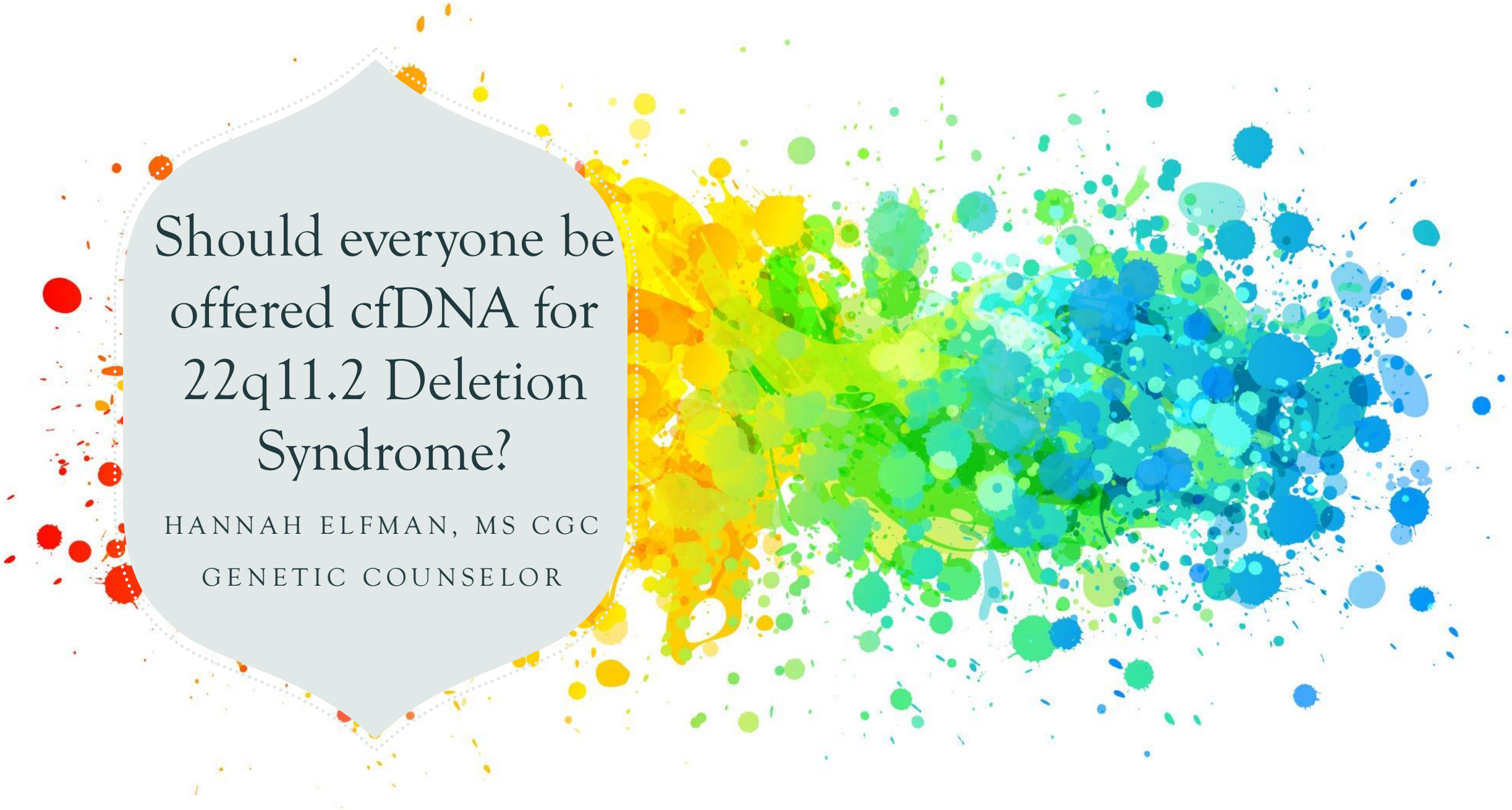
Should everyone be offered cfDNA for 22q11.2 Deletion Syndrome?

HANNAH ELFMAN, MS CGC

GENETIC COUNSELOR



No Disclosures

Objectives

- Identify cardinal features of 22q11.2 deletion syndrome pre- and post-natally.
- Assess the merits and limitations of prenatal screening for 22q11.2 deletion syndrome.
- Review updates in test performance for cfDNA for 22q11.2.
- Outline emerging evidence supporting improved clinical outcomes in patients with 22q that have early diagnosis.

22q11.2 deletion syndrome

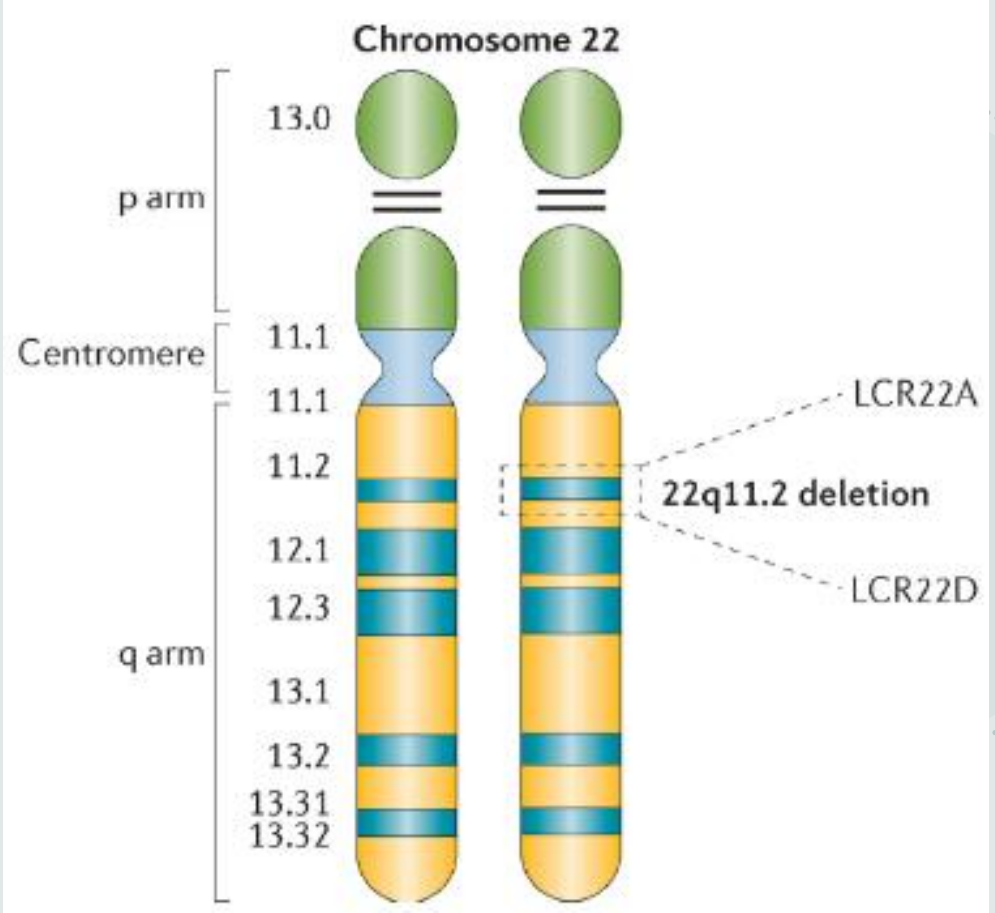
- The most common microdeletion syndrome

