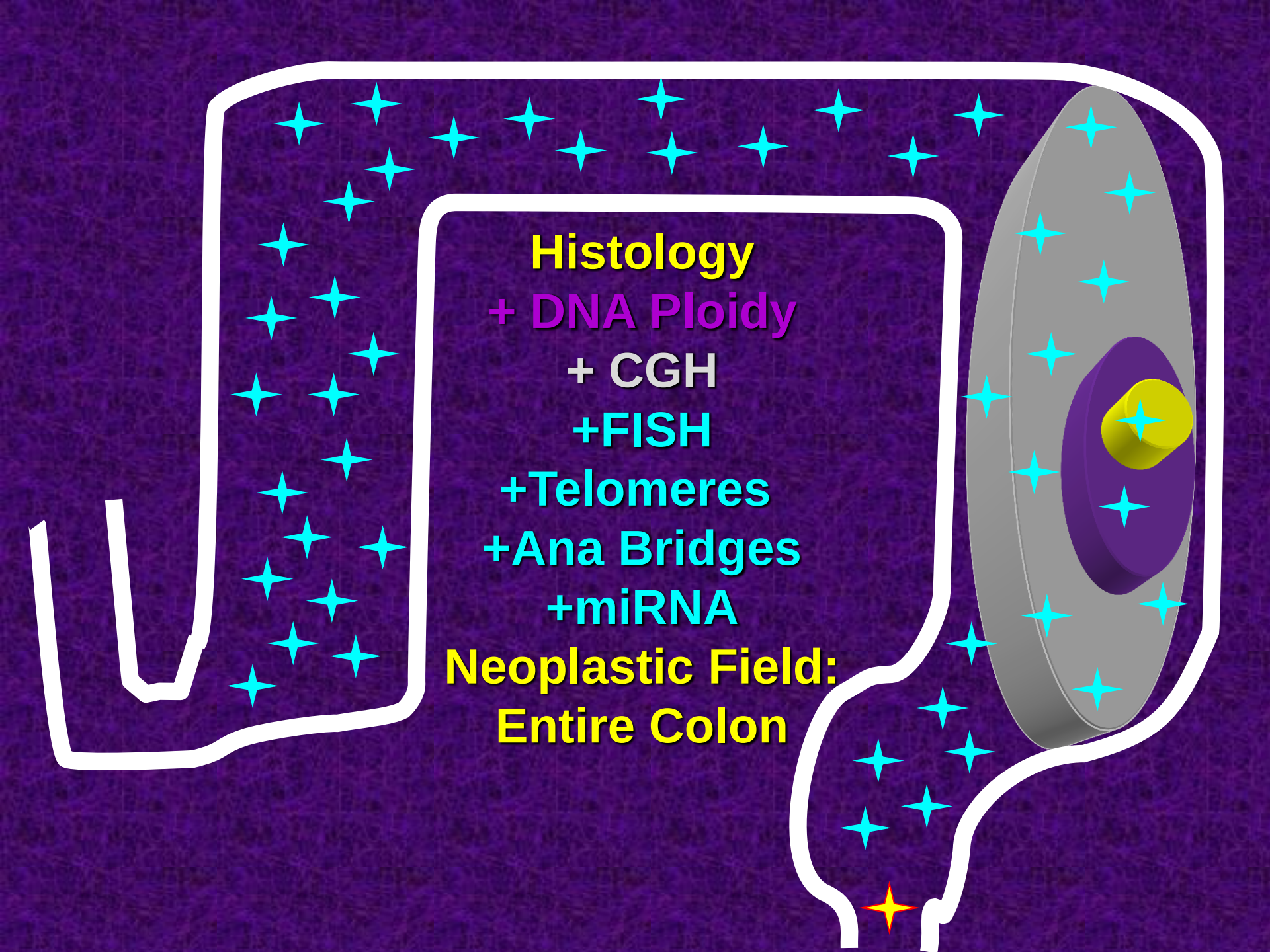
Histology
+ DNA Ploidy
+ CGH
+FISH
+Telomeres
+Ana Bridges
+miRNA
Neoplastic Field:
Entire Colon

UC Polypoid Dysplasia

You're dalmed if you do, and dalmed if you don't

Teri Brentnall,MD

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Dysplasia in UC vs Adenoma

- No clinical features
- No endoscopic features
- No pathologic features
- No molecular tests

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HOWEVER

- If the lesion can be demonstrably completely removed endoscopically
- Has only Low-Grade Dysplasia
- There is no other dysplasia on adequate sampling
- Then, careful follow-up may be considered

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UC Dysplasia Management

Continue Surveillance with adequate sampling:

- Single site LGD while in surveillance
- Indefinite of negative for dysplasia

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UC Dysplasia Management

Consider Colectomy:

