New diagnostic strategies to distinguish Crohn's disease and gastrointestinal tuberculosis

Himanshu Narang, Saurabh Kedia and Vineet Ahuja

Purpose of review
Despite advances in our radiological, histological and microbiological armamentarium, distinguishing between Crohn's disease (CD) and intestinal tuberculosis (ITB), especially in a TB endemic country, continues to be a challenging exercise in a significant number of patients. This review aims to summarize current available evidence on novel diagnostic techniques which have a potential to fill the gap in our knowledge of differentiating between ITB and CD.

Recent findings
Both ITB and CD are associated with altered host immune responses, and detection of these altered innate and adaptive immune cells has potential to distinguish ITB from CD. ITB and CD have different epigenetic, proteomic and metabolomic signatures, and recent research has focused on detecting these differences. In addition, the gut microbiome, which is involved in mucosal immunity and inflammatory responses, is considerably altered in both ITB and CD, and is another potential frontier, which can be tapped to discriminate between the two diseases. With technological advancements, we have newer radiological modalities including perfusion CT and dual-layer spectral detector CT enterography and evidence is emerging of their role in differentiating ITB from CD. Finally, time will tell whether the advent of artificial intelligence, with rapidly accumulating data in this field, will be the gamechanger in solving this puzzle of diagnostic dilemma between ITB and Crohn's disease.

Summary
Recent advances need to be clinically validated before they can be used as novel diagnostic measures to differentiate Intestinal TB from CD.

Keywords
artificial intelligence, Crohn's disease, diagnosis, gut microbiome, intestinal tuberculosis, metabolome

INTRODUCTION

Diagnosing intestinal tuberculosis (ITB) has not been easy since it is a paucibacillary disease. Despite advances in our radiological, microbiological, and pathological armamentarium, the intestinal tuberculosis vs. Crohn's disease (CD) conundrum continues to perplex clinicians in a significant number of patients.

Chronicling the key steps in diagnostic strategies (Table 1), we find that the criteria laid down by Paustian were representative of Koch's postulates, however they did not take into account the poor sensitivity of diagnostic tests for TB due to paucibacillary nature of ITB [1]. Hence, Logan came up with modified criteria which suggested that response to anti tubercular therapy would be a key factor in establishing the diagnosis of ITB [2]. This suggestion was valid but failed to consider the perplexing observation that one third of patients with Crohn's disease have a symptomatic response to antitubercular therapy (ATT) even if ill sustained. Hence just a symptomatic response to ATT was not sufficient to differentiate ITB from CD. Mouli *et al.* put forward the seminal observation that a combination of symptomatic response as well as mucosal healing was required to differentiate ITB from CD and this strategy has gained popularity in clinics [3]. A follow-up of this cohort by Gupta *et al.* revealed an interesting observation that patients who were eventually diagnosed to have CD after nonresponse to ATT trial had a more aggressive course

Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India

Correspondence to Vineet Ahuja, Professor, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India. Tel: +91 11 26594615; e-mail: vineet.aiims@gmail.com

Curr Opin Infect Dis 2024, 37:392–401

DOI:10.1097/QCO.0000000000001054

KEY POINTS

- Differentiating Crohn's disease and intestinal tuberculosis remains a challenging task for clinicians.
- Current diagnostic modalities and predictive models based on clinical, endoscopic, radiologic and histologic features have limited applicability due to lack of external validation.
- Endoscopic and clinical response to antitubercular therapy remains the gold standard
- Novel diagnostic modalities including multiomics, immune based tests on biopsy, newer microbiological tests, serologic techniques, and radiologic features can improve diagnostic differentiation.
- Artificial intelligence-based models may further improve the upfront diagnosis of both diseases.

subsequently [4]. A propensity case-matched analysis showed that patients with CD who were given ATT trial to confirm the diagnosis developed higher proportion of strictures and a more complicated disease course including requirement for surgery. The increased rate of development of strictures appeared to be caused by ATT itself and was independent of the diagnostic delay caused by the administration of ATT. Hence based on this study it was recommended that a patient with clinical resolution as well as mucosal healing on colonoscopy at 8–12 weeks after starting a trial of ATT could be diagnosed as having ITB. . This was subsequently confirmed in a cohort study by Hilmi *et al.* [5▪] A lot of research has also been done elucidating the clinical, radiological, and pathological features that point towards one disease entity over the other (Table 1a and 1b, Supplemental Digital Content, http://links.lww.com/COID/A52) [44,45,47,50–55]. Based on a combination of these features, many models have also been explored for clinical use (Table 2, Supplemental Digital Content, http://links.lww.com/COID/A52) [5▪,6,9–11,43,46,48,49,56–59,61–64]. However, external validation for such models is lacking.

The following sections will aim to bring forth emerging and recent research in various fields ranging from immunology to gut microbiome to radiomics and artificial intelligence, all focusing to differentiate intestinal tuberculosis from Crohn's disease.

GENETICS AND EPIGENETICS – ROLE OF microRNAs AND DNA METHYLATION

MicroRNAs, small RNA molecules regulating gene expression, have been explored as biomarkers to differentiate ITB from CD. In a study comparing plasma and ileocecal/terminal ileal biopsy samples, plasma miR-375-3p was found to be significantly elevated in ITB compared with CD, while the reverse was true for tissue samples [12]. Plasma miR-375-3p has previously been shown to be increased in pulmonary tuberculosis as well [13].

In a genome-wide association study conducted to identify differentially methylated positions (DMPs) in whole blood DNA of patients with CD, ITB and healthy controls ($n=22$), researchers found that in both CD and ITB, DNA was hypomethylated compared to controls [14]. They further found that hypermethylation in KCNJ15 could be a potential CD-specific biomarker. However, the limited sample size, high cost involved and need for validation by other centers are major impediments before these tools can be brought to clinical use.