  Prevalence is 1/990-1/2,148
- Autosomal dominant

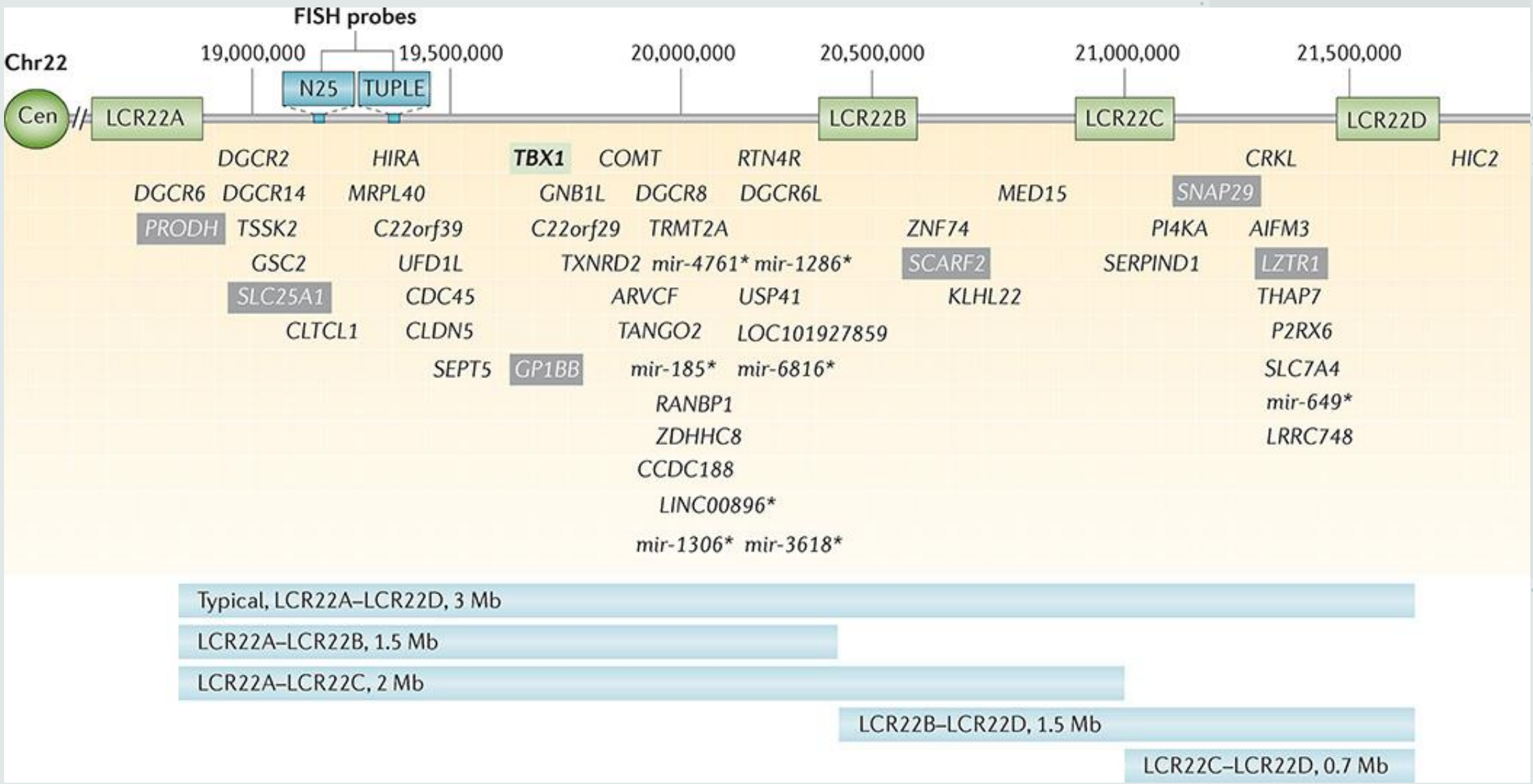
  5-10% of cases are inherited
- Complete penetrance

  Significant inter- and intra- familial clinical variability
- Deletions are located between low copy repeats (LCR)

  ~3Mb A-D deletion in 85%



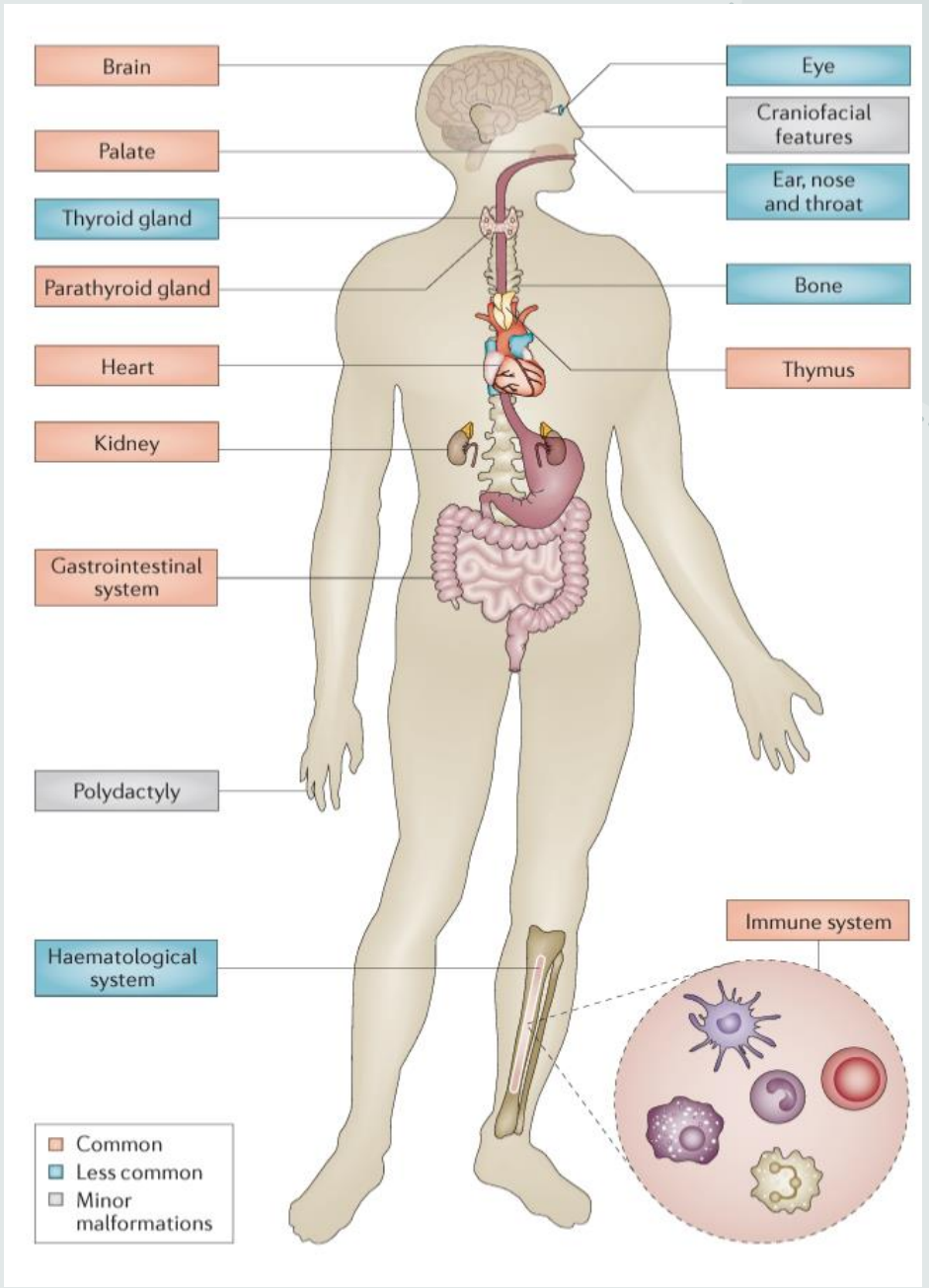
(McDonald-Mcginn, Sullivan et al. 2015)



(Blagowidow, Nowakowska et al. 2023)

