‘NIPT vs Molecular Karyotype’

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InterGenetics
ΔΙΑΓΝΩΣΤΙΚΟ ΚΕΝΤΡΟ ΓΕΝΕΤΙΚΗΣ

7th Advanced Course of Ultrasound
12th MEDUOG Congress

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Greek Branch
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12th MEDUOG CONGRESS

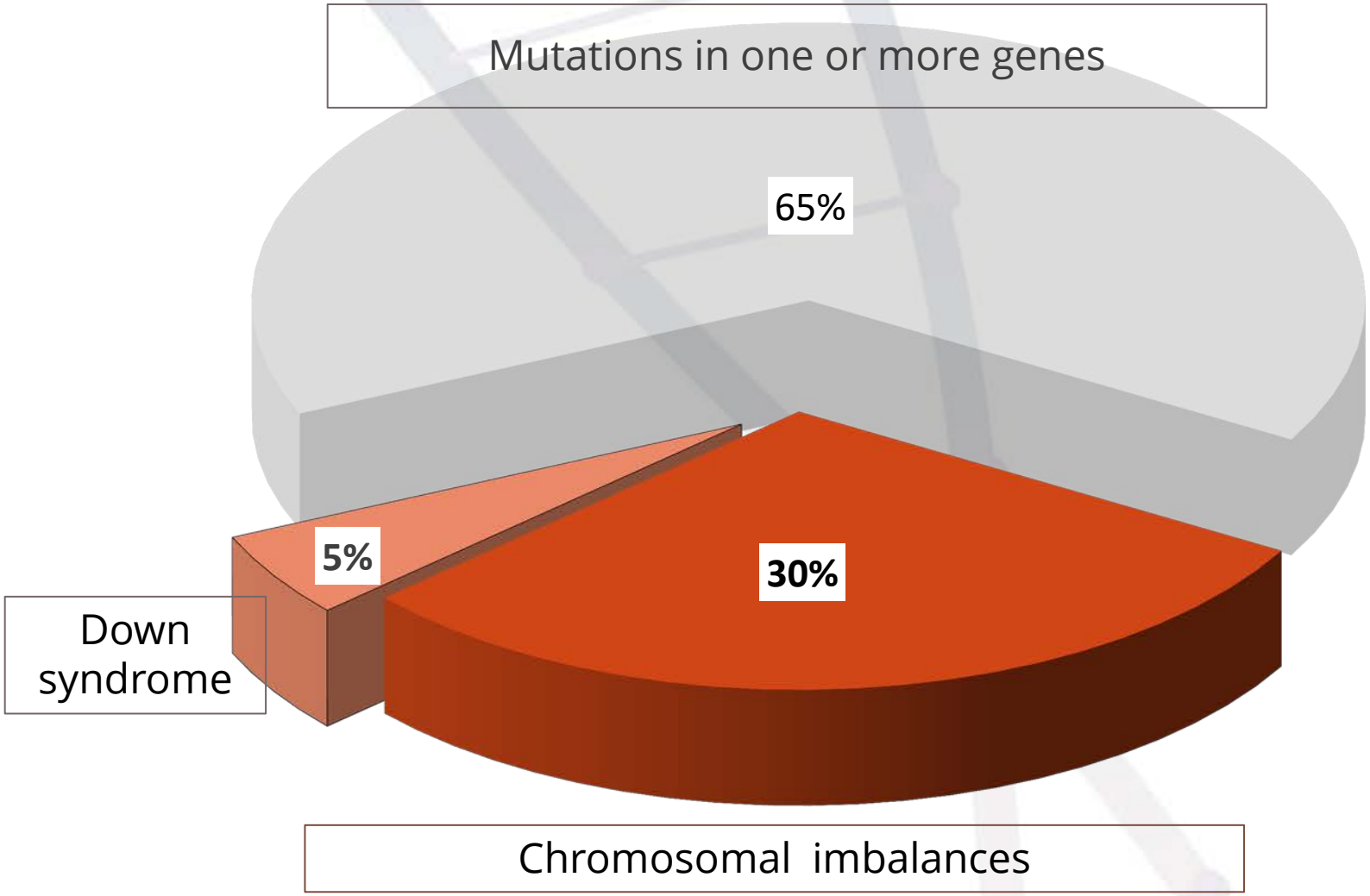
What does society wish today regarding the prevention of genetic diseases through prenatal diagnosis and therefore what can we as geneticists justifiably do towards this end ?

Several international surveys have shown that 80-90% of respondent women wish prenatal screening for all possible debilitating genetic diseases

