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# What is the real "price" of more prenatal screening and fewer diagnostic procedures?

*Costs and trade-offs in the genomic era.*

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In the accompanying commentary[1], two trends in prenatal testing are framed as competing – the reduction in diagnostic testing due to cell-free DNA-based (cfDNA) screening, and the increased diagnostic capacity of chromosomal microarrays (CMA). They provide a simplified cost-benefit analysis of universal diagnostic testing with CMA combined with the option of pregnancy termination for pathogenic findings and conclude that this may be more cost-effective than screening approaches.

## 1. Have women really "paid a price" for embracing cfDNA?

Evans and colleagues refer to the recent changes in practice as a "shift from diagnostics to screening". While "shift" may describe the numerical trends in prenatal testing, our fundamental screening paradigm has not changed. Rather, screening has improved enough that for many women, this is adequate and is preferable to diagnostic testing. Diagnostic tests are still positioned as follow-up confirmation after

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screening, including screening with maternal age alone, and universal diagnostic testing is not a recommended approach that is being abandoned in favor of screening. Any screening approach, including with cfDNA, will have inferior detection compared with 100% diagnostic testing with CMA.

It is important to recognize that the decrease in diagnostic testing is a trend that began before the introduction of cfDNA screening. Population-based data from the Australian state of Victoria, as well as from the Kaiser Permanente health system in Northern California, demonstrate that the reduction in diagnostic testing is a long-standing trend that predated cfDNA. In Victoria, diagnostic testing rates peaked at 8.9% of all births in the 1990s when maternal age and second trimester serum screening were the most common indications for testing, and began to decline following the introduction of combined first trimester screening (CFTS) in 2000 (Figure 1A).[2] In the Kaiser system, similarly, decreases in rates of diagnostic testing were seen in the decade before the introduction of cfDNA screening.[3]

So, has the overall decline in testing led to a reduction in the prenatal detection of major chromosome abnormalities? Our data suggest that this is not the case. CfDNA screening in Victoria is a self-funded choice that women may choose as a first or second line screen, within a well-established paradigm of CFTS, first and second trimester ultrasound, and high utilization of CMA (> 85% of all diagnostic tests in 2015).[4] State-wide data show that the prenatal detection of fetal chromosome

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abnormalities has continued to climb since cfDNA became available in 2013, despite the dramatic decline in diagnostic procedures (Figure 2A). Furthermore, this trend is largely driven by an increase in major chromosome abnormalities other than trisomy 21 (52% of abnormalities in 2015) (Figure 2B). These other abnormalities included trisomy 18 (11%), pathogenic CNVs (10%), level III mosaicism (9%), sex chromosome abnormalities (7%), triploidy (4%) and trisomy 13 (4%).[4] When the state cohort of 100,418 women undergoing CFTS during the years 2014-15 was analysed, 90% of major chromosome abnormalities not detectable by standard cfDNA (ie other than trisomies 21,18,13 and sex chromosome abnormalities) would have been detected if diagnostic testing were performed in women with: CFTS risk > 1 in 100, serum PaPP-A or beta-HCG < 0.2 MoM, or fetal abnormality on first or second trimester ultrasound.[5]

Therefore, in our population, women have reaped the benefits of advances in both screening (CFTS +/or cfDNA + ultrasound) and diagnostic testing (CMA), though the benefits of cfDNA may not be equitably distributed across all socioeconomic groups.[6] These complementary – not competing - advances have resulted in record yields from diagnostic testing: in the most recent published data, only 5 diagnostic tests were needed to detect each major chromosome abnormality.[4] In fact, it could be argued that the “price” of performing fewer diagnostic tests has actually been borne by the medical profession via its downstream effect on training, skills maintenance and clinical practice volume.[7]

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**2. Should all women be offered universal diagnostic testing as an alternative to screening?**