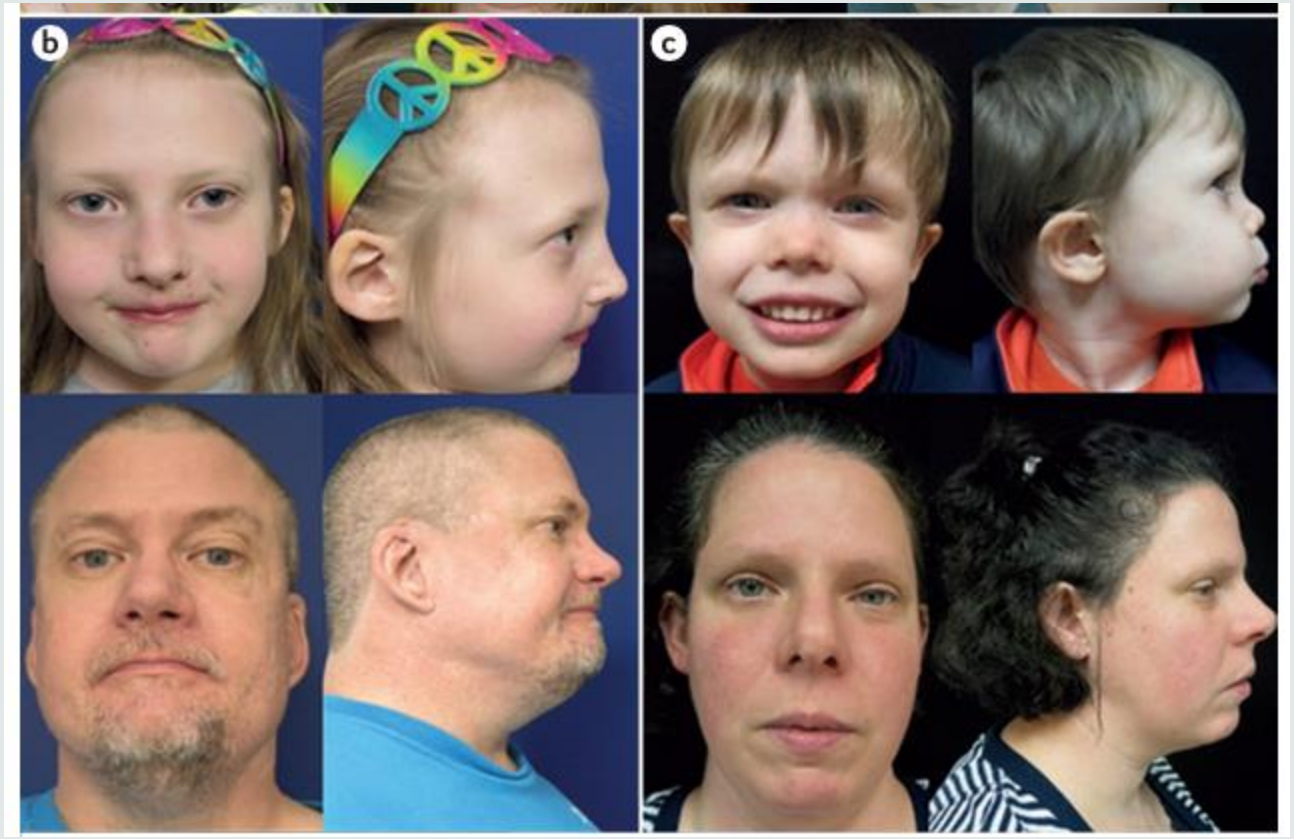
Symptoms

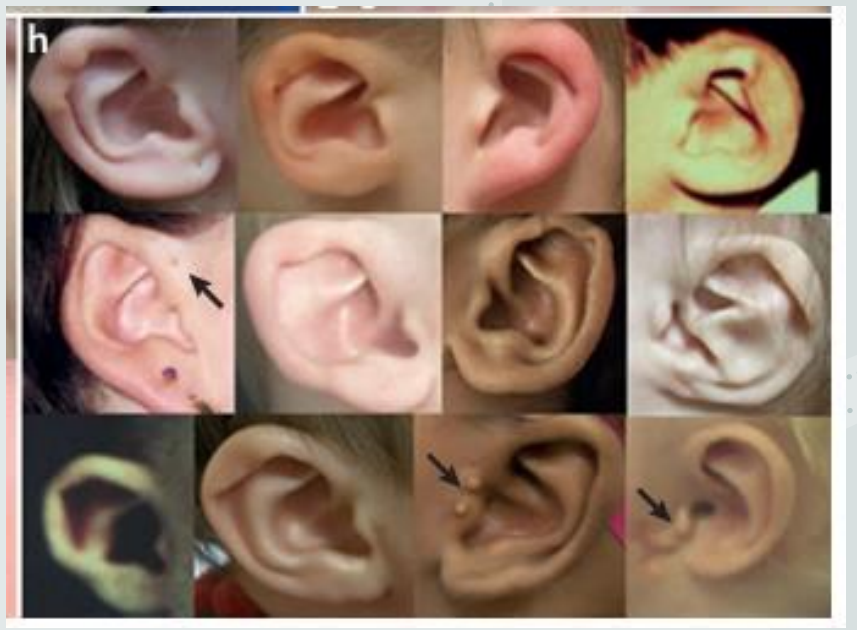
- Congenital heart defects (64%)
- Immunodeficiency (75%)
- Palatal Abnormalities (65%)
- Hypoparathyroidism (50-65%)
- Gastrointestinal abnormalities (30%)
- Genitourinary abnormalities (33%)
- Developmental delays are common
- Neurodevelopmental disorder (30%)
- Schizophrenia (25%)
- Other

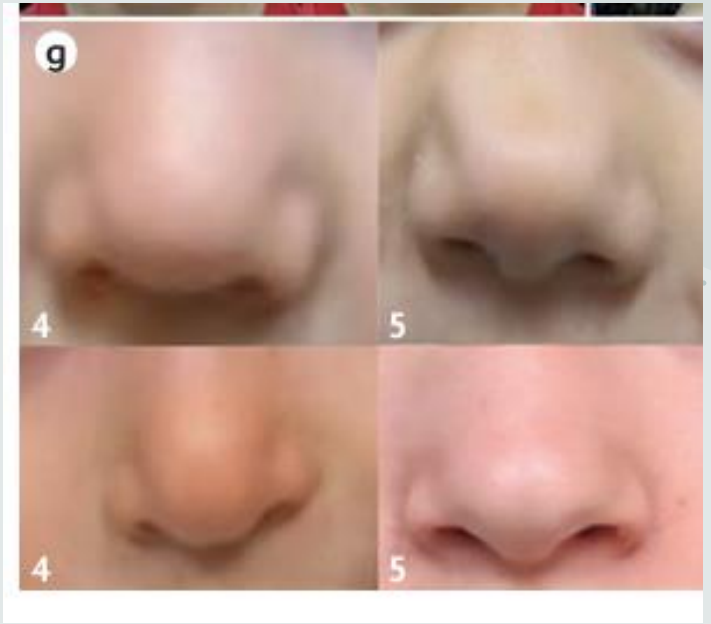


(McDonald-Mcginn, Sullivan et al. 2015)

Craniofacial Features







(McDonald-Mcginn, Sullivan et al. 2015)

Mortality

- 4% infant mortality primarily due to cardiac disease
- Lower life expectancy

  Probability of survival to age 45 years ~72% for those with major CHD and 95% for those with no major CHD (Van et al. 2019)

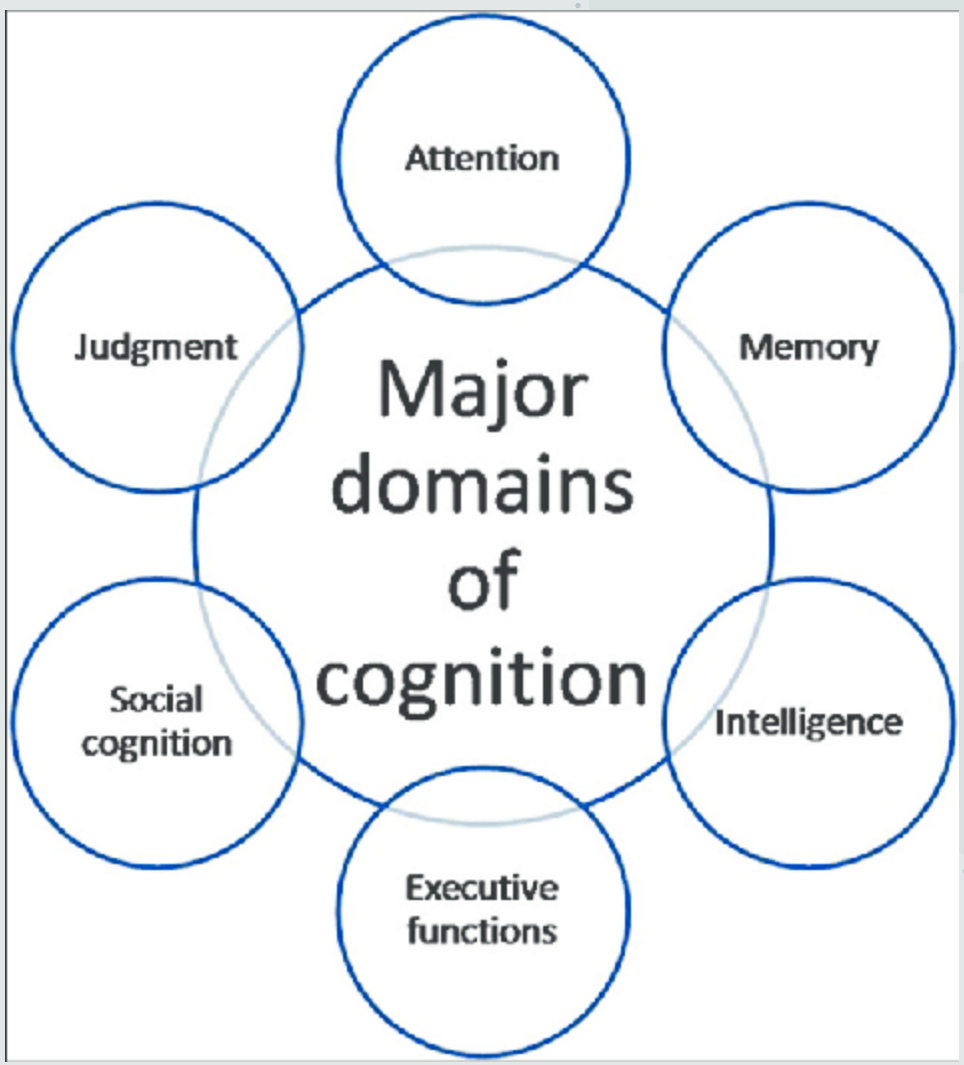
  Sudden cardiac death most common cause of mortality, with or without CHD

