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Newborn Screening for Cystic Fibrosis: A Lesson in public health disparities

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Keywords

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Introduction

In the US, Newborn screening (NBS) for cystic fibrosis (CF) has rapidly expanded since the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children [1] voted to recommend to the Secretary of the Department of Health and Human Services the uniform NBS panel proposed by the American College of Medical Genetics (ACMG)/ Health Resources and Services Administration (HRSA) committee.[2] The decision to include CF as one of the 29 core conditions in the uniform panel was strengthened by data presented at a CDC workshop in 2003.[3] Whereas 11 states offered screening in 2002,[4] by January 2008, 34 states offer screening and another 7 require testing but have not yet implemented it.[5] In Europe, the UK, France, Italy, Spain, Austria, Poland and the Czech republic have newborn programs for CF either regionally or nationally [6] as does Australia and New Zealand.[7] The introduction of NBS for CF has been mired in debate focused on whether screening provides adequate clinical benefit[3,8–12] and whether these benefits outweigh the clinical and psychosocial risks of screening.[4,12–14] There has been less debate about how screening should take place,[15–18] particularly about how the different methodologies have different impact on different racial and ethnic communities.[19] This is of utmost importance because NBS is a universal screening program that is mandated in most US states. Unless the differential impact of the different CF screening methodologies on members of different racial and ethnic communities is considered, health care disparities may become entrenched, albeit unconsciously, into public health programs.

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Methodologies for newborn screening for CF

In the US, three different methodologies are used to screen for CF in newborns. In all programs, the first stage of screening entails measurement of immunoreactive trypsinogen (IRT) on dried blood spots.[20] An elevated IRT level indicates an increased risk of CF. In some states, the second stage involves a repeat IRT. If the repeat is elevated, the child is referred for a sweat test. In other states, the second stage involves a DNA test for CF mutations on the original blood spot.[21] Over 1000 CF mutations have been discovered,[22] and the genetic test may include as few as one mutation (delta F508) or several dozen.[4] Because many mutations are not included, children are referred for sweat tests if only one mutation is found or if the IRT is so high as to be suspicious. Some states do 3 stages including 2 IRT tests plus DNA analysis to minimize the number of children who need to undergo sweat testing. In Europe, 19 of the 26 programs incorporated DNA analysis, but at least one program only does one IRT and goes immediately to sweat test, and another program includes two IRT tests, DNA analysis and the measurement of meconium proteins.[6] Australia and New Zealand use an IRT/DNA approach with regional variability in the number of mutations included.[7]

When deciding between these methodologies, one must be cognizant that screening may lead to delayed diagnoses of those with a false negative result because many physicians are reassured by a negative screening test even though it is not meant to be diagnostic.[13,23,24] The impact of false negatives, then, may differ between racial and ethnic communities. CF is the most common genetic condition in non-Hispanic Caucasians with a frequency of approximately one in 3300.[25] The rate is similar in Ashkenazi Jews, although the mutations that account for the disease are different.[26] However, the frequency is much lower in other ethnic communities including Hispanics (1 in 8000–9500), African Americans (one in 15 300) and Asian Americans (1 in 32 100).[25] The decreased frequency means that the diagnosis may be delayed in these individuals both when no screening program exists [27] and when an infant screens negative [13] because physicians may seek other diagnoses to explain the clinical symptoms. Thus, it is important to ensure that the screening methodology has a low rate of false negatives, particularly in ethnic communities.

Pros and Cons of each method

IRT/IRT

There are advantages and disadvantages for each method of screening. All methods that include two IRT-tests require a second sample. Although this is easier in the 9 US states that routinely require a second sample,[28,29] it is more complicated in states that only require at risk children to return for a second test. Data reveal that when the second sample is not mandatory, many families do not return;[30] and for those families who do return, there is moderate anxiety.[30–32] In states that have mandatory second samples, reports indicate that they are also useful for detecting some endocrine conditions (like secondary hypothyroidism [33] and some cases of CAH[34]) and other inborn errors of metabolism.[35]

A screening test is not meant to be diagnostic and therefore will always have some “false positives”, regardless of methodology. All children who screen positive undergo a diagnostic sweat test. When the IRT/IRT method is used, many of the false positives will be children with perinatal asphyxia or other perinatal health problems.[36] On average, African American children have higher IRT than do Caucasian children even though they have a much lower risk for CF.[16,36,37] False positives, then, will be more common in African Americans. How to quantitatively calculate the harm is unclear although there are some data to show parental anxiety persists despite reassurance of a negative sweat test.[32,38,39]

