Genetics Corner: Down Syndrome Tool Kit- a Resource for Physicians Taking Care of Neonates

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Case summary

A 40-year-old mother delivered monochorionic -diamniotic twin girls at 34 weeks gestation who were admitted to the NICU for prematurity. Their prenatal history was significant for a positive maternal serum screen for Down syndrome in the second trimester (California Integrated screen). Subsequently, non-invasive prenatal screening (NIPS) returned a low risk for Down syndrome. The NICU ordered chromosome microarray analysis on both identical twins to evaluate for Down syndrome, presumably because of the lower sensitivity of prenatal screening in twin gestations. There was no comment on the physical exam about features suggesting Down syndrome. The microarray was negative for trisomy 21 but detected a variant of uncertain significance (VUS) on chromosome 8 at 8p23.3. Parental follow-up testing was recommended to help inform the clinical significance of this variant. Many attempts were needed by the Genetics nursing staff after discharge in order to complete parental testing. The VUS was determined to be maternally inherited and reinterpreted to be likely benign. The parents want to test their 18-year-old daughter for the variant as they are concerned and curious to know if she had inherited it as well and it was explained to them that this is not clinically indicated.

This case illustrates several important points about the importance of making a clinical diagnosis of Down syndrome, the appropriate use of different testing modalities and the concerns raised by prenatal screening, even when negative. To better address, these questions, the Genetics service at Loma Linda University Health created a tool kit for Down syndrome as a resource for pediatricians in the newborn nursery and neonatologists to be able to recognize the features of Down syndrome and order appropriate cytogenetic testing and other assessments.

Discussion:

Down syndrome is the most common autosomal aneuploidy, with an incidence of 1/700 liveborn infants. It is also the most common cause of intellectual disability and congenital heart defects. The essential components of the tool kit include clinical and dysmorphic features seen in typical neonates with Down syndrome, pictures of karyotypes (normal and Down syndrome), summary of clinical concerns, setting up the informing interview with parents to deliver the news, summary of health supervision guidelines for Down syndrome from the American Academy of Pediatrics (including growth charts), and Down syndrome resources and support group information.

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Physical exam:

The physical exam is the mainstay of diagnosis in Down syndrome. Infants with Down syndrome have characteristic facial features, which facilitates diagnosis in the neonate. They include upslanting palpebral fissures, epicanthal folds, low nasal bridge, protruding tongue, "sandal gap" between the first and second toes, and single transverse palmar crease. The diagnosis is confirmed cytogenetically by routine karyotyping.

Pediatricians and neonatologists can be confident and comfortable in making an assessment for Down syndrome as >95% of infants with the diagnosis have typical and recognizable features. A Genetics consult should be reserved for atypical patients and those with unusual and/or additional features in the patient or family members, that may not be consistent with the diagnosis or that may raise suspicion for a dual diagnosis.

Testing:

We want to highlight that chromosome analysis remains the first-tier test for Down syndrome; microarray analysis should be reserved for those with atypical features or if there is a family history suspicious of a chromosome abnormality. When the diagnosis is