(Van, Heung et al. 2019)

Cognitive Functioning

- Impaired functioning in several cognitive domains
- Most with IQ in borderline range (70-85)

  30-40% with mild IQ
- Consider neurodevelopmental and psychiatric comorbidities



https://www.researchgate.net/figure/Major-domains-of-cognition_fig1_294137969

Adaptive Functioning

- School aged years

  Most in mainstream schooling, often require IEP

- Adulthood

  >60% have jobs (about half assisted employment)
  Most need help managing finances and are not financially independent

Vineland Adaptive Behavior Scales (VABS)

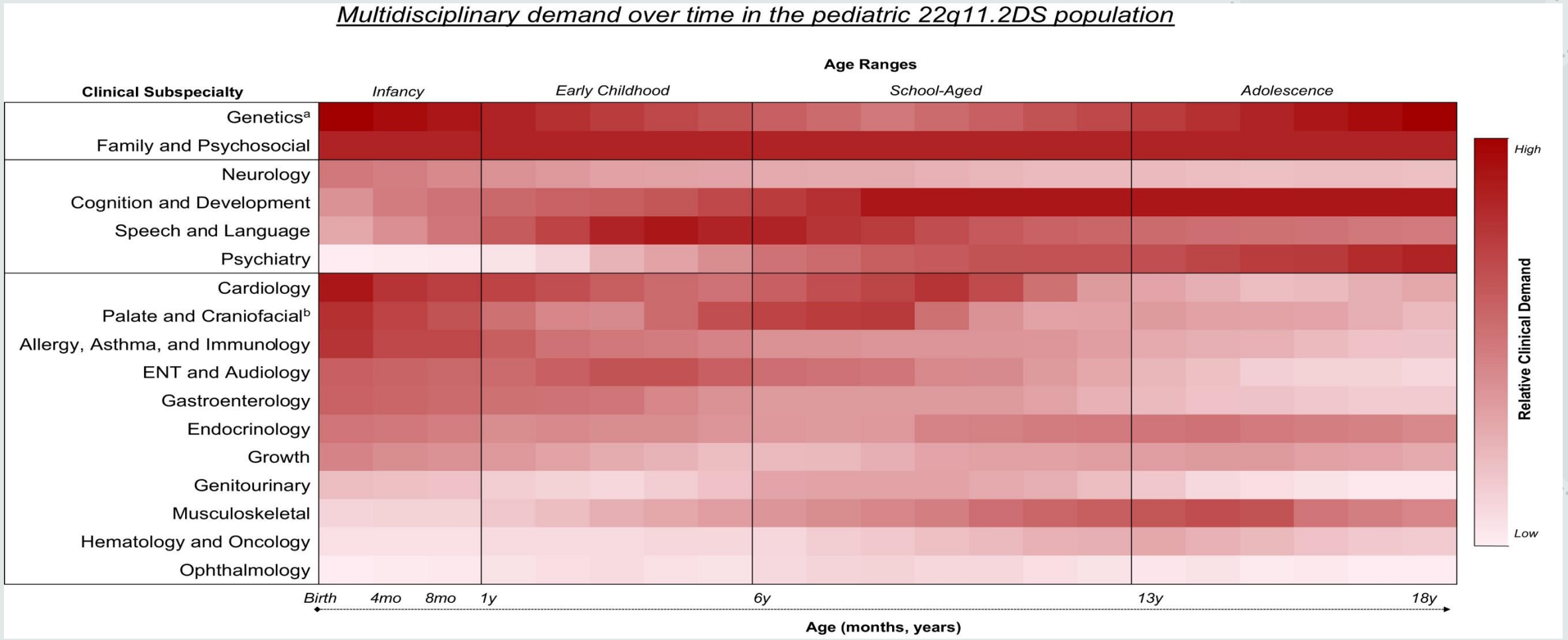
1) Daily Living Skills
2) Socialization
3) Communication

VABS score <78 indicates functional difficulty

- Most scored 76 (moderately low)
- Mean daily living 81.3
- Mean socialization 67.2
- Mean communication 60.5

(Butcher, Chow et al. 2012)

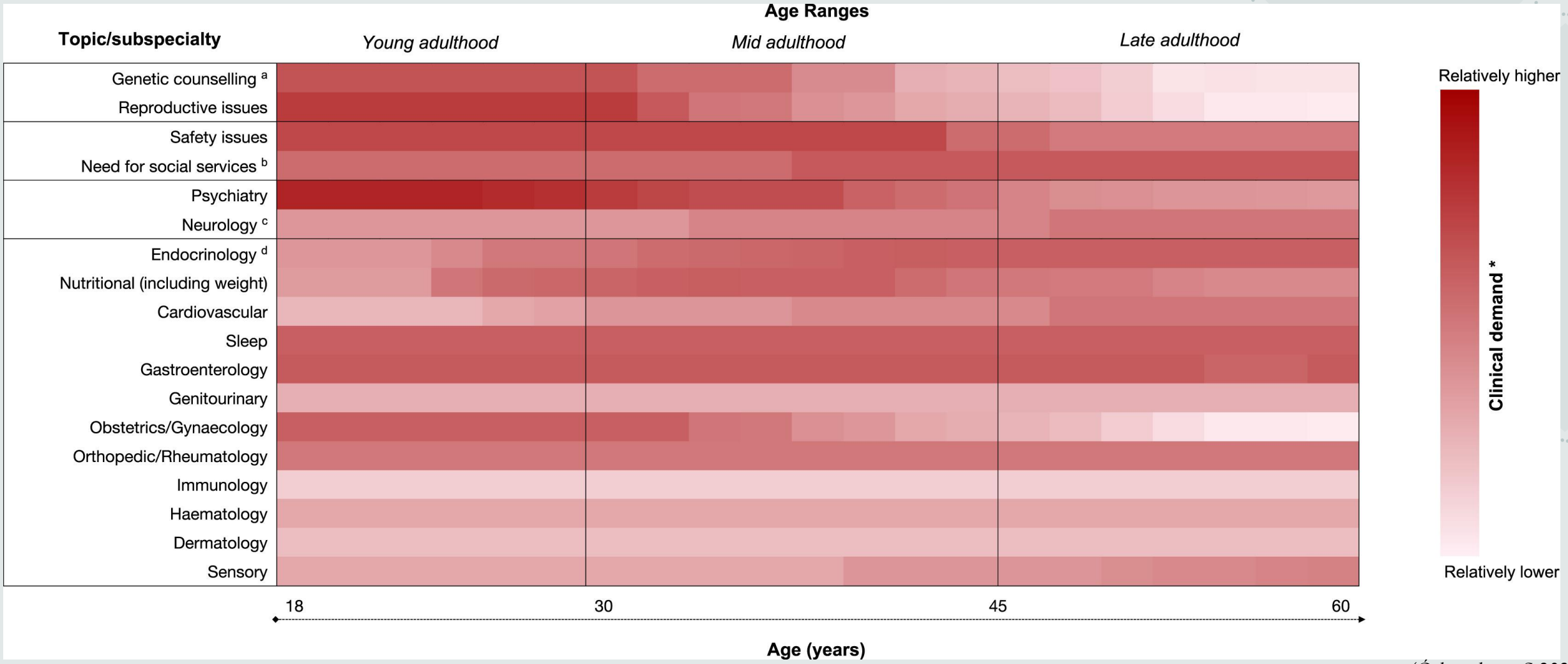
Clinical Practice Recommendations



Recently updated clinical practice recommendations for managing children and adults with 22q11.2 deletion, published in Genetics in Medicine (2023)

