Hirschsprung Disease: Still Searching for the Therapeutic Holy Grail

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Outline
• Brief overview of HD
• Genetics of HD
• History of surgical therapies for HD
• Current surgical techniques
• Complications
• Treatment of complications
• Future Challenges

Symptoms of Hirschsprung Disease
• Constipation
• Bowel obstruction
• Abdominal distention
• Episodes of diarrhea
• Vomiting
• Dehydration
• Death

Hirschsprung Disease
• Congenital form of constipation
  – Absence of ganglion cells in myenteric and submucosal plexuses
  – Described in 1886
Hirschsprung Disease

- Incidence 1 in 4400 to 7000 live births
- Sporadic (80-90%) and familial forms
- Associations
  - Trisomy 21 (4.5-16%)
  - Intestinal atresia
  - Trisomy 18
  - Ondine’s curse (central hypoventilation)
- Variable length of intestine affected
  - Total colonic (3-12%)

Genetics of Hirschsprung’s Disease

- Genetically heterogeneous condition:
  - AD, AR, sex-modified inheritance, polygenic subtypes with variable penetrance

Hirschsprung Disease

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- Associations
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  - Total colonic (3-12%)

Genetics of Hirschsprung’s Disease

- 1992 Martucciello et al localized total colonic aganglionosis in chromosome 10
- 1994 Edery et al and Romeo et al found point mutations in the RET protooncogene (chr 10) in patients with familial and sporadic HD
  - Incompletely penetrant
  - Dominant effect
RET

- RET gene encodes for a receptor tyrosine kinase that is critical in the development of neural crest cells and is responsible for MEN 2A & 2B

Hirschsprung Disease

- Identified gene mutations
  - RET
    - 35% of sporadic, 49% of familial cases
    - 75% of long-segment, 32% of short-segment cases
  - Other mutations (5-10% of patients)
    - EDNRB (Endothelin receptor B)
    - GDNF (Glial cell line-derived neurotrophic factor)
    - SOX10 (Sex-determining region Y-related HMG-box gene 10)

Early Descriptions of H.D.

- Ruysch, 1691
  - 5 yo girl who died with massive colon distention
Early Descriptions of H.D.

- Battini, 1800
  - Child followed for 10 years who died with massive colon distention
- Jacobi, 1862—Described 2 children with severe constipation that responded to enemas and transverse colostomy

Early Descriptions of H.D.

- Scattered reports of severe constipation in childhood with subsequent death by Ebers(1836), Gee(1884), Bristowe(1885)

Harald Hirschsprung--Pioneer

- Chief of Pediatrics
  - Queen Louise Children’s Hospital, Copenhagen
- Other contributions
  - Pyloric stenosis, Intussusception, Intestinal atresia
- Strong personality
  - Defied the Queen’s wish to hang pictures of saints in the hospital in favor of pictures of animals

Early Descriptions of H.D.

- Harald Hirschsprung(1886)
  - “Constipation in newborns due to due to dilatation and hypertrophy of the colon”
  - Presented to the Society of Pediatrics in Berlin, Germany
**Hirschsprung’s Description**
- Case reports of two infant boys
- Both had constipation from birth
- Enemas relieved their abdominal distention
- One boy had intermittent diarrhea

**Hirschsprung’s Description**
- Both boys died in infancy
- Both had enormously dilated colons
- One had a “normal” sized rectum

**Etiology of Hirschsprung Disease**
- Hirschsprung (1904)
  - No comment on etiology – focused on dilated colon
- Fenwick (1900)
  - “Spasm of anal sphincters”
- Tittel (1901)
  - Sparse development of nerve plexuses in the colon

**Etiology of Hirschsprung Disease**
- Dalla Valla (1920)
  - Absence of ganglion cells in distal sigmoid colon with normal ganglion cells in proximal colon
- Ishikawa (1923)
  - Absence of parasympathetic nerves in the pelvis
Early Surgical Attempts to Cure H.D.

- Finney (1908)
  - Resection of dilated colon

- Barrington-Ward
  - Resection of dilated colon

"In the 1930’s we had 9 patients who were treated by resection of the transverse colon or an enlarged sigmoid loop. One of these patients died of peritonitis. In one there was no change and in one there was slight improvement. One was in a very satisfactory state for fourteen years, after which there was a recurrence and involvement of other parts of the colon. Five were greatly improved and in excellent condition when last seen one, four, seven, eleven and twelve years respectively, after operation."

