European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

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Rare but relevant – colon carcinoma and cancer predisposition in childhood

Moderation:
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SIOPE YOUNG

St. Anna Kinderkrebs Forschung

COI declaration

- No COI to declare.

Case presentation

- 17 year old male
  - presenting with right-sided lower abdominal pain (3 days) and fever (40°C, 1 day)
  - increased sweating at night (2 days)

  Examination:
  - reduced general condition, pale
  - pain on pressure in the right lower abdomen
  - no palpable resistance or hepatosplenomegaly

Case presentation

- Diagnostics for suspected appendicitis
  - Lab:
    - C-reactive protein: 9.2 mg/dl ↑ (<0.5)
    - Hemoglobin: 7.7 g/dl ↓ (14-18) → microcytic and hypochromic
    - normal counts for leukocytes/platelets, normal LDH and uric acid
  - Ultrasound:
    - right lower abdomen: long wall thickening of the colon; subtotal luminal obstruction
    - surrounding mesenteric lymphadenopathy
    - slightly enlarged liver and spleen

} referral to our pediatric oncology department on suspicion of lymphoma

Case presentation

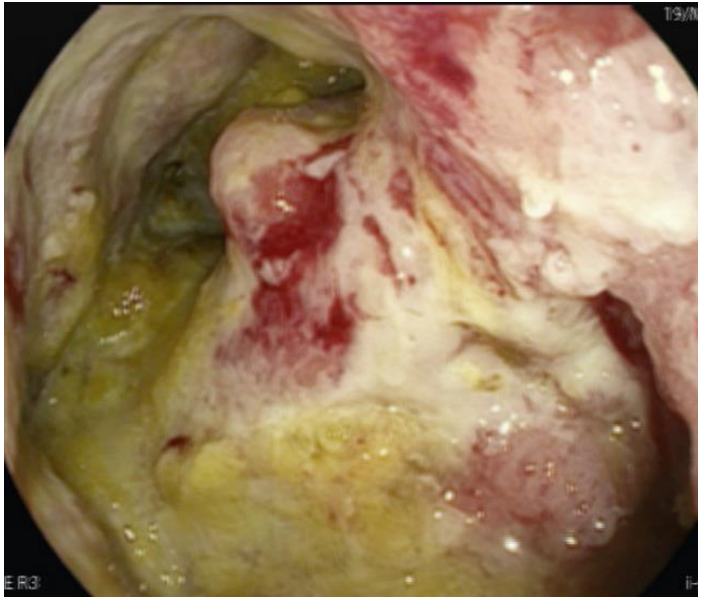
- extended anamnesis
  - weight loss of about 20 kg in the last 6 months as part of a deliberate diet (now normal weight)
  - no traces of blood/black discoloration of the stool
  - no pre-existing conditions
  - no early onset cancers in family history

Case presentation

- decision for endoscopic biopsy
  - macroscopic: tumor in the ascending colon

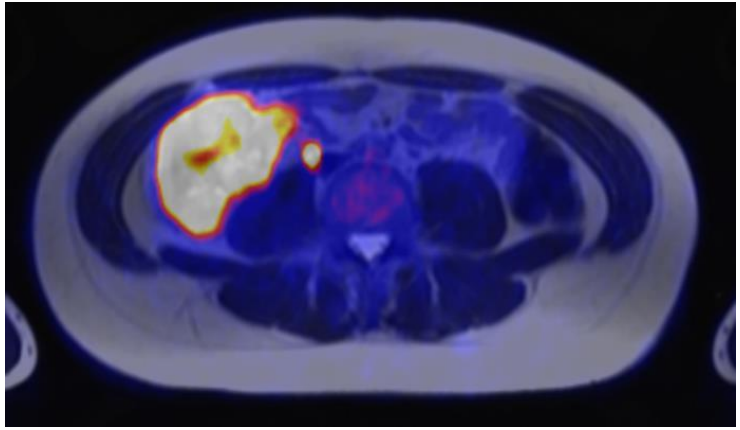
    with subtotal narrowing of the lumen

