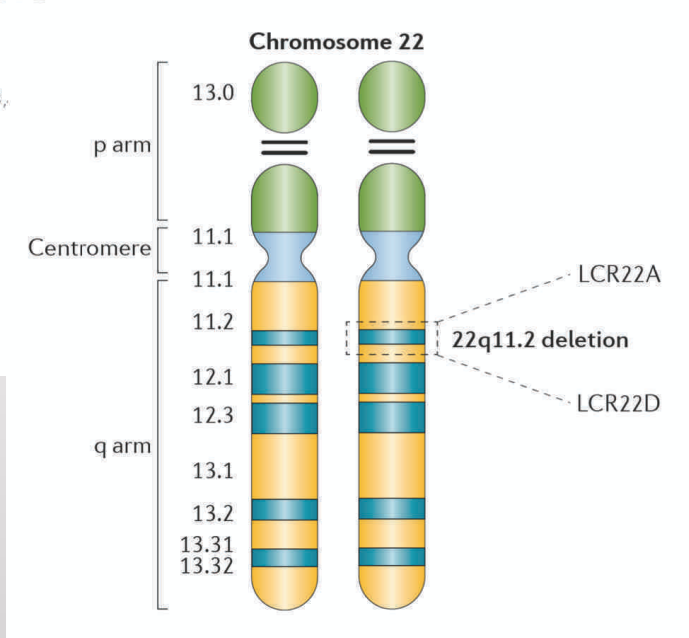
Screening 1p36, 5p, 15q, 22q11.2

Clinical outcome of subchromosomal events detected by whole-genome noninvasive prenatal testing

J. Helgeson[1], J. Wardrop[1], T. Boomer[1], E. Almasri[1], W. B. Paxton[1], J. S. Saldivar[1], N. Dharajiya[1], T. J. Monroe[2], D. H. Farkas[3], D. S. Grosu[1] and R. M. McCullough[1]*

[1]Sequenom Laboratories, San Diego, CA, USA
[2]Sequenom Laboratories, Morrisville, NC, USA
[3]Sequenom Laboratories, Grand Rapids, MI, USA
[4]Department of Obstetrics, Gynecology and Reproductive Medicine, Michigan State University, East Lansing, MI, USA
*Correspondence to: R. M. McCullough. E-mail: rmccullough@sequenom.com



n=175.393 Sequenom cfDNA-Screening
1p36, 5p, 15q, 22q11.2 del

22q11.2 32 (0,02%) positiv
davon 20 maternal (1:8.770)
12 fetal (1:14.616)

Helgeson 2015 Prenat Diagn

Ultrasound Obstet Gynecol 2016; 47: 177–183
Published online 5 January 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.15754. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Clinical experience with single-nucleotide polymorphism-based non-invasive prenatal screening for 22q11.2 deletion syndrome

S. J. GROSS*, M. STOSIC*, D. M. MCDONALD-MCGINN†, A. S. BASSETT‡, A. NORVEZ*, R. DHAMANKAR*, K. KOBARA*, E. KIRKIZLAR*, B. ZIMMERMANN*, N. WAYHAM*, J. E. BABIARZ*, A. RYAN*, K. N. JINNETT*, Z. DEMKO* and P. BENN§

**Natera Inc, San Carlos, CA, USA; †Division of Human Genetics, The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; ‡Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; §Division of Human Genetics, Department of Genetics and Genome Sciences, University of Connecticut Health Center, Farmington, CT, USA*

del 22q11.2

SNP Array n=20.776 Prävalenz 1:950

95 (0,5%) positive Befunde 34 kein outcome

11 richtig positiv fetal 2 maternale Deletionen

50 (0,2%) falsch positivPPV=18%

Nachträgliche Erhöhung der Sequenziertiefe: PPV 18% → 42%

Gross 2016 UOG

Genetics in Medicine Official Journal of the American College of Medical Genetics and Genomics

GENETICS IN MEDICINE | LETTER TO THE EDITOR

Expanding noninvasive prenatal testing to include microdeletions and segmental aneuploidy: cause for concern?

