



**NIDDK IBD
Genetics Consortium:**

Phenotype Operating Manual: Guidelines for recruiting individuals to the IBD Genetics Consortium and detailed forms for phenotyping Crohn's disease, Ulcerative Colitis, Indeterminate Colitis and Unaffected Controls.

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IBDGC Overview

The NIDDK Inflammatory Bowel Disease Genetics Consortium (IBDGC) consist of six genetic research centers (GRC) and a data coordinating center (DCC). The six principal investigators are Judy Cho (Yale, also head of DCC), Steven Brant (Johns Hopkins), Richard Duerr (University of Pittsburgh), John Rioux (University of Montreal), Mark Silverberg (University of Toronto), and Dermot McGovern (Cedars Sinai Medical Center). The Consortium's scientific representative at NIDDK is Robert Karp.

Major decisions are made by the Steering Committee (GRC PIs, lead analysts, DCC director and programmers, IBDGC administrator, and NIDDK representatives). The Steering Committee is also responsible for the formation of subcommittees for analysis, genotyping, phenotyping, publication, human subjects, and recruitment.

The Consortium has two primary responsibilities:

- 1) Recruitment of Crohn's disease and ulcerative colitis cases, and controls. Cells and DNA are available strictly to consortium members for a limited time, and then become available to the scientific community. Per NIDDK rules, all collected cells and DNA are maintained at an NIDDK DNA Repository. IBDGC samples are housed at the Rutgers University Cell and DNA Repository (RUCDR), and datasets are stored at the RTI International Data Repository.
- 2) Conducting genetic analyses to identify genes and loci associated with Inflammatory Bowel Disease.

The Consortium is involved with several independent genetic research studies and actively works with members of the IBD and genetic communities on collaborative projects. Below is the contact information for key Consortium members.

| <u>Contact</u> | <u>IBDGC Role</u> | <u>Email</u> |
|-----------------------|--------------------------|--|
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Recruitment Overview

The recruitment goals for the Consortium are primarily focused on recruiting individuals for phenotype data, DNA, and serum, from people of Caucasian (European ancestry) descent. The recruitment totals for each GRC during the first funding period (2003-2007) are presented below. Table 1 shows the total cases recruited regardless of race and European ancestry controls. Cell lines from these cohorts will be available to the scientific community, by request from NIDDK and the Rutgers University Cell and DNA Repository (RUCDR). Access to samples and any de-identified data can be acquired following procedures established by the NIDDK for its central genetics and data repositories (<https://www.niddkrepository.org/niddk/home.do>).

Table 1: Recruitment totals for funding period 2003-2007.

| Recruitment for Funding Period 2003-2007 | YUGRC | UPGRC | UMGRC | UTGRC | JHGRC | CSGRC | Total |
|--|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| CD Recruitment (2003-2007) | | | | | | | |
| CD Recruitment (Trios/Cases) EA (J + NJ) | 179 | 198 | 224 | 231 | 6 | 0 | 838 |
| CD Recruitment (Trios/Cases) AA | 8 | 5 | 1 | 8 | 194 | 1 | 217 |
| CD Recruitment (Trios/Cases) PR/HI | 5 | 1 | 0 | 0 | 1 | 258 | 265 |
| CD Recruitment (Trios/Cases) Other/Unphenotyped | 6 | 1 | 10 | 39 | 20 | 11 | 87 |
| Total CD Recruitment (Trios/Cases) | 198 | 205 | 235 | 278 | 221 | 270 | 1407 |
| UC Recruitment (2003-2007) | | | | | | | |
| UC Recruitment (Trios/Cases) EA (J + NJ) | 178 | 250 | 167 | 262 | 17 | 0 | 874 |
| UC Recruitment (Trios/Cases) AA | 13 | 4 | 0 | 5 | 59 | 1 | 82 |
| UC Recruitment (Trios/Cases) PR/HI | 9 | 3 | 0 | 3 | 0 | 170 | 185 |
| UC Recruitment (Trios/Cases) Other/Unphenotyped | 14 | 4 | 11 | 70 | 14 | 2 | 115 |
| Total UC Recruitment (Trios/Cases) | 214 | 261 | 178 | 340 | 90 | 173 | 1256 |
| Total IBD Case Recruitment (2003-2007) | 412 | 466 | 413 | 618 | 311 | 443 | 2663 |
| Unrelated Control Recruitment (2003-2007) EA only | | | | | | | |
| Unrelated EA Controls | 128 | 167 | 186 | 81 | 10 | 0 | 572 |
| Total Recruitment (cases/controls) (2003-2007) | 540 | 633 | 599 | 699 | 321 | 443 | 3235 |
| EA = European Ancestry; AA = African American; PR = Puerto Rican; HI = Hispanic; J = Jewish; NJ = Non-Jewish | | | | | | | |

The Steering Committee approved new recruitment targets (Table 2) for the current funding period (2008-2012). Pittsburgh, Hopkins, Cedars and Yale received American Recovery and Reinvestment Act (ARRA) funds for increased recruitment. The numbers in Table 2 were modified to reflect the additional funding.

Consistent with the NIDDK mandate the recruitment focus for 5 of the GRCs is European ancestry (EA). Johns Hopkins will primarily recruit African Americans but still contribute to EA recruitment. Cedars Sinai will now recruit primarily Caucasians but can also continue Puerto Rican recruitment. The recruitment targets include adults and children. There are no restrictions on age. While the numbers in table 2 are for DNA and subsequent cell lines, it is expected that serum will also be collected from as many cases and controls as possible. There is no longer a focus on trio recruitment.

Additionally, only one member per family can be recruited to the Consortium as an unaffected control.

Table 2: Targeted recruitment for second grant funding period.

| Recruitment Targets 2008-2012 (ARRA modified- July 2010) | YA/UC | UP | UM | UT | JH | CS | Total |
|--|--------------|------------|------------|------------|------------|-------------|--------------|
| CD Recruitment | | | | | | | |
| CD Cases - European Ancestry (J + NJ) | 250 | 310 | 250 | 250 | 100 | 250 | 1410 |
| CD Cases - African American | 45 | 5 | 0 | 0 | 350 | 5 | 405 |
| CD Cases - Puerto Rican/Hispanic | 5 | 5 | 0 | 0 | 5 | 200 | 215 |
| Total CD Recruitment Proposed (Cases) | 300 | 320 | 250 | 250 | 455 | 455 | 2030 |
| UC Recruitment | | | | | | | |
| UC Cases - European Ancestry (J + NJ) | 300 | 310 | 250 | 250 | 50 | 250 | 1410 |
| UC Cases - African American | 25 | 5 | 0 | 0 | 300 | 5 | 335 |
| UC Cases - Puerto Rican/Hispanic | 5 | 5 | 0 | 0 | 5 | 150 | 165 |
| Total UC Recruitment Proposed (Cases) | 330 | 320 | 250 | 250 | 355 | 405 | 1530 |
| Targeted IBD Case Recruitment | 630 | 640 | 500 | 500 | 810 | 860 | 3560 |
| PSC Cases | 30 | | | | | | |
| Unrelated Control Recruitment | | | | | | | |
| Proposed Unrelated EA controls | 200 | 200 | 200 | 200 | 50 | 50 | 900 |
| Proposed Unrelated AA/PR controls | 0 | 0 | 0 | 0 | 150 | 105 | 255 |
| Total Targeted Recruitment (cases/controls) | 860 | 840 | 700 | 700 | 860 | 1015 | 4975 |
| ***Parental controls will no longer be recruited, effective immediately. Cedars is recruiting AA and PR controls. | | | | | | | |

Recruitment Methodology

General Overview:

Subjects are recruited in clinics at the GRCs or their affiliated satellite centers. Participating physicians identify and inform the GRCs of patients. After patients give their consent they then complete the appropriate NIDDK IBDGC questionnaire/phenotype form. Each GRC has also chosen to design institution specific forms which also include the data collected for the NIDDK IBD-GC. All phenotype forms have full Internal Review Board (IRB) approval, and adhere to standards from the IBDGC Phenotype forms and Manual.

