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

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Abstract: The highly variable 22q11 deletion syndrome has been proposed for addition to newborn screening panels. A literature review investigated the incidence and prevalence, clinical features, and prognosis of 22q11 deletion syndrome and other issues related to newborn screening. Severe complications that could potentially be helped by screening include cardiac defects in 80% (with 20% having no outward signs to aid detection), hypocalcemia that can lead to seizures in 20% (though hypocalcemia is routinely investigated in sick newborns), and severe immune deficiency in <1% (which would be identified by some states' severe combined immunodeficiency screens). Other benefits that do not fit traditional goals of newborn screening include treatment for complications such as failure to thrive and developmental delay or preventing a "diagnostic odyssey." Although universal screening may prove the incidence to be >1:5000, undetected life-threatening effects occur in a minority of 22q11 deletion syndrome patients. Concerns include an untested screening technique, difficulty obtaining results in time for cardiac intervention, the chance of "vulnerable child syndrome" in mild cases, and possibly detecting congenital heart disease more efficiently by other means. Because addition of tests for highly variable conditions such as 22q11 deletion syndrome is likely to set a precedent for other syndromes, reevaluation of newborn screening criteria should be considered. ***Genet Med*** **2010:12(3):135–144.**

Key Words: *deletion 22q11, DiGeorge syndrome, newborn screening, public health, velocardiofacial syndrome*

Since the 1960s, newborn screening for phenylketonuria (PKU) and other disorders has become commonplace. The addition of new tests to screening panels continues at a rapid pace and is beginning to incorporate more genetic-based testing, as this technology advances. For example, Wisconsin has recently begun screening infants for severe combined immunodeficiency (SCID) through genetic analysis of T-cell receptor excision circles.[1] It seems likely that other tests will continue to be proposed and added to the screening panel, especially as technology continues to develop. A recently proposed test is for 22q11 deletion syndrome (22q11DS), a genetic disorder with a complex and variable presentation. Currently, suitable screening for 22q11DS does not exist but is under development by at least one group (A. Mitchell, personal communication).

Although newborn screening is ubiquitous across the United States, disorders for which screening is mandated vary among states. Criteria for addition of disorders also vary somewhat between states, though most follow the World Health Organization Wilson-Jungner criteria for general screening programs, which include the following important points:

- Knowledge of the disease
- Treatment of the disease
- Knowledge of the test
- Cost considerations.[2]

The initial impetus for this project was to assess the proposed addition of 22q11DS to Wisconsin's Newborn Screen; however, the issue is nationally pertinent as other states also consider expanded screening for a wide range of conditions, some of which, such as 22q11DS, are variable and may not always require neonatal treatment. This article will discuss the criteria for newborn screening with relation to 22q11DS to facilitate judgment on development of a screening test and potential addition of the syndrome to newborn screening panels.

KNOWLEDGE OF THE DISEASE

The effects of deletion of chromosome 22q11.2 have long been recognized clinically. However, before recognition of the underlying chromosomal deletion, several different terms including DiGeorge syndrome, Velocardiofacial syndrome, conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB Syndrome, Sedlackova syndrome, and Shprintzen syndrome were used, depending on the presenting clinical features. With advances in genetic testing, it has become clear that a 22q11 deletion is the underlying cause in most patients with these syndromes. For our purposes, the term "22q11 deletion syndrome" (22q11DS) will be used.

Although the deletion is identical in most patients studied, the phenotype varies greatly. Goodship et al.[3] report a case of monozygotic twins with 22q11DS where one twin's phenotype is more severe, showing that genotype alone does not account for the presence or absence of various features of 22q11DS.

More than 180 clinical findings have been associated with 22q11DS.[4] It is outside the scope of this article to describe each possible manifestation in detail; instead, it will cover the most common and most severe aspects of the phenotype. Examples of abnormalities that will not be described in detail include renal (36% of patients)[5] and skeletal anomalies (17%).[5]

Both the number of organ systems involved and severity of involvement vary. Severe cases may result in neonatal death, whereas mildly affected individuals may remain undiagnosed, even as adults.

In most cases, 22q11.2 deletion occurs de novo. However, in about 10% of cases, a parent is found to have the deletion.[4] In fact, mild cases are often recognized only after a relative is found to carry the deletion. Inheritance is autosomal dominant. As advances in medical care allow more patients to survive to adulthood,[6] the issue of passing the deletion to offspring will become more important. Prenatal testing and preimplantation diagnosis are family planning options for affected individuals.[7]

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INCIDENCE AND PREVALENCE

Because the phenotype of 22q11DS is so varied and diagnosis is often delayed, it is difficult to accurately assess the incidence and prevalence of the deletion. Because cost has precluded large population testing of asymptomatic individuals, these estimates are almost certainly a minimum approximation, with the true prevalence of the deletion more common than is seen in clinical cases. This is especially relevant to the discussion of newborn screening, because testing of all newborns is likely to uncover mild cases in which the affected individual may never have otherwise known he carried the deletion.

