A Test That Is 99.9 % Accurate and Wrong Half the Time: Predictive Value of Cell-Free DNA Prenatal Screening across Maternal Age and Condition

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Abstract

Background: Cell-free DNA prenatal screening is marketed and frequently explained to women in terms of its accuracy, sensitivity and specificity. The quantity a woman with a positive result actually needs is the positive predictive value, which depends on the prevalence of the condition in her circumstances and therefore varies with her age and with which condition was screened for. That dependence is arithmetic, is large, and is not conveyed by the figures usually quoted.

Objective. To quantify how the predictive value of cell-free DNA screening varies across maternal age and across the conditions on contemporary panels, and to evaluate two policy alternatives: contingent screening and panel expansion.

Methods: A decision-analytic model was constructed using literature-typical test characteristics (trisomy 21: sensitivity 99.7 %, specificity 99.90 %; trisomy 18: 97.8 %, 99.90 %; trisomy 13: 99.0 %, 99.90 %; 22q11.2 deletion: 75.0 %, 99.50 %) and a conventional maternal-age gradient of trisomy 21 prevalence. Positive and negative predictive values, screen-positive composition per 100,000 pregnancies, and the number of screen positives per true positive were computed across ages 20 to 45. Sensitivity analysis varied specificity from 99.50 % to 99.99 %. A contingent strategy applying cell-free DNA only after a positive first-line combined test, and panel expansion by up to 20 additional rare conditions, were modelled.

Results: Positive predictive value for trisomy 21 rose from 45.4 % at age 20 to 97.6 % at age 45, while sensitivity, specificity and overall accuracy were unchanged by construction; overall accuracy was 99.9 % at every age. For 22q11.2 deletion the predictive value was 7.0 % at every age, so approximately 14 screen positives arose per affected fetus. Per 100,000 pregnancies at age 25, trisomy 21 screening produced 91 true and 100 false positives; the 22q11.2 component of the same panel produced 38 true and 500 false positives. Specificity dominated: at age 25, moving specificity from 99.50 % to 99.99 % raised predictive value from 15.4 % to 90.1 %, while the reported sensitivity was irrelevant to it. Contingent screening raised predictive value at age 25 from 47.6 % to 93.9 % using cell-free DNA in 51 of every 1000 pregnancies, at the cost of detection falling from 99.7 % to 84.7 %. Adding 20 rare conditions raised the probability of any false-positive result from 3.0 to 98.1 per 1000 while adding 3.0 true positives per 1000.

Conclusions: Predictive value, not accuracy, is the quantity a positive result requires, and it ranges from 7 % to 98 % across the conditions and ages examined. Reporting should be individualised to age and condition, and expanded panels should be evaluated against the false positives they generate rather than the conditions they nominally cover.

Keywords: Cell-Free DNA Screening, Non-Invasive Prenatal Testing, Positive Predictive Value, Trisomy 21, 22q11.2 Deletion, Prenatal Diagnosis.

1. INTRODUCTION

Cell-free DNA screening has changed prenatal care faster than almost any recent obstetric technology. A maternal blood sample from ten weeks, analysed for fetal fragments circulating in the plasma, detects the common autosomal trisomies with a sensitivity that no earlier screening approach approached, and it has substantially reduced the number of invasive procedures performed for screening indications.

It is also explained to women, and advertised to them, in a way that systematically misleads. The figures that appear in patient material are accuracy, sensitivity and specificity — typically expressed as some version of "over 99 % accurate". Those are properties of the test. The question a woman asks when her result is positive is a different one: given this result, what is the probability that my fetus is affected? That quantity is the positive predictive value, and it depends on how common the condition is among women like her.

The dependence is not a subtlety. Trisomy 21 is roughly forty times more common at 45 than at 20, so the same result carries a very different meaning for two women receiving it on the same day from the same laboratory. Contemporary panels have also expanded well beyond the common trisomies to include microdeletion syndromes that are individually rare, and for those the arithmetic is harsher still, because prevalence in the denominator falls while the false-positive rate does not.

This study quantifies the problem and evaluates two responses to it. Three questions are addressed: how far predictive value varies across maternal age and across the conditions on current panels; which test property actually governs it; and what contingent screening and panel expansion do to the balance of true and false positives.

