ECS Impact on Indication Profile & Expanding Application of PGT-M

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Reproductive Genetic Innovations

USA

LEUVEN, 2025

PGT-M: Traditional and Novel Indications

- Autosomal recessive & dominant disorders
- X-linked diseases

- Late onset diseases:
  - Cancer
  - Cardiac diseases
  - Neurodegenerative conditions

- HLA GENOTYPING

Present RGI PGT experience (1990-2024)

Over 38,000 performed for 817conditions

11,437 - Mendelian disorders (PGT-M)

Including:

650 - *DE NOVO* mutations

1651 - Cancer

1247 - Neurodegenerative

204 - Cardiac Conditions

581 – HLA

6457 - combined with PGT-A

27,167 - (PGT-A)

Why are PGT-M Cycles Increasing?

- **Expanded Carrier Screening identifies increasing # couples at risk**

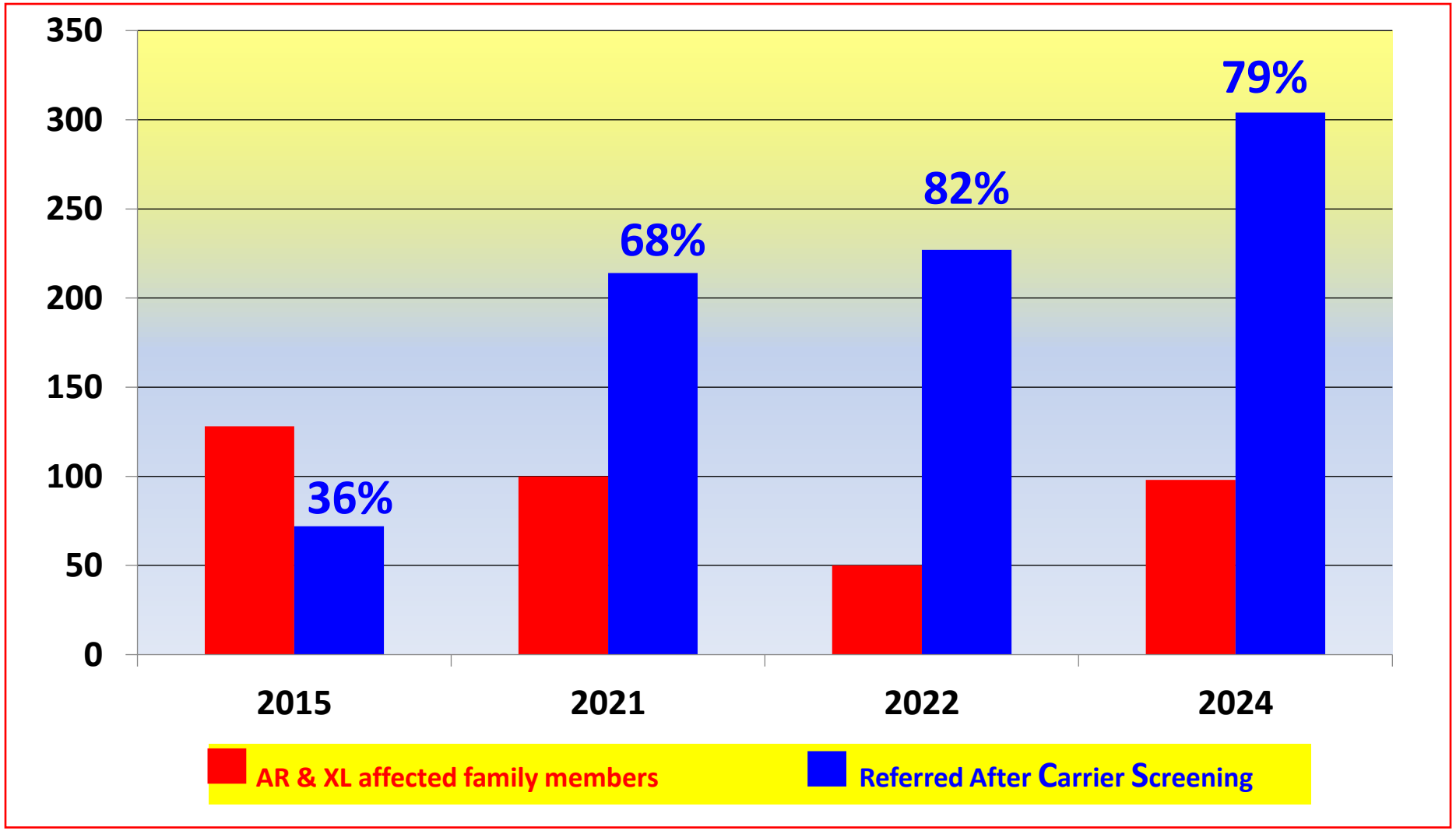
  1 in 300 pregnancies; 1 in 22 couples at risk

- **Recognition that embryo selection is achievable following a De Novo mutation in a single family member**

- **Disease-specific gene panels identify adults with heritable cancers and whose learn that their offspring are at risk for Late-onset single gene disorders**

INCREASED UTILIZATION OF PGT-M THROUGH PAN-ETHNIC EXPANDED CARRIER SCREENING

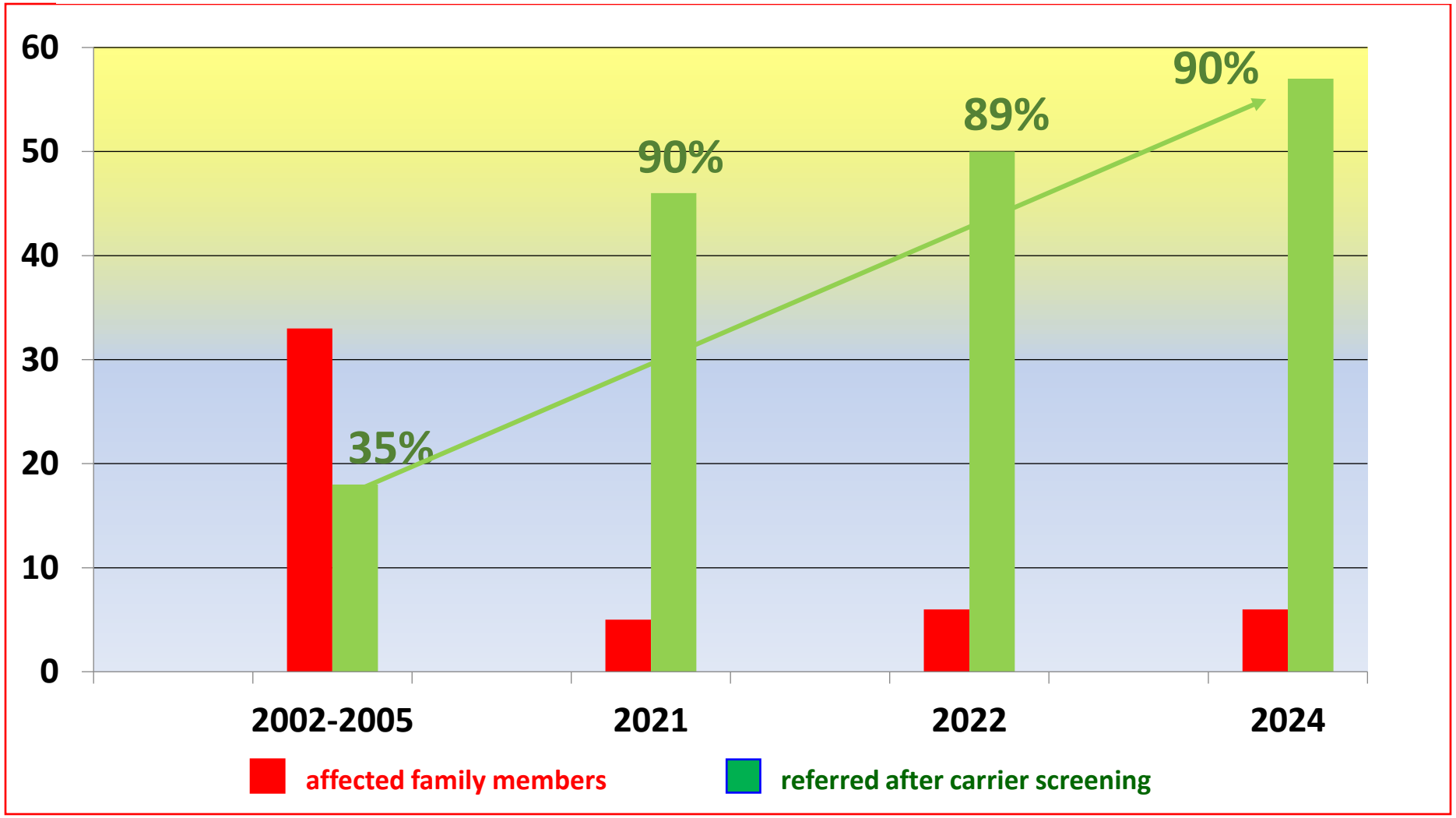
1 in 300 affected pregnancies
1 in 22 couples at risk



