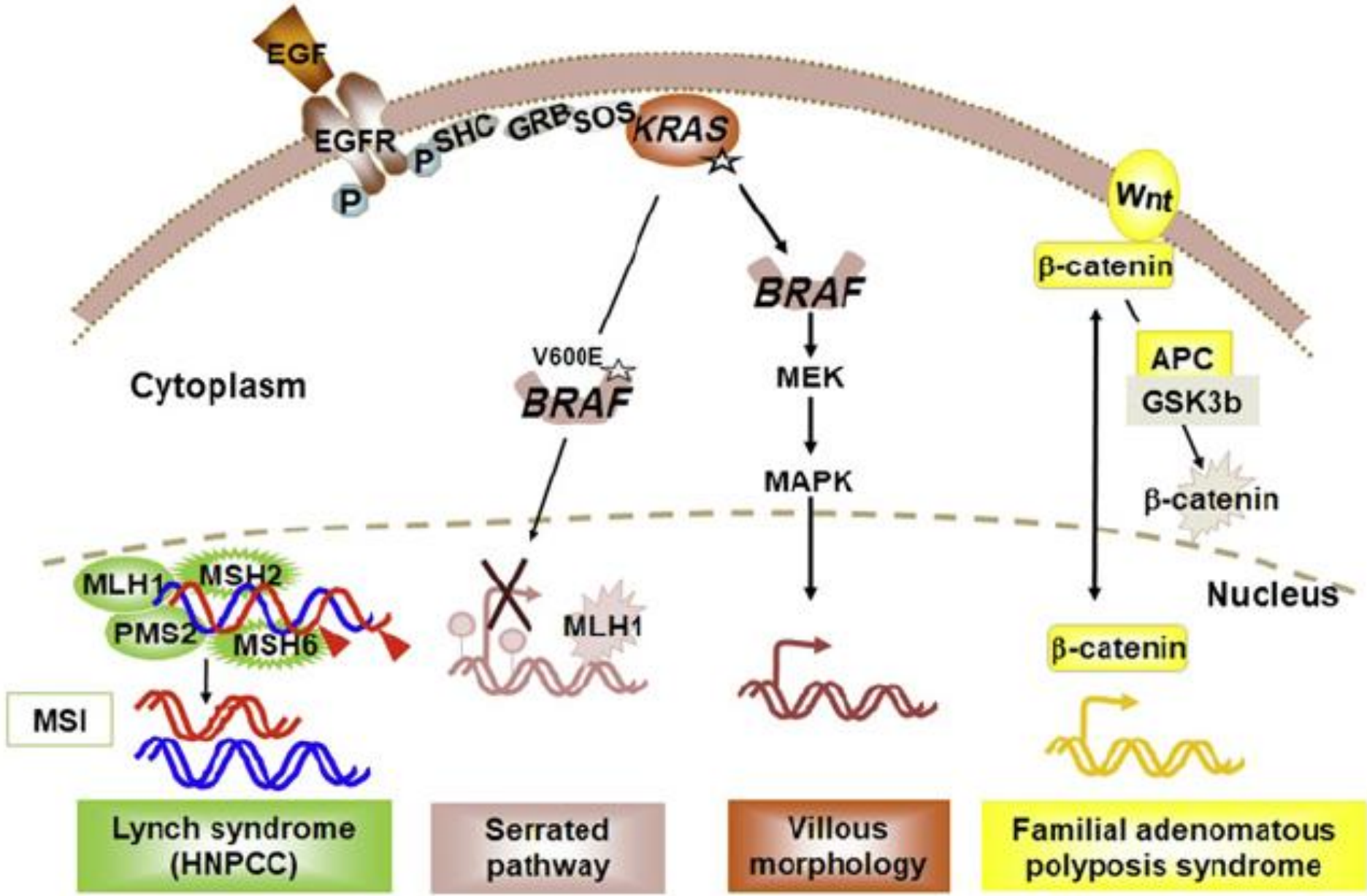
LA DIAGNOSI ISTOLOGICA DELLE LESIONI SERRATE DEL COLON: STUDIO DI CONCORDANZA INTERREGIONALE

Michelangelo Fiorentino
Università di Bologna
Anatomia Patologica Ospedale Maggiore, AUSL di Bologna

