Ulcerative colitis
State of the art

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University Paris VII
Beaujon Hospital, Clichy
1.5 million patients with IBD
Prevalence 1/1000
Incidence of UC

- Swedish study from Uppsala County
- Increased incidence from 2 to 19.2 new cases/100,000 habitants/year

Röönblohm et al. J Crohn's Colitis 2010

- 20 studies in UC:
  - 4 (20.0%) : increasing
  - 13 (65.0%) : stability
  - 3 (15.0%) : decreasing

Benchimol et al. Inflamm Bowel Dis 2011
Physiopathology of IBD

Shanahan F. Gastroenterology 2001;120:622-35.
Environmental factors in IBD

Very bad for CD
Good for UC!

Protect to UC
Ulcerative colitis

• UC is a relapsing non-transmural inflammatory disease that is restricted to the colon.

• Patients typically present with bloody diarrhoea (often nocturnal and postprandial), passage of pus, mucus, or both, and abdominal cramping during bowel movements.

• Severe symptoms are less common in left-sided colitis and proctitis.
Extensive colitis (20%)

Extensive colitis (30%)

Proctitis (50%)

Left sided colitis (20%)
Ileocolonoscopy with biopsies is the 1st line investigation for IBD diagnosis
Differential diagnosis of UC and CD

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematochezia</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Passage of mucus or pus</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Small-bowel disease</td>
<td>No (except backwash ileitis)</td>
<td>Yes</td>
</tr>
<tr>
<td>Can affect upper-gastrointestinal tract</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Rare</td>
<td>Sometimes in right lower quadrant</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Small-bowel obstruction</td>
<td>Rarely</td>
<td>Common</td>
</tr>
<tr>
<td>Colonic obstruction</td>
<td>Rarely</td>
<td>Common</td>
</tr>
<tr>
<td>Fistulas and perianal disease</td>
<td>No</td>
<td>Common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical features</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-neutrophil cytoplasmic antibodies</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Anti-seccharomyces cerevisiae antibodies</td>
<td>Rarely</td>
<td>Common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological features</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural mucosal inflammation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Distorted crypt architecture</td>
<td>Yes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cryptitis and crypt abscesses</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Granulomas</td>
<td>No</td>
<td>Yes, but rarely in mucosal biopsies</td>
</tr>
<tr>
<td>Fissures and skip lesions</td>
<td>Rarely</td>
<td>Common</td>
</tr>
</tbody>
</table>
Up to 25% patients with UC will develop extraintestinal manifestations
UC EVOLUTION IN POPULATION BASED STUDY

Danish Population based study
(IBSEN study), n=423/519, suivi 10 ans

Progressive improvement
- 55%

Progressive worsening
- 1%

Recurrent relapses
- 37%

chronic active
- 6%

Solberg, Scand J Gastro 2009; 44: 431
The natural history of surgery for UC in a population-based cohort

*Olmsted County, Minnesota (1940 – 2001)*

Incident cases, n=368; Follow up 15.1 (0.1-58) years; surgery 21%

Dhillon S et al. AJG 2005;100:S303
Mucosal healing at 1 years decreases the risk of colectomy

- Prospective follow up in a norwich study cohort between 1990-94 (before biothérapies)

- 354 UC with endoscopical evaluation à 1 year : 175 MH+, 163 MH-

- New clinical evaluation at 5 years

  MH+: 3 colectomies /178 (2%)
  MH -:13 colectomies /176 (7%)

__Froslie K.F et al Gastroenterology, 2007; 133: 412-22__
The therapeutic goal in UC is the clinical/endoscopic remission

**ECCO consensus 2008**

Endoscopic remission is defined by the Endoscopic Mayo Score

\[ RE = \text{sous-score endoscopique} \leq 1 \]

0 Normal or inactive disease

1 Mild disease (erythema, decreased vascular pattern, mild friability)

2 Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3 Severe disease (spontaneous bleeding, ulcerations)