Increase in PGT-M requests for Cystic Fibrosis after carrier screening

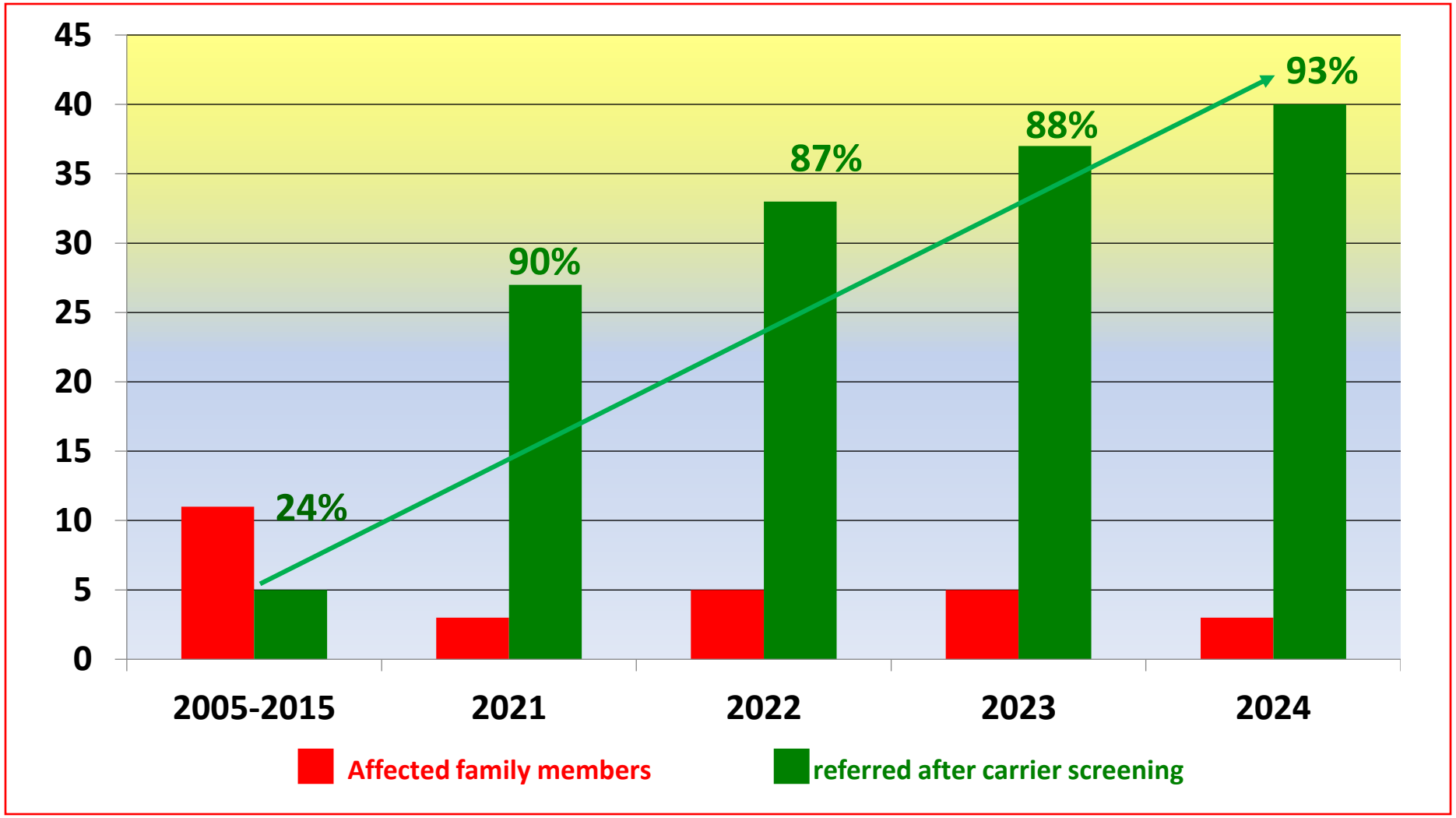
Frequency of live birthCaucasian: 1 in 2,500 to 3,500, African American: 1 in 17,000, Asian American: 1 in 31,000, and Hispanic: 1 in 4,000 to 10,000.

Carrier frequency : Caucasians: 1 in 25; **Ashkenazi Jews:** 1 in 29; **Hispanic Americans:** 1 in 46;**African Americans:** 1 in 61;**Asian Americans:** 1 in 90



Increase in PGT-M requests for Non syndromic hearing loss (*GJB2* gene) after carrier screening

Incidence of **between 1 in 500 and 1 in 1000 live births**.

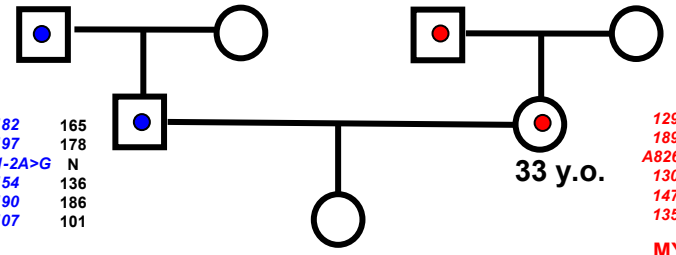


Type of GJB2 mutations for which PGT-M was performed

MUTATION TYPE	# CARRIERS
MISSENCE MUTATIONS: V37I+M34T	297 (58%)
13 OTHER MISSENCE MUTATIONS	25
2 SPLICING MUTATIONS	13
DEL35, DEL167, DEL235	169 (32%)
OTHER DELETION	10 (2%)
TOTAL	514

PGT for USHER SYNDROME (MYO7A and USH2A genes) and PGT-A by NGS

A. Family pedigree



Markers:	MYO7A		USH2A	
D11S4081	129	133	*182*	165
D11S1321	187	189	*197*	178
MYO7A	N	N	*IVS61-2A>G*	N
D11S4186	128	132	*154*	136
D11S911	136	128	*190*	186
D11S947	142	142	*107*	101

PGT
(embryo #4)
Normal USH2A & MYO7A,
46, XX

	MYO7A		USH2A	
	129	121	182	174
	189	195	182	182
	A826T	N	N	N
	130	134	147	147
	147	105	184	193
	135	148	107	105

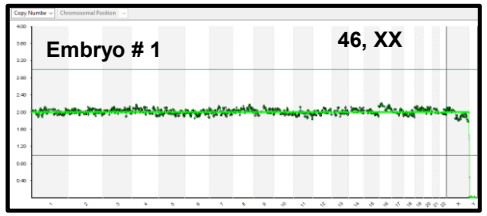
Markers:
D1S419
D1S237
USH2A
D1S229
D1S490
D1S227

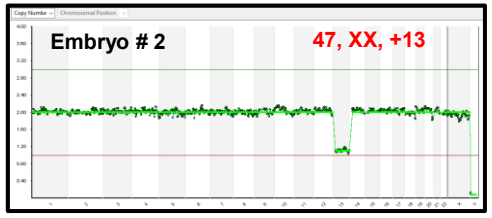
TOTAL -6
NORMAL or CARRIER USH2A -6
NORMAL or carrier MYO7A– 6
EUPLOIUD – 3
For transfer - 3

B. Trophectoderm analysis

Cycle #1

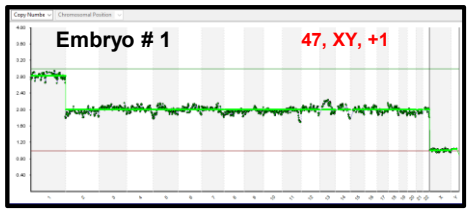
Embryo #	1	2
USH2A	165 182 178 182 N N 136 147 186 184 101 107	165 174 178 182 N N 136 147 186 193 101 105
MYO7A	133 *129* 189 *189* N *A826T* 132 *130* 128 *147* 142 *135*	129 121 187 195 N N 128 134 136 105 142 148
NGS	46, XX	47, XX, +13
	FET1	

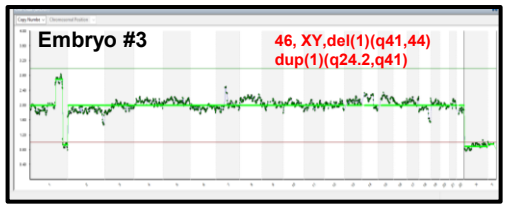


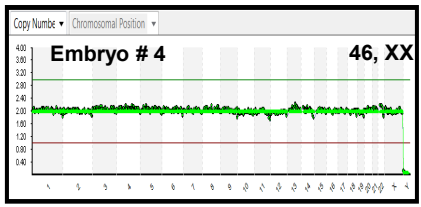


Cycle #2

	1	2	3	4
	165 174 178 182 N N 136 147 186 193 101 105	165 182 178 182 N N 136 147 186 184 101 107	*182* 182 *197* 182 *IVS61-2A>G* N *154* 147 *190* 184 *107* 107	165 182 178 182 N N 136 147 186 184 101 107
	129 121 187 195 N N 128 134 136 105 142 148	133 121 189 195 N N 132 134 128 105 142 148	133 121 189 195 N N 132 134 128 105 142 148	129 121 187 195 N N 128 134 136 105 142 148
	47, XY, +1	46, XY	46, XY,del(1)(q41,44) dup(1)(q24.2,q41)	46, XX
				FET2







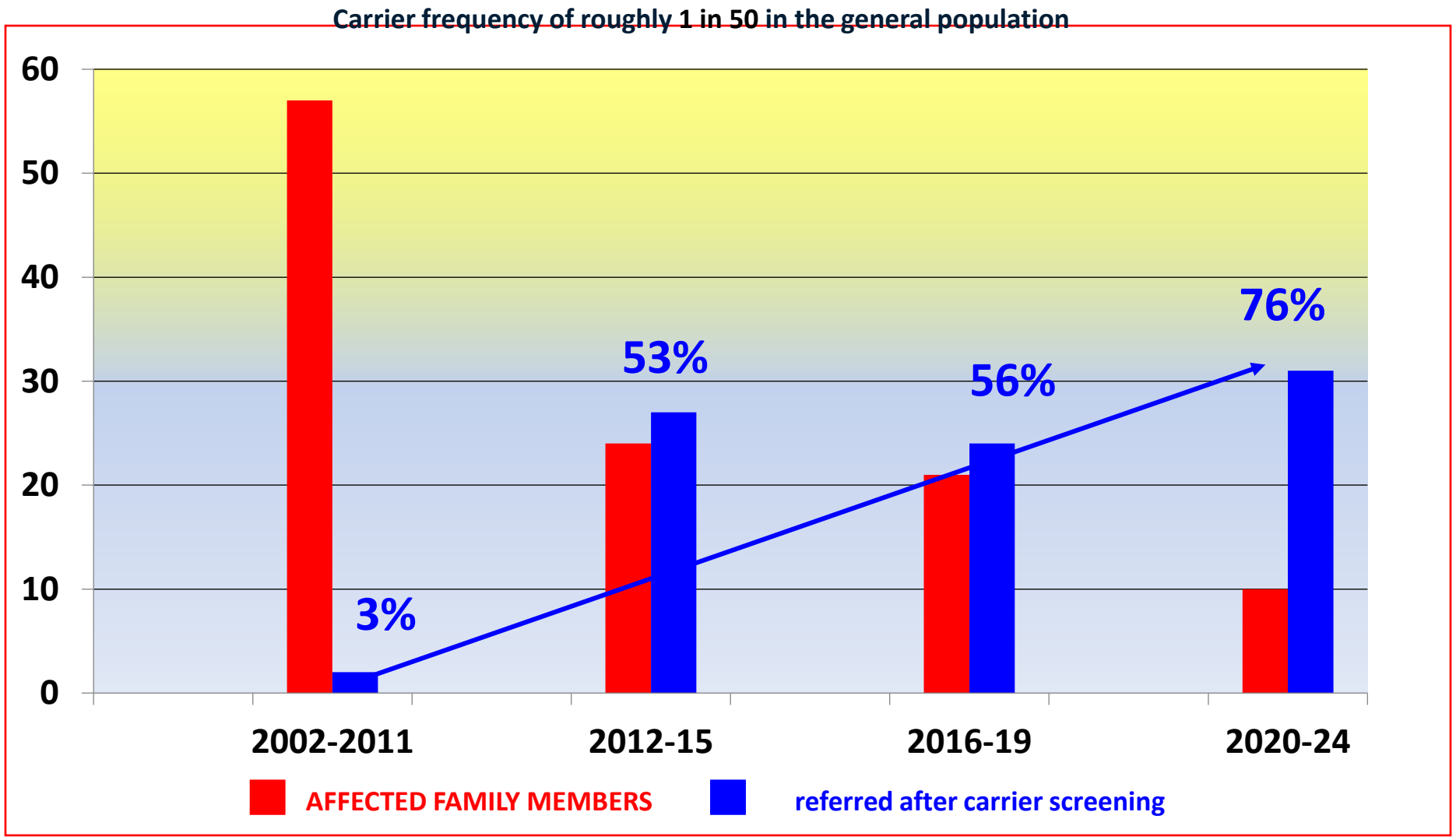
OUTCOME OF PGT-M for HEREDITARY DEAFNESS (HD)

