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COMMENTARY

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The price of abandoning diagnostic testing for cell-free fetal DNA screening

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Over 50 years, prenatal diagnosis procedures and screening have become safer and diagnostic laboratory capabilities have dramatically expanded,[1-5] Recently, cell-free fetal DNA (cffDNA) utilization has gained considerable market share. While officially, companies state that cffDNA is screening and not diagnostic, much of the sales "hype" and patient and physician understanding is that cffDNA is a replacement—not an adjunct to chorionic villus sampling (CVS) and amniocentesis.

In parallel, chromosomal microarrays (CMAs) have essentially replaced karyotypes in pediatrics.[6] The National Institute of Child Health and Human Development trial and others show that in fetuses with normal ultrasounds and karyotype, the detection of CNVs of well documented pathology is about 1.5%.[4,7] High risk has been defined as age 35, so now "everyone's risk" is over 35.[1,8]

There is an extensive literature on medical cost estimates, but it is of questionable accuracy for many rare disorders.[9] Economic models, while fraught with uncertainty, are used routinely by companies and governments studying the impact on practice and economics of medicine. However, actual incorporation of technology often occurs at a variance from conventional wisdom.

Here, we analyzed hypothetical populations of 1 million pregnancies each assigning, reasonable, approximate managed care costs for varied procedures. We estimated overall Down syndrome (DS) incidence of 0.2% and CMA detectible, significant disorders at 1.5%. For cffDNA, we modeled a detection rate of 99% for DS and several termination rates for anomalies.

We modeled 3 groups:

1. patients having no screening or testing;
2. patients having universal screening with cffDNA for DS; and
3. patients having universal CVS or amniocentesis with CMA.

We modeled financial implications by termination rates.

We ignored the relatively minor costs of terminations and diagnostic procedures to confirm abnormal cffDNA results. We anticipate that karyotypes will disappear as the primary cytogenetic technique. Managed care costs were estimated at $1 million per DS child, $500,000 for severe CNV abnormalities, and $1000 each for clinical CVS, cffDNA, and CMA lab costs.[1,4,] Given the complexity and evolution of technologies, we then raised and lowered estimates to create ranges of expected costs.

For 1 million patients without screening or testing, actuarial data suggest 2000 DS babies and 15,000 abnormal CNVs. Care of such children would cost $9.5 billion.

Universal cffDNA would find 99% of DS but no CNV abnormalities. The cost at $1000/patient is $1 billion. Assuming no terminations and a sensitivity of 99%, the cost of care of 20 DS children is $20 million, but there is no detection of the abnormal CNVs. Those costs, while not generally incorporated, increase overall program costs to $9.52 billion. Universal CVS/amnio and CMA diagnostic costs are $2 billion. For 15,000 abnormal CNVs, the costs reach $11.5 billion (Table 1).

There are a multitude of disorders for which cffDNA cannot screen. These disorders carry a significant economic burden and loss of contributions from those affected. Lifetime costs range from $581,256 for Beta-thalassemia major to $3,220,398 for Prader Willi. Cystic fibrosis lifetime costs are $2,029,628; Marfan syndrome costs $1,705,470.[9] For hundreds of disorders, estimated costs are undocumented, but of several disorders investigated, average lifetime cost was $1.6 million.[9-12]

Next, we modeled the impact of patients' choices when they have options following prenatal diagnosis. At 1 extreme, at a 100% termination rate for DS and CNVs, the $9.5 billion of care would be eliminated. At 50%, medical costs would be $6.75 billion, and at 20%, $7.6 billion.[9] For CNVs, universal cffDNA does not have impact as those conditions

TABLE 1 Economic modeling for cohorts of 1 million patients each

Cohorts of A million patients	Incidence	Prenatal Costs	Detection	Pediatric Costs	Total Costs (0% Terminations)	Assume (50% Terminations)	Assume (100% Terminations)
No screening or testing	2000 DS	$0	0%	$2 billion			
	15,000 CNVs		0%	$7.5 billion			
					$9.5 billion		
Universal	2000 DS	$1 billion	99%	$2 billion			
cffDNA	15,000 CNVs		0%	$7.5 billion			
					$10.5 billion	$9.49 billion	$8.5 billion
Universal CMA	2000 DS	$2 billion	100%	$2 billion			
	15,000 CNVs		100%	$7.5 billion			
					$11.5 billion	$6.75 billion	$2.0 billion
Savings by CMA						$4.75 billion	$9.5 billion

Modeling: Per 1 million patients, we expect the following: 2000 Down syndrome cases, 15,000 abnormal copy number variations (CNVs), medical costs for DS patients: $1 million, and medical costs for abnormal CNV patients: $500,000. CMA, chromosomal microarrays; cffDNA, cell-free fetal DNA.

are not detected. Some laboratories now offer a small number of microdeletion tests, but these do not have a significant impact upon the overall incidence and therefore costs.[9-12]

At the 50% termination rate, universal cffDNA lowers costs by $1 billion. However, CVS/amnio and aCGH lower it by $4.75 billion. At 20%, the costs would be lowered by $1.9 billion. Even cutting our modeled costs of CNV disorders by 50%, the savings would be $2.37 billion. We believe that actual medical costs are likely higher than we model, and thus savings, depending upon patient's choices, could be higher.