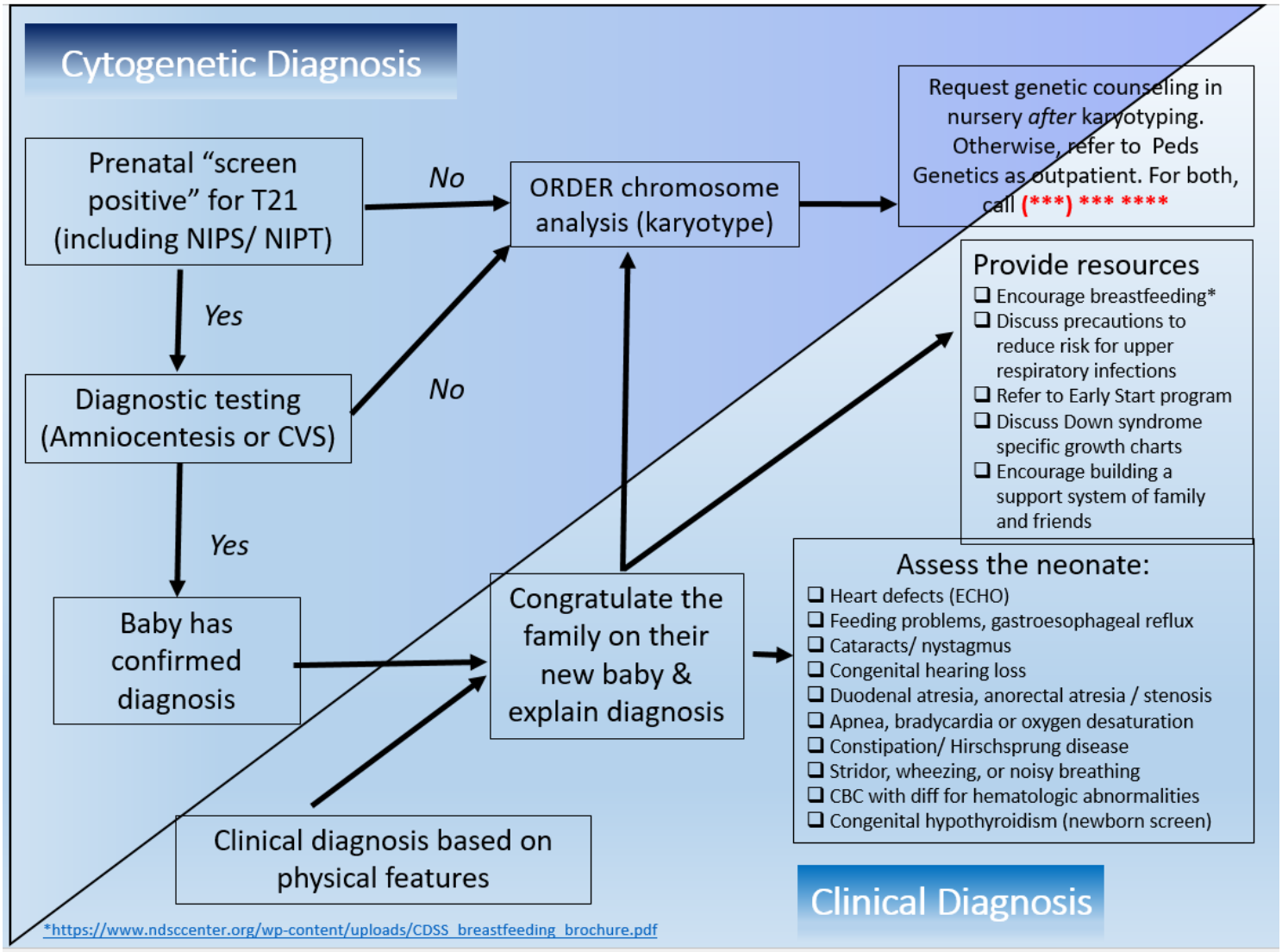

Figure 1: Overview of clinical and cytogenetic diagnostic components

clinically apparent, the parents should be informed and appropriate clinical assessments made in the neonate, as outlined in Figure 1.

Chromosome analysis is usually a confirmatory test, but it also distinguishes the more common trisomy 21 from the less common translocation and mosaic Down syndrome (which differ in their recurrence risks and id therefore necessary for providing appropriate genetic counseling)

The majority of individuals with Down syndrome (95%) have trisomy 21 due to meiotic nondisjunction, and the karyotype is written as:

47,XX,+21 or 47,XY,+21

Parental chromosome analysis is not indicated when the diagnosis is trisomy 21. The risk of recurrence for Down syndrome is low, approaching about 1% for women in their mid-thirties.

In about 4% of cases, Down syndrome is due to a translocation involving chromosome 21. An example of a karyotype for translocation Down syndrome is:

46,XX,der(14;21),+21

In this situation, parental chromosome analysis is recommended, and recurrence risks will be based on whether the chromosome translocation was de novo or inherited, derived from a parent with a balanced chromosome translocation. If the mother is a carrier, the risk to have a liveborn child with Down syndrome is about 10%, while the risk is about 1% if the father is a carrier.

Mosaic Down syndrome accounts for about 1 to 2%, with a karyotype of 47,XX,+21/46,XX (for example) due to postzygotic nondisjunction. The recurrence risk is low and is usually quoted to be similar to that for trisomy 21. Individuals with mosaic Down syndrome may or may not have milder features; karyotyping in the blood is not predictive of the degree of mosaicism in other tissues.