(Óskarsdóttir S 2023)

Management for Adults



(Óskarsdóttir S 2023)

Pathway to Diagnosis

Prenatal	Infancy	Childhood	Adolescence/Adulthood
Heart defect	Heart defect	Recurrent infections	Scoliosis
Polyhydramnios	Hypotonia	Nasal regurgitation	Psychiatric illness
Cleft Lip/Palate	Hypocalcemia	Hypernasal speech	Dysmorphic features
Polydactyly	Recurrent infections	Developmental delays	Sudden death/heart failure
Diaphragmatic Hernia	Nasal regurgitation	Language delays	Birth of affected child
Neural tube defect	Hypernasal speech	Behavioral differences	Chronic sinus infection
	Feeding difficulties		

Prenatal Detection

- Ultrasound (60-95%)
- Cell Free DNA Screening / Non-Invasive Prenatal Testing (74%-83%)
- Prenatal Diagnostic Testing (>99.99%)

Prenatal Ultrasound

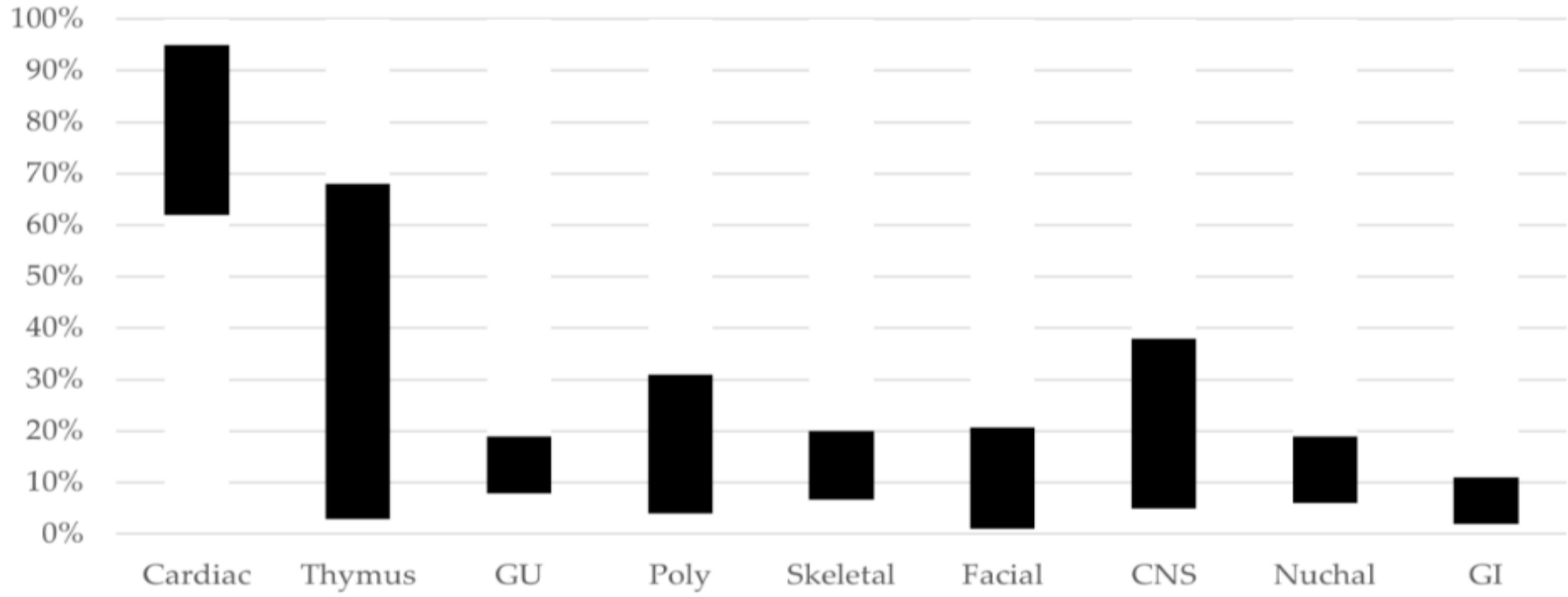


Figure 4. 22q11.2DS Structural Findings. Range of proportion of fetuses with prenatal structural findings in nine categories, later found to have a diagnosis of 22q11.2DS. Based on data from studies with 40 or more patients [6,11,38,39,41]. Legend: GU, genito-urinary tract; Poly: polyhydramnios; CNS: central nervous system, GI: gastrointestinal.

(Blagowidow, Nowakowska et al. 2023)

Congenital heart defect

- CHD is an isolated finding in over half of cases

Heart Defect	% of CHD with 22q11.2 DS
Interrupted aortic arch, Type B	50-80%
Tetralogy of Fallot	10-15%
Pulmonary atresia + VSD + MAPCAs	30-45%
Truncus arteriosus	30-50%
Isolated aortic arch anomalies	25%
Double outlet right ventricle	Up to 7%
Right aortic arch	3-4%

(Unolt, Versacci et al. 2018)

OBSTETRICS

Cell-free DNA screening for prenatal detection of 22q11.2 deletion syndrome

Pe'er Dar, MD; Bo Jacobsson, MD, PhD; Rebecca Clifton, PhD; Melissa Egbert, MS; Fergal Malone, MD; Ronald J. Wapner, MD; Ashley S. Roman, MD; Asma Khalil, MD; Revital Faro, MD; Rajeevi Madankumar, MD; Lance Edwards, MD; Noel Strong, MD; Sina Haeri, MD; Robert Silver, MD; Nidhi Vohra, MD; Jon Hyett, MD; Zachary Demko, PhD; Kimberly Martin, MD; Matthew Rabinowitz, PhD; Karen Flood, MD; Ylva Carlsson, MD, PhD; Georgios Doulaveris, MD; Sean Daly, MD; Maria Hallingström, PhD; Cora MacPherson, PhD; Charlly Kao, PhD; Hakon Hakonarson, MD, PhD; Mary E. Norton, MD

- SNP-based Microdeletion and Aneuploidy RegisTry (SMART study)
- Multicenter prospective observational study
- 20,877 participants
- Requirement of singleton pregnancy and postnatal test confirmation, ideally with microarray
- Primary outcome: test perform for detection of deletion >500kb in A-D region
- Secondary outcome: prevalence of disease and performance of an updated screening algorithm

(Dar, Jacobsson et al. 2022)

Table 3. cfDNA test performance for detection of ≥ 500 kb 22q11.2 deletions in the LCR22 A–D region with the algorithm applied at enrollment and with the updated algorithm

Test parameter	Original algorithm used at enrollment (n=18,014)	Updated algorithm implemented after study completion (n=18,043)
Sensitivity	75.0% (9/12; 95% CI, 42.8–94.5)	83.3% (10/12; 95% CI, 51.6–97.9)
Specificity	99.84% (17,973/18,002; 95% CI, 99.77–99.89)	99.95% (18,022/18,031; 95% CI, 99.91–99.98)
PPV	23.7% (9/38; 95% CI, 11.4–40.2)	52.6% (10/19; 95% CI, 28.9–75.6)
NPV	99.98% (17,973/17,976; 95% CI, 99.95–100)	99.99% (18,022/18,024; 95% CI, 99.96–100)
Positive likelihood ratio[a]	468.75	1666.00
Negative likelihood ratio[a]	0.25	0.17

LCR, low-copy repeats; *NPV*, negative predictive value; *PPV*, positive predictive value.

