MaterniT21™ PLUS

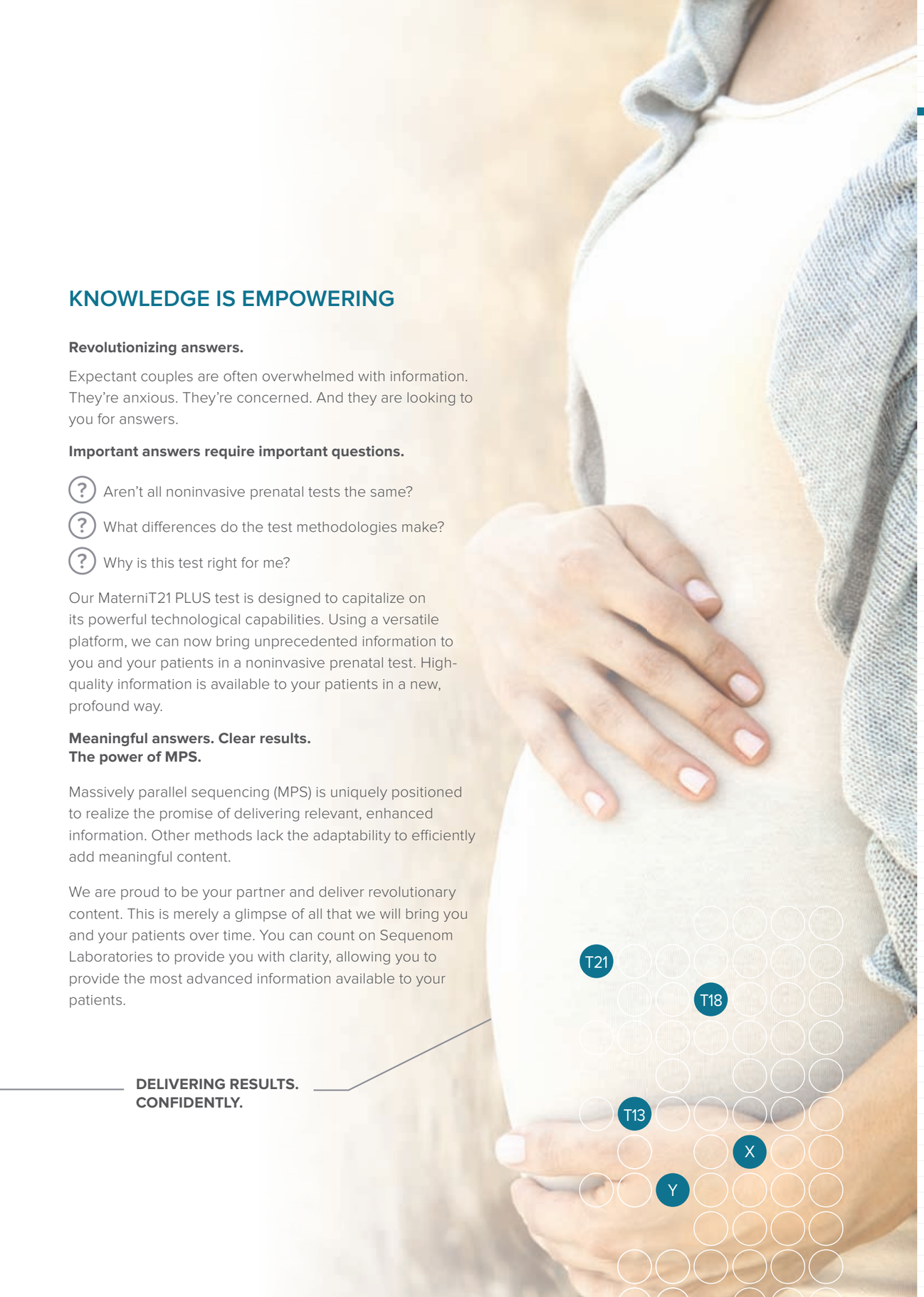
Noninvasive test for chromosomal abnormalities

Delivering results. Confidently.

Meaningful answers. Clear results.

QUALITY OF SCIENCE

sequenom Laboratories



KNOWLEDGE IS EMPOWERING

Revolutionizing answers.

Expectant couples are often overwhelmed with information. They're anxious. They're concerned. And they are looking to you for answers.

Important answers require important questions.

- Aren't all noninvasive prenatal tests the same?
- What differences do the test methodologies make?
- Why is this test right for me?