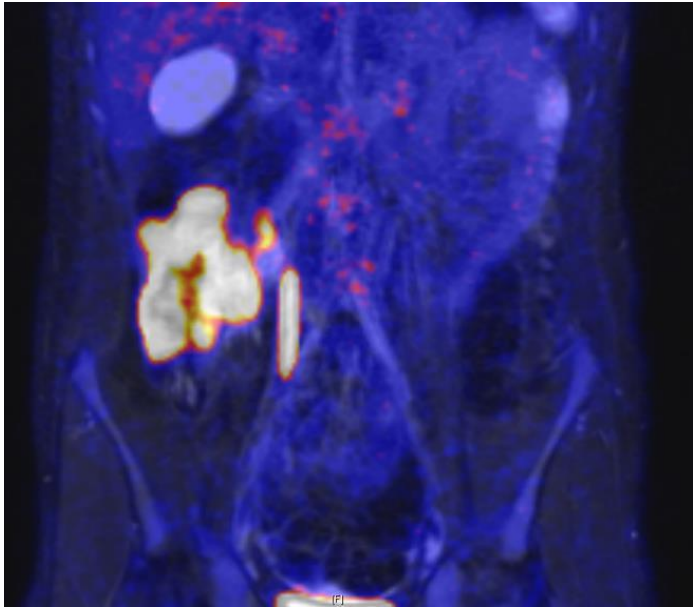
  - histology: adenocarcinoma of the intestinal type



Case presentation

- Staging by whole body PET MRI





Case presentation

- Staging by whole body PET MRI
  - **10 x 6.5 x 7 cm circular mass** extending around the ascending colon, with a margin that absorbs contrast agent and shows clearly restricted diffusion. […] Adjacent to this, **suspicious lymph nodes** in the morphological sequences, which are lost in the tumor conglomerate in the PET.
  - no distant metastases
- CEA 1.8µg/l (<5)

→ right hemicolectomy with lymphadenectomy

Case presentation

- Histopathologic report
  - Adenocarcinoma of the ascending colon, grading: G2

    TNM: pT3 (subserosal infiltration), pN1b (2/33)

    R1 (retrocecal dissection)

Question 1

What should be analyzed in histopathologic examination additionally? (1 is correct)

a) PD-L1 expression

b) Microsatellite instability

c) TP53 alteration

d) VEGF expression

Case presentation

- Histopathologic report
  - Adenocarcinoma of the ascending colon, grading: G2

    TNM: pT3 (subserosal infiltration), pN1b (2/33) → **Stage IIIB**

    R1 (retrocecal dissection)

    MSH2 and MSH6 status: preserved. MLH1 and PMS2 status: loss.

    Microsatellite status: unstable (MSI high)

    (*BRAF* status: codon 600 WT)

Question 2

What further action should be taken? (1 is correct)

a) adjuvant chemotherapy

b) re-resection

c) checkpoint inhibitor treatment

d) adjuvant chemotherapy + checkpoint inhibitor treatment

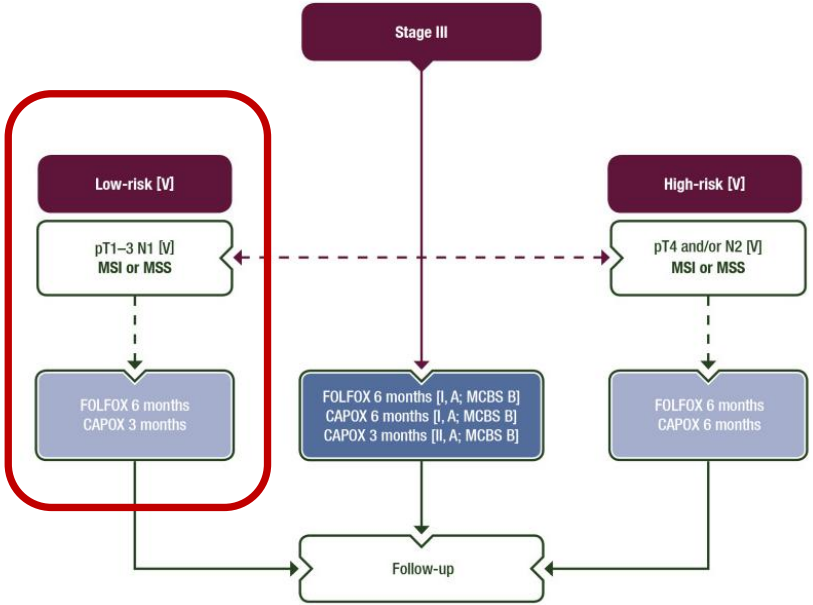
e) follow-up

Case presentation

- Adjuvant treatment
  - 4 cycles of capecitabine + oxaliplatin (CAPOX)