Disease	Gene	Omim	Number of Patients	Number of Cycles	Number of transfers	Number of embryos tranferred	Pegnancy	SAB	Number of Deliveries	Number of Babies
AURICULOCONDYLAR SYNDROME 2; ARCND2	PLCB4	614669	1	3	3	5	2	1	1	1
DEAFNESS, AUTOSOMAL DOMINANT 3B; DFNA3B	GJB6	612643	1	2	2	3	1	0	1	1
DEAFNESS, AUTOSOMAL RECESSIVE 3; DFNB3	MYO15A	600316	2	6	5	5	2	0	2	2
DEAFNESS, AUTOSOMAL RECESSIVE 8; DFNB8	TMPRSS3	601072	2	3	3	3	3	1	2	2
DEAFNESS, NEUROSENSORY, AUTOSOMAL RECESSIVE 1; DFNB1	GJB2	220290	140	324	314	353	208	22	186	190
DEAFNESS, X-LINKED 1; DFNX1	PRPS1	304500	1	1	1	1	1	0	1	1
PENDRED SYNDROME; PDS	SLC26A4	274600	7	10	10	9	4	0	4	4
USHER SYNDROME, TYPE I; USH1	MYO7A	276900	4	4	4	4	2	0	2	2
USHER SYNDROME, TYPE IF; USH1F	PCDH15	602083	3	8	5	7	4	2	2	2
USHER SYNDROME, TYPE IIA; USH2A	USH2A	276901	20	36	38	46	22	3	19	19
USHER SYNDROME, TYPE IIC; USH2C	ADGRV1	605472	1	2	2	3	1	0	1	1
WAARDENBURG SYNDROME, TYPE 2A; WS2A	MITF	193510	3	7	7	9	5	1	4	4
WOLFRAM SYNDROME 1; WFS1	WFS1	222300	1	2	1	1	1	0	1	1
TOTAL	(13 genes)		186	408	395	449 (1.1)	256 (65%)	30 (12%)	226 (88%)	230

PGT-M for GJB2 COMBINED WITH OTHER CONDITIONS

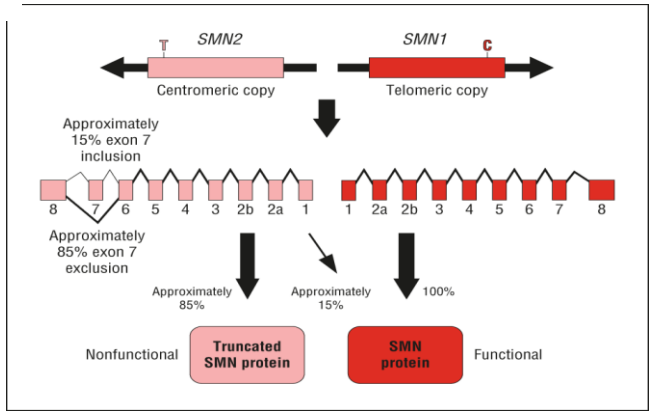
CONDITIONS	GENE		# FAMILIES
FAMILIAL ADENOMATOUS POLYPOSIS 1; FAP1	APC	AD	1
RETINOBLASTOMA	RB1	AD	1
BREAST-OVARIAN CANCER, FAMILIAL	BRCA1	AD	1
TUMOR PREDISPOSITION SYNDROME 4; TPDS4	CHEK2	AD	1
POLYCYSTIC KIDNEY DISEASE 1	PKD1	AD	1
BREAST-OVARIAN CANCER, FAMILIAL	BRCA2	AD	1
MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 23, ATAXIA-TELANGIECTASIA; AT	LAMA2 ATM	AR	1
MITOCHONDRIAL COMPLEX II DEFICIENCY, NUCLEAR TYPE 4; MC2DN4	SDHB	AR	2
ALPORT SYNDROME 1, X-LINKED; ATS1	COL4A5	AR	3
STARGARDT DISEASE 1; STGD1	ABCA4	AR	1
FABRY DISEASE	GLA	AR	1
CYSTIC FIBROSIS; CF	CFTR	AR	1
DRENAL HYPERPLASIA, CONGENITAL, DUE TO 21-HYDROXYLASE DEFICIENCY	CYP21A2	AR	1
HEMOPHILIA A	F8	XL	1
FRAGILE X SYNDROME; FXS	FMR1	XL	1
MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD	DMD	XL	1
TOTAL	17		19

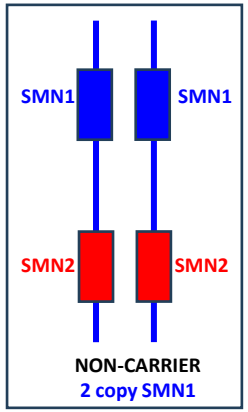
Increase in PGT-M requests for Spinal Muscular Dystrophy after carrier screening

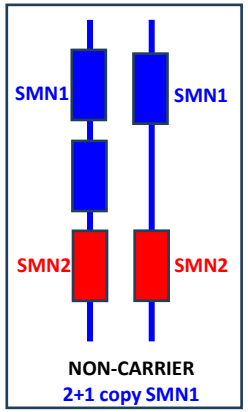


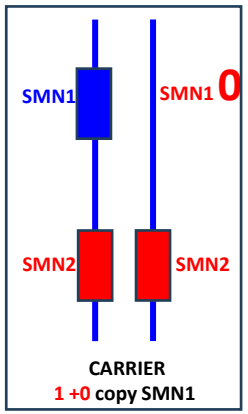
PGT-M STRATEGIES for SILENT MUTATION (2+0) IN *SMN1* GENE

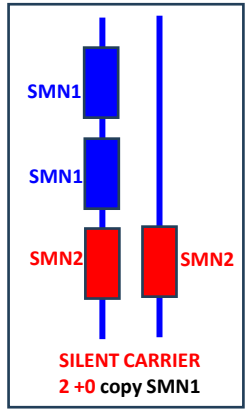
SMA frequency: 1 in 6,000 to 1 in 10,000 live births and a carrier frequency of 1 in 40 to 1 in 60 people





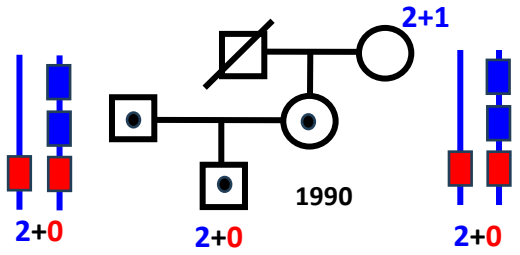




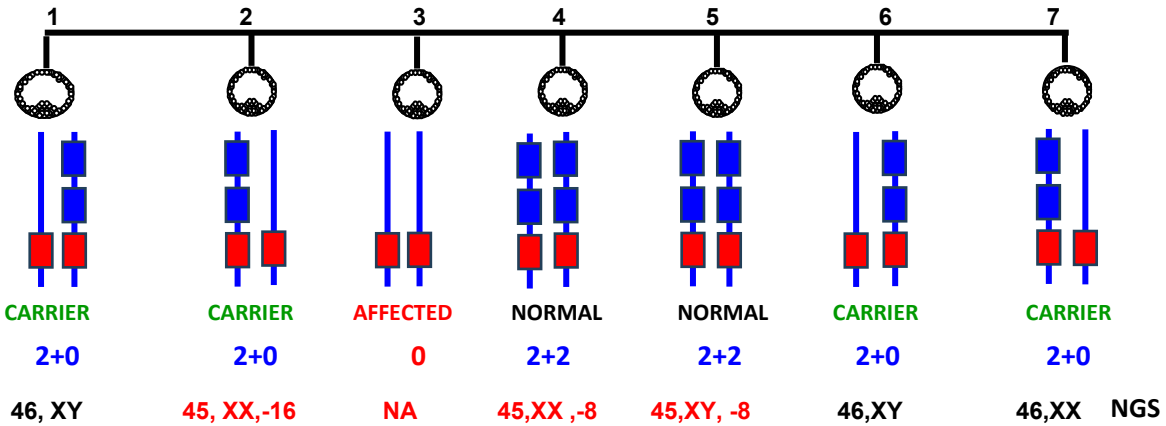


FAMILY A.