Two large population studies have attempted to assess the prevalence of 22q11DS in the general population. During the 10-year period, using the comprehensive medical records in the Western Gotland Region of Sweden, Oskarsdóttir et al.[8] found an estimated prevalence of 1 in 7081 for clinically recognized 22q11DS. However, the authors note that the prevalence is higher for children born in the first half of the study period (1 in 5500), and more of these patients lack heart defects. This provides evidence that milder cases, including those without major cardiac abnormalities, are diagnosed later in life. Presumably, some cases remain unrecognized even after 10 years. A study based on Atlanta birth defects registry data during a 5-year period[9] yielded similar results, with a 1 in 5950 birth incidence of the deletion. As in the Swedish study, the prevalence of clinically recognized 22q11DS was higher (1 in 5000) in those born in the earlier part of the study.

Higher estimates of incidence, ranging from 1 in 4000 to 1 in 2000,[4,10] are based on calculations involving occurrence of symptoms such as cleft palate and heart disease in 22q11DS and the general population. For this investigation, data substantiated by population evidence are more useful. Both of the population studies referenced above found similar prevalence of clinically recognized 22q11DS in the older groups of their studies (1 in 5000). This number will be used throughout the remainder of this article, with the understanding that it represents a minimum estimate.

By most estimates, the deletion seems to be equally common in all ethnic groups. In a few studies, the deletion has been found to be less common in African Americans and more common in Hispanics, but this is likely due to chance and ascertainment bias.[11]

ASSOCIATED SYMPTOMS

Cardiac defects

Cardiac abnormalities are a frequent and sometimes severe feature of 22q11DS, occurring in approximately 75–80% of cases.[12,13] However, this may be an overestimate of the actual population prevalence, because patients with major cardiac anomalies are more likely to be recognized by clinicians as possible 22q11DS patients. 22q11DS patients with heart defects are diagnosed earlier in life than those without heart abnormalities.[8] Cardiac defects associated with 22q11DS are typically conotruncal anomalies (Table 1).

Early detection and intervention in congenital heart defects is generally seen to improve outcomes and for certain ductus-dependent lesions may prevent early death. Presymptomatic intervention reduces clinical deterioration and prevents collapse, which ultimately reduces length of stay in the intensive care unit, while improving mortality and neurologic outcome in the postoperative period and long term.[17]

However, the extent to which screening for 22q11DS will prevent adverse cardiac outcomes is less clear. As shown in Table 1, most of the common cardiac abnormalities cause a murmur and/or cyanosis and, therefore, should be detectable on physical exam. Only about 20%, mainly interrupted aortic arch, do not display these physical findings that would indicate a need for further examination. Nonetheless, there is evidence that signs such as murmurs and cyanosis are not reliably detected on neonatal examinations.[18] Therefore, it is difficult to know what proportion of heart defects due to 22q11DS would be detected by other means.

Table 1 Cardiac defects in 22q11DS

Defects	Incidence in 22q11DS[14]	Incidence of 22q11DS in heart defect[14]	Murmur[15]	Cyanosis[15]
Tetralogy of fallot	17%	16%	X	X
Pulmonary atresia	10%	16–40%[16]	Variable	X
Ventricular septal defect	14%	25%	X	
Interrupted aortic arch	14%	50%		Variable
Truncus arteriosus	9%	33%	X	X

X, feature is present.

Immune system

Patients with 22q11DS frequently have a small or absent thymus and up to 80% have at least minor T-cell abnormalities.[19] However, severe T-cell deficiency due to thymic aplasia occurs in only about 0.5% of patients. Because these patients are at risk for graft-versus-host disease if they receive nonirradiated blood products and are also susceptible to opportunistic infections, rapid treatment is required.[12] It is important to note that Wisconsin has newborn screening for SCID,[1] and other states have recently added, or are considering adding, this syndrome to their newborn screening. The measurement of T-cell receptor excision circles would identify the most severe immune deficiencies from 22q11DS. In fact, because the SCID screen began in Wisconsin, a few cases of 22q11DS with immune deficiency have already been identified (M. Baker, personal communication). In other areas where a SCID screen is not in place, a 22q11DS screen may identify patients with severe immune deficiency, but the number is small.