Our MaterniT21 PLUS test is designed to capitalize on its powerful technological capabilities. Using a versatile platform, we can now bring unprecedented information to you and your patients in a noninvasive prenatal test. High-quality information is available to your patients in a new, profound way.

Meaningful answers. Clear results.
The power of MPS.

Massively parallel sequencing (MPS) is uniquely positioned to realize the promise of delivering relevant, enhanced information. Other methods lack the adaptability to efficiently add meaningful content.

We are proud to be your partner and deliver revolutionary content. This is merely a glimpse of all that we will bring you and your patients over time. You can count on Sequenom Laboratories to provide you with clarity, allowing you to provide the most advanced information available to your patients.

DELIVERING RESULTS. CONFIDENTLY.

MaterniT21 PLUS

DELIVERING ON THE PROMISE OF OUR TECHNOLOGY

OUR PERFORMANCE MAKES THE DIFFERENCE

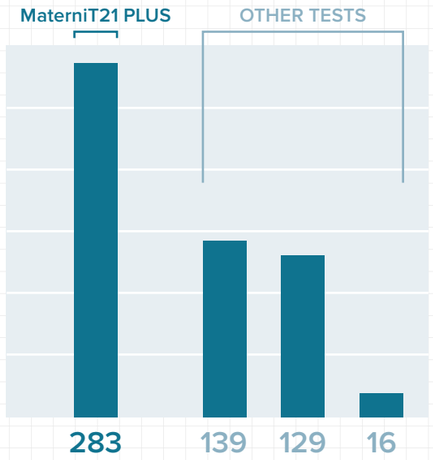
Meaningful content.
Sequenom Laboratories continues to be at the forefront of innovation. With the introduction of our Enhanced Sequencing Series, we report on fetal chromosomal abnormalities; from common (trisomies 21, 18 and 13) to rare (sex aneuploidies, trisomies 16 and 22, and select copy number variants). All of the information that we report is clinically relevant.

The power of a comprehensive platform.
We obtain millions of pieces of sequence data from chromosomes across the genome. When coupled with elegant bioinformatic analysis, the raw data becomes a highly accurate and distinct clinical picture. We generate critical information and deliver it clearly. The platform is built for today and for the future.

We stand behind our test.
The most comprehensive data of its kind to date. Our research has been validated in the largest of-its-kind, independently designed, analyzed, and published clinical study with 4,664 pregnant women at increased risk for fetal chromosomal aneuploidies. Our robust data is derived from testing more than 2,800 pregnant women's blood samples and 375 trisomies. No other published data comes close in terms of scale.

When speed matters.
Our test can be utilized as early as 10 weeks' gestation.[1] The results are turned around in 7 business days from receipt of sample in the lab.

TRISOMIES ANALYZED IN VALIDATION STUDIES

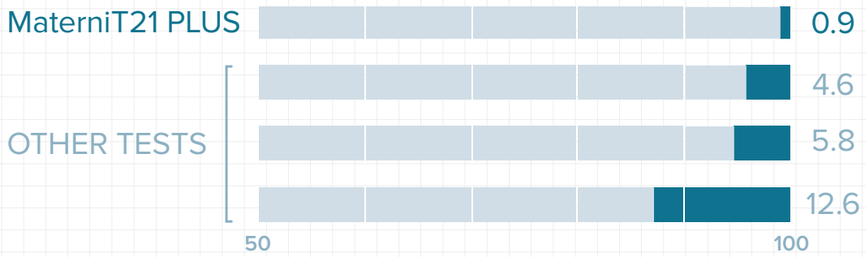


*Includes chromosomes 21, 18 and 13
References: Ashoor[2], Bianchi[3], Norton[4], Palomaki[1,5], Zimmermann[6]

INDEPENDENT VALIDATION[1,5,7,8,9]

POSITIVE RESULTS	SENSITIVITY	SPECIFICITY
210 of 212 trisomy 21	99.1%	99.9%
59 of 59 trisomy 18	>99.9%	99.6%
11 of 12 trisomy 13	91.7%	99.7%
8 of 8 multiple gestations: 7 of trisomy 21 1 of trisomy 13	>99.9% detection rate	
Y chromosome	99.4% accuracy	
25 of 26 combined sex aneuploidies	96.2%	99.7%

VALIDATION STUDY NON-REPORTABLE RATES (%)



References: Bianchi[3], Norton[4], Palomaki[1,5], Zimmermann[6]

NO ROOM FOR MAYBE

The answers you need.
Other prenatal tests offer risk percentages or unclear results. The MaterniT21 PLUS test reports results as positive or negative, providing you and your patients with clear, direct results.