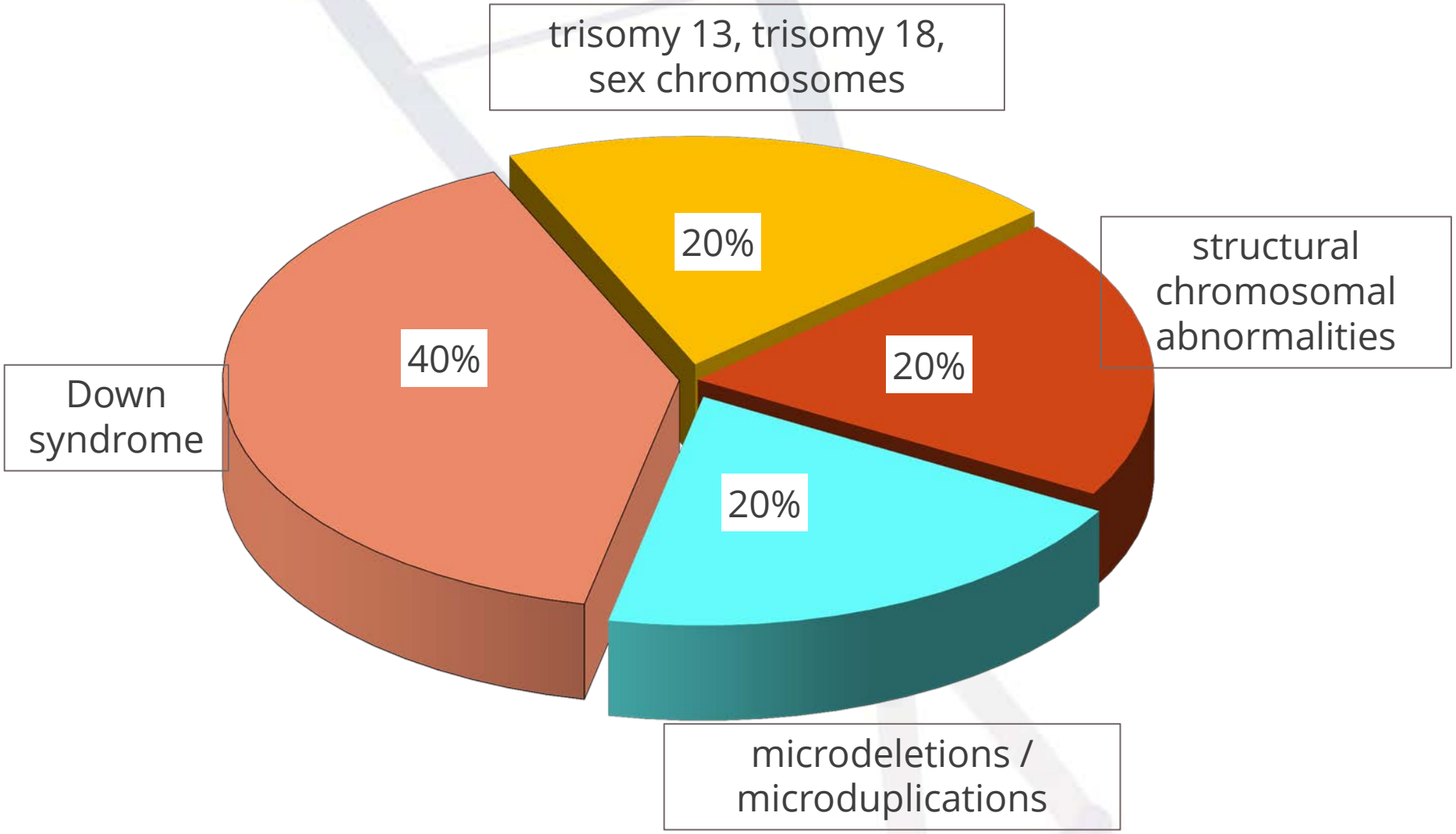
What can genetics offer today

Geneticists, recognizing these needs and coming into daily contact with families burdened with genetic disorders, have now developed the necessary tools and tests permitting the safe diagnosis of hundreds of chromosomal and gene disorders in the fetus

Genetic disorders



Chromosomal abnormalities



What did we learn up until 2005 ?

Classic karyotype analysis will reveal:

~1,8% (1/56) affected fetuses

(avg. of 1st and 2nd trimester, ~84.000 cases 1979-2013 of InterGenetics)

harboring microscopically visible

pathogenic chromosomal abnormalities

PRENATAL DIAGNOSIS
Prenat Diagn 2011; **31**: 571–577.
Published online 29 March 2011 in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/pd.2750

Uncovering recurrent microdeletion syndromes and subtelomeric deletions/duplications through non-selective application of a MLPA-based extended prenatal panel in routine prenatal diagnosis

Christopher Konialis*, Birgitta Hagnefelt, Sophia Sevastidou†, Sophia Karapanou†, Katerina Pispili, Aggeliki Markaki and Constantinos Pangalos

InterGenetics - Diagnostic Genetics Centre, Athens, Greece

Diagnostic yield of *EPP®*

1 in180

of all PCD cases, irrespective of indication, are likely to harbor a genomic aberration, detectable through this MLPA panel of first-tier extended targeted testing and undetectable by conventional karyotype analysis

Increase in diagnostic yield through *EPP®*

Classic karyotype

1 / 56
(1.8%)

+ 1 / 180 =

Extended Prenatal Panel

1 / 43
(2.3%)

the next step forward ....

routine application of standalone prenatal molecular karyotype (aCGH) in PCD

it includes 120 syndromes and report in 4-5 days

Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther
DOI: 10.1159/000368604

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Dilemmas in Prenatal Chromosomal Diagnosis Revealed Through a Single Center's 30 Years' Experience and 90,000 Cases

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Referral reasons and prenatal aCGH results

Referral reason*		Pathogenic		AF	Pathogenic		CVS	Pathogenic	
	N (%)	A	B	N (%)	A	B	N (%)	A	B
AMA/anx	2102	46 2,2%	12 0,6%	1767	37 2,0%	12 0,7%	320	9 2,8%	-
High-risk biochemical marker screening	325	9 2,7%	2 0,6%	282	5 1,8%	2 0,7%	41	4 9,3%	-
Ultarsound abnormalities (including NT)	440	23 5,1%	7 1,5%	373	6 1,6%	6 1,6%	66	17 25,3%	1 1,5%
Family history with a genetic abnormality	243	4 1,6%	-	174	1 0,5%	-	87	3 3,4%	-
TOTAL	3110	82 2,6%	21 0,7%	2596	49 1,9%	20 0,8%	514	34 6,5%	

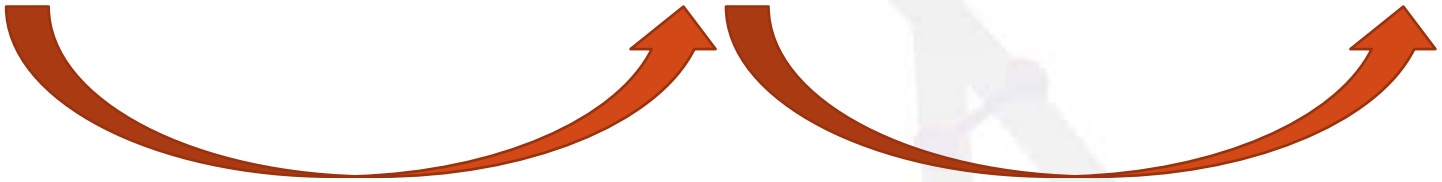
•as stated on the test requisition fom

•A = pathogenic, DETECTABLE by classic karyotype
•B = pathogenic, NOT DETECTABLE by classic karyotype

InterGenetics
DIAGNOSTIC GENETIC CENTER

Further increase in diagnostic yield by prenatal aCGH

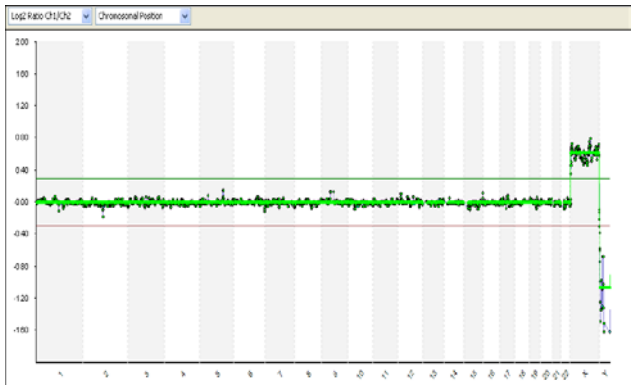
Classic karyotype		*Extended Prenatal Panel*		*Molecular karyotype*
1 / 56 (1.8%)	+ 1 / 180 =	1 / 43 (2.3%)	+ 1 / 125 =	1 / 30 (3.3%)