That CMA is capable of detecting clinically significant copy number variants (CNV) in ~1% of fetuses with no structural abnormalities challenges the existing approach of offering a screening test prior to diagnostic testing, as there is currently no accepted screening test for these genome wide CNVs. Offering all pregnant women diagnostic testing with CMA as an alternative to aneuploidy screening would represent a significant paradigm shift, by labelling all pregnancies as being at sufficient risk to warrant diagnostic testing. The opportunity for diagnostic testing may be welcomed by women who seek information, while it may increase anxiety for others. Regardless of what miscarriage risk is quoted, most women do not welcome the idea of an invasive test and will make their decision based on their personal preferences for information and avoiding procedure-related complications.

The challenges inherent in offering diagnostic testing to all pregnant women include ensuring informed consent and equity of access, managing uncertain and unexpected findings, and providing well-supported clinical pathways for those with abnormal results. In this respect, a universal prenatal diagnostic program should aim to be as accessible and uniform as newborn screening programs. However, universal prenatal diagnosis will never achieve the same uptake as newborn

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screening as the test itself is not as acceptable, in part because the risks, benefits and available choices are very different.

Another particular challenge raised by universal diagnostic testing in low risk pregnancies is the current shotgun approach to detection of any dosage aberration. The limitations in current knowledge of the natural history of many CNVs means that variations of uncertain significance are likely to outnumber pathogenic findings. The potential for short and long-term harm – both financial and psychological – is a major consideration when considering implementation of universal diagnostic testing.[8] Couples who receive a diagnosis of a variant of unknown or uncertain significance (VUS) may then experience a difficult and stressful pregnancy, whether or not they ultimately deliver a healthy infant. Furthermore, this anxiety may continue for years as the parents watch their child for the emergence of a suspected phenotype.[9] It could certainly be argued that this is a hidden "price" to be paid for offering universal diagnostic testing and abandoning the presumption of a normal infant in otherwise uncomplicated pregnancies.

**3. Cost-utility and the importance of patient preferences**

The paper by Evans et al does not address or consider the role of patient preferences; but the values and preferences of the women who choose to undergo or to decline these tests, are of paramount importance and are an important driver of relative test volumes. An assumption of his commentary is that women would, if they

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understood the benefits of diagnostic testing, prefer CMA over cfDNA screening. However, data indicate that this is not always the case.

In a randomized trial published in 2014, Kuppermann and colleagues conducted a study of the impact of comprehensive patient education and counseling on prenatal testing decisions.[10] A cohort of women was randomized to either view a comprehensive, computerized informational tool that explained the risks and benefits of all the available aneuploidy screening and diagnostic testing options, or to receive usual care; this usually consisted of a brief conversation with the provider and provision of a brochure. All costs were covered, and the results demonstrated that women who received more comprehensive information had a better understanding of the testing options but were less likely to choose diagnostic testing and were, in fact, more likely to decline testing altogether. While neither cfDNA nor CMA were available at the time this study was conducted, the results demonstrated clearly that this cohort of women generally felt that the additional information or certainty gained through diagnostic testing was not enough to justify undergoing an invasive procedure. On a broader scale, this is reflected in the trends seen in prenatal diagnosis and screening.

Furthermore, when women do decide to have an invasive procedure, they may not wish to have maximum genomic information about their fetus. A clinical study offering women a choice between targeted and extended analysis by CMA showed

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that 40.5% of women chose to receive information only on pathogenic CNVs with 100% penetrance, and to forgo information on VUS and susceptibility genes.[11]

In another recent study, a cost utility analysis was performed to assess outcomes of six testing strategies, including diagnostic testing with CMA, cfDNA screening, or traditional serum and nuchal translucency based screening, alone, in combination, or in sequence.[12] Quality adjusted life years were measured in a cohort of women using time trade-off utilities, and outcomes considered included birth of a child with a chromosome abnormality, as well as miscarriage, detection of a VUS, and termination of an abnormal fetus, among others. The probabilities for each of these outcomes were obtained from the literature. Although diagnostic testing resulted in the most abnormalities detected, interestingly, cfDNA or traditional screening with low risk results had a higher utility than diagnostic testing with normal results. Furthermore, traditional screening was the most cost effective until maternal age 40, when cfDNA was the optimal test and most cost effective. Again, this model, which was far more complex and considered many more outcomes than that described by Evans et al, had quite different (and somewhat surprising) results when women's preferences were measured and considered.

