be expected to have coeliac disease. I hope that the authors can confirm that some at least were diagnosed and given appropriate management.

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References

Response
Sir,
We appreciate Dr Harvey’s interest in our paper, and wholeheartedly agree that coeliac disease is an important cause of iron-deficiency anaemia; this diagnosis will have been considered and pursued where appropriate in the patients in our study. However, the purpose of our study was not to expound every presumed cause of iron-deficiency anaemia in our large series of patients. Such a report would not have added any new information to the existing literature on iron-deficiency anaemia. Rather, our purpose was to compare diagnostic yields for malignant disease from upper and lower gastrointestinal investigation among patients presenting with iron-deficiency anaemia and, more importantly, to compare patient outcomes following a diagnosis of upper or lower gastrointestinal malignancy as a cause for the anaemia.

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AIDS and the Black Death
Sir,
Cohn and Weaver1 assert that recent publications suggesting that the medieval Black Death could be responsible for the origin of the CCR5-Δ32 allele among present-day descendents parallels the severity of the Black Death in 1348…’ and ‘it is erroneous to assert that the plague mortalities exhibit a north–south cline; rather the opposite seems to be the case’. It is unclear who is supposed to have made these assumptions, or asserted this north–south cline. Published research indicates such assumptions to be unsubstantiated and counter to modern Black Death understanding.

Cohn and Weaver argue that if the Black Death were responsible for the spread of the CCR5-Δ32 allele, then present-day frequencies of the allele should correlate positively with recorded mortality during the Black Death. As Italy suffered greater mortality than Scandinavia during the time of the Black Death, yet but has a lower sampled CCR5-Δ32 allele frequency, the Black Death cannot be responsible. However, it is not clear that this argument is conclusive.

Firstly, it is not obvious whether we should expect high Black Death mortality to correlate with high levels of CCR5-Δ32 (because of the Black Death selectively killing those who lacked the allele) or low levels (because populations lacking the allele would be more at risk from the disease). In other words, how much the distribution has been shaped by selection, and how much it reflects pre-Black Death variation. As we do not know the frequency of the CCR5-Δ32 allele in European populations at the time of the Black Death, this question seems unanswerable.

Secondly, it is unclear to what extent the present-day distribution of the allele reflects that 700 years ago. It is general knowledge, for example, that immigration and population mixing over that time have been far more pronounced in southern and central Europe than in Scandinavia. Over time, migration would be expected to dilute selection effects from disease, once those diseases were no longer epidemic. ‘Black Death’ epidemics in Scandinavia continued well beyond the time at which they died out in southern Europe.2 As Cohn and Weaver note, Finland did not experience the plague until 1440, almost 100 years after the disease entered southern Europe. This would tend to favour a higher level of CCR5-Δ32 allele in Scandinavia, as observed. Other diseases may also have affected this distribution, although modelling suggests that smallpox3 could not have elevated CCR5-Δ32 allele frequencies to those witnessed in Europe today.3

Martinson et al.6 found a cline of the indigenous population demonstrating detectable levels (>1.5%) of the CCR5-Δ32 allele, from central Asia through southern Europe and extending up to the Arctic.
The greatest recorded historical epidemic. More questions than answers about the world’s relationship between the Black Death and the CCR5-Δ32 allele seems at best premature. In time, the posited connection between plague and the HIV-resistant allele may indeed turn out to be a red herring. For now, multiple lines of research continue to raise more questions than answers about the world’s greatest recorded historical epidemic.

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References
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Response

Sir,

Dr. Bossak alleges that ‘it is unclear who is supposed to have made these assumptions’—that the Black Death provoked a genetic shift that bestowed greater resistance to HIV for Europeans, and in particular those from northern Europe—we think our references leave no doubt as to who supports this thesis (references 1–5, 7–10 from the original article).

Dr. Bossak asserts: ‘Cohn and Weaver argue that if the Black Death were responsible for the spread of the CCR5-Δ32 allele, then present-day frequencies of the allele should correlate positively with recorded mortality during the Black Death’. We do not make any such positive claim; rather, we have questioned those who have assumed that Black Death mortalities followed a north–south cline matching that of the geographical distribution of CCR5-Δ32 in present-day descendants. By turning to historical research (references 15, 17, 27, 28, 29, 31, 32, 34 and particularly 16 from the original article, which relies on >40 000 death records across Europe) we show that the Black Death mortalities as well as plague mortalities through the early modern period more likely reflect the opposite cline, with the highest mortalities most often recorded in the Mediterranean and little or no evidence of plague in the highlands of Scotland or the northern parts of Scandinavia and especially Finland.

Dr. Bossak also raises questions about using genotype evidence from present-day descendants to study characteristics of historical and pre-historical populations, as though we were the pioneers in such research and methodology. Unfortunately, we cannot make any such grandiose claims. With regard to the question of CCR5 distributions and the Black Death, we have pointed out the limitations of this particular genotype evidence (original article, referenced above, p. 501). Those who developed these methods, however, are aware of the problems of subsequent migration. Indeed, several decades ago, scientists such as Luigi Cavalli-Sforza used such evidence and methods to establish new findings about global migration and long-term transcontinental integration and communication of races and societies in pre-historical times. More recently, his students and others have devised genetic methods for distinguishing the effects of recent immigration among populations.

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