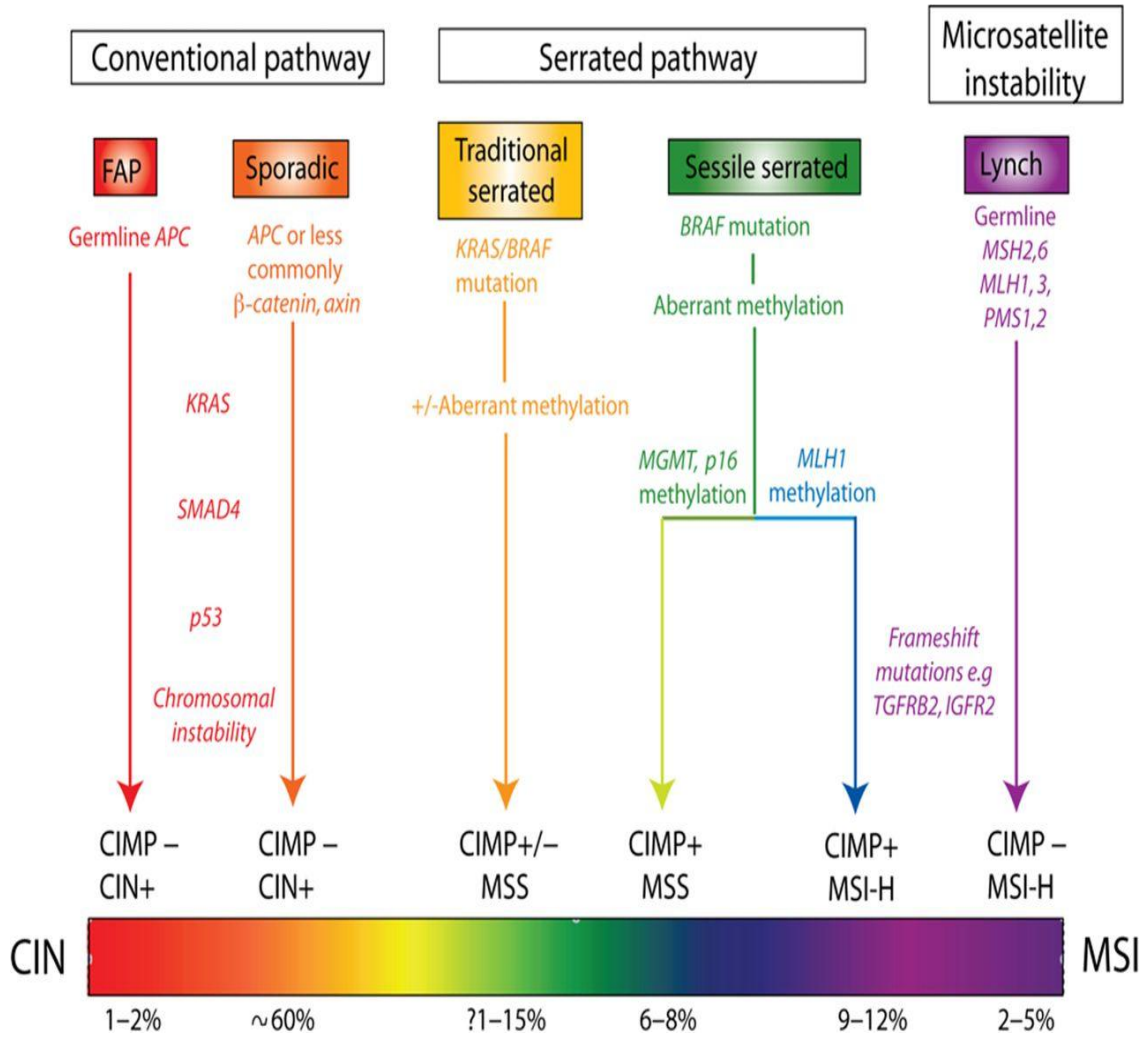
Normal colonic mucosa

MSI affects proliferation of the crypts
APC loss affects differentiation



From Chen cancer Genetics 2011

Considering the spectrum of colorectal cancer (CRC)—conventional adenomas progress by the sequential accumulation of genetic mutations and chromosomal instability causing microsatellite stable (MSS) tumours.