Obviously, such models are complex, and individuals will often indicate a planned, hypothetical behavior that is different than what they actual choose when faced with real life circumstances. This is often the case with prenatal testing, in which women

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may state a preference for obtaining the most information, but when actually pregnant and needing to make a decision, they are willing to rely on a screening test and accept a modestly lower detection rate.

**Conclusion**

CfDNA screening should not be seen as a threat to informed choice. Rather, we must acknowledge that as screening methods have become so much better – more specific and sensitive – women are comfortable relying on such screening to put them in a low risk category, and many do not feel they need the certainty of a diagnostic test. These changes have not led to a decline in detection of fetal chromosome abnormalities – in fact, we are now seeing historically high yields from prenatal testing.

That being said, for *some* women, comprehensive information and certainty is important. Offering such women all options, with a careful and comprehensive explanation of the risks and benefits of each, results in outcomes that are best aligned with women's preferences while at the same time, requiring fewer diagnostic tests and therefore lowering costs. This is one of the primary challenges of the modern era of prenatal testing - to ensure that women understand their choices and and have adequate and accurate information on which to make informed decisions.

**Disclosures**

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## Figure legends

Figure 1. Rates of prenatal diagnostic testing in Victoria, Australia

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(Data courtesy of the Murdoch Children's Research Institute)

Figure 1A. Rates of prenatal diagnostic testing as a percentage of all births in Victoria 1976-2015.

Figure 1B. Rates of prenatal diagnostic testing in Victoria according to combined first trimester screening risk for trisomy 21 in 2002-04 and 2014-15.

CFTS, combined first trimester screening with nuchal translucency, serum PaPP-A and beta HCG.

Figure adapted from *Lindquist A, Poulton A, Jane Halliday, Hui L. Prenatal diagnostic testing and atypical chromosome abnormalities following combined first trimester screening: implications for contingent models of non-invasive prenatal testing. Ultrasound Obstet Gynecol. 2017; DOI: 10.1002/uog.18979.*

Figure 2. Annual prenatal diagnoses of major chromosome abnormalities in Victoria (2000-2015) (Data courtesy of the Murdoch Children's Research Institute)

Figure 2A. Annual numbers of trisomy 21 and other major chromosome abnormalities detected by amniocentesis or chorionic villus sampling.

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Definition of major abnormality includes: autosomal trisomy and monosomy, pathogenic copy number variation, level III mosaicism, sex chromosome aneuploidy, triploidy (excludes variants of unknown/uncertain significance, confined placental mosaicism, benign copy number variants, balanced rearrangements)

Figure 2B. Annual rate of prenatal major chromosome abnormalities per 1000 births

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**Fig. 1A Annual prenatal diagnosis rate (% of births)**

