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Viral success for Grail but not with core tech

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Grail has proven that its DNA-based blood test can be used to screen for cancer. However, the DNA it has used to identify patients with nasopharyngeal carcinoma was not shed by the tumour itself. Instead the test picked up DNA from the Epstein-Barr virus (EBV), the organism which causes the condition.

The Illumina spinout could launch the test in southeast Asia in the coming months, whereupon it will become Grail's first commercial product. This is good news in itself, but it represents a divergence from Grail's core technology of detecting circulating tumour DNA.

Feasible

Nasopharyngeal carcinoma is far more prevalent in southern China, including Hong Kong, than in other areas; 61% of cases diagnosed each year occur in this region compared with 1% in northern Europe, the US and Japan combined. The study of Grail's EBV test was conducted by Hong Kong-based Cirina, acquired by Grail in June.

Cirina's – now Grail's – test was used to screen 20,174 asymptomatic individuals and detected EBV DNA in plasma samples obtained from 1,112 of them. EBV DNA in plasma is an established marker for nasopharyngeal carcinoma but can also occur transiently in patients who come down with the virus but do not develop cancer. It was thus necessary to re-test patients four weeks later to find those in whom the EBV DNA persisted.

The data, published in the *New England Journal of Medicine*, showed that 309 patients had positive results on repeated tests, and 300 underwent further examination with endoscopic examination and/or MRI. Nasopharyngeal carcinoma was ultimately diagnosed in 34 patients.

A factor in the test's favour is that it permitted diagnoses to be made earlier than they might otherwise have been. Nasopharyngeal carcinoma is fairly easy to cure if caught early enough, and the screened patients had a significantly higher proportion of early disease – stage I or II – compared with historical controls (71% vs. 20%). 16 patients (47%) had stage I disease at diagnosis, a much higher rate than the roughly 6% reported in literature.

Cancer developed in only one of the 19,865 screen-negative individuals within a year of testing, giving a negative predictive value for the screen of 99.995%. With 275 false positives to 34 true, however, the test does not appear enormously specific – its positive predictive value was just 11%. But as an initial, low-cost screening test – compared with endoscopy and MRI – it does not have to be.

Trial results		
Finding	**Screen-positive (308)**	**Screen-Negative (19,865)**
Confirmed nasopharyngeal carcinoma by the screening protocol or nasopharyngeal carcinoma reported to have developed within 1yr	34	1
No nasopharyngeal carcinoma within 1 yr after screening	274	19,864
Sensitivity	97.1% (95% CI 95.5–98.7)	
Specificity	98.6% (95% CI 98.6–98.7)	
Positive predictive value	11.0% (95% CI 10.7–11.3)	
Negative predictive value	99.995% (95% CI 99.99–100.00)	
Proportion of stage I/II disease in the 34 cases of nasopharyngeal carcinoma identified by screening	70.6% (95% CI 69.6–72.5)	
Source: NEJM.		

The blood test costs $30, compared with $80 for endoscopy and $1,000 for MRI. According to the researchers, to detect one case, 593 participants would need to be screened at a cost of $28,600. They state that this would be feasible in regions with a high incidence of the disease.

In an editorial commenting on the results, Richard Ambinder, an oncologist at Johns Hopkins School of Medicine, wrote that the findings were clinically important and the data suggest that lives had been saved by the screening.

Leerink analysts believe that Grail will launch a nasopharyngeal carcinoma screen in Asian markets in the near to medium term.

Implications

The success of this blood test says little or nothing about Grail's core technology. This test employs PCR rather than Grail's USP, next-generation sequencing, since deep sequencing is not necessary for the small EBV genome.

Moreover, nasopharyngeal tumours are stuffed with EBV DNA: a single tumour cell might have 50 copies of the virus's genome. If Grail wants to screen for a non-viral cancer – breast cancer, for instance, in which it has begun a 120,000-patient study – it will only have one copy per cell.

Grail's ultimate goal is to use next-gen sequencing to screen healthy people for unsuspected cancer by detecting tumour DNA – liquid biopsy. The test it has gained from Cirina uses a different technology to find more plentiful DNA from a different source. A win is a win, but when it comes to its stated mission, Grail still has much to prove.

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