PROTEOMICS AND METABOLOMICS

Proteomics assessment with matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) on serum of patients with CD, ITB, and healthy controls ($n=81$) was done in a study from China [15]. Among 332 differently expressed protein peaks between CD and ITB

Table 1. Key studies in diagnosing intestinal tuberculosis from Crohn's disease

Year	Key studies	How to diagnose intestinal TB
1959 [1]	Paustian's criteria	Demonstrating AFB
1969 [2]	Logan's Criteria	Symptomatic response to ATT
2017 [3]	Mouli VP, New Delhi	Mucosal as well as symptomatic response to ATT
2017 [56]	Limsrivilai J, Thailand	Meta-Analytic Bayesian Model
2020 [4]	Gupta A, New Delhi	3 months mucosal response after ATT to prevent strictures
2023 [5▪]	Hilmi I, Malaysia	Prospective application of simplified algorithm

ATT, antitubercular therapy.

patients, a diagnostic model utilizing three proteins achieved 80.0% sensitivity and 76.2% specificity in distinguishing between the two conditions. Additionally, tandem mass tag labeled proteomic analysis revealed increased levels of tumor necrosis factor ligand superfamily member 13, peroxiredoxin-5, T-complex protein 1 subunit gamma, CutA, and Fibulin-5 in CD compared to ITB [16].

Furthermore, our group explored the utility of proteome profile in colonic biopsy in differentiating CD from ITB [17], and found at least 11 differentially expressed proteins. However, none of them could be validated in a subsequent study. Clearly, we need larger studies with more homogenous samples before we can decide on the clinical utilities of these techniques.

A study based on metabolomics utilized liquid chromatography-mass spectrometry to investigate differences in serum metabolites in CD compared with healthy controls (68 CD patients, 56 healthy controls in training cohort; 110 CD patients, 90 controls in validation cohort) [18▪]. Five metabolic biomarkers (pyruvate, phenylacetylglutamine, isolithocholic acid, taurodeoxycholic acid, and glycolithocholic acid) were identified that distinguished CD patients from healthy controls. Furthermore, these metabolic biomarkers also distinguished CD from intestinal tuberculosis and other chronic gastrointestinal inflammatory diseases, suggesting metabolomics' potential as a tool to differentiate between these conditions.

GUT MICROBIOME ALTERATION

Two studies have shown promising role of fecal microbiome in differentiating ITB from CD. One study utilizing mucosal samples and 16srRNA sequencing, found distinct differences in gut microbiota composition in patients with ITB, CD, and healthy controls [19]. Although patients with ITB exhibited predominance of Proteobacteria and reduced Firmicutes, *Fecalibacterium*, *Rosburia*, and *Ruminococcus*, patients with IBD-CD showed increased *Bacterioides*, *Fecalibacterium*, *Collinsella*, and *Klebsiella* species. The study achieved an area under the curve (AUC) of 97.6% in discriminating between the two conditions.

Our group had analyzed fecal samples using 16s amplicon sequencing and observed reduced alpha and beta diversity indices in ITB and CD patients compared to healthy controls, with no significant differences between the two diseases [20]. Both conditions displayed decreased Firmicutes and Bacteroidetes, with increased Actinobacteria and Proteobacteria. However, differential abundance analysis revealed distinct microbial expansion in each condition. A random forest-based machine learning model developed using this microbiome data achieved a 93% AUC in distinguishing between CD and ITB [20].

Thus, clearly the gut microbiome signature is distinct between CD and ITB and this can be a tool to differentiate between the two diseases. However, the major limitation today in incorporating –omics technology in our clinical algorithms for routine use is the lack of availability of the 16srRNA sequencing and other techniques and the high cost involved. These factors limit utilization of these techniques only to research settings.

IMMUNOLOGY – ALTERATIONS IN INNATE AND ADAPTIVE IMMUNE RESPONSES

It is well known that classic M1 macrophages are associated with inflammation, whereas M2 macrophage activation is associated with anti-inflammatory effects. Studies have investigated immune cell alterations for distinguishing between ITB and CD. We had conducted a study examining colonic biopsy samples from 29 ITB, 50 CD, and 19 control patients to assess M1 and M2 macrophage ratios using immunohistochemistry [21]. We discovered elevated pro-inflammatory M1 macrophages in CD compared to ITB and controls, with higher M1 polarization correlating with increased inflammatory response in peripheral blood monocyte cells. A similar study analyzed immune marker expression in biopsy samples from 5 patients each with ITB, Behcet disease, and CD [22]. It found that dendritic cell expression was highest in ITB and lowest in Behcet's disease, while cytotoxic T cells, helper T cells, and regulatory T cells showed similar expression levels across all diseases. However, the small sample size may have limited the identification of differences between the groups. These findings suggest potential utility of immune cell profiling for differentiating between ITB and CD. However, studies with larger sample sizes are needed to validate these results, before these techniques can be taken to the clinics. Also, the cost of these investigations will need consideration before they can be employed for routine use. These advanced techniques may be helpful in cases where diagnosis remains elusive even after routine radiological, histological and microbiological investigations.

$CD4^{+}CD25^{+}FOXP3^{+}$ T regulatory cells have been shown to be increased in pulmonary tuberculosis [23,24]. Our group prospectively recruited patients with intestinal tuberculosis and CD and assessed $FOXP3^{+}$ T cell levels by flow cytometry [25]. Results showed a significant increase in $FOXP3^{+}$ T-regulatory cells in peripheral blood and

colonic mucosa of ITB compared to CD. A cut-off value of 32.5% in peripheral blood had a sensitivity of 75% and specificity of 90% for differentiating between the two conditions. We subsequently conducted a validation study involving 47 ITB and 23 CD patients, and found similar results with FOXP3$^+$ T-regulatory cell level of 32.37% having sensitivity and specificity of 87% and 95%, respectively, to differentiate between the two conditions [26]. While elevated levels are not sacrosanct for diagnosis of tuberculosis, this investigation does provide supportive evidence in favor of tuberculosis in doubtful cases.

SERIAL FECAL CALPROTECTIN LEVELS

Currently, early mucosal response to antituberculosis therapy trial is used as a diagnostic test to differentiate intestinal tuberculosis from CD. In a prospective study, investigators assessed utility of fecal calprotectin and CRP at 2 and 6 months of ATT to differentiate ITB from alternative diagnoses [27]. The study found AUC of 0.82 and 0.6 for FCP and CRP, respectively at 2 months for diagnosis of ITB. Another retrospective study found FCP to be <100 mcg/g in all patients with ITB even after 1 month of ATT [28].

Fecal calprotectin has become a part of clinical practice in IBD because of its noninvasive nature, increasing accessibility and affordable costs. If validated by multicenter high quality studies, then serial FCP can very well become part of diagnostic algorithm of ITB vs. CD.

RADIOLOGY

Multiple recent advances in radiology, if validated in larger studies, have the potential to be easily incorporated in our diagnostic algorithms for ITB and CD, with minimal additional logistics expenditures (Table 2).