Chromosomal abnormalities in fetuses

trisomy 13, trisomy 18, sex chromosomes

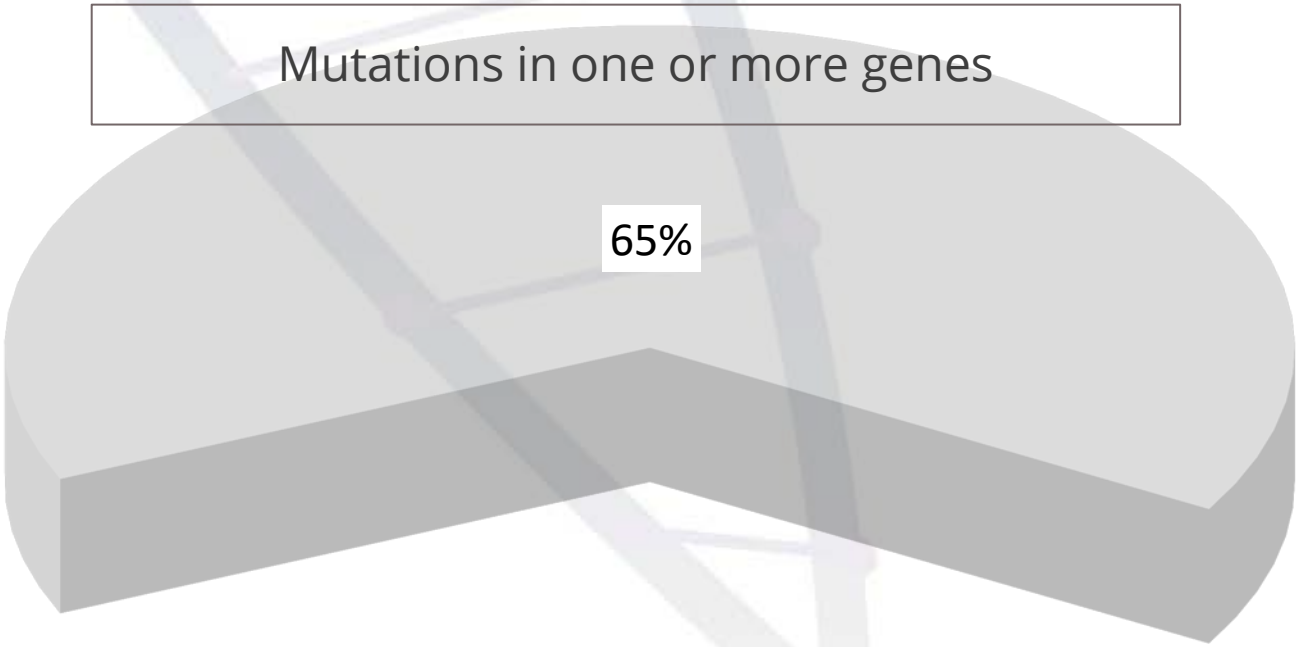
Down syndrome



Structural chromosomal abnormalities

Microdeletions / microduplications

Gene disorders in the fetus



Fetalis®

by InterGenetics

prenatal genomic testing
(exome sequencing) of 685 genes
associated with troubling U/S findings

U/S finding	Genetic disorder(s)	Genes
Cystic hygroma, Elevated N.T., Cardiac anomalies, Macrosomia, Polyhydramnios, Lymphoedema	Noonan syndrome	BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, SOS1
Holoprosencephaly	Non-syndromic or syndromic holoprosencephaly	SHH, SIX3, TGIF, ZIC2, GLI2, PTCH1, DISP1, FGF8, FOXH1, NODAL, TDGF1, GAS1, DLL1, CDON, …..
Renal abnormalities - renal dysplasia/agenesis	Townes-Brocks syndrome, Duane-Radial-Ray syndrome, Acro-renal-ocular syndrome Renal Hypodysplasia/Aplasia 1, AR Nephronophthisis, Renal agenesis/dysgenesis	ATRX,CHD7,DHCR7,EYA1,FANCA,FANCB,FANCC, FANCD2,FANCE,FGF10,FGFR2, FGFR3, GDF6, HNF1B,HOXD13, INSL3,KAL1,KCTD1,LRP4, MBTPS2,MKS1,PAX2,PROKR2,PTPN11,PUF60,RET, RPL26,RXFP2,SALL4,SEMA3E,SF3B4,TBC1D24, TBX1,TFAP2A,TP63,UPK3A,WNT3,WNT4SALL1, SALL4, EYA1,ITGA8,NPHP1,NPHP4,OCRL,PAX2, RET,SIX5, VIPAS39,VPS33B,WNT4, …..
Ambiguous genitalia, sex reversal, hypospadia	Androgen Insensitivity syndrome (AIS) Campomelic dysplasia, 5-Alpha Reductase Deficiency, XY Complete or Partial Gonadal Dysgenesis 17 Alpha-Hydroxylase/17,20-Lyase Deficiency 46,XY Disorder of Sex Development, 46,XY Gonadal Dysgenesis (SRY-related), 46,XY Gonadal Dysgenesis +/- adrenal insufficiency , 46,XY Gonadal Dysgenesis +/- polyneuropathy, 5-Alpha Reductase Deficiency, Adrenal Hypoplasia Congenita (AHC), X-linked, Androgen Insensitivity Syndrome (AIS), Antley-Bixler Syndrome (ABS), Aromatase Deficiency, Campomelic Dysplasia, Cytochrome P450 Oxidoreductase (POR) Deficiency, Smith-Lemli-Opitz Syndrome, Testicular Feminization Syndrome (TFM)	CYP17A1,NR0B1,SRY,NR5A1,DHH,SRD5A2, AR,POR,CYP19A1,SOX9, DHCR7, SRD5A2, SRY, AKR1C2,ARX,ATRX,BDNF,BUB1,BUB1B, BUB3, CEP41,CEP57,COX7B,CYP11B1, CYP17A1,DHCR24, DHCR7,DYNC2H1,FRAS1, FREM2, GATA4,GRIP1, HCCS,HOXD13,HSD17B3, ICK,IFT80,IRF6, LHB, MAP3K1,MKS1,NEK1,NR0B1,NR5A1,PAX6,POR, RIPK4,SC5D,SHH,SOX3,SOX9,SRD5A2,SRY, TBX15, TNXB,TSPYL1,VANGL1,WDR34,WDR35,WDR60, WT1,WWOX, …..
Skeletal dysplasias, limb abnormalities	Achondroplasia, Hypochondroplasia, Ectrodactyly-Ectodermal Dysplasia-Cleft Lip/Palate (EEC), Split Hand-Split Foot Malformation (SHFM), Hay-Wells syndrome, κι άλλα πολλά	BMP2,BMPR1B,CHSY1,COL11A1,COL11A2, COL2A1,DYNC2H1,EFNB1, EVC1, EVC2, FANCA,FANCB,FANCC, FANCD2, FANCE,FANCF, FANCG,FANCI,FANCL, FANCM,FGFR2,FGFR3,GDF5, GJA1, GLI3,HOXD13, HPGD,IHH, LMBR1,LRP4, NEK1,NOG,SKI,SLC26A2, TP6 WDR19,WDR35, ……

