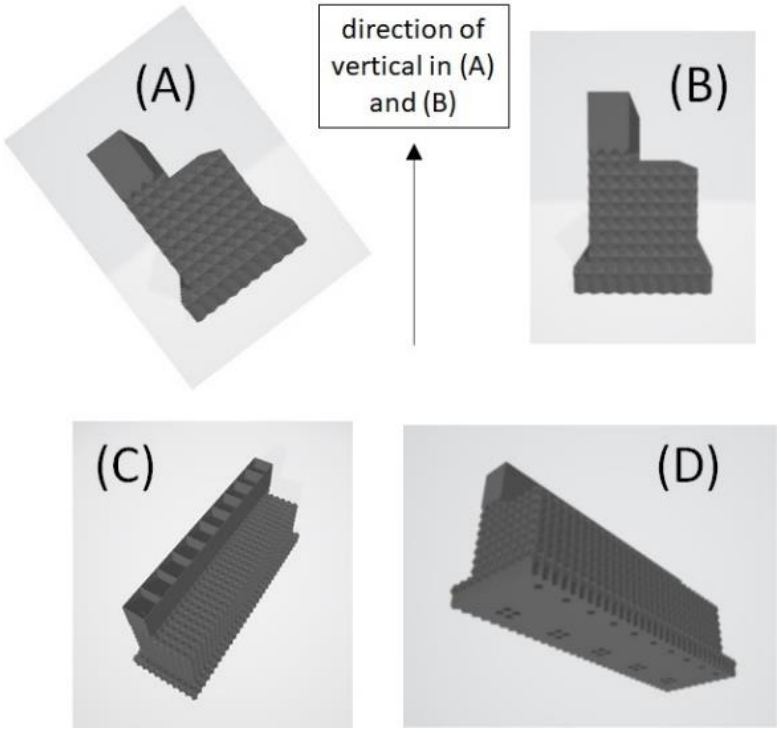
Group testing equipment designs for Covid-19 (or other epidemiological) testing

The development and roll-out of Covid-19 vaccines has substantially diminished the impact of the Covid-19 pandemic in many but not all countries. Where vaccination rates are lower, testing remains an important mitigation strategy. Cost-effective testing protocols are appealing and would likely take on added importance in future pandemics.

Many commentators have highlighted the potential merits of group testing for this purpose. In this context, this involves taking samples from the different individuals being tested, splitting each sample into one or more sub-samples, mixing the sub-samples in a controlled manner, applying tests to these mixtures (rather than to each of the original samples) and then deriving from the results of these grouped tests which of the individuals being tested is infected. In principle, group testing often allows us to identify the test status of every individual to be tested using fewer tests on average than the number of individuals being tested. In practice, current ways of applying group testing in this context often involve extensive pipetting and can be laborious and prone to operator error.

Illustrated below, from different angles, is a simple "concept" 3d printable device that Nematrian has developed whilst exploring ways of addressing these challenges.

Figure 1: Visualisation of a 3d printable design potentially able to assist with Covid-19 group testing



Note: In this visualisation, (A) and (B) are views from side on. (A) provides a view in the "closed" orientation (i.e. the orientation in which samples are inserted into the sample wells at the top of the device). (B) provides a view in the "open" orientation (tilting the device from the "closed" to the "open" position initiates the creation of the relevant sub-sample mixtures). (C) is an oblique view from above showing (in this case) the 10 wells into which samples from 10 individuals can be placed. (D) is an oblique view from below showing (in this case) 5 separate groups of 4 holes (which in combination output the mixtures of sub-samples that are tested in the first round of the group testing) and a further 10 individual holes (under which would be placed 10 containers, collecting 10 unmixed sub-samples for second round testing where needed).