Blood is drawn locally if possible. The recruitment coordinator or external laboratory ships blood samples labeled only with a single, pre-printed ID (called the NIDDK ID) label to the RUCDR. RUCDR assigns their own internal ID (called the K number), immortalizes the lymphocytes to create a cell line and extract DNA. Eventually, aliquots of DNA samples will be shipped back to all centers (all centers will get all samples, regardless of the recruiting center).

Data are initially stored locally and is under the control of the Principal Investigator and the data coordinator. Data is also transferred to the DCC via a secure web-based data entry system. DOB, initials and diagnosis are required for registry into the

NIDDK IBDGC website. Full phenotype data can be entered online via a secure web-based form or uploaded via a secure connection from a center's internal database. This website and its security are strictly controlled by Phil Schumm at the University of Chicago.

The purpose of recruitment is to create a repository of IBD-related samples and unaffected controls for the scientific community to use. At the end of recruitment, data that the IBDGC has collected must be shared with RUCDR/NIDDK/NIH. No personal health information (PHI) will be shared. The GRCs involved have sole use of these samples for 2-3 years after recruitment, after which the samples can be used by any NIDDK-approved researcher.

Recruitment of IBD Cases and Controls for DNA and Serum:

Do not recruit blood-related index subjects, e.g. if a father and son are both affected and can be recruited, but the mother cannot, you may only recruit *either* the father *or* the son as an index subject. Once an index subject has been recruited to donate blood, a phenotyping form must be completed with the careful questioning of the patient and with the aid of a clinician. In some cases, (e.g. adopted index subjects), family IBD status will be unknown. This is simple for the *father*, *mother* and *second-degree relatives* sections, but for the *siblings* section, you must enter "0" for all fields. While this does not document the true answer ('unknown'), scientifically it is as accurate as for someone who does not have any siblings (neither has known affected siblings; neither has known unaffected siblings).

The *Macroscopic Disease Location*, *Surgery* and *Extra-intestinal Manifestations* sections must be completed by a clinician reviewing the patient's chart.

Controls should be collected from the general population. Recruitment for the Consortium will no longer focus on unaffected family members. Only one person from a family can be recruited as a control.

Following notification that Rutgers University Cell and DNA Repository (RUCDR) has received a subject or control blood sample, you may proceed with registering him/her on the IBDGC website. Following registration on the IBDGC website, you may enter phenotype data using the IBDGC website interface.

Inflammatory Bowel Disease (IBD) Definitions for Diagnosis

The following diagnostic criteria are provided as guidelines to complete documentation on individuals with Crohn's disease, Ulcerative Colitis and Indeterminate Colitis enrolled in the NIDDK IBD Genetics Consortium:

- A) Symptoms including one or more: diarrhea, rectal bleeding, abdominal pain, fever, complicated perianal disease, extraintestinal manifestations, weight loss or failure to thrive.

AND

- B) Symptoms on two or more occasions separated by at least 8 weeks or ongoing symptoms of at least 6 weeks duration. When there has been a single episode of colitis (in some instances less than 6 weeks duration) resulting in colectomy and resolution of disease symptoms, pathology on the colectomy specimen should be consistent with idiopathic IBD and microbiology studies should be negative.

AND

- C) One or more of the following providing *objective* evidence of inflammation:

Endoscopic: Mucosal edema, erythema, loss of normal submucosal vasculature, friability, ulceration, stricture formation, pseudopolyps, mucosal edema, erythema. *Where there are only minor changes (mucosal edema, erythema, loss of normal submucosal vasculature, friability) mucosal biopsies should have been done to confirm the presence of IBD.*

Radiologic: Mucosal thickening and/or nodularity, ulceration, stricture, pseudopolyps, fistula formation, pseudosacculation. Minor changes alone (mucosal thickening and/or nodularity) should not be sufficient to make a diagnosis of IBD.

Histologic: Mucosal erosion or ulceration, architectural changes of crypts, Paneth cell metaplasia (in colon), transmural inflammatory infiltrate*, fibrosis of muscularis propria*, noncaseating granuloma*.

* *Crohn's disease*

Individuals with IBD should be classified into one of three categories, based on most recent diagnosis:

Crohn's disease (CD):

- 1) Evidence of small intestinal inflammation with endoscopically, radiologically or histologically demonstrated ulcerations, fistulization, mucosal fissuring, nodularity or cobblestoning, stricture formation or histologically demonstrated transmural inflammation with or without granuloma formation.

- 2) Isolated esophageal, gastric or duodenal inflammation with the finding of non-caseating granuloma.
- 3) Colonic inflammation which is patchy (normal segments separating areas of inflammation, as described above) or associated with one or more of the following features: complete rectal sparing, multiple (>10) aphthoid ulcers, deep ulceration (into the muscularis propria), transmural inflammation, extensive fibrosis and wall thickening, fistulization, non-caseating granuloma. (N.B. See note below regarding patchiness of endoscopically observed inflammation in patients with partially treated ulcerative colitis.)
- 4) The presence of complex suppurative perianal disease (i.e. more than a superficial fistula or uncomplicated superficial abscess).
- 5) If there are fewer than 10 aphthoid ulcers in the cecum (and the rest of the colon appears normal) in a patient with small bowel disease then this should be called small bowel disease only. Similarly, if the colon is normal except for the presence of a fistula extending from inflamed small bowel, the patient should be said to have small bowel disease alone. If the cecum is involved with ulcers larger than aphthoid ulcers or ulcers that are deep or if the involvement has resulted in deformity of the cecum this would be considered to be colonic involvement.

Ulcerative Colitis (UC)

- 1) Superficial inflammation and/or ulceration (involving only the mucosa and submucosa) of the colon which is continuous from the rectum extending proximally without skip lesions or complete rectal sparing (*N.B.* Relative rectal sparing is allowed for patients receiving topical rectal therapy; patchiness of endoscopic inflammation may be observed in patients with partially treated ulcerative colitis).
- 2) In patients with proctitis or left-sided ulcerative colitis there may be an area of inflammation in the cecum, usually surrounding the appendiceal orifice.
- 3) No inflammation of the small intestine (“backwash ileitis” is allowed - non-stenosing superficial inflammation of the terminal ileal mucosa associated with severe pancolitis which resolves following medical or surgical treatment of the colitis).
- 4) No features of Crohn’s disease listed above.

Indeterminate Colitis (IC):

- 1) *Confirmed* IBD by A, B and C above.
- 2) Physician unable to classify individual into either CD or UC based on above criteria and/or patient has features of both CD and UC with none of the features diagnostic of one or the other.