Trilochan Sahoo MD, Karine Hovanes PhD, Michelle N. Strecker MS, Natasa Dzidic MS, Sara Commander MS & Mary K. Travis MS

Affiliations | Corresponding author

Genetics in Medicine (2016) 18, 275–276 | doi:10.1038/gim.2015.196

Most read

Standards a
interpretati
consensus
College of
and the Ass
Genetics in M

Sahoo 2016 Genet Med

Table 1 Invasive testing results for cases with microdeletions or segmental aneuploidies reported by NIPT

	Array/karyotype results			
	Concordant (6)	Discordant (17)		Concordant + structural abnormality (3)
Abnormal NIPT results (26)		No.	Description (discordant results)	
22q11.2 Deletion (7)	2	5	All normal	0
5p Deletion (6)	1	5	All normal	0
1p36 Deletion (4)	1	3	All normal	0
4p Deletion (1)	0	1	Normal	0
8q24 Deletion (1)	NA	NA	NA	NA
15q Deletion (1)	1	0		
9p Duplication (1)	0	0		1 (idic 9p)
13q Deletion (1)	1	0		
18p Deletion + 18q deletion (1)	0	1	14-Mb deletion: 18p11.32p11.21	
Trisomy 18q (1)	0	0		1, 18p11.21q23(14,419,130-78,077,248)x3; 46,XY,der(13;18)(q10;q10),+18
21q Partial deletion (1)	0	1		Duplication 21q11.2-q21.1 (9.2 Mb), ins(14;21)(p11.2;q11.2q21.1)
No result for chromosome 13 (1)	0	1	ROH chromosome 13/?UPD13	

idic, isodicentric; NA, data not available; NIPT, noninvasive prenatal testing; ROH, region(s) of homozygosity.

Fetal Diagnosis and Therapy

Original Paper

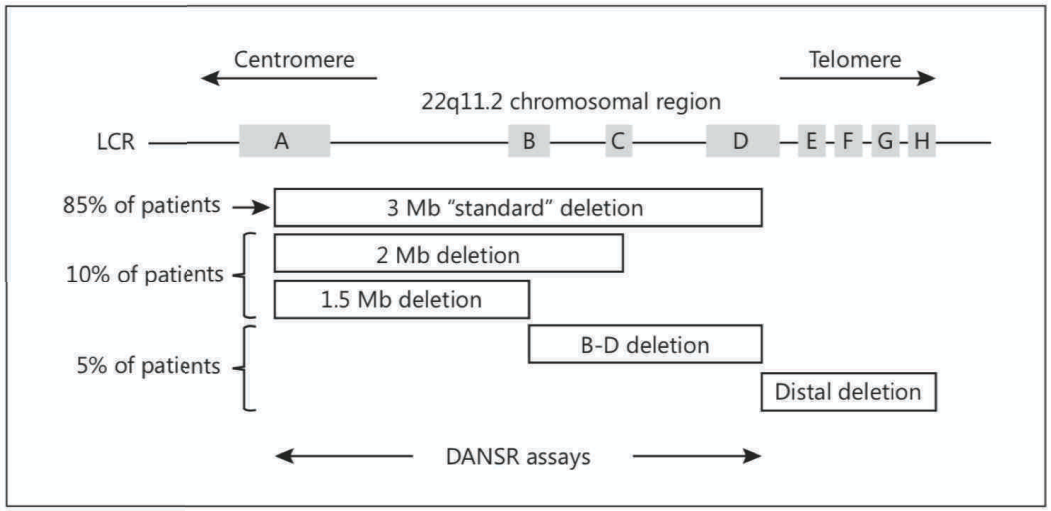
Fetal Diagn Ther
DOI: 10.1159/000484317

Received: August 15, 2017
Accepted after revision: October 17, 2017
Published online: November 8, 2017

Prenatal Screening for 22q11.2 Deletion Using a Targeted Microarray-Based Cell-Free DNA Test