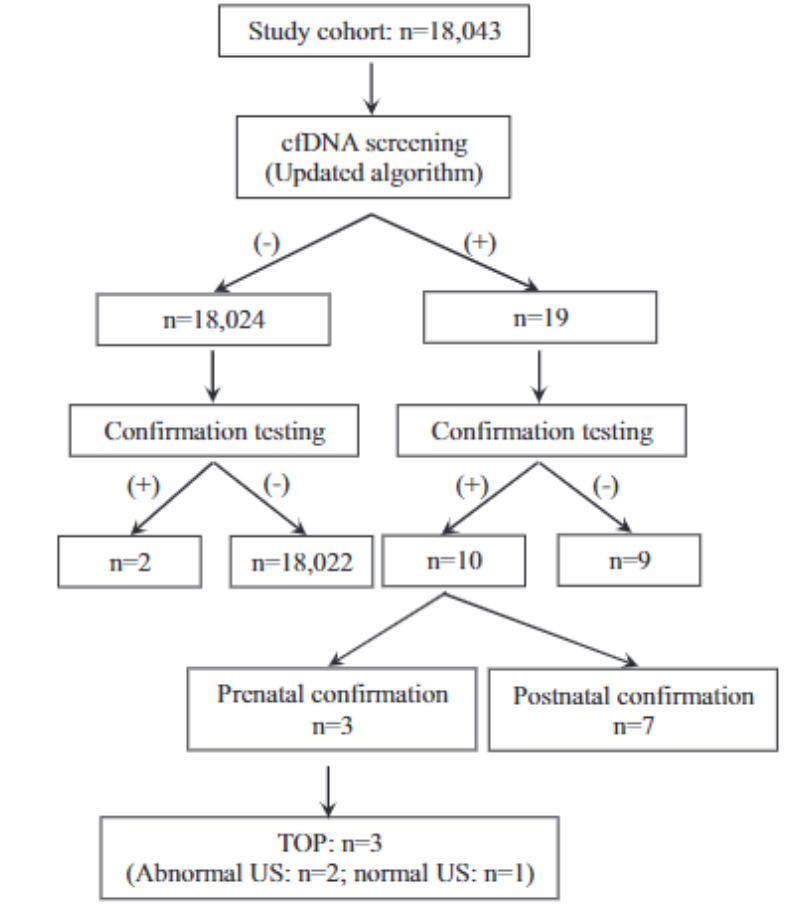
Dar et al. Performance of cell-free DNA prenatal screening for 22q11.2 deletion syndrome. Am J Obstet Gynecol 2022.

a Positive likelihood ratio is calculated as sensitivity/100–specificity and the negative likelihood ratio is calculated as 100–sensitivity/specificity.

(Dar, Jacobsson et al. 2022)

FIGURE

The performance of an updated algorithm with cfDNA in screening for fetal 22q11.2DS in the study by Dar et al.[3]



DR = 83.3% (10/12); PPV = 52.6% (10/19); SPR = 0.10% (19/18,043)

cfDNA, cell-free DNA; *DR*, detection rate; *PPV*, positive predictive value; *SPR*, screening positive rate; *TOP*, termination of pregnancy; *US*, ultrasound.

Pan. Single nucleotide polymorphism–based cell-free DNA prenatal screening for 22q11.2 deletion syndrome. Am J Obstet Gynecol 2022.

1.5% failure rate after second attempt

1/1,000 screen positive rate

.05% false positive rate

(Dar, Jacobsson et al. 2022)

TABLE 2

Pre- and postnatal characteristics of confirmed 22q11.2 deletions >500 kb in the LCR22 A-D region

Case	Deletion size and location	Stage of confirmation	Test	GA at cfDNA (wk)	Fetal fraction	Identified by cfDNA	First trimester ultrasound	Fetal anomaly detected before cfDNA	Fetal anomaly detected after cfDNA	Outcome	GA at delivery	Birthweight
1.	A-D 2.6 Mb	Postnatal	CMA	20	13.7%	Yes	Normal	Interrupted aortic arch, VSD (20 wk)	None	Live birth	Term	AGA
2.	A-D 2.6 Mb	Postnatal	CMA	31	9.7%	Yes	Normal	Truncus arteriosus at (31 wk)	None	Live birth	Late preterm[a]	AGA
3.	A-D 2.6 Mb	Postnatal	CMA	10	7.5%	Yes	Normal	None	None	Live birth	Term	SGA
4.	A-D 2.6 Mb	Postnatal	CMA	17	7.0%	Yes	Not done	Truncus arteriosus, VSD (17 wk)	Bowel obstruction (31 wk)	Live birth	Late preterm[a]	AGA
5.	Unknown[b]	Prenatal CVS	BoB	10	6.9%	Yes	Normal	None	Atrioventricular canal (20 wk)	TOP		
6.	Unknown[b]	Prenatal amniocentesis	BoB	11	6.9%	Yes	Normal	None	No additional ultrasound	TOP		
7.	Unknown[b]	Postnatal	FISH	21	14.4%	Yes	Normal	Tetralogy of Fallot (21 wk)	No additional ultrasound	NND	Term	SGA
8.	A-C 2.06 Mb	Prenatal amniocentesis	MLPA	10	7.6%	Yes	Normal	None	VSD (18 wk)	TOP		
9.	A-B 1.47 Mb	Postnatal	CMA	20	13.3%	Yes	Normal	None	No additional ultrasound	Live birth	Term	AGA
10.	A-B 1.47 Mb	Postnatal	CMA	11	17.5%	No	Normal	None	None	Live birth	Term	AGA
11.	B-D 0.73 Mb	Postnatal	CMA	15	4.9%	No[c]	Normal	None	Unilateral renal agenesis (22 wk)	Live birth	Term	AGA
12.	B-D 0.73 Mb	Postnatal	CMA	12	8.5%	No	Normal	None	None	Live birth	Term	SGA

AGA, appropriate for gestational age; *BoB*, bacterial artificial chromosomes (BACs)-on-Beads; *CMA*, chromosomal microarray; *CVS*, chorionic villous sampling; *FF*, fetal fraction; *FISH*, fluorescence in situ hybridization; *GA*, gestational age; *MLPA*, multiplex ligation-dependent probe amplification; *NND*, neonatal death; *SGA*, small for gestational age (birthweight <10th percentile for gestational age); *TOP*, termination of pregnancy; *VSD*, ventricular septal defect.

[a] Late preterm birth was defined as birth at 34 to 37 weeks' gestation; [b] Probes localized to the A-B region; [c] This case was identified by the updated algorithm.

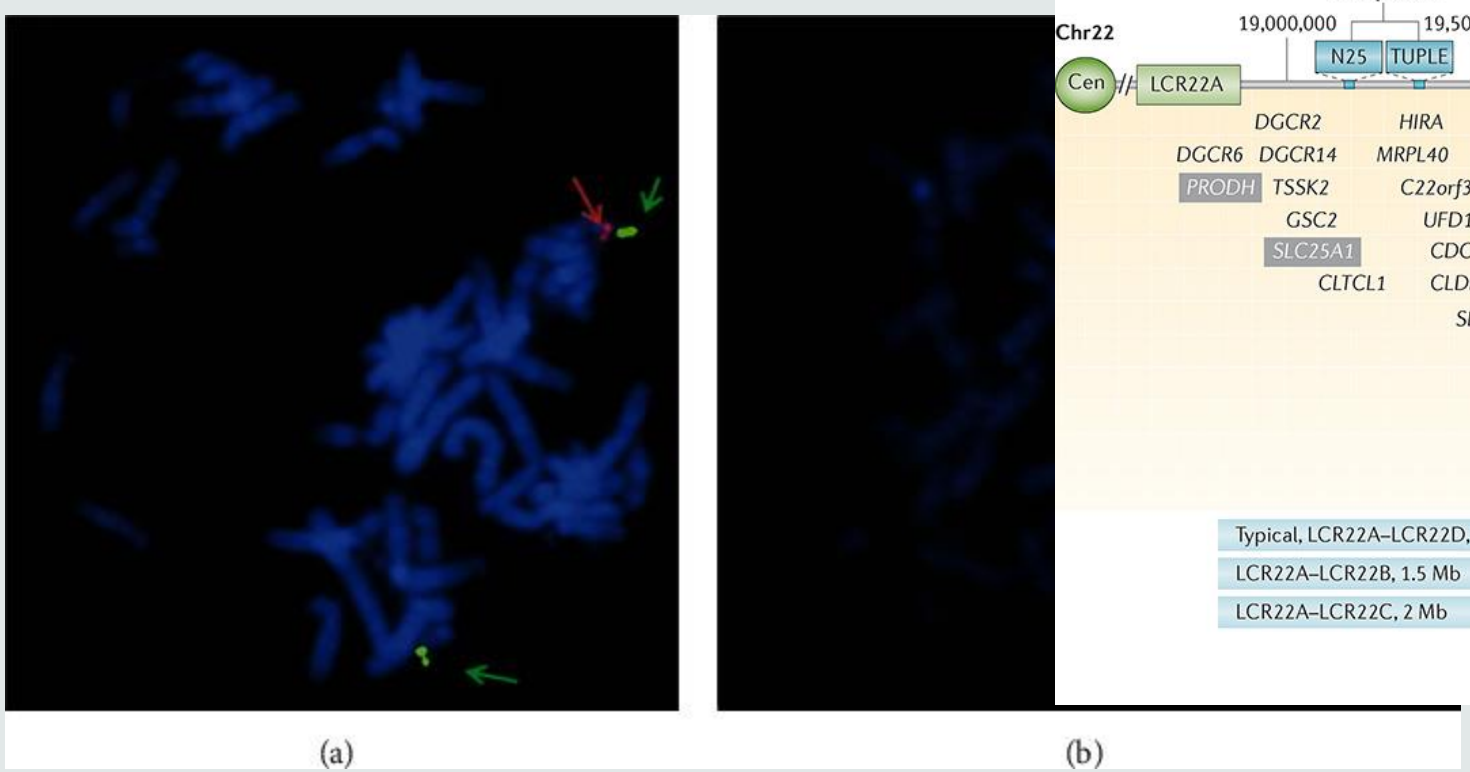
Dar et al. Performance of cell-free DNA prenatal screening for 22q11.2 deletion syndrome. Am J Obstet Gynecol 2022.