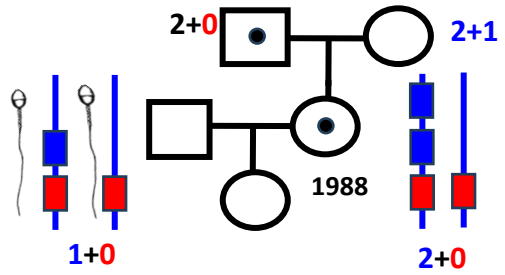
MARKERS ORDER:
D5S2019
D5S1967
D5S1414
EXON7
g.27134 (TorG)
g.27706 delAG
D5S637
D5S2122

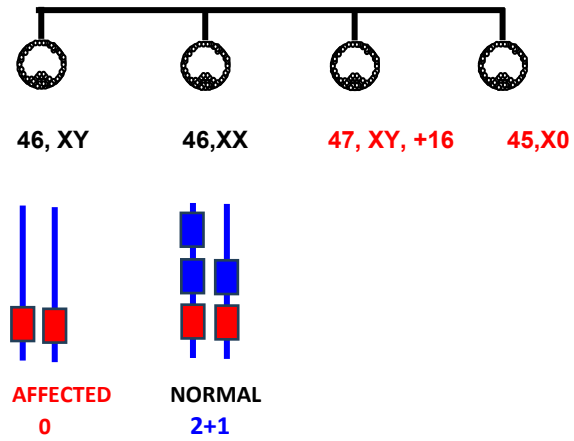


EMBRYOS



FAMILY B.

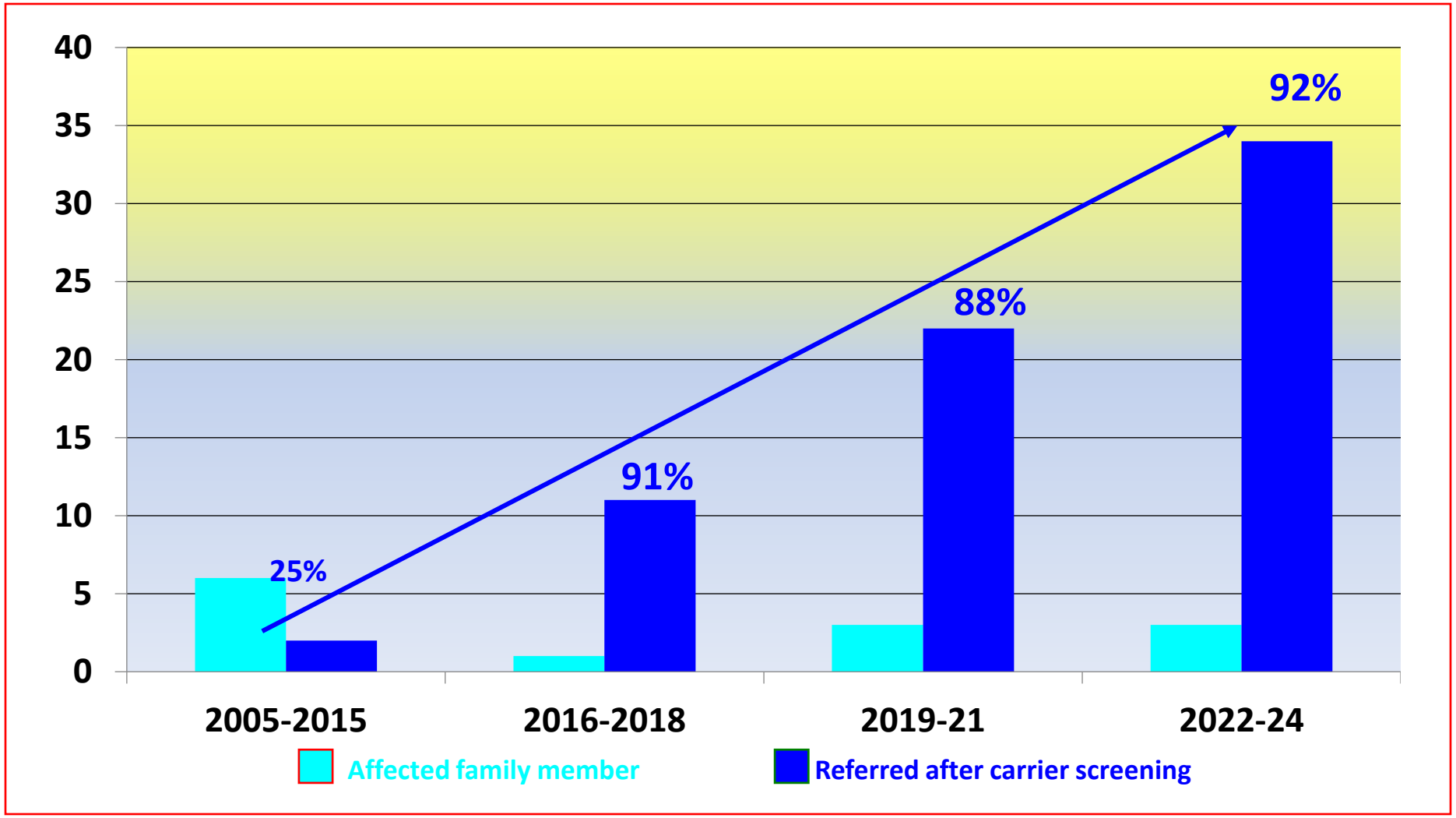




Increase of prospective PGT for PHENYLKETONURIA after expanded carrier screening (ECS)

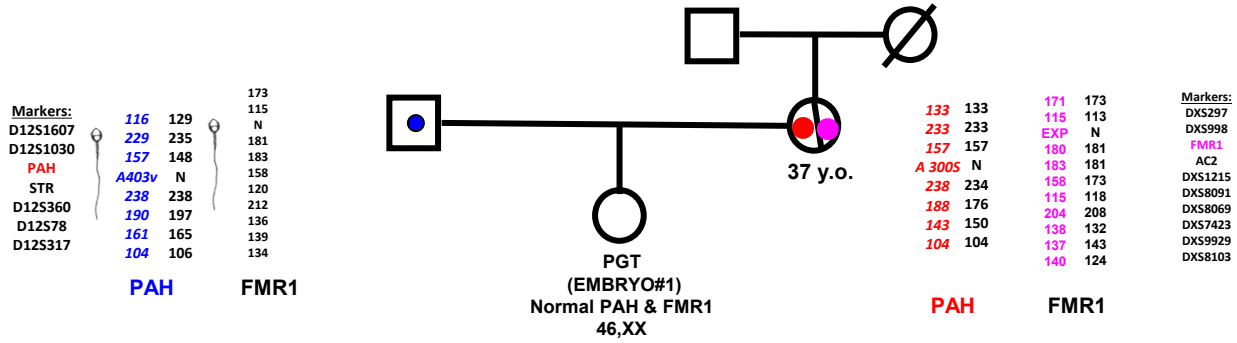
Globally: The average carrier frequency is estimated to be around 1 in 50; Caucasians: The carrier frequency is higher, around 1 in 56;

Ashkenazi Jews: The carrier frequency is even higher, around 1 in 22.

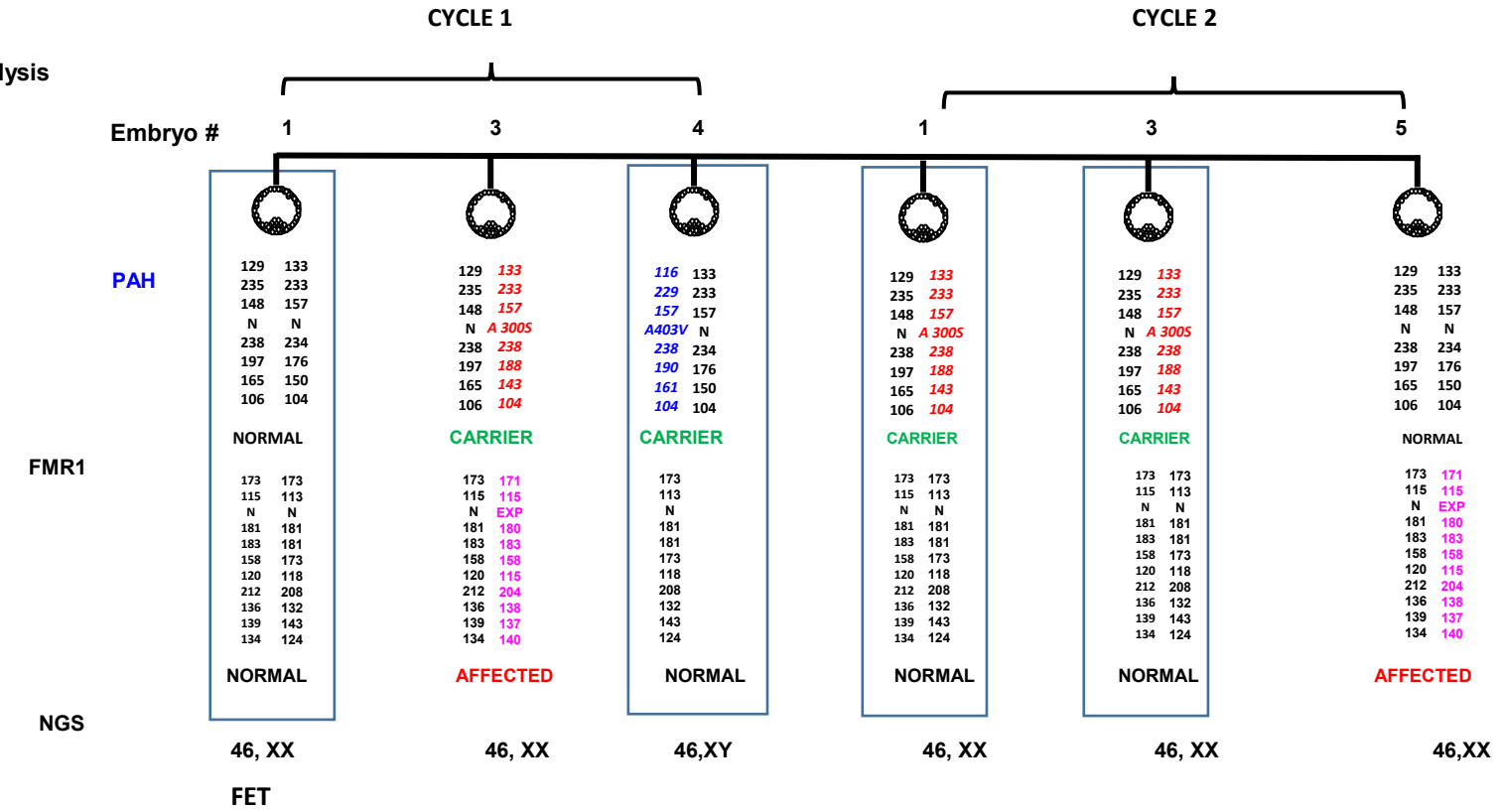


SEQUENTIAL PGT-A by NGS followed by PGT for PHENYLKETONURIA and FRAGILE-X syndrome

