Nomination and Prioritization Workgroup Report on 22q11.2 Deletion Syndrome (22q11.2DS; DiGeorge Syndrome, DGS-1)

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SACHDNC Meeting
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Nomination of 22q11.2DS

Proponents: - John Routes, MD (primary contact) and
James Verbsky, MD, PhD

Medical College of Wisconsin, Milwaukee, WI

- Kathleen Sullivan, MD and
Donna McDonald-McGinn, MS, CGC

Children's Hospital of Philadelphia, PA

Supporting Organizations:

- Jeffrey Modell Foundation
- Immune Deficiency Foundation
- International 22q11.2DS Foundation
- Dempster Family Foundation

Nomination of 22q11.2DS for NBS

Condition:

22q11.2 Deletion Syndrome (22q11.2DS; DiGeorge syndrome, Velocardiofacial syndrome, etc.)

Genetics:

- autosomal dominant
- >90% de novo deletion
- <10% inherited from parent

Prevalence:

1 in ca. 4,000 live births; panethnic

Phenotype:

- variable (mild to severe)
- intrafamililal variability as well

Treatment: symptomatic

TABLE 3. Major Phenotypic Features*

Feature	Frequency (%)
Cardiac anomaly	77
Tetralogy of Fallot	20
Ventriculoseptal defect	21
Interrupted aortic arch	12
Truncus arteriosus	6
Vascular ring	6
Immune deficiency	77
T-cell lymphopenia	67
Delayed IgG production	10
Thymic aplasia with absent T cells	<0.5
Palatal defects	
Velopharyngeal insufficiency	42
Submucous cleft palate	16
Overt cleft palate	11
Cleft lip and palate	2
Weschler IQ	
Average	18
Low average	20
Borderline	32
Mentally retarded	30

*Data taken from the CHOP cohort, n = 906.

22q11.2DS
Clinical Concerns over Time

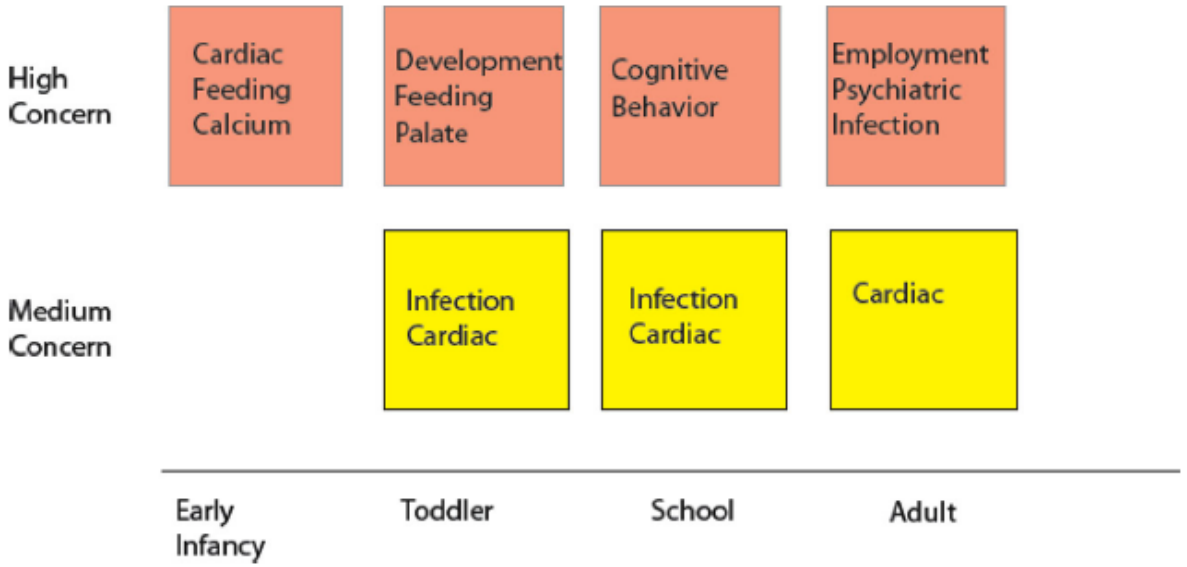

FIGURE 5. The dynamic nature of health concerns in patients with chromosome 22q11.2 deletion syndrome. Each age has a typical set of concerns that change over time.