(Dar, Jacobsson et al. 2022)

Diagnostic Testing

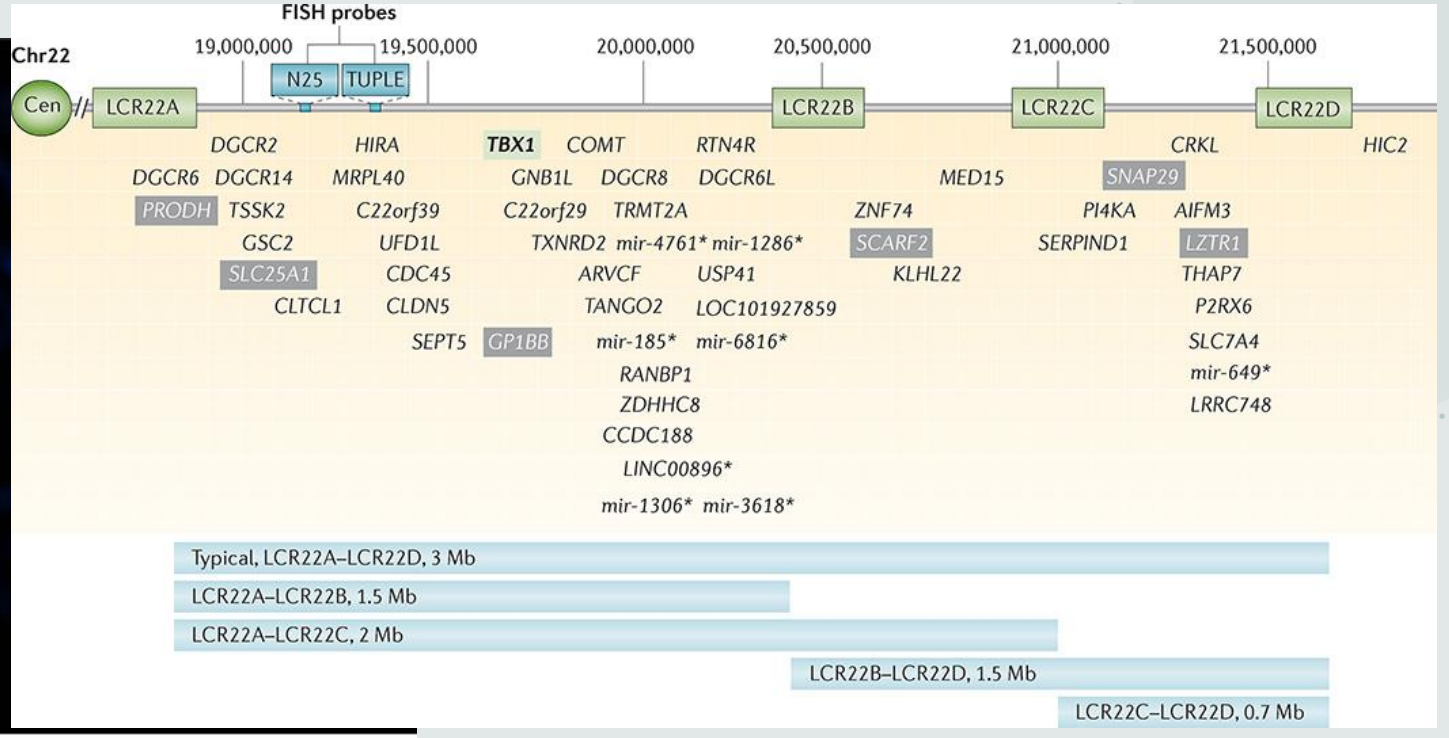
Step 1: FISH

2-3 days, detect 80-85%



Step 2: Microarray

1-3 weeks, detect >99.9%



(Maran, Faten et al. 2020)

Original Research ajog.org

OBSTETRICS

Prenatal vs postnatal diagnosis of 22q11.2 deletion syndrome: cardiac and noncardiac outcomes through 1 year of age

Lindsay R. Freud, MD; Stephanie Galloway, MS, CGC; T. Blaine Crowley; Julie Moldenhauer, MD; Ann Swillen, PhD; Jeroen Breckpot, MD, PhD; Antoni Borrell, MD, PhD; Neeta L. Vora, MD; Bettina Cuneo, MD; Hilary Hoffman, CCRC; Lisa Gilbert, BS, RDCS; Beata Nowakowska, PhD; Maciej Geremek, MD, PhD; Anna Kutkowska-Kaźmierczak, MD, PhD; Joris R. Vermeesch, PhD; Koen Devriendt, MD, PhD; Tiffany Busa, MD; Sabine Sigaudy, MD; Trisha Vigneswaran, MBBS; John M. Simpson, MD; Jeffrey Dungan, MD; Nina Gotteiner, MD; Karl-Philipp Gloning, MD; Maria Cristina Digilio, MD; Marta Unolt, MD; Carolina Putotto, MD; Bruno Marino, MD; Gabriela Repetto, MD; Magdalena Fadic; Sixto Garcia-Minaur, MD; Ana Achón Buil; Mary Ann Thomas, MD; Deborah Fruitman, MD; Taylor Beecroft, MS, CGC; Pui Wah Hui, MD; Solveig Oskarsdottir, MD, PhD; Rachael Bradshaw, MS, CGC; Amanda Criebaum, MSN, RN; Mary E. Norton, MD; Tiffany Lee, MPH; Miwa Geiger, MD; Leslie Dunnington, MS, CGC; Jacqueline Isaac, MS, CGC; Louise Wilkins-Haug, MD, PhD; Lindsey Hunter, MBChB; Claudia Izzi, MD; Marika Toscano, MD; Tullio Ghi, PhD; Julie McGlynn, MS, CGC; Francesca Romana Grati, MSc, PhD; Beverly S. Emanuel, PhD; Kimberly Gaiser, BS; J. William Gaynor, MD; Elizabeth Goldmuntz, MD; Daniel E. McGinn, BS; Erica Schindewolf, MS, LCGC; Oanh Tran, BS; Elaine H. Zackai, MD; Qi Yan, PhD; Anne S. Bassett, MD; Ronald Wapner, MD; Donna M. McDonald-McGinn, MS, LCGC