A. Family pedigree



B. Trophectoderm analysis



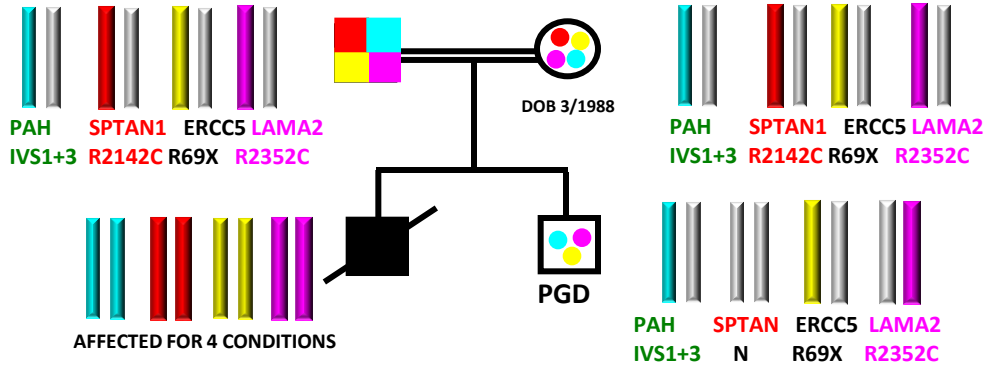
TOTAL 6
CARRIER or NORMAL PAH -6
NORMAL FX 4
For transfer -4

PGT-M for PHENYLKETONURIA COMBINED WITH OTHER CONDITIONS

SECOND CONDITIONS	GENE	INHERITANCE	# FAMILIES
CYSTIC FIBROSIS; CF	CFTR	AR	1
PROPIONIC ACIDEMIA	PCCA	AR	1
ADRENAL HYPERPLASIA, CONGENITAL	CYP21A2	AR	1
FAMILIAL MEDITERRANEAN FEVER	MEFV	AR	1
WILSON DISEASE	ATP7B	AR	1
DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 5; DEE5 XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP G; MUSCULAR DYSTROPHY, CONGENITAL	SPTAN1 ERCC5, LAMA2	AR	1
BRCA1	BRCA1	AD	2
MYOTONIC DYSTROPHY 1 (DMPK)	DMPK	AD	3
FRAGILE X MENTAL RETARDATION	FMR1	XL	1
TRANSLOCATION			1
TOTAL	11		13

PGD FOR 4 AUTOSOMAL RECESSIVE CONDITIONS AND 24 CHROMOSOME TESTING BY NGS

Family pedigree

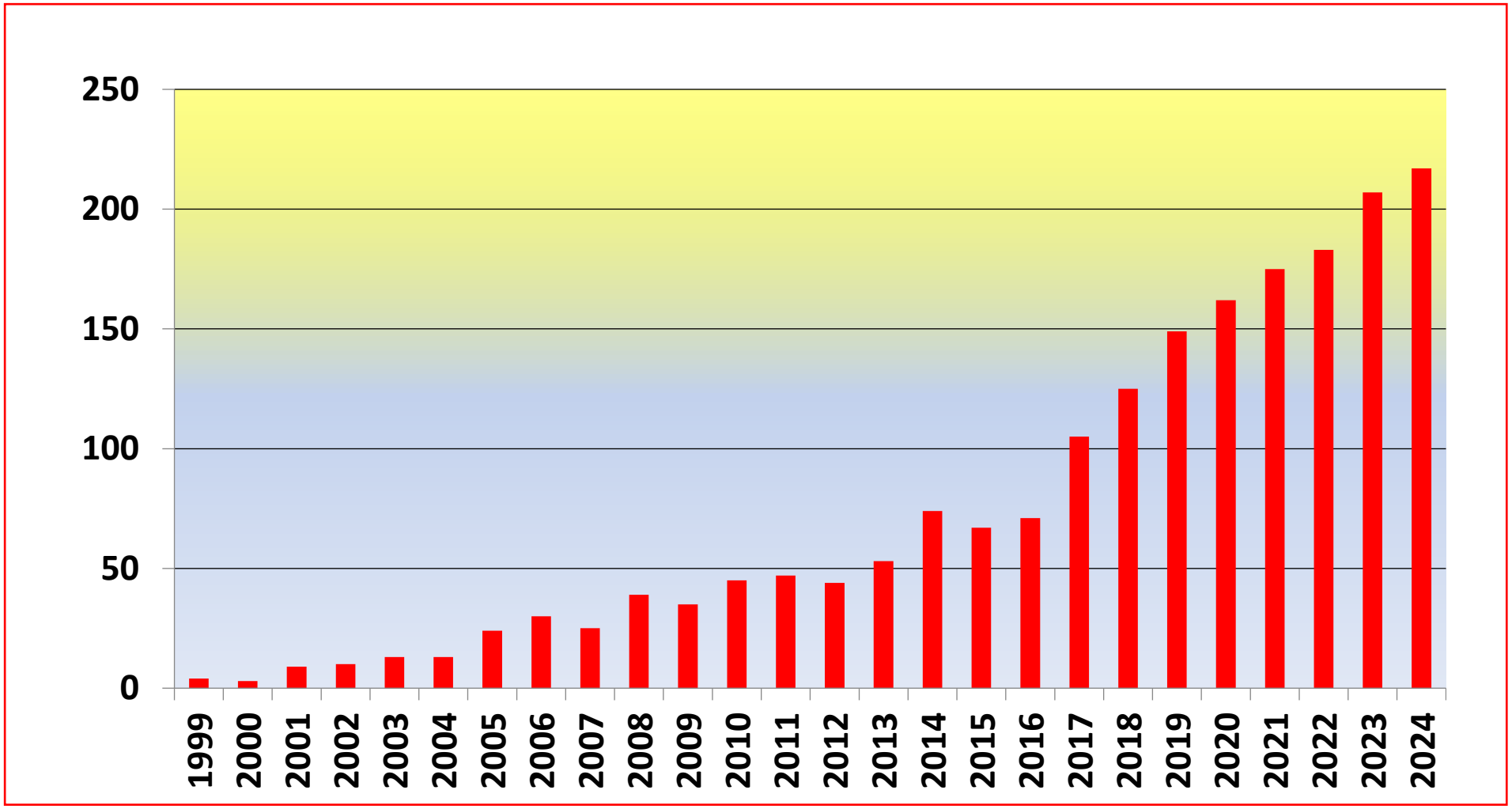


CHANCES TO FIND EMBRYO
FREE FROM PKU ¾
FREE FROM EIEE5 ¾
FREE FROM XPG ¾
FREE FROM MDCA1 ¾
FREE FROM ALL CONDITIONS: ¾ x ¾ x ¾ x ¾ = 81/256 (31.6%)
AFFECTED FOR ALL 4 CONDITIONS: ¼ x ¼ x ¼ x ¼= 1/256 (0.4%)

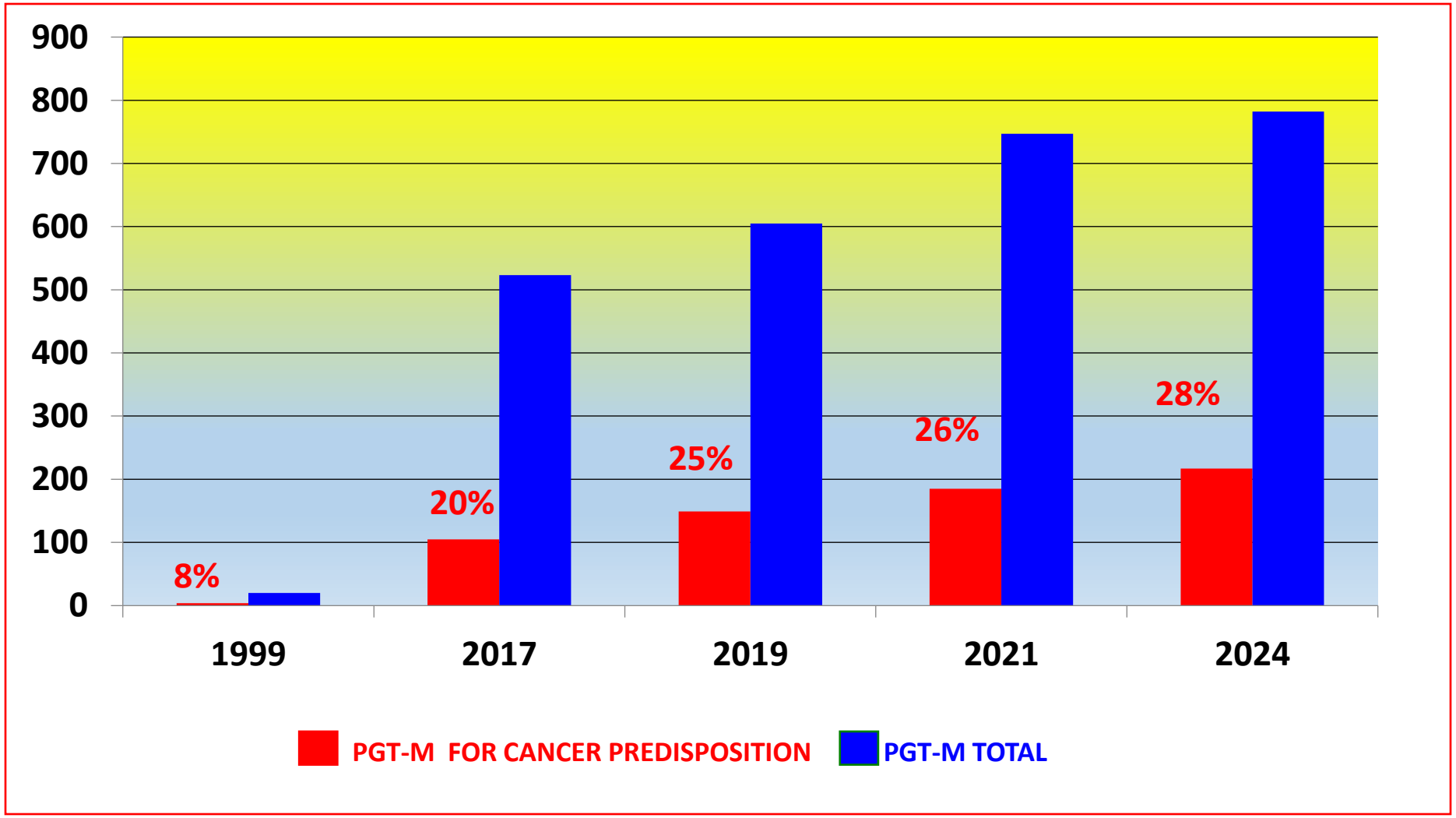
	1	3	4	5	6	7	8	9	10	11	12	16
PAH- 12q22-24.2	AFFECTED	CARRIER	CARRIER	AFFECTED	CARRIER	AFFECTED	CARRIER	NORMAL	AFFECTED	CARRIER	AFFECTED	CARRIER
SPTAN1 9q34.11	CARRIER	NORMAL	AFFECTED	NORMAL	NORMAL	CARRIER	NORMAL	CARRIER	CARRIER	AFFECTED	CARRIER	NORMAL
ERCC5 13q33.1	CARRIER	CARRIER	CARRIER	CARRIER	CARRIER	CARRIER	CARRIER	AFFECTED	CARRIER	NORMAL	AFFECTED	AFFECTED
LAMA2 6q22-23	AFFECTED	CARRIER	CARRIER	CARRIER	CARRIER	NORMAL	AFFECTED	CARRIER	AFFECTED	0	NORMAL	NORMAL
NGS	45, XX,-22	46,XY FET	46,XX	46,XX	47,XX+13	46,XY	46,XY	48,XX+21,+22	47XY,+22	44,XX-2,-6	46,XX	47,XY+13

