

Implementation of Cystic Fibrosis Newborn Screening in North Carolina

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Abstract

Cystic Fibrosis (CF) is one of the most common life-shortening genetic diseases in the United States, with an incidence of one in 2,500 (1), and a carrier frequency of one in 25. Newborn Screening for CF has been shown to improve the patient's nutritional status and growth, reduces hospitalizations, and decrease the risk of life-threatening complications or death. Due to these benefits and the recommendations of several organizations including the Center for Disease Control and Prevention (CDC) (2), the American College of Medical Genetics (ACMG), the March of Dimes and the North Carolina Newborn Screening Advisory Committee, we proposed to add CF to the state newborn screening panel.

This study project presents the development and implementation of CF Newborn Screening in North Carolina. The process includes seeking resources, writing a proposal, building partnerships with medical centers and community groups, preparing for implementation, implementing the test and evaluating the outcomes. The major funding comes from Medicaid reimbursement and the newborn screening fee, which has increased from \$14 to \$19 per newborn. Three new positions related to laboratory testing and two new positions related to follow-up have been requested. Due to the current budget crisis, two positions have been approved and posted, but the remaining three are still pending. After extensive research and discussions, a two-tiered testing algorithm using Immunoreactive trypsinogen (IRT) and DNA mutation assay was proposed. We have collaborated with Women's and Children's Health Section and three major medical centers in the state to establish the follow-up protocol. In addition, we also partnered with the CF Foundation, the March of Dimes, the North Carolina Medical Genetics Association (NCMGA) and other advocacy groups to promote CF testing.

To date, we have succeeded in obtaining the approval of state legislators in August 2008 and are in the stage of preparation for launching this important testing. CF Newborn Screening is scheduled to start early 2009.

During this project, I have interacted with or led a variety of individuals, including clinicians, parents, testing and follow up staff, and others. I have strengthened my leadership skills in facing changes, communication, collaboration, innovation and other areas of leadership. I ultimately wish to successfully implement this testing early next year.

Introduction

Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians occurring 1 in 2,500 births (1). It is estimated that as many as 36 newborns per year in North Carolina would be identified to have this disorder. CF usually manifests as progressive lung dysfunction, pancreatic insufficiency, and intestinal disease (3). It was originally thought that CF newborn screening had little or no benefit to CF patients. As more clinical data was accumulated and results indicated the benefits of screening, the CDC made the recommendation for CF screening in 2004 (2). It stated “The magnitude of the health benefits from screening of CF is sufficient that states should consider including routine newborn screening for CF in conjunction with systems to ensure access to high-quality care.” This recommendation was further supported by ACMG, the March of Dimes and the NC Newborn Screening Advisory Committee.

CF was traditionally diagnosed clinically, either because of a family history or occurrence of meconium ileus, or as a result of intestinal malabsorption and chronic pulmonary disease. In 1979, it was discovered that immunoreactive trypsinogen (IRT) was increased in neonatal dried-blood specimens on Guthrie cards (5), making it possible to screen neonates. The DNA- based genetic testing became available after the gene and protein for CF were discovered in 1989. Several countries in Europe, Australia, and Canada started to adopt CF newborn screening programs to identify CF patients after birth (5). As expected, many benefits have been observed due to the early identification of CF patients, including improved survival, better lung function and growth with less intensive therapy, and reduced cost of therapy. In March 2008, there are 42 states (4 and [Appendix 1](#)) in the United States which have adopted similar programs in the hopes of improving CF outcomes. Unfortunately, North Carolina is not one of them. To improve outcomes in the quality and quantity of life of CF patients in North Carolina, we have proposed to implement CF Newborn Screening.

Methods

The implementation plan will include the following steps: Forming the workgroup, writing the CF proposal and submitting for approval, contacting advocacy groups to help promote CF newborn screening, researching and evaluating methodologies, purchasing instruments and reagent kits, setting up Quality Assurance (QA) and Quality Control program, hiring and training testing and follow-up personnel, educating parents and health care providers (HCP) and evaluating the outcomes.