Affected Registration and Demographics Form

Registration Information:

1. *Individual ID, Mother's ID, Father's ID and Family ID* are all optional. Each center may choose to assign these or disregard.
2. *Gender*.
3. *Date of Birth* is in format MM/DD/YYYY.
4. The *Consortium ID* is generated upon registration of the subject using the Consortium web interface, and serves as the primary identifier for all subjects recruited into the repository or otherwise registered online.
5. The *Date of Diagnosis* refers to the month and year in which a definitive diagnosis of IBD was made. In a case in which a patient is initially diagnosed with one form of IBD and subsequently has the diagnosis changed from one form of IBD to another form of IBD, the date of original diagnosis of IBD should be used. However, the most recent disease diagnosis (CD, UC or IC) should be used.
6. *Inception Case* refers to someone recruited within the first two years following diagnosis. For inception cases the month and year of diagnosis should be obtained and recorded. For non-inception cases (recruited more than 2 years after diagnosis) only the year of diagnosis is required. However, month of diagnosis, if known, may be recorded.

Demographic and Early Childhood Information:

1. *Hispanic/Latino* status ('Yes' / 'No') is self-reported.
2. *Jewish* status ('Yes' / 'No') is self-reported. Jewish heritage of grandparents is required.
3. *Race* is self-reported. Choose 'Other' under *Race* for multiracial individuals.
4. *Birth Order* is the temporal birth rank of the subject within his/her family. Where there are half-siblings from the same mother and who are living in the same household the birth order should include the half-siblings.
5. *Breast feeding* should be marked as 'yes' or 'no' depending on whether the subject received breast feeding for a period of at least 4 weeks. Mark 'unknown' where there is no information about breast feeding history. Also indicate the period of time the subject received exclusive breast feeding without any other supplemental sources of nutrition. Also indicate the age (in months) when the subject was completely weaned from breast feeding. Mark 'unknown' where there is no information regarding duration of exclusive breast feeding or age of weaning.

Family History of IBD

1. *Family History of IBD* as reported by the individual for all relatives listed. Relatives must have been diagnosed with IBD to qualify under 'CD', 'UC/IC' or 'IBD affected type unclear'. This does not require confirmation by relative or relative's medical chart. 'IBD Affected, type unclear' refers to a relative whom the individual knows has been diagnosed with IBD but isn't sure/cannot recall what type of IBD affection as reported by the patient/participant. UC or IC in any 1st or 2nd degree relative would indicate mixed family type. *1st degree relatives* include parents, full siblings, and children. *2nd degree relatives* include grandparents, aunts/uncles and nieces/nephews and half-siblings.

Smoking History Prior to Diagnosis:

1. *Smoking at Diagnosis* is defined as smoking, on average, at least 1 cigarette daily for a period of at least 3 months prior to diagnosis and who continued to smoke up until within three months of diagnosis. Pipe and cigar smoking are not included. An *Ex-smoker* at diagnosis is defined as someone who had stopped smoking at least 3 months prior to diagnosis and was not smoking at diagnosis.
2. *Year Started* and *Year Stopped*. If patient has had multiple episodes of quitting and starting smoking cigarettes indicate the year when first started and the year last quit (even if it is after the year of diagnosis).
3. If patient is a *Smoker* but dates of start and stop are unknown, leave dates blank. If patient has never smoked indicate 'No', and leave *Year Started/Year Stopped* blank. If smoking history is unknown, check 'Unknown', and leave *Year Started/Year Stopped* blank.
4. *No. of cigarettes per day*: indicate the number of cigarettes smoked daily. Where smoking amount has changed over time use the amount at diagnosis (if known). If not known, use the amount smoked at the date closest to the time of diagnosis. If *Ex-smoker* at diagnosis use the estimated mean number of cigarettes per day prior to quitting. If subject is a *Smoker* or *Ex-smoker* but the number of cigarettes per day is not known please indicate 'Unknown'. If patient had never smoked at diagnosis or smoking history is unknown please leave field empty.
5. *Regular Second-Hand Smoke Exposure at Home (for pediatric module)*: Indicate 'yes' if subject has lived in the same household with a smoker for a period of more than one year prior to diagnosis. Record year when last lived with smoker. If ongoing passive household exposure indicate year of ascertainment.

Crohn's Disease Intake Phenotype Form

1. The Date of Diagnosis refers to the month and year in which a definitive diagnosis of IBD was made. In a case in which a patient is initially diagnosed with one form of IBD and subsequently has the diagnosis changed from one form of IBD to another form of IBD, the date of original diagnosis of IBD should be used.

2. The date of the **Latest Clinical Exam/Encounter** indicates the date of the most recent clinical, endoscopic, radiologic and/or pathologic records in the study participant's record, and is recorded as MM/DD/YYYY.

- **Macroscopic Disease Location:** Must be completed by a clinician and confirmed by medical records. If region has not been examined for disease, enter 'Unknown' for that region. Check all areas of **macroscopic** disease at any time during the course of disease. All sites should be completed based on the available information and not left blank.
- Mucosal erythema, friability or granularity is not considered to be indicative of involvement. Mucosal ulceration, cobblestoning, stricturing or bowel wall thickening typically indicates involvement. Acceptable sources of information for classification are endoscopy procedure reports, diagnostic imaging (e.g. barium X-rays, CT scans, MRIs) reports, operative reports and pathology resection specimen reports. In cases where there is no information or missing information regarding evaluation of a portion of the GI tract, extent should be classified as 'Unknown' for that location. Operative descriptions of normal appearing small bowel or colon should not be used to classify 'No' for a site if that site has not been adequately visualized by endoscopy or diagnostic imaging modalities.
- Perianal disease location is said to be present when an individual has a history of perianal or perineal abscess(es) and/or fistula, anal canal ulcers, anal stenosis or chronic edematous and violaceous skin tags. This can be documented by clinical examination, examination under anesthesia and/or diagnostic imaging. Perianal disease location does not include the presence of only anal fissures or hemorrhoids.
- Jejunal involvement is the proximal 2/3 of small intestine beyond the ligament of Treitz (duodenojejunal flexure).
- Ileal involvement (distal 1/3 of small intestine) should be subclassified if possible. The distal ileum is considered to be the last 100 cm of ileum (approximately half of the total length of ileum). The terminal ileum is that part of the ileum leading up to and contiguous with the ileocecal valve. It is not necessarily defined by a certain distance proximal to the ileocecal valve. When the distal ileum is involved but the terminal portion leading up to and contiguous with the ileocecal valve is not involved there is said to be involvement of the distal ileum but not of the terminal ileum. If there are fewer than 10 aphthoid ulcers in the cecum (and the rest of the colon distal to the

cecum appears normal) in a patient with terminal ileal disease then this should not be considered to be indicative of the presence of colorectal involvement. If the cecum is involved with ulcers larger than aphthoid ulcers or ulcers that are deep or if the involvement has resulted in deformity of the cecum this would be considered to be cecal involvement.

- If there are a few aphthoid ulcers in the cecum (and the rest of the colon appears normal) in a patient with terminal ileal disease then this should not be considered to be indicative of the presence of colorectal involvement. If the cecum is involved with ulcers larger than aphthoid ulcers or ulcers that are deep or if the involvement has resulted in deformity of the cecum this would be considered to be cecal involvement.
- If the colon in between, but not including, the cecum and rectum is affected based upon the criteria for macroscopic involvement this should be indicated separate from that of the ‘cecum’ or ‘rectum’.
- Macroscopic involvement of the rectum should be indicated separate from that of the ‘colon (not including cecum and rectum)’.
- If the colon is normal except for the presence of a fistula extending from inflamed small bowel, the patient should be said to have small bowel disease (ileal or jejunal) only.