-6

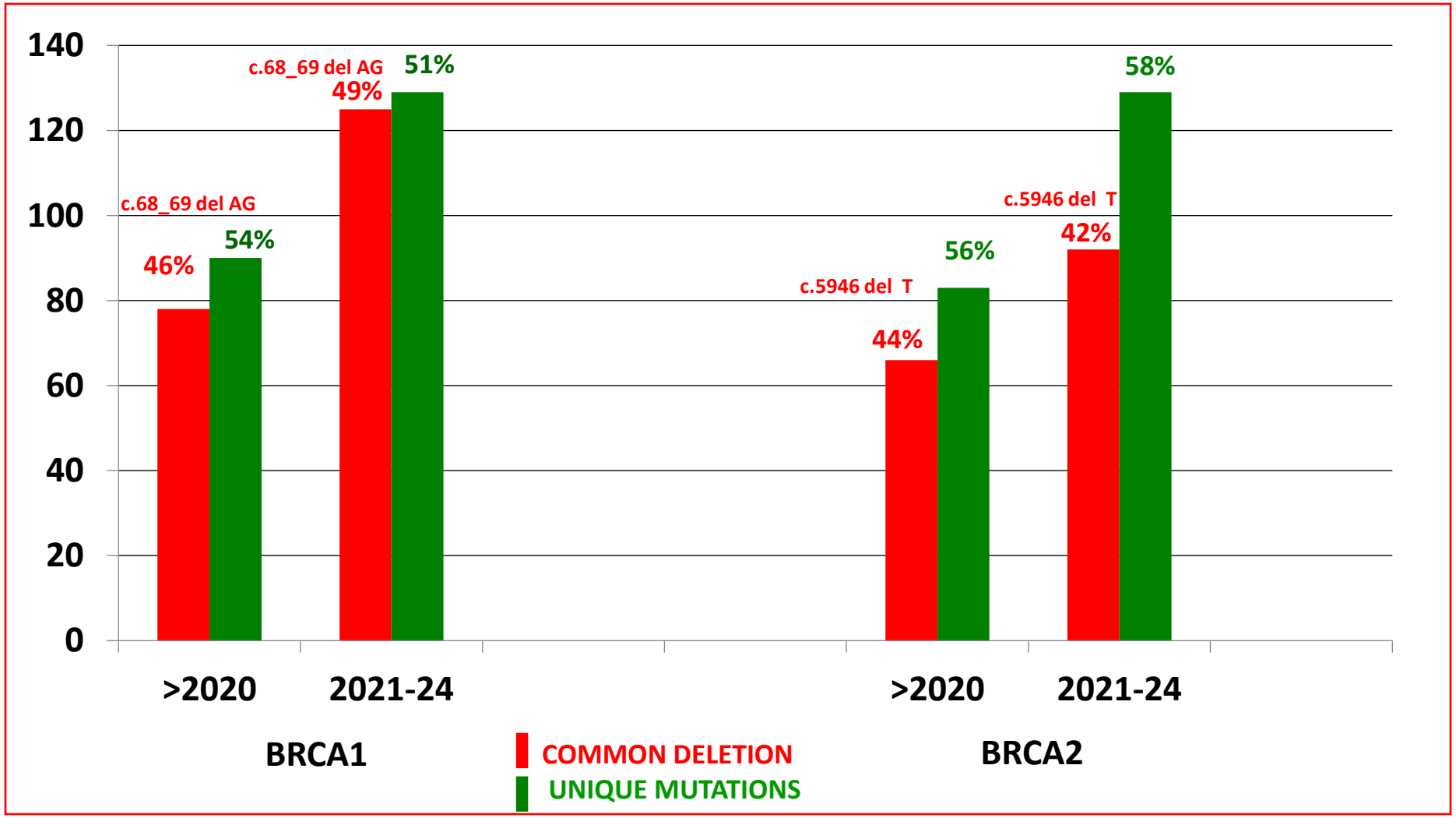
Steady Increase of PGT-M Cycles For Cancer Predisposition (45 conditions, 56 genes)



PROPORTION OF PGT-M cycles for cancer from ALL PGT-M CYCLES



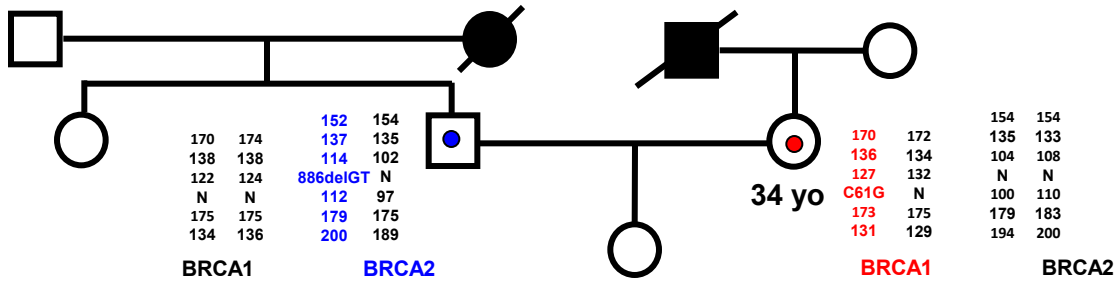
Distribution of most common and unique mutations in BRCA1 and BRCA2 genes



COMBINED PGT-M and PGT-A for BRCA1 and BRCA2 mutations

A.

Family pedigree



PGT

Normal BRCA1 &BRCA2

TOTAL -6

NORMAl BRCA1- 4

NORMAL BRCA2 – 5

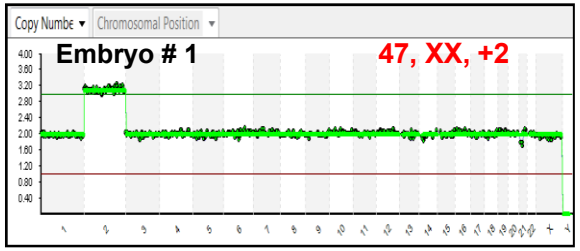
EUPLOIUD – 4

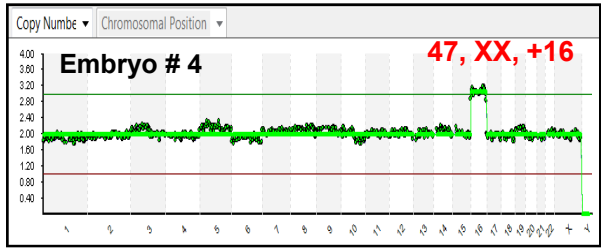
SUTABLE FET - 1

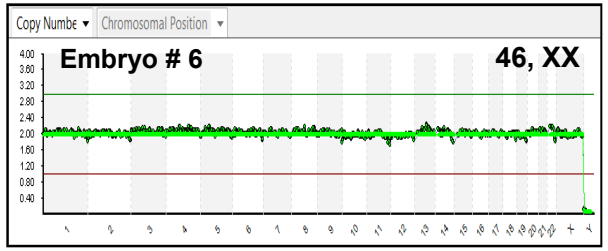
B. Trophectoderm analysis

Embryo #	1	2	3	4	5	6
BRCA 1	170 172 138 134 122 132 N N 175 175 134 129	170 170 138 136 122 127 N C61G 175 173 134 131	170 170 138 136 122 127 N C61G 175 173 134 131	174 172 138 134 124 132 N N 175 175 136 129	170 172 138 134 122 132 N N 175 175 134 129	174 172 138 134 124 132 N N 175 175 136 129
BRCA 2	154 154 135 135 102 104 N N 97 100 175 179 189 194	154 154 135 135 102 104 N N 97 100 175 179 189 194	154 154 135 135 102 104 N N 97 100 175 179 189 194	154 154 135 135 102 104 N N 97 100 175 179 189 194	152 154 137 133 114 108 886delGT N 112 110 179 183 200 200	154 154 135 135 102 104 N N 97 100 175 179 189 194
NGS	47, XX, +2	46, XX	46, XY	47, XX, +16	46, XX	46, XX FET

C.