    according to adult guidelines

→ clinical/radiological remission



Argilés et al. 2020, Localised colon cancer ESMO guidelines, Annals of Oncology

Question 3

What further action should be taken? (1 is correct)

a) analysis of CEA every 3-6 months

b) cross-section imaging every 6-12 months

c) colonoscopy every 3-5 years

d) germline genetic sequencing

e) all of the above

Case presentation

- Germline genetic sequencing for tumor predisposition, e.g.:

  - Lynch syndrome (formerly HNPCC) = mono-allelic alteration in a mismatch repair gene:

    MLH1, MSH2, MSH6 or *PMS2*

    (or epithelial cell adhesion molecule EPCAM, which causes epigenetic silencing of *MSH2*)

  - Constitutional mismatch repair-deficiency syndrome (HNPCC) = bi-allelic alteration in a mismatch repair gene

  - Familial adenomatous polyposis (FAP) = germline mutation in the *APC* gene

Case presentation

- Germline genetic sequencing for tumor predisposition:
  - heterozygous pathogenic frameshift variant in the *MLH1* gene, corresponding to a Lynch syndrome (HNPCC)

→ necessity of appropriate screening

(e.g. according to Stjepanovic et al. Annals of Oncology 2019)

Table 2. LS surveillance recommendations

Site	Technique	Age (years)	Interval (years)
Colorectum	Colonoscopy	• *MLH1/MSH2*: 25[a,b] • *MSH6/PMS2*: 35	1–2
Uterus	TV US Endometrial biopsy	30–35	1
Ovaries	CA 125 + TV US	30–35	1
Stomach	UGI endoscopy[c] Consider testing *Helicobacter pylori*	30–35	1–3
Other LS-associated cancers	None[d]		

[a]Or 5 years before the earliest CRC, if diagnosis <25 years.
[b]Consider later age for *MSH6* carriers.
[c]Consider in high-incidence countries or family history of gastric cancer.
[d]Consider pancreatic/urinary tract cancer surveillance if family history.
CA 125, cancer antigen 125; CRC, colorectal cancer; LS, Lynch syndrome; TV, transvaginal; UGI, upper gastrointestinal; US, ultrasound.

