A Decision-Tree Approach to Cost Comparison of Newborn Screening Strategies for Cystic Fibrosis

AUTHORS: Janelle Wells, MD, MPH,^a Marjorie Rosenberg, PhD, FSA,^{b,c} Gary Hoffman, BS,^d Michael Anstead, MD,^e and Philip M. Farrell, MD, PhD^{a,f}

Departments of ^aPopulation Health Sciences, ^bBiostatistics and Medical Informatics, and ^cPediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin;

^bWisconsin School of Business, University of Wisconsin, Madison, Wisconsin; ^dWisconsin State Laboratory of Hygiene, Madison, Wisconsin; and ^eDepartment of Pediatrics, University of Kentucky College of Medicine, Lexington, Kentucky

KEY WORDS

cystic fibrosis, immunoreactive trypsinogen, DNA, newborn screening, costs, sensitivity

ABBREVIATIONS

CF—cystic fibrosis

CFTR—cystic fibrosis transmembrane conductance regulator

IRT—immunoreactive trypsinogen

NBS—newborn screening

All authors meet the following criteria for authorship: (1) they have all substantially contributed to conception and design, acquisition of data, or analysis and interpretation of data; (2) they all participated in drafting the article and/or revising it critically for important intellectual content; and (3) they all gave the corresponding author approval of the final version submitted for publication. Thus, Dr Wells, Dr Rosenberg, Mr Hoffman, Dr Anstead, and Dr Farrell have all made substantive intellectual contributions to the study. In addition, they will all approve the version to be published.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0096

doi:10.1542/peds.2011-0096

Accepted for publication Oct 7, 2011

Address correspondence to Philip M. Farrell, MD, PhD, University of Wisconsin School of Medicine and Public Health, WARF Building, Room No. 785, 610 Walnut St, Madison, WI 53706. E-mail: pmfarrell@wisc.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Funded by the National Institutes of Health (NIH).

WHAT'S KNOWN ON THIS SUBJECT: Although it has been shown that cystic fibrosis newborn screening is beneficial, the strategies vary widely, and there has been uncertainty about the costs and consequences of different algorithms and whether screening methods/decisions should be based on assumed cost differences.

WHAT THIS STUDY ADDS: This study contributes by offering a comparison of both costs, assessed comprehensively, and the consequences associated with the 2 most popular screening methodologies, immunoreactive trypsinogen/immunoreactive trypsinogen and immunoreactive trypsinogen/DNA, by using a decision-tree framework allowing variation in the model parameters.

abstract

OBJECTIVES: Because cystic fibrosis can be difficult to diagnose and treat early, newborn screening programs have rapidly developed nationwide but methods vary widely. We therefore investigated the costs and consequences or specific outcomes of the 2 most commonly used methods.

METHODS: With available data on screening and follow-up, we used a simulation approach with decision trees to compare immunoreactive trypsinogen (IRT) screening followed by a second IRT test against an IRT/DNA analysis. By using a Monte Carlo simulation program, variation in the model parameters for counts at various nodes of the decision trees, as well as for costs, are included and applied to fictional cohorts of 100 000 newborns. The outcome measures included the numbers of newborns given a diagnosis of cystic fibrosis and costs of screening strategy at each branch and cost per newborn.

RESULTS: Simulations revealed a substantial number of potential missed diagnoses for the IRT/IRT system versus IRT/DNA. Although the IRT/IRT strategy with commonly used cutoff values offers an average overall cost savings of \$2.30 per newborn, a breakdown of costs by societal segments demonstrated higher out-of-pocket costs for families. Two potential system failures causing delayed diagnoses were identified relating to the screening protocols and the follow-up system.

CONCLUSIONS: The IRT/IRT screening algorithm reduces the costs to laboratories and insurance companies but has more system failures. IRT/DNA offers other advantages, including fewer delayed diagnoses and lower out-of-pocket costs to families. *Pediatrics* 2012;129:e339–e347

