MYRIAD

Prequel™

Prenatal Screen

EXECUTIVE SUMMARY

Every pregnant woman and her doctor share the goal of delivering a healthy, full-term baby. During pregnancy, however, chromosomal abnormalities can occur that cause serious birth defects, health problems and/or intellectual disabilities. Conventional prenatal screening methods, such as maternal serum screening with or without specialized ultrasound assessment, have traditionally had an overall false positive rate of around 5%, resulting in unnecessary and costly invasive diagnostic procedures and patient anxiety.[1]

Non-invasive prenatal screening (NIPS) is a newer method of identifying pregnancies at increased risk for genetic abnormalities via analysis of cell-free DNA (cfDNA). NIPS requires only a blood sample from the mother, and because chromosomal abnormalities occur in the earliest stages of development, screening can be done as early as ten weeks. Compared to maternal serum screening, NIPS has a positive predictive value (PPV) – the likelihood that a positive test result is associated with an affected pregnancy – that is 20x higher, with 100x fewer false positives.[1] Professional societies including the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) now recognize NIPS as a screening method for all women, regardless of age or risk.[2,3]

The Prequel™ Prenatal Screen from Myriad Genetics, Inc. detects pregnancies at increased risk for certain chromosome conditions with extremely high accuracy.[4]

Prequel provides reliable results with unmatched accuracy. Prequel has an industry-leading test failure rate of 0.1%[4] and validated accuracy across patient types, including those with high body mass index (BMI) who have test-fail rates up to 24% with other NIPS offerings.[5,6] Low test failure and high accuracy lead to fewer redraws, fewer invasive diagnostic procedures, shorter overall turnaround time, and less patient anxiety.[7-9]

Prequel provides patients with more accurate, actionable information. NIPS identifies 15% more trisomy cases, reduces invasive diagnostic procedures by 88%, and reduces fetal loss due to those procedures by 94%, compared to maternal serum screening.[10]

Prequel supports responsible healthcare cost management. Multiple studies have concluded that NIPS is an economical alternative to first-tier conventional screening in the general population.[10-12]

TEST DESCRIPTION

All women, including those with high body-mass index (BMI), an ovum donor, a surrogate, or a twin pregnancy can be offered Prequel. The test requires a single blood sample from the mother, and results are available in approximately one week.

Prequel uses whole-genome sequencing of cfDNA to detect the presence of the following chromosome abnormalities:

Trisomies:
- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)

Sex Chromosomes:
- Monosomy X (Turner syndrome)
- XXY (Klinefelter syndrome)
- Trisomy X (Triple X syndrome)
- XYY (Jacob syndrome)

INTENDED USE POPULATION

The Prequel Prenatal Screen is intended for all pregnant women, regardless of age, risk, or body mass index (BMI), as early as ten weeks of pregnancy until term. Prequel is appropriate for singleton or twin pregnancies, as well as those pregnancies achieved with an ovum donor or surrogate.

ANALYTICAL VALIDITY

Numerous studies demonstrate that NIPS is a highly accurate method of detecting presence (or absence) of common fetal aneuploidies.[13-15] Independent test performance studies of Prequel using reference lab data and clinical outcomes data showed reproducible results with high precision.[16]

CLINICAL VALIDITY

Prequel's unique and superior clinical test performance, particularly at low fetal fraction levels, was highlighted by Hancock et al. in a retrospective analysis of 58,105 samples from the general obstetric population. In the full cohort, inferred sensitivities for T21, T18, and T13 were 99.7%, 96.8%, and 94.3%, respectively, and PPVs were 93.1%, 85.2%, and 48.4%, respectively. Prequel yielded a result for 99.9% of patients, meaning that only 1 in 1000 patients received a test failure.[4] Additionally, Muzzey et al. used the same cohort to show that irrespective of BMI, the sensitivity of Prequel for common aneuploidies exceeds that of traditional screening.[5]

CLINICAL UTILITY

The clinical utility of aneuploidy screening in the general population has been well established. For women whose tests show the potential of a chromosomal abnormality, having this information in advance allows them and their partners to pursue additional diagnostic testing, speak with specialists, or find the ideal place to deliver. Due to its accuracy and safety, NIPS is rapidly replacing older aneuploidy screening modalities. Clinical studies show high patient uptake rates and understanding of the basic concept of NIPS, making for easy incorporation into routine obstetrical practices.[21]