Pineton de Chambrun, G. et al. NRGH 2010; 7:15–29
Mild to moderate UC
## Treatment of mild to moderate UC

<table>
<thead>
<tr>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA topics</td>
<td>5-ASA oral</td>
</tr>
<tr>
<td>5-ASA oral</td>
<td>Anti-TNFs</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>Corticoïds topics</td>
</tr>
<tr>
<td>Systemic Corticoïds</td>
<td></td>
</tr>
</tbody>
</table>
Induction of remission
Rectal 5-ASA in distal UC

Figure 5. Forest plot of comparison: Rectal 5-ASA vs Placebo, outcome: Symptomatic Remission.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rectal 5-ASA</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campieri 1990a</td>
<td>45</td>
<td>63</td>
<td>17.4%</td>
<td>3.95 (1.60, 9.80)</td>
</tr>
<tr>
<td>Campieri 1990b</td>
<td>13</td>
<td>32</td>
<td>10.3%</td>
<td>15.00 (3.65, 88.75)</td>
</tr>
<tr>
<td>Campieri 1991a</td>
<td>12</td>
<td>18</td>
<td>6.5%</td>
<td>26.00 (7.72, 74.53)</td>
</tr>
<tr>
<td>Campieri 1991b</td>
<td>38</td>
<td>36</td>
<td>13.1%</td>
<td>10.57 (4.00, 29.73)</td>
</tr>
<tr>
<td>Hanauer 1998</td>
<td>101</td>
<td>217</td>
<td>16.7%</td>
<td>5.22 (2.54, 10.74)</td>
</tr>
<tr>
<td>Moller 1978</td>
<td>13</td>
<td>16</td>
<td>8.0%</td>
<td>26.00 (3.68, 183.42)</td>
</tr>
<tr>
<td>Poltronbela 2000</td>
<td>35</td>
<td>54</td>
<td>57.1%</td>
<td>2.72 (1.26, 5.80)</td>
</tr>
<tr>
<td>Williams 1987</td>
<td>11</td>
<td>14</td>
<td>5.9%</td>
<td>44.00 (3.97, 488.19)</td>
</tr>
</tbody>
</table>

Total (95% CI) 506 256 100.0% 8.30 [4.28, 16.12]

Figure 6. Forest plot of comparison: Rectal 5-ASA vs Placebo, outcome: Endoscopic Remission.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rectal 5-ASA</th>
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<th>Odds Ratio</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Campieri 1990a</td>
<td>36</td>
<td>63</td>
<td>16.0%</td>
<td>4.57 (1.72, 12.16)</td>
</tr>
<tr>
<td>Campieri 1990b</td>
<td>13</td>
<td>32</td>
<td>6.7%</td>
<td>9.56 (1.94, 47.30)</td>
</tr>
<tr>
<td>Campieri 1991a</td>
<td>10</td>
<td>18</td>
<td>2.6%</td>
<td>35.82 (1.86, 691.79)</td>
</tr>
<tr>
<td>Campieri 1991b</td>
<td>40</td>
<td>86</td>
<td>9.7%</td>
<td>10.87 (2.42, 48.78)</td>
</tr>
<tr>
<td>Hanauer 1998</td>
<td>137</td>
<td>217</td>
<td>29.4%</td>
<td>5.34 (2.30, 9.65)</td>
</tr>
<tr>
<td>Moller 1978</td>
<td>12</td>
<td>16</td>
<td>7.8%</td>
<td>11.00 (2.00, 60.57)</td>
</tr>
<tr>
<td>Poltronbela 2000</td>
<td>26</td>
<td>54</td>
<td>23.5%</td>
<td>2.18 (1.00, 4.76)</td>
</tr>
</tbody>
</table>

Total (95% CI) 486 243 100.0% 5.31 [3.15, 8.92]

Rectal 5-ASA vs rectal corticosteroid in distal UC

Rectal vs oral 5-ASA in proctitis

• A 4-week, randomized trial (n=58): Rectal 400 mg or oral 800 mg 3 times per day