Recurrent infections are common in 22q11DS and do not seem to be correlated with the laboratory measures of T-cell function, so even patients with sufficient T-cell levels may be at increased risk of infection.[20] It seems likely that additional factors such as anatomic defects, reflux, allergies, cardiac disease, and poor nutrition, contribute to recurrent infection.[19] Fortunately, patients with mild to moderate T-cell deficiency do not seem to suffer from the serious opportunistic infections that afflict the more severe cases.[21]

In general, humoral (antibody mediated) immunity seems to be intact,[12] though some studies have found decreased humoral function in some patients.[22] The extent of this deficiency and its impact on the overall health are not yet clear, although a correlation between the frequency of infections and degree of decrease in humoral immunity has been identified.[22]

Immune problems in 22q11DS can also manifest as a general increase in the frequency of autoimmune disorders.[23] Juvenile rheumatoid arthritis, immune thrombocytopenia, and Reynaud's phenomenon have been described as more common in 22q11DS,[12] as are diabetes mellitus type I and Graves disease.[23] The frequency of clinical autoimmune disease is estimated to be approximately 10–20% of 22q11DS patients.[20,24]

Endocrine

The most common endocrine manifestation in 22q11DS is hypocalcemia, usually due to hypoparathyroidism. Many cases of hypocalcemia occur in the neonatal period but resolve with age, whereas others do not present until later in life.[25] Hypocalcemia occurs sometime in the life of about 50–60% of all 22q11DS patients,[5,26] most commonly during the neonatal period. Although most cases of neonatal hypocalcemia are benign and are detected during routine laboratory work, some patients may present with seizures, tremor, or rigidity.[25] Unrecognized hypocalcemia can also cause arrhythmia, syncope, or death, especially in patients with congenital heart defects.[27] High phosphate or low parathyroid hormone levels in conjunction with hypocalcemia can help identify hypocalcemia due to 22q11DS versus hypocalcemia of other causes.[25]

Seizures have been found to occur in >20% of patients with 22q11DS.[5,28] The most common cause of these seizures is hypocalcemia (40–70% of seizures are due to hypocalcemia),[5,28] but there are other causes including fever, hypoxia, or recent surgery.[28] Of all patients who experience hypocalcemia at some point, only about 10–15% develop seizures.[28] Once the cause of seizure is discovered, treatment is generally straightforward, usually calcium supplementation or anticonvulsants.[4]

Individuals with 22q11DS are generally smaller than average in size.[5] Disrupted growth is sometimes due to specific treatable endocrine abnormalities such as growth hormone deficiency,[29] autoimmune thyroid disease, or congenital hypothyroidism.[25,30] Other causes of small stature include feeding difficulty and intrauterine growth restriction.[31]

Craniofacial anomalies

One of the earliest recognized features of 22q11DS was a characteristic facial appearance. Although these features are not usually clinically significant in their own right, they are a consistent feature of the disease[32] and can be an indicator for genetic testing (assuming universal screening is not in place). Features occurring in more than half of patients include malar flatness, hooded eyelids, tubular nose with round nasal tip, and round, low-set ears with overfolded helices.[32] However, it is clear that facial features alone are not adequate for clinical diagnosis. Features are often less pronounced early in life and become apparent only as the child ages,[33] making timely diagnosis by appearance alone unlikely. Furthermore, the typical facial features are not always present or readily identified, especially in the African American population.[11]

Furthermore, palatal abnormalities are frequently present in 22q11DS, although the extent and frequency of various types of palate abnormalities is not clearly delineated. Overt clefts (usually cleft palate but occasionally cleft lip) occur in about 10% of cases.[5] More subtle palate problems such as submucous cleft palate or velopharyngeal insufficiency are more difficult to assess, because they are often found only if specific, invasive examinations are done. A large study by Ryan et al.[5] found these in about 37.5% of cases, but these data came from surveys and likely missed patients who did not have full palatal exams. With complete evaluation, these more subtle anomalies are found in about 60% of patients.[26,34]

Feeding/failure to thrive

There has been little study on the frequency of "failure to thrive" in infants with 22q11DS, but it has been clearly demonstrated that feeding problems are common. At least 30% of patients have serious feeding problems.[7,26,35] Some authors report feeding abnormalities in as many as 74% of patients.[36] It seems that many factors including palatal dysfunction, cardiac anomalies, gastrointestinal dysmotility, and incoordination, the presence of a vascular ring that impairs the esophagus,[35] and hypotonia can lead to feeding difficulty.[12]

Hearing

Recurrent otitis media, often requiring myringotomy or tympanostomy tubes, is common in 22q11DS patients, occurring in about 52%. Some degree of hearing loss, usually conductive, is found in about 31%.[34]

