
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.

higher variant allele frequencies (VAFs) compared to "subclonal" mutations in gastric and colorectal cancer, which offers opportunities for detection in ctDNA.[3,4] Multiregional sequencing of ESCCs also revealed that "clonal" mutations had high VAFs in all cases.[5] In our study, the clinical validity of ctDNA monitoring was confirmed in 91% (31/34) of ESCC patients, using fewer than 3 mutations per patient. Therefore, the selection of high-VAF mutations may be practical as a countermeasure for ctDNA analysis, which is still likely to reflect tumor heterogeneity.

On the other hand, as Du et al point out, it seems that there are some types of tumor relapse where it is difficult to detect ctDNA. It was suggested that disseminated recurrence, as seen in EC_10, may have a different DNA fragment-releasing mechanism and showed lower ctDNA levels compared to solid lesions.[6] Moreover, dormant cells induced in response to treatment (EC_24) may not have released ctDNA, despite the fact that residual cancer was observed during image diagnosis. Despite a high tumor volume, 3 cases (EC_25, EC_26, and EC_33) were ctDNA negative before treatment. The VAFs of all mutations in the primary tumors were lower than 10%. EC_33 showed ctDNA positivity just before death. It is possible that ctDNAs of mutations with low VAF in the tumor subpopulation become detectable when the tumor burden markedly increases. However, the clinical benefit of ctDNA monitoring for patients with undetectable pretreatment levels of ctDNA may be limited to a long-term follow-up for relapse prediction (EC_1). Continuous ctDNA positivity is recognized as a clinical warning sign in our ctDNA monitoring system. Regarding transient positivity in EC_21, we hypothesized that the patient had minimal residual disease when ctDNA positive but that the disease was cleared by the immune system.

Third, it has been reported that *ZNF750* is one of the driver genes for ESCC, and its "clonal" mutation has been observed.[5,7] *ZNF750* mutations also have been observed throughout the gene without hotspots in approximately 10% of ESCC cases.[1,2,5,7] Nonetheless, *ZNF750* mutations in ctDNA might be well traceable in patients (EC_13, EC_29, and EC_32) who had the highest VAFs in *ZNF750* from the primary tumor. In contrast, *TP53* mutation is observed in more than 90% of ESCC cases, and many of them are recurrent among patients with cancer. We have established dPCR primer/probe sets for more than 100 *TP53* mutations. Furthermore, in ESCC, "clonal" mutations most frequently occurred in *TP53*.[7] Among 17 cases monitored with multiple ctDNA mutations, *TP53* ctDNA mutations were the most quantifiable, even if the VAFs of other gene mutations were higher than that of *TP53* in the tumor. Therefore, we have prioritized *TP53* mutations with high VAF for ctDNA monitoring in ESCC.

Information about early relapse prediction, treatment efficacy evaluation, and relapse-free corroboration can be obtained by ctDNA monitoring in patients with ESCC. Although further studies are needed to fully establish the clinical utility of ctDNA, we believe that patient-specific ctDNA monitoring by dPCR is the most refined tumor marker at present.

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# Winter Is Coming and COVID-19 Vaccine Is Available! The Role of Gastroenterologist in Increasing COVID-19 Vaccine Acceptability Among IBD Patients

Dear Editors:

We read with interest the inspiring and timely commentary by Melmed et al[1] in which they explained the benefits and provided practical recommendations to get patients with inflammatory bowel disease (IBD) vaccinated for influenza and pneumococcus, particularly during the COVID-19 pandemic. Furthermore, the authors realistically described the future COVID-19 vaccination scenario for

patients with IBD. The intrinsic immune-mediated nature of, as well as the need for, immunomodulating or biologic therapies in patients with IBD has raised several questions about the safety and efficacy of the COVID-19 vaccine.[1]

In this context, we would like to dissect some specific points covered in this commentary, also considering the new available data coming from recently published phase III trials.[2] First, we believe that, given the unprecedented development rapidity of COVID-19 vaccines, the answers on their performance in particular groups of patients (eg, patients with IBD) will be addressed over time. At the beginning of December 2020, the first COVID-19 vaccine (Pfizer-BioNTech vaccine) was approved in the United Kingdom, then in the United States, and finally in the European Union. The vaccination campaign started from the front-line health care personnel, home care staff, and residents.[3] Subsequently, a second mRNA vaccine (Moderna) has also been approved in the United States.[4] We are now waiting for the approval of a third vaccine with a different mechanism of action (Oxford-AstraZeneca vaccine), consisting of a replication-deficient chimpanzee adenoviral vector containing the gene for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein.[2] On one hand, the efficacy data coming from phase III trials certainly have fueled the expectation of drastically reducing the spread of SARS-CoV-2 infection. On the other hand, no specific data for patients with IBD are yet available in these studies. We still need to extrapolate concepts of safety and efficacy from studies conducted in IBD populations with different vaccines. Undoubtedly new accumulating reports obtained from real-world data of vaccinated patients in appropriate post-marketing registers with eventual adverse reactions will clarify their safety both in the short-, and especially, long-term.[3] In addition, the possibility of having different vaccines obtained from distinctive platforms will also allow their comparison and therefore the identification of the most effective and safe solution according to demographic characteristics and comorbidities, including IBD. Another crucial point is how to achieve the highest acceptance rate for the COVID-19 vaccine according to a predefined list of priorities, even in patients with immune-mediated inflammatory diseases (ie, IBD). This will not consider those with earlier access to the vaccine for reasons not connected to IBD, such as age, work activity, or presence of other comorbidities. Factors associated with the likelihood of accepting COVID-19 vaccination have been studied extensively in large population cohorts in order to drive public health information campaigns and to address vaccine hesitancy.[5] The role of health care providers in recommending the vaccination results among the most significant factors in driving the compliance to vaccination.[6] This means that an essential task in reducing IBD patients' hesitancy to get vaccinated against COVID-19 will be played by gastroenterologists who will have to educate and inform their patients on the usefulness of vaccination, as already reported in the past for other vaccine recommendations.[7] Again, on this point, we believe that the open declaration of having been vaccinated (eg, through the use of "I'm vaccinated" pins or stickers or social media campaigns) would be an important motivator tool in orienting patients' choice toward vaccination.[8] Finally, as part of the exhaustive information, gastroenterologists will have to alert patients that the vaccine does not give 100% protection against COVID-19 and that we are not sure that it prevents the transmission of SARS-CoV-2. It will be essential to follow the preventive measures adopted so far until herd immunity will be achieved.

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**Reply.** We thank Papa et al for their thoughtful comments about our commentary. The broad considerations about these new vaccines are being actively discussed in many populations, and Papa et al outline very important concerns. First, we agree with their assessment that the exclusion of patients with inflammatory bowel disease (IBD) who are receiving