- Multiple LGD sites
- LGD on more than one endoscopy
- LGD at initial colonoscopy
- Excessive inflammatory polyps

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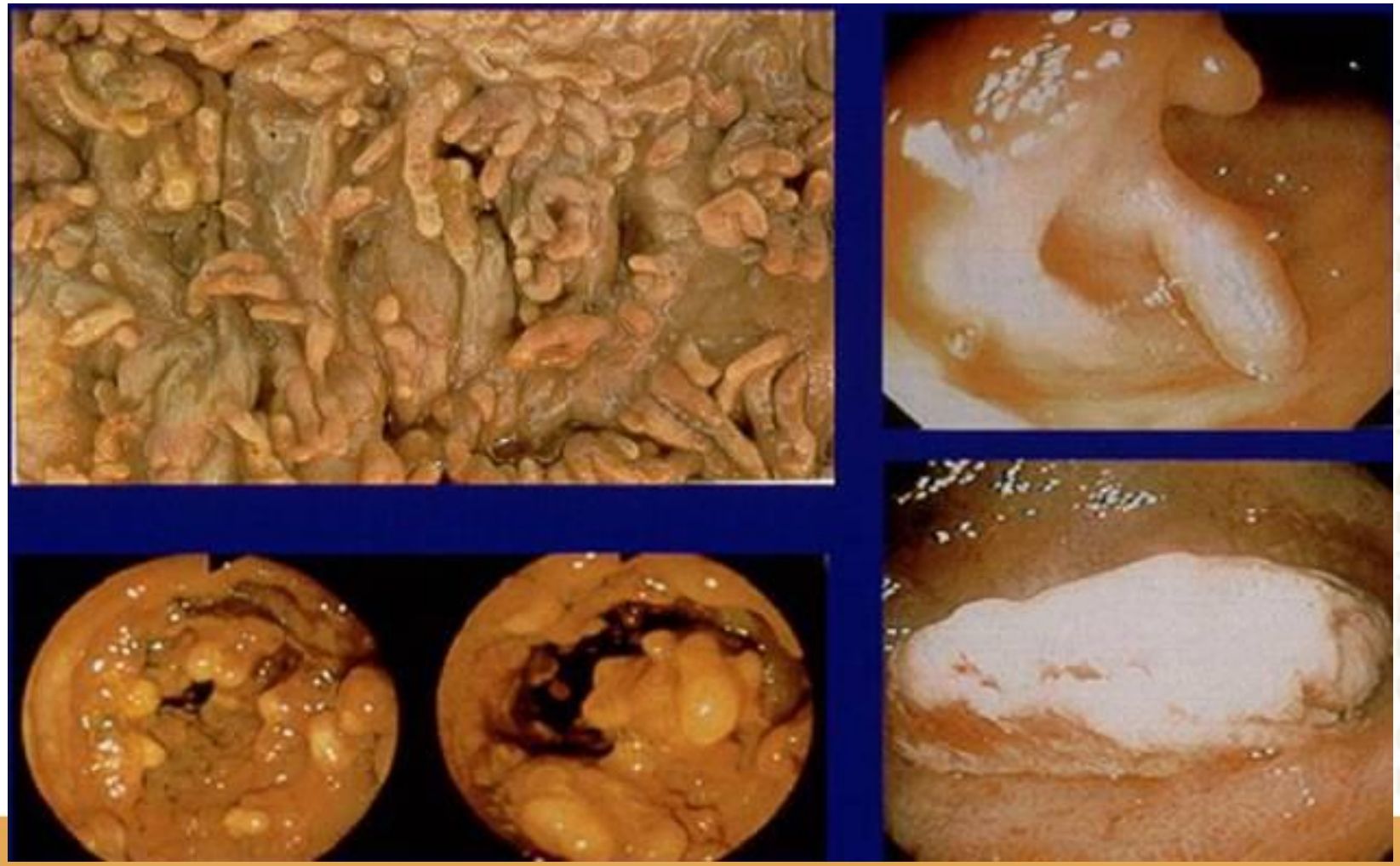
Inflammatory Polyps



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UC Dysplasia Management

Colectomy Indicated:

- HGD
- Endoscopically unresectable dysplastic lesion

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Conclusions

- Molecular alterations are widespread in UC, CD, CP, HP, HCV
- Single non-dysplastic bx alterations show promise for reducing sampling error
- Paradigm for cancer in chronic inflammatory disease

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Further Work:

- Reproducibility
- Longitudinal analyses
- Prospective validation
- High throughput
- Reduced numbers of markers
- Mechanism: *why progressors*?

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Thanks To My Colleagues:

Bonnie Shadrach

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Ru Chen
David Crispin
Rosana Risques
Jacintha O'Sullivan

Noah Welker
Keith Lai
Danielle Elsberry
Ryan O'Connell
June Round
John Valentine

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