2. METHODS

2.1 Model

For a condition of prevalence π at the time of screening, and a test of sensitivity Se and specificity Sp, the positive and negative predictive values follow from Bayes' theorem:

$$PPV = \pi Se / [\pi Se + (1 - \pi)(1 - Sp)] \quad (1)$$

$$NPV = (1 - \pi) Sp / [(1 - \pi) Sp + \pi (1 - Se)] \quad (2)$$

The number of screen positives per true positive, which is the number of women who must be counselled and offered confirmatory testing for each affected fetus identified, is the reciprocal of the positive predictive value. No parameter of the test appears in the prevalence term, which is the reason the same test performs differently in different women.

2.2 Parameters

Table 1. Model parameters

Condition	Sensitivity	Specificity	Prevalence assumed
Trisomy 21	99.7 %	99.90 %	Maternal-age gradient (Table 2)
Trisomy 18	97.8 %	99.90 %	0.25 × the trisomy 21 prevalence
Trisomy 13	99.0 %	99.90 %	0.10 × the trisomy 21 prevalence
22q11.2 deletion	75.0 %	99.50 %	1 in 2000, independent of age
First-line combined test (contingent strategy)	85.0 %	95.0 %	—
Additional rare conditions (panel expansion)	75.0 %	99.50 %	1 in 5000 each

Note. Test characteristics are literature-typical assumptions selected to be representative rather than estimates from any particular assay or laboratory. Specificity is varied from 99.50 % to 99.99 % in sensitivity analysis because it is the parameter that governs the results and the one that differs most between reported series.

Table 2. Assumed prevalence of trisomy 21 at screening, by maternal age

Age (years)	20	25	30	32	35	37	40	42	45
Prevalence (1 in N)	1200	1100	800	600	320	200	85	45	25

Note. Values represent the conventional maternal-age gradient and are illustrative. Prevalence at screening exceeds prevalence at birth because of fetal loss between the first trimester and delivery; absolute values differ between populations and reference series, and no result here should be read as a population estimate.

2.3 Analyses

Four analyses were performed. Predictive values were computed across nine maternal ages for each of four conditions. A cohort analysis expressed the results as counts per 100,000 pregnancies at ages 25, 35 and 40, decomposing the screen-positive group into true and false positives. A sensitivity analysis varied specificity across the reported range. Finally, two policy alternatives were modelled: a contingent strategy in which cell-free DNA is offered only to women positive on a first-line combined test, and panel expansion by up to twenty additional rare conditions. All computation was performed in Python and reproduces exactly from the parameters in Tables 1 and 2.

3. RESULTS

3.1 Predictive value across age and condition

Table 3. Positive predictive value (%) by maternal age and condition

Condition	20	25	30	32	35	37	40	42	45
Trisomy 21	45.4	47.6	55.5	62.5	75.8	83.4	92.2	95.8	97.6
Trisomy 18	16.9	18.2	23.4	29.0	43.3	55.0	74.3	84.5	90.8
Trisomy 13	7.6	8.3	11.0	14.2	23.6	33.1	53.8	68.8	79.9
22q11.2 deletion	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0