McDonald-McGinn DM & Sullivan KE.
Medicine 2011;90: 1-18

22q11.2DS Treatment

More significant issues relate to management of patients once the diagnosis is established. The varied presentations and the varied phenotypic constellations *mandate that each patient have a nearly unique management strategy*. Nevertheless, coordinated care and comprehensive approaches are possible. The promise, and the possibility of improved interventions for neuropsychiatric needs could lead to enhanced adult function.

McDonald-McGinn DM & Sullivan KE. Medicine 2011;90: 1-18

NBS for 22q11.2DS

- Proposed Method:
  - Multiplex quantitative RT-PCR for TBX1 copy number
  - 1/8-inch (3.2 mm) punch/test
- Overlap with existing NBS methods?

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CCHD

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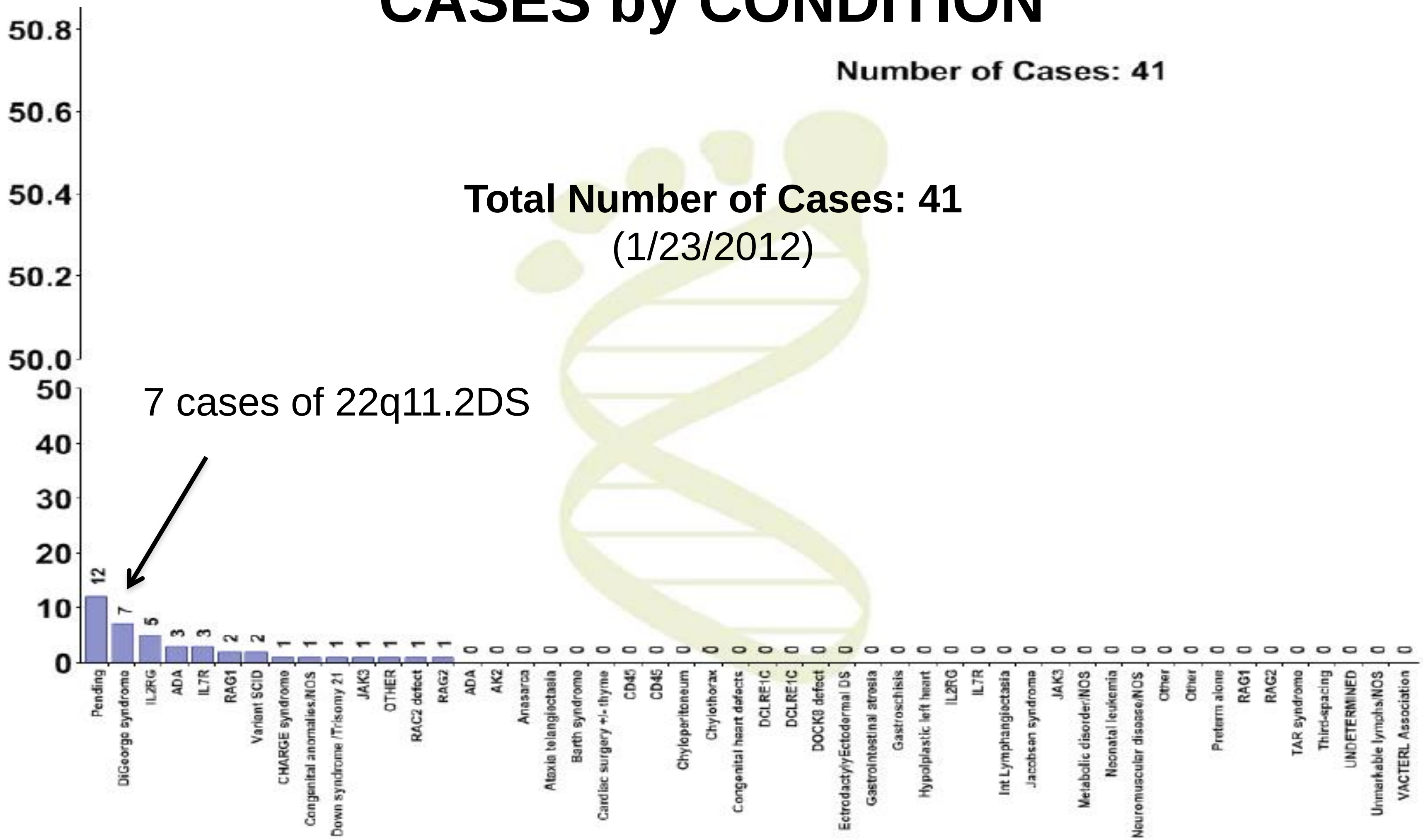
  - Pulseoximetry for CCHD:

    At least 50% of patients with 22q11.2DS have a cyanotic heart defect
  - SCID screening:

CASES by CONDITION



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  - Pulseoximetry for CCHD:

    At least 50% of patients with 22q11.2DS have a cyanotic heart defect
  - SCID screening:

    67% of 22q11.2DS have T-cell lymphopenia

NBS for 22q11.2DS

- Proposed Method:
  - Multiplex quantitative RT-PCR for TBX1 copy number
  - DNA
  - 1/8-inch (3.2 mm) blood spot punch/test
- SCID screening:
  - Quantitative RT-PCR for T-cell receptor excision circle (TRECs) analysis
  - DNA
  - 1/8-inch (3.2 mm) blood spot punch/test

Newborn screening programs: should 22q11 deletion syndrome be added?

Bales AM, Zaleski CA, McPherson EW.

Genet Med. 2010;12:135-44

Table 2 Quick summary of benefits and risks of newborn screening for 22q11DS

	Benefits	Risks
Societal	Consideration of adding screening provides impetus for development of effective inexpensive screening for a potentially serious problem that now is often unrecognized	Untested screening technique. Sensitivity, specificity, and cost not fully known
	Societal benefit of delineating full phenotypic spectrum and natural history of 22q11DS	False positives may affect cost and cause unnecessary anxiety
		Individual values and principles ignored (some families may prefer not to know of medical conditions for which urgent treatment may not be needed)
		Early interruption of parent/child relationship (effects on bonding, stress)
		Possibility of detecting incidental findings, including 22q11 duplication
		May set precedent for other syndromes
Individual	Early detection/treatment of cardiac defects	May be alternate, more effective ways to detect congenital heart disease Reporting and confirmation may not be possible within critical 1 week window Possible detection of defects that would resolve without treatment
	Prevent seizures secondary to unrecognized hypocalcemia	Neonatal seizures may occur before reporting of 22q11DS
	Early detection/treatment for severe immune deficiency	Immune deficiency screening already in place in some states. Detection of 22q11DS may lead to unnecessary evaluation of children with minimal immune deficiency
	Early detection and intervention for palatal abnormalities affecting feeding and speech	Confirmation of velopharyngeal insufficiency difficult in a young child
	Early intervention for developmental delay	Risk of labeling child who might prove mildly affected
	Early, timely recognition of treatable complications (i.e., mental illness and learning disabilities)	Educational strategies are not unique to condition and are similar to those for other children with similar disabilities
		Identification of increased risk of mental illness is unintended consequence
	Adaption of surgical techniques as necessary (cardiac and palate repairs)	
Family	Prevent "diagnostic odyssey" for families	Concerns of creating "vulnerable child syndrome" for mild cases
	Recognition of familial cases, recurrence risk counseling	Phenotype varies and difficulty to predict presence of absence of features, therefore cost associated with interventions that may not be necessary for every patient
		Anxiety with false positives or mild cases not requiring urgent treatment
		Access to genetic counseling from trained individuals may not be universally available
Cost-effectiveness	Early diagnosis and intervention may minimize complications and resultant costs of treatment	Costs of confirmatory testing and follow-up care

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NBS for 22q11.2DS

- No prospective study performed to date
  - How well does the test perform (false positive rate, false negative rate, positive predictive value, specificity, sensitivity)?
  - Will it detect individuals with 22q11.2 duplications (which can be of NO clinical consequence)?
- Significant number of cases expected to be identified through NBS for SCID and CCHD

  Must other presentations of 22q11.2DS be detected?
- Limited number of experienced, multi-center clinical centers
- Proposal is for 1 DBS punch for 1 condition

  Potential waste of specimen; consider combining with NBS for other condition(s), such as SCID, to save DBS

Nomination of 22q11.2DS for NBS - *Recommendation to SACHDNC* -

- Do not initiate External Evidence Review yet
- Suggest to proponents/NBS community to conduct a prospective NBS study for 22q11/2DS to determine
  - test performance metrics;
  - if current NBS for SCID and CCHD is sufficient to detect *clinically significant* 22q11.2DS cases;
  - if testing for 22q11.2DS could be multiplexed with other DNA based NBS assays, in particular SCID;
  - Development of ACT SHEETS and algorithms (www.acmg.net).
- Recommend to NBS programs that already test for SCID to participate in Region 4 SCID project.