MEDICAL SOCIETY GUIDELINES

Most professional societies, including the ACOG, ACMG, SMFM, the National Society of Genetic Counselors (NSGC), and the International Society for Prenatal Diagnosis (ISPD) recognize and support offering NIPS as an option to pregnant women, regardless of a priori risk.[2,3, 23, 24] The ACMG updated its position statement in 2016 to recommend informing all pregnant women that NIPS is the most sensitive screening option for traditionally-screen aneuploidies involving chromosomes 13, 18, and 21.[3]

HEALTH ECONOMICS

Multiple studies demonstrate that NIPS can be a cost-effective alternative to conventional screening. Because NIPS is a more accurate alternative, its use can substantially reduce the number of unnecessary invasive

diagnostic procedures such as amniocentesis and chorionic villus sampling (CVS). A study based on decision-analytic modeling for 4 million pregnancies estimated an 88% reduction in invasive procedures.[10] Another study, based on more than 13,000 pregnancies, found that NIPS reduced invasive procedures by 60% and the number of procedure-related euploid fetal losses by 73.5%.[11] A third study (based on over 12,000 pregnancies in the baseline year and over 7,000 in follow-up year) showed a 42% increase in NIPS tests ordered coincided with a 15% decrease in invasive diagnostic tests for trisomy syndromes.[12]

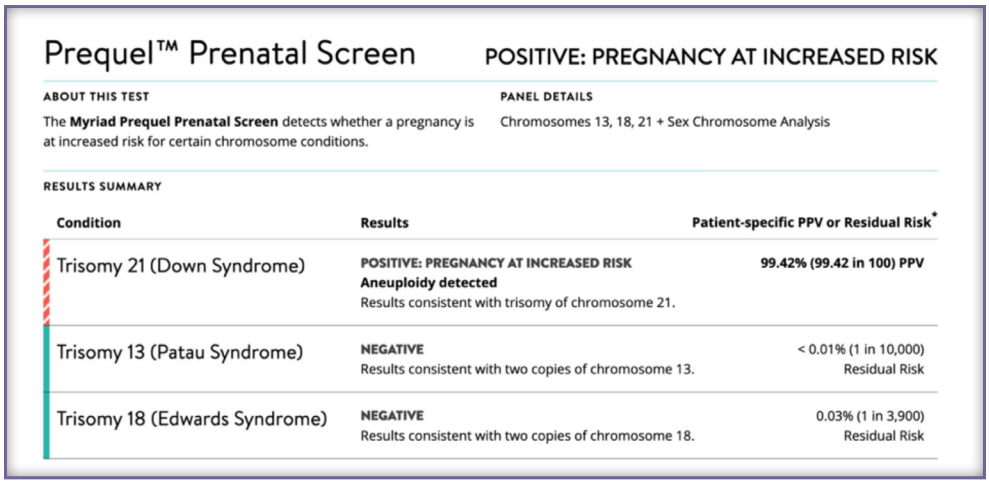
The key determining factors in the economics of NIPS are the timing of screening, cost of the test, and pregnancy termination rates.[10-12, 25]

TEST REPORT

The Prequel report offers clear risk assessment with individualized PPVs and residual risk estimates, so your providers can help patients decide on next steps. Test results can be securely accessed online by both your physicians and members via Myriad Complete, our patient-friendly online portal. Myriad also provides consults with Patient Educators, tailored to help answer any questions the patients may have.

To further facilitate results delivery, Myriad Genetics developed an automated results delivery platform shown to effectively manage large-scale return of NIPS results in a manner that satisfies patients and providers.[22]