Cognitive/development

Early developmental milestones are often delayed in 22q11DS patients. Approximately 80% of patients have been found to have motor or speech delay.[5] Hypotonia and decreased cognitive function may play a role in motor delay.[37,38] Speech development may be complicated by palate abnormalities, which contribute to hypernasal speech and articulation errors.[33,39]

Learning problems persist in school age children and adults. Most studies show that only about 13% of school-age patients have intelligent quotients (IQ scores) in the average range, whereas about 25% have low average scores, approximately 33% have borderline IQ scores, and the remaining 29% have IQ scores that are classified as mentally retarded.[26,33] Mental retardation is generally mild, with <1% of all patients having severe mental retardation, and only about 7% having moderate mental retardation.[33] Learning disability is frequently found, especially nonverbal learning disorder, though there is variation in the type and extent of learning disability.[26,33,40]

Further complicating learning and school performance is the fact that attention deficit hyperactivity disorder (ADHD) is more common in 22q11DS patients than in the general population. One study found that ADHD occurs in about 30% of patients with 22q11DS.[41]

Mental illness

Patients with 22q11DS are at a higher than average risk of developing mental illness, often classified as schizophrenia.[42] It is clear that patients with comorbidities of 22q11DS and schizophrenia have more problems than either diagnosis alone.[43] Two relatively small studies indicate that the lifetime prevalence of schizophrenia is 25–30% for people with 22q11DS.[43–46] Compared with 22q11DS patients, only individuals who have a monozygotic co-twin with schizophrenia or two parents with schizophrenia have greater risk of developing schizophrenia.[43]

Although schizophrenia is usually considered as an adult-onset disorder, psychiatric disorders in childhood also occur in those with 22q11DS. Vorstman et al.[47] found that in a group of 60 22q11DS patients younger than 18 years, 3% had schizophrenia. An additional 8% were diagnosed with "psychosis not otherwise specified."[48] Baker et al.[48] found high prevalence of hallucinatory phenomena and other psychopathology in adolescents with 22q11DS. Although some of these patients were older than 13 and thus did not meet the specific criteria for childhood-onset schizophrenia,[49] it is still notable that in 22q11DS psychoses can manifest before adulthood.

Autism

Autism and autism-spectrum disorders (ASDs) are more frequently seen in 22q11DS than in the general population. The largest existing studies (~100 patients) have screened patients and performed standardized diagnostic assessments for autism and found that about 5–10% of patients have autism, and another 15–20% have any ASD.[41,50] Still, although autism assessments have been revised to discriminate from disorders such as Fragile X, they may not be able to reliably discriminate autism from 22q11DS.[50]

In the study by Vorstman et al.[47] of psychosis in 22q11DS, as in the general population, ASDs are linked to schizophrenia, especially childhood-onset schizophrenia. There is evidence that the phenotype of autism seen in 22q11DS is different in some ways from the phenotype of autistic patients without this deletion.[51] Some autism symptoms in 22q11DS could be prodromal features of schizophrenia or severe expression of obsessive compulsive disorder and not a distinct element.[47,52]

In addition to schizophrenia and autism, it seems that children with 22q11DS have increased rates of ADHD, anxiety, obsessive-compulsive disorder and mood disorders, (ADHD can be seen in about 30% of patients with 22q11DS[41]), although it has been hypothesized that this may be secondary to the syndrome and its developmental delays.[53] Children with 22q11DS are similar to children with other developmental disabilities in terms of rate of psychiatric disorders; however, 22q11DS patients do not show the same improvement in mental health in early adulthood as other young adults with developmental disabilities. They are also more likely to have psychotic disorders.[53] It is difficult to quantify the juvenile mental health problems, because reports vary by study design and the largest studies tend not to do very in-depth analysis of mental health.

TREATMENT OF THE DISEASE

Because the missing genetic material cannot be replaced throughout the body, there is clearly no cure for 22q11DS. Once the syndrome is identified, the goal is detection and management of treatable complications. Evaluation by a cardiologist including chest x-ray, electrocardiogram, and echocardiogram is indicated.[7] Although interventions for heart defects in 22q11DS patients usually do not differ from the interventions for other patients with the same cardiac defect, the presence of the deletion can create a unique situation. In about 50% of cases, other cardiovascular anomalies, such as aberrant vessels, are present and usually require adaptation of surgical technique (this applies to other surgeries as well, including palate repairs). Immune problems may also play a role, contributing to infectious complications and making irradiated blood a necessity. It is not clear what role these complications play in surgical outcome, especially since use of irradiated blood products is now almost universal in neonates. Although some studies indicate 22q11DS patients have worse outcome due to their multiple medical problems,[54] most studies have found the surgical results are not significantly different.[55,56]

Once the diagnosis is made, immunologic evaluation is also recommended. Only the most severely immune deficient patients (<0.5%) require bone marrow or thymus transplantation, which seems to be effective in restoring normal immune function.[23] Immunization of patients with immune deficiency could be a cause for concern, but studies show that in the absence of severe immune deficiency, 22q11DS patients do not have increased adverse effects and vaccines are effective in this population.[57,58] Evaluation and treatment for autoimmune disease is limited to symptomatic individuals.