Get an answer. The first time.
Enjoy the confidence that comes with the lowest published and commercial non-reportable rates to date. Other noninvasive prenatal tests hide their inaccuracies in "suspected" report results, unclear risk scores and have clinically, published high non-reportable rates. With the MaterniT21 PLUS test, your patients can count on accuracy and potentially avoid a retest or an unnecessary invasive procedure.

DESIGNED FOR INCREASED RISK PREGNANCIES

We continue to follow the American College of Obstetricians and Gynecologists (ACOG) Committee on Genetics and the Society for Maternal-Fetal Medicine (SMFM) Publications Committee Joint Committee Opinion and offer this test for increased risk pregnancies with one or more of the following conditions:[10]

- Advanced maternal age
- Personal or family history of chromosomal abnormalities
- Fetal ultrasound abnormality suggestive of aneuploidy
- Positive serum screening test

10 WEEKS' GESTATION
Know more earlier

Provides clear, direct results

7 BUSINESS DAY TURNAROUND
Results when you need them

We know you can't outsource excellent service. Our lab personnel are committed to follow up on every single positive result. When you have a question, you're talking to one of our employees who has a vested interest in providing you and your patients with the best service.

WE BACK UP OUR SCIENCE WITH THE BEST PERSONAL SUPPORT

We enable you to focus on the medicine.
Our dedicated customer service is outstanding and will always follow through, leaving you free to focus on what's important—the health and well-being of your patients.

We are committed to medical education.
We want to ensure that you have the most up-to-date information and can make informed decisions.

The MaterniT21 PLUS test is performed exclusively by Sequenom Laboratories.

INTRODUCING: THE ENHANCED SEQUENCING SERIES
EXCLUSIVELY FOR THE MATERNIT21 PLUS TEST

TECHNOLOGY AT THE FOREFRONT OF INNOVATION

Capitalizing on our revolutionary technological capabilities, the MaterniT21 PLUS test can now provide you and your patients with unprecedented information in a noninvasive prenatal test.

INNOVATION TRANSLATING TO PREMIUM CONTENT

In addition to content that you have come to rely on (chromosomes 21, 18, 13, X and Y),[11,12,13,14] the Enhanced Sequencing Series debut includes:

- 22q11.2 deletion syndrome (DiGeorge)
- Cri-du-chat syndrome (5p minus)
- Prader-Willi/Angelman syndrome
- 1p36 deletion syndrome
- Trisomy 16
- Trisomy 22

Findings of uncertain significance will not be reported.

REPORTING METHOD YOU HAVE COME TO EXPECT

As you have come to expect with previous enhancements like sex chromosome aneuploidy reporting, we will similarly report this information as an Additional Finding. Multiple gestations can be included for analysis. Limited prevalence in the general population precludes us from reporting detailed performance characteristics for extended content.

Though additional enhanced content is forthcoming, the analysis is restricted to these syndromes at this time. This testing is not intended to be diagnostic. The absence of an Additional Finding does not indicate a negative result. There are other etiologies (uniparental disomy, single gene mutations, etc.) not addressed by this analysis.

CAN I OPT-OUT FOR REPORTING OF MICRODELETIONS / TRISOMY 22 / TRISOMY 16?

Yes, you can check the relevant opt-out box on the prenatal test requisition form that you do not want this information reported for selected patients.

ENHANCED SEQUENCING SERIES PERFORMANCE

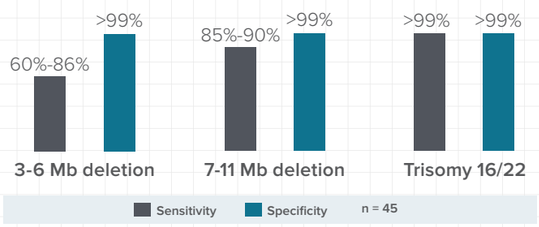
METHOD VALIDATION			
Sensitivity	94%	95% CI (71-99%)	17 of 18
Specificity	99%	95% CI (95-99%)	156 of 157

Method Validation:

- Blinded plasma samples with karyotypic anomalies were used for the genome-wide method validation study.
- The study was designed to test a range of microdeletion/duplication sizes ranging from 3Mb-40Mb, not syndrome-specific deletions/duplications due to low prevalence rates.