U/S finding	Genetic disorder(s)	Genes
Cleft lip – cleft palate	Orofacial cleft 5, AD, Cleft lip/palate-Ectodermal dysplasia syndrome, Orofacial cleft 7, AR	BMP4,MSX1,PVRL1,SUMO1,TBX22,TP63,UBB, …..
Hydrocephalus and/or aqueductal stenosis	X-linked hydrocephalus, MASA syndrome, CRASH syndrome, κι άλλα πολλά	AHI1,AKT3,ALG13,ALX3, AMER1,AP1S2,ARHGAP31, ARL13B, ARSB, ATXN10, B3GALNT2, B3GALTL, B3GAT3, B3GNT1, B4GALT1,B9D1,B9D2,BRAF,BRIP1,BUB1B,C5ORF42,CC2D2A, CCDC88C,CEP290,CEP41,CLCN7,CLIC2,COL18A1,COL4A1, COX7B,CSPP1,CTSK,DHCR24,DHCR7,DMPK, DNAI1, DNMT3B, DOCK6,DOK7,EOGT,ERCC4,ERCC6, ERCC8,ERF, ESCO2,EZH2,FAM111A,FAM20C, FANCA, FANCB, FANCC, FANCD2,FANCE,FANCF, FANCG,FANCI, FANCL,FANCM, FGFR1,FGFR2, FGFR3,FKRP,FKTN, FLNA, FLT4,FLVCR2,FRAS1, FREM2, FTO, FUZ,GALC,GBA, GFAP, GLI2,GLI3, GMPPB, GPC3, GPSM2,GRIP1,GUSB, HCCS,HDAC6,HRAS,HYLS1, ICK,IDS,IDUA,IFT172,IFT88, INPP5E,ISPD,KDM6A,KIAA0196, KIF7, MT2D,KRAS,L1CAM, LAMB1,LARGE,MAP2K1, MAP2K2, MBTPS2,MED12,MIPOL1,MKS1,MMACHC, MPDZ,MTM1, NF1, NOTCH2, NPHP1, OFD1,OGDH, OSTM1, PALB2, PIGV, PIK3CA,PIK3R2,PLG, POMGNT1, POMGNT2, POMK,POMT1, POMT2,PORCN, PRKAR1A, PTCH1, PTDSS1,PTEN,PYCR1, RAD51C, RAPSN, RBPJ, RECQL4,RNASEH2A,ROGDI,RPGRIP1, RPGRIP1L, SF3B4,SHOC2,SKI,SLC17A5,SLX4,SMARCB1, SMOC1,SNX10,SOX18,SOX2,SOX9,SUMF1,TBX15, TCIRG1, TCTN1,TCTN2,TGFBR1,TGFBR2,TMEM138, TMEM216, TMEM231,TMEM237,TMEM5,TMEM67,TNFSF11,TP53,TREM2,TRPV4,TSC1,TSC2, TYROBP, VANGL1,VANGL2,VHL,VSX1, WDPCP,WNT3, ZBTB24,ZIC2,ZIC3,ZNF423,…….
Heart abnormalities / dysplasias	Hypoplastic left heart syndrome, Hypoplastic right heart syndrome, Endocardial fibroelastosis, Complete heart block (AD) Supravalvular aortic stenosis (AR), Wolff-Parkinson-White syndrome, Apert, Noonan, Holt-Oram, Marfan, Osteogenesis imperfecta, Tuberous Sclerosis, Ehlers-Danlos syndromes, Ellis-Van Creveld, Carpenter, Meckel-Gruber, Laurence-Moon-Biedl syndromes, Duchenne/Becker and Dreifus muscular dystrophies	COL1A1,COL1A2,COL3A1, DMD, ELN, EMD,FBLN5,FBN1, GATA4, GATA6, GDF1, GJA1,JAG1,LMNA, NKX2-5, PRKAG2, SYNE1,SYNE2, TAZ, BX1,TSC1, TSC2, ZFPM2, ……..

U/S finding	Genetic disorder(s)	Genes
Abnormalities/dysplasia of the eyes (anophthalmia, microphthalmia)	Anophthalmia / Microphthalmia	ALDH1A3,BMP4,FKTN,GDF6, MFRP,OTX2,PAX6,POMT1, POMT2 PRSS56,RAX,SOX2,VSX2, OTX2
IUGR		ARID1A,ARID1B,ARVCF,ASXL1,ATP6V0A2 ATP7A, ATR, ATRIP, B3GALTL, BCS1L, BLM, BMPER, BRAF, BRIP1, BUB1, BUB1B,BUB3,CCDC8,CDC6,CDKN1C,CENPJ,CEP152,CEP57, CHD7, CHRNA1, CHRND, CHRNG,COMT, CTC1,CTDP1,CUL7,DDX11,DHCR24,DHCR7, DKC1,DLL3,DNAJC19,DOK7, EIF2AK3, EMG1,EPHX1,ERCC1, ERCC2,ERCC4,ERCC5, ERCC6,ERCC8,ESCO2,EVC,EVC2,FAM111A, FAM20C, FANCA, FANCB,FANCC,FANCD2, FANCE,FANCF,FANCG,FANCI,FANCL,FANCM,FBN1,FGFR1,FGFR3,FIG4, FLNB, FLVCR2, GBA,GCK, GDF1,GFM1,GLI3,GLIS3,GP1BB,HDAC6,HDAC8,HES7,HIRA,HMGA2,HOXD13, ……..

InterGenetics 2015

yet another step forward ....

FetalSafe®

comprehensive prenatal testing

The new genomic test *FetalSafe*® may be applied to all pregnancies requesting prenatal diagnosis,

as a complement to

prenatal molecular karyotype

What is the new genomic test *FetalSafe®*

The *FetalSafe®* genomic test analyzes through massive parallel sequencing (NGS), all the exons of ~350 genes with a turnaround time of 5 days and in parallel with the prenatal molecular karyotype, covering, in addition to all possible chromosomal abnormalities, a large number of severe and debilitating gene disorders, which may manifest in the child, without any previous family history

What is analyzed through *FetalSafe®*

The genes and the associated genetic diseases correspond to approximately:

- 210 recessive genetic diseases, such as:
  - thalassemia
  - cystic fibrosis
  - several types of deafness
  - Duchenne/Becker muscular dystrophy
  - retinopathies
- 110 dominant genetic diseases, such as:
  - Marfan syndrome
  - neurofibromatosis
  - polycystic kidney disease, adult type
  - Noonan syndrome
  - Treacher-Collins syndrome

Which disease entities are included in *FetalSafe®*

- ~170 neurogenetic-neurological diseases
- ~22 metabolic diseases
- ~90 severe pediatric diseases, and
- ~140 genetic diseases presenting with U/S findings during pregnancy (Noonan syndrome, Smith-Lemli-Opitz syndrome, infantile recessive polycysatic kidney disease, osteogenesis imperfecta, etc.).