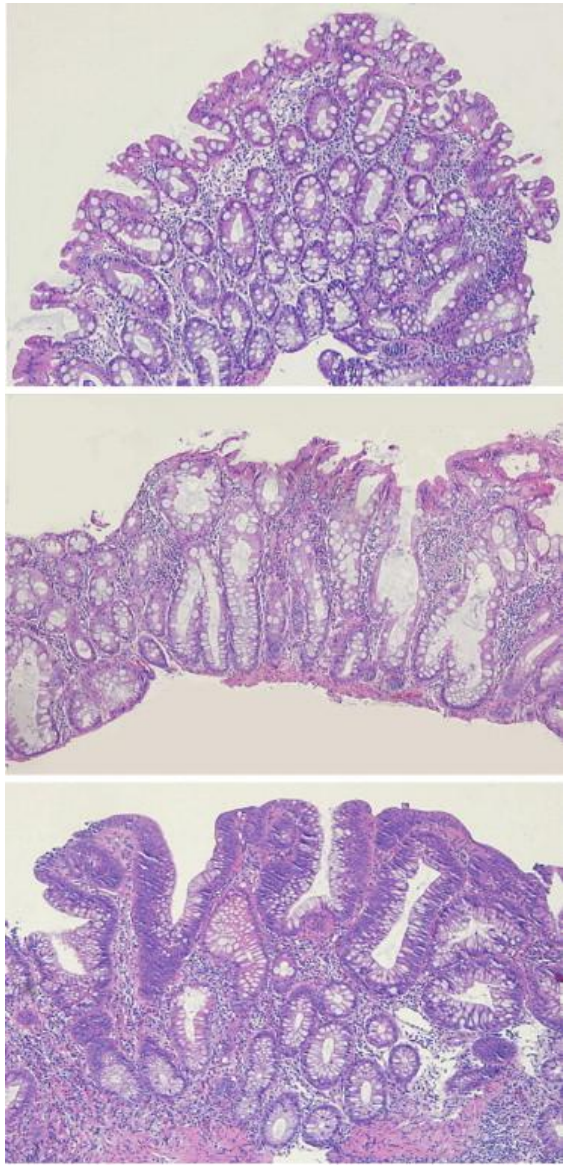
James E East et al. Gut 2017;66:1181-1196