MICRODELETION	
SYNDROME	FREQUENT DELETION SIZE
Cri-du-chat (Cri-du-chat critical region locus)	9-11Mb[15]
Prader-Willi/Angelman	5-6Mb[16]
1p36	3-5Mb[17] (40% of occurrences)
22q11	3.0Mb[18] (85% of occurrences)

ANALYTICAL PERFORMANCE BASED ON SIZE OF ABNORMALITY*



* gDNA/plasma mixtures used to calculate expected performance due to limited clinical prevalence. Performance dependent on size of deletion, number of reads, fetal fraction, etc.

SELECTED MICRODELETIONS AND TRISOMIES REPORTED AS ADDITIONAL FINDINGS

NAME	SITE OF ANOMALY	FREQUENCY OF LIVE BIRTHS	DESCRIPTION
DiGeorge syndrome[19]	**22q11**	**1** in **4,000**	An autosomal dominant condition caused by a submicroscopic deletion of the long arm of chromosome 22. The disorder is characterized by cardiac abnormalities, abnormal facies, thymic aplasia, cleft palate, hypocalcemia (CATCH-22). Most cases are not inherited (*de novo*) but transmission from a parent carrying the 22q11 deletion is seen in ~7% of cases.
Cri-du-chat syndrome[20]	**5p**	**1** in **50,000**	Cri-du-chat (5p minus) is caused by a partial deletion of the short arm of chromosome 5. The disorder is characterized by intellectual disability, developmental delay, microcephaly, hypotonia, distinctive facies, heart defects, and a characteristic cat-like cry. This condition affects all ethnicities and is more frequent in females. Most cases are not inherited (*de novo*) but transmission from an unaffected parent carrying a balanced translocation is seen in ~10% of cases.
Angelman syndrome[21] and Prader-Willi syndrome[22]	**15q**	**1** in **20,000**	Both Angelman (AS) and Prader-Willi (PWS) syndromes may be caused by deletions on the long arm of chromosome 15. Maternal deletions lead to AS while paternal deletions result in PWS. Seventy percent of both AS and PWS are caused by deletions on the long arm of chromosome 15. These disorders affect the nervous system and, while both result in developmental delay, each presents with its own unique clinical features. The severity of these syndromes warrants additional studies, FISH and/or methylation PCR, for appropriate diagnosis and to facilitate relevant genetic counseling.
1p36 deletion syndrome[23]	**1p**	**1** in **10,000**	1p36 deletion syndrome (monosomy 1p36 syndrome) is characterized by a deletion on the short arm of chromosome 1. The disorder is characterized by dysmorphic craniofacial features, developmental delay, brain abnormalities, short feet, congenital heart defects, hypotonia, and brachy/camptodactyly. This condition is more common in females and the recurrence risk depends on the origin of the deletion. In 20% of affected individuals, the deletion is inherited from an unaffected parent. Most cases are not inherited (*de novo*).
Trisomy 16[24,25]	**Chromosome 16**	**1** in **50,000**	Full trisomy 16 is not compatible with life and is the most common cause of miscarriage. Mosaic trisomy 16 may present with intrauterine growth retardation, developmental delay, and congenital heart defects. Most frequent cause of spontaneous miscarriage and IUFD. Cardiac defects can be common.
Trisomy 22[26]	**Chromosome 22**	**1** in **40,000**	Full trisomy 22 is rarely compatible with life and most individuals die before birth or shortly after. Mosaic trisomy 22 may present with growth retardation, malformations of the head and face, cardiac abnormalities, and developmental delay.

No test is perfect. DNA test results do not provide a definitive genetic risk in all individuals. Cell-free fetal DNA does not replace the accuracy and precision of prenatal diagnosis with CVS or amniocentesis. A patient with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results. A negative test result does not ensure an unaffected pregnancy. The absence of an Additional Finding does not indicate a negative result. While results of this testing are highly accurate, not all chromosomal abnormalities may be detected due to placental, maternal or fetal mosaicism, or other causes. Sex chromosomal aneuploidies are not reportable for known multiple gestations. The health care provider is responsible for the use of this information in the management of their patient.

ABOUT THE COMPANY

Sequenom Laboratories, a wholly-owned subsidiary of Sequenom, Inc., is a CAP-accredited and CLIA-certified molecular diagnostics laboratory dedicated to improving patient outcomes by offering revolutionary laboratory-developed tests for a variety of prenatal and eye conditions. Sequenom Laboratories pioneered NIPT with the launch of its MaterniT21 PLUS test for fetal aneuploidies, and offers a full menu of prenatal tests.