Maximilian Schmid[a] Eric Wang[a] Patrick E. Bogard[a] Elisa Bevilacqua[b] Coleen Hacker[a] Susie Wang[a] Jigna Doshi[a] Karen White[a] Jennifer Kaplan[a] Andrew Sparks[a] Jacques C. Jani[b] Renee Stokowski[a]

[a]Ariosa Diagnostics Inc., Roche Sequencing Solutions, Inc., San Jose, CA, USA; [b]Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium



Validierungsgruppe:
122 Plasmaproben, davon 120 „simulated" und 2 prospektiv
Klinische Gruppe:
217 Plasmaproben mit bekanntem 22q11.2 Status
5/7 Betroffenen richtig positiv (71%)
210 Nichtbetroffene korrekt klassifiziert

Keine Daten zur postpartalen Überprüfung

Schmid 2017 Fetal Diagn Ther

PLOS | ONE

RESEARCH ARTICLE

Validation of a SNP-based non-invasive prenatal test to detect the fetal 22q11.2 deletion in maternal plasma samples

Harini Ravi[1], Gabriel McNeill[1], Shruti Goel[1], Steven D. Meltzer[2], Nathan Hunkapiller[1], Allison Ryan[1], Brynn Levy[3], Zachary P. Demko[1]*

1 Natera, Inc., San Carlos, CA, United Statesof America, **2** The Woman's Hospital of Texas, Houston, TX, United States of America, **3** Department of Pathology and Cell Biology, Columbia University, New York, NY, United States of America

* zdemko@natera.com

Check for updates

Abstract

OPEN ACCESS

Citation: Ravi H, McNeill G, Goel S, Meltzer SD, Hunkapiller N, Ryan A, et al. (2018) Validation of a SNP-based non-invasive prenatal test to detect the fetal 22q11.2 deletion in maternal plasma samples. PLoS ONE 13(2): e0193476. https://doi.org/10.1371/journal.pone.0193476

Editor: Kelvin Yuen Kwong Chan, Hospital Authority, CHINA

Received: October 17, 2017

Accepted: February 12, 2018

Published: February 23, 2018

9/10 richtig positiv

9 im US auffällig

1/390 falsch positiv

überwiegend hohe SSW

Table 1. Clinical information for affected samples.

No.	Deletion Syndrome	MA (Years)	GA (Weeks)	FF (%)	Procedure for Sample Procurement	DiagnosticTest	Deletion Size (Mb)	Time Between Invasive Test and Blood Draw (Days)	NIPT Call	Deleted Haplotype
1	22q11.2	N/A	22.0	13.3	Amnio	CMA	2.55	15	High risk	Paternal
2	22q11.2	19	15.6	11.7	CVS	mmPCR	≥2.91	0*	High risk	Paternal
3	22q11.2	20	30.4	15.4	Amnio	FISH	N/A	53	High risk	Maternal
4	22q11.2	21	21.5	39.7	Amnio	CMA	2.55	14	High risk	Maternal
5	22q11.2	35	13.3	19.4	CVS	FISH	N/A	6	High risk	Maternal
6	22q11.2	31	20.2	7.9	Amnio	CMA	2.55	0*	High risk	Maternal
7	22q11.2	35	25.1	8.0	Amnio	CMA	3.15	15	Low risk	N/A
8	22q11.2	30	16.2	21.4	Amnio	FISH	N/A	6	High risk	Maternal
9	22q11.2	31	14.0	9.6	CVS	FISH	N/A	2	High risk	Paternal
10	22q11.2	31	37.4	19.3	Amnio	CMA	2.55	109	High risk	Maternal

Amnio, amniocentesis; CMA, chromosomal microarray; CVS, chorionic villus sampling; FF, fetal fraction; FISH, fluorescence in situ hybridization; GA, gestational age; MA, maternal age; mmPCR, massively-multiplexed polymerase chain reaction; N/A, not available, NIPT, non-invasive prenatal testing.