Visceral fat quantification

Mesenteric fat proliferation and fat wrapping, notably seen in CD over tuberculosis, is visualized as fibrofatty proliferation on CT scan. Our group assessed visceral fat (VF) and subcutaneous fat (SC) area on CT to determine utility of VF/SC ratio in differentiating CD from ITB, and found the cut-off of 0.63 to be simple, cost-effective, noninvasive and single objective parameter with a good sensitivity (81%) and specificity (78%) [8,60]. The ratio has been utilized in pediatric population as well, with cut-off of 0.6 having good sensitivity and specificity to predict IBD-CD (sensitivity 75%, specificity 86%, AUROC 0.79) [29■■].

Table 2. Specific findings on different radiologic modalities which are helpful in differentiating CD from ITB

Study	Feature	Remarks
Kedia *et al.* 2015 [7]	3 CT findings- • Long segment involvement • Ileocecal region involvement • LN > 1 cm	Risk score for CD 3: Sensitivity 37%, Specificity 90% Risk score for ITB 0: Sensitivity 14%, Specificity 100%
Yadav *et al.* 2017 [8] Seetharaman *et al.* 2023 [29■■]	Visceral and subcutaneous fat quantification Ratio of visceral to subcutaneous fat (VF/SC ratio)	Higher VF/SC ratio favors diagnosis of CD. A cut of 0.63 in adults and 0.609 in children has a good diagnostic accuracy in differentiating CD from ITB
Kedia *et al.* 2018 [60]	3 CT or CTE findings- • VF/SC ratio > 0.63 • Long segment involvement • Necrotic lymph nodes	Training- Score 0 for ITB – Sensitivity 85%, Specificity 79% Score 2 for CD – Sensitivity 52% Specificity 100% Validation- Score 0 for ITB –Sensitivity 56%, Specificity 84% Score 2 for CD- Sensitivity 50%, Specificity 100%
Seth *et al.* 2023 [30]	Perfusion CT of the ileocaecal region. Blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability.	Blood flow, permeability had excellent while MTT had reasonable diagnostic accuracy in differentiating CD from ITB.
Huang *et al.* 2024 [31]	CT images were obtained at the enteric phases and portal phases. Quantitative energy spectrum parameters were iodine density (ID), normalized ID (NID), virtual noncontrast (VNC) value, and effective atomic number (Z-eff).	Enteric phase NID and portal phase Z-eff had the highest accuracy in differentiating CD from ITB. AUC value was highest when the four parameters were combined

CD, Crohn's disease; ITB, intestinal tuberculosis; CD, Crohn's disease.

Perfusion CT

Perfusion CT imaging involves measuring blood flow, blood volume and permeability of tissue. While initially used in neurological imaging, it has recently caught interest of radiologists for its utility in diseases of small and large bowel. Recently, a study evaluating 26 patients (15 CD, 11 ITB) with perfusion CT imaging, found blood flow and permeability to have 100% sensitivity and specificity while mean transit time (MTT) had 60–100% sensitivity and 70–100% specificity in differentiating between the 2 conditions [30]. Although promising, larger studies are needed for validation. Also, increased radiation exposure limits its use as a routine investigation in our clinics. Literature is scarce on the role of perfusion MRI, which overcomes limitation of radiation exposure, in differentiating between the 2 conditions.

Dual-layer spectral detector CT enterography

Dual-layer spectral detector CT enterography is an advanced imaging technology that incorporates two layers of detectors within the CT scanner. Each layer is designed to absorb photons at different energy levels. The top layer of detectors is optimized to absorb low-energy photons, while the bottom layer is specialized to absorb high-energy photons. By capturing data from two different energy levels simultaneously, the dual-layer spectral detector CT scanner can provide detailed information about the composition of tissues and materials within the body. One study collected clinical and CTE data from 182 CD and 51 ITB patients and found it to have high sensitivity and specificity in differentiating CD and ITB, with AUC exceeding 0.93 [31].

Radiomics

Radiomics is the field of medical imaging that deals with extraction of quantitative features from medical images and their analysis and storage as data that can be used for assisting in diagnosis, severity, prognosis and treatment response assessment of disease. Medical images including those from computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan are converted to mineable data using advanced computational methods.

Two studies from China have explored potential of radiomics in differentiating CD from ITB. The first study used CT enterography and radiomics to extract features from lesions in ileocecal region (region of interest) [32]. A radiomics score was created and a clinical-radiomics model was made using nine radiomics signatures. In both training (110 patients) and validation (50 patients) cohorts, the model achieved high discriminatory accuracy with area under the receiver operating characteristic curve (AUROC) values of 0.96 and 0.93, respectively. Similarly, the second study used CT enterography-based multiregional radiomics model derived from data of 105 patients (61 CD, 44 ITB) [33]. A clinical radiomic combined model was created using one radiomic signature each from intestinal wall, lymph node, involved bowel segments on CT enterography, and longitudinal ulcer on endoscopy. The model had good diagnostic accuracy, with AUROC values of 0.98 and 0.96 in training and validation cohorts, respectively.

Various diagnostic modalities differentiating ITB and CD have been described in Table 3a, Supplemental Digital Content, http://links.lww.com/COID/A52 [8,12,14–16,18▪,19–22,25–33,65–76].

ROLE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) is the field of computer science concerned with the development of programs that can perform tasks that traditionally required human intelligence, like reasoning and problem-solving. Machine learning (ML) is a subfield of AI that gives the computer the ability to learn, i.e. predict future results using past data, without being explicitly programmed. Deep learning is a subset of machine learning that learns features directly from the raw data, without being hand-engineered, as was traditional ML.

Multiple studies have evaluated the role of AI and ML in differentiating CD from ITB using endoscopy and radiological images [32,34–40,42,77–79,80▪] (Table 3b, Supplemental Digital Content, http://links.lww.com/COID/A52). A recent systematic review and meta-analysis found that such AI-based models had high predictive value for differentiating CD from ITB, with accuracy ranging from 70–100% [41▪]. Similar studies are also evaluating role of AI in reviewing histopathological whole slide images from intestinal specimens, with encouraging results [42].

Thus, there is a growing body of evidence to suggest that artificial intelligence is a potential tool which can assist us in differentiating between ITB and CD without need for any new additional expensive lab test.