Cystic fibrosis (CF) is a relatively common, life-threatening, autosomal recessive disease that can now be diagnosed routinely through newborn screening (NBS) by using immunoreactive trypsinogen (IRT)¹ as the primary analyte or first tier. After both the Centers for Disease Control and Prevention² and CF Foundation³ endorsed universal adoption of CF screening, it was included in the list of 29 core disorders recommended by the Health Resources and Services Administration for all state NBS programs.⁴ Thus, by 2010 all states plus DC were screening for CF. With nationwide CF NBS underway, the research climate shifted from one focused on identifying the benefits of screening to one focused on identifying the best screening methodology.^{5–7} Although wide variations in screening methods and cutoff values currently exist throughout the United States and across the world,^{6,8} almost all algorithms begin by evaluating IRT¹ levels by using a dried blood specimen collected between 1 and 5 days of age with the second tier being either a second IRT or DNA analysis for CF transmembrane conductance regulator (*CFTR*) mutations.⁹ Further testing and referrals are then made based on the particular screening method in use by the state. More specifically, the US screening protocols being used in 2010 were as follows: IRT/IRT in 15 states plus DC and IRT/DNA in 33 states; in addition, there is a recent variation of IRT/DNA, namely IRT/IRT/DNA (Colorado, Texas, and Utah). The IRT/IRT and IRT/IRT/DNA algorithms require collection of a second blood specimen to confirm hypertrypsinogenemia, whereas the IRT/DNA algorithms allow completion of the screening on a single/initial blood NBS specimen.

NBS programs have chosen their screening methods based on limited information regarding the impact their choice of method can have on costs and consequences.^{10–12} In the IRT/IRT algorithm,

there have been wide variations in definitions of the level at which an IRT screen is considered “abnormal” and in the processes for follow-up evaluation. For those states using IRT/DNA analyses, the IRT cutoff values are much lower and more consistent, but choices must be made as to the number and types of *CFTR* mutations identified in the second tier of the screening test. Further research of these protocols and their many variations is urgently needed to aid in identification of the best screening strategy. An important issue relates to whether decisions to use IRT/IRT or IRT/DNA screening should be based predominately on assumed cost differences. This study contributes to the current research by offering a comparison of the costs and consequences, or outcomes, associated with the 2 most popular screening methodologies in the United States by using a decision-tree framework that allows for variation in the model parameters. A

decision tree visually shows the process of the path a newborn may follow under a screening program. Average assumptions, in terms of rates, are shown for moving along a path, and costs at each point of the process are determined. These results can then be summarized to evaluate the effectiveness of a screening program.

METHODS

Data for Decision Tree Analyses

Baseline costs for this study consisted of the (1) expenses of screening laboratories, (2) costs borne by families, and (3) costs usually covered by insurance (Table 1). The costs to the screening laboratory obtained from the Wisconsin State Laboratory of Hygiene included building costs, laboratory equipment, reagents, personnel, administration, shipping/postage, maintenance, and overhead. Sweat test costs were based on those reported previously.¹⁰

TABLE 1 Cost Data for Components of CF NBS^a

Group	Type of Expense	IRT/IRT		IRT/DNA	
		Cost per newborn	% of total	Cost per newborn	% of total
State laboratory	IRT equipment and maintenance	0.39	8.6	0.39	5.8
	IRT reagent	1.57	34.4	1.57	23.2
	DNA reagent	—	0.0	1.64	2.41
	Laboratory personnel (laboratory technician, administration, and data entry)	0.88	19.3	1.39	20.5
	Shipping postage and consumables	0.68	14.8	0.68	10.0
	Capital expense	0.08	1.7	0.08	1.1
	Building and interdepartmental expenses	0.04	0.8	0.06	0.9
	Travel for second DBS	0.12	2.7	—	0.0
	Work missed for second DBS	0.05	1.1	—	0.0
Family	Blood draw fee for second DBS	0.09	2.1	—	0.0
	Genetic counseling	—	0.0	0.04	0.6
	Travel for sweat tests	0.04	1.0	0.10	1.4
	Work missed for sweat tests	0.05	1.0	0.10	1.5
	Sweat tests	0.30	6.5	0.66	9.7
Insurance	Missed diagnoses	0.27	6.0	0.08	1.1
	Total cost per newborn	4.57	100	6.79	100

^a Family costs from the Kentucky survey of 26 families with abnormal initial IRT screens included the costs of the second dried blood specimen collection (out-of-pocket laboratory fee for blood collection, travel, and work missed) and travel and work missed for the sweat test. Out-of-pocket family expenses for the second dried blood specimen collection were obtained from the University of Kentucky, where a survey of 26 families with abnormal initial IRT screens was conducted. Answers were obtained from all families regarding round-trip mileage, fees paid to the laboratory for collection of the second blood specimen, and the average hours of work missed. Information on sweat test travel costs and work missed were obtained through data collected during the Wisconsin randomized controlled trial.^{37,49} DBS, dried blood specimen. Empty cells indicate that data are not available because the expense type does not apply to that method.