Ravi 2018

Screening auf Mikrodeletionen / CNVs

TABLE 1 Recurrent microdeletion syndromes with prevalence and deletion size

Syndrome	Location	Estimated Prevalence	Deletion Size	% ≥3 Mb
DiGeorge	22q-	1/2,000	1.5-3 MB	85%
Wolf-Hirschorn	4p-	1/50,000-1/20,000	1.9-3.5 Mb	97%
Cri du Chat	5p-	1/50,000	10-30 Mb	99%
Prader-Willi/Angelman	Del 15q11.2	1/20,000	5.0-6.0 Mb	70%
1p36 deletion	1p36-	1/5,000	1.5-10 Mb	85%
Miller Dieker	Del 17p13.3	~1/100,000	0.4-2.Mb	Very rare

TABLE 2 Sensitivity, false positive rate and positive predictive value for copy number variants detected by cell free DNA

Study	Cohort	Sample Details	Sensitivity	False-Positive Rate	Positive Predictive Value
Zhao (2015)[15]	18 maternal plasma with known CNVs	CNV size 3 to 40 Mb	94.4%	N/A	N/A
Wapner (2015)[10]	358 maternal plasma and 111 maternal plasma spiked	"Normals" not confirmed by microarray	97.8% of known 22q- (including artificial samples)	0.76% for 22q- 0.24% for 5p-	3.8% 17%
Lo (2015)[16]	31 maternal plasma with known CNVs	CNVs 3 to 40 Mb genome wide (3 maternally inherited)	64.5% (83% ≥6 Mb, 20% <6 Mb)	0.4%	N/A
Gross (2016)[11]	20,776 maternal plasma screened with NIPT	22q- only reported, 30% LTFU, "normals" not confirmed by chromosomal microarray	Unknown	0.4%, 22q- only reported	18% overall 89% in fetuses with ultrasound anomalies 4.9% when normal ultrasound
Li (2016)[17]	Maternal plasma, 11 with known CNVs and 99 normal on microarray	CNVs 1.4 to 38 Mb across the genome	61% (90% ≥5 Mb, 14% <5 Mb)	5%	71% high risk
Yin (2015)[18]	1,456 maternal plasma with microarray results. 78 abnormal	Semiconductor sequencing detected 56/78	71.8%	3.8%	50% high risk
Lefkowitz (2016)[19]	1166 reportable cases at high risk for aneuploidy	43 cases with a CNV >7 Mb or rare trisomy	97.7%	N/A	97% high risk
Helgeson (2015)[20]	175,393 maternal plasma screened by NIPT. Normals not confirmed by microarray	53 microdeletion positive, 20 maternally inherited	Not known	0.0017%	60%-100%

CNV, copy number variant; LTFU, lost to follow-up; N/A, not applicable.

Chitty 2018 Prenat Diagn

Screening auf Mikrodeletionen / CNVs

Received: 24 August 2017 | Revised: 7 January 2018 | Accepted: 8 January 2018
DOI: 10.1002/pd.5217

ORIGINAL ARTICLE

WILEY PRENATAL DIAGNOSIS

Clinical experience of laboratory follow-up with noninvasive prenatal testing using cell-free DNA and positive microdeletion results in 349 cases

S. Schwartz[1] | M. Kohan[2] | R. Pasion[1] | P. R. Papenhausen[1] | L. D. Platt[3,4]

Deletion	screenpositiv *	richtig positiv CVS oder AC	PPV (%)
1p36	21	1	5
4p	6	1	17
5p	45	6	13
15q	80	5	6
22q11.2	183	12	7

