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The epidemic of abnormal copy number variant cases missed because of reliance upon noninvasive prenatal screening

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Abstract

Objective: To assess the implications of increasing utilization of noninvasive prenatal screening (NIPS), which may reach 50% with the concomitant decrease in diagnostic procedures (DPs) for its impact on detection of chromosomal abnormalities.

Methods: We studied our program's statistics over 5 years for DPs and utilization of array comparative genomic hybridization (aCGH). We then modeled the implications in our program if DP had not fallen and nationally of a 50% DP and aCGH testing rate using well-vetted expectations for the diagnosis of abnormal copy number variants (CNVs).

Results: Our DP fell 40% from 2013-2017. Utilization of aCGH for DP nearly tripled. We detected 28 abnormal CNVs. If DP had not fallen, we likely would have detected 60. With 4 million US births per year, 2 million DPs would detect 30 000 abnormal CNVs and 4000 standard aneuploidies. At a 1/500 complication—pregnancy loss rate, the detection/complication ratio is 8.5/1.

Conclusions: Noninvasive prenatal screening has significantly changed the practice of prenatal screening. However, while increasing the detection of Down syndrome, the concomitant decrease in DP and lack of aCGH results in missing many more abnormalities than the increase in Down syndrome and complications of DP combined. From a public health perspective, such represents a missed opportunity for overall health care delivery.

1 | INTRODUCTION

From the introduction of diagnostic prenatal procedures for chromosome abnormalities and Mendelian disorders in the late 1960s/early 1970s, utilization increased steadily for about 3 decades.[1] However, there has always been reticence over "invasive" diagnostic procedures (DPs) such as amniocentesis and chorionic villus sampling (CVS) both because of the risk of complications including pregnancy loss and patient needle phobia.[1] In the United States, for example, utilization has also correlated with "red state/blue state" divide, ie, conservative vs liberal areas for both utilization of diagnostic techniques and deciding upon termination following the diagnosis of anomalies.[2] A major theoretical advantage of noninvasive prenatal screening (NIPS) would be that the same answers might be achievable without DPs.[3] Our concerns center on patients and physicians not recognizing the significantly increased diagnostic capabilities now possible for conditions that can result in children with serious impairments and physicians not offering their patients the opportunity to investigate for those primarily.

Utilization rates of DP slowed with the introduction of second-trimester Down syndrome (DS) screening.[4] With the introduction of first-trimester combined screening with free β hCG, PAPP-A, and nuchal translucency, there was a further impact on procedural rates. In some locations, DPs dropped as much as 40%.[5] Although designed principally to help identify and risk stratify the low-risk patient who now was "high risk," the actual application was more for high-risk patients to believe they were low risk and to decline procedures following low-risk screening results.[6] A decade ago, we published that

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reliance upon such biochemical and ultrasound screening had led to a precipitous drop in procedures in Colorado but a doubling of the DS birth rate for women over 35.[4] Analysis of that data showed that it was related to missed diagnoses rather than patients choosing to continue after a correct diagnosis of DS.

Over the past 5 years, utilization of NIPS has dramatically increased with a further DP drop of at least 30% to 50% nationally.[6-8] It has very good performance metrics for DS (≈99%) and some other common aneuploidies but much poorer for copy number variants (CNVs). With increasing experience, its applications have increased but with variable results.[7-13]

Concomitantly, much higher resolution of gains and losses of material, ie, CNVs, has become possible with microarrays (array comparative genomic hybridization [aCGH]). Since the NICHD collaborative trial published in 2012, offering aCGH on all DPs has been accepted as routine by geneticists although there continues to be reticence among many obstetricians, patients, and insurance companies to accept and pay for the new technology.[6,14,15] Nevertheless, the quality of the aCGH results, which requires specimens from CVS or amniocentesis, has steadily improved particularly as increased experience has dramatically lowered the number of variants of uncertain significance.[16] Improvements in performance have paralleled that previously seen with new ultrasound markers such as echogenic focus and choroid plexus cysts, which were first introduced 3 decades ago.[17] Data suggest that in the presence of an ultrasound abnormality that aCGH increases the yield of diagnosed abnormalities by about 6% to 8% by finding abnormal CNVs, but even in the absence of any risk factors (history, age, and ultrasound) finds at least a 1% to 1.7% incidence of significant CNV abnormalities not otherwise diagnosable.[14-16]