Any analysis which includes a discussion and quantification of patients' reproductive decisions will be considered controversial by many. However, we believe that without such frank analysis, public policy and medical practice cannot be rigorously studied and improved. We present here a range of statistical scenarios which can be used for such modeling while completely respecting the clear tenet of genetics as being nondirective.

For cffDNA, never before have we seen one technology substantially replace another (diagnostic tests) when it is both simultaneously less efficacious and more expensive.[8] The shift from diagnostics to screening is not new, however. Over 2 decades, ultrasound reliance has also decreased diagnostic testing but has resulted in more anomalies being missed.[13] We have voiced serious concerns about quality control of nuchal translucency and have proposed methods to improve it. Overall, laboratory tests have higher performance metrics than ultrasound.[13]

An argument for cffDNA is that has no procedural risks. While true, in experienced hands, risks of both CVS and amniocentesis are very low (1/500 or lower) and CVS is just as safe (or safer) than amniocentesis.[8,14] We counsel all patients that in the middle 99%, it actually does not matter if they have screening or testing; everything will be "fine." The issue is, if they are going to be wrong, which way would they rather be wrong? Would they rather take a small risk of having a baby with a serious problem, or a small risk of a complication because they wanted to know that. Not surprisingly, there is a strong liberal/conservative divide on how patients act.[15] We would expect with 1 million CVS/amnios that there would be 2000 losses, but 17,000 serious problems could be identified (ratio 8.5/1). We believe that most couples would find this ratio to be acceptable—provided they are actually presented with these data.[8]

Cell-free fetal DNA has high performance for DS but much less for other conditions.[16] Although originally proposed for only the high-risk population, its use had migrated to routine. By definition, all screening tests have poorer performance for lower incidence conditions and are less cost beneficial.[1] Our own work and others have suggested that the cost of finding additional DS cases over combined screening may be about $3 million per case.[8] Aetna insurance company began coverage for CffDNA for "routine" pregnancies in 2015 but, in August 2017, reversed their decision. We believe this was a reasonable decision.

In our programs, the proportion of patients having procedures after counseling has not changed.[1,8] What has changed is that fewer patients actually receive genetic counseling. Nationally, most patients are unaware of difference between screening and diagnostic tests, sensitivity versus positive predictive values, and other genetic conditions that karyotypes or CMA can detect that cffDNA cannot.

Economic modeling must be taken cautiously, but the general trend is clear. Identification of serious problems affords patients control over their reproductive choices. The $1 million estimate for the care of a child with DS has been well vetted.[17] Our 50% estimate for abnormal CMA CNVs is an educated guess given that there are hundreds of disorders. By limiting to those cases with confirmed pathological CNVs, we deliberately skewed the group toward the more severe end. We identify fewer patients, but they have higher costs. The $500,000 estimate may be too low.

The "goal posts" of what can be diagnosed by CMA analysis have increased dramatically. About 1% of all children develop neurological developmental delays, and over 1% develop autism.[18] Chromosomal microarray studies suggest that as much as 50% of neurological developmental delays and 20% of autism can be identified.[19] The 2012 National Institute of Child Health and Human Development data showed that, at the most conservative, 0.5% of patients with no other findings had a well-documented, pathological CNVs. Approximately 1.7% had a CNV that was either well documented or likely to be pathological. We believe 1.5% is a reasonable, conservative number. Modeling variable detection, costs, and patient choices allows us to develop both high- and low-cost estimates under differing scenarios.

If, as an extreme hypothetical, all patients underwent CVS and CMA and all with anomalies chose to terminate, the health-care system could save about $7 billion per year per 1 million patients. In the United States, with approximately 4 million births per year, theoretically, the savings could be $28 billion. Even reducing costs by 50% would still suggest $14 billion savings.

About two-thirds of patients undergo screening,[20] but much fewer have diagnostic tests even when known to be "high risk."[1,5,8] We believe that over the next several years, a larger proportion of patients will become educated as to the increased diagnostic capabilities with CMA and the safety of diagnostic procedures when performed by experienced and talented clinicians. As such, the pendulum may swing back from cffDNA to CVS and CMA. Only when cffDNA or intact fetal cells can match the depth of sequencing to equal the diagnostic capabilities of CMA will noninvasive screening methods of screening approach the yield of CVS and amniocentesis with CMA.

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