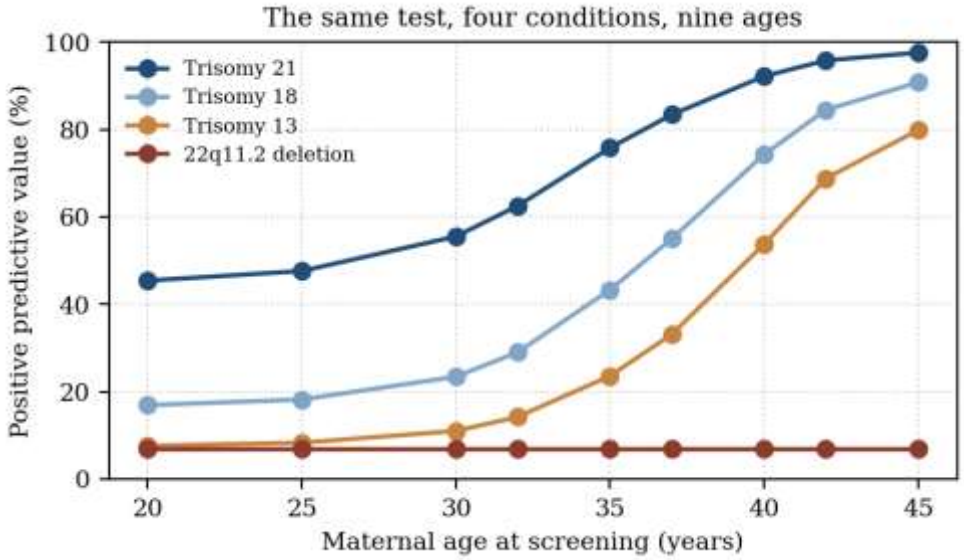

Figure 1. Positive predictive value by maternal age for four conditions on a contemporary panel

The range across the table is from 7.0 % to 97.6 %, produced by a single unchanged test. A 20-year-old with a positive trisomy 21 result has a fetus more likely unaffected than affected; a 45-year-old with the identical result is nearly certain. For trisomy 13 the predictive value remains below a quarter until the mid-thirties. The flat line for 22q11.2 deletion is the most consequential row. Because the condition does not vary with maternal age, no woman screened for it receives a result with a predictive value above about 7 %: roughly fourteen women are told their screen is positive for every affected fetus. That is a property of the condition's rarity and the assay's specificity, not of the woman.

3.2 Accuracy conceals the variation

Table 4. Four metrics for trisomy 21 screening at three maternal ages

Metric	Age 25	Age 35	Age 40	Varies with age?
Sensitivity	99.7 %	99.7 %	99.7 %	No
Specificity	99.90 %	99.90 %	99.90 %	No
Overall accuracy	99.90 %	99.90 %	99.90 %	No
Negative predictive value	99.9997 %	99.9991 %	99.9964 %	Negligibly
Positive predictive value	47.6 %	75.8 %	92.2 %	Yes, substantially

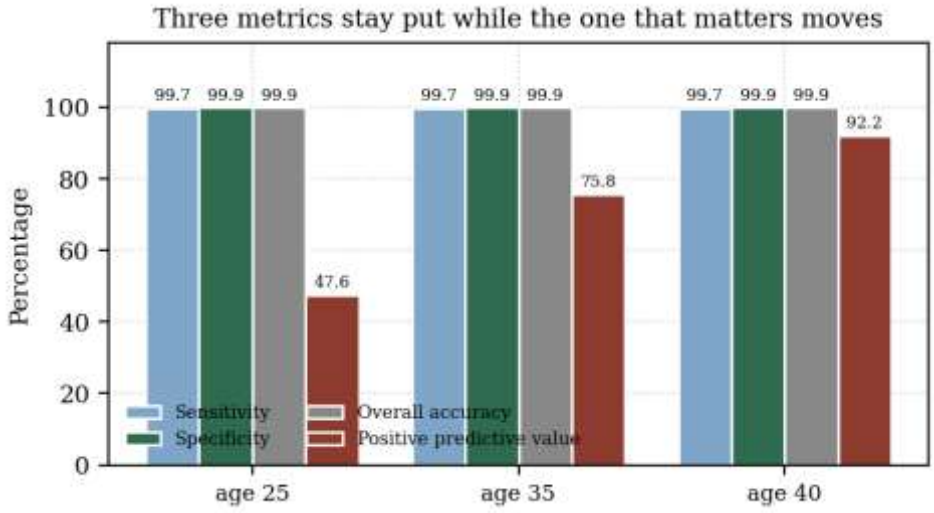

Figure 2. Sensitivity, specificity, overall accuracy and positive predictive value at three maternal ages

Four of the five metrics in Table 4 are effectively constant and the fifth doubles. The four that do not move are the four that appear in patient information and marketing. The one that moves is the one a woman with a positive result is asking about.

The negative predictive value deserves separate comment because it is the metric most often quoted as reassurance and is nearly uninformative here. It exceeds 99.99 % at every age, which sounds impressive and is close to what it would be for a test with no discriminating ability at all, because the condition is rare. A negative result is genuinely reassuring; the figure quoted to convey that is not doing the work it appears to do.

