Figure 1 (facing page). Two Predicted Truncated Proteins Generated by Nonsense Mutations of Human *ABCB1*.

Panel A shows the location of the altered residues on the two-dimensional structure of human ABCB1 (NP_000918.2). The protein contains 1280 residues (circles), organized in 12 transmembrane domains, and canonical nucleotide-binding domains 1 and 2 (NBD1 and NBD2) with two symmetric ATP-binding sites, essential for coupling ATP hydrolysis to drug efflux pump activity. ABC-specific conserved sequence motifs (i.e., A loop, Walker A, Q loop, ABC signature [yellow], Walker B, D loop, and H switch) in the NBD1 domain (blue) and NBD2 domain (green) are shown. The altered residues (Arg794 and Il1018) are indicated by arrows. The p.(Arg794Ter) substitution generates a stop codon (asterisk) and a truncated protein of 793 residues. The p.(Ile1018ThrfsTer8) deletion causes a frameshift starting from the Ile1018 codon and a new reading frame ending 8 amino acids downstream, resulting in a truncated protein of 1024 residues. The topologic plot was generated with the use of Protter software. SNP denotes single-nucleotide polymorphism. Panel B shows the results of the family *ABCB1* genetic study. Genetic screening of *ABCB1* (NC_000007.13, NM_000927.4) was undertaken in three members of the family with the use of next-generation sequencing (Agilent SureSelectQXT reagent for Illumina MiSeq). The mutations detected were p.(Arg794Ter) and p.(Ile1018ThrfsTer8) in exons 20 and 25, respectively. These mutations were subsequently confirmed with the use of Sanger sequencing. The proband (arrow) had inherited the chromosome bearing the c.2380C→T allele from his mother and the chromosome with the c.3053_3056delTTGA deletion from his father. Genetic analysis was not performed in the younger brother because of ethical reasons. The equal sign denotes a normal allele.

after the administration of a usual dose. The seriousness of the intoxication in the child implies that caution is warranted regarding medical prescriptions of ivermectin and other ABCB1 substrates (see the Supplementary Data 2 section in the Supplementary Appendix). Our findings highlight the importance of pharmacovigilance and the benefit of *ABCB1* genotyping to identify clinically significant *ABCB1* mutations related to a well-circumscribed phenotype and to explain an unexpected response to a drug.

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New-Onset Diabetes in Covid-19

TO THE EDITOR: There is a bidirectional relationship between Covid-19 and diabetes. On the one hand, diabetes is associated with an increased risk of severe Covid-19. On the other hand, new-onset diabetes and severe metabolic complications of preexisting diabetes, including diabetic ketoacidosis and hyperosmolarity for which exceptionally high doses of insulin are warranted, have been observed in patients with Covid-19.[1-3] These manifestations of diabetes pose challenges in clinical management and suggest a complex pathophysiology of Covid-19–related diabetes.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19, binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, and the kidneys.[4] Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of disease.

There are also several precedents for a viral

cause of ketosis-prone diabetes, including other coronaviruses that bind to ACE2 receptors.[5] Greater incidences of fasting glycemia and acute-onset diabetes have been reported among patients with SARS coronavirus 1 pneumonia than among those with non-SARS pneumonia.[5]

In the aggregate, these observations provide support for the hypothesis of a potential diabetogenic effect of Covid-19, beyond the well-recognized stress response associated with severe illness. However, whether the alterations of glucose metabolism that occur with a sudden onset in severe Covid-19 persist or remit when the infection resolves is unclear. How frequent is the phenomenon of new-onset diabetes, and is it classic type 1 or type 2 diabetes or a new type of diabetes? Do these patients remain at higher risk for diabetes or diabetic ketoacidosis? In patients with preexisting diabetes, does Covid-19 change the underlying pathophysiology and the natural history of the disease? Answering these questions in order to inform the immediate clinical care, follow-up, and monitoring of affected patients is a priority.

To address these issues, an international group of leading diabetes researchers participating in the CoviDIAB Project have established a global registry of patients with Covid-19–related diabetes (covidiab.e-dendrite.com). The goal of the registry is to establish the extent and phenotype of new-onset diabetes that is defined by hyperglycemia, confirmed Covid-19, a negative history of diabetes, and a history of a normal glycated hemoglobin level. The registry, which will be expanded to include patients with preexisting diabetes who present with severe acute metabolic disturbance, may also be used to investigate the epidemiologic features and pathogenesis of Covid-19–related diabetes and to gain clues regarding appropriate care for patients during and after the course of Covid-19. Given the very short history of human infection with SARS-CoV-2, an understanding of how Covid-19–related diabetes develops, the natural history of this disease, and appropriate management will be helpful. The study of Covid-19–related diabetes may also uncover novel mechanisms of disease.

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Randomized Trial of Lactin-V to Prevent Recurrence of Bacterial Vaginosis

TO THE EDITOR: In their trial of *Lactobacillus crispatus* CTV-05 (Lactin-V), Cohen et al. (May 14 issue) offer hope for the prevention of bacterial vaginosis.[1] The protective effect of the treatment was modest, similar to twice-weekly metronidazole,[2,3] but the *L. crispatus* CTV-05 strain could still be detected in 48% of participants 13 weeks after the last administration. This finding is encouraging, but in order to interpret the effects of Lactin-V properly, we would like to see additional data. First, previous trials of lactobacilli-containing vaginal probiotics have shown large variability in treatment responses among women, as well as fluctuations in response in individual women, over time.[4] Cohen et al. report a cumulative incidence according to treatment group, thereby overlooking these variabilities. Second, sequencing or other data on the composition of the molecular vaginal microbiome — preferably quantified — are essential for interpretation.[3,4] Unlike microscopy, molecular methods can differentiate between autologous and biotherapeutic lactobacilli, which enables microbiome data obtained at all trial visits, including those that occurred during treatment with Lactin-V, to be used in longitudinal modeling. Molecular methods also enable estimation of the relative abundance of lactobacilli and bacterial vaginosis–associated anaerobes over time. Clinical symptoms are important outcomes in their own right, but microscopy-based Amsel criteria and Nugent scores should be accompanied by molecular data.

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TO THE EDITOR: Cohen et al. report on a potential treatment for recurrent bacterial vaginosis. Women arrived at the trial screening clinic. (I could not find a description of the way in which they were recruited.) Bacterial vaginosis was diagnosed on the basis of the Amsel criteria and the Gram's staining–based Nugent score; the presence of symptoms was not required for diagnosis. I could not find how many participants had symptoms at entry nor whether treatment affected the symptoms in the participants who had them. Some symptoms of bacterial vaginosis were reported as adverse events in some participants.

The U.S. Preventive Services Task Force recommends against screening for bacterial vaginosis in pregnant women who are not at risk for preterm delivery; for pregnant women who have such a risk, no recommendation is made, because current evidence is insufficient.[1] I could find no recommendation for or against screening in nonpregnant women.

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