Genetic counseling costs were based on publicly reported Wisconsin salary data, in addition to CF center expert opinion of the time required to counsel parents of infants who are identified as carriers of CF. The data obtained from the Wisconsin State Laboratory of Hygiene were used to calculate screening test costs of IRT/DNA and IRT/IRT. Family costs from the Kentucky CF center survey of 26 families with abnormal initial IRT screens included the costs of the second dried blood specimen collection (out-of-pocket laboratory fee for blood collection, travel, and work missed) and travel and work missed for the sweat test. The cost for missed diagnoses were based on the UK study of Sims et al^{13,14} by using their conversion method (\$1.69/£) to US dollars. For our analyses and decision trees, we updated all costs to \$2010 US.

Decision trees were constructed^{15–17} for the IRT/IRT and IRT/DNA methods to compute the total cost for a variety of outcomes, either dependent or independent on the sensitivity/specificity of the particular screening test, and were based on data obtained from screening laboratories, the University of Wisconsin Hospitals, and published data.^{18–36} The decision-trees contain nodes, or decision-points, where the process is diverted along different paths. For our analyses, 100 000 newborns started the process and at each node or branch these newborns were followed with the aid of the decision trees. We assumed CF incidence in the US population was 1 in 4000 newborns^{5,6,18} and expected that 25 newborns of the 100 000 would have CF, with 5 newborns predicted to have meconium ileus³⁷ and who immediately would be given a diagnosis without NBS; thus, they were removed from the decision trees before initiation of the screening processes. Although some recent surveys suggest the possibility that prenatal screening may reduce the incidence of

CF,^{19–21} other observations have not confirmed this effect, and many reports provide a rationale for using 1:4000^{22–24}; in fact, regions with a higher incidence such as the Republic of Ireland and the UK (with ~1:1500–2500)^{24,25} can still use the decision trees provided herein by simply adjusting the second branches.

The decision tree used for the IRT/IRT method (Fig 1) was based on the currently most common screening process²⁷ in which the threshold levels for identifying abnormal screens were set at 105 ng/mL and 70 ng/mL for the first and second IRT levels, respectively. Based on a large database analysis in a state with ongoing CF surveillance,³⁷ a survey, and reviewing the literature, Kloosterboer et al (2009)⁶ reported an average sensitivity of 80% for an initial IRT cutoff level of 105 ng/mL. For the current study, to assess sensitivity further, we reviewed all the CF NBS articles available through PubMed, focusing on those with CF false negative screening test results,^{28–35} and determined from worldwide reports^{28,32} that a 78% to 85% range of sensitivity has been observed; then we took into account data presented at a recent conference (Evaluation of IRT as a Biomarker for Cystic Fibrosis: Methodological Issues and Practical Challenges for Newborn Screening; May 23–24, 2011) and concluded that 80% is a reasonable value to apply in the decision tree, despite a claim of higher sensitivity.²⁶

In addition, reports from Colorado describe significant loss to follow-up at the second stage of the IRT/IRT method related to collection of the second dried blood specimen depending on the presence (2% loss) or absence (20% loss) of a state-mandated second dried blood specimen collection.^{26,27} Surveys of current IRT/IRT screening programs by 1 of the authors (Dr Farrell) have revealed that none of them claim 100% return of the second dried blood specimen and that the range observed

is 2% to 16% failure to complete IRT follow-up procedures (because of a variety of causes such as the inability to contact the family due to relocation, name changes, lack of cooperation, or even death of the infant). Consequently, for the purposes of our simulation, we used an estimated loss to follow-up average of 10%. Although the percentage of infants with a second IRT above 70 ng/mL has not specifically been reported in the literature, based on expert opinion and mathematical deduction,⁶ we estimated that 12.25% of infants with an initially high IRT will have a second high IRT based on expert opinions and mathematical deduction. Infants with a second high IRT are referred for a sweat test for diagnostic evaluation, but this step generally requires a referral, which provides another area for loss to follow-up and delayed diagnosis. From Wisconsin⁶ and Massachusetts²³ data, we assumed that 5% of infants would be lost at this step.