CD Disease Behavior:

1. *B1* (Non-stricturing non-penetrating disease) is defined as uncomplicated inflammatory disease without evidence of stricturing or penetrating disease.
2. *B2* (Stricturing Disease) is defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic, or surgical examination combined with prestenotic dilation and/or obstructive signs or symptoms but without evidence of penetrating disease.
3. *B3* (Penetrating Disease) is defined as the occurrence of bowel perforation, intra-abdominal fistulas, inflammatory masses and/or abscesses at any time in the course of the disease, and not secondary postoperative intra-abdominal complication. Stricturing and penetrating should be classified B3.

NB Perianal and rectovaginal fistula(s) do not count, by themselves, as ‘penetrating fistulizing’ or as indicating a B3 disease behavior.

Surgery: Must be completed by a clinician.

1. *Surgery for complication or treatment of CD* must be confirmed by chart. If unconfirmed, then check ‘No’. If no information, check ‘Unknown’.
If Yes:

2. *Small Bowel resection* includes:
 - a) Resection of stricturing disease in small bowel.
 - b) Resection of small bowel disease that has been complicated by fistula or abscess.
 - c) Resection of small bowel disease segment for refractory symptoms in the absence of stricturing, fistula or abscess formation or for other complications of small bowel disease (e.g., hemorrhage)

3. *Large Bowel resection* includes resection of all or part of the large bowel (colon) and/or rectum (with the exception of resection of the cecum when this is performed along with a resection of the terminal ileum):

4. *Strictureplasty* involves surgically increasing the lumen of a strictured segment of intestine (almost always small intestine).

5. *Diversion* includes:
 - a) Diversion procedures performed prior to definitive surgery such as resection.
 - b) Diversion procedures performed to allow healing of perineal disease.
 - c) Diversion procedures performed at the time of other surgical procedure (e.g. bowel resection, abscess drainage and/or anastomosis) to allow healing of a distal anastomosis or because the presence of intra-abdominal sepsis made the creation of an anastomosis unsafe at the time.

6. Permanent stoma includes creation of a stoma of small or large intestine that is intended to be lifelong without a possibility of restoring continence (i.e. not a temporary diversion).

7. *Gastroenterostomy* is the creation of a surgical connection between the stomach and small bowel. It is usually used for gastric outlet obstruction (i.e. obstruction in the gastric antrum, pylorus or duodenum).

8. *Surgery for Abdominal Fistula/Abscess* includes:
 - a. Surgical resection of a complicated fistula (e.g. enterovesical fistula).
 - b. Surgical drainage of an abscess (e.g. intra-abdominal, iliopsoas).
 - c. Percutaneous drainage of an intra-abdominal abscess that is followed by surgical resection of involved intestine.

Surgery for Abdominal Fistula / Abscess does not include:

 - a. Percutaneous drainage of intra-abdominal abscess without resection of involved intestine within 12 months.
 - b. Incidental resection of an enteroenteric fistula that occurs as part of an intestinal resection.

9. *Surgery for Perineal Fistula/Abscess* includes:
 - a. Surgical fistulotomy.
 - b. Placement of a seton.
 - c. Intestinal diversion to permit healing of perineal disease.

Surgery for Perineal Fistula/Abscess does not include:

- a. Simple incision and drainage of a perianal abscess performed using only local anesthetic.
10. *Surgery for dysplasia/cancer*: When dysplasia or cancer is only found postoperatively on the surgical specimen but the indication for surgery was either acute fulminant or chronic continuous disease, dysplasia/cancer should not be included as an indication for surgery. However the presence of dysplasia/ cancer should be indicated in the appropriate field.
11. *Date of First Operation*: month and year of first **abdominal** surgery at or after diagnosis. If only year is known indicate the year and indicate '99' for the month. If neither month nor year are known please tick 'unknown'.
12. *No. of operations for abdominal disease*: (i.e. resection, strictureplasty, abscess drainage): a single operation may include two types of surgeries (e.g., a single operation during which both 'bowel resection' and 'abscess drainage' were performed).
13. *No. of operations for perineal disease (including diversions)*: a single operation may include two types of surgeries (e.g. a single surgery for perineal abscess and diversion) and still be counted as one.
14. *Appendectomy*: Should be noted as 'Yes' even if removal was part of another surgery such as a right hemicolectomy. If yes, indicate year.

Pubertal Stage at Diagnosis (Pediatric Onset Cases Only)

Pubertal stage assessment is based upon Tanner Stages of 1 to 5 for pubic hair, genital development and breast development (for females) at the time of diagnosis (or within one month of diagnosis). Where this is not recorded in the chart or if the chart is not available please indicate 'unknown'.

Height at diagnosis (or within one month of diagnosis) should be recorded. The unit of measure can be either inches or centimeters but should be indicated. Where height has not been recorded in the chart please indicate 'unknown'.

Weight at diagnosis (or within one month of diagnosis) should be recorded. The unit of measure can be either pounds or kilograms but should be indicated. Where weight has not been recorded in the chart please indicate 'unknown'.

Disease Activity and Treatment: These items should be determined from chart /medical record review preferentially and rarely use patient self-reporting:

1. *Current disease activity* should be the physician's global assessment of the disease activity at most recent assessment or clinical encounter. This should be based upon the elements of the Harvey Bradshaw Index as recorded in the

chart/medical record. These items (subject's general well being, abdominal pain, number of liquid stools, abdominal mass, complications and extraintestinal manifestations) are recorded individually in the CD Phenotype Intake Form (see Item 9 below). Where insufficient information is available in the chart/medical record to allow a determination of *current disease activity* this should be recorded as 'unknown'. It is recognized that, in some instances, the symptoms included in the assessment of disease activity (general well being, abdominal pain and number of liquid stools) may be explained or caused by other factors not directly related to intestinal inflammation. In these instances an attempt should be made to discount these particular symptoms when assessing disease activity.

2. *Physician global assessment of disease activity since diagnosis* should be an overall assessment of the course of disease which integrates the occurrence of periods of remission and the severity of disease flares or exacerbations. This is not intended to include the presenting flare at the time of diagnosis. For example, if a patient presented with a severe flare at first diagnosis but has had only quiescent disease in remission since then he/she should be categorized as having "*Continuously quiescent*" disease. It is also recognized that patients may experience changes in the course of their disease over time and that this assessment may be difficult to place into a single category. However, an attempt should be made to assign the dominant pattern. The severity of the flares should generally be determined using the assessments applied in the Harvey Bradshaw Index. Where a patient has had both periods of flares and remissions since diagnosis he/she should be categorized as having "*Mild with Remissions*" or "*Moderate or Severe Exacerbations but Remissions*". If a patient has had only mild disease flares or exacerbations he/she should be categorized as having "*Mild with Remissions*". If he/she has had any flares or exacerbations that were of moderate to severe activity he/she should be categorized as having "*Moderate or Severe Exacerbations or Remissions*". Where the patient has not had significant periods of remission he/she could be considered as having had chronically active disease.
3. *Hospitalizations since diagnosis* are the number of hospitalizations for the management of IBD or one of its complications. This would include a hospitalization for investigation or treatment of symptoms that turn out to be due to newly diagnosed IBD. It does not include Emergency Department visits in which the subject is treated and discharged from the Emergency Department and not admitted to an in-patient unit.
4. *Medication use since diagnosis* should be indicated as 'yes', 'no' or 'unknown' for each class of therapy depending on whether it has been used between the time of diagnosis and the most recent evaluation. A medication is considered to have been used if it has been administered for at least 5 days (for those medications administered at least once daily), for 2 weeks (for those administered weekly) or for one dose (for those administered less often than every week). As indicated in the introduction to this section, the use of the chart/medical records to confirm the use of a medication is preferred but patient or family reporting can also be

used to make these determinations in instances where medication use is not directly available from the medical record.