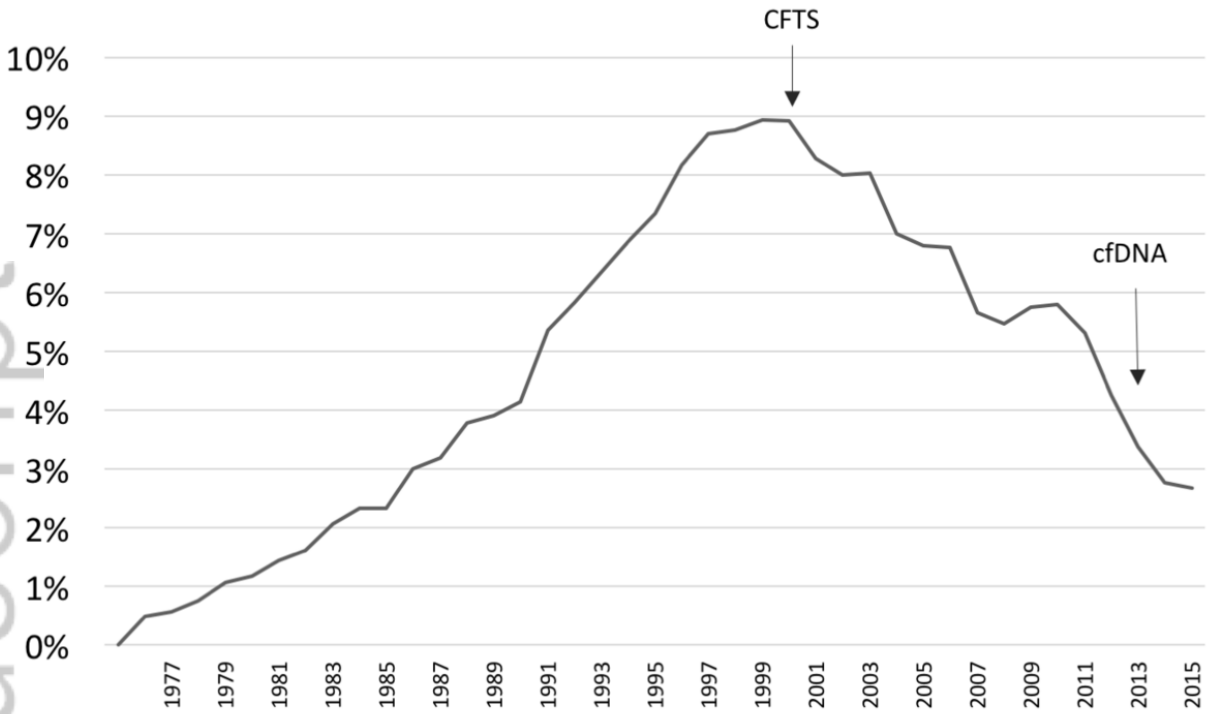