• Improvement in mean DAI scores and rates of histologic remission were significantly greater at weeks 2 and 4 with suppos compared with oral mesalazine

Oral 5-ASA for induction of remission in mild to moderate UC: The ASCEND 1 trial

E2+E3

Figure 2) Asacol (Proctor & Gamble Pharmaceuticals, USA) treatment outcomes at weeks 3 and 6 in all patients with mildly to moderately active ulcerative colitis

The ASCEND 1 trial: Analysis restricted to moderate UC

Figure 4) Treatment success in the subgroup of patients with moderately active ulcerative colitis who were administered delayed-release oral mesalazine (Asacol, Proctor & Gamble Pharmaceuticals, USA) at a dose of either 2.4 g/day or 4.8 g/day. *Significant difference in between-treatment comparison using Wilcoxon’s signed rank test (P=0.0384)

Rectal + oral 5-ASA in extensive UC (n=127)

What to do in case of failure of 5-ASA (topical + oral) and rectal steroids?
Steroids for refractory UC

- 63 patients with UC
- Population-based cohort, Olmsted County, MN, US
- 1970-93

<table>
<thead>
<tr>
<th>Complete remission:</th>
<th>Partial remission:</th>
<th>No response:</th>
</tr>
</thead>
<tbody>
<tr>
<td>54%</td>
<td>30%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Faubion et al. Gastroenterology 2001
Infliximab for UC: ACT 1 and 2 trials

Randomization of Patients (n=364/trial)

<table>
<thead>
<tr>
<th>Visits</th>
<th>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 6</td>
<td></td>
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<td></td>
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<td>Week 8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 30</td>
<td></td>
<td>ACT 2</td>
<td>Final Evaluation</td>
</tr>
<tr>
<td>Week 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 54</td>
<td></td>
<td>ACT 1</td>
<td>Final Evaluation</td>
</tr>
</tbody>
</table>

- Infusions

Rutgeerts et al. NEJM 2005
Infliximab for UC: ACT 1 and 2 trials

Sustained Response

Sustained Remission

Rutgeerts et al. NEJM 2005
Infliximab for UC: ACT 1 and 2 trials

% of patients with no colectomy

Placebo

244 243 234 210 197 191 178 170 158

Infliximab

484 484 477 457 443 419 401 391 372

Time from Study Drug Administration (Weeks)

10% vs. 17% after 54 weeks

Maintenance of remission
ECCO Consensus UC
Maintenance therapy

ECCO statement 6A
The goal of maintenance therapy in UC is to maintain steroid-free remission, clinically [EL1, RG A] and endoscopically defined [EL2, RG B]

ECCO statement 6B
Maintenance treatment is recommended for all patients [EL1a, RG A]. Intermittent therapy is acceptable in a few patients with disease of limited extent [EL5, RG D]

ECCO Consensus UC
Maintenance therapy

<table>
<thead>
<tr>
<th>ECCO statement 6D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral 5-aminosalicylate (5-ASA) containing compounds are the first line maintenance treatment in patients responding to 5-ASA or steroids (oral or rectal) [EL1a, RG A]. Maintenance with topical 5-ASA is a valuable alternative in proctitis and left-sided colitis [EL1b, RG A]. A combination of oral and rectal 5-ASA can be used as a second line maintenance treatment [EL1b, RG B]</td>
</tr>
</tbody>
</table>
Consensus RCH
Durée du traitement d’entretien

ECCO statement 6J
The general recommendation is to continue 5-ASA maintenance treatment long-term [EL3b, RG C] since this may reduce the risk of colon cancer [EL4, RG D]

ECCO statement 6 K
Due to lack of evidence, no recommendation can be given for the duration of treatment with azathioprine or infliximab, although prolonged use of these medications may be considered if needed [EL4, RG D]
Oral 5-ASA for maintenance of remission

Clinical and endoscopic remission

47%

Sutherland and Mac Donald. Cochrane 2010 (In Press)
Asacol once vs twice daily

- Multicenter, randomized, 12-month trial
- Mild to moderate UC in clinical remission
- N=1023
- Oral mesalamine (400-mg tablet):
  - 1.6-2.4 g/d once or twice daily

Thiopurines as maintenance therapy in UC

Clinical remission

59.7%

Figure 2. Meta-analysis of randomized clinical trials evaluating the efficacy of azathioprine (AZA) and mercaptopurine (MP) for the maintenance of clinical remission of ulcerative colitis.