CONCLUSION

Certainly, starting from the initial days when CD was first described, we have made great strides in diagnosis and management of the disease. However,

Table 3. Diagnostic utility of newly developed parameters in differentiating CD from ITB

	Evidence	**Remarks**
Immune response based tests-		
Colonic biopsy Immunohistochemistry (IHC) for immune profiling	Das *et al.* 2018 [21]	Proinflammatory M1ϕ polarization was more common in colonic mucosa of CD patients, especially in the presence of mucosal granulomas.
	Yoo *et al.* 2023 [22]	Expression of immune cells, including M1 macrophages and dendritic cells, was different between CD, intestinal Behcet's disease, and ITB.
Serum FOX-P3+ T cells levels Tiwari *et al.* [25] Rampal *et al.* [26]	Tiwari *et al.* 2018 [25]	A cut-off value of 32.5% in peripheral blood had a sensitivity and specificity of 75% and 90%, respectively, to differentiate ITB from CD.
	Rampal *et al.* 2021 [26]	Cutoff of 32.37% had sensitivity and specificity of 87% and 95% respectively, to differentiate ITB from CD.
Flowcytometry for $CD4^+$ cell apoptosis	Nayak *et al.* 2020 [65]	Best sensitivity, specificity, and positive and negative predictive values for the diagnosis of ITB were seen with $CD4^+$ cell percentage (82.6%, 82.4%, 86.4%, 77.8%, respectively) and the proportion of early apoptotic cells (73.9%, 70.6%, 77.3%, 66.7%, respectively).
Genetics and Epigenetics		
MiRNAs (Plasma miR-375-3p levels)	Roy *et al.* 2021 [12]	Combination of miR-375-3p + Eotaxin-1/CCL11 + SDF-1α /CXCL12 + G-CSF showed an AUC of 0.83, with 100% specificity and positive predictive value while sensitivity, negative predictive value, and accuracy were 56%, 69%, and 78% respectively in distinguishing ITB from CD
KCNJ15 hypermethylation in blood	Wu *et al.* 2020 [14]	Hypermethylation of cg03122532 (5'UTR of KCNJ15) could be a potential CD-specific biomarker
Proteome and metabolome analysis		
Serum and tissue proteome profile – MALDI-ToF-MS	Zhang *et al.* 2016 [15]	A differential diagnostic model comprising three potential biomarkers protein peaks (M/Z 4267, 4223, 1541) could distinguish CD and ITB patients, with a specificity and sensitivity of 76.2% and 80.0% respectively.
	Ning *et al.* 2019 [16]	There were increased levels of tumor necrosis factor ligand superfamily member 13, peroxiredoxin-5, T-complex protein 1 subunit gamma, CutA, and Fibulin-5 in CD compared to ITB.
	Rukmangadachar *et al.* 2016 [17]	11 proteins were differentially expressed between CD and ITB in more than one set of experiments. Six proteins used for validation using immunohistochemistry in a larger cohort of patients; were not differentially expressed in patients with ITB and CD.
Serum metabolome profile – LC-MS	Ma *et al.* 2023 [18▪]	A panel of 5 metabolites (pyruvate, phenylacetylglutamine, isolithocholic acid, taurodeoxycholic acid, and glycolithocholic acid) could distinguish patients with CD and ITB with high diagnostic accuracy (AUC: 0.963)
Gut microbiome		
Gut microbiome assessment	He *et al.* 2021 [19]	Microbial structure in CD was distinctly different from ITB, characterized by lower alpha diversity and increased abundance of *Bacteroides*, *Faecalibacterium*, *Collinsella*, and *Klebsiella*. These four bacterial markers distinguished ITB from CD with an area under the curve of 97.6%.
	Markandey *et al.* 2022 [20]	Differential Abundance Analysis between CD and ITB groups revealed expansion of *Succinivibrio dextrinisolvens, Odoribacter splanchnicus, Megasphaera massiliensis, Bacteroides uniformis* and *B.xylanisolvens* in CD, while *Clostridium sp., Haemophilus parainfluenzae* and *Bifidobacterium sp.* were elevated in ITB. Random Forest-based ML model showed predictive accuracy of 0.78 (AUC = 93%).
Colonic biopsy for pathobionts; Host gene polymorphisms	Khan *et al.* 2021 [66]	*Listeria monocytogenes* and *Yersinia enterocolitica* were significantly associated with CD than ITB ($P = 0.02$). All three SNPs in IRGM (rs13361189, rs10065172, and rs4958847), one SNP in ATG16L1 (rs2241880) and TNFRSF1A (rs4149570) had a significant difference in frequency in CD compared with ITB and controls ($P < 0.05$).

Table 3 (*Continued*)

