UCCH Pathway

UCCH Guideline
Hereditary Colorectal Cancer

2.03.01 Anlage 36

Version Jan/2022

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Guideline Hereditary Colorectal Cancer

Version 05, Jan/2022

According to TNM classification 8th edition

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Implemented	May/2017
Revised	Feb/2018, Jun/2018, May 2020, Jan 2022
Next planned review	Jan/2024

Legend of Colours

= Therapeutic procedure

= Clinical or diagnostical condition

= Diagnostic procedure

= Clinical trial

= Supportive measure

= Referral

TB

= Tumorboard (including post tumorboard interaction with patient that follows the principles of shared decision-making)

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Pathway: Hereditary Colorectal Cancer

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Work up

Preconditions for further risk evaluation:

- Known mutation in the family
- Individuals affected with colorectal or endometrial cancer according to Amsterdam or revised Bethesda criteria[1]
- Age at diagnosis of colorectal cancer <= 50 years
- Individuals with colorectal cancer and >10 adenomas
- Individuals with a first degree relative with polyposis
- Individuals with a desmoid tumor, multifocal or bilateral CHRPE, cribriform-morular variant of papillary thyroid cancer or hepatoblastoma
- Individuals with multiple GI hamartomatous polyps or serrated polyposis syndrome

Baseline:

- History (incl. medical and surgical history)
- Family history (incl. Pedigree of first, second and third degree relatives of proband)
- Physical examination (incl. direct examination of related manifestations)
- Genetic counseling including risk counseling and discussion of genetic testing

Supportive:

- Offer contact to self help group
- Offer psychooncological/ psychosocial support

HNPCC/ Lynch syndrome → Pathway page 2

Adenomatous polyposis syndromes
- Familial adenomatous polyposis (FAP)
- MUTYH-associated polyposis
- Attenuated polyposis

→ Pathway page 3

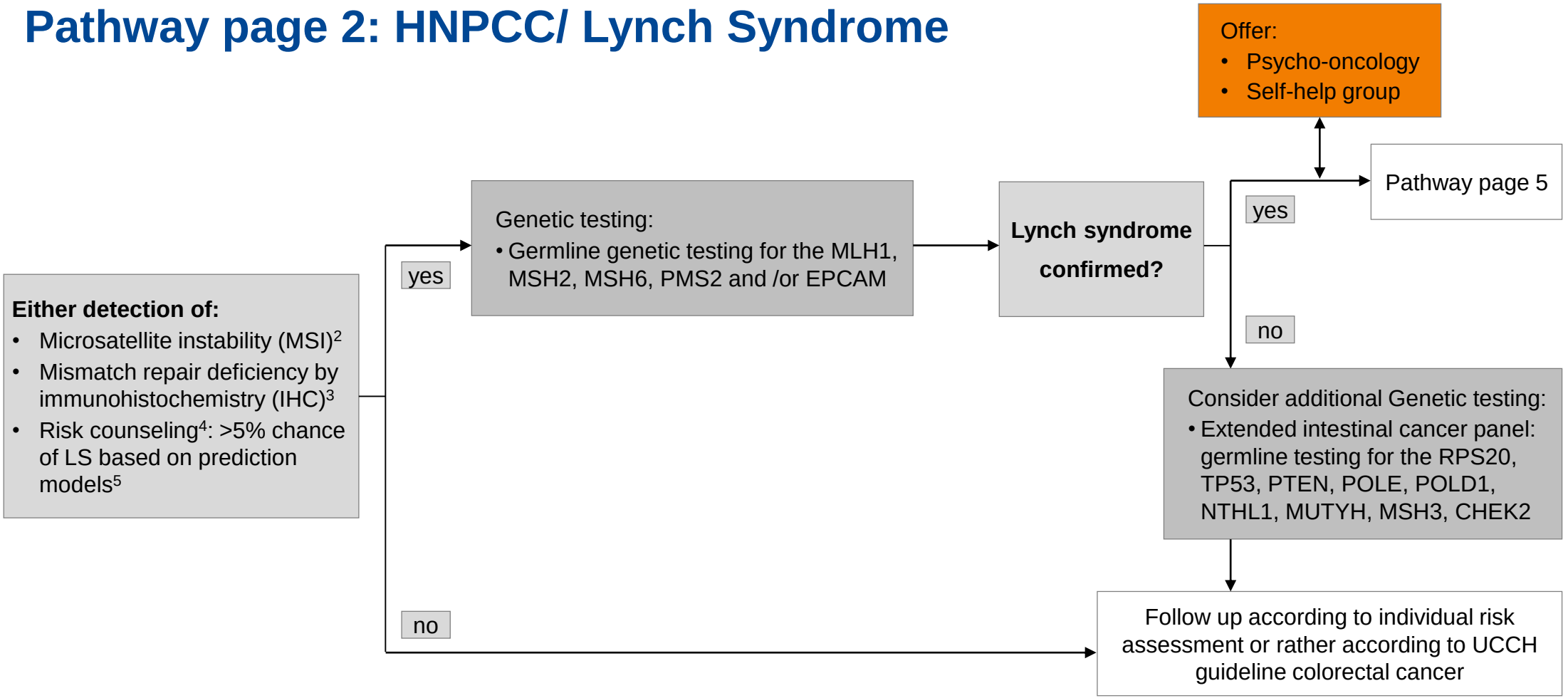
Non-Adenomatous polyposis syndromes
- Peutz-Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Cowden syndrome (PTEN hamartoma tumor syndrome)
- Serrated/hyperplastic polyposis syndrome