The FetalSafe® genomic test is addressed to parents wishing the most comprehensive testing of genetic diseases, which may affect their future child

Thus, it may now be envisaged that the prevention of severe genetic diseases by genetic testing of the fetus is nearly complete and effective

However….prerequisites

- Based on current technology, a prerequisite for the diagnostic application of the above, with the required diagnostic precision for implementation in daily clinical practice, is the existence of sufficient quality and quantity of fetal DNA

- The way in which we ensure this belongs to the specialist obstetricians practicing maternal-fetal medicine, who are primarily responsible for proposing safe (invasive ?) methods for obtaining embryonic cells

Approaches for obtaining fetal DNA

- Today, two approaches are basically available for the collection of fetal DNA for the purpose of prenatal diagnosis / testing of genetic disorders:
  1. invasive collection of fetal cells
  2. analysis of free fetal DNA in maternal blood

First option: invasive prenatal diagnosis

- This option of invasive collection of fetal cells, through biopsy of chorionic villi in the 1st trimester or by drawing amniotic fluid in the 2nd and 3rd trimester, permits the accurate diagnostic detection of all possible chromosomal and gene disorders of the fetus

- This proven approach has been in use for decades, albeit reportedly accompanied by some degree of risk for pregnancy loss, determined initially at 1-2% for chorionic villi biopsy and 1% for amniotic fluid sampling, forming the criterion for prenatal diagnosis

However, undisputable recent scientific data, place the risk of invasive amniotic fluid sampling at 1/350 - 1/1000, i.e. 3.5-10 times lower than that quoted previously..

…. and therefore this risk should now form the new criterion for performing prenatal diagnosis through amniocentesis…..

….. by comparing the likelihood of a genetic defect in the fetus versus the risk of pregnancy loss

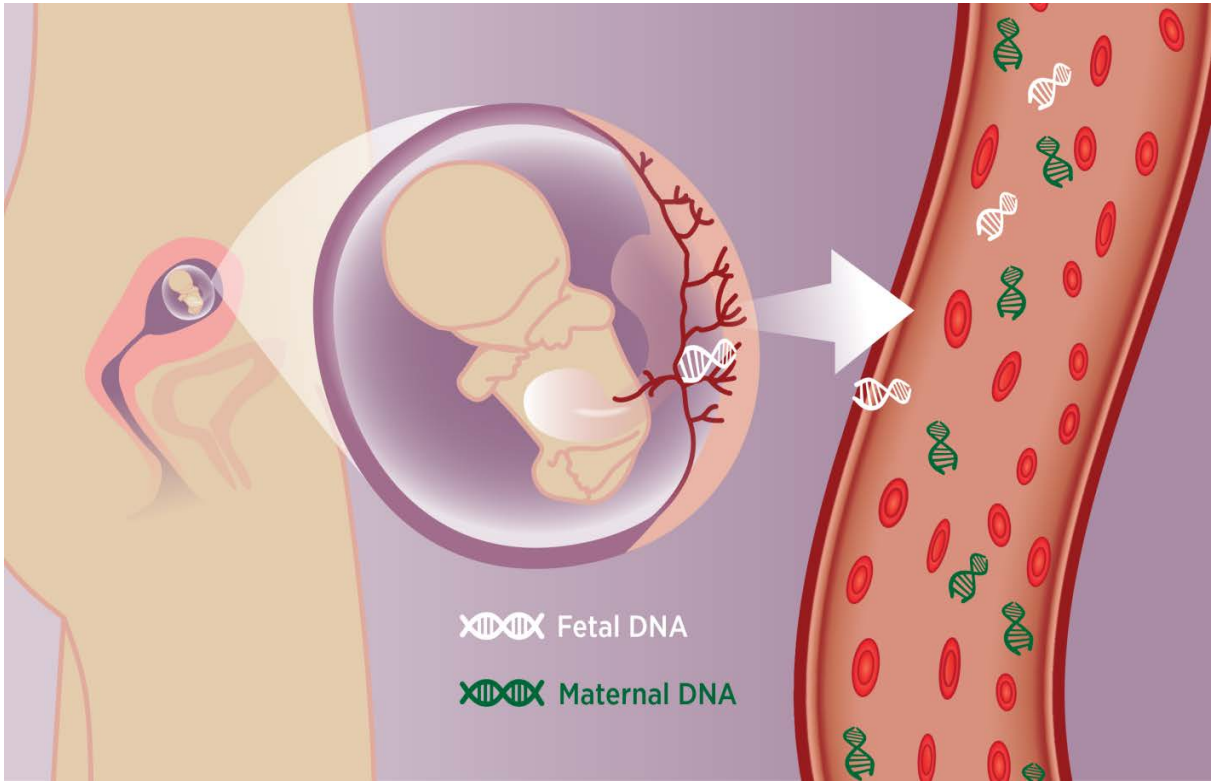
In other words, any genetic defect that has by itself, or in aggregate with other discoverable genetic abnormalities, an incidence of >1/350 should be tested through invasive procedures

Second option: non-invasive prenatal diagnosis

- This option rejects any invasive risk, favoring the analysis of free fetal DNA in the blood of pregnant women, which is performed non-invasively by obtaining a maternal peripheral blood sample (NIPT test)

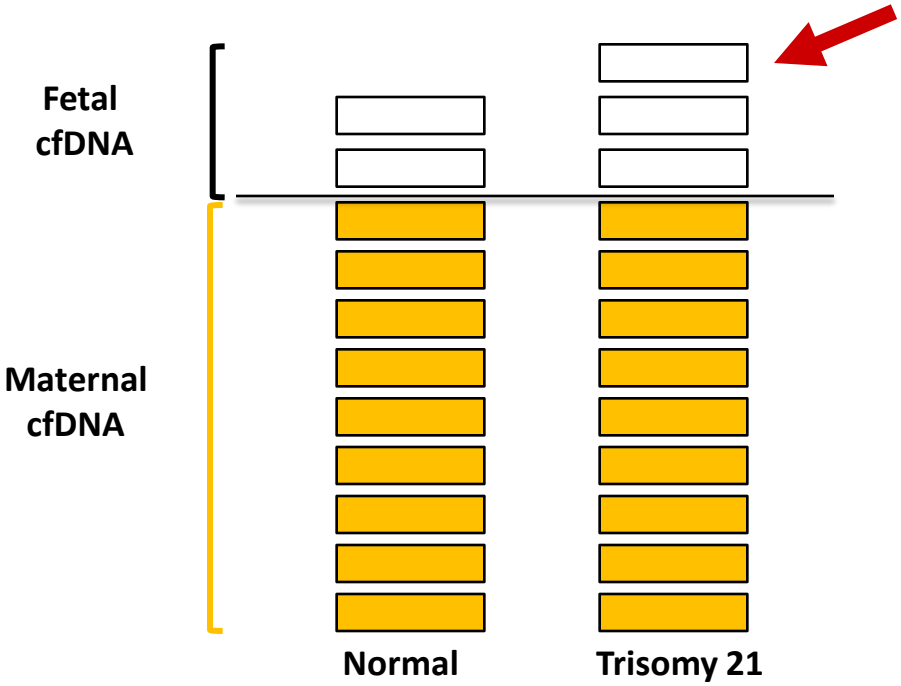
- It allows the collection of fetal DNA, but in insufficient quantity and quality to allow the abovementioned necessary accurate routine diagnostic genetic testing, affording only the statistical evaluation of the risk, rather than diagnosis, for specific chromosomal abnormalities and basically for Down syndrome only, i.e. trisomy of chromosome 21