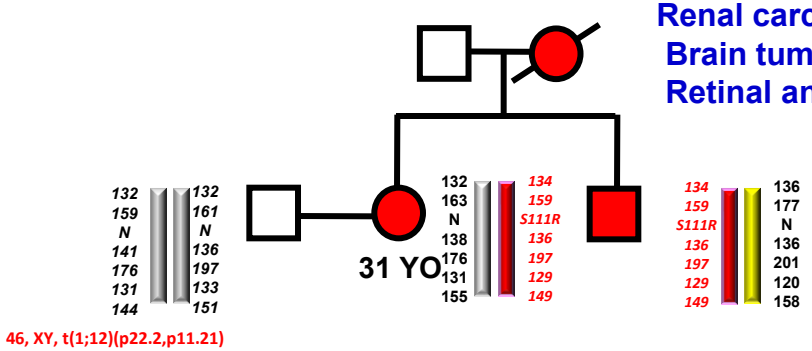




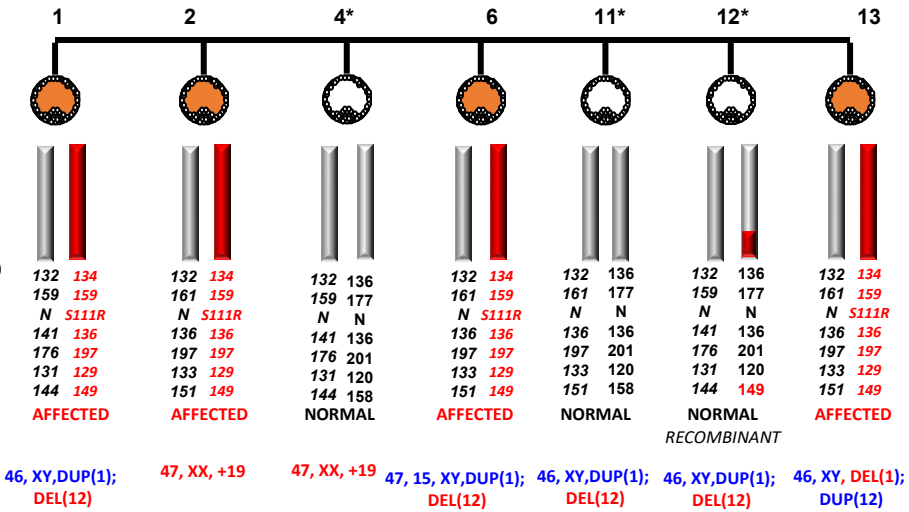


Incidental finding of Structural rearrangements During PGT-M +PGT-A for Von Hippel Lindau Syndrome.

Family Pedigree

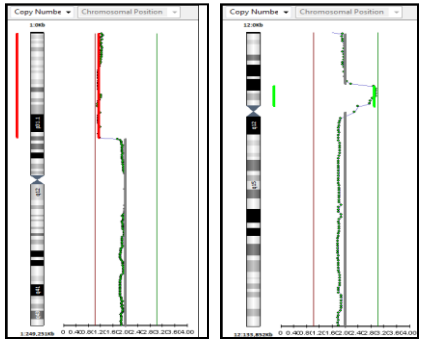


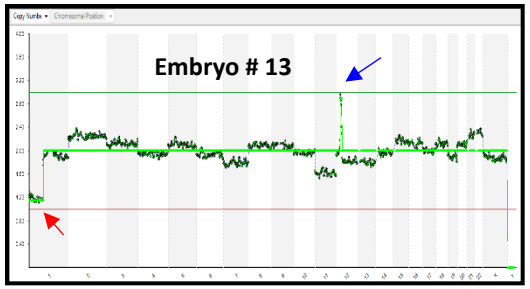
Trophectoderm analysis

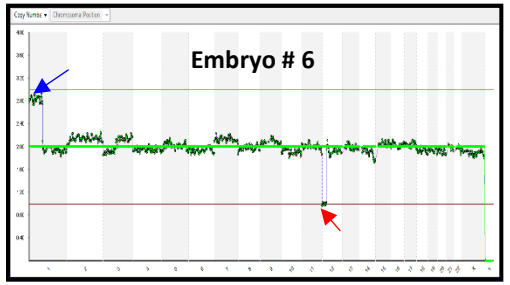


3 without mutation
4 affected
5 with translocation
2 aneuploid

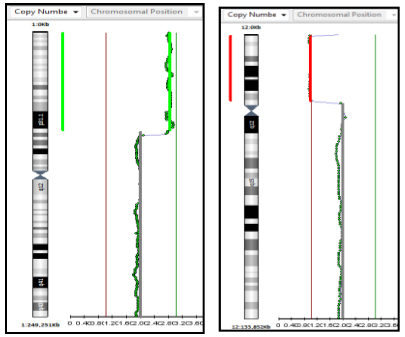
46, XX,DEL(1)(p22.2;36.33); DUP(12)(p11.21;13.33)







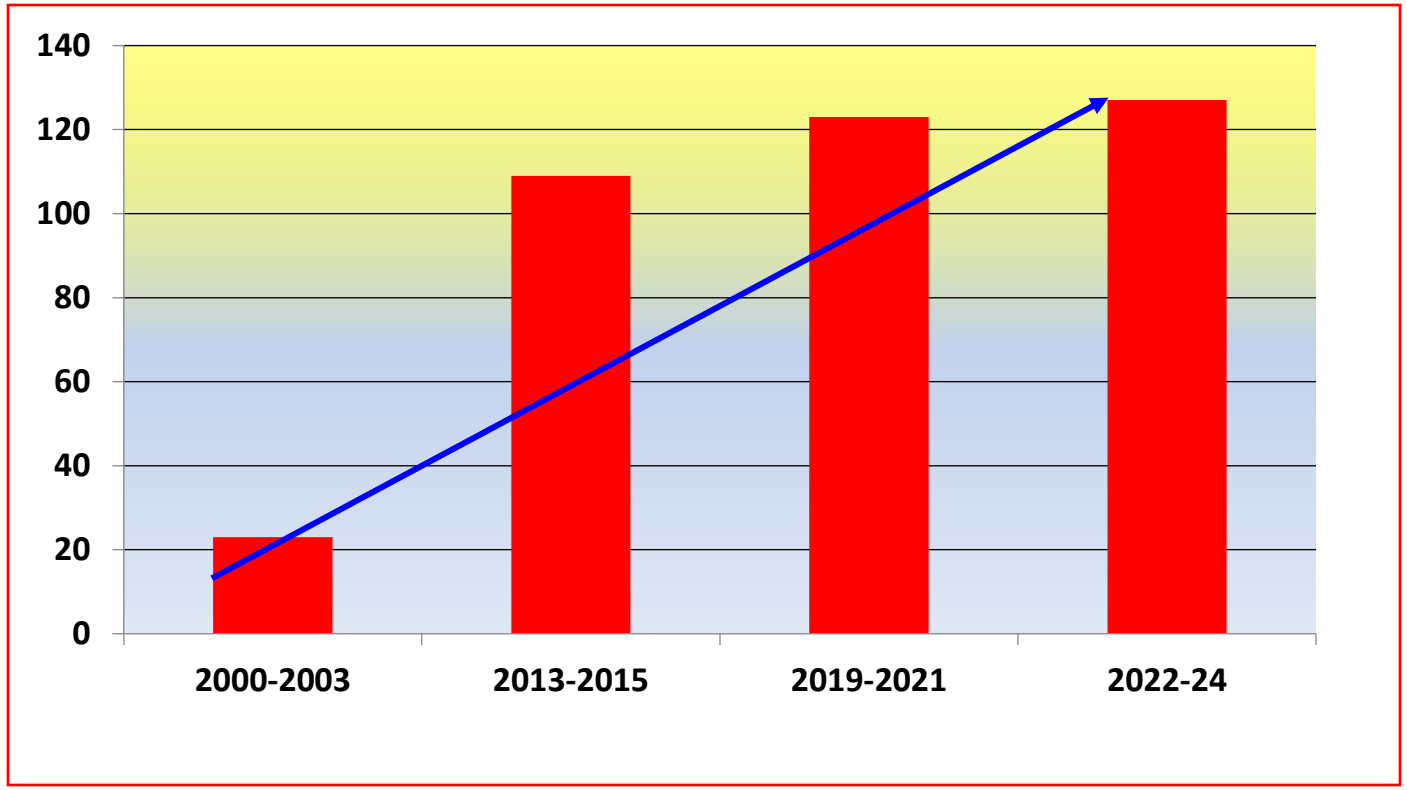
46, XX,DUP(1)(p22.2;36.33) -80 Mb DEL(12)(p11.21;13.33 -30 Mb



STRUCTURAL REARRANGMENTS DETECTED in PGT-A or PGT-M combined with PGT-A cases

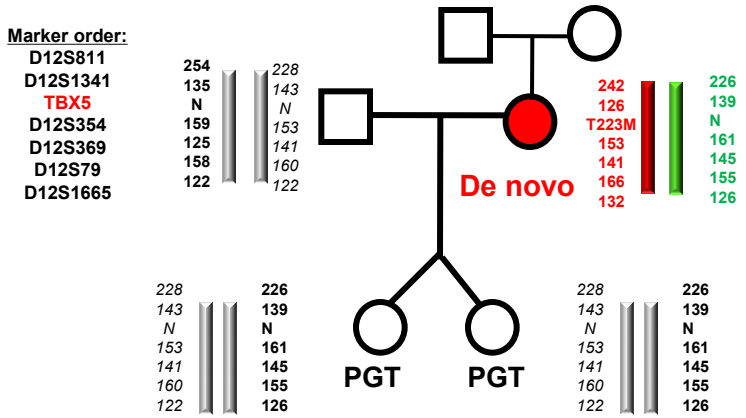
Confirmed Karyotypes:
46, XX, t(1;14)(p13.1;q11.2)
46, XY, t(7,8)(q21.2;q12)
46, XX, t(4,15)(q25q15)
46, XY, t(1,22)(p13.3;q11.2)
46, XX, t(2;13)(q13;q22); t(7,11)(q22,q24)
46, XY, t(1;16)(p34.1; p13.1)
46, XY,t(7,11)(q11.23; p11.2)
46, XX, t(1,16)(q21.1;q12.1)
46, XY, t(3,5)(q23,q13)
46, XY, t(1,12)(p22.2,p11.21)
46, XY, inv (2)(p4.2q22.2)
46, XY, t(7;10)(q36.1;p15.3)
46, XY, t(17;22)(q25;q11.2)
46, XX, t(8;13)(q21.1;q14.1)
46, XX, t(8;22)(q24.13;q11.2)
TOTAL: 32 CASES SUSPECTED, 15 CONFIRMED, 16 DECLINED, 1 NORMAL KARYOTYPE