For the IRT/DNA method, we based the process on the method used in Wisconsin, which has been applied in 32 states, by using both published^{5,6,10,11,37} and some unpublished data available from that program. In the decision tree we created, the newborns were selected for 23 *CFTR* mutation DNA analyses²² by a cutoff for the initial IRT based on the daily 96th percentile. Kloosterboer et al (2009)⁶ reported a sensitivity of 96% with the use of a daily top 4% IRT floating cutoff. Other programs^{22,33} have a similar sensitivity and also report^{30,32} a substantially higher sensitivity for IRT/DNA compared with IRT/IRT. In addition, according to data reported from Wisconsin from 2002 to 2003, 93.9% of infants receiving a mutation analysis have no mutations, whereas 4.6% show 1 *CFTR* mutation, and 0.3% 2 mutations.³⁸ Predicted percentages of children with 1 or 2 mutations who experienced a true negative diagnosis, delayed diagnosis (due to a loss to follow-up), or early

FIGURE 1

IRT/IRT decision tree. For the IRT/IRT method, newborns were divided between those with an IRT level above or below a defined cutoff value. If the IRT value for the newborn is below the cutoff value, then the newborn either has CF or not, with the former group defined as a “missed diagnosis.” For those newborns above the cutoff level, a repeat IRT was needed. As described in the Methods section, an estimated 10% of newborns were “lost to follow-up” and were classified as having CF or not. For those newborns having a repeat IRT, the results distribute into 1 of 3 categories: (a) low IRT, (b) high IRT, or (c) delayed second blood sample. For either the low IRT or delayed second blood sample categories, the newborn classified as either not having CF or as a missed diagnosis. The outcome of the simulation demonstrated that up to 50% of screened infants with CF may experience either a delay in diagnosis or a false negative result. The simulation also demonstrated that second-tier testing is requested in 600 of the 100 000 infants initially screened; assuming a 10% loss to follow-up for this step, 540 of these second-level tests would be completed. Further diagnostic testing via sweat tests would be requested in 66 infants, of which 63 will be completed.

diagnosis of CF were also obtained from numbers published from Rock et al (2005)³⁸ and again a 5% loss was assumed for sweat tests.

Simulation Model

We conducted a 2-part computer-based simulation of 100 000 newborns screened with the IRT/IRT and

IRT/DNA protocols shown in Figs 1 and 2, respectively. The first part of the model simulated the flow of the newborns through the decision-tree, whereas the second part attributed costs for each newborn at each branch of the tree. Part 1 of the decision tree model provided a complete analysis of the system design of each screening method and

allowed for identification of specific system errors that create opportunities for delayed or missed diagnoses. Part 2 of the simulation applied a cost simulation framework to the decision tree simulation, resulting in projected societal costs of the IRT/IRT and IRT/DNA systems.

From the literature^{18–36} or from our data,⁶ we identified the percentages of

FIGURE 2

IRT/DNA decision tree. For the IRT/DNA method, we based the process on the method used in Wisconsin, which has been applied in 32 states, by using both published and unpublished data available from that program. The newborns were divided by a cutoff for the initial IRT based on the daily 96th percentile. Infants with IRT values below the cutoff value were missed diagnoses or would not have CF. Those newborns with IRT values above the cutoff would have a DNA mutation analysis. A sensitivity of 96% with the use of a daily top 4% IRT floating cutoff was applied from data in the literature^{5,6,8} and it was assumed from other data²³ that 93.9% of infants receiving a DNA analysis have no mutations, whereas 4.6% show 1 *CFTR* mutation, and 0.3% 2 mutations. If the test revealed no mutations, the newborn was classified as either not having CF or missed. If the test showed 2 mutations, the newborn was classified as having CF and either diagnosed through early screening or missed. The final step of the IRT/DNA screening system led to sweat test referrals for all infants with 1 mutation. Consistent with data from Massachusetts, which was also used in the IRT/IRT decision tree, 95% of infants completed a sweat test.²¹ Outcomes for this part of the tree include diagnosis through early screening, missed diagnosis, or identifying CF carriers. Note that 17 of the 20 infants with CF were given a diagnosis with no delays or false negative results, resulting in 15% of the affected infants categorized as a potential missed diagnosis. DNA mutation analyses were completed in 100%, or 3999 infants, where 185 were found to have 1 mutation and were referred for a diagnostic sweat test; 175 (95%) were expected to complete the sweat test and 169 of these would be negative.

newborns who move from 1 node to another for part 1, whereas for part 2 we have the costs at each node. To allow for recognition that there may be variation of these values, we simulate a value for the percentages and the costs. For each run of the simulation, percentages and costs per newborn

were generated on average, equal to the numbers that we gleaned from the literature or our own data. Then the outcomes from each run were combined to report as results. Thus, the method has a built-in sensitivity analysis by taking into account that the original estimates are variable.