Children with two elevated IRT measurements who have a negative sweat test are reassured that they do not have CF. Although there are data to show that the higher the IRT, the greater the risk of being a carrier,[40] unless counseling and education are provided, families may leave the sweat test unaware of their possible carrier status. There are no data regarding what percentage of families with a negative sweat test following an abnormal IRT/IRT screen receive genetic counseling or whether it is even recommended given the non-genetic methodology. Whether reproductive counseling of parents is or ought to be viewed as a component of NBS programs, and if so, whether it should be understood as a benefit or harm is controversial [41] and discussed in the next section.

IRT/DNA

Methods that include genetic testing can be done using a single sample. The controversy is the appropriate number of mutations to include in the genetic test. The answer depends in part on the heterogeneity of the population. The most common CF mutation is delta F508. It is found in 72% of the US Non-Hispanic Caucasian CF population, but in much lower percentages of patients with CF from other ethnicities (Hispanic Caucasian, 54%; African American, 44%; Asian American, 39%; Ashekenazi Jewish, 31%).[26] In 2001, the American College of Medical Genetics Cystic Fibrosis Carrier Screening Working Group recommended a panel of 25 mutations which would account for > 80% of CF alleles in the pan-ethnic US population with CF.[42] This panel was updated in 2004 based on a larger more pan-ethnic CF data-base that now finds 6 additional mutations with a frequency > 0.10% percent and another 14 that occurred at slightly lower frequency (.09-.01) but would be useful for specific ethnic minority communities.[26] Adding mutations will improve sensitivity but decrease specificity. The selection of mutation panels, then, is not a simple medical decision.

Under current IRT/DNA methodology, all children with an elevated IRT and one DNA mutation are advised to undergo a sweat test. Those who have a negative sweat test are reassured about this child's health. Genetic counseling should be provided because the child has been diagnosed as a carrier, and counseling can provide parents with information about their child's and their own reproductive risks.[43,44] Although the percentage of families that undergoes counseling varies widely between centers, the majority receive no counseling.[45,46] It is also the case that counseling leaves some parents with residual anxiety.[39,47]

Whether to include carrier detection and its potential use in reproductive planning as a benefit or harm of a NBS program is complex[31,48] because the empirical data to date show that a significant minority of parents whose children are diagnosed as carriers misunderstand recurrence risks despite counseling and this misunderstanding has reproductive implications. [44] It is also of questionable cost-effectiveness in an era in which most women and couples are offered prenatal testing for CF carrier status.[49] If the reduction of the number of children with CF is viewed as an economic gain, then the use of IRT/DNA and the identification of carriers and the option of cascade testing of parents and other relatives will be preferred. However, it is important to realize that the current methods do not seek to maximize the number of parent carriers detected as genetic testing is only done on children with elevated IRT. Carrier children (and possibly some affected children) with a normal IRT will be missed. Thus, if one wanted to detect all carriers, DNA testing would be performed on all specimens and not just those with an elevated IRT.

However, one can question the utility of carrier detection of infants for 3 different reasons: 1) antenatal screening is widely available [49] making carrier detection in newborns somewhat redundant; 2) the carrier detection of infants ignores the rights of parents not to know their own carrier status;[50,51] and 3) the disclosure of carrier detection of infants ignores the child's right to decide for him- or herself whether he or she wants this information as an adult,[52, 53] The identification of newborns as carriers is particularly problematic given the mandatory

nature of NBS in contrast with prenatal carrier programs that require a voluntary and informed consent.

If an IRT/DNA method is used, the number of carriers detected will depend on the number of mutations included in the screening test. The more mutations included, the more children will be identified with one common mutation. Some of these children will have a borderline sweat test. These children will be in limbo as they undergo further testing and re-testing. Even those with one common mutation and a negative sweat test are left with some residual uncertainty as they may be a compound heterozygote with a mild or even atypical phenotype.[54–56]