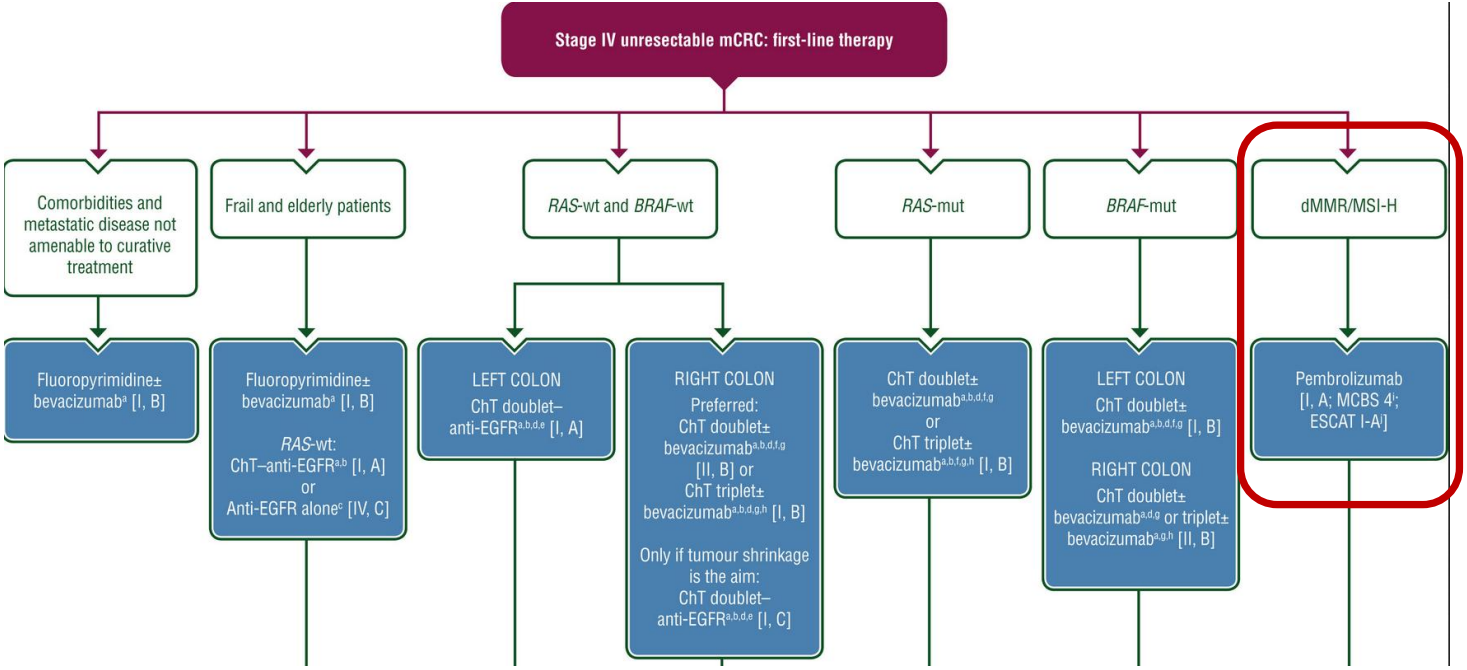
Case presentation

→ 5 months after end of treatment: local recurrence in the lymph nodes

→ decision for checkpoint inhibition due to proven microsatellite instability

→ Pembrolizumab over 2 years (initially every three weeks, then every six weeks)

Case presentation



Cervantes et al. 2023, Metastatic colorectal cancer ESMO guidelines, Annals of Oncology

Case presentation

→ 5 months after end of treatment: local recurrence in the lymph nodes

→ decision for checkpoint inhibition due to proven microsatellite instability

→ Pembrolizumab over 2 years (initially every three weeks, then every six weeks)

→ lasting clinical/radiological remission

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DISCUSSION

Funded by the European Union's Health Programme

Take home messages

- → colon carcinoma often presents with unspecific symptoms in childhood
- → colon carcinoma is an important differential diagnosis in patients with ileus/bowel wall thickening and mesenteric lymphadenopathy
- → histopathologic analysis must include analysis of microsatellite instability

  (as well as sequencing for *BRAF*, *KRAS* and *NRAS* alterations at least in stage IV cancer without MSI)
- → treatment should be discussed interdisciplinary together with medical oncologists, e.g. within the ERN CPMS; therapy is currently still based on adult guidelines for colon cancer *(…though biological differences are noted…)*
- → analysis for germline cancer predisposition must be performed to conduct appropriate screening

STEP data

41 STEP patients <18 years (analyzed along with further population-based data)

- Genetic tumor syndrome (Lynch, CMMRD, FAP):

  35-50%! vs. 7% for adults

  → especially in patients with MSI tumors: 11/13

- more frequently distant metastases (44% vs. 15-20%), primarily in MSS tumors
- more frequently “unfavorable” histology (34% vs. 10-20%)
- more frequently MSI tumors (35-40% vs. 15%)

publication in preparation

STEP data

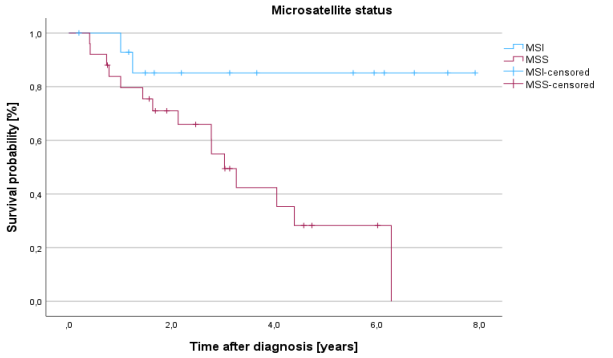
Kaplan-Meier curves for estimating the survival of pediatric patients from STEP cohort differing between