5. For those medications that have been used since diagnosis, the *use within the first month* following diagnosis should be determined and indicated as 'yes', 'no' or 'unknown' for each class of therapy. As indicated in the introduction to this section, the use of the chart/medical records to confirm the use of a medication in the first month following diagnosis is preferred but patient or family reporting can also be used to make these determinations in instances where medication use is not directly available from the medical record.
6. For those medications that have been used since diagnosis, the *current use* should be indicated as 'yes', 'no' or 'unknown' for each class of therapy for the date of the most recent assessment. This information should be obtained from the chart/medical record.
7. For *biologic therapy* other than an anti-TNF agent please indicate the generic name in the open text field.
8. Topical *steroid therapy* is not recorded.
9. Items from the *Harvey Bradshaw Index* should be completed based upon the subject's current status at the time of ascertainment or most recent clinical evaluation. Where information is missing 'unknown' should generally be indicated (e.g. if it appears that a physical examination was not performed then 'abdominal mass' should be 'unknown.' However, if complications (aphthous ulcers, anal fissure, new fistula or abscess) are not mentioned in a clinical note, it can be assumed that they are not present. *Aphthous ulcers* refer to ulcers in the mouth or oropharynx and do not refer to similar ulcers that may be seen elsewhere in the gastrointestinal tract.

Extra-Intestinal Manifestations: Must be completed by a clinician.

Extraintestinal manifestations (EIM) should be documented in medical records (e.g. clinical note, radiology report, surgical report, pathology report).

1. *Joints*: pauciarticular (less than 5 joints involved with evidence of effusion or swelling – usually large joints - and associated with relapses of IBD); polyarticular (5 joints or more, symmetric involvement with effusion or swelling - usually small joint - runs a course independent of IBD often lasting many months).
 - a. *Large joint disease related to disease activity*: Fewer than 5 (usually large) joints with evidence of inflammation (effusion and/or swelling) related to disease activity.
 - b. *Small joint unrelated to disease activity*: Five or more (usually small) joints with evidence of inflammation (effusion and/or swelling) unrelated to disease activity.

- c. *Ankylosing spondylitis*: requires radiologic documentation of typical findings of sacroiliac inflammation, narrowing or sclerosis and/or inflammation or fusion of vertebral bodies.
 - d. *Sacro-iliitis*: also requires radiologic documentation of typical findings of sacroiliac inflammation, narrowing or sclerosis and/or inflammation or fusion of vertebral bodies.
 - e. *Non-specific joint inflammation*: evidence of effusion or swelling but does not fit any of the above categories.
 - f. *Non-specific*: arthralgias (joint pains) in the absence of other markers of active joint inflammation such as effusion or swelling.
2. *Skin*:
- a. *Erythema nodosum*: typically appear as raised, tender, red or violet subcutaneous nodules that are 1 to 5 cm in diameter. The nodules are most commonly located on the extensor surfaces of the extremities, particularly over the anterior tibial area.
 - b. *Pyoderma*: ulcerative disease of the skin. There may be one or multiple lesions. They occur most commonly on the legs, especially the pretibial area, but can develop in any area of the body, including the abdominal wall adjacent to the stoma after colectomy.
3. *Eyes*:
- a. *Uveitis*: intraocular inflammation. Diagnosis requires documentation of typical findings. A slit lamp examination is preferable.
 - b. *Episcleritis*: Defined by the abrupt onset of mild inflammation of the episclera of the eye. Requires documentation of typical findings of localized inflammation (erythema, increased vascularity, nodularity) of the episcleral tissues.
 - c. *Undiagnosed ocular inflammation*: Where there has been eye inflammation but the presentation or findings have not been typical or where the nature of the inflammation cannot be classified based upon the available information.
4. *Liver*:
- a. *Primary sclerosing cholangitis*: should be documented with typical dye cholangiographic or MRCP findings in someone with no other known causes of secondary cholangitis. Abnormal liver enzymes or liver biopsy alone are not sufficient evidence of sclerosing cholangitis.

Ulcerative/Indeterminate Colitis (UC/IC) Intake Phenotype Form

1. The Date of Diagnosis refers to the month and year in which a definitive diagnosis of IBD was made. In a case in which a patient is initially diagnosed with one form of IBD and subsequently has the diagnosis changed from one form of IBD to another form of IBD, the date of original diagnosis of IBD should be used.

2. The date of the **Latest Clinical Exam/Encounter** indicates the date of the most recent clinical, endoscopic, radiologic and/or pathologic records in the study participant's record, and is recorded as MM/DD/YYYY.

Macroscopic Disease Location:

Must be completed by a clinician and confirmed by medical records. If region has not been examined for disease, enter 'Unknown' for that region. Check all areas of **macroscopic** disease that apply at any time during the course of disease. Acceptable sources of information for classification are colonoscopy reports, barium enemas, or colectomy gross pathology reports.

1. *Proctitis*: inflammation extending up to no further than 15 cm proximal to the anorectal junction.
2. *Left-sided* (to splenic flexure): inflammation extending up to, but not proximal to, the splenic flexure. If this category is checked, so should *Proctitis*.
3. *Extensive* (beyond splenic flexure): inflammation extending proximal to the splenic flexure but not to the cecum. If this category is checked for a UC patient, *Proctitis* and *Left-sided* should be as well.
4. *Pancolitis* indicates inflammation extending from the rectum to the cecum and would include *periappendiceal inflammation* (see below).
5. *Periappendiceal inflammation*: documented by colonoscopy with or without biopsy. It is always present in patients with *Pancolitis* where there is continuous inflammation from rectum to cecum and should be checked off in that instance. Periappendiceal inflammation may also accompany *Proctitis*, *Left-sided disease* or *Extensive* disease.
6. *Terminal Ileum visualized*. If yes, determine condition and check if a biopsy was obtained.

NB: Furthermore, patients with left-sided disease or proctitis and with an isolated patch of inflammation in the cecum should be recorded as having *Left-sided* disease only or *Proctitis* only, respectively.

Surgery: Must be completed by a clinician.

1. *Surgery for complication or treatment of UC*: must be confirmed by chart. If unconfirmed, then check 'No'. If no information, check 'Unknown'.

If Yes (i.e. if surgery for complication or treatment of UC has been confirmed) then complete the following fields:

2. *Surgery for dysplasia/cancer:* When dysplasia or cancer is only found postoperatively on the surgical specimen but the indication for surgery was either acute fulminant or chronic continuous disease, dysplasia/cancer should not be included as an indication for surgery. However the presence of dysplasia/ cancer should be indicated in the appropriate field.
3. *Surgery for chronic continuous disease:* should be indicated when there is neither an indication for acute severe / fulminant colitis nor for dysplasia/cancer.
4. *Surgery for acute or fulminant disease:* fulminant colitis implies an acute or subacute onset of severe colitis (with or without signs of toxicity). This may occur over a period of 2 - 12 weeks in someone without a prior diagnosis of ulcerative colitis or in someone with a prior diagnosis of ulcerative colitis in whom the disease had been quiescent or stable prior to the fulminant exacerbation of disease activity.
5. *Date of surgery (colectomy):* month and year of first abdominal surgery at or after diagnosis (typically this will be a colectomy +/- proctectomy +/- ileal pouch construction). If year of surgery is known but month is not known please indicate the year and indicate '99' for the month. Indicate 'unknown' only if surgery has been confirmed but the year is not known.
6. *Pouchitis* is defined as the occurrence of increased stool frequency, abdominal cramps and fecal urgency lasting for more than 5 days. Patients may also experience fever, pelvic discomfort and extraintestinal manifestations of IBD. For a symptomatic episode to be considered to be confirmed as 'pouchitis' there should have been either a documented response to a course of antibiotics or endoscopic confirmation of inflammatory mucosal changes in the pouch.
7. *Diagnosis of dysplasia/cancer (colorectal):* If the patient has had disease less than 10 years or a negative surveillance colonoscopy then the answer is "no". If the patient has had disease more than 10 years and no surveillance (i.e. no biopsy after 10 years of disease or biopsy results not available) the answer is "unknown". If the patient has had confirmed dysplasia/cancer the answer is "yes".
8. *Appendectomy:* Should be noted as 'Yes' even if removal was part of another surgery. *If Yes, indicate year.*