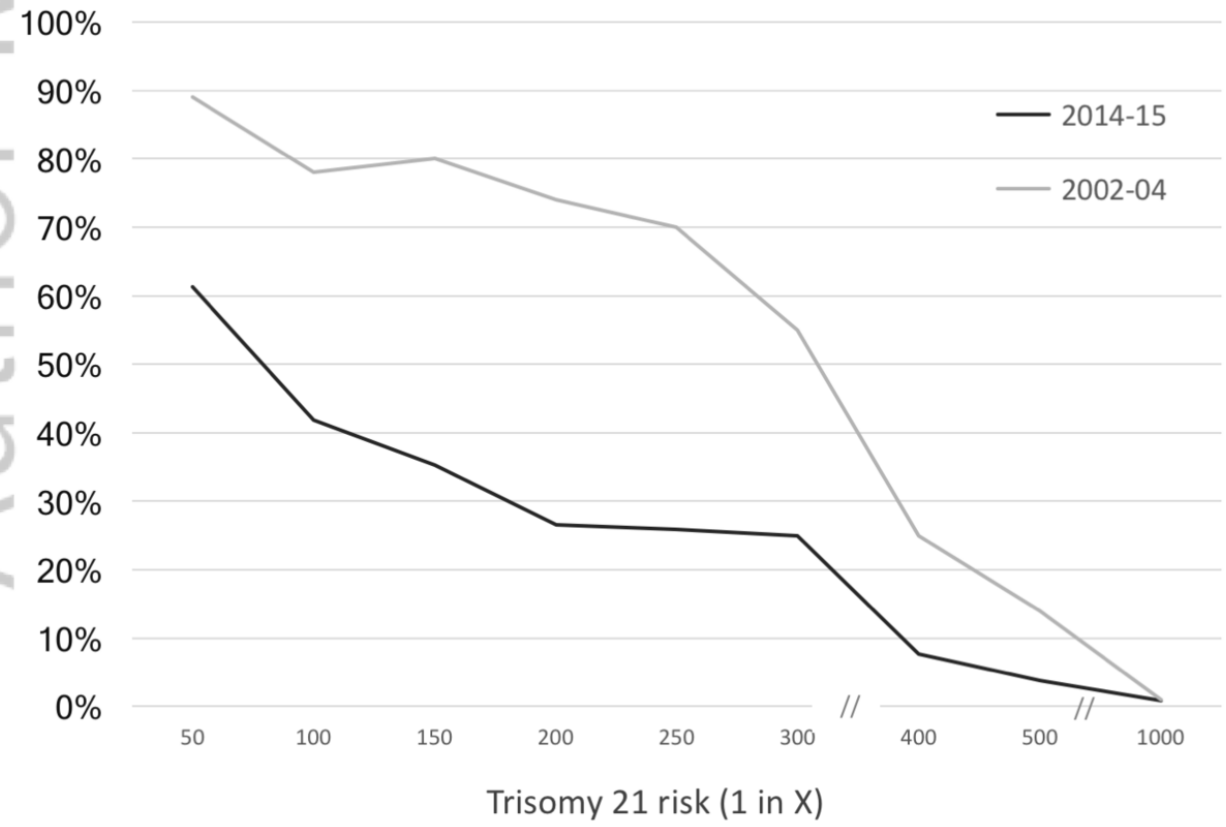