3.3 What the screen-positive group contains

Table 5. Per 100,000 pregnancies screened

Age	Condition	Affected fetuses	Screen positives	True positives	False positives	Missed	Screen positives per affected fetus
25	Trisomy 21	90.9	190.5	90.6	99.9	0.27	2.1
25	22q11.2 deletion	50.0	537.3	37.5	499.8	12.5	14.3
35	Trisomy 21	312.5	411.3	311.6	99.7	0.94	1.3
35	22q11.2 deletion	50.0	537.3	37.5	499.8	12.5	14.3
40	Trisomy 21	1176.5	1271.8	1172.9	98.8	3.53	1.1
40	22q11.2 deletion	50.0	537.3	37.5	499.8	12.5	14.3

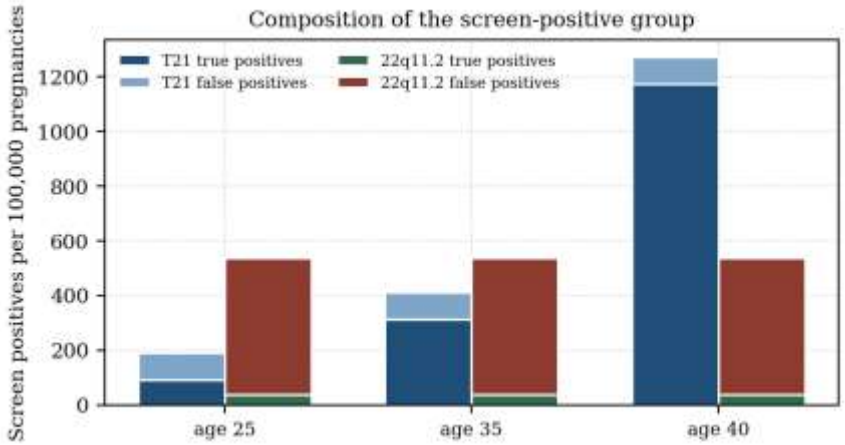

Figure 3. Composition of the screen-positive group at three maternal ages, for trisomy 21 and 22q11.2 deletion

The false-positive count for trisomy 21 is essentially constant across age — about 100 per 100,000 — because it is generated by the 0.10 % of unaffected pregnancies that test positive, and unaffected pregnancies are the overwhelming majority at every age. What changes is the number of true positives sitting alongside them, from 91 at age 25 to 1,173 at age 40. Predictive value improves with age not because the test performs better but because the true positives come to outnumber a fixed background of false ones. The 22q11.2 rows are identical at every age by construction and are worth reading against the trisomy 21 row directly above them. At age 25 the same blood sample generates 91 true trisomy 21 positives and 38 true 22q11.2 positives, alongside 100 and 500 false ones respectively. The microdeletion component of the panel contributes five times the false positives and less than half the true ones.

3.4 Specificity is the governing parameter

Table 6. Positive predictive value for trisomy 21 by assumed specificity

Specificity	Age 25	Age 35	Age 40
99.50 %	15.4	38.5	70.4
99.80 %	31.2	61.0	85.6
99.90 %	47.6	75.8	92.2
99.95 %	64.5	86.2	96.0
99.99 %	90.1	96.9	99.2

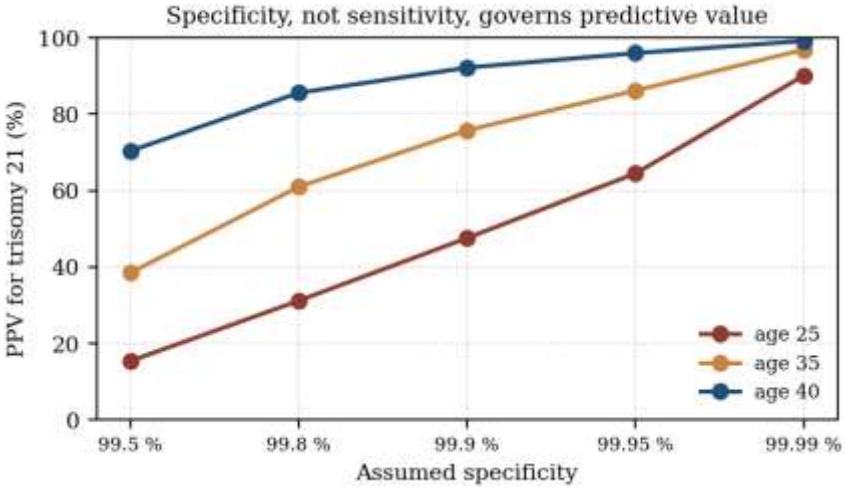

Figure 4. Effect of specificity on predictive value at three maternal ages

Across the range of specificity reported for different assays and laboratories, predictive value at age 25 moves from 15.4 % to 90.1 % — a sixfold change produced by a parameter that differs in the third decimal place. Sensitivity has almost no influence on this quantity, because at these prevalences the denominator of equation (1) is dominated by false positives.