Free fetal DNA in maternal blood



- ~2-30% of cell-free DNA in maternal plasma is of fetal origin
- Is the result of apoptosis of syncytiotrophoblastic cells of the placenta
- It is released in the blood-stream in small fragments, approx. ~150-200bp
- Present >7th week
- It disappears in a few hours postpartum

NIPT: the importance of fetal fraction



Fetal fraction	Expected difference in trisomy
[illegible]	[illegible]
10%	1.05
20%	1.10
40%	1.20

Low yield for sex chromosomes

Bianchi *et al.*, 2012 (Verinata)	No call rate 9.5% (T21 1.4%)	DR 8/9	FPR 0%
Mazloom *et al.*, 2013 (Sequenom)	No call rate 5.1% (T21 1.0%)	DR 8/8	FPR 0%
Samango-Sprouse *et al.*, 2013 (Natera)	Failure rate 7.0% (T21 5.4%)	DR 3/3	FPR 0%
Jiang *et al.*, 2012 (BGI)	Failure rate 0.0% (T21 0.0%)	DR 3/3	FPR 0%
Liang *et al.*, 2013 (Berry Genomics)	Failure rate 2.8% (T21 2.8%)	DR 3/3	FPR 0%
Nicolaides *et al.*, 2013 (Ariosa)	Failure rate 2.8% (T21 2.8%)	DR 9/9	FPR .9%

~50% of sex-chromosome aneuploidies are mosaics

(similarities with CVS)

also ..... analysis failures

Company	Insufficient fetal DNA	Assay failure	Total No Result
Sequenom[1]	0.9%	1.1%	2%
Verinata[2]	3.0%	?	5.6%
Ariosa[3]	1.8%	2.8%	4.6%
Natera[4]	?	?	12.6%

1) Palomaki et al, Genet Med 2012 & Sequenom CMM
2) Bianchi et al, Obstet Gynecol 2012
3) Norton et al, Am J Obstet Gynecol 2012
4) Zimmermann et al, Prenat Diagn, 2012

Gestational Age and Maternal Weight Effects on Fetal Cell-Free DNA in Maternal Plasma

Wang E, Batey A, Struble C, Musci T, Song K, Oliphant A. Prenat Diagn. 2013 Jul;33(7):662-6.

Results

- 1.9% of pregnant women had insufficient fetal cfDNA amounts (<4% cfDNA fraction) for testing on the first blood draw.
- Increasing maternal weight is associated with lower fetal fraction of cfDNA.

Cell-Free DNA Analysis for Trisomy Risk Assessment in First-Trimester Twin Pregnancies

M Gil, M Quezada, B Bregant, B Bregant A Syngelaki, and K Nicolaides. Fetal Diagn Ther. 2013 Nov 15. [Epub ahead of print]

Retrospective Group

- Results were correctly classified in 191/192 cases with known karyotype
  - No false positive results.
- Correctly classified 9 of 10 trisomy 21 cases, with risk scores of >99% in 8 cases and a 72% risk in 1 case
  - There was one false negative trisomy 21 case with a risk of 1:714 (0.14%).

Prospective Group

- Risk scores provided for 63/68 samples (92.6%); risk scores not provided in 5/68 samples (7.3%) due to low fetal fraction.
  - In 60/63 cases with a result, risk score for T21, T18 and T13 was <0.01%.
  - In 2/63 cases, risk score for T21 was >99%.
  - In 1/63 cases, risk score for T18 was 59%.

SEQUENOM® MaterniT21 PLUS

Microdeletions:

	1:x births
• DiGeorge syndrome (22q11.2 deletion) [3 Mb]	2,000
• 1p36 deletion syndrome [3-5 Mb]	5,000
• Prader-Willi (pat15q11-13 del) [5-6 Mb]	15,000
• Angelman syndrome (mat15q11-13 del) [5-6 Mb]	15,000
• Cri-du-chat syndrome (5p deletion) [9-11Mb]	50,000

DR 60-80%

DR 85-90%

FPR 1%

natera Panorama™

Microdeletions:

	1:x births
• DiGeorge syndrome (22q11.2 deletion)	2,000
• 1p36 deletion syndrome	5,000
• Prader-Willi (pat15q11-13 deletion)	15,000
• Angelman syndrome (mat15q11-13 deletion)	15,000
• Cri-du-chat syndrome (5p deletion)	50,000
• Wolf-Hirschhorn (4p16.3 deletion)	50,000
• Phelan-McDermid (22q13.3 deletion)	<100,000
• Miller-Dieker syndrome (17p13.2 deletion)	<100,000

DR 97.8% (45/46)
FPR 0.8% (3/392)

DR 96.9% (63/65)
FPR 0.7% (3/404)

Total FPT 1.5%
No result 6.0%

- *Very low sensitivity, and*
- *Large number of false positives, leading to an increase of invasive procedures !*

Results issued … even without a fetus

Ultrasound Obstet Gynecol 2014
Published online in Wiley Online Library (wileyonlinelibrary.com).

Letter to the Editor

Performance of non-invasive prenatal testing when fetal cell-free DNA is absent

Table 1 Non-invasive prenatal test (NIPT) results for two non-pregnant women from five commercial laboratories

	Patient 1		*Patient 2*	
Laboratory	*Test result available*	*Details*	*Test result available*	*Details*
Lab A	No	Insufficient fetal cfDNA for accurate NIPT evaluation	No	Insufficient fetal cfDNA for accurate NIPT evaluation
Lab B	No	Unable to report due to low fetal fraction (fetal fraction reported as 0.6%)	No	Unable to report due to low fetal fraction (fetal fraction reported as 0.6%)
Lab C	Yes	Negative, consistent with female fetus (fetal fraction 4.3% reported on request)	Yes	Negative, consistent with female fetus (fetal fraction 3.9% reported on request)
Lab D	Yes	No aneuploidy detected, two sex chromosomes (XX)	Yes	No aneuploidy detected, two sex chromosomes (XX)
Lab E	Yes	No aneuploidy detected, two sex chromosomes (XX)	Yes	No aneuploidy detected, two sex chromosomes (XX)

The complex finances of NIPT

Maternal cfDNA screening for Down syndrome – a cost sensitivity analysis

Prenatal Diagnosis 2013, 33, 636–642

Howard Cuckle[1]*, Peter Benn[2] and Eugene Pergament[3]

WHAT DOES THIS STUDY ADD?

- On the basis of modeling, it was concluded that expansion of cfDNA testing would be economically justifiable if offered as a contingent test to 10% to 20% of women at moderate or high risk.
- The cost of cfDNA testing needs to fall substantially before it should be offered to all women, regardless of risk.