Additional evaluation includes measurement of serum calcium levels, which are easily treated with calcium and vitamin D once hypocalcemia is recognized. Short stature and other endocrine problems are evaluated and treated the same as in chromosomally normal individuals.[7] Recommended screening for other medical complications includes renal ultrasound, chest x-ray to identify vertebral anomalies, and spine films at the age of 4 years to check for cervical spine anomalies.[7]

Starting in infancy, evaluations for feeding, speech, and language problems are recommended to identify individuals who require intervention such as physical, occupational, or speech therapy. Treatment strategies for feeding problems are similar to those for other children with similar feeding difficulties and may include postural therapy, spoon placement modifications, medication, or gastrostomy or nasogastric tube placement.[26] Despite considerable literature on learning disabilities in 22q11DS, educational strategies are comparable with those for other children with similar disabilities. Evaluation for psychiatric illness is recommended whenever symptoms are noted.[7] Although cooccurring health problems can complicate matters, it seems that psychiatric disorders are generally responsive to standard medications, though there is some conflicting data.[43] Overall, treatment for most aspects of 22q11DS is comparable with that for individuals in the general population who experience similar physical or mental health problems. The major advantage in early detection of 22q11DS is early recognition and treatment of associated problems. In general, with appropriate treatment, prognosis is good for patients with 22q11DS.[59]

Genetic counseling by trained individuals is also an essential part of follow-up, both at diagnosis and later in life. Because the syndrome is so varied, accurate and client-centered counseling at diagnosis is critical to ensure that parents understand the diagnosis and its implications. Access to ongoing genetics services should be available to address later concerns.

KNOWLEDGE OF THE TEST

A critical part of any screening program is the characteristics of the test to be used. Under development is a real-time polymerase chain reaction test that would detect the number of copies of the 22q11 region in each sample to identify the presence of a deletion (A. Mitchell, personal communication). Sensitivity, specificity, and cost need to be accurately known before a decision can be made regarding implementation of screening. The current gold-standard test and proposed confirmatory test after an abnormal screen is fluorescence in situ hybridization (FISH). Turn-around time is about 3–5 days.[60]

One additional consideration for screening tests is whether the test will identify individuals with a disease other than the intended disease (in this case 22q11 deletion). It seems possible that the screening test for 22q11 deletion might also detect some cases of 22q11 duplication. Although it involves the same region as 22q11DS, 22q11 duplication syndrome is quite distinct. The phenotypic range for the duplication syndrome is much wider than 22q11DS, with many seemingly normal people having been identified with the duplication. Clinical features that are sometimes associated with the duplication include mental retardation and learning disability, developmental delay, growth retardation, and hypotonia. Prevalence is uncertain but was observed to be about 1:700 in a population with mental retardation or developmental delay.[61] This was only recently recognized as a genetic syndrome, so literature on the subject is minimal and subject to ascertainment bias.

COST CONSIDERATIONS

Benefits

Historically, newborn screening has been used to identify "hidden" disorders that benefit from presymptomatic treatment in the newborn period. PKU and hypothyroidism are classic examples: affected babies show no signs at birth, but early treatment can prevent irreversible harms (e.g., mental retardation) and result in substantial benefit to the child, family, and society.[62]

Using this rationale, new disorders added to the screening panel should be proven to require treatment in the newborn period (as opposed to later in life) to avoid adverse outcomes. In some ways, 22q11DS meets this requirement, because a large proportion of patients have serious heart defects and presumably can benefit from early diagnosis and medical or surgical intervention. Additionally, endocrine manifestations, especially hypocalcemia, are common, and monitoring calcium levels in the newborn period and throughout life may help prevent seizures and other complications. (Severe immune deficiency is a life-threatening complication of 22q11DS, but these children would be identified by SCID screens in some states. Because it is quite rare, it will not be considered further in this discussion.) It is not clear whether these complications are severe or time sensitive enough to warrant mandated newborn screening. For example, although approximately 75% of those with the deletion have a significant heart defect, the nature of cardiac problems varies widely. Some of these defects would be expected to cause a murmur or cyanosis. Therefore, they are not truly "hidden" as they could potentially be identified by auscultation or visual examination. Furthermore, not all cardiac defects require immediate treatment. Hypocalcemia is common, but only causes symptoms in a small proportion of patients, occurs at all ages (not just in the newborn period), and may improve spontaneously. Intervention in infancy would only make a difference in a subset of patients.