Breaking the news to parents and family:

We provided practical tips on breaking bad news when setting up an interview with parents to inform them of the diagnosis in the nursery, based on the SPIKES 6-step protocol. This is best done in person, before discharge.

Set up the interview	Maintain privacy, sit down, have enough chairs for everyone, involve significant family members, as desired by parents, minimize interruptions, have tissues handy	
Assess parent perceptions	Ask parents how they think the infant is doing What is their understanding of the situation	
Invite participation	Give parents the choice of how much information they would like to receive at that time	
Communicate effectively	Avoid jargon (aneuploidy, trisomy, syndrome), pause frequently to allow a response, use drawings or pictures, avoid being excessively blunt	
	Use: "I'm sorry to have to tell you this" "I know this is not good news for you" "	**Avoid:** "You knew....this was a possibility" "I see this all of the time" "I know what this must be like"
Address parents' emotions	Listen, observe and acknowledge their emotions	
Provide summary of information and resources	End with a summary of recommendations. Keep it simple. Give written information.	

Figure 2: Breaking bad news

At our institution, parents of infants with Down syndrome due to trisomy 21 with typical clinical features are referred for genetic counseling, either while inpatient or in the outpatient Pediatric Genetics clinic. Genetic counseling is best done ideally AFTER karyotype analysis to allow for appropriate genetic counseling regarding recurrence risks in the family. Most pediatricians should be able to provide the basic information about the test result, recurrence risk, and options for prenatal screening and diagnosis in future offspring for parents.

When to order a Genetic consult:

We recommend a Genetics consult when:

- The baby has features that are NOT typical for Down syndrome with an abnormal chromosome analysis result
- The karyotype confirms translocation or mosaic Down syndrome
- The family history is positive for Down syndrome in another close family member

Resources for parents:
A companion tool kit was also prepared for parents of newly diagnosed infants which include a fact sheet, a short summary of clinical information, support group information, and resources:

- *Fact Sheet about Down Syndrome for New and Expectant Parents*
- *Breastfeeding a baby with Down syndrome*
- Understanding a Down syndrome diagnosis: *https://understandingdownsyndrome.org/*
- National Down Syndrome Society *https://www.ndss.org/*
- Down's Syndrome Association: *http://downs-syndrome.org.uk*
- Sibling Support: *https://www.siblingsupport.org/*
- National Down Syndrome Adoption Network: *https://www.ndsan.org/*
- Reeces Rainbow Adoption Ministry: *https://reecesrainbow.org/*
- *Welcome to Holland by Emery Perl Kingsley*

We also included a table on developmental milestones in Down syndrome (*ndss.org*):

Practical applications:

Milestone	Range for Children with Down Syndrome	Typical Range
GROSS MOTOR		
Sits Alone	6 – 30 Months	5 – 9 Months
Crawls	8 – 22 Months	6 – 12 Months
Stands	1 – 3.25 Years	8 – 17 Months
Walks Alone	1 – 4 Years	9 – 18 Months
LANGUAGE		
First Word	1 – 4 Years	1 – 3 Years
Two-Word Phrases	2 – 7.5 Years	15 – 32 Months
SOCIAL/SELF-HELP		
Responsive Smile	1.5 – 5 Months	1 – 3 Months
Finger Feeds	10 – 24 Months	7 – 14 Months
Drinks From Cup Unassisted	12 – 32 Months	9 – 17 Months
Uses Spoon	13 – 39 Months	12 – 20 Months
Bowel Control	2 – 7 Years	16 – 42 Months
Dresses Self Unassisted	3.5 – 8.5 Years	3.25 – 5 Years

"You have to forget the timetable you reserve for your other kids. This child will succeed at his own pace."

Figure 3. Table on developmental milestones in Down's Syndrome

1. Examine the infant for typical features of Down syndrome
2. Chromosome analysis is recommended in typical Down syndrome cases
3. Avoid ordering of chromosome microarray analysis in these typical infants
4. Request a Genetics consult if the infant has atypical features and/or if there is a family history that may suggest a dual diagnosis.

References:

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