Randomised controlled trial of azathioprine and 5-ASA for treatment of steroid dependent UC

% remission off steroids at month 6

Non observance of treatment = Main factor of relapse

RR X 5 of relapse

99 UC in remission with 5-ASA prospective follow up of 24 months
Observance: > 80% of consumption 5-ASA

*Kane S et al. Am J Med 2003*
Methotrexate as maintenance therapy in UC

« Only 1 study reported a prospective randomized placebo-controlled trial using methotrexate at a dose of 12.5 mg orally with no significant clinical benefit.

The majority of uncontrolled retrospective analyses suggest a clinical response to methotrexate therapy in a range of 30%-80% when the drug is applied by parenteral route in doses between 20-25 mg. Uncontrolled, retrospective studies using doses and routes of administration similar to those employed in CD suggest benefit.

Well-designed, prospective, placebo-controlled trials of methotrexate in UC are needed. »

Herfarth HH et al. IBD 2010;16:1421-30
METEOR
MULTICENTER PLACEBO RANDOMIZED DOUBLE BLIND CLINICAL TRIAL OF METHOTREXATE vs PLACEBO FOR STEROID-DEPENDENT ULCERATIVE COLITIS
Severe UC: 15% of patients
Treatment of acute severe UC

Steroids

Cyclosporine

Infliximab

OR?

Failure

Failure

Infliximab?

Infliximab

Colectomy

Cyclosporine?

Cyclosporine

Colectomy

Rule out CMV and C. Difficile infection +++

Always consider surgery
Severe UC: IV cyclosporin

Intravenous CsA:
Severe Active Steroid-Refractory UC

Clinical Response at Week 2*

- Placebo
- CsA 4 mg/kg

% of Patients

Lichtiger Score at Week

- Placebo
- CsA 4 mg/kg

N=20

*Lichtiger score <10 points for 2 consecutive days

Infliximab as Rescue Therapy for UC

- Hospitalized patients failed 3d of IV steroids with moderate to severe disease
- RCT – infliximab versus placebo
- Single dose of infliximab 5mg/kg
- Primary outcome – Colectomy or death within 90 days:

Ø deaths

Essai CYSIF

Screening
-5 0 7 14 28 42 98 jours 1 an

Réponse
Rémission

Cyclo.  IV oral
IFX
AZA
CYSIF: Failure rate at D98

- Ciclosporine (n=55): 60% failure rate
- Infliximab (n=56): 54% failure rate

p = 0.49

Laharie et al., JFHOD 2011
CYSIF: Response rate at D7

![Bar chart showing response rate distribution between Cyclosporin (n=55) and Infliximab (n=56).]

Laharie et al., JFHOD 2011
The GETAID experience: Is a third line possible?

- 86 patients
- Median follow-up: 4.6 months
- CYS-IFX (n=65) or IFX-CYS (n=21)

**Efficacy:**
- 48 (57%) patients underwent colectomy during follow-up

**Safety:**
- One death (pulmonary embolism one day after surgery) in the CYS-IFX group
- 8 infections (7 in the CYS-IFX group), including 2 sepsis on central line and 5 post-operative infections
- No cases of opportunistic infections after second line therapy

Leblanc et al. Submitted
Special Situations

- C. difficile
- Cancer
- Thrombosis
- Surgery
A National Survey of the Prevalence and Impact of Clostridium difficile Infection Among Hospitalized Inflammatory Bowel Disease Patients

Prevalence of Clostridium difficile

- UC: 37.3 per 1,000
- CD: 10.9 per 1,000
- Gastro: 4.8 per 1,000
- non gastro: 4.5 per 1,000

↑ incidence C. difficile in UC

Increased mortality

- RCH (OR=3.79 [2.84–5.06])
- MC (OR 1.66 [0.75–3.66], NS)

After 8-10 years of evolution, the risk increases from 0.5 to 18%.