* Pathologische Mikroarrays in 11 Fällen

Schwartz 2018 Prenat Diagn

natera Conceive. Deliver. vistara POINT MUTATION NIPT Products Menu

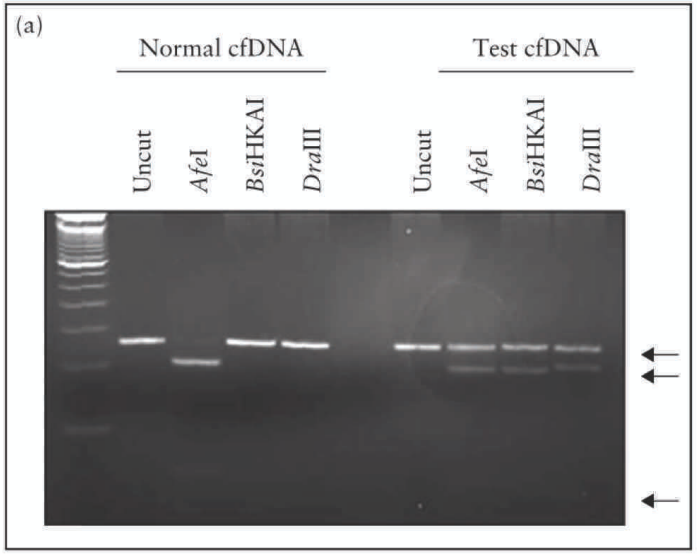
Vistara non-invasive prenatal screen

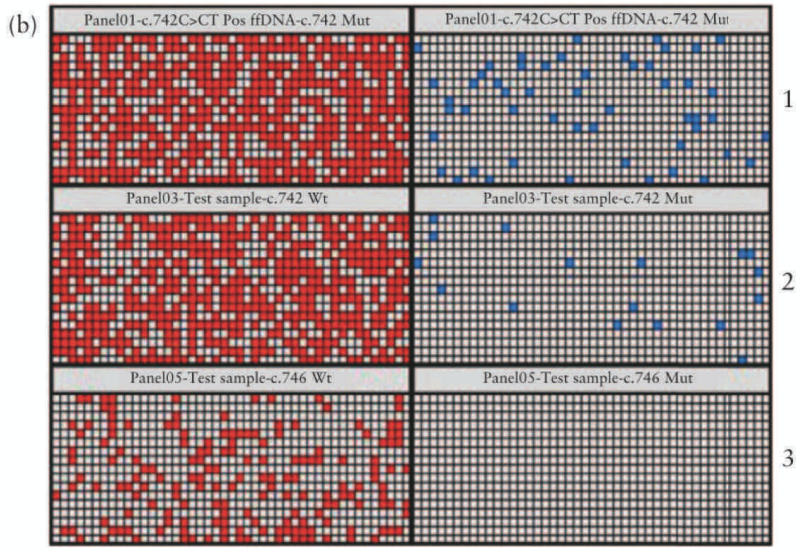
Vistara identifes risk for conditions that may have otherwise gone undetected until after birth or into childhood.
All conditions are inherited in an autosomal or X-linked dominant fashion, which means that if the mutation is present, the child will be affected by the condition and experience related symptoms.

Condition[1] *Gene(s)*	Clinical synopsis[2,3]	Cases caused by de novo mutations[2,3]	Ultrasound findings[2,3]			Clinical actionability	Detection rate for gene[1]
			None	Late gestation	Non-specific		
Achondroplasia *FGFR3*	The most common form of skeletal dysplasia; may cause hydrocephalus, delayed motor milestones, and spinal stenosis	80%		●	●	Labor and delivery management, monitor for spinal stenosis, early sleep studies to reduce risk of SIDS	>96%
Alagille syndrome *JAG1*	Affects multiple organ systems and may cause growth problems, congenital heart defects, and vertebral differences	50% to 70%	◐		◐	Symptom-based treatment	>79%
Antley Bixler syndrome *FGFR2*	A type of craniosynostosis; also causes premature fusion of the arm bones, blockage of the nasal passage, and permanently flexed or extended joints	more severe forms		●		Fetal MRI, avoid instrumented delivery, corrective surgery, monitor for hydrocephalus	>96%
Apert syndrome *FGFR2*	A type of craniosynostosis; also causes abnormal formation of the fingers, toes, and vertebrae, and other organ anomalies	more severe forms		●		Fetal MRI, avoid instrumented delivery, corrective surgery, monitor for hydrocephalus	>96%
Cardiofaciocu-taneous syndrome 1,3,4 *BRAF, MAP2K1, MAP2K2*	Causes abnormalities of the heart, face, skin, and hair; may cause developmental delays and intellectual disability	majority		●	●	Fetal echocardiogram	>96%
CATSHL syndrome *FGFR3*	Acronym stands for camptodactyly, tall stature, scoliosis, and hearing loss; may increase risk for intellectual disability	unknown	●			Early adoptionof sign language and behavioral intervention	>96%
CHARGE syndrome *CHD7*	Acronym stands for coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital abnormality, ear abnormalities; may cause hearing loss, developmental delays,	majority	◐	◐	◐	Early referral to endocrinology, adoption of sign language, and behavioral intervention	>91%