Sample report



Prequel™ Prenatal Screen

POSITIVE: PREGNANCY AT INCREASED RISK

ABOUT THIS TEST

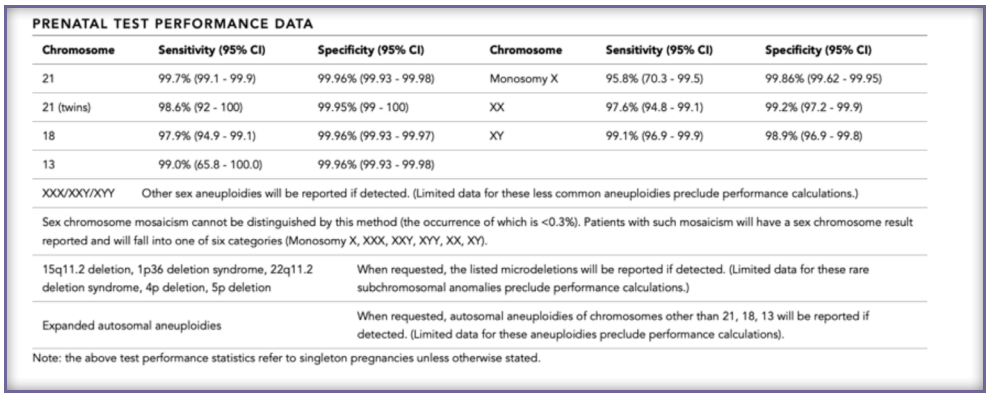
The **Myriad Prequel Prenatal Screen** detects whether a pregnancy is at increased risk for certain chromosome conditions.

PANEL DETAILS

Chromosomes 13, 18, 21 + Sex Chromosome Analysis

RESULTS SUMMARY

Condition	Results	Patient-specific PPV or Residual Risk*
Trisomy 21 (Down Syndrome)	**POSITIVE: PREGNANCY AT INCREASED RISK** **Aneuploidy detected** Results consistent with trisomy of chromosome 21.	**99.42% (99.42 in 100) PPV**
Trisomy 13 (Patau Syndrome)	**NEGATIVE** Results consistent with two copies of chromosome 13.	< 0.01% (1 in 10,000) Residual Risk
Trisomy 18 (Edwards Syndrome)	**NEGATIVE** Results consistent with two copies of chromosome 18.	0.03% (1 in 3,900) Residual Risk



PRENATAL TEST PERFORMANCE DATA

Chromosome	Sensitivity (95% CI)	Specificity (95% CI)	Chromosome	Sensitivity (95% CI)	Specificity (95% CI)
21	99.7% (99.1 - 99.9)	99.96% (99.93 - 99.98)	Monosomy X	95.8% (70.3 - 99.5)	99.86% (99.62 - 99.95)
21 (twins)	98.6% (92 - 100)	99.95% (99 - 100)	XX	97.6% (94.8 - 99.1)	99.2% (97.2 - 99.9)
18	97.9% (94.9 - 99.1)	99.96% (99.93 - 99.97)	XY	99.1% (96.9 - 99.9)	98.9% (96.9 - 99.8)
13	99.0% (65.8 - 100.0)	99.96% (99.93 - 99.98)			

XXX/XXY/XYY	Other sex aneuploidies will be reported if detected. (Limited data for these less common aneuploidies preclude performance calculations.)
Sex chromosome mosaicism cannot be distinguished by this method (the occurrence of which is <0.3%). Patients with such mosaicism will have a sex chromosome result reported and will fall into one of six categories (Monosomy X, XXX, XXY, XYY, XX, XY).	
15q11.2 deletion, 1p36 deletion syndrome, 22q11.2 deletion syndrome, 4p deletion, 5p deletion	When requested, the listed microdeletions will be reported if detected. (Limited data for these rare subchromosomal anomalies preclude performance calculations.)
Expanded autosomal aneuploidies	When requested, autosomal aneuploidies of chromosomes other than 21, 18, 13 will be reported if detected. (Limited data for these aneuploidies preclude performance calculations).

Note: the above test performance statistics refer to singleton pregnancies unless otherwise stated.