Clinical utility of NIPT ?

	Overall ranges		
	T21	T18	T13
Specificity (%)	99-100	99-100	99-100
Sensitivity (%)	98-100	97-100	79-100
Positive Predictive Value [PPV] - true positives (%)	90-95*	84*	52*
Negative Predictive Value [NPV] – true negativ	99.9	99	100

- **If positive predictive value**, 99% sensitivity and 0.2% false positives
  - → If 1/50 risk → 90.8%
  - → If 1/500 risk → 49.7%

*ASHG Oct 2013 platform presentation – data from BGI China; 63,543 pregnancies

ACOG
THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

SMFM Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 545 • December 2012

The American College of Obstetricians and Gynecologists Committee on Genetics
The Society for Maternal-Fetal Medicine Publications Committee

- cfDNA should not be part of routine prenatal lab assessment, but should be an informed patient choice after pretest counseling
- cfDNA should not be offered to low-risk women or women with multiple gestations – not yet sufficiently evaluated
- Negative cfDNA test result does not ensure an unaffected pregnancy
- Patient with a positive test should be referred for genetic counseling and offered invasive PND for confirmation
- cfDNA does not replace the accuracy and diagnostic precision of PND w/ CVS or amnio

ISPD Position Statement April 2013

•Reliable cfDNA screening methods have only been reported for trisomy 21 and 18.

•cfDNA screening results have also been reported for sex chromosome aneuploidy and the efficacy is unacceptably low.

•The tests should not be considered to be fully diagnostic and therefore are not a replacement for amniocentesis and CVS.

•Efficacy in low risk populations has not yet been fully demonstrated.

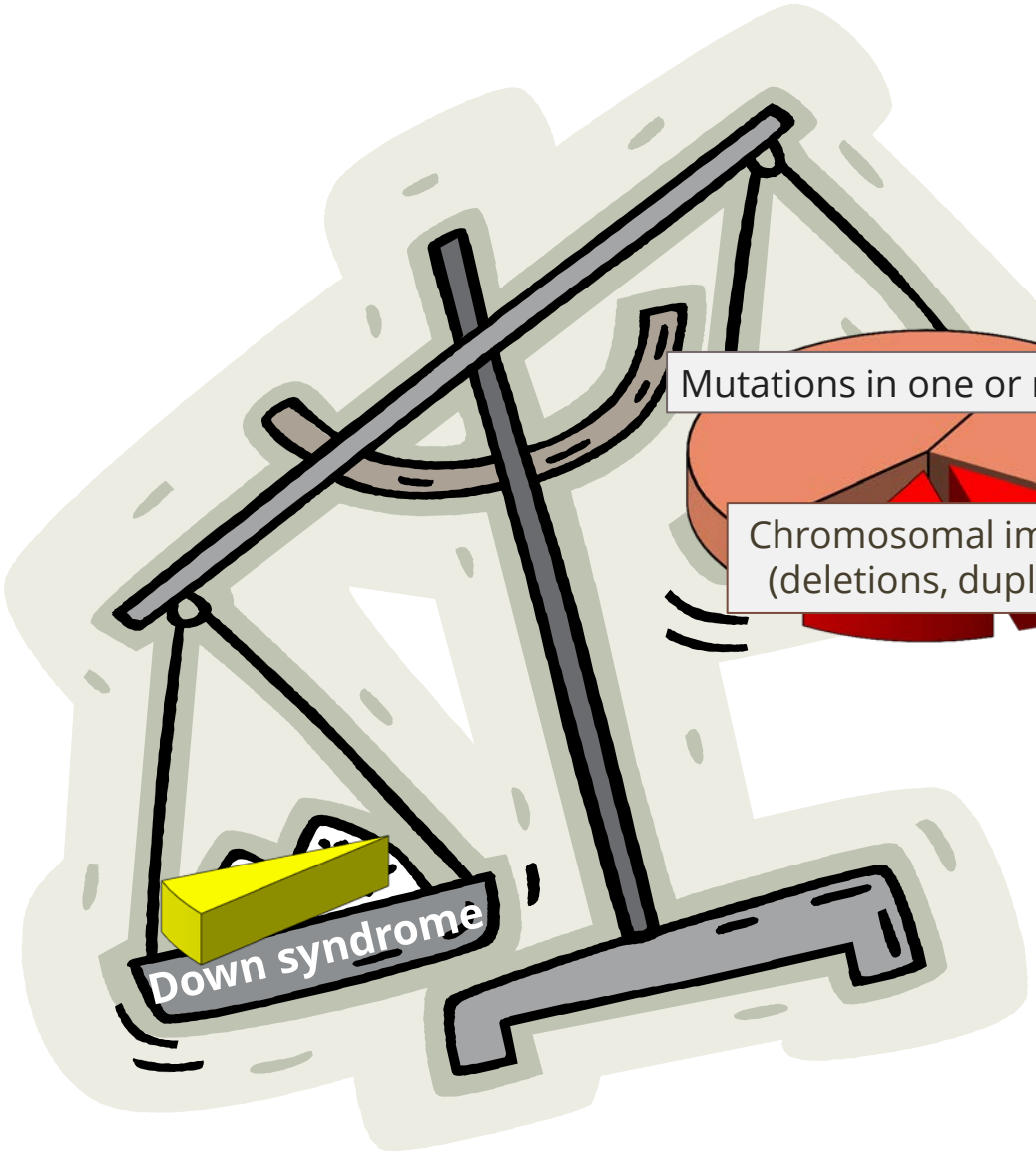
•There is insufficient information to know how well the test will perform in multiple gestation pregnancies.

•It has not been demonstrated that the test can be provided in a cost-effective, timely, and equitable manner to total populations.

Therefore….
it appears that NIPT is not particularly useful in low-risk pregnancies….

…but pregnancies at risk for what ..??