1. CF Newborn Screening Workgroup: A workgroup was assembled to determine the screening algorithms, diagnostic testing and follow-up protocol. The workgroup consists of the state newborn screening program staff, CF specialists, metabolic specialists, diagnostic testing specialists and parent representatives. The meetings were held in conjunction with the Newborn Screening Advisory Committee Meeting on January 25, May 16 and September 26, 2008. The agenda for these meetings are in [Appendix 2](#).
2. Cost analysis: The cost to perform the CF testing was calculated as the sum of estimated cost for instrument/reagent, personnel and Information Technology

(IT). The equipment/reagent cost was estimated based on the cost per test provided by the vendors. The IT cost was provided by the IT manager and the personnel cost was estimated from the mid-range salary of each salary grade for each position.

3. CF proposal: The CF proposal was written to include justifications for CF screening, cost, funding sources, and personnel requirements.
4. Methodology evaluations: The methodologies available for both IRT and DNA mutation analysis and their feasibilities were researched through literatures and consultation with directors from other state newborn screening laboratories. The vendors for reagent kits were contacted and the arrangements were made to perform the on site evaluation. An internal laboratory workgroup was assembled to plan and perform the methodology evaluations.
5. Purchase of equipment and reagent kits: According to the state regulations, purchase of equipment and reagents is subject to open bidding. The specifications for both IRT and DNA mutation analysis were written and sent to the Purchase & Contract Department for bidding.
6. Information Technology (IT): Manager was consulted regarding exporting data from instruments to the Laboratory Information Management System (LIMS) and adding CF results to the current result report.
7. Quality assurance (QA) and quality control (QC) program: The CDC Newborn Screening Quality Assurance Program (NSQAP) was contacted and the control materials were requested to set up the CF QA/QC program in the laboratory. The proficiency testing will be performed once we start the CF testing.
8. New positions: The job descriptions for the requested positions were written and submitted for approval. The positions were posted after obtaining approval from Budget Office and Human Resources Office.
9. Training: The on-site trainings for both IRT and DNA mutation analysis were set up in March and May. The off-site trainings which were sponsored by the Association for Public Health Laboratory (APHL) and National Newborn Screening and Genetics Resource Center (NNSGRC) were also arranged for May, August, and November 2009. The training for follow-up staff will be provided by CF Follow-up Workshop sponsored by APHL and NNSGRC.
10. Partner with community and advocacy groups: CDC, CF Foundation, March of Dimes and North Carolina Medical Genetics Association (NCMGA) were contacted to help promote the CF newborn screening.
11. Networking with other state CF newborn screening programs: In addition to the regular phone or e-mail communications, I attended a CF conference entitled

“Newborn Screening Issues and Answers Series: Cystic Fibrosis” sponsored by NNSGRC on January 16, 2008.

12. Follow-up protocol: CF specialists from the major medical centers across the state were consulted to establish the follow-up protocol.
13. Education of parents and health care providers (HCP): Information regarding CF newborn screening will be added to the existing NC Newborn Screening pamphlet to be distributed to the parents at prenatal clinics or hospitals. The education of the HCP was provided during the Education Section at the NC Pediatric Society Annual Meeting. Well-written educational materials from ACMG and Health Resources and Services Administration (HRSA) are also available for pediatricians. The pre-screening education for the parents and HCP will be in the form of a public service announcement. The announcement will be made shortly before starting CF NBS testing. The post-screening education for the parents and HCP will be provided by NBS follow-up staff, and/or genetic counselors when a positive CF screen result is notified.

Results and Discussion:

The CF NBS Workgroup was assembled to include those who will have operational responsibility for the local CF NBS program. In our workgroup, we included the state NBS laboratory staff, NBS coordinator from Women’s and Children’s Health Section, diagnostic testing specialists and all of the center directors of the CF clinical care programs in the state. It has become an information resource and the operational arm of NC NBS Advisory Committee. After several meetings and discussions, it was agreed that a two-tiered testing algorithm should be performed: an initial IRT test followed by DNA mutation analysis. The diagnosis will be made by performing sweat testing. The proposed testing algorithm, diagnostic testing and the follow-up protocol are illustrated in [Appendix 3 and 4](#). It is proposed that all newborns (~135,732) would be tested for IRT and the top 5% of newborns (~6,787) with elevated IRT would then be tested for DNA mutation. Newborns with one or two mutations or with ultra-high IRT ($\geq 99.9\%$), which is considered presumptive positive, will be subject to sweat testing to confirm if they have CF (Appendix 3). The certified sites for sweat testing across the state are also identified, including the CF Centers at University of North Carolina at Chapel Hill, Duke University, Wake Forest University and two satellite sites in Charlotte and Asheville. A future satellite site may be set up in Greenville or Wilmington.