natera.com
10.04.2018

Mutationen





(c)

	ffDNA
Exon6wt	21386
Exon6c742c-t	703
Exon6c746C-G	0
Exon6c749C-G	2
c.749C>T	1

Table 3 Shift from invasive to non-invasive prenatal testing (NIPT) for achondroplasia and thanatophoric dysplasia in the UK from 2009 to 2013, as tests became validated and approved for use in the North East Thames Regional National Health Service genetics laboratory

	Achondroplasia		*Thanatophoric dysplasia*	
Year	*Invasive*	*NIPT*	*Invasive*	*NIPT*
2009–2010	28	0	16	0
2010–2011	27	13	21	0
2011–2012	28	14	25	2
2012–2013	20	22	17	11
2013–	10	14	7	18

Data are given as *n*. Other conditions for which NIPT has been performed in high-risk families include Apert syndrome ($n=7$), Crouzon syndrome ($n=2$), Fraser's syndrome ($n=4$), autosomal polycystic kidney disease, osteogenesis imperfecta ($n=2$) and cystic fibrosis.

Everett T, Chitty L UOG 2015

DOI: 10.1002/pd.4583 PRENATAL DIAGNOSIS

ORIGINAL ARTICLE

Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach

Lyn S. Chitty[1,2]*, Sarah Mason[3], Angela N. Barrett[3], Fiona McKay[3], Nicholas Lench[3], Rebecca Daley[2] and Lucy A. Jenkins[3]

[1]UCL Institute of Child Health, Genetics and Ger
[2]University College London Hospitals NHS Foun
[3]N-E Thames Regional Genetics Service, Great (
*Correspondence to: Lyn S. Chitty. E-mail: l.chitt
The copyright line in this article was changed on

Table 2 The performance of the PCR–RED and NGS panel for the detection of *FGFR3* mutations causing achondroplasia and thanatophoric dysplasia with confirmed postnatal diagnoses

		Prenatal test result					
		PCR–RED			NGS panel		
Confirmed postnatal diagnosis	Mutation	True positive	False negative	Inconclusive	True positive	False negative	Inconclusive
Achondroplasia	c.1138G>A (p.Gly380Arg)	14	0	1	8	0	0
	c.835A>T (p.Ser279Cys)	ND	ND	ND	0	1[a]	0
Thanatophoric dysplasia	c.742C>CT (p.Arg248Cys)	6[b]	1[c]	1[b]	9[b]	0	0
	c.1948A>AT (p.Lys650Glu)	3	0	0	3	0	0
	c.1118A>G (p.Tyr373Cys)	ND	ND	ND	2	0	0
	c.746C>G (p.Ser249Cys)	ND	ND	ND	2	0	0
	c.2419T>A (p.*807Argext*101)	ND	ND	ND	1	0	0
[a]Does not carry *FGFR3* mutation	No mutant allele detected	43[b]	0	3	20[b]	0	0
	Total	66	1	5	46	1	0
	Sensitivity	88.6% (95% CI 71–96) taking inconclusive that were positive as false negative			96.2% (81–99)		
	Specificity	100% (92–100)			100% (85–100)		
	Positive predictive value	100% (86–100)			100% (87–100)		
	Negative predictive value	93.9 (83.5–97.9) taking inconclusive that were positive as false negative			95.5% (78.2–99.2)		
	Inconclusive rate	7%			0		

Chitty 2015 Prenat Diagn