	Evidence	Remarks
Serologic		
Quantitative IGRA	Zhao *et al.* 2020 [67]	TB-IGRA ⩾ 100 pg/ml indicated a high possibility of ITB, with a sensitivity of 88% and a specificity of 74%.
Interferon gamma release assay (IGRA)	Sachdeva *et al.* 2023 [68]	For diagnosing ITB, IGRA showed a sensitivity, specificity, positive and negative predictive values of 40.68%, 75.51%, 66.67%, and 51.39%, respectively. The area under the curve of IGRA for ITB diagnosis was 0.66 indicating poor diagnostic accuracy in TB endemic areas.
Enterogenous Microbiotic Markers (ASCA IgG, ASCA IgA, ACCA, Anti-I2 and AMCA)	Jiang *et al.* 2022 [69]	For differentiating CD from ITB, AMCA and Anti-I2 demonstrated AUC of 0.712 and 0.691, with the sensitivity of 71.8% and 64.1%, specificity of 77.8 and 77.8%, respectively. The cut-off parameters of these two antibodies were 45.5 and 0.419.
Antizymogen granule glycoprotein GP2 (aGP2)	Zhang *et al.* 2018 [70]	IgA GP2 exhibited the highest positive likelihood ratio (LR+) of 3.67 in differentiating ileal CD from ITB, followed by IgG GP2 (LR+, 2.94)
Microbiological tests		
GeneXpert MTB/RIF Ultra	Risco *et al.* 2018 [71] Bouzouita *et al.* 2024 [72]	GeneXpert MTB/RIF Ultra has not been evaluated in patients with ITB. Is a potential biomarker for diagnosis of ITB and differentiating ITB from CD.
Tissue biopsy IHC - MPT64 antigen	Fei *et al.* China, 2021 [73]	The sensitivity and specificity of parallelly combined detection of tuberculosis protein MPT64 and Xpert MTB/RIF in diagnosing ITB was 50.0% and 85% respectively.
TB-PCR	Jin *et al.* 2017 [74] INDEX-TB Guidelines, 2016 [75]	TB-PCR has high specificity but very low sensitivity, with variable diagnostic accuracy. Hence, authors of this review support INDEX-TB guidelines [74,75] in recommending against routine use of TB-PCR in clinical practice
Radiological		
Visceral fat/ Subcutaneous fat ratio > 0.63	Yadav *et al.* 2017 [8]	A cut-off of 0.63 for VF/SC ratio in the development cohort had a high sensitivity (82%) and specificity (81%) in differentiating CD and ITB. Similar sensitivity (81%) and specificity (78%) were seen when this cut-off was applied in the validation cohort.
	Seetharaman *et al.* 2023 [29▪▪]	A VF/SF ratio of 0.609 predicted CD with a good sensitivity [75%] and specificity [86.4%] (AUC: 0.795)
Perfusion CT	Seth *et al.* 2023 [30]	Blood Flow and permeability at perfusion CT had 100% sensitivity and 100% specificity, while mean transit time (MTT) had 61.5–100% sensitivity and 70–100% specificity for differentiating ITB from active CD and active from inactive CD.
Dual-layer spectral detector CT enterography	Huang *et al.* 2024 [31]	Quantitative energy spectrum parameters were iodine density (ID), normalized ID (NID), virtual noncontrast (VNC) value, and effective atomic number (Z-eff). Enteric phase NID (AUC, 0.906; $P<0.001$) and portal phase Z-eff (AUC, 0.947; $P<0.001$) had the highest accuracy in differentiating CD from ITB.
Radiomics	Zhu *et al.* 2021 [32]	Clinical radiomics nomogram based on the 9 radiomics signature and two clinical factors had an AUC of 0.96 in training and 0.93 in validation cohort to differentiate CD from ITB.
	Gong *et al.* 2023 [33]	Clinical-radiomic combined model comprising one radiomic signature from intestinal wall, one radiomic signature from LN, involved bowel segments on CTE, and longitudinal ulcer on endoscopy showed an AUC of 0.975 in the training and 0.958 in the validation cohort in differentiating CD from ITB.
	Cheng *et al.* 2024 [77]	The arterial-venous combined deep learning radiomics model for differentiating between CD and ITB showed a high prediction quality with AUCs of 0.800 - 0.885.
Others		
Serial FCP on ATT	Sharma *et al.* 2021 [27]	Serial measurement of FCP at 2 and 6 months of ATT had an AUC of 0.82 for differentiating ITB from other diagnoses.
	Jo *et al.* 2022 [28]	FC levels decreased to below 100 μg/g in all patients after one month of ATT.

ATT, antitubercular therapy; CD, Crohn's disease; ITB, intestinal tuberculosis.

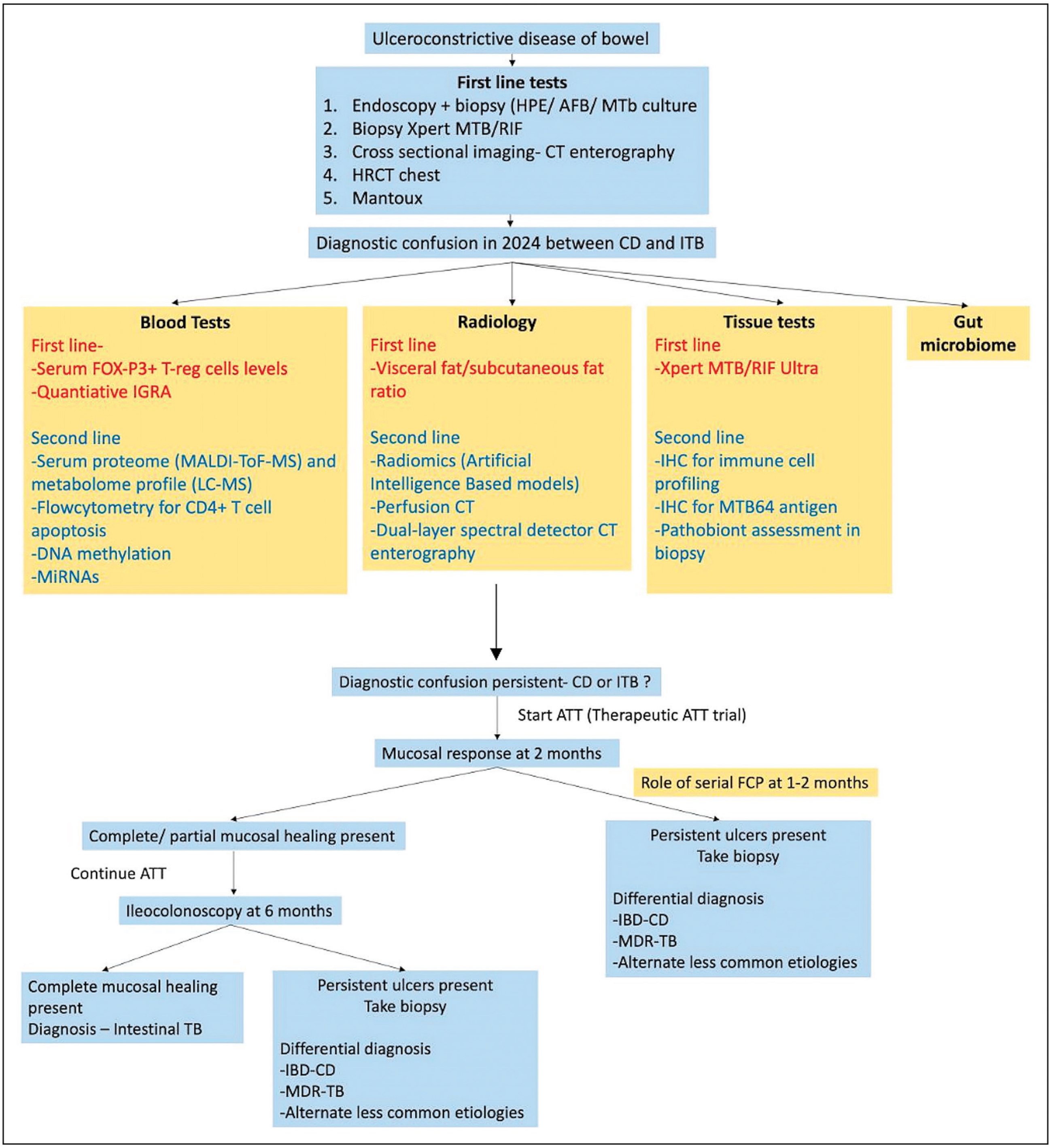

FIGURE 1. Diagnostic algorithm in 2024 to differentiate tuberculosis from Crohn's disease.

with rising incidence of CD in developing countries, and tuberculosis in immunocompromised patients in developed countries, differentiating between the two conditions continues to be a perplexing challenge in a sizable proportion of patients even for experienced clinicians. The numerous diagnostic modalities outlined in this review (Table 3), once validated, promise to augment our diagnostic arsenal for distinguishing between these 2 closely mimicking conditions (Fig. 1). Additionally, the artificial intelligence-based models being developed will further be important pieces in solving this puzzle of ITB vs. CD.

