Not-so-free testing for cell-free DNA

Darryl Huang MD Karen Lundgard MD CCFP Michael R. Kolber MD CCFP MSc

Clinical question

Can cell-free DNA (CF-DNA) tests, also known as noninvasive prenatal tests (NIPTs), be recommended to women to screen for trisomies?

Bottom line

Best evidence suggests that CF-DNA testing at 10 to 14 weeks' gestation is more sensitive (100%) and specific (99.9%) than current screening for trisomy 21 and approaches the accuracy of amniocentesis. Use might be limited by high cost and lack of provincial coverage.

Evidence

A multicontinent prospective study of 18955 women with singleton pregnancies compared standard first-trimester screening (plasma protein A and β–human chorionic gonadotropin levels, nuchal translucency) with maternal blood CF-DNA tests for detecting trisomies 21, 18, and 13.[1]

- Patients and physicians were aware of standard test results (not CF-DNA). Decisions were made according to standard clinical practice.
- A CF-DNA test was done at 10 to 14 weeks' gestation by staff blinded to the other test results. Results were reported after delivery.
- Outcome assessors (blinded to test results) reviewed newborn examination and genetic test records.
- The CF-DNA results identified trisomy 21 in all 38 cases; standard screening identified 30 of 38 (79%).
- False-positive results were identified by standard screening in 5% of cases and by CF-DNA testing in less than 0.1%. The CF-DNA test had sensitivity of 100%, specificity of 99.9%, a positive likelihood ratio (LR+) of 1756, and a negative likelihood ratio (LR-) of 0. Standard testing had sensitivity of 78.9%, specificity of 94.6%, LR+ of 15, and LR- of 0.22.
- A CF-DNA test accurately detected trisomies 18 and 13 in 12 cases (LR+ >5000, LR- <0.1).
- In 3% of cases, unusable CF-DNA was found; this subgroup had a higher rate of aneuploidy (2.7% vs 0.4%).
- The CF-DNA test manufacturer supported the study.
- An earlier meta-analysis of 37 studies (N = 22 659) found similar results.[2]

Context

- Risk of trisomy 21 increases with maternal age.[3]
- Risk of pregnancy loss with amniocentesis is about 0.5% and with chorionic villus sampling is 1% to 2%.[3,4]
- The Society of Obstetricians and Gynaecologists of Canada recommends discussing screening for trisomies with all pregnant mothers[5]; CF-DNA testing could be used instead of amniocentesis but termination decisions should not be based only on its results.[6]
- Coverage of CF-DNA varies across Canada, with self-pay costing about $500. Compared with standard screening, CF-DNA testing is likely cost effective.[7]

Implementation

Most pregnant women would use NIPTs if available,[8,9] including more than half who previously refused prenatal screening.[10] Studies cite test safety and accuracy, and a possible reduction in invasive procedures as reasons to offer NIPTs to all pregnant women.[9] In some areas of Canada, CF-DNA tests are covered for women who had a positive initial result, are older than 40 years, or had a previous trisomy pregnancy.[3,8] It takes time to perform a test, receive results, and discuss these results and explore patient preferences. Decision aids increase patients' involvement in health care decisions and improve risk estimates and patient satisfaction.[11]

Dr Huang was a family medicine resident at the University of Alberta in Fort McMurray. **Dr Lundgard** is a rural family physician in Peace River, Alta. **Dr Kolber** is Associate Professor in the Department of Family Medicine at the University of Alberta in Edmonton.

Competing interests
None declared

References

1. Norton ME, Jacobsson B, Swamy GK, Laurent LC, Ranzini AC, Brar H, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med* 2015;372(17):1589-97.
2. Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol* 2015;45(3):249-66.
3. BC Prenatal Genetic Screening Program. *Perinatal Services BC obstetric guideline: prenatal screening for Down syndrome, trisomy 18 and open neural tube defects.* Vancouver, BC: Perinatal Services BC; 2016.
4. Caughey AB, Hopkins LM, Norton ME. Chorionic villus sampling compared with amniocentesis and the difference in the rate of pregnancy loss. *Obstet Gynecol* 2006;108(3 Pt 1):612-6.
5. Chitayat D, Langlois S, Wilson RD; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada; Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists. Prenatal screening for fetal aneuploidy in singleton pregnancies. *J Obstet Gynaecol Can* 2011;33(7):736-50.
6. Langlois S, Brock JA; Genetics Committee, Wilson RD, Audibert F, Brock JA, et al. Current status in non-invasive prenatal detection of Down syndrome, trisomy 18, and trisomy 13 using cell-free DNA in maternal plasma. *J Obstet Gynaecol Can* 2013;35(2):177-83.
7. Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. *J Matern Fetal Neonatal Med* 2016;29(7):1160-4.
8. Pariente G, Hasan L, Gadot Y, De Souza LR, Lebovic G, Berger H. Canadian women's attitudes toward noninvasive prenatal testing of fetal DNA in maternal plasma. *J Matern Fetal Neonatal Med* 2016 Mar 4. Epub ahead of print.
9. Lewis C, Hill M, Chitty LS. Women's experiences and preferences for service delivery of non-invasive prenatal testing for aneuploidy in a public health setting: a mixed methods study. *PLoS One* 2016;11(4):e0153147.
10. Verweij EJ, Oepkes D, de Vries M, van den Akker ME, van den Akker ES, de Boer MA. Non-invasive prenatal screening for trisomy 21: what women want and are willing to pay. *Patient Educ Couns* 2013;93(3):641-5.
11. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2014;(1):CD001431.

Tools for Practice articles in *Canadian Family Physician (CFP)* are adapted from articles published on the Alberta College of Family Physicians (ACFP) website, summarizing medical evidence with a focus on topical issues and practice-modifying information. The ACFP summaries and the series in *CFP* are coordinated by **Dr G. Michael Allan**, and the summaries are co-authored by at least 1 practising family physician and are peer reviewed. Feedback is welcome and can be sent to **toolsforpractice@cfpc.ca**. Archived articles are available on the ACFP website: **www.acfp.ca.**