The number of newborns with abnormal newborn screening results, confirmed carrier and CF were estimated based on the experiences of other state newborn screening programs. It is estimated that there will be about 699 infants per year with abnormal screens that require sweat testing. Among these, about 529 newborns will be carriers and 36 will be identified as having CF (Appendix 3 and 4). It is important to predict these numbers as this information allows the follow-up staff and CF centers to plan for proper

staffing to accommodate the increase in the workload and avoid overloading resources in the system.

CF Newborn Screening is not just performing the screen to identify the infants with abnormal results. It is beneficial only if infants identified by the screen receive a prompt diagnosis and treatment. When the infants are identified as having abnormal screening results (one or two mutations or with ultra high IRT), the laboratory staff will notify the CF follow-up staff immediately. The follow-up staff will in turn contact the HCP and CF center to arrange the sweat testing and genetic counseling ([Appendix 4](#)). The follow-up staff is responsible for tracking the infant to assure compliance with the recommendation for evaluation and to document the diagnostic outcome.

After consulting with upper managers and financial officers, it was determined that the major funding for CF testing would come from Medicaid reimbursement and the newborn screening fee. The cost to perform CF testing was estimated to be \$767,481 per year; \$517,458 would come from Medicaid reimbursement. The estimated Medicaid reimbursement was calculated based on 21% of newborns screened claiming Medicaid reimbursement and the amount of reimbursement for each CPT (Current Procedural Terminology) code. The remaining would come from the newborn screening fee. The newborn screening fee has thus increased from \$14 to \$19 per newborn.

CF Newborn Screening proposal ([Appendix 5](#)) includes the justifications for adopting CF testing, detailed resources, numbers of positions required and salary grade for each position. The organizational charts ([Appendix 6](#)) indicating the relationship between these positions and the organization are also attached. Three technical positions are requested: one medical technologist II position (salary grade 70), one medical specialist (salary grade 73) and one newborn screening laboratory consultant (salary grade 73). Two follow-up positions (salary grade 71) were requested in a separate proposal submitted by the Children and Youth Branch of Women's and Children's Health Section. The job description for these positions were written and submitted for approval. Two positions for testing personnel were recently approved and posted. The laboratory consultant position and two follow-up positions are still pending due to hiring freezes.

To expedite the laboratory process, an internal laboratory group from the existing workforce was established to plan and perform method evaluations. There is only one commercial source for IRT reagent kits. The method evaluation for IRT was completed in March 2008. Two commercial sources were available for DNA mutation kits. One of these companies was contacted and method evaluation was completed in May 2008. The other one was not available for on-site testing; however, it was available for method evaluation at CF workshop sponsored by APHL and NNSGRC in May and August 2008.

The decision to use reagent rental rather than purchasing equipment has great advantage, since it enables us to quickly adopt new technology should it become available. According to the state regulations, this has to be subject to open bidding. The specifications were written and sent to Purchase & Contract Department for bidding.

The CDC Newborn Screening Quality Assurance Program (NSQAP) of CDC was contacted. The control materials were requested to set up the CF QA/QC program. The proficiency testing will be performed once we start the CF testing.

The on-site training for testing personnel has been completed and two staff members have completed the off-site training sponsored by APHL and NNSGRC (May and August 2008). One will attend the workshop in November 2008. The training for follow-up staff will be arranged once the new follow-up staff members are on board.

To promote CF newborn screening, we have partnered with the federal government, community and advocacy groups including CDC, CF Foundation, March of Dimes and North Carolina Medical Genetics Association (NCMGA). As a result of these partnerships, Dr. Philip M. Farrell, a well-known Cystic Fibrosis specialist from the University of Wisconsin, was invited to come to North Carolina and made a presentation at the University of North Carolina (UNC) Hospitals and NC Newborn Screening Advisory Committee Meeting in May 2008 ([Appendix 2](#)). I have made a presentation at NCMGA Spring Meeting at Asheville, NC ([Appendix 7](#)). The March of Dimes and the NC Perinatal Association set June 3, 2008 as Advocacy Day to support adding Cystic Fibrosis to the Newborn Screening Panel. The package that the March and Dimes distributed to its members is shown in [Appendix 8](#). The package included the fact sheet, advocacy day flyer, and directions to the state legislative building.