Two consequences follow for practice. A laboratory's specificity, which is rarely stated in the patient-facing material and is frequently reported only as "greater than 99 %", is the single most important determinant of what a positive result means. And an assay improvement that raises sensitivity from 99.0 % to 99.7 % — the kind of change that is marketed — alters predictive value negligibly, while a specificity improvement of the same apparent magnitude transforms it.

3.5 Contingent screening

Table 7. Universal against contingent cell-free DNA screening for trisomy 21

Age	Prevalence before test	Prevalence among first-line positives	PPV, universal	PPV, contingent	cfDNA tests per 1000	Detection rate
25	0.091 %	1.52 %	47.6 %	93.9 %	50.7	84.7 %
35	0.312 %	5.06 %	75.8 %	98.2 %	52.5	84.7 %
40	1.176 %	16.83 %	92.2 %	99.5 %	59.4	84.7 %

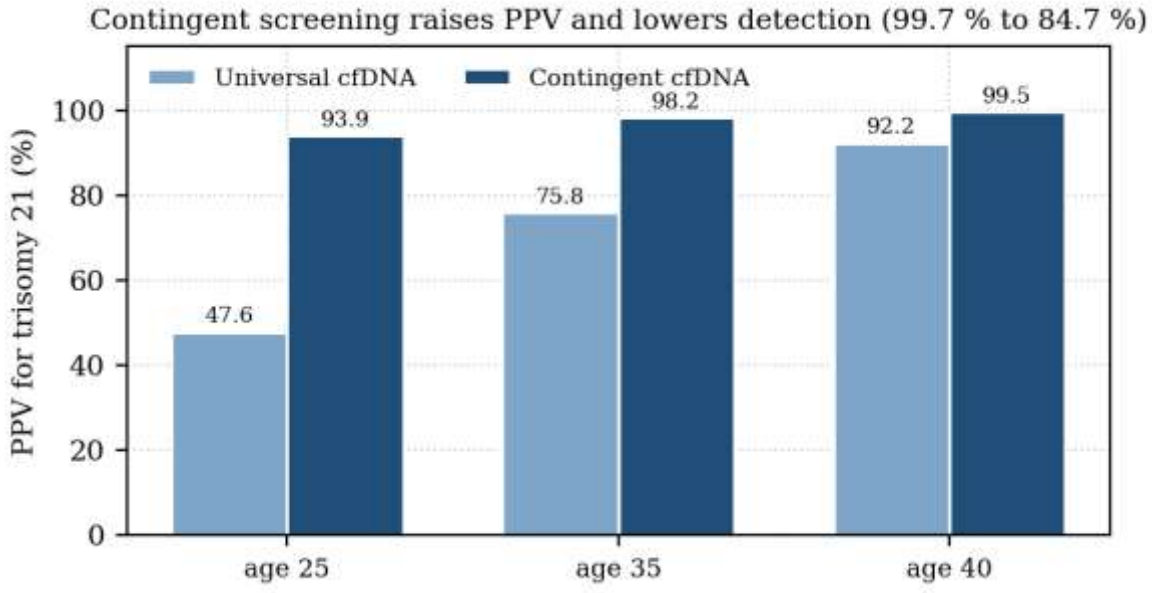

Figure 5. Predictive value under universal and contingent strategies

Restricting cell-free DNA to women positive on a first-line combined test raises the prevalence in the tested group by a factor of sixteen at age 25, and with it the predictive value from 47.6 % to 93.9 %. It does so while performing cell-free DNA in only about five per cent of pregnancies.

The cost is detection. Because the first-line test misses fifteen per cent of affected pregnancies before cell-free DNA is ever offered, overall detection falls from 99.7 % to 84.7 %, and those missed cases are missed silently. This is a genuine trade rather than a dominated option: contingent screening buys interpretability and cost at the price of detection, and which side of that trade a service should sit on depends on how it weighs a false positive against a missed diagnosis. The model quantifies the exchange rate rather than resolving it.