We have previously reported that based on our experience, and consistent with statements of the American College of Medical Genetics and American Congress of Obstetricians and Gynecologists that all patients regardless of age should be offered a DP, we began routinely offering aCGH in 2012 to all our DP patients undergoing CVS because of the increased detection of abnormalities.[6,18,19] Then we modeled the economic impact of (1) offering no screening, (2) universal NIPS, and (3) universal DPs on cohorts of 1 million patients each. Using reasonable high and low estimates for use of tests and how abnormalities are managed, we demonstrated considerable savings for the cohorts by diagnostic testing.[20]

We believe we are living in the middle of an unrecognized epidemic of genetic abnormalities that cannot be addressed until we recognize them as a cohort—no different than many other conditions for which we are expending considerable public health efforts and have an enormous financial burden. Here, we studied the number of consults to our service, utilization of DP, and opting for aCGH from 2013 to 2017 and then used that data to extrapolate our findings to model nationwide projections.

What's already known about this topic?

- Noninvasive prenatal screening and array comparative genomic hybridization (aCGH) are disruptive technologies for prenatal diagnosis and screening, which have dramatically impacted the practice of obstetrics. Noninvasive prenatal screening utilization has decreased diagnostic procedures (DPs) by over 40%. Array comparative genomic hybridization has increased the diagnostic capabilities from fetal tissue. We have previously argued that increased use of aCGH would result in considerable economic savings in health care costs.

What does this study add?

- Our procedures dropped 40%, but aCGH utilization has tripled. If DPs were stable with increased aCGH, we would have more than doubled abnormal copy number variant detection. Extrapolating nationally, if half the pregnancies in the United States had DPs, 30 000 currently undetected abnormal copy number variants could be found. The ratio of finding abnormalities to procedure complications is 8.5 to 1, which, from a public health perspective, many consider to be reasonable.

2 | METHODS

Our program primarily services an upper socioeconomic status, sophisticated population, and is located in New York City. We provide genetic consults, prenatal screening for chromosomal and Mendelian disorders, ultrasounds, CVS, amniocenteses, fetal tissue biopsies, and fetal reductions. Most of our routine singleton patients come from the New York/New Jersey metropolitan area. More complex patients such as multiples come from all over the United States and abroad.

We studied the number of our patients having CVS and amniocenteses over 5 years from 2013-2017. We then studied the number of patients electing aCGH as part of the laboratory studies from those procedures and the number of abnormalities detected on those laboratory studies. We differentiated them by severity and whether they were de novo or inherited.

We modeled what the number of aCGH would have been over the 5-year period if referrals to our service had not dropped but using the higher rate of acceptance of aCGH seen at the end of the period. We then extrapolated those numbers to what we would have expected in our referral area and nationally in the United States. Statistical analyses were performed by χ^2.

3 | RESULTS

Over the 5-year period, referrals to our service for genetic counseling and consideration of DP dropped by about 40%. Acceptance of DP after counseling has not changed (≈80%), and aCGH utilization steadily increased from 30% in 2013 to 76% in 2017 ($P < .001$). As

such, the absolute number of aCGH tests remained stable until 2017 when it increased despite falling procedures (Table 1). The vast majority of our procedures (94%) are CVS, but the utilization of aCGH particularly at the beginning of this series was higher for amniocentesis as a disproportionate share of amniocenteses were referred to us following second-trimester ultrasounds suggesting concerns.

Overall, we found abnormal aCGH in 4% of patients: 1.5% were inherited, and 2.5% were de novo. Only 1 of the CNVs was of sufficient size as to be seen on karyotype (Table 2).

We then modeled as if referrals had not dropped but acceptance of aCGH had been at current levels for the entire 5 years (Table 3). Had referrals not decreased—mostly, we believe attributable to NIPS, we would have performed 2060 procedures instead of 1461 and done 1039 aCGH vs 710. We would have detected more than double the number of abnormal CNVs.