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ABOUT THE MATERNIT21 PLUS TEST

The MaterniT21™ PLUS test is a laboratory-developed test that was developed, validated and performed exclusively by Sequenom Laboratories in the USA. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although laboratory-developed tests to date have not been subject to US FDA regulation, certification of the laboratory is required under CLIA to ensure the quality and validity of the tests. Sequenom Laboratories is certified under the U.S. Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing and accredited by the College of American Pathologists (CAP).

REFERENCES

1. Palomaki GE, et al. DNA sequencing of maternal plasma to detect Down syndrome: An international clinical validation study. *Genet Med*. 2011;13(11):913-920.
2. Ashoor G, et al. Trisomy 13 detection in the first trimester of pregnancy using a chromosome-selective cell-free DNA analysis method. *Ultrasound Obstet Gynecol*. 2013;41(1):21-25.
3. Bianchi DW, et al. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstet Gynecol*. 2012;119(5):890-901.
4. Norton ME, et al. Non-invasive chromosomal evaluation (nice) study: results of a multicenter, prospective, study for detection of fetal trisomy 21 and trisomy 18. *Am J Obstet Gynecol*. 2012;207:137. e1-8.
5. Palomaki GE, et al. DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13, as well as Down syndrome: An international collaborative study. *Genet Med*. 2012;14(3):296-305.
6. Zimmermann B, et al. Noninvasive prenatal aneuploidy testing of chromosomes 13, 18, 21, X and Y, using targeted sequencing of polymorphic loci. *Prenat Diagn*. 2012;32(13):1233-4121.
7. Canick JA, et al. DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. *Prenat Diagn*. 2012;32(8):730-734.
8. Mazloom AR, et al. Accuracy of noninvasive prenatal sex determination using massively parallel sequencing in samples from a large clinical validation study. Poster presented at: 62nd Annual Meeting of the American Society of Human Genetics; 2012 Nov 6-10; San Francisco, CA.
9. Mazloom AR, Dzakula Z, Oeth P, Wang H , et al. Noninvasive prenatal detection of sex chromosomal aneuploidies by sequencing circulating cell-free DNA from maternal plasma. *Prenat Diagn*. 2013;33(6):591-597.
10. Committee Opinion No. 545: Noninvasive prenatal testing for fetal aneuploidy. *Obstet Gynecol*. 2012;120(6):1532-1534.
11. Palomaki GE, et al. DNA sequencing of maternal plasma to detect Down syndrome: An international clinical validation study. *Genet Med*. 2011;13(11):913-920.
12. Palomaki GE, et al. DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13, as well as Down syndrome: An international collaborative study. *Genet Med*. 2012;14(3):296-305.
13. Canick JA, et al. DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. *Prenat Diagn*. 2012;32(8):730-734.
14. Mazloom AR, et al. Accuracy of Noninvasive Prenatal Sex Determination using Massively Parallel Sequencing in Samples from a Large Clinical Validation Study. Poster presented at the 2012 Annual American Society of Human Genetics Meeting, November 6-10, 2012; San Francisco, CA.
15. Zhang X, et al. High-resolution mapping of genotype-phenotype relationships in cri du chat syndrome using array comparative genomic hybridization. *Am J Hum Genet*. 2005;76(2):312-326.
16. Kim SJ, et al. Unique and atypical deletions in Prader-Willi syndrome reveal distinct phenotypes. *Eur J Hum Genet*. 2012;20(3):283-290.
17. Heilstedt HA, et al. Physical map of 1p36, placement of breakpoints in monosomy 1p36, and clinical characterization of the syndrome. *Am J Hum Genet*. 2003;72(5):1200-2012.
18. McDonald-McGinn DM, et al. Genetic counseling for the 22q11.2 deletion. *Dev Disabil Res Rev*. 2008;14(1):69-74.
19. http://www.ncbi.nlm.nih.gov/books/NBK1523. (DiGeorge)
20. http://omim.org/entry/123450. (Cri-du-chat)
21. http://www.ncbi.nlm.nih.gov/books/NBK1144. (AS)
22. http://www.ncbi.nlm.nih.gov/books/NBK1330. (PW)
23. http://www.ncbi.nlm.nih.gov/books/NBK1191. (1p36)
24. http://www.trisomy16.org.
25. http://ghr.nlm.nih.gov/chromosome/16.
26. http://rarediseases.info.nih.gov/gard/6085/mosaic-trisomy-22/resources/1.

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