3.6 Panel expansion

Table 8. Effect of adding rare conditions to the panel, per 1000 pregnancies

Additional conditions	Probability of any false-positive result	Additional true positives	False positives per additional true positive
0	3.0	—	—
2	12.9	0.30	43.1
5	27.7	0.75	36.9
10	51.7	1.50	34.5
20	98.1	3.00	32.7

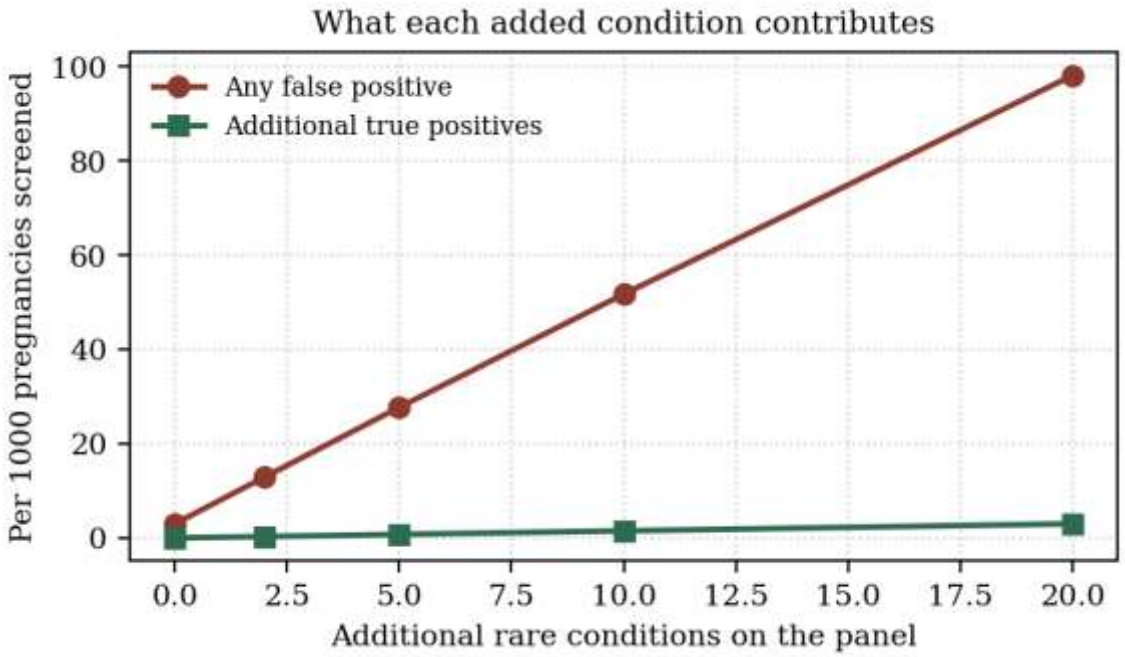

Figure 6. False positives and additional true positives as conditions are added to the panel

Each rare condition added to a panel contributes a small number of true positives and a much larger number of false ones, and because false positives accumulate multiplicatively across conditions the probability that a woman receives at least one false-positive result rises steeply. At twenty additional conditions, 98.1 per 1000 pregnancies — approximately one in ten women screened — receive a false-positive result somewhere on the panel, against 3.0 per 1000 receiving a true one.

The ratio of roughly 33 false positives per additional true positive is stable across panel size because it is determined by the prevalence and specificity assumed for each condition rather than by how many are added. The number of women affected is what scales.

4. DISCUSSION

4.1 Principal findings

Predictive value for trisomy 21 ranged from 45.4 % at age 20 to 97.6 % at age 45 while sensitivity, specificity, accuracy and negative predictive value were effectively constant. For 22q11.2 deletion the predictive value was 7.0 % at every age, implying roughly fourteen screen positives per affected fetus. Specificity, not sensitivity, governed predictive value, moving it sixfold at age 25 across the reported range. Contingent screening nearly doubled predictive value at younger ages while reducing detection from 99.7 % to 84.7 %. And panel expansion generated about 33 false positives for each additional true positive.