GUT

Hyperplastic Polyp, no mandatory screening

Serrated lesions (somatic BRAF mutation, MSI) mandatory screening

Adenomatous dysplastic polyp (KRAS mut) mandatory screening



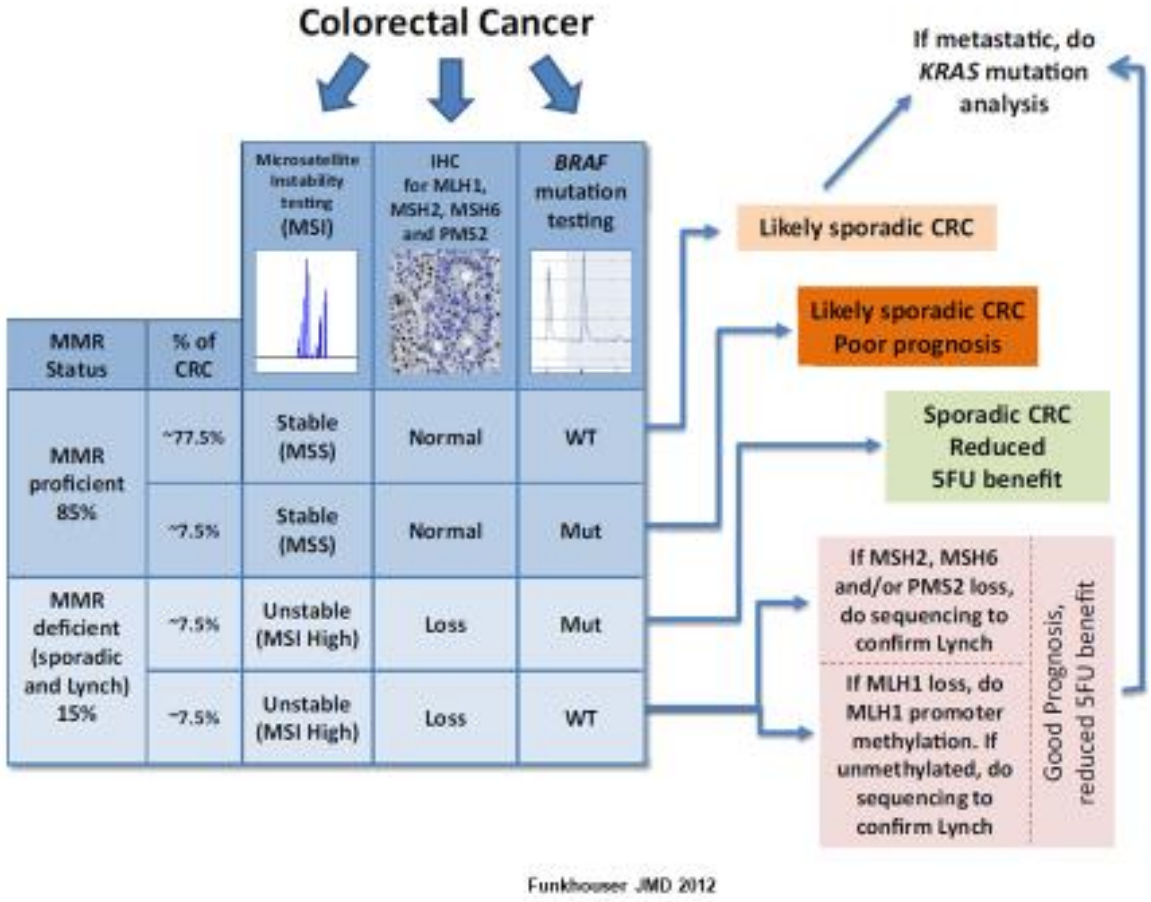
From Boparai Gastroenterology 2008

Definitions of lesions with serrated morphology

- ***Hyperplastic polyp:*** **epithelial cells with hypermucinous microvesicular cytoplasm only or mixed with goblet cells with maintained maturation towards the surface. Crypts are straight, dilatation/serration is confined in the more luminal aspects, crypt bases are narrow with symmetrical proliferative activity and interspersed neuroendocrine cells.**
- ***Sessile serrated adenoma/polyp*****: minimum of one crypt with clear dilatation and/or serration extending to the crypt base, with or without branching (L-, inverted T- or anchor-shape) of the crypts and abnormal proliferation (proliferative zone located on the side, frequently asymmetrical) showing goblet cells or gastric foveolar cells in the crypt basis. In addition, absence or presence of cytologic dysplasia is determined.**
- ***Traditional serrated adenoma:*** **villiform growth pattern with serration due to infolding, budding and papillary tufting, composed of tall columnar cells with pencillated nucleus and hypereosinophilic cytoplasm with interspersed goblet cells. In addition, the grade of cytologic dysplasia is determined.**

Evidence to support serrated pathway in CRC carcinonogenesis

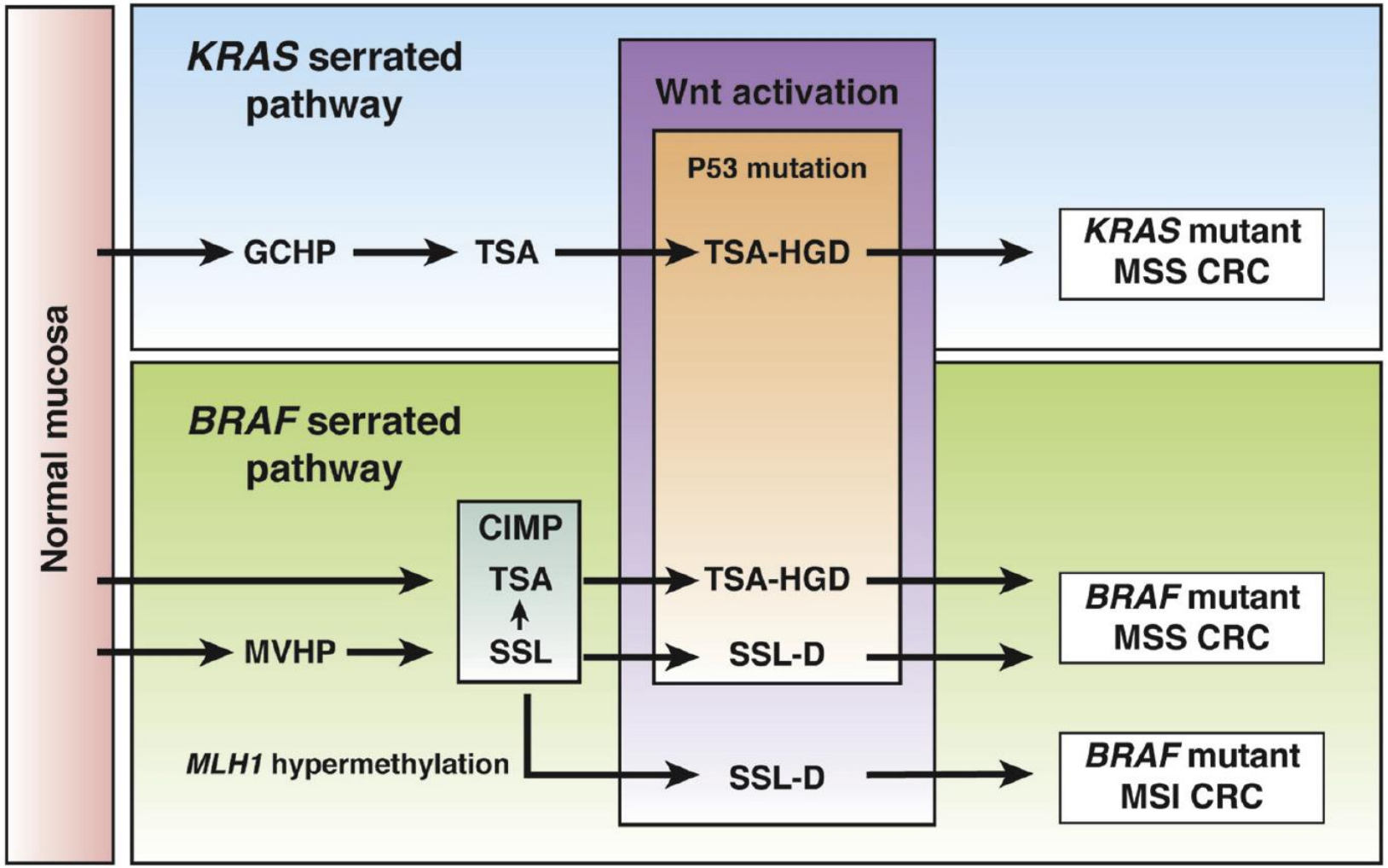
- Patients with numerous serrated polyps are at increased risk of colorectal carcinoma (CRC).
- Large serrated polyps are associated with synchronous advanced polyps and CRC
- Serrated polyps are present in areas that subsequently developed MSI-H CRC.
- Patients with MSI-H CRC often have serrated polyps elsewhere in the colon.
- Serrated polyps can develop dysplasia and are seen adjacent to some CRC.
- Serrated polyps have molecular features similar to MSI-H CRC