Pubertal Stage at Diagnosis (Pediatric onset cases only– prior to age 18):

1. Pubertal stage assessment is based upon Tanner Stages of 1 to 5 for pubic hair, genital development and breast development (for females) at the time of

diagnosis (or within one month of diagnosis). Where this is not recorded in the chart or if the chart is not available please indicate ‘Unknown’.

2. Height at Diagnosis. Record height (in centimeters or inches) at diagnosis. Record ‘Unknown’ if height not documented at diagnosis.
3. Weight at Diagnosis (for pediatric module). Record weight (in kilograms or pounds) at diagnosis. Record ‘Unknown’ if weight not documented at diagnosis.

Disease Activity and Treatment (including Partial Mayo Index): These items should be determined from chart/medical record review preferentially and rarely use patient self-reporting:

1. *Current disease activity* should be the physician’s global assessment of the disease activity at most recent assessment or clinical encounter. This should be based upon the elements of the Partial Mayo Index as recorded in the chart/medical record. These items (stool frequency, rectal bleeding) are recorded individually in the UC Phenotype Intake Form (see Item 9 below). Where insufficient information is available in the chart/medical record to allow a determination of *current disease activity* this should be recorded as ‘unknown’. It is recognized that, in some instances, the symptoms included in the assessment of disease activity (number of stools, rectal bleeding) may be explained or caused by other factors not directly related to intestinal inflammation. In these instances an attempt should be made to discount these particular symptoms when assessing disease activity.
2. *Physician global assessment of disease activity since diagnosis* should be an overall assessment of the course of disease which integrates the occurrence of periods of remission and the severity of disease flares or exacerbations. This is not intended to include the presenting flare at the time of diagnosis. For example, if a patient presented with a severe flare at first diagnosis but has had only quiescent disease in remission since then he/she should be categorized as having “*Continuously quiescent*” disease. It is also recognized that patients may experience changes in the course of their disease over time and that this assessment may be difficult to place into a single category. However, an attempt should be made to assign the dominant pattern. The severity of the flares should generally be determined using the assessments applied in the Partial Mayo Index. Where a patient has had both periods of flares and remissions since diagnosis he/she should be categorized as having “*Mild with Remissions*” or “*Moderate or Severe Exacerbations but Remissions*”. If a patient has had only mild disease flares or exacerbations he/she should be categorized as having “*Mild with Remissions*”. If he/she has had any flares or exacerbations that were of moderate to severe activity he/she should be categorized as having “*Moderate or Severe Exacerbations or Remissions*”. Where the patient has not had significant periods of remission he/she could be considered as having had chronically active disease.
3. *Hospitalizations since diagnosis* are the number of hospitalizations for the management of IBD or one of its complications. This would include a hospitalization for investigation or treatment of symptoms that turn out to be

due to newly diagnosed IBD. It does not include Emergency Department visits in which the subject is treated and discharged from the Emergency Department and not admitted to an in-patient unit.

4. *Medication use since diagnosis* should be indicated as ‘yes’, ‘no’ or ‘unknown’ for each class of therapy depending on whether it has been used between the time of diagnosis and the most recent evaluation. A medication is considered to have been used if it has been administered for at least 5 days (for those medications administered at least once daily), for 2 weeks (for those administered weekly) or for one dose (for those administered less often than every week). As indicated in the introduction to this section, the use of the chart/medical records to confirm the use of a medication is preferred but patient or family reporting can also be used to make these determinations in instances where medication use is not directly available from the medical record
5. For those medications that have been used since diagnosis, the *use within the first month* following diagnosis should be determined and indicated as ‘yes’, ‘no’ or ‘unknown’ for each class of therapy. As indicated in the introduction to this section, the use of the chart/medical records to confirm the use of a medication in the first month following diagnosis is preferred but patient or family reporting can also be used to make these determinations in instances where medication use is not directly available from the medical record
6. For those medications that have been used since diagnosis, the *current use* should be indicated as ‘yes’, ‘no’ or ‘unknown’ for each class of therapy for the date of the most recent assessment. This information should be obtained from the chart/medical record.
7. For *biologic therapy* other than an anti-TNF agent, please indicate the generic name in the open text field.
8. Topical *steroid therapy* is not recorded
9. Items from the *Partial Mayo Index* should be completed based upon the subject’s current status at the time of ascertainment or most recent clinical evaluation. Where information is missing, ‘unknown’ should generally be indicated. In instances where a patient has undergone an ileostomy (usually following a colectomy for management of the ulcerative colitis) the items in the *Partial Mayo Index* should be marked as ‘unknown’.

Smoking History Prior to Diagnosis:

1. *Smoking at Diagnosis* is defined as smoking, on average, at least 1 cigarette daily for a period of at least 3 months prior to diagnosis. Pipe and cigar smoking are not included. An *Ex-smoker* at diagnosis is defined as someone who had stopped smoking at least 3 months prior to diagnosis and was not smoking at diagnosis.
2. *Year Started* and *Year Stopped*. If patient has had multiple episodes of quitting and starting smoking cigarettes indicate the year when first started and the year last quit (even if it is after the year of diagnosis).
3. If patient is a *Smoker* but dates of start and stop are unknown, leave dates blank. If patient has never smoked indicate ‘No’, and leave *Year Started/Year*

Stopped blank. If smoking history is unknown, check 'Unknown', and leave *Year Started/Year Stopped* blank.

4. *No. of cigarettes per day*: indicate the number of cigarettes smoked daily. Where smoking amount has changed over time use the amount at diagnosis (if known). If not known, use the amount smoked at the date closest to the time of diagnosis. If Ex-smoker at diagnosis use the estimated mean number of cigarettes per day prior to quitting. If subject is a *Smoker* or *Ex-smoker* but the number of cigarettes per day is not known please indicate 'Unknown'. If patient had never smoked at diagnosis or smoking history is unknown please leave field empty.
5. *Regular Second-Hand Smoke Exposure at Home (for pediatric module)*: Indicate 'yes' if subject has lived in the same household with a smoker for a period of more than one year prior to diagnosis. Record year when last lived with smoker. If ongoing passive household exposure indicate year of ascertainment.

Extra-Intestinal Manifestations: Must be completed by a clinician.

Extraintestinal manifestations (EIM) should be documented in medical records (e.g. clinical note, radiology report, surgical report, pathology report).