Ancient UC are more at risk to develop colorectal cancer.

## Risk of venous thromboembolic disease

<table>
<thead>
<tr>
<th></th>
<th>Events (n)</th>
<th>Person-years of follow-up</th>
<th>Risk per 1000 person-years (unadjusted)</th>
<th>Hazard ratio* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All periods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall inflammatory bowel disease</td>
<td>139</td>
<td>53534.5</td>
<td>2.6</td>
<td>3.4 (2.7-4.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Flare</td>
<td>34</td>
<td>3782.3</td>
<td>9.0</td>
<td>8.4 (5.5-12.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic activity</td>
<td>45</td>
<td>8358.7</td>
<td>5.4</td>
<td>6.5 (4.6-9.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remission</td>
<td>60</td>
<td>41393.5</td>
<td>1.4</td>
<td>2.1 (1.6-2.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Control</td>
<td>165</td>
<td>279772.2</td>
<td>0.6</td>
<td>1.0</td>
<td>..</td>
</tr>
<tr>
<td><strong>Hospitalised periods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall inflammatory bowel disease</td>
<td>48</td>
<td>1907.5</td>
<td>25.2</td>
<td>2.1 (1.4-3.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Flare</td>
<td>12</td>
<td>320.3</td>
<td>37.5</td>
<td>3.2 (1.7-6.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Chronic activity</td>
<td>13</td>
<td>443.0</td>
<td>29.3</td>
<td>2.8 (1.5-5.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Remission</td>
<td>23</td>
<td>1102.2</td>
<td>20.9</td>
<td>1.7 (1.1-2.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Control</td>
<td>49</td>
<td>3532.2</td>
<td>13.9</td>
<td>1.0</td>
<td>..</td>
</tr>
<tr>
<td><strong>Ambulatory periods</strong></td>
<td></td>
<td></td>
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<tr>
<td>Overall inflammatory bowel disease</td>
<td>91</td>
<td>51669.0</td>
<td>1.8</td>
<td>4.3 (3.3-5.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Flare</td>
<td>22</td>
<td>3462.1</td>
<td>6.4</td>
<td>15.8 (9.8-25.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic activity</td>
<td>32</td>
<td>7915.7</td>
<td>4.0</td>
<td>9.9 (6.7-147)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remission</td>
<td>37</td>
<td>40291.2</td>
<td>0.9</td>
<td>2.2 (1.5-3.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Control</td>
<td>116</td>
<td>276239.2</td>
<td>0.4</td>
<td>1.0</td>
<td>..</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, body-mass index (<25 kg/m², 25–30 kg/m², >30 kg/m², information missing), smoking (current smoker, non-smoker, information missing), cancer diagnosis (in exposure period or before study), and history of pulmonary embolism or deep vein thrombosis.

Surgery in acute severe UC

Subtotal colectomy

no anastomosis first

ileosigmoidostomy

Rectal treatment of excluded rectum

2-3 months

IRA or IAA following aspect of rectum

Thank you for your attention
**Where are we now with the objectives?**

<table>
<thead>
<tr>
<th>Objective</th>
<th>1990</th>
<th>2000</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control symptoms</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Maintain remission</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Improve QoL</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Limit drug toxicities</td>
<td>+</td>
<td>+</td>
<td>↑</td>
</tr>
<tr>
<td>Heal lesions</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Decrease hospitalizations</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Stop progression of irreversible lesions</td>
<td>-</td>
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<tr>
<td>Limit complications</td>
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<td>Limit surgery</td>
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<tr>
<td>Prevent cancer</td>
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<tr>
<td>Decrease mortality</td>
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<tr>
<td>Cure the disease…</td>
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