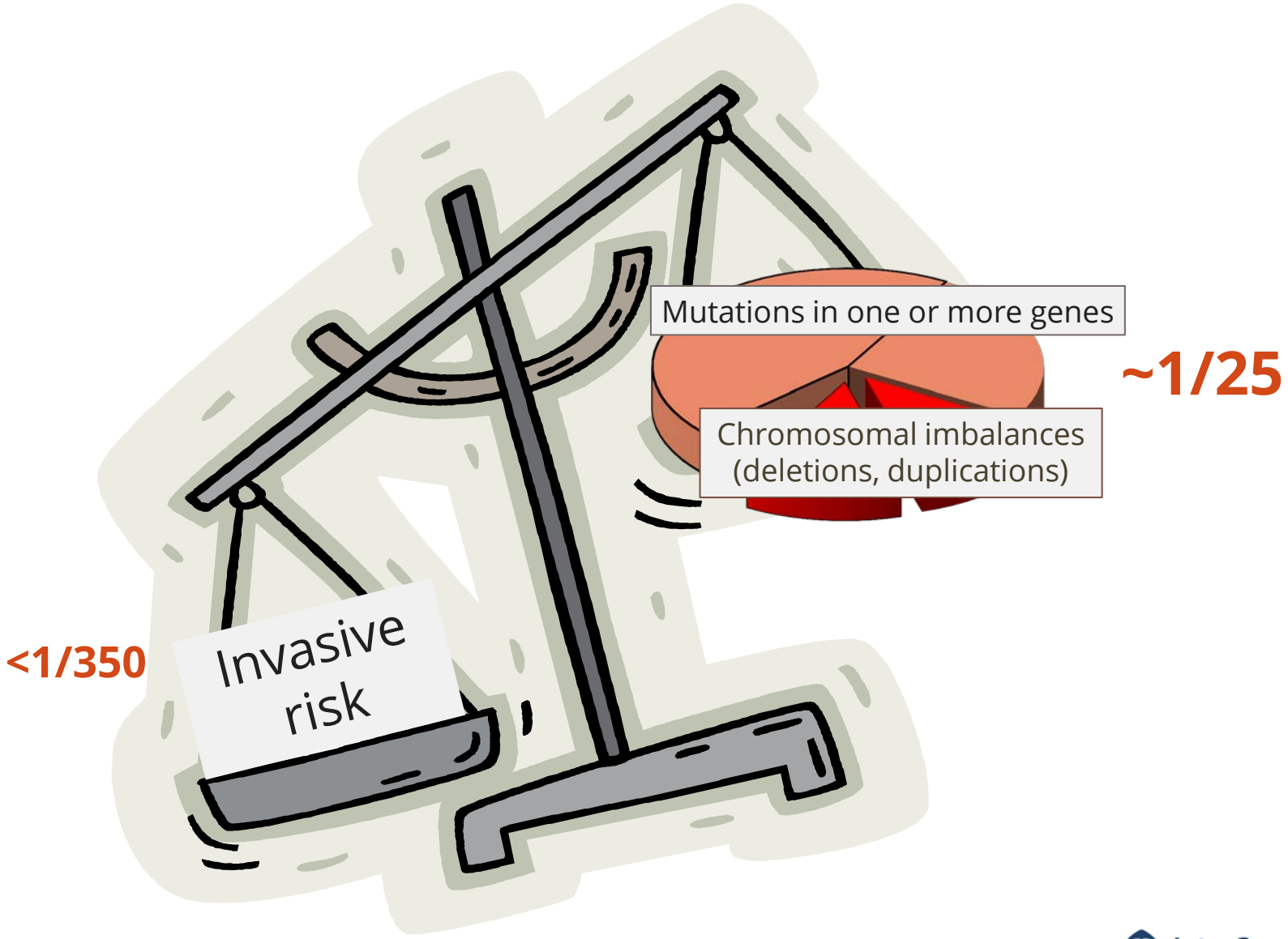
Balance of risks ....!!!



~3%

<1%

Balance of risks ....!!!



Residual risks of NIPT

- Pregnancies in which NIPT has been applied are left practically exposed to a residual risk of 2-3% for serious genetic disorders, that would have otherwise been diagnosed through invasive testing

- These disorders affect the quality of life of the newborn child, also disturbing the everyday life of the family and leading to a serious social and economic burden

Troubling limitations of NIPT

- The nature of NIPT, as already mentioned, is inherently non-diagnostic
- It is risk assessment practically for Down syndrome only, an approach comparable to the classical 1st trimester screening
- This drawback has led to the birth of children with Down syndrome, to which an invasive test had not been performed because of a false negative test result, while many pregnant women have terminated pregnancies without confirmatory invasive testing

- Unfortunately, pregnant women are not fully informed of the aforementioned limitations, due to the low awareness (and potentially punishable by law) of obstetricians-gynecologists and fetal medicine practitioners worldwide

- Furthermore, women are also often reassured that 'all is well' in this gestation, in terms of genetic diseases of the fetus, when in fact they have only been assessed for the risk for Down syndrome

- To all the above, we must add the alarming and overt commercialization of NIPT testing (overselling) of various foreign companies, who rushed to patent their analytical methods in order to maximize their profits,

- …. while also misinforming medical practitioners and the general public regarding the true value and the limitations of NIPT

NIFTY™

华大健康

BGI health

panorama™

prenatal test

Down syndrome	>99%
Edwards syndrome	
Patau syndrome	
Turner syndrome	2/2
Triploidy	1/1

verinata Health®

an Illumina® company

An advanced blood test to assess the risk of common fetal trisomies.

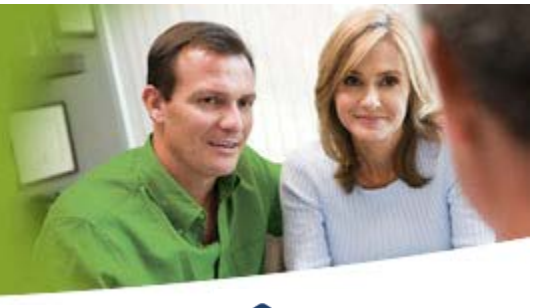
Harmony™ PRENATAL TEST

SEQUENOM® CMM®

CENTER FOR MOLECULAR MEDICINE

MaterniT21™ PLUS

A noninvasive prenatal laboratory-developed test for fetal aneuploidies



InterGenetics

DIAGNOSTIC GENETIC CENTER

Diagnostic comparison
Invasive vs. Non-Invasive

Genetic disorders	Invasive testing	NIPT
Common trisomies	+	+ **(with confirmation)**
Microdeltion/microduplication syndromes	+	-
Gene disorders	+	-
Pregnancy loss per 10.000	10-20	2-3
Diagnostic yield per 10.000	400 (4%)	60-80 (<1%)

The introduction of NIPT from 2012 onwards,

is causing serious problems

in the proper genetic counseling of pregnant women and

ultimately in the

prevention of genetic disorders

of the fetus

Current dilemmas in PCD

- Now more than ever, careful consideration is warranted as to how PCD risks and the concomitant dilemmas are communicated to couples, by offering as few as possible, concrete, well documented and personalized options, which will help them to reach an informed decision
- In parallel, it would appear that in this new era the role of professionals with a solid background in medical genetics should play a decisive role in pre- and post-test prenatal counseling, while obstetricians should also be better informed about the new diagnostic capabilities and their benefits and limitations

The major current dilemma in PCD

In conclusion, there appears to be one current major dilemma, embodying all the data presented herein, relating on the one hand to reaping the benefits from the high detection rate of several clinically important disorders through aCGH, but accepting a necessary comparatively lower invasive risk, and, on the other hand, providing a lower detection rate practically for DS only, with the benefit of avoiding the invasive risk. Although this dilemma is formulated and will be debated by medical professionals active in PCD, the answer will surely come from the properly informed couple.

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Dilemmas in Prenatal Chromosomal Diagnosis Revealed Through a Single Center's 30 Years' Experience and 90,000 Cases

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Thank you for your attention