Steady Increase of PGT cycles for De Novo Mutations after first description in 2000



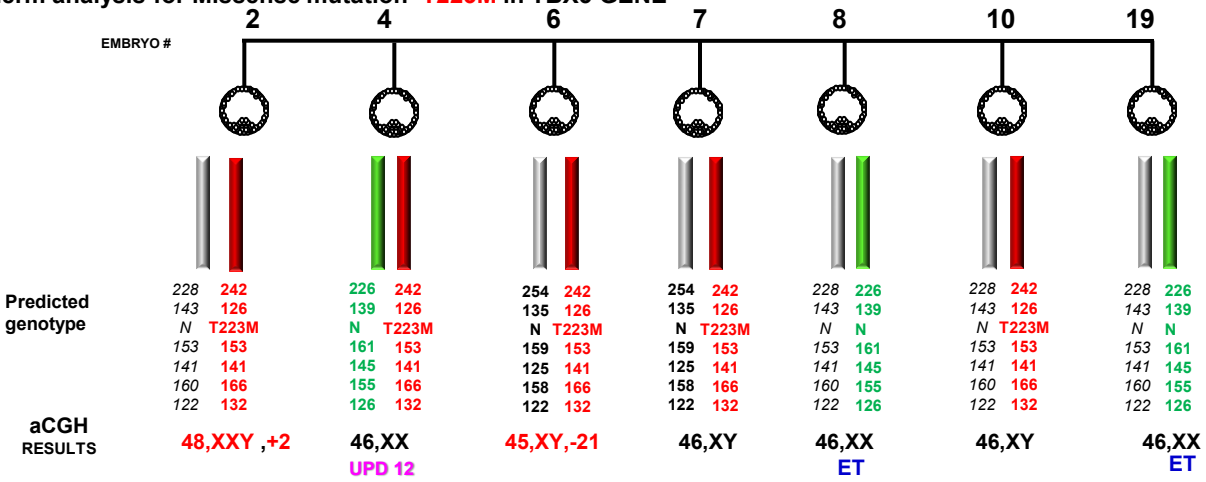
PGT-M for Holt – Oram Syndrome;

1. Family pedigree

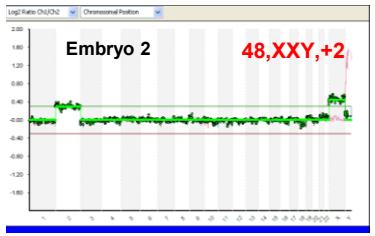


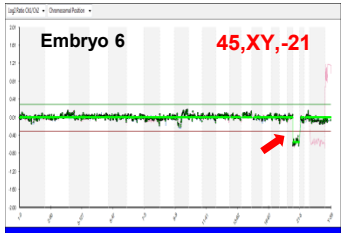
Heritable adult-onset cardiac disorders are usually pleiotropic and characterized by structural abnormalities in multiple organ systems: thumb anomaly and atrial septal defects

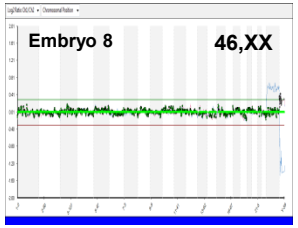
2. Trophectoderm analysis for Missense mutation T223M in TBX5 GENE

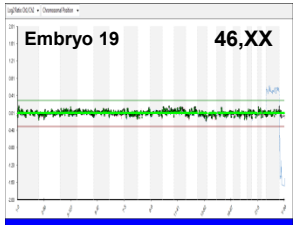


TOTAL – 7
NORMAL – 2
Affected - 5
EUPLOID – 4
UPD – 1
FET - 2

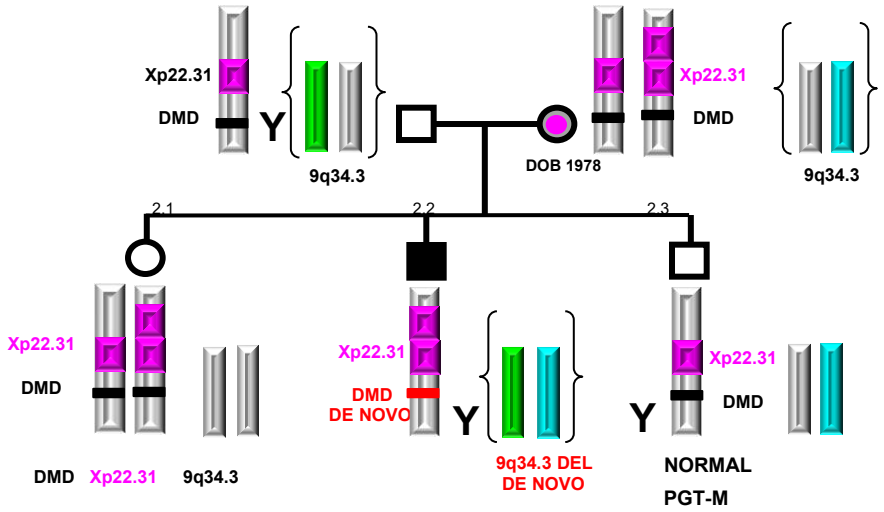






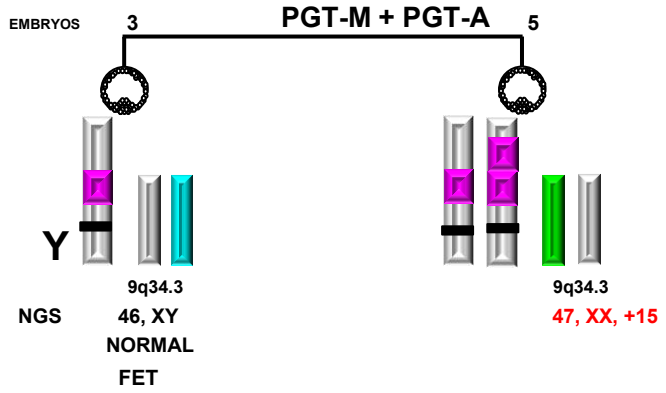


PGT-M for TWO DE NOVO MATERNAL DELETIONS: DMD – exon 8-9 and 9q34.3 (Kleefstra syndrome) and Xp22.31 duplication



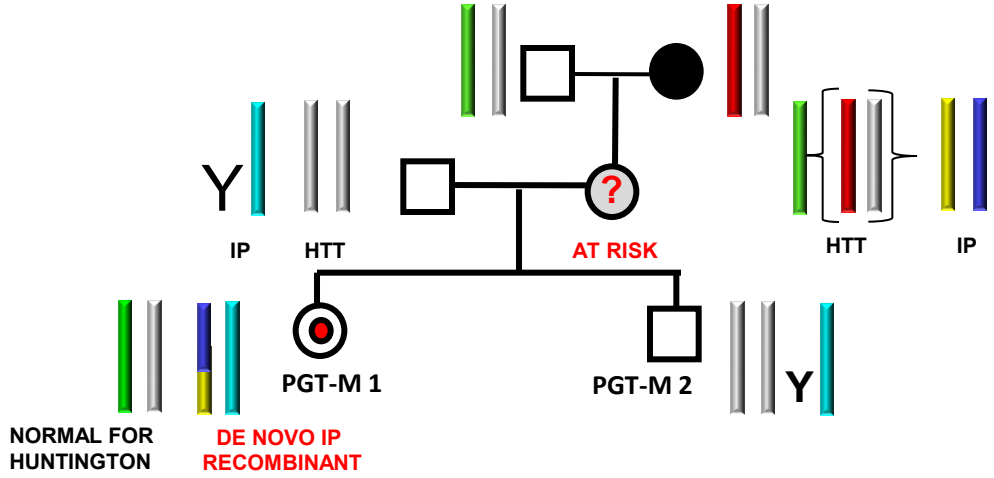
Kleefstra syndrome (KS) is a genetic disorder characterized by intellectual disability, childhood hypotonia, severe expressive speech delay and a distinctive facial appearance with a spectrum of additional clinical features.

Caused by a microdeletion in the chromosome region 9q34.3 (seen in >85% of cases), leading to the loss of the entire gene. This gene encodes an enzyme that modifies histone function and is essential for normal development.



DE NOVO IP MUTATION INDIRECT NON-DISCLOSURE HUNTINGTON DISEASE PGT-M

1. Family pedigree



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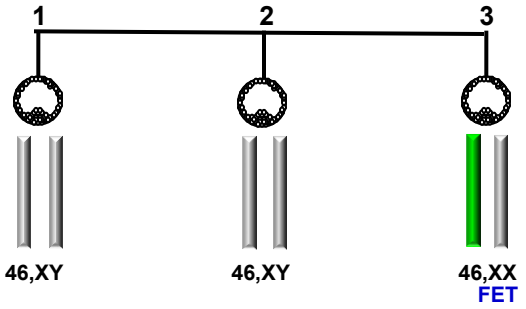
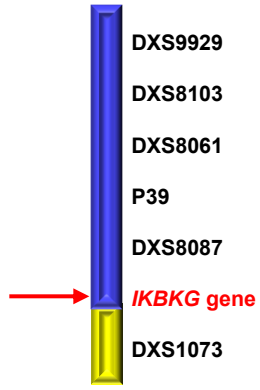
2. PGT-M +PGT-A

CYCLE 1

EMBRYO #

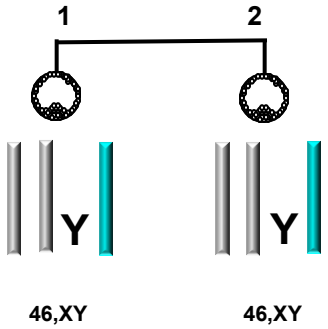
HTT +NGS





Recombinant X chromosome

CYCLE 2



CONCLUSIONS:

- PGT-M referral profile significantly changes with introduction of ECS

- Prospective referrals more than doubled in the last 5 years overall and even tripled for some selected conditions

- ECS impacts spectrum of PGT-M indications with the shift to the late onset conditions, such as cancer and cardiac disease.

- There is a shift in spectrum PGT-M mutations tested, from common to unique ones as seen for mutations causing breast cancer both BRCA1 and BRCA2.

- A wider application of ECS improves PGT-M uptake, turning it from retrospective approach to a prospective avoidance of the genetic disease in those with unknown risk.

THANK YOU

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