Of the 17 de novo abnormal CNVs, by traditional metrics, we considered 9 (1.27% of total cases) to be significant and 8 (1.13%) to be of low to middle risk. We modeled that 12 significant cases were never detected (Table 4). Clearly, most of these have been born. At a hospital performing 5000 deliveries per year using our observed incidence of serious CNVs, one would expect 55 such births. Adding the middle risk cases to the high ones, there would be 85.

TABLE 1 Utilization of procedures and aCGH

Year	All CVS	CVS aCGH	%	All AMN	AMN aCGH	%	All Procedures	All aCGH	%
2013	369	114	30.89	43	26	60.47	412	140	33.98
2014	284	116	40.50	20	12	60.00	304	128	42.10
2015	281	119	42.35	36	20	55.56	317	139	43.85
2016	220	135	61.36	24	17	70.83	244	152	62.30
2017	216	164	75.90	19	16	84.20	235	180	76.60
Totals	1370	648	52.80	142	91	64.10	1461	739	50.58
Δ% 2013 to 2017	−41.5	56.2	145.3	−55.9	−38.5	39.2	−33	28.6	125.4

Abbreviations: aCGH, array comparative genomic hybridization; CVS, chorionic villus sampling; AMN, amniocentesis.

TABLE 2 aCGH results

	aCGH Normal	Abnormal aCGH	Abnormal %	De Novo	De Novo %	Inherited	Inherited %	On Karyotype
2013	137	3	2.14	2	1.43	1	0.71	1
2014	123	5	3.91	3	2.34	2	1.56	0
2015	131	8	5.76	4	2.88	4	2.88	0
2016	139	7	4.61	5	3.29	2	1.32	0
2017	180	5	2.78	3	1.67	2	1.11	0
Totals	710	28	3.94	17	2.39	11	1.54	1

Abbreviation: aCGH, array comparative genomic hybridization.

TABLE 3 Modeled for our center

	All CVS	CVS aCGH	% aCGH	All Amnios	AMN aCGH	% aCGH	All Procedures	All aCGH	% aCGH
Totals	1370	648	52.80	142	91	64.10	1461	739	48.90
Modeled	1845	1400	75.9	215	186	86.7	2060	1615	78.40
	aCGH NL	aCGH Abnormal	Abnormal %	De Novo	De Novo %	Inherited	Inherited %	On Karyotype	aCGH Normal
Totals	710	28	3.94	17	2.40	11	1.54	1	Totals
Modeled	1039	60	5.82	36	3.46	23	2.21	2	Modeled

Abbreviations: aCGH, array comparative genomic hybridization; CVS, chorionic villus sampling; NL, normal.

TABLE 4 Our "missed" cases

	Actual		Modeled		# "Missed Cases"
Total abnormals	28/710	3.94%	60/1039	4.09%	32
Total de novo	17/710	2.39%	36/1039	3.46%	12
High risk	9/710	1.27%	19/1039	1.83%	5
Low to middle risk	8/710	1.13%	17/1039	1.64%	**7**
Inherited	11/710	1.61%	19/1039	1.83%	**7**
Abnormal US	2/18	11.10%			

Abbreviation: US, ultrasound.

Nationally, for decades, about 67% screening use has been seen for biochemistry and ultrasound. Noninvasive prenatal screening use might eventually reach 50%.[1] However, if there were 50% use of DP and aCGH, on 4 million births per year in the United States, that would mean 2 million aCGHs is being performed.[21] Using a 1.5% detection rate of abnormal CNVs, we would expect to diagnose 30 000 such abnormalities. On top of these abnormal CNVs, there would be about 4000 aneuploidies for a total of 34 000 abnormalities (Table 5). Using a 1/500 risk of procedures (which is likely an overestimate for well-trained operators), we would expect 4000 losses. Thus, the ratio of detection to complications including pregnancy loss is about 8.5/1. Even if the procedure rate were 25% instead of 50%, the ratio of detection to complications would remain the same. The societal economic benefits would be lower, however. Assuming our model to be reasonable, it is straightforward to change any number and adjust resultant effects.

