Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Third, we interrogated the cell-type–specific contexts of intestinal *ACE2* and *TMPRSS2* expression. Using bulk RNA sequencing data, we quantified cell-type proportions and observed that an enrichment of epithelial cells is associated with increased expression of *ACE2* and *TMPRSS2* in both ileum and colon (all $P < .004$). Using single-cell RNA sequencing data from colonic biopsies, we observed that *TMPRSS2* is mainly expressed by absorptive enterocytes, and that intestinal inflammation is associated with increased *TMPRSS2* expression within absorptive enterocytes ($P = 3.2 \times 10^{-22}$). *ACE2* was also primarily expressed by absorptive enterocytes, but expression was not affected by intestinal inflammation.

In conclusion, ACE2 and TMPRSS2 are key proteins for cellular entry of SARS-CoV-2, and are highly expressed in the intestinal mucosa. Next to intestinal inflammation, age, sex, and anatomic location, the use of tumor necrosis factor alpha antagonists and aminosalicylates influence intestinal expression of *TMPRSS2* as well. We demonstrate that intestinal inflammation is associated with an increased expression of *TMPRSS2* in absorptive enterocytes, suggesting that the increased expression is not merely an effect of change in cellular composition during inflammation. Altered intestinal expression could render patients with IBD particularly susceptible to COVID-19 and absorptive enterocytes could provide targets for interventional studies. Indeed, clinical studies are needed to monitor the impact of COVID-19 on patients with IBD.

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Conflicts of interest
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Reply. We read with great interest the letter by Bangma et al, who corroborated our previous findings, and extended these by demonstrating increased expression of *TMPRSS2* in the ileal mucosa of patients with inflammatory bowel disease (IBD) receiving antagonists of tumor necrosis factor α (TNFα). Bangma et al also demonstrate that 5-aminosalicylates (5-ASA) use may be associated with increased colonic *TMPRSS2* expression.

The translational implications of these emerging data in terms of the prediction of susceptibility and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in IBD are now key issues, which remain to be established. The observed effect of anti-TNFα therapy on *TMPRSS2* expression in Bangma's report are difficult to reconcile with conclusions from a recent IBD meta-analysis,[1] wherein anti-TNFα agents associated with a 3-fold decrease in the risk of hospitalization for coronavirus disease 2019 (COVID-19). Further investigation is clearly required, focusing both on the gut as well as extraintestinal effects, notably in the respiratory system. For example, can it be that any "negative" effects of TMPRSS2-related facilitation of viral entry in the intestine are more than offset by the effects of TNF blockade in curtailing inflammation in the lungs? This question and related uncertainties in assessing the translational relevance will need to be answered by exploring gene function and expression in parallel with clinical observations, including outcomes from ongoing trials of infliximab in COVID-19 (NCT04425538, NCT04593940).

The potential contribution of 5-ASA therapy to the course of COVID-19 is also proving to be complex to unravel. The meta-analysis revealed an increased risk of COVID-19 hospitalization in IBD related to 5-ASA therapy (by 59%).[1] In the SECURE-IBD registry, severe COVID-19 was more frequent in patients receiving 5-ASA (adjusted odds ratio of 1.7).[2] In discussing the initial SECURE-IBD report,[3] Magro et al pointed out[4] that binding of peroxisome proliferator-activated receptor gamma by 5-ASA could induce *ACE2* and inhibit *TMPRSS2* expression. Here, Bangma et al, to the contrary, indicate increased colonic *TMPRSS2* expression in patients with ulcerative colitis receiving aminosalicylates. Again, we suggest that consideration of *TMPRSS2* expression in the ileum might not be key for the systemic course of COVID-19.

We suggest that it is important to consider the implications and pathogenesis of multiorgan involvement in COVID-

19. It is possible that the crucial interaction between 5-ASA and COVID-19 determining outcome does not occur in the intestine, but in the lungs. Mesalazine-induced respiratory disease is unusual, but well-recognised, and may be severe.[4] It is interesting to consider the hypothesis that SARS-CoV-2 infection might decrease the threshold for 5-ASA–associated respiratory disease. In susceptible patients, salicylates could augment the production of cysteinyl leukotrienes, thus leading to a stronger inflammatory response. If this hypothesis is valid, then leukotriene antagonists might prove beneficial in patients on 5-ASA with severe COVID-19, or in COVID-19 overall. Hopefully, the trial of montelukast in COVID-19 will provide much-needed answers to this question (NCT04389411).

Although ACE2 and TMPRSS2 are known to be main molecules of SARS-CoV-2 entry, other molecular modifiers also are involved; more recently neuropilin-1 (NRP1) was implicated.[5] Our preliminary re-analysis highlights increased *NRP1* expression both in active Crohn's disease of the ileum and in the mucosa of active ulcerative colitis in data from Vancamelbeke et al.[6] A greater expression of *NRP1* in Crohn's disease of the ileum compared with ulcerative colitis or controls can be found in data from Haberman et al.[7] In ileal biopsies of anti–TNFα-refractory Crohn's disease patients gathered by Peters et al,[8] inflamed ileal mucosa had a greater expression of *NRP1* relative to uninflamed tissue ($P = .002$).[8] Of interest, oncostatin M receptor, which allows oncostatin M to exhibit TNFα-like effects in the presence of anti-TNFα, consistently and strongly correlated with *NRP1* in the ileal and colonic mucosa in these 3 datasets (Pearson's $r > 0.7$ and $P < 10^{-22}$).

Overall, the evidence for the increased susceptibility to SARS-CoV-2 entry in the inflamed intestine is growing, and our understanding is further strengthened by additional details, such as involvement of specific cell types described by Bangma et al. Defining the relevance of these observations to clinical observation and practice represents an important area for immediate translational research in IBD, and more generally in patients with multisystem COVID-19 illness.

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The Usefulness of Fecal Calprotectin in the era of the COVID-19 Pandemic

Dear Editors:

The coronavirus disease 2019 (COVID-19) pandemic has caused significant modifications in patient management, especially for chronically immunocompromised individuals. With approximately 3 million patients in the United States with inflammatory bowel disease (IBD) and the absence of substantial data in the era of coronavirus,