The Surgery of Infancy and Childhood, 1953, p. 338
Robert E. Gross, MD
Theories of Causation

“In the light of recent work on the sympathetic system, all the theories of the past, except the neuromuscular, can be discarded. There is now abundant clinical evidence to show that the sympathetic or parasympathetic nerve supply to the colon and rectum is at fault, and that surgical measures directed to that fault relieve the disease.”

The Abdominal Surgery of Children, 2nd Ed., 1937, p.276
Sir Lancelot Barrington-Ward

Early Surgical Attempts to Cure H.D.

- Wade and Royle (1927)
  - Lumbar sympathectomy

- (1930’s)
  - Spinal anesthetic
Etiology of Hirschsprung Disease

• Tiffin(1940)
  – Absence of ganglion cells in myenteric plexus of involved colon with ganglion cells above and below this segment

• (1940’s)
  – Marked disagreement about the importance of a neurogenic disturbance in HD

Swenson’s Pull-through for H.D.

• Became interested in patients with severe constipation

• Some patients had a sympathectomy

• Some patients had a sigmoid colectomy

Swenson’s Pull-through for H.D.

• Dr. Ladd admitted these therapies didn’t work

• A failing patient was treated with a colostomy

• The patient improved
Swenson’s Pull-through for H.D.
- Swenson identified peristalsis in the proximal bowel
- No peristalsis found in the distal segment

Swenson’s Pull-through for H.D.
- The colostomy was closed and the deterioration returned

"While we formerly believed that cecostomy might be used in some cases as a temporary decompression (over a period of one or two years), and that the colon would collapse or regain normal tone and activity making it possible for it to function reasonably well after closure of the colostomy, we now are sure that this is a forlorn hope."

The Surgery of Infancy and Childhood, 1953, p. 338
Robert E. Gross, MD

Swenson’s Pull-through for H.D.
- Swenson and radiologist Neuhauser studied other similar patients with a trickle BE
Swenson’s Pull-through for H.D.

- The “spastic distal colon was identified for the first time”
- No identification of aganglionosis was made

Swenson’s Pull-through for H.D.

- A technique for proctectomy with pull-through was worked out in pigs
- Swenson presented his proposed surgical cure for HD to authorities at Boston Children’s Hospital but was not allowed perform the “pull-through” on a patient
- Two other patients had a similar bad outcome after colostomy formation followed by colostomy closure

Swenson’s Pull-through for H.D.

- Swenson was finally given approval to perform his new operation

Swenson’s Technique
Swenson’s Pull-through for H.D.

- Grob’s modification dividing part of the internal sphincter

- Swenson’s modification dividing part of the sphincter posteriorly and using a diagonal anastomosis to avoid stricture

Etiology of Hirschsprung Disease

- Zuelzer and Wilson (1948)
  - Absence of ganglion cells in distal bowel and recommended diversion therapy

- Bodian (1949)
  - Histologically separated HD from other causes of constipation in children

- Hiatt (1951)
  - Manometric studies confirmed loss of anorectal reflex
State’s Anterior Resection

- Developed as a “safer” cure for HD
- Good early response in many patients
- Eventually failed in most patients
- Abandoned when recurrence of symptoms noted to be so high

Duhamel’s Technique

Duhamel’s Bypass Technique

- Designed to avoid the “long, delicate and tedious operation” devised by Swenson
- Retrorectal pull-through and end to side anastomosis on the posterior rectal wall and entire internal anal sphincter
Duhamel’s Bypass Technique

- Modified by Grob with end to side anastomosis above the internal sphincter
- Led to fecal impaction in aganglionic backwater
Duhamel’s Bypass Technique

- Duhamel modified technique by preserving about one-half of the internal sphincter posteriorly
- Grob and Louw reduced the size if the aganglionic blind pouch

Duhamel’s Bypass Technique

- Modification by multiple surgeons to completely obliterate septum between the two segments of bowel
- Modification by Steichen, Talbert and Ravitch using a stapler to divide the septum
Hirschsprung’s Disease

Surgical Treatment
- Leveling colostomy
- Proctectomy and pull-through
- Colostomy closure

Pediatric Laparoscopic Colorectal Surgery
Hirschsprung’s Disease
Laparoscopic Pull-through: Diagnosis

- Barium enema
- Rectal biopsy
- Ganglion cells
  - Hypertrophic nerves

One-Stage Pull-Through in the Neonate

- So et al 1981
- Carcasonne 1982

Georgeson’s Technique
Laparoscopic assisted Transanal Pull-through
Hirschsprung’s Disease
Laparoscopic Pull-through: Results