Acknowledgements

None.

Financial support and sponsorship

Indian Council of Medical Research, Center for Advanced Research and Excellence in Intestinal Diseases (grant number 55/4/11/CARE-ID/2018-NCD).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
▪ of special interest
▪▪ of outstanding interest

1. Paustian FF. Tuberculosis of the intestine. In: Bockus HL, editors. Gastroenterology, Vol. 311, 2nd ed. Philadelphia: WB Saunders Co.; 1964.
2. Logan VS. Anorectal tuberculosis. Proc R Soc Med 1969; 62:1227–1230.
3. Pratap Mouli V, Munot K, Ananthakrishnan A, *et al.* Endoscopic and clinical responses to antitubercular therapy can differentiate intestinal tuberculosis from Crohn's disease. Aliment Pharmacol Ther 2017; 45:27–36.
4. Gupta A, Pratap Mouli V, Mohta S, *et al.* Antitubercular therapy given to differentiate Crohn's disease from intestinal tuberculosis predisposes to stricture formation. J Crohns Colitis 2020; 14:1611–1618.
5. ▪ Hilmi IN, Nik Muhamad Affendi NA, Shahrani S, *et al.* High accuracy of a simplified, practical algorithm in differentiating Crohn's disease from intestinal tuberculosis. Dig Dis 2023; 41:581–588.

A practical algorithm consisting of history, examination, ileocolonoscopy with biopsies and tuberculosis workup had an accuracy of 89.6% in initial diagnosis.

6. Makharia GK, Srivastava S, Das P, *et al.* Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. Am J Gastroenterol 2010; 105:642–651.
7. Kedia S, Sharma R, Nagi B, *et al.* Computerized tomography-based predictive model for differentiation of Crohn's disease from intestinal tuberculosis. Indian J Gastroenterol 2015; 34:135–143.
8. Yadav DP, Madhusudhan KS, Kedia S, *et al.* Development and validation of visceral fat quantification as a surrogate marker for differentiation of Crohn's disease and intestinal tuberculosis. J Gastroenterol Hepatol 2017; 32:420–426.
9. Jung Y, Hwangbo Y, Yoon SM, *et al.* Predictive factors for differentiating between Crohn's disease and intestinal tuberculosis in Koreans. Am J Gastroenterol 2016; 111:1156–1164.
10. Li X, Liu X, Zou Y, *et al.* Predictors of clinical and endoscopic findings in differentiating Crohn's disease from intestinal tuberculosis. Dig Dis Sci 2011; 56:188–196.
11. Lei Y, Yi FM, Zhao J, *et al.* Utility of in vitro interferon-(release assay in differential diagnosis between intestinal tuberculosis and Crohn's disease. J Dig Dis 2013; 14:68–75.
12. Roy S, Ghosh S, Banerjee M, *et al.* A combination of circulating microRNA-375-3p and chemokines CCL11, CXCL12, and G-CSF differentiate Crohn's disease and intestinal tuberculosis. Sci Rep 2021; 11:23303.
13. Wang L, Xiong Y, Fu B, *et al.* MicroRNAs as immune regulators and biomarkers in tuberculosis. Front Immunol 2022; 13:1027472.
14. Wu H, Chen Y, Liu T, Shen X. Mo1116 genome-wide DNA methylation profiling in differentiating Crohn's disease from intestinal tuberculosis. Genes Genomics 2022; 44:603–615.
15. Zhang F, Xu C, Ning L, *et al.* Exploration of serum proteomic profiling and diagnostic model that differentiate Crohn's disease and intestinal tuberculosis. PLoS One 2016; 11:e0167109.
16. Ning L, Shan G, Sun Z, *et al.* Serum proteome profiles to differentiate Crohn disease from intestinal tuberculosis and primary intestinal lymphoma: a pilot study. Medicine (Baltimore) 2019; 98:e18304.
17. Rukmangadachar LA, Makharia GK, Mishra A, *et al.* Proteome analysis of the macroscopically affected colonic mucosa of Crohn's disease and intestinal tuberculosis. Sci Rep 2016; 6:23162.
18. ▪ Ma R, Zhu Y, Li X, *et al.* A novel serum metabolomic panel for the diagnosis of Crohn's disease. Inflamm Bowel Dis 2023; 29:1524–1535.

The study identified 5 metabolites which could differentiate CD from other diagnoses with excellent diagnostic accuracy.

19. He C, Wang H, Yu C, *et al.* Alterations of gut microbiota in patients with intestinal tuberculosis that different from Crohn's disease. Front Bioeng Biotechnol 2021; 9:673691.
20. Markandey M, Bajaj A, Vuyyuru SK, *et al.* P709 distinct pattern of gut microbial dysbiosis in Crohn's disease and intestinal tuberculosis – a machine learning-based classification model. J Crohns Colitis 2022; 16 (Suppl 1):i606–i607.
21. Das P, Rampal R, Udinia S, *et al.* Selective M1 macrophage polarization in granuloma-positive and granuloma-negative Crohn's disease, in comparison to intestinal tuberculosis. Intest Res 2018; 16:426–435.
22. Yoo JW, Jo SI, Shin DW, *et al.* Clinical usefulness of immune profiling for differential diagnosis between Crohn's disease, intestinal tuberculosis, and Behcet's disease. Diagnostics 2023; 13:2904.
23. Cardona P, Cardona PJ. Regulatory T cells in *Mycobacterium tuberculosis* infection. Front Immunol 2019; 10:2139.
24. Chen X, Zhou B, Li M, *et al.* CD4+CD25+FoxP3+ regulatory T cells suppress *Mycobacterium tuberculosis* immunity in patients with active disease. Clin Immunol 2007; 123:50–59.
25. Tiwari V, Kedia S, Garg SK, *et al.* CD4+ CD25+ FOXP3+ T cell frequency in the peripheral blood is a biomarker that distinguishes intestinal tuberculosis from Crohn's disease. PLoS One 2018; 13:e0193433.
26. Rampal R, Kedia S, Wari MN, *et al.* Prospective validation of CD4+CD25+FOXP3+ T-regulatory cells as an immunological marker to differentiate intestinal tuberculosis from Crohn's disease. Intest Res 2021; 19:232–238.
27. Sharma V, Verma S, Kumar MP, *et al.* Serial measurements of faecal calprotectin may discriminate intestinal tuberculosis and Crohn's disease in patients started on antitubercular therapy. Eur J Gastroenterol Hepatol 2021; 33:334–338.
28. Jo HH, Kim EY, Jung JT, *et al.* Value of fecal calprotectin measurement during the initial period of therapeutic anti-tubercular trial. Clin Endosc 2022; 55:256–262.
29. ▪▪ Seetharaman J, Srivastava A, Yadav RR, *et al.* Visceral fat indices: do they help differentiate Crohn's disease and intestinal tuberculosis in children? J Crohns Colitis 2023; 17:2026–2032.