1. *Joints*: pauciarticular (less than 5 joints involved with evidence of effusion or swelling – usually large joints - and associated with relapses of IBD); polyarticular (5 joints or more, symmetric involvement with effusion or swelling - usually small joint - runs a course independent of IBD often lasting many months).
 - b. *Large joint disease related to disease activity*: Fewer than 5 (usually large) joints with evidence of inflammation (effusion and/or swelling) related to disease activity.
 - c. *Small joint unrelated to disease activity*: Five or more (usually small) joints with evidence of inflammation (effusion and/or swelling) unrelated to disease activity.
 - d. *Ankylosing spondylitis*: requires radiologic documentation of typical findings of sacroiliac inflammation, narrowing or sclerosis and/or inflammation or fusion of vertebral bodies.
 - e. *Sacro-iliitis*: also requires radiologic documentation of typical findings of sacroiliac inflammation, narrowing or sclerosis and/or inflammation or fusion of vertebral bodies.
 - f. *Non-specific joint inflammation*: evidence of effusion or swelling but does not fit any of the above categories.
 - g. *Non-specific*: arthralgias (joint pains) in the absence of other markers of active joint inflammation such as effusion or swelling.
2. *Skin*:
 - a. *Erythema nodosum*: typically appear as raised, tender, red or violet subcutaneous nodules that are 1 to 5 cm in diameter. The nodules are most commonly located on the extensor surfaces of the extremities, particularly over the anterior tibial area.
 - b. *Pyoderma*: ulcerative disease of the skin. There may be one or multiple lesions. They occur most commonly on the legs, especially the pretibial

area, but can develop in any area of the body, including the abdominal wall adjacent to the stoma after colectomy.

3. *Eyes:*
 - a. *Uveitis:* intraocular inflammation. Diagnosis requires documentation of typical findings. A slit lamp examination is preferable.
 - b. *Episcleritis:* Defined by the abrupt onset of mild inflammation of the episclera of the eye. Requires documentation of typical findings of localized inflammation (erythema, increased vascularity, nodularity) of the episcleral tissues.
 - c. *Undiagnosed ocular inflammation:* Where there has been eye inflammation but the presentation or findings have not been typical or where the nature of the inflammation cannot be classified based upon the available information.
4. *Liver:*
 - a. *Primary sclerosing cholangitis:* should be documented with typical dye cholangiographic or MRCP findings in someone with no other known causes of secondary cholangitis. Abnormal liver enzymes or liver biopsy alone are not sufficient evidence of sclerosing cholangitis.

Disease Activity and Update Forms (CD and UC/IC)

The disease activity and update forms (formerly longitudinal forms) will be used to update the phenotypic information on study subjects, since the time of initial intake. This will be based upon a review of the clinical information available up until the time of reassessment. The information may be extracted from the patient chart and/or from local patient databases. This information will be especially useful for expression studies and projects looking at disease activity and progression.

Use the form that is appropriate for the current diagnosis (CD or UC/IC) even if the diagnosis has changed since the previous form completion.

Assessment Date

1. Date of Previous Assessment: Record the date of the latest exam/encounter from the previous Phenotype Intake Form or Disease Activity and Update Form.
2. Date of Latest Clinical Exam/Encounter: Record the date of the most recent clinical exam or encounter upon which the current assessment is based.
3. Disease Type: Indicate whether the disease diagnosis has changed or not changed since the time of the last form completion.

For UC/IC, if the diagnosis has not changed indicate whether the diagnosis is UC (unchanged) or IC (unchanged). Where the diagnosis has changed indicate whether it has “changed to UC” or “changed to IC”.

Family History Update

Indicate any changes to family history since the previous form completion. Please note that where a subject’s diagnosis has changed this may necessitate a change in the ‘family type’.

Current Smoking Status

Indicate any current smoking status and year of starting and stopping, as indicated.

Macroscopic Disease Location

Reassess disease location including any new information obtained since last form completion. Criteria used should be as described above for Intake Forms. This is intended to reflect the disease location at any time since diagnosis and not simply since the time of previous form completion.

CD Disease Behavior

Update the CD disease behavior based upon the most recent information available. A subject cannot move from B2 or B3 back to B1. For example, if someone has undergone ileocecal resection for B2 or B3 disease he/she does not have B1 disease behavior if the disease recurs in the ileum in the absence of stricturing or penetration (fistulization).

Surgical History Update

Indicate any operations for IBD since last form completion. Definition of operations is as described above for Intake Forms. Indicate dates of any operations performed for IBD since the previous form completion. If there have been abdominal surgery since the previous form completion ‘*Date of first operation*’ should be the date of the first operation since the previous form completion and ‘*Date of second operation*’ should be the date of the second operation since the previous form completion. The ‘*Number of operations for abdominal disease*’ and the ‘*Number of operations for perineal disease*’ should be the number of these types of operations since the previous form completion. For ulcerative colitis the ‘*Date of surgery (colectomy)*’ should be the date of colectomy which is, in general, the first operation for ulcerative colitis.

Indicate if there has been a new diagnosis of colorectal dysplasia or cancer since the previous form completion and the date of diagnosis.

Indicate whether patient has undergone an appendectomy and, if so, the date of the procedure.

Current Pubertal Stage (Pediatric subjects only):

1. Tanner Stage: Indicate Tanner Stage (1 through 5), for breast development and pubic hair development for females, and genitalia and pubic hair development for males, at time of latest clinical evaluation. If information is not available please indicate ‘Unknown’.
2. Height at Diagnosis. Record height (in centimeters or inches) at latest clinical evaluation. Record ‘Unknown’ if height not documented.
3. Weight at Diagnosis (for pediatric module). Record weight (in kilograms or pounds) at latest clinical evaluation. Record ‘Unknown’ if weight not documented.

Disease Activity and Treatment Since Last Assessment

1. Hospitalizations since last assessment: Indicate the number of hospitalizations for IBD or a complication of IBD since the date of the previous form completion. Hospitalization does not include Emergency Department visits in which the subject is treated and discharged from the Emergency Department and not admitted to an in-patient unit.
2. Physician global appraisal of disease activity since last assessment: This is intended to be an overall evaluation of the predominant disease course since the time of the previous form completion incorporating both the occurrence of disease remissions and the severity of flares/exacerbations. It is recognized that patients may experience changes in the course of their disease over time and that this assessment may be difficult to place into a single category. However, an attempt should be made to assign the dominant pattern. Where a patient has had both periods of flares and remissions since the last form completion he/she should be categorized as having “*Mild with Remissions*” or “*Moderate or Severe Exacerbations but Remissions*”. If a patient has had only mild disease flares or exacerbations he/she should be categorized as having “*Mild*

with Remissions". If he/she has had any flares or exacerbations that were of moderate to severe activity he/she should be categorized as having "*Moderate or Severe Exacerbations or Remissions*". Where the patient has not had significant periods of remission he/she could be considered as having had chronically active disease. Definitions of disease severity are as described below. Remission is considered to be a Harvey Bradshaw Index score of 3 or less for Crohn's disease and a Mayo Index score of 2 or less for ulcerative colitis.

3. Current Disease Activity: Provide overall assessment of disease activity at latest clinical exam / encounter. As a general guide, for Crohn's disease mild disease would correspond to a Harvey-Bradshaw Index score of 6 or less, moderate disease to a HBI score of 7 to 13 and severe disease to a HBI score of greater than 13. For ulcerative colitis, mild disease corresponds to a Mayo Index score of 4 or less, moderate disease to a Mayo Index score of 5 to 8 and severe disease to a Mayo Index score of 9 to 12. It is recognized that, in some instances, the symptoms included in the assessment of disease activity may be explained or caused by other factors not directly related to intestinal inflammation. In these instances an attempt should be made to discount these particular symptoms when assessing disease activity.