As new screening tests for disorders are becoming more available, there has been a movement to expand the goals of screening and consider additional potential benefits to affected individuals, families, and society. This view is not universally accepted, but it is worth considering these additional possible benefits and their relation to 22q11DS.

First, 22q11DS has many associated symptoms, and even those that do not require immediate treatment in the newborn period may benefit from early detection and intervention. For example, learning problems are a nearly uniform feature of the syndrome, and early intervention is important in bringing about the best possible outcome.[40] Early intervention services are appropriate for ensuring that these patients reach their highest potential, and a screening test could help make sure that all affected individuals are included in these programs. A definitive diagnosis may also be helpful in securing appropriate special education services for these children as they enter higher grades.

Early diagnosis may help with other problems, such as feeding difficulties or mental illness, for similar reasons. If parents are aware that certain problems may occur as a result of the syndrome and know that therapies are available, they may be more likely to recognize these problems and seek help in a timely manner. Communication with parents of 22q11DS patients has revealed many cases with problems early in childhood (nasal regurgitation of food, hypernasal speech, frequent ear infections, etc.), but parents either assumed or were told by primary providers that it was nothing to worry about (Bales, unpublished data). If the diagnosis was made at birth, unnecessary risks, such as adenoidectomy in children with unrecognized palatal abnormalities, could be avoided and appropriate interventions, such as assessments of palatal function or surgery, could be made sooner.

In addition to improving treatment for affected infants, newborn screening could also provide important information for families. For instance, identifying parents who are mildly affected may impact family planning choices by helping them understand the chance of having another affected child. Family planning is less of a factor in 22q11DS compared with some other conditions being considered for newborn screening such as Fragile X because, as most cases occur de novo, the risk to subsequent children is low. However, in the 10% of cases where a parent carries the deletion and there is a 50% risk to future children, parents might find this information useful. Similarly, affected babies will have a 50% recurrence risk for their own future children and screening could raise awareness of this risk. Furthermore, it may be helpful to families to be aware that their child has 22q11DS, so they are better able to make plans regarding future health care needs, though this is complicated by the variability of the phenotype.

Another potential benefit to early diagnosis is the ability to avoid a "diagnostic odyssey," a period of stress, and uncertainty for families when a child presents with nonspecific symptoms such as failure to thrive or developmental delay. This may be pertinent to discussion of 22q11DS, as primary providers often have difficulty recognizing the syndrome, because it is so variable in presentation. Early diagnosis could give parents and providers an explanation for the child's symptoms and avoid anxiety or inappropriate or unnecessary questioning of parenting skills.

The expanded benefits of newborn screening may extend to society in general. Screening would help delineate the full phenotypic spectrum and natural history of 22q11DS. (see Table 2 for a quick summary of the benefits and risks of newborn screening for 22q11DS.)

Risks

The extended view of possible benefits of newborn screening is intriguing but leads to several concerns. First, the mandatory nature of newborn screening seems less appropriate when benefits are uncertain. Furthermore, it ignores individual values and principles; some families may prefer not to know of medical conditions for which immediate treatment is not needed. Because many benefits are not time sensitive in infancy, screening at a later date may be more desirable.

It is possible that identification of a varied, often severe, genetic syndrome in the first days of life might negatively alter the parent/child relationship. Early notification of the presence of disease may affect bonding or stress to a greater extent than notification once clinical symptoms manifest (especially if there is no effective treatment to be started early in life). Anxiety is to be expected whether diagnosis is made by screening or by clinical signs, but it seems to subside with time.[63] Families whose child was diagnosed with cystic fibrosis (CF) by screening were not found to have different levels of stress or depression than children diagnosed clinically.[64] Diagnosis by screening may allow families to develop a better support system, as was found in families of children with biochemical disorders.[65]

Depending on test specificity, false-positive results may be an issue. An increase in parental stress levels has been observed at the initial notification of false-positive results.[66] In most studies, the negative emotional state seems to be temporary. Tluczek et al.[66] found higher clinical depressive symptoms in false-positive CF screen mothers, but these generally decreased by about 6 months. However, a study by Baroni et al.[64] found

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

that the false-positive CF group still had higher stress levels at 1 year of age. This is potentially significant, even if stress or depression eventually subside, because maternal depression in the neonatal period can alter parent-child attachments.[66] Children with false-positive biochemical screening have greater rates of hospitalization than normal screened children, suggesting that this early anxiety about health problems may affect future health,[65] but no other lasting effects have been reported. Because factors, such as the timing and method by which the parents learn about the abnormal screen, affect the level of parental distress,[66] refinements of notification protocol may help minimize the level of parental distress and potential lasting negative effects.