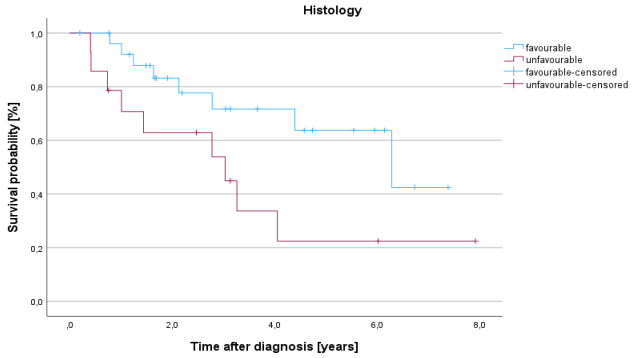
microsatellite status (p-value: 0.007)

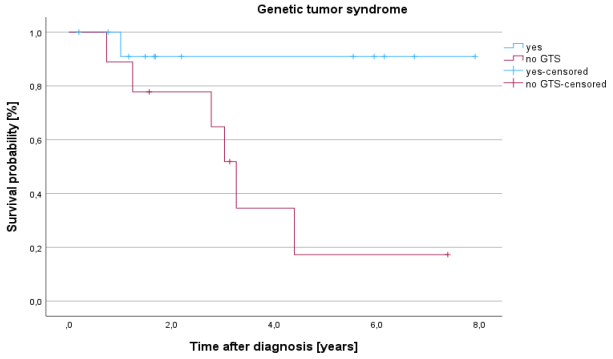
GTS (p-value: 0.022)

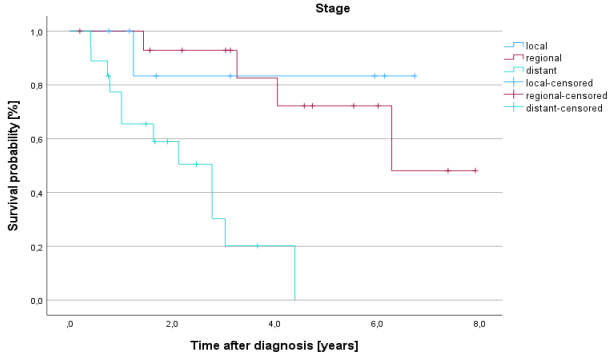
histology (p-value: 0.037)

stage (p-value: <0.001)