This concept device assumes access to suitable tests that can detect the presence of the SARS-COV-2 virus underlying Covid-19 in a given sample (or other agents for other epidemiological purposes). These might for, example, involve suitable lateral flow devices (LFD) or polymerase chain reaction (PCR) testing capabilities. We assume that we want to minimise the average number of such tests (per individual) needed to determine the test status of each individual being tested (e.g. because such tests are expensive or hard to access). The above device aims to test 10 individuals at a time in an operationally convenient manner using only slightly more than 5 tests on average, if the rate of infectivity in the population from which individual samples are being drawn is sufficiently low. The design is structured so that it can be printed using a wide range of 3d printers (both commercial and hobbyist), including FDM (fused deposition modelling) printers, as its structure (including internal pipework) involves no part with an overhang relative to the vertical greater than 45°.

This sort of device would be operated in two positions, one where it is tilted in a particular manner to the vertical (the "closed" position) and one where it is tilted back to being vertical (the "open" position). In the "closed" position, samples (e.g. sample fluid and sample swabs) from ten individuals are inserted separately into (in this case) the ten individual openings (i.e. "wells") towards the top of the device. By squeezing each swab against the wall of its own well in the presence of suitable fluid, samples can be transferred from the sample swab into the sample fluid. Or, samples can be transferred elsewhere from sample swabs into separate sample fluid containers with only the resulting fluid samples then inserted into the apparatus.

The apparatus is then moved to the "open" position causing each sample to be split into three sub-samples and causing two of each individual's sub-samples to be mixed in a defined way. In aggregate the internal pipework within the apparatus produces five different mixtures of sub-samples, each one containing sub-samples from four of the original ten individuals. Each individual's third sub-sample is kept separate, for second round testing if needed (see below). The bottom of the device thus has 30 exits, 5 x 4 relating to the 5 mixtures of sub-samples (with the 4 outputs per mixture close to each other to make routing to the same group test straightforward) and 10 relating to the unmixed sub-samples for potential second round testing (one for each starting sample). We initially apply five separate tests to each of the five mixtures, retaining the unmixed sub-samples in separate containers. In some cases, we subsequently also test some of the unmixed sub-samples.

The apparatus illustrated above uses the following relatively straightforward mixing approach. If the individuals are numbered 1 to 10 from left to right as shown in views (C) and (D) and the mixed sub-samples are numbered 1 to 5 also from left to right from the same viewpoint then the following individuals contribute to the following mixtures (here 1 = contributes, blank = doesn't contribute):

Individual	Mixture 1	Mixture 2	Mixture 3	Mixture 4	Mixture 5
1	1	1			
2		1	1		
3	1		1		
4				1	1
5	1				1
6	1			1	
7		1		1	
8			1		1
9			1	1	
10		1			1

The above approach is not optimal in terms of minimising the number of tests needed to be carried out to identify which of the original individuals is positive or not, particularly if the infection rate is

quite low. But it is relatively simple to explain, implement and operate. Assuming that the testing methodology (e.g. LFD or PCR) used in conjunction with such an apparatus is accurate and sensitive enough always to register positive if at least one of the four individuals contributing to a given mixture is positive (and to register negative if none of them are positive) then:

(a) If none of the five group tests is positive, none of the individuals is positive
(b) If just one of the five group tests is positive, something has gone wrong with the testing (since every individual contributes to two of the five tests) and the testing should be redone
(c) If just two of the five tests are positive, then only one individual is positive, i.e. the individual who has contributed to both of these tests
(d) If more than two of the five tests are positive, then more than one individual is positive and in a second round of testing we should test any individuals who don't contribute to a negative test. In the extreme case where all five tests are positive then we would need to retest all ten of the original individuals. But, there is no specific need to collect new samples from any of the individuals involved. Instead we can test the unmixed sub-samples the apparatus separated out and retained for second round testing.