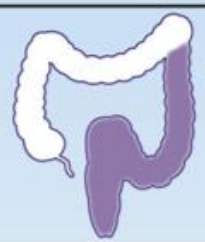
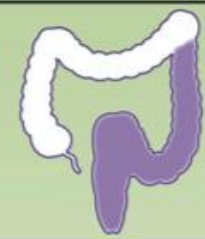
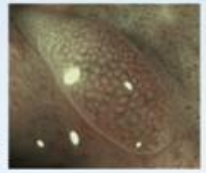
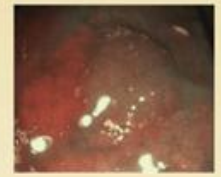
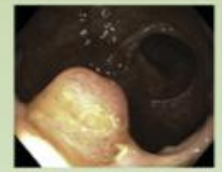
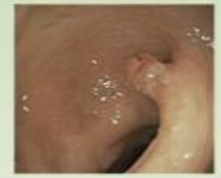
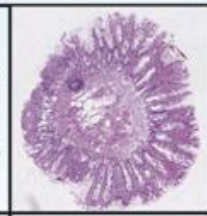
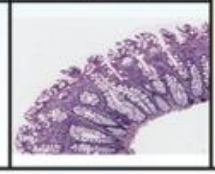
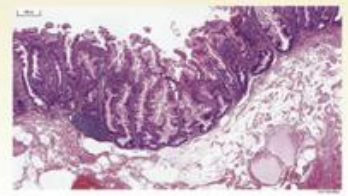
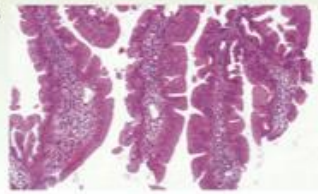