One specific concern about the effect of false-positive results is the potential for "vulnerable child syndrome." Vulnerable child syndrome occurs when parents view a healthy child as vulnerable, often with a specific event triggering parental anxiety. These children often develop separation anxiety, behavior problems, underachievement in school, misperception of their

own health, and other problems. False-positive results from newborn screening have been seen to occasionally be a trigger event for vulnerable child syndrome.[67]

Because 22q11DS is variable, identification of mildly affected individuals who might never require treatment is potentially a more significant concern than false positives, because there would be no immediate reassurance mechanism equivalent to confirmatory testing. Because the phenotype ranges widely in severity, it is possible that parents of a child with a mild phenotype might worry excessively about potential problems that never occur.

Early identification of individuals at increased risk for mental illness is an unintended consequence of screening for 22q11DS. Because the onset is typically in the teenage or adult years, and most patients with 22q11DS never develop mental illness at all, informing families of the risk of mental illness may be problematic. However, because onset can occur in childhood or adolescence,[47,68] prohibitions against screening children for adult onset disorders do not apply. The risk of mental illness in 22q11DS is similar to some familial risks (e.g., a parent with schizophrenia) for which counseling would usually be provided.[69] It is important to note that risk of mental illness should be included in counseling, because families will find out about the risk through other means,[70] and there are potential benefits to knowing the risk of mental illness. It is generally accepted that intervention early in the course of schizophrenia is more effective and has better outcomes than intervention later in the disease progression[71]; therefore, awareness of the risk may make families more able to seek help when signs first appear, which could result in better outcomes.[70]

Financial costs

Although the cost of the screening test itself is expected to be small, confirmatory testing and follow-up care can be much more costly. Because the net benefits of newborn screening for 22q11DS are not as clear-cut as in some other disorders, there may be greater concern that these funds could be better spent in other areas. For example, if the goal is reduction of infant morbidity and mortality from heart disease, other screening tools such as pulse oximetry may be more effective at identifying all heart defects not just those with genetic causes.[72] Obviously, the cost of confirmatory testing depends to a great extent on the rate of false positives, which can be minimized if the test is highly specific. If most patients with 22q11DS would eventually be detected and treated, to some extent the costs of confirmatory testing and follow-up care are not attributable to screening but to the incidence of the disorder. However, if there are significant numbers of mild cases that would not otherwise be diagnosed or treated, the costs for the diagnosis and follow-up of their screening are a major concern.

OTHER CONSIDERATIONS

The addition of a screen for 22q11DS to a newborn screen panel is likely feasible for most states if the test developed proves to have good sensitivity and specificity. However, several factors may complicate screening for 22q11DS.

Rapid reporting and confirmation of results are essential if the benefits of recognition of congenital heart disease before closure of the ductus arteriosus are to be realized. Because physician notification of abnormal results is expected to take about 5 days, it is unlikely that parental notification, confirmatory testing by FISH, and cardiology evaluation can be accomplished within approximately 1 week time window.[17] To protect at-risk infants, echocardiograms could be done on all positive screens even before FISH results are available, but this has the potential to substantially raise the cost of screening.

The extreme clinical variability may make it difficult for parents to truly grasp what it means to learn that their child has the syndrome. There is significant possibility for parents to be overwhelmed by the potential problems, even though most affected individuals have only some of the associated symptoms. Parents of very mildly affected infants may experience unnecessary anxiety. Primary providers may lack understanding of the syndrome as well and not be well equipped to provide comprehensive care. Genetics centers will likely be the best source of information and support, but access may be an issue for some patients.

Further evaluation of the clinical efficacy of screening for 22q11DS is vital, because there are still uncertainties regarding both the course of the disease and potential benefits of screening. Although it is generally assumed that early intervention will be beneficial, some newborn screening tests have been found to have fewer benefits and more harms than anticipated. An example of expected benefits that did not materialize is the case of 2-methybutyryl-CoA dehydrogenase deficiency (MBAD), an inborn error of metabolism that was added to the newborn screen with the advent of mass spectrometry. Previous literature reports of rare MBAD cases described severe effects that were theoretically treatable by diet, so it was assumed that screening for the disorder would improve prognosis in identified cases. However, an unexpectedly high number of cases (most of Hmong descent) were identified in the first few years of the screening, and even though adherence to the recommended diet has been variable in these cases, affected individuals were largely asymptomatic, indicating a wider clinical spectrum of MBAD than expected and less benefit from screening.[73] Newborn screening tests can also prove to have unanticipated harms, as in the CF trial in Wisconsin, where children in the screened group were found to have earlier exposure to *Pseudomonas aeruginosa* than patients diagnosed by clinical signs, as a result of increased exposure to other patients with CF in hospitals and clinics.[74] Because of this research phase, subsequent adjustment was made to screening and treatment protocols to minimize risk of infection. It may, then, be wise to undertake a research phase of screening for 22q11DS before adding the syndrome to the mandated panel for state-wide screening. Even if a formal research trial is not done, it would be important to make plans for assessing screening success after a period of time and reevaluating as needed.