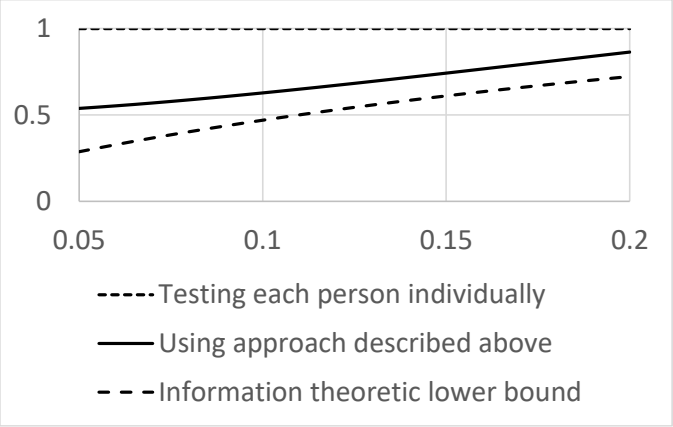
If p is the likelihood that an individual would test positive in isolation (assumed the same, and independent, for all individuals) and if we assume that we test individually in a second round each individual who might be positive given only the first-round results then the average number of tests (per individual) carried out to identify the status of each of the original 10 individuals is:

$$Average\ number\ of\ tests\ (per\ individual) = 0.5 + \frac{1}{10}\sum_{n=0}^{10} C_n p^n (1-p)^{10-n}$$

where $(C_0, C_1, \dots, C_{10}) = (0,0,180,810,1800,2400,2080,1200,450,100,10)$.

We show below this average for some different p. Also shown is the information-theoretic lower bound on the number of tests needed whatever the group testing approach being adopted, i.e. $p \log_2 p + (1-p) \log_2 p$.

Figure 2: Average number of tests (per individual) needed to identify every individual's test status



To get close to the information-theoretic lower bound, it is typically necessary to use a multi-stage group testing approach in which the choice of samples to be mixed in one stage depends on the results of tests in a previous stage. This is typically slow and difficult to handle operationally. If p is expected to be in the range say 0.08 to 0.15, the design illustrated above seems capable of meaningfully reducing the average number of tests needed (per individual) to not far above the

theoretical lower bound without adding much delay or extra complexity into the overall testing process.

Important notices

Please note:

(1) Nematrian has patent applications relating to group testing, to devices that initiate and accomplish mixing of fluid sub-samples by altering the device's inclination to the vertical and to devices where complex internal pipework is structured to have no overhangs anywhere exceeding 45° to the vertical making them easier to 3d print using simpler FDM 3d printers. Please contact contactus@nematrian.com if you wish to discuss with Nematrian the licencing of these technologies. No warranty is offered by Nematrian as to the effectiveness or reliability of the concept device described above for any purposes, diagnostic or otherwise.

(2) Group testing reduces, for a given individual, the amount in any given test of whatever active agent is being tested for in that individual's sample. This means that, depending on the testing approach used (LFD, PCR, …), group testing can increase the risk of incorrectly concluding that an individual is negative when in fact that individual is positive.

(3) Group testing offers potential cost savings because it reduces the average number of tests needed per individual being tested. However, overall costs may not scale in a similar manner. For example, group testing doesn't by itself reduce the overall number of swabs needed to be collected from the individuals being tested or the costs involved in this collection process.

(4) A two-round group testing approach as illustrated above will on average take somewhat more than one round of tests per person to identify individuals who are positive rather than negative. If the time taken to carry out an individual test is very lengthy then this will on average introduce some delay in the average length of time taken to confirm an individual's test status.

(5) To avoid risk of cross-contamination, different input wells and output channels should be kept strictly differentiated. If the device is 3d printed, slicing and printing parameters should be chosen to ensure that the internal walls in the device are watertight or if this is not possible a different manufacturing technique should be used.

(6) Another possible source of operator error is to misinterpret which individuals need testing in a second round of testing. With the design given above, if just zero or two of the group tests are positive then no individuals should need specific testing in a second round. However, if more than two of the group tests are positive there can be 3, 6 or 10 individuals needing testing in a second round. Tabulations or software automating identification of which individuals to test in a second round given observed first round test results may reduce the risk of this sort of error occurring.