To learn from the experiences of their implementation of CF screening, I have consulted with colleagues at other state CF newborn screening programs. It has been very beneficial to our decision making. In addition, I attended the "Newborn Screening Issues and Answers Series: Cystic Fibrosis" in January. This meeting not only provided me the opportunity to strengthen my knowledge about CF, but more importantly it provided me the opportunities to network with my colleagues at other states and the CF specialists across the US.

To date, we have completed most of the work initially required. Unfinished tasks include purchasing equipment and reagent kits, hiring, and IT work. The severe departmental budget cuts have some impact on our progress. Justifications of purchases and hiring may cause some delay in our schedule. Two technical positions have been posted and the closing date will be November 4, 2008; but the laboratory consultant position is still pending. Adding CF results to the existing result report has not been completed due to the delay in implementation of the new LIMS system.

As we struggle to cover all aspects of CF newborn screening, there are still questions remaining. These questions include whether there are enough genetic counselors to handle the caseload and whether health care personnel will have adequate time or training to convey the necessary information to the parents, especially for newborns with abnormal results or complicated mutation profiles.

After we start the CF NBS program, I feel there will be an opportunity and responsibility to conduct research to improve treatment and outcomes. NBS and early

diagnosis may be able to accelerate the adoption of new treatment for infants with CF, because CF Newborn Screening creates an opportunity to define a specific cohort from early in life for entry into clinical trials. In addition to clinical research, there must be continual evaluation of outcomes resulting from the initiation of CF NBS. Outcome measures for laboratory testing, diagnostic testing, follow-up, genetic counseling and patient care must be established. The outcome measures may include measures such as proportion of newborns having CF NBS screening, false positive and false negative rate for laboratory testing, proportion of sweat tests performed at accredited clinical laboratory, changes in numbers of sweat tests conducted annually before and after implementation of state CF NBS, number of inconclusive sweat tests, proportion of families of infants diagnosed with CF receiving genetic counseling, proportion of diagnosed infants followed at CF Foundation-accredited care centers, outpatient visit frequency, inpatient hospitalization frequency and others.

It is important to ensure that all necessary guidelines and resources for screening, follow-up, diagnosis, and care be in place prior to CF newborn screening implementation. All parties involved have to be working together to achieve this goal (6). So far, the NBS program and CF care centers staff seem to work well together. Continued cooperation among these groups should ensure the implementation of a successful program.

I am very fortunate to have my mentor, Dr. Leslie Wolf, who is involved in every aspect of this project. In the early stages of the project, I met with her to discuss the planning of this project and she has reviewed all documents, including my project proposal, CF proposal and job descriptions, and participated in most meetings and gave advice at each step of this project. During the budget crisis, she has helped prepare the justifications for the positions. She is also going to review the final project and evaluate the progress of this project.

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Leadership Development

This project has offered me opportunities to practice the leadership skills in the following aspects:

Organization and planning:

I have organized the internal laboratory workgroup and workgroup meetings. We have set the timelines for each step of preparing for implementation of CF testing in the laboratory. I have also organized the external CF workgroup which includes CF specialists, diagnostic specialists, advocacy groups, parents and the newborn screening staff. To bring such a diverse group to a meeting was not an easy task; however, it has given me the opportunity to enhance my organization and planning skill.

Chair the meetings:

I usually chair the internal staff meetings, but not a diverse workgroup meeting like CF Workgroup meetings. This project gave me an opportunity to chair diverse workgroup meetings and stay focused on our agenda.

Presentations:

With this project, I had a lot of opportunities to make presentations at workgroup meetings. I also had the opportunity to present at the NCMGA meeting and have received very positive remarks from the audience. These practices have sharpened my presentation skills. I have also learned to make my power point slides more effective for presentations.

Building the partnership with other organizations, especially advocacy groups:

This is probably the most important benefit that I gained from this project. As a laboratory manager, I have very limited opportunity to work with the community, especially advocacy groups. This project provides me the opportunities to work with diverse groups and I have enjoyed the results of the networking.