4. Components of *Harvey-Bradshaw Index* (for Crohn's disease) are to be determined based upon the most recent clinical exam/encounter. Where information is missing 'unknown' should generally be indicated (e.g., if it appears that a physical examination was not performed then 'abdominal mass' should be 'unknown.' However, if complications (aphthous ulcers, anal fissure, new fistula or abscess) are not mentioned in a clinical note it can be assumed that they are not present.

5. Items from the *Partial Mayo Index* (for ulcerative colitis) should be completed based upon the subject's status at the time of most recent clinical exam/encounter. Where information is missing, 'unknown' should generally be indicated.

6. Medication use since last assessment should be indicated as 'yes', 'no' or 'unknown' for each class of therapy depending on whether it has been used between the time of diagnosis and the most recent evaluation. A medication is considered to have been used if it has been administered for at least 5 days (for those medications administered at least once daily), for 2 weeks (for those administered weekly) or for one dose (for those administered less often than every week).

7. For those medications that have been used since last assessment, the *current use* should be indicated as 'yes', 'no' or 'unknown' for each.

Extraintestinal Manifestations

The previous occurrence or current expression of extraintestinal manifestations should be updated with inclusion of any additional information obtained since the time of the previous form completion. This is intended to reflect the occurrence of these manifestations at any time since diagnosis and not simply since the time of previous form completion. Definition of extraintestinal manifestations is as described above for Intake Forms.

Unaffected Phenotype Form for Controls

Registration Information:

1. *Individual ID* is optional. Each center may choose to assign these or disregard.
2. *Gender*.
3. *Date of Birth* is in format MM/DD/YYYY.
4. The *Consortium ID* is generated upon registration of the subject using the Consortium web interface, and serves as the primary identifier for all subjects recruited into the repository or otherwise registered online.
5. *Relationship to Proband*: Must be parent, spouse/domestic partner, friend* or population control*. Note: the Consortium is focusing on population controls; therefore controls cannot be parents of subjects. Domestic partner refers to a non-friend person, not married to but cohabitating with, the IBD subject.
6. *Population Control*: The Consortium is focusing on population controls therefore controls cannot be parents of subjects. Only one person per family can be recruited as a control.
7. *Control Checklist: Same race/ethnicity as index subject* is as self-reported. Matched Jewish ethnicity must also match Ashkenazi status (e.g. if proband has 2-4 Ashkenazi Jewish grandparents, control must have any of 2, 3 or 4 Ashkenazi grandparents. If proband has only 1 Ashkenazi grandparent but all are Jewish, control must have 1 or 0 Ashkenazi grandparents, but 2 or more must be Jewish). *No family history of IBD* refers to 1st and 2nd degree relatives (parents, siblings, offspring, aunts/uncles, grandparents, nieces/nephews).

Demographic Information:

1. *Hispanic/Latino* status ('Yes' / 'No') is self-reported.
2. *Jewish* status ('Yes' / 'No') is self-reported. Jewish heritage of grandparents is required.
3. *Race* is self-reported. Choose 'Other' under *Race* for multiracial individuals.
4. *Family History of IBD* as reported by the individual for all relatives listed. Relatives must have been diagnosed with IBD to qualify under 'CD', 'UC/IC' or 'IBD affected type unclear'. This does not require confirmation by relative or relative's medical chart. 'IBD Affected, type unclear' refers to a relative whom the individual knows has been diagnosed with IBD but isn't sure/cannot recall what type. IBD affection as reported by the patient/participant. UC or IC in any 1st or 2nd degree relative would indicate mixed family type. *1st degree relatives*

Unaffected

include parents, full siblings, and children. *2nd degree relatives* include grandparents, aunts/uncles and nieces/nephews and half-siblings.

Smoking History:

1. Indicate if control is *Current smoker, Ex-smoker, Non-smoker* or *Unknown*.
2. If control has smoked less than 100 cigarettes in his/her lifetime, he/she is considered to be a non-smoker.
3. If control has had multiple episodes of quitting and starting smoking cigarettes indicate the year when first started and the year last quit, unless currently smoking.
4. If *Current smoker*, leave *Year stopped* blank.

Surgery:

1. Indicate 'Yes', 'No' or 'Unknown' and enter year of appendectomy if known.

Glossary

Abscess: A localized collection of pus in part of the body formed by tissue disintegration and surrounded by an inflamed area.

Ankylosing Spondylitis: Arthritis of the axial skeleton manifested by back pain and progressive stiffness of the spine.

B1: CD Disease Behavior, nonstricturing, nonpenetrating. Defined as uncomplicated inflammatory disease without evidence of stricturing or penetrating disease.

B2: CD Disease Behavior, stricturing. Defined as the occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic, or surgical examination combined with prestenotic dilation and/or obstructive signs or symptoms but without evidence of penetrating disease.

B3: CD Disease Behavior, penetrating. Defined as the occurrence of bowel perforation, intraabdominal fistulas, inflammatory masses and/or abscesses at any time in the course of the disease, and not secondary postoperative intra-abdominal complication. NB Perianal and rectovaginal fistula(s) do not count, by themselves, as 'penetrating fistulizing'.

Cecum: The large blind pouch forming the beginning of the large intestine. Also called blind gut.

Endoscopy: Examination of the interior of a hollow body organ by use of an endoscope.

Episcleritis: Defined by the abrupt onset of mild inflammation of the episclera of the eye. Requires documentation of typical findings of localized inflammation (erythema, increased vascularity, nodularity) of the episcleral tissues. The episclera is a highly vascular connective tissue that is superficial to the sclera of the eye.

Erythema Nodosum: Typically appear as raised, tender, red or violet subcutaneous nodules that are 1 to 5 cm in diameter. The nodules are most commonly located on the extensor surfaces of the extremities, particularly over the anterior tibial area.

Ex-smoker: Someone who has smoked prior to diagnosis, but was not smoking at time of diagnosis.

Fistula: An abnormal duct or passage resulting from injury, disease, or a congenital disorder that connects an abscess, cavity, or hollow organ to the body surface or to another hollow organ.

Macroscopic: Large enough to be perceived or examined without microscopy.

Non-smoker: A person who has never smoked, at time of diagnosis.

Non-specific joint inflammation: Evidence of effusion or swelling but does not fit any of the other categories.

Percutaneous Drainage: Drainage performed through the skin or accomplished by a needle.

Population Control: Controls should be collected from the general population. Recruitment for the Consortium will no longer focus on unaffected family members. Only one person from a family can be recruited as a control.

Primary Sclerosing Cholangitis: A chronic progressive disorder of unknown etiology, characterized by inflammation, fibrosis, and stricturing of medium size and large ducts in the intrahepatic and extrahepatic biliary tree (bile ducts in- and outside the liver).

Pyoderma: Ulcerative disease of the skin. There may be one or multiple lesions. They occur most commonly on the legs, especially the pretibial area, but can develop in any area of the body, including the abdominal wall adjacent to the stoma after colectomy.

Resection: Excision of a portion or all of an organ or other structure.

Sacro-iliitis: Arthritis of the sacroiliac joint.

Seton: One or more threads or horsehairs or a strip of linen introduced beneath the skin by a knife or needle to provide drainage.

Smoker: Someone smoking at time of diagnosis.

Strictureplasty: Surgical procedure for widening a structured segment of intestine that involves incision and closure in opposing directions.

Undiagnosed ocular inflammation: Where there has been eye inflammation but the presentation or findings have not been typical or where the nature of the inflammation cannot be classified based upon the available information.

Uveitis: Intraocular inflammation. Diagnosis requires documentation of typical findings. A slit lamp examination is preferable.