Role of visceral fat quantification in differentiating CD from ITB in children was described for first time.

30. Seth R, Gupta P, Debi U, *et al.* Perfusion computed tomography may help in discriminating gastrointestinal tuberculosis and Crohn's disease. Diagnostics 2023; 13:1255.
31. Huang M, Tu L, Li J, *et al.* Differentiation of Crohn's disease, ulcerative colitis, and intestinal tuberculosis by dual-layer spectral detector CT enterography. Clin Radiol 2024; 79:e482–e489.
32. Zhu C, Yu Y, Wang S, *et al.* A novel clinical radiomics nomogram to identify Crohn's disease from intestinal tuberculosis. J Inflamm Res 2021; 14:6511–6521.
33. Gong T, Li M, Pu H, *et al.* Computed tomography enterography-based multiregional radiomics model for differential diagnosis of Crohn's disease from intestinal tuberculosis. Abdom Radiol (NY) 2023; 48:1900–1910.
34. Tong Y, Lu K, Yang Y, *et al.* Can natural language processing help differentiate inflammatory intestinal diseases in China? Models applying random forest and convolutional neural network approaches. BMC Med Inform Decis Mak 2020; 20:248.
35. Choi Yi, Kim YJ, Park DK. Su1787 – development of a deep learning algorithm for differential diagnosis between Crohn's disease and intestinal tuberculosis. Gastroenterology 2019; 156:S-611–S-612.
36. Kim JM, Kang JG, Kim S, Cheon JH. Deep-learning system for real-time differentiation between Crohn's disease, intestinal Behçet's disease, and intestinal tuberculosis. J Gastroenterol Hepatol 2021; 36:2141–2148.
37. Lu K, Tong Y, Yu S, *et al.* Building a trustworthy AI differential diagnosis application for Crohn's disease and intestinal tuberculosis. BMC Med Inform Decis Mak 2023; 23:160.
38. Lu Y, Chen Y, Peng X, *et al.* Development and validation of a new algorithm model for differential diagnosis between Crohn's disease and intestinal tuberculosis: a combination of laboratory, imaging and endoscopic characteristics. BMC Gastroenterol 2021; 21:291.
39. Weng F, Meng Y, Lu F, *et al.* Differentiation of intestinal tuberculosis and Crohn's disease through an explainable machine learning method. Sci Rep 2022; 12:1714.
40. Chen Y, Li Y, Wu M, *et al.* Differentiating Crohn's disease from intestinal tuberculosis using a fusion correlation neural network. Knowl-Based Syst 2022; 244:108570.
41. ▪ Sachan A, Kakadiya R, Mishra S, *et al.* Artificial intelligence for discrimination of Crohn's disease and gastrointestinal tuberculosis: A systematic review. J Gastroenterol Hepatol 2023; 39:422–430.

A systematic review describing the role of artificial intelligence and machine learning in differentiating CD from ITB.

42. Liu X, Li F, Xu J, *et al.* Deep learning model to differentiate Crohn's disease from intestinal tuberculosis using histopathological whole slide images from intestinal specimens. Virchows Arch. 2024 [cited 2024 Mar 14]; Available at: https://link.springer.com/10.1007/s00428-024-03740-9
43. Yu H, Liu Y, Wang Y, *et al.* Endoscopic and histological differentiations between Crohn's disease and intestinal tuberculosis. Digestion 2012; 85:202–209.
44. Dutta AK, Sahu MK, Gangadharan SK, Chacko A. Distinguishing Crohn's disease from intestinal tuberculosis–a prospective study. Trop Gastroenterol 2011; 32:204–209.
45. Liu YY, Chen MK, Cao Z, *et al.* Differential diagnosis of intestinal tuberculosis from Crohn's disease and primary intestinal lymphoma in China. Saudi J Gastroenterol 2014; 20:241.

