Conflating screening detection rates with the uptake of further testing: A potential source of confusion

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The screening performance of a screening or diagnostic test can be defined in terms of the detection rate for a given false-positive rate or the false-positive rate for a given detection rate. The detection rate (also known as the test sensitivity) is defined as the proportion of *affected* individuals with a positive test result. The false-positive rate is defined as the proportion of *unaffected* individuals with positive test results; it is the complement of the test specificity.

In the field of antenatal screening for Down's syndrome, the term "detection" has been used in a different way, namely as the number of affected individuals who have a screen positive result and who then proceed for a further test in a screened population of a given size.[1] For example, if 90% of affected individuals are screen positive and half then proceed to a further test the "detection" is 90% × 50%, i.e. 45%. Conflation of the test detection rate with the uptake of further testing is confusing and could label an excellent screening test a poor one simply because people choose not to proceed with subsequent testing. It is usual to separately report the screening performance of a test and the uptake of subsequent testing or intervention. The former is an objective parameter of a test, while the latter reflects individual decision making in a particular context.

The confusion is illustrated by the claim that in antenatal screening for Down's syndrome, the combined test used with a risk cut-off of 1 in 150 followed by an invasive diagnostic test has a lower level of "detection" than the same combined test used with the same risk cut-off followed by the option of second screening test based on a DNA analysis instead of an invasive diagnostic test (amniocentesis or chorionic villus sampling). It has been estimated that the latter detects 195 more affected pregnancies in England and Wales each year, a figure taken up by the Nuffield Council on Ethics.[2] However, the detection rate of the two tests in sequence can only be lower than that of the first test unless the second has a detection rate of 100%. The claim arises from the observation that only about half of women with a positive combined test choose to have an invasive diagnostic test but by offering a second screening test based on a DNA analysis about 90% of women choose further tests. The difference in the uptake of further testing is not surprising. A woman receiving a positive combined test result with a risk of an affected pregnancy of between 1 in 100 and 1 in 150 might rationally judge that despite being screen positive the risk is still rather low, and so decline an invasive diagnostic test to avoid possible adverse effects on her pregnancy. However, given the option of a DNA-based screening test prior to making a decision on having an invasive diagnostic test, about 90% accept further testing. This explains the extra estimated 195 pregnancies with Down's syndrome identified each year.[1] But this is not an improvement in test detection rate; it simply reflects an increase in the uptake of further testing.

Table 1 shows a comparison of four methods of antenatal screening for Down's syndrome limited to the effect in women with affected pregnancies. The comparison is based on 400,000 women screened (similar to the number screened in England and Wales each year) and test detection rates previously reported.[3]

Method 1 uses the combined test alone: 518 pregnancies are screen positive out of 640 affected pregnancies. Of these, 50% take up the offer of invasive diagnostic test, which identifies and diagnoses 259 affected pregnancies.

Method 2, "Recall DNA screening," offers the option of women returning for a second screening test based on DNA analysis which is likely to be taken up because the DNA analysis does not involve the risk of an invasive diagnostic test. The method identifies 466 affected pregnancies instead of 259 as in method 1.

Method 3, "Reflex DNA screening" is an alternative method of interposing a DNA analysis between a combined test and an invasive diagnostic test. In this method, a blood collection is divided into two samples. If the first sample yields a high risk using the combined test markers, plasma DNA analysis is performed on the second sample before a result is reported. The method identifies 518 affected pregnancies, higher than that achieved with method 1 or 2.

Table 1. Flowcharts comparing four methods of antenatal screening 400,000 women for Down's syndrome limited to the effect in women with ***affected*** pregnancies.

Method of screening	Women screened	Down's syndrome pregnancies at term without screening	Detection rate using combined test	Number with Risk ⩾ alone cut-off	Result reported at this stage	Uptake of further testing	Number having a further test
(1) Combined test only: cut-off 1 in 150	400,000	640	81% →	518	Yes	50% →	259 IDT
(2) Recall DNA: Combined test cut-off 1 in 150	400,000	640	81% →	518	Yes	90% →	466 DNA-ST or IDT
(3) Reflex DNA if: Combined test markers risk ⩾ 1 in 150	400,000	640	81% →	518	No	100% → (reflexed)	518 DNA-ST
(4) Reflex DNA if: Combined test markers risk ⩾ 1 in 800	400,000	640	97% →	621	No	100% → (reflexed)	621 DNA-ST

IDT: invasive diagnostic test; DNA-ST: DNA screening test.

Method 4 illustrates an advantage of the reflex DNA method of screening; the combined test risk level that triggers a DNA analysis can be reduced without causing the stress and anxiety of reporting a positive combined test result. If the combined risk cut-off is 1 in 800, the method identifies 621 affected pregnancies, higher than that achieved with methods 1, 2, or 3.

Not shown in the table is that the overall false-positive rate associated with methods 3 or 4 is about 2 per 10,000, much lower than the false-positive rates associated with method 1 or 2.[3]

The Reflex DNA method of screening avoids the confusion arising from reporting two screening test results, with two risk estimates (one based on the Combined Test, and the other on a DNA test). Instead, it provides a more accurate single estimate of risk by amalgamating information from the combined test markers and the DNA analysis. Making a single decision on whether to be screened instead of two avoids the stress of making an unnecessary choice, and receiving a single screening result instead of two avoids the dilemma faced by receiving two different risk estimates. With reflex DNA screening, women with unaffected pregnancies have extremely low risks and women with affected pregnancies have extremely high risks. This polarization of risk estimates goes a long way to reducing the uncertainty and stress of antenatal screening. Following the reflex DNA method, women have an odds of being affected with a positive reflex DNA result of about 25:1.[3]

In summary, different screening methods should be compared keeping the specific test performance (detection rate and false-positive rate) distinct from the uptake of further testing. Both are important, but conflating the two together under the term "detection" is potentially misleading and best avoided.

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