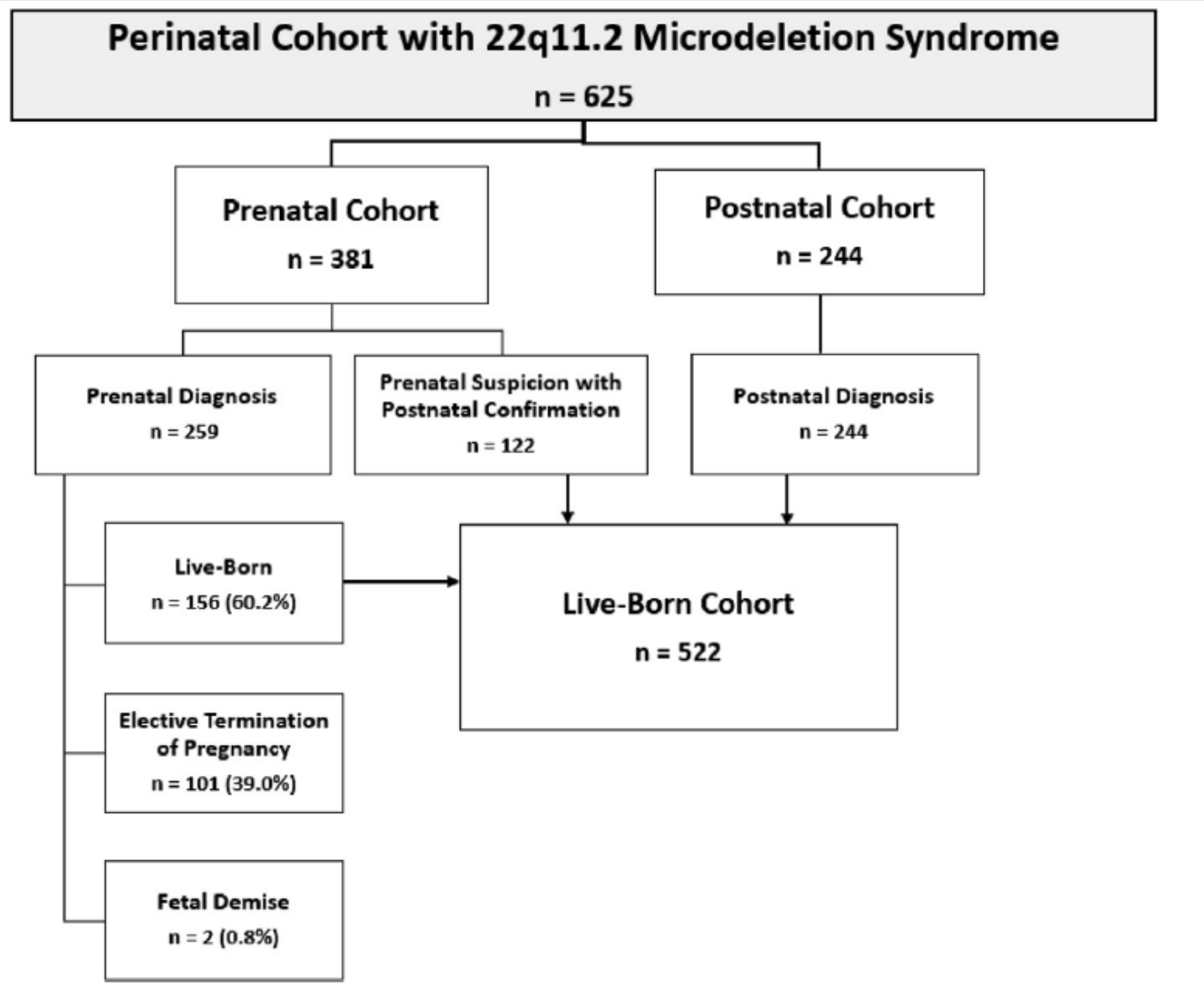
- Multicenter retrospective study
- First study to address if there is clinical benefit to prenatal detection versus postnatal
- Primary outcome: assess perinatal management, cardiac and noncardiac morbidity, and mortality by 1 year

(Freud, Galloway et al. 2024)

Materials and methods

- Prenatal cohort with diagnosis or suspicion based on ultrasound +/- cfDNA screening
- All required to have genetic testing confirmation
- Data collected
  - Delivery locations
  - Delivery complication
  - Neonatal mechanical ventilation
  - Neonatal cardiac decompensation
  - FTT/Dev Delay
- CHD categorized by pediatric cardiologist:
  - Critical (need intervention <= 30 days of age)
  - Noncritical

(Freud, Galloway et al. 2024)



(Freud, Galloway et al. 2024)

Outcomes

- Presence of critical CHD was the driver for mortality and morbidity
- Mortality rate 5.9%

TABLE 3
Perinatal and infant outcomes for 22q11.2 deletion syndrome by time of diagnosis (n = 522)

Outcomes	Prenatally diagnosed or suspected n=278[a]	Postnatally diagnosed n=244[a]	Unadjusted *P* value	Multivariable analysis[b] Adjusted *P* value	Odds ratio	95% confidence interval
Delivery outcomes						
Delivery at local community hospital (nontertiary center)	13 (5.14)	58 (38.16)	<.001	<.001	0.11	(0.06–0.23)
Delivery complication	46 (18.47)	43 (24.43)	.14	.03	0.56	(0.33–0.95)
Neonatal outcomes						
Cardiac decompensation	3 (1.31)	7 (4.96)	.05	.004	0.11	(0.03–0.49)
Mechanical ventilation unrelated to cardiac procedure	41 (17.52)	23 (16.55)	.81	.04	0.48	(0.24–0.95)
Major infection or sepsis	45 (17.93)	22 (12.43)	.12	.78	0.92	(0.50–1.69)
Kidney failure	5 (2.01)	2 (1.09)	.70	.45	1.97	(0.34–11.26)
Hypocalcemia	117 (45.53)	71 (37.77)	.10	.58	0.89	(0.58–1.36)
Seizure	19 (7.63)	15 (8.02)	.88	.41	0.72	(0.34–1.56)
Stroke	7 (2.79)	0 (0)	.04	.11	6.80	(0.70–919.73)
Infant outcomes						
Live vaccines not withheld for immunodeficiency concerns	115 (59.28)	114 (72.15)	.01	.36	0.79	(0.48–1.31)
Failure to thrive	88 (43.35)	92 (50.27)	.17	.02	0.58	(0.36–0.91)
Developmental delay	143 (84.12)	134 (85.35)	.76	.09	0.55	(0.28–1.10)
Length of hospitalization(s) ≥30 d	151 (54.32)	104 (42.62)	.01	.74	0.93	(0.62–1.41)
Death	19 (7.22)	12 (5.02)	.31	.77	0.88	(0.38–2.04)

(Freud, Galloway et al. 2024)

Why is early detection important?

- Allow for pregnancy decision making
- Prepare expectant parents
- Plan delivery and postnatal care at tertiary care facility
- May shorten the diagnostic odyssey and ensure access to multidisciplinary care
- Evidence of clinical benefits for prenatal cohorts versus postnatal
  - Improved delivery management
  - Less cardiac and noncardiac morbidity

Argument for including 22q11.2 on cfDNA

- American College of Medical Genetics recommends offering 22q11.2 deletion for all (conditional and based on moderate evidence)
- Disease associated with severe morbidity
- Prevalence of 22q11.2 in prenatal cohort is 1 in 1,000
- PPV for Trisomy 13 is lower (30%) and has higher prenatal u/s detection rate 96-99%
- Timely referral for detailed ultrasound and fetal echo
- Improved clinical outcomes with early diagnosis

  More studies expected in the future

Questions? Thoughts?

References

Blagowidow, N., et al. (2023). "Prenatal Screening and Diagnostic Considerations for 22q11.2 Microdeletions." Genes **14**(1): 160.

Butcher, N. J., et al. (2012). "Functional outcomes of adults with 22q11.2 deletion syndrome." Genetics In Medicine **14**(10): 836-843.

Dar, P. E., et al. (2022). "Cell-free DNA screening for prenatal detection of 22q11.2 deletion syndrome." American Journal of Obstetrics and Gynecology **227**(1): 79.e71-79.e11.

Dar, P. E. and M. E. Norton (2022). "Performance of noninvasive prenatal screening for 22q11.2 deletion syndrome in the SMART study." American Journal of Obstetrics and Gynecology **227**(1): 124-125.

McDonald-Mcginn, D. M., et al. (2015). "22q11.2 deletion syndrome." Nature Reviews Disease Primers **1**(1): 15071.

Maran, S., et al. (2020). "Screening of 22q11.2DS Using Multiplex Ligation-Dependent Probe Amplification as an Alternative Diagnostic Method." BioMed Research International **2020**: 1-6.

Óskarsdóttir S, B. E., Crowley TB, Loo JCY, Arganbright JM, Armando M, Baylis AL, Breetvelt EJ, Castelein RM, Chadehumbe M, Cielo CM, de Reuver S, Eliez S, Fiksinski AM, Forbes BJ, Gallagher E, Hopkins SE, Jackson OA, Levitz-Katz L, Klingberg G, Lambert MP, Marino B, Mascarenhas MR, Moldenhauer J, Moss EM, Nowakowska BA, Orchanian-Cheff A, Putotto C, Repetto GM, Schindewolf E, Schneider M, Solot CB, Sullivan KE, Swillen A, Unolt M, Van Batavia JP, Vingerhoets C, Vorstman J, Bassett AS, McDonald-McGinn DM (2023). "Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome." Genetics In Medicine **25**(3).

Unolt, M., et al. (2018). "Congenital heart diseases and cardiovascular abnormalities in 22q11.2 deletion syndrome: From well-established knowledge to new frontiers." American Journal of Medical Genetics Part A **176**(10): 2087-2098.

Van, L., et al. (2019). "All-cause mortality and survival in adults with 22q11.2 deletion syndrome." Genetics In Medicine **21**(10): 2328-2335.