46. Mao R, Liao WDI, He Y, *et al.* Computed tomographic enterography adds value to colonoscopy in differentiating Crohn's disease from intestinal tuberculosis: a potential diagnostic algorithm. Endoscopy 2015; 47:322–329.
47. Larsson G. Routine diagnosis of intestinal tuberculosis and Crohn's disease in Southern India. World J Gastroenterol 2014; 20:5017–5024.
48. Lee Y, Yang SK, Byeon JS, *et al.* Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy 2006; 38:592–597.
49. Bae JH, Park SH, Ye BD, *et al.* Development and validation of a novel prediction model for differential diagnosis between Crohn's disease and intestinal tuberculosis. Inflamm Bowel Dis 2017; 23:1614–1623.
50. Gan HT, Chen YQ, Ouyang Q, *et al.* Differentiation between intestinal tuberculosis and Crohn's disease in endoscopic biopsy specimens by polymerase chain reaction. Am J Gastroenterol 2002; 97:1446–1451.
51. Pulimood AB, Peter S, Ramakrishna B, *et al.* Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. J Gastroenterol Hepatol 2005; 20:688–696.
52. Kirsch R. Role of colonoscopic biopsy in distinguishing between Crohn's disease and intestinal tuberculosis. J Clin Pathol 2006; 59:840–844.
53. Jin XJ, Kim JM, Kim HK, *et al.* Histopathology and TB-PCR kit analysis in differentiating the diagnosis of intestinal tuberculosis and Crohn's disease. World J Gastroenterol 2010; 16:2496–2503.
54. Ye Z, Lin Y, Cao Q, *et al.* Granulomas as the most useful histopathological feature in distinguishing between Crohn's disease and intestinal tuberculosis in endoscopic biopsy specimens. Medicine (Baltimore) 2015; 94:e2157.
55. Kedia S, Sharma R, Sreenivas V, *et al.* Accuracy of computed tomographic features in differentiating intestinal tuberculosis from Crohn's disease: a systematic review with meta-analysis. Intest Res 2017; 15:149.
56. Limsrivilai J, Shreiner AB, Pongpaibul A, *et al.* Meta-analytic Bayesian model for differentiating intestinal tuberculosis from Crohn's disease. Am J Gastroenterol 2017; 112:415–427.
57. Zhao XS, Wang ZT, Wu ZY, *et al.* Differentiation of Crohn's disease from intestinal tuberculosis by clinical and CT enterographic models. Inflamm Bowel Dis 2014; 20:916–925.
58. Zhang T, Fan R, Wang Z, *et al.* Differential diagnosis between Crohn's disease and intestinal tuberculosis using integrated parameters including clinical manifestations, T-SPOT, endoscopy and CT enterography. Int J Clin Exp Med 2015; 8:17578–17589.
59. Huang X. Differences in clinical features of Crohn's disease and intestinal tuberculosis. World J Gastroenterol 2015; 21:3650–3656.
60. Kedia S, Madhusudhan KS, Sharma R, *et al.* Combination of increased visceral fat and long segment involvement: Development and validation of an updated imaging marker for differentiating Crohn's disease from intestinal tuberculosis. J Gastroenterol Hepatol 2018; 33:1234–1241.
61. Wu X, Huang H, Hou H, *et al.* Diagnostic performance of a 5-marker predictive model for differential diagnosis between intestinal tuberculosis and Crohn's disease. Inflamm Bowel Dis 2018; 24:2452–2460.
62. He Y, Zhu Z, Chen Y, *et al.* Development and validation of a novel diagnostic nomogram to differentiate between intestinal tuberculosis and Crohn's disease: a 6-year prospective multicenter study. Am J Gastroenterol 2019; 114:490–499.
63. Watermeyer G, Thomson S. Differentiating Crohn's disease from intestinal tuberculosis at presentation in patients with tissue granulomas. S Afr Med J 2018; 108:399–402.
64. Zeng S, Lin Y, Guo J, *et al.* Differential diagnosis of Crohn's disease and intestinal tuberculosis: development and assessment of a nomogram prediction model. BMC Gastroenterol 2022; 22:461.
65. Nayak SS, Shetty MV, Pai CG, *et al.* Apoptosis in peripheral blood lymphocytes in intestinal tuberculosis and Crohn's disease: Implications to diagnostic differentiation. Indian J Gastroenterol 2020; 39:338–345.
66. Khan IA, Nayak B, Markandey M, *et al.* Differential prevalence of pathobionts and host gene polymorphisms in chronic inflammatory intestinal diseases: Crohn's disease and intestinal tuberculosis. PLoS One 2021; 16:e0256098.
67. Zhao Y, Xu M, Chen L, *et al.* Levels of TB-IGRA may help to differentiate between intestinal tuberculosis and Crohn's disease in patients with positive results. Ther Adv Gastroenterol 2020; 13:175628482092200.
68. Sachdeva K, Kumar P, Kante B, *et al.* Interferon-gamma release assay has poor diagnostic accuracy in differentiating intestinal tuberculosis from Crohn's disease in tuberculosis endemic areas. Intest Res 2023; 21:226–234.
69. Jiang M, Zeng Z, Chen K, *et al.* Enterogenous microbiotic markers in the differential diagnosis of Crohn's disease and intestinal tuberculosis. Front Immunol 2022; 13:820891.
70. Zhang S, Luo J, Wu Z, *et al.* Antibodies against glycoprotein 2 display diagnostic advantages over ASCA in distinguishing CD from intestinal tuberculosis and intestinal Behçet's disease. Clin Transl Gastroenterol 2018; 9:e133.
71. Perez-Risco D, Rodriguez-Temporal D, Valledor-Sanchez I, Alcaide F. Evaluation of the Xpert MTB/RIF ultra assay for direct detection of *Mycobacterium tuberculosis* complex in smear-negative extrapulmonary samples. J Clin Microbiol 2018; 56:e00659–e00718.
72. Bouzouita I, Ghariani A, Dhaou KB, *et al.* Usefulness of Xpert MTB/RIF Ultra for rapid diagnosis of extrapulmonary tuberculosis in Tunisia. Sci Rep 2024; 14:2217.
73. Fei B, Zhou L, Zhang Y, *et al.* Application value of tissue tuberculosis antigen combined with Xpert MTB/RIF detection in differential diagnoses of intestinal tuberculosis and Crohn's disease. BMC Infect Dis 2021; 21:498.
74. Jin T, Fei B, Zhang Y, He X. The diagnostic value of polymerase chain reaction for *Mycobacterium tuberculosis* to distinguish intestinal tuberculosis from crohn's disease: a meta-analysis. Saudi J Gastroenterol 2017; 23:3.
75. Central TB Division Ministry of Health and Family Welfare, Government of India. Index-TB guidelines: guidelines on extra-pulmonary tuberculosis in India. 2016.
76. Central TB Division Ministry of Health and Family Welfare, Government of India. Training module on extrapulmonary tuberculosis 2023.
77. Cheng M, Zhang H, Huang W, *et al.* Deep learning radiomics analysis of CT imaging for differentiating between Crohn's disease and intestinal tuberculosis. J Imaging Inform Med. 2024 [cited 2024 Apr 17]; Available at: https://link.springer.com/10.1007/s10278-024-01059-0
78. Park JJ, Park SJ, Hong SP, *et al.* Su1932 differential diagnosis between intestinal tuberculosis and Crohn's disease by ileocolonoscopic findings. Gastroenterology 2012; 142:S539.
79. Li YP, Lu TY, Huang FR, *et al.* Differential diagnosis of Crohn's disease and intestinal tuberculosis based on ATR-FTIR spectroscopy combined with machine learning. World J Gastroenterol 2024; 30:1377–1392.
80. ■ Lin J, Zhu S, Yin M, *et al.* Few-shot learning for the classification of intestinal tuberculosis and Crohn's disease on endoscopic images: a novel learn-to-learn framework. Heliyon 2024; 10:e26559.

AI based zero shot algorithm to differentiate CD from ITB.