(N=80)
- Operative time: 147 minutes
- Blood loss: <10 cc’s
- Blood transfusion: 1 (1%)

Hirschsprung’s Disease
Laparoscopic Pull-through

- Bowel movement in first 24 hours: 74/80
- Average time to full feeds: 28 hours
- Mean time to discharge: 3.7 days

Early Complications

(N=80)
- Converted: 2 (2.5%)
- Enterocolitis: 6 (7.5%)
- Chronic diarrhea: 6 (7.5%)
- Anastomotic leak: 2 (2.5%)
- Bleeding: 1 (1%)
- Recurrent constipation: 1 (1%)

4 Important Points
Avoid tension on neorectum to preserve anorectal angle
4 Important Points

Avoid tension on neorectum to preserve anorectal angle
Avoid distorting the external anus by starting transanal dissection at the top of rectal columns
4 Important Points

Avoid tension on neorectum to preserve anorectal angle
Avoid distorting external anus by starting transanal dissection at the top of rectal columns
Don’t overstretch muscle sphincter complex during transanal dissection
4 Important Points
Avoid tension on neorectum to preserve anorectal angle
Avoid distorting external anus by starting transanal dissection at the top of rectal columns
Don’t overstretch muscle sphincter complex during transanal dissection
Split or resect posterior aspect of aganglionic cuff to level of anastomosis

Hirschsprung’s Disease
Laparoscopic Pull-through

Total excision of posterior rectal cuff

- Total excision of the posterior rectal cuff is mandatory during laparoscopy-assisted pull-through for HD to eliminate risk for post-operative stenosis.

- Splitting alone is not enough !!

Total excision of posterior rectal cuff

de la Torre’s Technique

Transanal Pull-through
Transanal Pull-through

- Biopsy taken after rectal ablation
- No abdominal dissection
- No “ugly abdominal pock marks”
- Otherwise similar to LATAP
- Several modifications advocated

Primary Transanal Pull-through

“I am very concerned about surgeons performing a rectal dissection without first defining the transition zone.”

Ovar Swenson

Hirschsprung’s Disease

Laparoscopic Pull-through

- BE unreliable indicator of transition zone
  - Procter et al, JPS, 2003
    - Radiologic and histologic concordance of transition zone—65%, Long seg—25%
  - Jamieson et al, Ped Rad, 2004

Hirschsprung’s Disease

Basic Surgical Principles

- Resect dysfunctional bowel
- Connect normal bowel to the anus
- Preserve fecal continence
- Preserve urinary and sexual function
Pediatric Laparoscopic Colorectal Surgery

**Hirschsprung’s Disease**

*Recent Trends in Surgery*

- Early definitive repair
- One-stage procedure
- Minimally invasive procedures

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**Laparoscopic Primary Pullthrough for Hirschsprung’s disease**

- Conventional staged pullthrough
- Laparoscopic primary pullthrough

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**Hirschsprung’s Disease**

*Complications of Primary vs Staged Repair*

<table>
<thead>
<tr>
<th></th>
<th>One stage</th>
<th>Multistage</th>
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</thead>
<tbody>
<tr>
<td>Complications per patient</td>
<td>0.93</td>
<td>2.13</td>
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</tbody>
</table>

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**Laparoscopic-Assisted Pull-Through for Hirschsprung’s Disease**

*Indications For Surgery*

- Diagnosis established by suction rectal biopsy
- No contraindications for primary procedure

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**Pediatric Laparoscopic Colorectal Surgery**

**Hirschsprung’s Disease**

*Laparoscopic Pull-through: Indications for a Colostomy*

- Associated life threatening anomalies
- Deteriorating general health
- Severe enterocolitis
- Massive dilation and hypertrophy of the proximal bowel

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**Hirschsprung’s Disease**

*Preferred Colostomy Technique*

- Leveling end colostomy
- Long aganglionic segment - resect aganglionic segment to peritoneal reflection
- Short aganglionic segment - leave aganglionic colon in place
- Laparoscopic pull-through in 4-6 months
Postoperative Outcomes

- Single or multiple institution case series
- Procedures, complication definitions vary
- Variable stringency in followup
  - chart review vs. patient interview/questionnaire
  - % of patients included/responding

Enthusiastic surgeons usually lack data
Surgeons with data usually lack enthusiasm