→ Pathway page 4

CHRPE Congenital hypertrophy of the retinal pigment epithelium

[1] Amsterdam- and revised Bethesda criteria see pathway page 9

Pathway page 2: HNPCC/ Lynch Syndrome



MSI Microsatellite instability IHC Immunohistochemistry

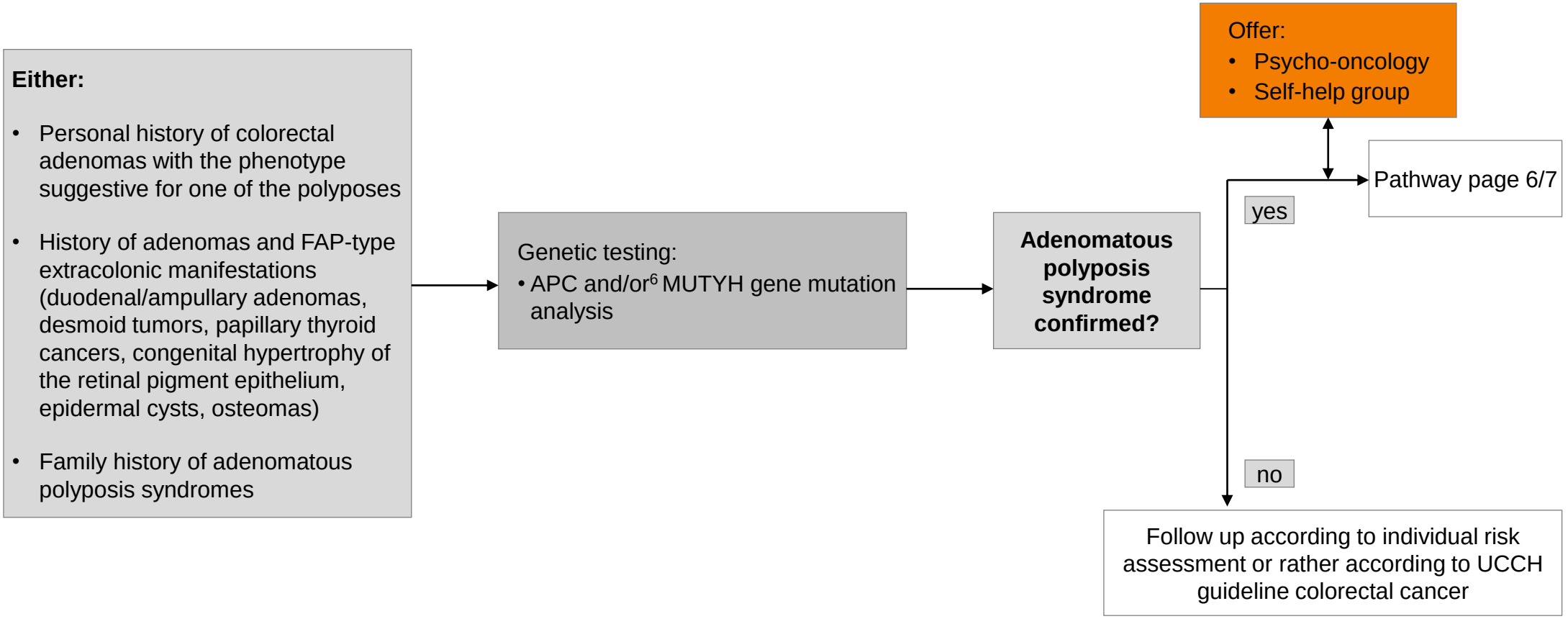
2 All newly diagnosed colorectal cancers according to Amsterdam- and revised Bethesda criteria. Apart from that MSI status is determined in all newly diagnosed colorectal cancers UCCH internally