Molecular Features of the Serrated Pathway

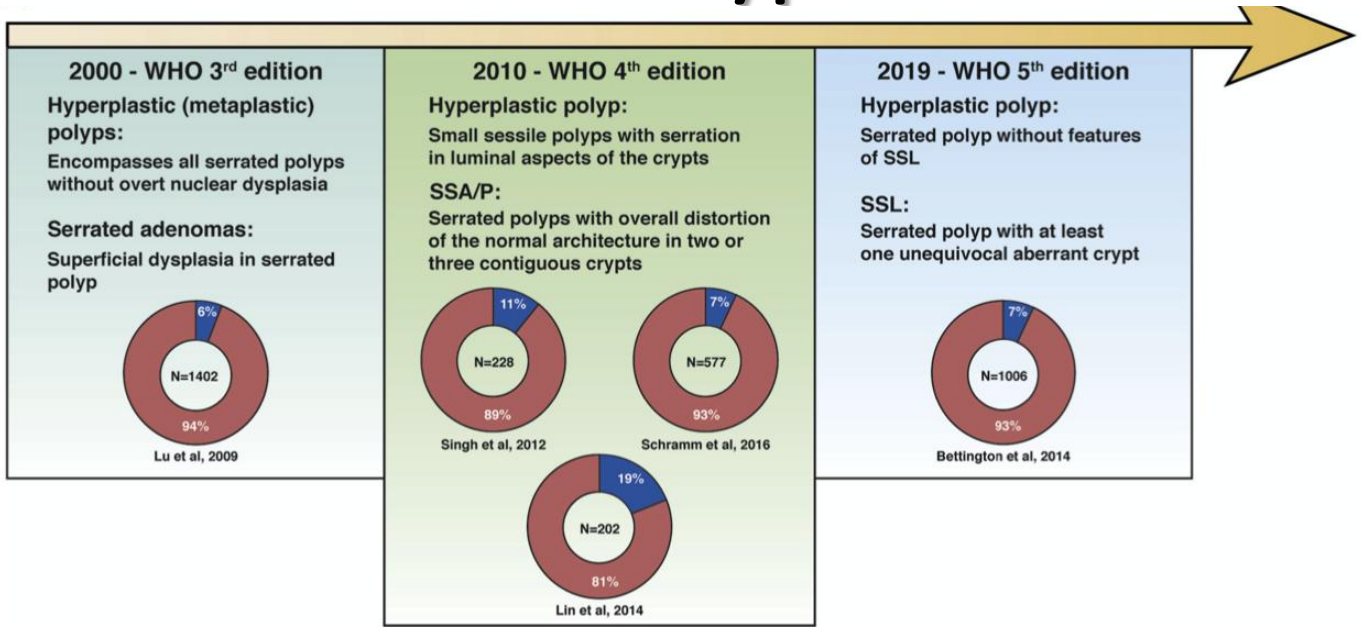
- The serrated pathway is characterized by a sequence of genetic and epigenetic changes that accompany polyp progression, tracked by histologic features
- The first step of the pathway is believed to be acquisition of a mutation in a gene that regulates mitogen-activated protein kinase pathway (such as in KRAS or in most cases BRAF)
- Activating mutations in BRAF result in widespread methylation of CpG islands, called the a CpG island methylator phenotype (CIMP). CIMP results in silencing of many genes, including some tumor suppressor genes.
- Hypermethylation of CDKN2A (which encodes P16) occurs more frequently in TSAs than SSLs, in particular in the advanced lesions with BRAF mutations
- Hypermethylation of the promoter of the MLH1 occurs only in SSLs.
- Approximately 75% of SSL-D have microsatellite instability (MSI), resulting from this specific hypermethylation. Thus, immunostaining for MLH1 protein can identify dysplasia!!!
- Progression of serrated polyps is associated with activation of the WNT signaling pathway

Colorectal tumors arising from serrated lesions can exhibit different molecular features and at least 3 subgroups of CRCs, based on molecular features can be identified:



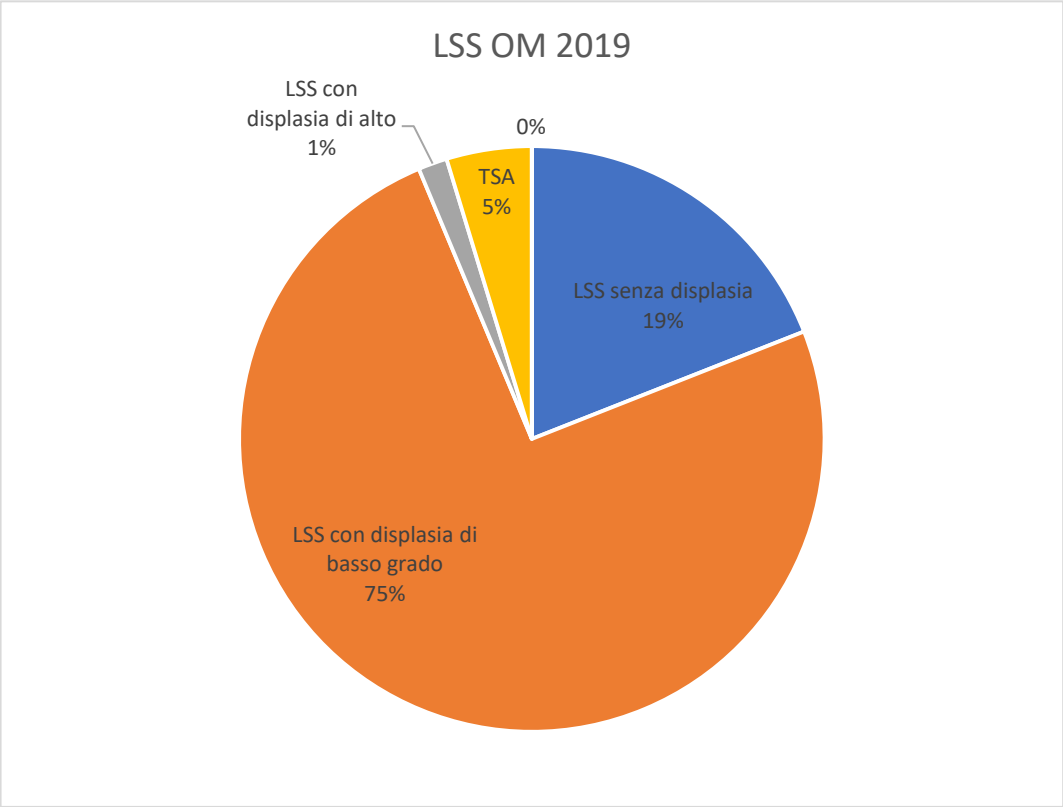
Features	Hyperplastic polyps (HPs)	Sessile serrated lesions (SSLs)	Traditional serrated adenomas (TSAs)
Clinical characteristics	• Prevalence: 20%–30% • Size: Usually small or diminutive (≤ 5mm) • Morphology: Flat or sessile	• Prevalence: 5%–15% • Size: Usually larger than HPs, mean diameter= 5–7mm • Morphology: Flat (45%) or sessile	• Prevalence: <1% • Size: Usually larger than SSLs • Morphology: Polypoid or pedunculated
Location	 70%–80% distal	 75%–90% proximal	 Mostly distal
Endoscopic appearance	White light: • Pale or same color as surrounding mucosa • Round or oval shape • Flatten with insufflation • Absent or fine, lacy vessels Narrow band imaging: • NICE type 1 • Uniform dark or white spots  	White light: • Mucus cap • Ring of debris • Cloud-like surface • Irregular shape Narrow band imaging: • NICE type 1 • WASP criteria • Dark spots in crypts  	White light: • Erythematous • Multilobulated • "Pine cone" appearance • Type IV-S pit pattern Narrow band imaging characterisitics not well defined  
Histopathology	Microvesicular HP (MVHP): • Narrow, uniform basal crypt • Serrated upper crypt • Eosinophilic mucin droplets in cytoplasm  Goblet cell rich HP (GCHP): • Goblet cells predominate epithelium • Less serrated than MVHP 	• Serration extending to base of crypts • Dilated and inverted "T" or boot shaped crypts • Crypt branching 	• Pseudostratification • Villous pattern with stretched or pencillate nuclei • Eosinophilic predominant • Ectopic crypts 