Early Complications

<table>
<thead>
<tr>
<th>Year</th>
<th>Operation</th>
<th>n</th>
<th>Wound Infect</th>
<th>Anast Leak</th>
<th>Preop HAEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sherman 1989</td>
<td>Swenson</td>
<td>880</td>
<td>7%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Tang 1991</td>
<td>ERPT</td>
<td>60</td>
<td>7</td>
<td>7</td>
<td></td>
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<tr>
<td>Rescorla 1992</td>
<td>Multiple</td>
<td>280</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Marty 1995</td>
<td>Multiple</td>
<td>135</td>
<td>1</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Reding 1997</td>
<td>Multiple</td>
<td>59</td>
<td>4</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Ballie 1999</td>
<td>Duhamel</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yanchar 1999</td>
<td>Multiple</td>
<td>107</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Shankar 2000</td>
<td>ERPT</td>
<td>136</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetedbaum 2000</td>
<td>ERPT</td>
<td>181</td>
<td>4</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>1909</td>
<td>4</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
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Adapted from Pediatric Surgery and Urology: Long-term Outcomes, 2006

Hirschsprung Disease Associated Enterocolitis

- Presentation
  - Abdominal distension
  - Fever
  - Explosive diarrhea
  - Septic shock (severe form)
  - Chronic – failure to thrive

<table>
<thead>
<tr>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explosive diarrhea</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Systemic signs</td>
<td>None</td>
<td>Mild-moderate</td>
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</tbody>
</table>

Hirschsprung Disease Associated Enterocolitis

At Diagnosis After Rectal Washouts
Hirschsprung Disease Associated Enterocolitis

**Grade Findings**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>normal mucosa</td>
</tr>
<tr>
<td>I</td>
<td>crypt dilation; mucin retention</td>
</tr>
<tr>
<td>II</td>
<td>cryptitis or &lt;= 2 crypt abscesses per HPF</td>
</tr>
<tr>
<td>III</td>
<td>multiple crypt abscesses per HPF</td>
</tr>
<tr>
<td>IV</td>
<td>fibrinopurulent debris, mucosal ulceration</td>
</tr>
<tr>
<td>V</td>
<td>transluminal necrosis or perforation</td>
</tr>
</tbody>
</table>

Photographs provided by Dr. D. Kelly

**Proposed mechanisms**

- Mechanical
- Infectious
  - *C. difficile*
  - Rotavirus
- Ischemic
- Immunologic
  - Reduced mucin production/turnover
  - Altered sIgA production
  - Neutrophil dysfunction

**Incidence**

- 17-50% patients
- Clinical definition varies

**Mortality**

- Up to 30% reported in literature
- Generally lower in case series from more recent era
At 3 years, 70% without stricture had no HAEC admission, compared to 36% with stricture. Haricharan, Barnhart, Saito et al, JPS

Overall 5 year survival without HAEC admission 63%
50% of HAEC admissions occurred within 3.5 months of ERPT
Haricharan, Barnhart, Saito et al, JPS

Outcomes for HD are not as good as most pediatric surgeons think they are.

Multivariate analysis
- Proportional hazards regression modeling
- HAEC admission risk
  - Decreased by doubling of age at surgery (hazard ratio 0.68)
  - Increased by stricture (hazard ratio 9.4)
  - Impact of staged procedure lost when controlled for age at surgery
  - Down syndrome, aganglionic length not significant
Haricharan, Barnhart, Saito et al, JPS

“Nearly Normal” - 65%
Chronic Encopresis and/or Enterocolitis - 10%
Hirschsprung Disease

- Complications
  - Early
    - Wound infection
    - Anorectal/anastomotic stricture
    - Intestinal obstruction
    - Anastomotic disruption
  - Long-term
    - Anorectal/anastomotic stricture
    - Fecal incontinence
    - Enterocolitis
    - Constipation

Hirschsprung Disease Associated Enterocolitis

- Treatment
  - Local irrigation — rectal washouts
  - Antibiotics
    - Enteral
    - Intravenous
  - Chronic/recurrent
    - Look for distal obstruction
      - Anal dilation/sphincterotomy
      - Botox into anal sphincters
      - Chronic PO flagyl
      - Redo pull through or diversion

PO Hirschsprung Disease Associated Constipation

- Treatment
  - Local irrigation — rectal washouts
  - Miralax or Senna
- Chronic/recurrent
  - Look for distal obstruction — scars, dysmotility
  - Anal dilation
  - Botox into anal sphincters
  - Bowel management
  - Redo pull through