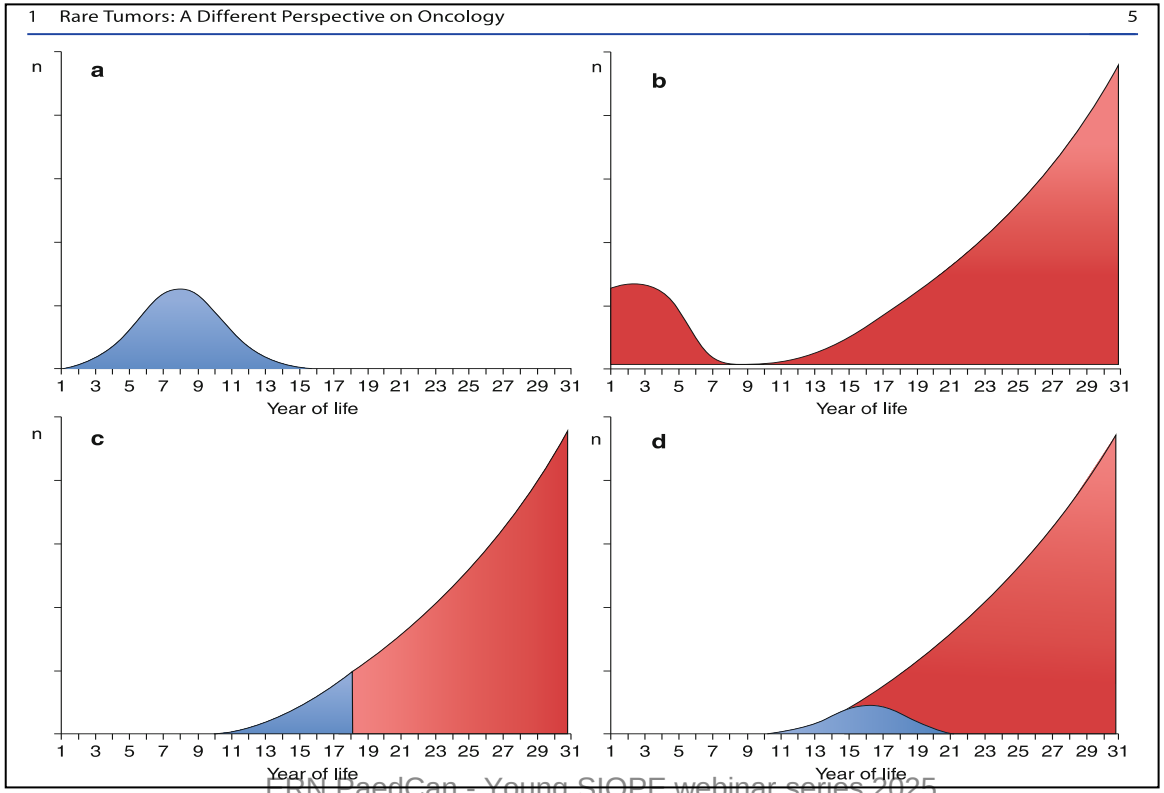
publication in preparation

STEP data

- inferior outcome in pediatric patients with CRC compared to adults (5-y OS: 48% vs. 65%)
- trend indicating a poorer prognosis for pediatric patients with MSS-CRC compared to young adults with MSS-CRC
- very favorable outcome for children with MSI-CRC, which exceeds the disease-specific survival of adults with MSI-CRC

publication in preparation

General Considerations:
When adult cancers occur in children



Schneider et al,
Rare Tumors in Children and Adolescents, Springer 2022

General Considerations:
When rare cancers occur in your clinic

International Consultation Platform of the European Pediatric Rare Tumour Group (EXPERT)

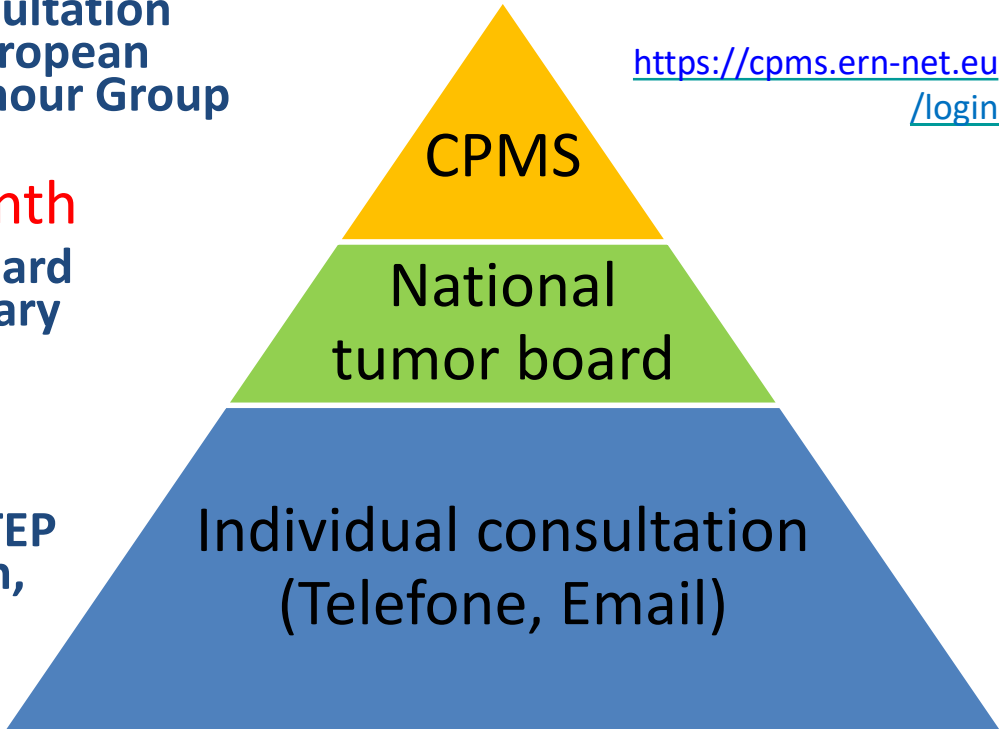
1 week – 1 month

National tumor board with interdisciplinary experts

< 1 week

Consultation by STEP chairs, information, literature

< 24 hours



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