“Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing”
(Diana W. Bianchi, MD, Lawrence D. Platt, MD, James D. Goldberg, MD, Alfred Z. Abuhamad, MD, Amy J. Sehnert, MD, and Richard P. Rava, PhD, on behalf of the Maternal Blood IS Source to Accurately diagnose fetal aneuploidy (MELISSA) Study Group)  
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1. The authors contrast their study to other sequencing studies in that theirs is prospective. Is it important for this type of study to be prospective? Why or why not?

2. The authors explain their sample size in the methods section. Define sensitivity, specificity, and precision. Explore why a larger number of unaffected controls (~4:1 ratio) would estimate the specificity with greater precision.

3. The MPS laboratory that ran the maternal samples is described as “blinded.” What do the authors mean by “blinded”? Is it important? What procedures can be used for blinding?

4. Review how the MPS lab identified aneuploidy and sex chromosome status using the maternal blood. How do they address the issue of maternal DNA mixed with fetal DNA?

5. Review the results of the study. What was the sensitivity and specificity of the test for detection of T21, T18, T13? (Review definitions and calculations of sensitivity and specificity if needed). How does this compare to other tests?

6. Review the entry for this trial in clinicaltrials.gov (NCT01122524). Were the primary and secondary outcomes reported in the manuscript? Discuss the planned enrollment stated in the clinicaltrials.gov listing and the final enrollment in the manuscript. Why is there a discrepancy, and would that discrepancy affect a case-control study?

7. The authors recommend utilizing this test after a positive first- or second-trimester screening result. Why?

8. At this time, with the currently available data, should this test be considered the primary screening and noninvasive diagnostic test for fetal aneuploidy? Why or why not?

9. The authors studied women with high-risk pregnancies. Discuss why this study was performed with women with high-risk pregnancies (see Discussion section). What are the implications for low-risk women?

10. Describe how you would counsel a woman interested in this test. What are the limitations of the test? What are the implications of the results? Is an invasive test ever needed?

11. Will the findings from this analysis change your practice? How?