3 Immunohistochemical testing for MLH1/MSH2/MSH6/PMS2. Tumors that demonstrate loss of MLH1 and PMS2 should undergo testing for BRAF (V600E) and MLH1 promoter hypermethylation

4 Based on risk prediction models (e.g. Cancer Gene)

5 Consider direct germline testing of an unaffected at-risk individual whose risk is calculated to be ≥5% in families where LS is a consideration and no tumor material is available for analysis

Pathway page 3: Adenomatous polyposis syndromes



[6] Depending on history/ family history and clinical/ pathological phenotype of polyposis. Testing for MUTYH should be performed in all cases with clinically adenomatous polyposis without detection of an underlying APC mutation

Pathway page 4: Non-Adenomatous polyposis syndromes

Peutz-Jeghers syndrome (PJS)
- Individuals with perioral or buccal pigmentation and/ or
- Histologically characteristic gastrointestinal hamartomatous polyps
- Or family history of PJS

Juvenile polyposis syndrome (JPS):
- Five or more juvenile polyps in the colorectum or any juvenile polyps in other parts of the GI tract

Cowden syndrome (PTEN hamartoma tumor syndrome):
- Multiple gastrointestinal hamartomas or ganglioneuromas

Serrated/ hyperplastic polyposis syndrome:
- At least 5 serrated polyps proximal to the sigmoid colon (≥2 of these being >10 mm)
- Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
- >20 serrated polyps of any size, distributed throughout the large intestine
- Exclusion of $BRAF^{V600E}$ mutation

→

Genetic testing:
- STK11/LKB1 gene mutation analysis (PJS)
- SMAD4 and BMPR1A gene mutation analysis (JPS)
- PTEN gene mutation analysis (Cowden syndrome)
- MUTYH, PTEN, BMPR1A (SMAD4, APC when indicated) gene mutation analysis (serrated/ hyperplastic polyposis syndrome)

→

Non-Adenomatous polyposis syndrome confirmed?

yes →

Offer:
- Psycho-oncology
- Self-help group

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Pathway page 8

no →

Follow up according to individual risk assessment or rather according to UCCH guideline colorectal cancer

Page 5: Lynch syndrome management and surveillance

Lynch syndrome:

- In case of colorectal carcinoma: Subtotal colectomy with ileorectal anastomosis. Segmental colectomy is an option in patients unsuitable for total colectomy if regular postoperative surveillance is conducted
- Annual colonoscopy starting at the age of 25 years
- Yearly screening for endometrial and ovarian cancer including vaginal ultrasound and cervical cytology starting at age of 25 years, endometrial biopsy beginning with the age of 35 years
- Depending on genotype: Offer prophylactic hysterectomy and bilateral salpingo-oophorectomy in women > 40 years or respectively 5 years before the earliest disease onset
- EGD with extended duodenoscopy every 3-5 years beginning at age of 30-35 years
- Recommend genetic counseling and consideration of genetic testing for at risk relatives (first- and second degree relatives)