**Fig 2B. Diagnostic testing after combined first trimester screening (2002-04 vs 2014-15)**




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**Fig 2A. Annual numbers of prenatal chromosome abnormalities**

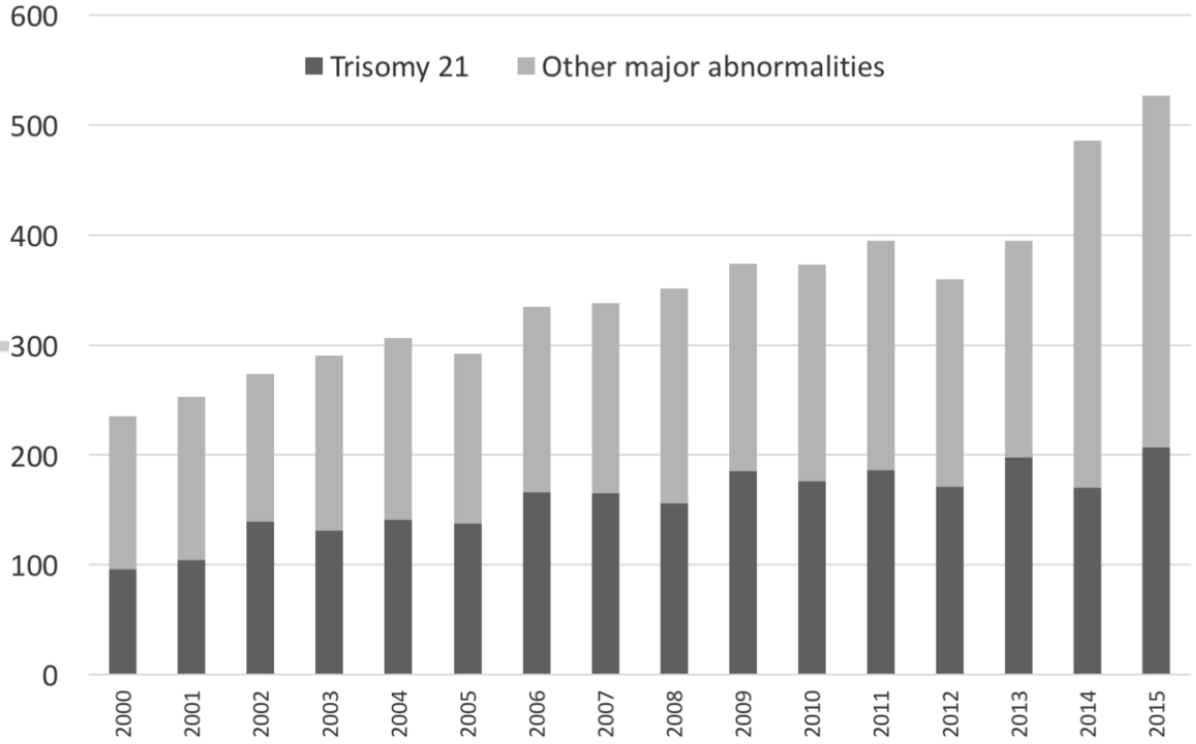
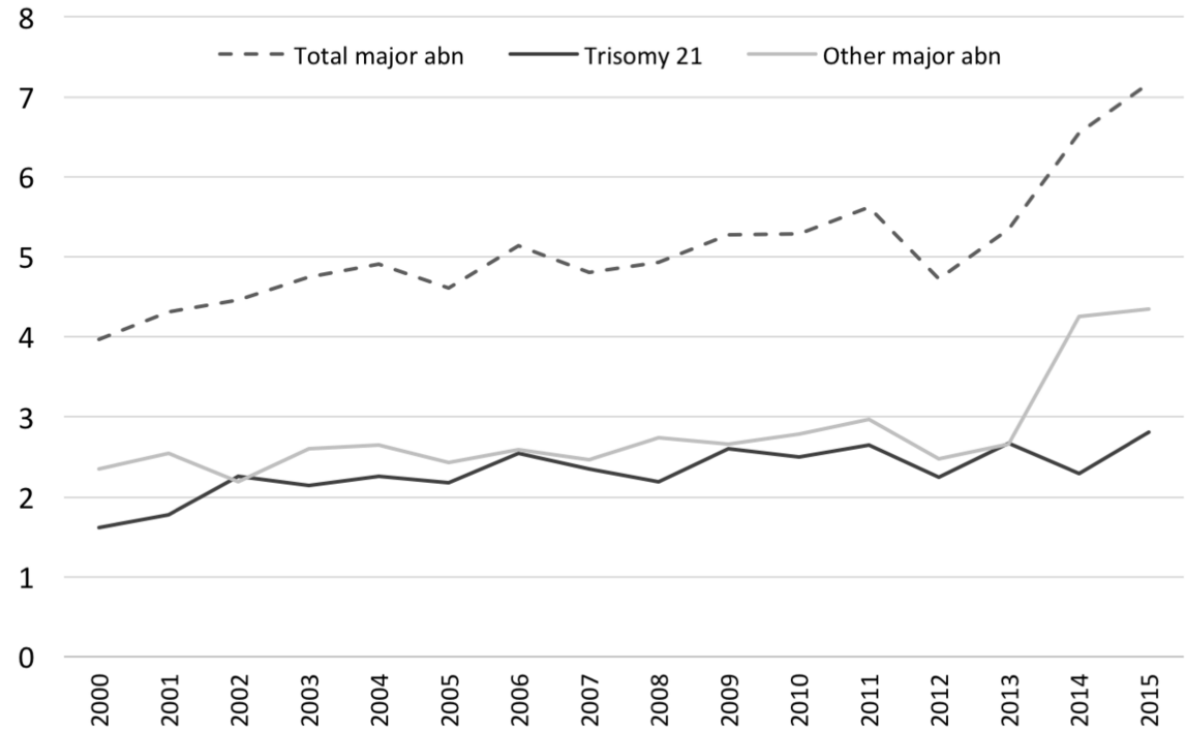



**Fig 2B. Prenatal chromosome abnormalities /1000 births**




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