4.2 Implications

Table 9. Implications for practice

Finding	Implication	Recommendation
PPV ranged 45.4–97.6 % for trisomy 21	A positive result means different things at different ages	Report PPV individualised to age and condition, not accuracy
Accuracy was 99.9 % at every age	The headline figure is uninformative for a positive result	Remove "accuracy" from patient-facing material
22q11.2 PPV was 7.0 % at every age	Most microdeletion positives are false	Counsel microdeletion results explicitly as low-probability
NPV exceeded 99.99 % throughout	A high NPV reflects rarity, not test quality	Do not quote NPV as evidence of assay performance
Specificity moved PPV sixfold	Laboratory specificity determines what a result means	Require laboratories to state specificity to two decimal places
Contingent screening doubled PPV, cut detection to 84.7 %	The strategies trade interpretability against detection	Choose explicitly and state the detection rate
Panel expansion gave 33 false positives per true positive	Added conditions carry a large counselling burden	Justify each added condition against its own false-positive yield

The first row is achievable immediately and requires no new data. Every laboratory reporting a positive result knows the woman's age and the condition detected, and equation (1) requires nothing else. A report stating that the probability of an affected fetus is approximately 48 % conveys what a report stating "positive, test accuracy over 99 %" does not, and the difference between those two sentences is the difference between a woman understanding her situation and misunderstanding it.

The third row carries the greatest potential for harm. A microdeletion screen positive with a 7 % predictive value is, in the great majority of cases, a false alarm delivered to a woman in the first trimester, and the anxiety and the pressure toward invasive testing that follow are real costs borne mostly by women whose pregnancies are unaffected. This does not argue that microdeletion screening should not be offered, but it argues that the offer should be accompanied by the number.

4.3 Limitations

This is a model and its outputs are conditional on its inputs. Test characteristics are literature-typical assumptions rather than measurements from any specific assay, and real-world specificity varies between laboratories and with gestational age, maternal weight and fetal fraction; the sensitivity analysis in Section 3.4 covers this range but a particular laboratory may sit outside it. The prevalence gradient is illustrative of the conventional maternal-age relationship and is not a population estimate for any setting, and prevalence at screening rather than at birth is the appropriate denominator here, which differs between published series.

Several features of real screening are omitted. Test failures and no-call results, which occur in a small percentage of samples and are themselves associated with aneuploidy, are not modelled and would alter the effective performance of every strategy. Confined placental mosaicism, vanishing twin and maternal malignancy are recognised causes of discordant results and are subsumed here into the specificity parameter rather than modelled mechanistically. Multiple gestation, in which fetal fraction and interpretation both differ, is excluded entirely.

The contingent strategy is modelled with a single set of first-line characteristics and a fixed risk threshold; real contingent policies use a risk cut-off that determines both the proportion referred for cell-free DNA and the enrichment achieved, and optimising that threshold would improve on the single point examined

here. The panel-expansion analysis assumes independence between conditions and equal prevalence and specificity for each added condition, which is a simplification that understates the variation between real microdeletion syndromes.

Finally, the model addresses test performance and not outcomes. It says nothing about what women do with the information, about the psychological consequences of a false-positive result, about the downstream invasive-procedure-related loss rate, or about the substantial ethical questions raised by expanding prenatal screening. Those are the questions that determine whether a screening programme is worthwhile, and an arithmetic analysis is a precondition for addressing them rather than a substitute.

5. CONCLUSION

A cell-free DNA screen described as 99.9 % accurate returns a positive trisomy 21 result that is correct 45 % of the time at age 20 and 98 % of the time at age 45, and a positive 22q11.2 result that is correct 7 % of the time at any age. The metrics quoted to women — accuracy, sensitivity, negative predictive value — are precisely the ones that do not change across that range.

Two changes follow and neither requires new evidence. Positive results should be reported with a predictive value calculated for that woman's age and that condition, which is a single line of arithmetic from information the laboratory already holds. And expanded panels should be justified condition by condition against the false positives each generates, because on these assumptions adding twenty rare conditions gives one woman in ten a false-positive result somewhere on the panel in order to identify three true ones per thousand. The screening is valuable; the way its performance is described is not.

Declarations

Ethical approval: Not applicable.

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Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Omar Qahtan Yaseen	✓	✓	✓	✓	✓		✓	✓		✓		✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

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