Page 6: Adenomatous Polyposis Syndromes management and surveillance

FAP:

- In individuals at risk (relatives of a patient with a known autosomal dominant germline mutation) genetic counseling and genetic testing. Offer genetic testing also during childhood. After exclusion of a familial APC the general recommendations for cancer screening are applied.
- Yearly recto- sigmoidoscopy starting at the age of 10 years in APC-mutation positive (or unknown) individuals. In case of adenoma detection colonoscopy should be proceeded (yearly)
- In case of classical FAP prophylactic proctocolectomy (continence preserving whenever possible) after puberty with subsequent yearly endoscopy of rectum or ileal pouch is recommended.
- Screening for gastric and small bowel tumors should be done using upper endoscopy including duodenoscopy starting at age 25-30 years.
- Annual thyroid screening by ultrasound
- Offer hepatoblastoma screening (AFP and ultrasound biannually) in early infancy (until age of 7 years).
- Recommend genetic counseling and consideration of genetic testing for at risk relatives (first- and second degree relatives)

Attenuated polyposis:

- Individual recommendation with respect to age, number of polyps, and histological classification. In case of endoscopically not manageable polyposis a colectomy is indicated.
- Baseline colonoscopy at the age of 15 years. If there´s no polyposis continue with yearly colonoscopy at the age of 20 years.

Page 7: Adenomatous Polyposis Syndromes management and surveillance

MUTYH-associated polyposis:

- Recommend genetic counseling and consideration of genetic testing for at risk relatives (autosomal recessive inheritance)
- After genetically exclusion of MUTYH mutation APC the general recommendations for cancer screening are applied.
- Heterozygous MUTYH carriers should undergo colonoscopy every ten years, beginning at the age of 40-45 years (or 10 years before earliest diagnosis of CRC)
- Asymptomatic biallelic MUTYH carriers should undergo baseline colonoscopy at the age of 18-20 years with subsequent regular monitoring depending on the findings.
- Individual recommendation with respect to age, number of polyps, and histological classification. In case of endoscopically not manageable polyposis a colectomy is indicated.
- EGD and Duodenoscopy every three years starting at the age of 25-30 years.

Page 8: Non-Adenomatous Polyposis Syndromes management and surveillance

Non-Adenomatous polyposis syndromes:

- Peutz-Jegers syndrome: Surveillance in affected or at risk PJS patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix and testes cancer. Genetic counseling and consideration of genetic testing for at risk relatives (autosomal dominant inheritance)
- Juvenile polyposis syndrome: Surveillance should include screening for colon, stomach and small bowel cancers.
- Cowden syndrome: Surveillance should include screening for colon, stomach, small bowel, thyroid, breast, uterine, kidney and skin cancers
- Serrated/ hyperplastic polyposis syndrome: Colonoscopy every 1-3 years with attempted removal of polyps >5 mm. Surgical referral is necessary if colonoscopic treatment is inadequate or if high grade dysplasia occurs.

Page 9: Amsterdam criteria and revised Bethesda guidelines

Amsterdam II criteria (all criteria have to be fulfilled)
There are at least three relatives with an HNPCC-associated cancer (large bowel, endometrium, small bowel, ureter or renal pelvis)
At least two successive generations are affected
One affected person is a first-degree relative of the other two
At least one person was diagnosed before the age of 50 years
Familial adenomatous polyposis has been excluded

Revised Bethesda criteria (MSI and at least one criterion is met)
Colorectal cancer diagnosed in a patient who is less than 50 years of age
Presence of synchronous, metachronous colorectal or other HNPCC-associated tumors (colorectal, endometrial, gastric, ovarian, pancreatic, ureter/ renal pelvis, biliary tract and brain tumors, sebaceous gland adenomas and keratoacanthomas and carcinoma of the small bowel) regardless of age
Colorectal cancer with the MSI-high histology (Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern) diagnosed in a patient who is less than 60 years of age
Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years
Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Vasen, H.F., et al., The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum, 1991. 34(5): p. 424-5.

Umar, A., et al., Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst, 2004. 96(4): p. 261-8.