RECOMMENDATIONS FOR FURTHER DATA AND DECISION MAKING

At this time, it is premature to add 22q11DS to any newborn screening panel. Although 22q11DS and other microdeletion syndromes were not considered in the deliberations of the American College of Medical Genetics (ACMG) Newborn Screening Expert Group[75] and thus were not subjected to the evaluation process by multiple experts and other stakeholders, it is evident that only a minority of 22q11DS patients meet traditional screening criteria of disease otherwise undetectable in the newborn period for which urgent treatment can prevent mortality or severe morbidity. If criteria similar to that used by the ACMG Newborn Screening Expert Group are applied to 22q11DS, it seems likely that the ranking would be similar to conditions such as Turner syndrome, Alpha-1-antitrypsin deficiency, and Fragile X for which medical, nutritional, and/or educational intervention during infancy may be beneficial but is

not fully corrective. None of these conditions were deemed appropriate for addition to the standard mandatory newborn screening panel.

An optional screen for 22q11DS could be considered. In states where optional screening through fee for service laboratories is already available for other disorders, screening for 22q11DS, if available at a reasonable cost, could be added. Where optional newborn screening is not currently available for other disorders, establishment of such a precedent would take time, and issues of consent, follow-up, and third party reimbursement would have to be addressed.

Because newborn screening may not be the best way to identify 22q11DS patients for early intervention, several other screening options could be considered. If timing problems cannot be resolved to identify cardiac problems early, screening at a few months old may allow parents to plan for their child's needs and prevent a diagnostic odyssey, while avoiding the bonding disruption that may occur from stress in the newborn period. This would be more difficult because there is not currently infrastructure in place for screening after birth, but it may become a more useful alternative as additional screening tests are proposed.

Implementing a 22q11DS screen for all children with recognized delays, but who are not yet diagnosed could also be useful. Alternatively, it may be possible to identify more cases of 22q11DS by lowering the index of suspicion at which genetics evaluation is pursued. For example, by routinely evaluating children with feeding problems, developmental delay, or other commonly associated features of 22q11DS, diagnosis may be made in a timelier manner. This is already recommended in certain cases of conotruncal heart disease[76] but not for other features of 22q11DS.

There are also many logistical issues to be addressed before adding 22q11DS to a newborn screening panel. Test characteristics need to be determined. Timing needs to be considered to determine whether babies with cardiac problems or hypocalcemia will be identified early enough for interventions to be most effective. Furthermore, accessibility to follow-up care, including genetic counseling and cardiac assessments, should be evaluated. The issue of possible identification of 22q11 duplication (or other incidental findings) needs to be addressed as well: to what extent will it be found, how will the cases be reported, and what follow-up would be indicated?

It is not clear that benefits of screening significantly outweigh the risks that would result from false positives and identification of mild cases. To better assess the use of screening, it may be prudent to undertake a research phase to ensure screening is logistically feasible, anticipated benefits are observed, and that no unforeseen harms result.

A major argument in favor of screening for 22q11DS is recognition of infants with cardiac defects, although alternative screens to identify cardiac defects could also be considered. For example, universal pulse oximetry may better identify babies who need cardiac interventions and would provide more equitable care by not only finding infants with chromosomal abnormalities. There may also be less expensive ways to improve physicians' ability to detect signs of cardiac disease.

Addition of 22q11DS would likely set a precedent for the addition of other chromosomal diseases. The current newborn screening criteria are vague and provide an inadequate guide for decisions about rapid expansion of newborn screening. It has been a few years since the ACMG Newborn Screening Expert group has convened,[75] and we recommend reconsidering the criteria for adding condition to make them more applicable to today's technology. In conjunction with a decision about adding 22q11DS, newborn screening guidelines should be reevaluated. Furthermore, many states have their own guidelines for newborn screening programs, and it would be wise to reevaluate them as well. Particular issues to be addressed include the role of nontraditional benefits when starting medical or nutritional therapy as an infant is not fully corrective, consideration of a tiered system to include optional conditions, ethical issues involving large-scale genetic testing, screening for disorders that are highly variable or not fully understood, and maintaining cost-effectiveness in expanded screening. Although newborn screening has historically been an effective public health program, the evolution in the past 40 years should be considered.

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