4 | DISCUSSION

In our own program, more than 30 abnormal CNVs could have been detected had patients come for counseling and followed the same 80% procedure acceptance we have seen for 30 years. What has changed is these patients are not coming for consultations, not that their decisions after genetic counseling have changed.[5]

Noninvasive prenatal screening and aCGH are both disruptive technologies that have had major impact upon the practice of obstetrics and gynecology and reproductive genetics. The introduction of NIPS has been primarily industry driven with large-scale studies done mostly after widespread clinical introduction and extensive marketing.[22] Array comparative genomic hybridization has followed the more traditional paradigm of academic studies, grant funding, and large-scale multicenter investigations before introduction and has not had the mass sales force efforts of NIPS. Noninvasive prenatal screening also allows the primary provider to be able to "work around" the subspecialists and maintain more control of their patients. However, we believe this practice generally does a disservice to patients who desires a complete diagnostic evaluation, but who often do not know there is more available than what they are being offered.[6,22]

Our data are consistent with a general theme we have espoused for several years that the focus of prenatal diagnosis needs to move beyond DS to consider all sources of neurologic and structural impairments.[6,22] With the advent of screening for preeclampsia, further progress is also being added to maternal health disorder screening.[23] The incidence of abnormal CNVs is actually greater than the standard aneuploidies. Particularly for younger women, the detection of abnormal CNVs can be 10 times the expected yield of NIPS.[5,20] Eventually, with deeper next generation sequencing and whole exome sequencing, noninvasive methods may approximate the diagnostic capabilities of DP and aCGH.[23,24] Until that time, however, literally tens of thousands of aCNVs are not being detected because of reliance upon the screening practices of NIPS today.[5,20]

From a public health perspective, including public policy, cost/benefit analysis, and maximizing patient autonomy, moving towards the direction of much higher diagnostic capabilities at the risk of complications including pregnancy loss with a ratio of 8.5/1 would often be considered very compelling. In a diverse society, however, there will never be a uniform acceptance of any stance on this subject. The concept of taking a procedure risk for diagnostic capabilities has been at the center of genetic counseling and prenatal diagnosis for 50 years.[1,6,18] The issues for NIPS vs aCGH are no different than many that have come previously—just the names of the conditions that can be discovered and what resources are used and risks taken to find them.

We have recently estimated that the cost of care of an abnormal CNVs might be about $500 000.[20] Hard data on the costs of numerous serious genetic disorders are generally not available.[25] However, this number is half the generally accepted $1 million for a DS baby. If we compare these numbers against estimated costs for several other medical conditions, it becomes apparent that abnormal CNVs, for which we are doing very little as a public health measure, are costing the medical "system" far more than many issues, for which we devote tremendous efforts to detect and prevent.[20,25] Cumulatively, abnormal CNVs are 3 times the cost of DS and cerebral palsy.[19] The incidences of auto fatalities, gunshot deaths, and HIV are comparable with abnormal CNVs, and the cost of HIV are roughly comparable (Table 6).[26-29] Far more public health efforts are being directed at

TABLE 5 Modeled nationally

	Observed %	National Diagnoses
Total abnormals	3.9	80 000
Total de novo	2.5	50 000
High risk	1.3	22 000
Low to middle risk	1.1	28 000
Inherited	1.1	32 000
Modeled from NICHD	1.7	34 000

TABLE 6 US societal comparisons

	Cases per Year	Cost Lifetime per Case	Total Costs
Down syndrome births	6000	$1 000 000	$6 billion
Cerebral palsy	8000	$1 000 000	$8 billion
HIV cases	40 000	$400 000	$16 billion
Auto fatalities	38 000	$0	$0
Gunshot deaths	34 000	$0	$0
Missed CNVs	34 000	$500 000	$17 billion

Abbreviation: CNV, copy number variant.

these other situations such that the tremendous expense for NIPS for DS represents a very inefficient use of health care dollars.

5 | CONCLUSIONS

In routine obstetrical and genetic practices, there is an unappreciated epidemic of detectable, but not generally detected, CNVs that have significant phenotypic consequences. These occur even in patients for whom there are no other findings as they have normal ultrasounds and karyotypes. Such cases are actually far more prevalent than well-recognized conditions such as DS. We believe that it is time to take a step back and view prenatal screening and diagnosis from the wider perspective of its impact upon society in more than just the strict statistical performance metrics. However, it is impossible to address an epidemic until one recognizes that it exists.

CONFLICT OF INTEREST

One of the author's practice (M.I.E.) includes performing diagnostic procedures described in this manuscript.

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