If an IRT/DNA method is used, the panel will need to include more rather than less mutations to avoid disproportionate number of missed screened cases (false negatives) in US ethnic minorities. In fact, to capture a high percentage of cases involving ethnic minorities might even require full sequencing of the cystic fibrosis transmembrane conductance regulator [CFTR] gene. Kammesheidt et al. have shown the feasibility of temporal temperature gradient electrophoresis-based full sequence analysis and targeted sequencing from DNA in newborn blood specimens which can increase the identification of mutations in ethnic minorities.[57] This method would permit a more comprehensive diagnosis on one blood sample because only children with two mutations and/or variants would need to undergo sweat testing. It should reduce the overall number of cases referred for sweat tests, unless questionable variants are more common than previously anticipated. However, it will identify individuals with one clear mutation and one questionable variant or even two questionable variants and they will need to undergo sweat testing and their parents will need counseling about their ambiguous risk status. Many families will be reassured by a negative sweat test,[57] but some will have equivocal sweat tests results and need to undergo repeat testing. Depending on whether full sequencing is done as a first step in screening or only in conjunction with an elevated IRT, the number of children who will need genetic counseling may increase significantly. Who will do the counseling and how it will be funded are unanswered given the shortage of genetic professionals and the lack of adequate reimbursement for their services.[58]

Finally, many programs that use an IRT/DNA methodology also recommend sweat testing on children with a very high IRT without mutations in an attempt to capture children who have rare mutations. This safeguard will reduce the number of false negatives.

IRT/DNA/IRT or IRT/IRT/DNA

There are two methods that use both DNA testing and 2 IRT measurements. The first method, IRT/DNA/IRT, applies a mutation panel to primary samples with an elevated IRT. Children whose sample has at least one mutation or whose sample has a very high initial IRT measurement are asked to provide a second sample for a second IRT measurement. Only those with an elevated IRT on the second sample undergo sweat testing. The second method, IRT/IRT/DNA, recalls all children with an elevated IRT and performs a second IRT. Mutation analysis is performed if the second IRT sample is elevated. Again, only those with at least one identified DNA mutation undergo sweat testing. Both the IRT/DNA/IRT and the IRT/IRT/DNA methods have the same goal: To reduce the number of sweat tests performed because they are costly and raise parental anxiety.

The IRT/DNA/IRT and IRT/IRT/DNA methods have the disadvantages of requiring two tests (as is true of all methods involving two IRT measurements) and of diagnosing parental carriers (as is true of all methods involving DNA genotyping). The main benefits of these methods over a single IRT/DNA methodology is that they reduce 1) the number of children who need to undergo sweat testing; and 2) the number of parents who are informed of their child’s carrier status and need genetic counseling. However, if one believes that carrier identification of newborns and their parents is a primary benefit of newborn screening, this method reduces the

benefit. By reducing the number of carrier families detected, the methodology may leave individuals with a false sense of security.

Because both methods involve DNA testing, they have the same problem as a single IRT/DNA in that they fail to detect ethnic minorities with rare mutations. Some ethnic minority children with rare mutations may still be detected to the extent that the IRT/IRT/DNA method employs the safeguard of recommending sweat testing of children with a very high IRT measurement even if no mutations are detected. Modeling in different ethnic communities using different DNA panels would be necessary to determine whether the costs of the extra laboratory testing are outweighed by the benefits achieved by reducing the number of children who need to undergo sweat testing and genetic counseling.

IRT/Pancreatic Associated Proteins [PAP]

There is an alternative methodology developed in France that uses the IRT/pancreatic associate protein [PAP] method.[59,60] IRT/PAP can be done on one sample and preliminary data show comparable sensitivity and specificity with the other methods using the Guthrie cards. However, to-date it has not been tested outside of Europe and its benefits and harms in a pan-ethnic community have not been clarified. Clearly, given the benefits and risks of the two current screening methods in the US, this method should at least be studied.

Economics of CF NBS

The costs of various NBS methodologies have been studied. Three cost-effectiveness studies from the USA and one from the UK in the 1990s all found that the cost per infant diagnosed was between $7000–$11 000 and that there was not much difference between the IRT/IRT and the various IRT/DNA methodologies.[31] However, as one increases the number of mutations for which screening is performed, the costs increase due to the increased number of false positives that are located and the number of additional sweat tests and genetic counseling sessions that are needed. The cost-benefit calculation for each testing methodology, then, will vary considerably but so will the number of missed diagnoses. A recent cost-effectiveness modeling exercise of four different neonatal CF screening protocols was conducted in 2006. The modelers found that the cost per life year ranged from 24 800 to 39 800 euros depending on which of 4 testing strategies (IRT/IRT; IRT/DNA; IRT-DNA-IRT; and IRT-DNA by denaturing gel electrophoresis] were utilized,[61] all of which are comparable or more cost-effective than many other public health screening programs.[62] And both US and UK studies find significant cost savings from NBS compared with clinical diagnosis, particularly if indirect cost savings are included.[63,64] Yet how these models account for false positives, false negatives and the diagnosis of mild phenotypes are controversial.