REFERENCES

1. Norton, M. et al Cell-free DNA analysis for noninvasive examination of trisomy. The New England Journal of Medicine April 2015; 372: 1589-97.
2. Practice Bulletin No. 163: Screening for fetal aneuploidy. Obstet Gynecol. 2016;127(5):e123-37.
3. Gregg AR. et al. Noninvasive prenatal screening for fetal aneuploidy. 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016;18(10):1056-1065.
4. Hancock S, Ben-Shachar R, Adusei C, Oyolu CB, Evans EA, Kang HP, Haverty C, Muzzey D. "Clinical experience across the fetal-fraction spectrum for a non-invasive prenatal screen with low test-failure rate." Ultrasound Obstet Gynecol. 2019 Oct 31. doi: 10.1002/uog.21904.
5. Muzzey D, Goldberg JD, Haverty C.Noninvasive prenatal screening for patients with high bodymass index: Evaluating the impact of a customized wholegenome sequencing workflow on sensitivity and residual risk.PrenatalDiagnosis. 2019;1–9.https://doi.org/10.1002/pd.5603MUZZEYET AL.9
6. Yared E, Dinsmoor MJ, Endres LK, Vanden Berg MJ, Maier Hoell CJ, Lapin B, Plunkett BA, "Obesity Increases the Risk of Failure of Non-Invasive Prenatal Screening Regardless of Gestational Age", American Journal of Obstetrics and Gynecology (2016), doi: 10.1016/ j.ajog.2016.03.018.
7. Taneja et al. Noninvasive prenatal testing in the general obstetric population: clinical performance and counseling over 85,000 cases†. Prenatal Diagnosis 2016, 36, 1 -7.
8. Bianchi DW, Parker RL, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. The New England Journal of Medicine. 2014: 370(9):799-808.
9. Artieri, C.G. et al. (2017) Noninvasive Prenatal Screening at Low Fetal Fraction: Comparing whole-genome sequencing and single-nucleotide polymorphism methods. Prenat Diagn, doi: 10.1002/pd.503.
10. Fairbrother G, Burigo J, Sharon T, and 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; 29:1160-4.
11. Benn P, Chapman S, Curnow KJ, Hornberger J, Michalopoulos SN, and Rabinowitz M. An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. PloS One. 2015; 10:e0132313.
12. Walker BS, Ashwood ER, Grenache DG, Jackson BR, Nelson RE, and Schmidt RL. "A Cost-Effectiveness Analysis of First Trimester Non-Invasive Prenatal Screening for Fetal Trisomies in the United States." PloS One. 2015; 10:e0131402. PMID: 26133556.
13. Chiu Chiu RW, Akolekar R, Zheng YW, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. BMJ. 2011;342:c7401
14. Ehrich M, Deciu C, Zwiefelhofer T, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. Am J Obstet Gynecol 2011; 204:205.e1-11.
15. Sehnert AJ, Rhees B, Comstock D, et al. Optimal detection of fetal chromosomal abnormalities by massively parallel DNA sequencing of cell-free fetal DNA from maternal blood. Clin Chem. 2011;57(7):1042-1049.
16. Data on file.
17. Bianchi DW, Platt LD, Goldberg JD, et al. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol 2012; 119: 890– 901.
18. Futch T, Bhatt S, de Feo E, Rava RP, Sehnert AJ, and Spinosa J. Initial clinical laboratory experience in noninvasive prenatal testing for fetal aneuploidy from maternal plasma DNA samples. Prenat Diagn. 2013;33:569-74. PMID: 23592485.
19. Bianchi DW, CARE Study Group, Chudova DI, Craig JA, Das AF, Devers PL, et al. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med. 2014;370:799-808. PMID: 24571752.
20. Gil MM, Accurti V, Nicolaides KH, Plana MN, and Santacruz B. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2017;50:302-14. PMID: 28397325.
21. Palomaki GE, Eklund EE, Kloza EM, Lambert-Messerlian GM, and O'Brien BM. The Clinical Utility of DNA-Based Screening for Fetal Aneuploidy by Primary Obstetrical Care Providers in the General Pregnancy Population. Genet Med. 2017;19:778-86. PMID: 28079901.
22. Arjunan A, Ben-Shachar R, Kostialik J, et al. Technology-Driven Noninvasive Prenatal Screening Results Disclosure and Management. Telemed J E Health. 2019. https://doi.org/10.1089/tmj.2018.0253.
23. National Society of Genetic Counselors. Position Statements: Prenatal Cell-Free DNA Screening. 2016. https://www.nsgc.org/p/bl/et/blogaid=805 (accessed 10/28/19).
24. Benn P, Borrell A, Chiu RW, Cuckle H, Dugoff H, Fass B, et al. Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. 2015;35:725-34. PMID: 25970088.
25. McQueen R. B., Schroeder B, Wright G, Barlow J, Sherman M. (2019) Evaluation of Coverage Expansion for Non-Invasive Prenatal Testing Through a Performance-Based Risk Sharing Agreement.

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