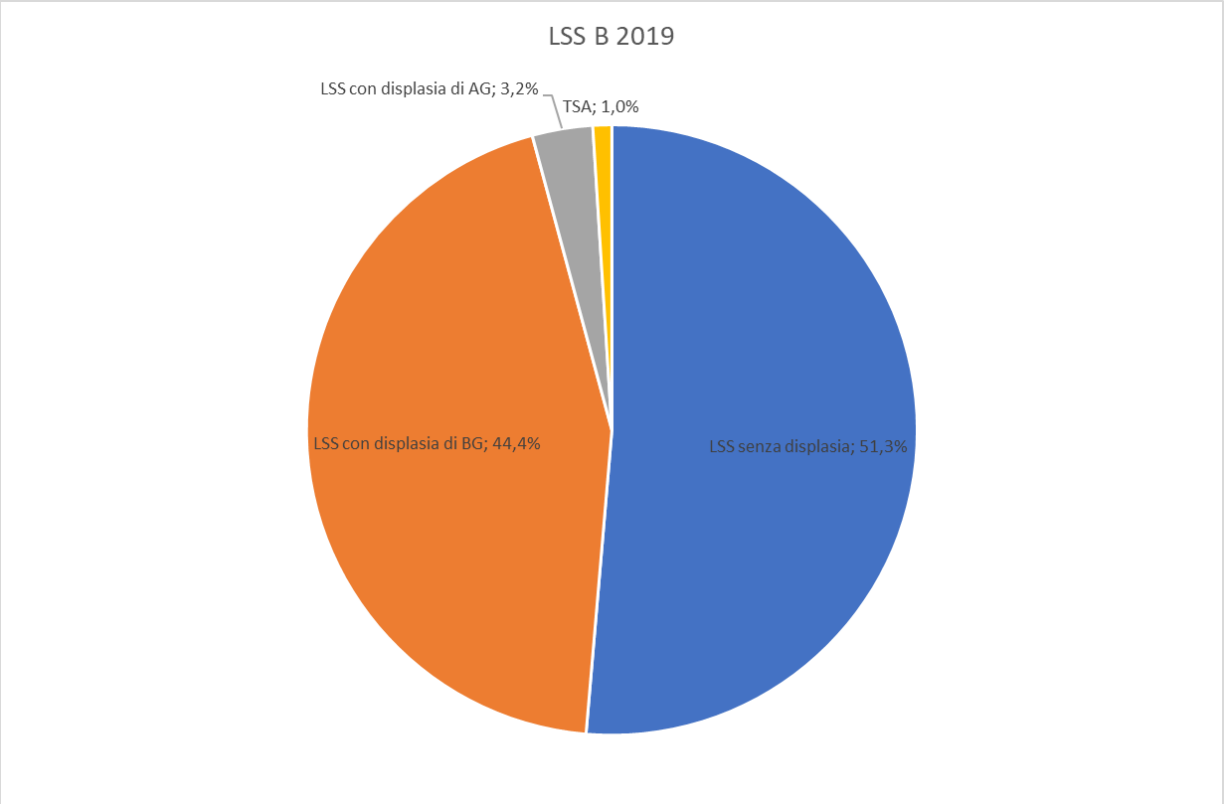
Classification of Serrated Polyps



- After SSLs were included in the WHO classification of 2010, 8%–19% of HPs were reclassified as SSLs.
- Application of the 1 crypt rule, per the recent revised WHO criteria, likely increases the sensitivity of detection of SSLs further.
- theapplication of this criterion resulted in a 7% increase in the proportion of serrated polyps classified as SSLs.
- An ad ditional benefit of this new definition is improved inter-observer agreement compared with the 4th edition WHO criteria.
- Inter-observer agreement can be further improved by better orientation of polyps and by training

Interobserver variability in two hospitals of the AUSL Bologna





Serrated lesions: Diagnostic Issues

Histologic agreement among 7 GI pathologists on 109 serrated polyps

Polyp	Overall Kappa	Individual Kappa	95% CI	Interpretation
All polyps	0.5		0.47-0.52	Moderate
HP		0.52	0.48-0.57	Moderate
SSP		0.56	0.51-0.60	Moderate
SSP with cytologic dysplasia		0.8	0.75-0.84	Excellent

Only moderate interobserver agreement

Gonzalo, DH, et al. J Pathol. 2013 Aug;230(4):420-9

CONCORDANCE STUDY ON SERRATED LESIONE AMONG EXPERIENCED AND IN-TRAINING PATHOLOGISTS

- 50 H&E imagines of polyps with serrated features, no immunohistochemistry.
- Imagines scanned and made available on a server for remote assessment
- 50 pathologists enrolled in the survey with different experience and from different Regions
  - 41 Staff Pathologists (from Ascoli, Bari, Bologna, Bolzano, Brescia, Ferrara, Forlì, Modena, Parma, Pesaro, Piacenza, Ravenna, Reggio Emilia, Trento)
  - 9 Residents in pathology from the Residency Program of the University of Bologna
- Pathologists asked to fill a form and choosing from the following fixed answers:
  - Hyperplastic Polyp
  - Sessile serrated lesion without dysplasia
  - Sessile serrated lesion with dysplasia
  - Traditional Serrated Adenoma

TIMELINE

- The COVID emergency has delayed of more than one year the original timeline
- Slides have been chosen and scanned in 2021
- The funds from RER have been used for the maintenance of the Aperio slide scanner at Maggiore Hospital and for a new server for remote access to the images (4000 Euro) and for a 1 year fellowship of a young biologist (12.000 Euro) who prepared and scanned the slides and took care of the IT setting for the survey
- The access to the images has been given on April 1st to the pathologist and the survey is expected to be closed on May 31st
- Data will be analyzed in the summer
- A meeting for the discussion of the results will be held (hopefully in person) in September 2022