How then does one decide which methodology to use?

NBS is one of the largest and most successful public health initiatives of the past 40 years.[65] In 1968, Wilson and Jungner delineated 10 criteria that should be examined in determining whether a condition meets a public health program.[66] More recently, attempts have been made to modify these criteria and with the development of tandem mass spectrometry, some have argued that some of these criteria are no longer justifiable.[67,68]

The goals of public health programs are to reduce disease and premature death and disability in human populations. The emphasis is at the population level, and in this regard, the concept of social justice is integral to its structure and function.[69] NBS is a mandatory program in most states which helps to ensure universal access. Although there have been some NBS programs that began as programs targeted to particular racial/ethnic communities (e.g. hemoglobinopathy screening),[70,71] both concerns of justice and concerns of stigmatization

have led to a more universal approach with, not surprising, detection of hemoglobinopathies in a wider community than originally hypothesized.[72]

Given that the goal is for universal access, methodology matters. If one method of screening (IRT/DNA) is very effective in non-Hispanic Caucasians but not for ethnic minorities and another method (IRT/IRT) is better able to diagnose CF in all racial and ethnic communities, then it may be justifiable to use the second method even if 1) the frequency of the disease is less common in these racial and ethnic communities; and 2) the alternate screening method costs more or is more cumbersome. This is particularly true for a condition like CF which has historically been perceived as a "white child's illness". One concern of a screening program is that it will lead to complacency in physicians that a child with failure to thrive has had "CF" ruled out in the newborn screen.[13] Even though physicians must know that a screen is just a screen and will have false positives and false negatives, false positives may lead to unnecessary psychological distress during a particularly vulnerable period (the newborn period) [32] and false negatives may lead to delays in diagnosis.[13,73] How significant these harms will be depends on which methodology is used and the heterogeneity of the population. If an IRT/DNA methodology is used, the false negatives will most likely include a disproportionate number of minorities. If the result is a delay in diagnosis mainly for minority children, then the methodology may cause more disproportionate harm than realized.

The IRT/IRT has the advantage that it will not lead to a disproportionate number of missed cases in ethnic minorities. In fact, the opposite is the case in that there are more false positives in the African American community. As such, one must determine how many false positives can be justified to avoid a false negative. In a program like PKU, where a missed diagnosis is almost always devastating, the answer may be different than in CF, where the diagnosis of a child only after he or she has become symptomatic, although not ideal, does not necessarily produce permanent or irreversible harm. That is, the shift from NBS as a public health emergency to a public health service ought to influence how we think about false positives and false negatives and the evaluation of costs, benefits, and risks.[74]

The IRT/IRT has the disadvantage that unless a state has a mandatory second screen, children may not return for a second screen and this could lead to more missed cases, particularly in the vulnerable populations that lack adequate access to health care. A routine second screen would facilitate the use of the IRT/IRT method by obviating the need to recall families for a second IRT with its attendant anxieties. It would thereby allow states to achieve greater equity in public health goals than they could do by using other screening methods. Although the recommendation for routine second screens has been raised at numerous meetings of the Secretary's Advisory Committee,[1] there is currently no proposal for universal adoption. Given the value of a second screen for the use of the IRT/IRT methodology in CF screening, concerns about justice may be the catalyst for supporting mandatory second screens nationally.

Conclusion: Methodology Matters

Whether or not one believes that there are compelling data to justify NBS for CF, its inclusion in the uniform panel and its adoption by the Secretary's Advisory Committee have led to its adoption into the NBS panels in the majority of states. Like most public health screening programs, the decision about which method to use for CF NBS involves trade-offs between sensitivity and specificity, between cost and uptake. Mandatory screening ensures that it is provided to virtually all infants. We now need to make sure that the methodology achieves an equitable distribution of both the benefits (early diagnosis) and harms (false positives and false negatives), particularly within racial and ethnic minority populations. The IRT/PAP needs further study. Until clinical utility and validity of the IRT/PAP have been established, however,

IRT measured during 2 mandatory screens may be the preferred public health solution from a racial and ethnic equity perspective.

List of abbreviations

CF, cystic fibrosis; IRT, immunoreactive trypsinogen; NBS, newborn screening; PAP, pancreatic associate protein.

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