PO Hirschsprung Disease Associated Diarrhea

- Early — suspect enterocolitis
- May have to wait for reservoir formation
- Barrier cream and oral cholestyramine
- Often associated with low anal anastomosis and incontinence
- Imodium or lomotil

Rintala Fecal Continence

<table>
<thead>
<tr>
<th>Hold Stool</th>
<th>Feel Urge</th>
<th>Freq of Stool</th>
<th>Soiling</th>
<th>Accidents</th>
<th>Constipation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.5</td>
<td>1.63</td>
<td>1.33</td>
<td>1.93</td>
<td>2.53</td>
<td>2.33</td>
</tr>
<tr>
<td>1.14</td>
<td>0.9</td>
<td>0.49</td>
<td>1.24</td>
<td>1.2</td>
<td>0.86</td>
<td>0.92</td>
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</table>

Results: Fecal Continence

<table>
<thead>
<tr>
<th>Score</th>
<th>Mean</th>
<th>SD</th>
<th>Category</th>
<th>Range (0-20)</th>
</tr>
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<tbody>
<tr>
<td>Rintala</td>
<td>14.3</td>
<td>4.8</td>
<td>Good</td>
<td>9-16</td>
</tr>
<tr>
<td>Fair</td>
<td>7.11</td>
<td>2.53</td>
<td>Poor</td>
<td>6-9</td>
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<table>
<thead>
<tr>
<th>Category</th>
<th>N [30]</th>
<th>%</th>
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<tbody>
<tr>
<td>Good</td>
<td>22</td>
<td>73%</td>
</tr>
<tr>
<td>Fair</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Poor</td>
<td>5</td>
<td>17%</td>
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</table>
PO Fecal Incontinence

- Prevent by starting dissection at the top of the anorectal columns
- Don’t overstretch the anal sphincters
- Check for overflow incontinence
- Check for chronic enterocolitis
- Slow diarrheal stool with lomotil and cholestyramine
- Bowel management or fecal diversion

Results: Quality of Life

<table>
<thead>
<tr>
<th>Score</th>
<th>Mean</th>
<th>SD</th>
<th>Category</th>
<th>Range (0-3)</th>
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</thead>
<tbody>
<tr>
<td>Templeton</td>
<td>2.8</td>
<td>0.6</td>
<td>Good</td>
<td>2.5-3</td>
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<table>
<thead>
<tr>
<th>Category</th>
<th>N (28)</th>
<th>%</th>
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<tbody>
<tr>
<td>Good</td>
<td>24</td>
<td>85%</td>
</tr>
<tr>
<td>Fair</td>
<td>3</td>
<td>11%</td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>4%</td>
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</table>

Conclusions

- Long-term critical evaluation of 30 patients (median 9yrs)
- Fair-Good fecal continence scores
- Good quality of life scores
- LATAP procedure results in good long-term quality of life and fecal continence
- Close follow-up of patients with Hirschsprung disease
- Critical evaluation of short & long-term outcomes data
- PO outcomes for all approaches to surgical therapy need to be improved

Hirschsprung’s Disease

Causes of Postoperative Complications

N = 49

- Acquired aganglionosis 10
- Severe colon dysmotility 10
- Internal sphincter achalasia 14
- Mechanical obstruction 7
- Functional megacolon 8

Langer, BAPS 2003
Frozen Section Analysis for Hirschsprung’s Disease

- Enzymatic analysis of ganglion cells considered better than anatomic analysis by some centers
  - Alpha-naphthylesterase
  - Acetylcholinesterase
  - LDH
  - H and E
  - Calretinin

Miller—APSA 2010

- Glial cell numbers and organization decreased proximal to transition zone

Gastric Emptying--Rintala

- Only 20% of normal in well-functioning adult HD patients decades after a pull-through operation

Systemic Neural Cristopathy

- Decreased vibratory sense
- Dysfunction of ENS
- Slow gastric emptying

Reality check: one size does not fit all…

Unsettled Issues in HD

- Genetics of HD
- Immune defenses in HD
- Motility of ganglionated bowel
- Pathophysiology of enterocolitis
New Paradigm for HD Surgery

- Better preoperative analysis of enzymatic activity, immune function and motility of the bowel proximal to the transition zone
- Preoperative genetic, motility and enzymatic profiling of the colon proximal to the transition zone may eventually lead to better individualized treatment strategies for HD
- Continued improvement in operative techniques