RESULTS

System Design and Outcome Simulations

The results from the IRT/IRT and IRT/DNA decision tree simulations showing the average counts are presented in Figs 1 and 2. Table 2 shows a summary of the

TABLE 2 Summary of Simulation Counts

	IRT/IRT		IRT/DNA	
	Average	Interquartile range	Average	Interquartile range
No. CF diagnosed	10.1	7.8–11.9	17.1	14.3–19.6
No. CF undiagnosed	10	7.7–11.9	2.9	1.7–3.7
Protocol definition error	6.6	4.7–8.1	2.0	1.6–2.6
Follow-up system error	3.4	2.1–4.4	0.9	0.4–1.2

numbers of newborns given a diagnosis by protocol, number of newborns not given a diagnosis by the screening protocol, and the 2 categories of errors. In addition, we provide the interquartile range (25th to 75th percentiles) to indicate the variation of the counts.

Analysis of the “potential missed diagnosis” category in both protocols was conducted to identify particular failures of the system design that might result in a delayed or missed diagnosis, and 2 significant issues were identified: (1) failure of the protocol definition and (2) errors in the follow-up system (particularly losses to follow-up, as shown in the decision trees). In the case of IRT/IRT screening, this is exemplified by the relatively low sensitivity resulting from high cutoff levels used for identifying abnormal IRT screens. In the case of IRT/DNA, this is exemplified both through the reduced sensitivity of the IRT screen and the decrease in sensitivity caused by not testing for all possible *CFTR* mutations. Protocol definition failures accounted for the largest percentage of potential misses with 6.6 (66% of undiagnosed) potential missed diagnoses in the IRT/IRT system and 2.0 (69% of undiagnosed) potential misses in the IRT/DNA system.

Cost Simulation

An overview of the results for the cost simulations are presented in Table 3. With a starting cohort of 100 000, the total cost of the IRT/IRT is projected as \$4.57 per newborn (interquartile prediction interval of \$4.43–\$4.71), equating to a total cost of ~\$457 000 for a cohort of 100 000 newborns. The largest contributors to the cost of the IRT/IRT program, accounting for nearly half of the total costs, include the IRT reagents (35%) and the collection of the second dried blood specimen (12%). The projected cost of the IRT/DNA program, on the other hand, is greater than the cost of the IRT/IRT program by \$2.31 per infant, with a total cost of \$6.78 per infant (interquartile prediction interval of \$6.60–\$6.96). The largest proportion of these costs is attributable to the IRT reagents, DNA reagents, and laboratory personnel.

Costs were also assessed according to payer source, defined as laboratory costs, family/individual costs, and insurance, to allow for further analysis of each screening system. Overall, the IRT/IRT program offered substantial cost savings for state laboratories and insurance as compared with IRT/DNA, while creating higher costs for individuals and

families. Average costs for running the laboratory portion of the IRT/IRT and IRT/DNA program were equal to \$3.63 per newborn and \$5.85, respectively. In terms of costs covered by insurance, IRT/IRT offered the higher cost savings, with a cost of \$0.57 per newborn, compared with \$0.73 per newborn. Finally, the cost to families of infants with an abnormal screen was lowest with the IRT/DNA strategy, totaling \$20 000 per year. The total family costs of the IRT/IRT program were nearly double that of IRT/DNA, with an average expense of ~\$36 000 per year. The IRT/IRT screening cost per diagnosis is equal to \$45 400, compared with \$39 700 per diagnosis in the IRT/DNA system.

DISCUSSION

This study of screening and diagnostic costs is 1 aspect of the global question on the cost effectiveness of CF NBS, whereas the care costs are still being investigated with utilization data that should allow us to reach conclusions about overall cost effectiveness. This comprehensive assessment of costs for diagnosis adds to the literature through novel inclusion of all procedures such as (1) the costs of procuring the second blood specimen in IRT/IRT; (2) costs for genetic counseling with IRT/DNA; (3) the outcomes associated with “loss to follow-up” and other flaws in the designs of both screening systems; (4) costs associated with missed diagnoses; (5) the overall costs of the screening program to various segments, such as the costs to families, insurers, and screening laboratories; and (6) creating more robust results by allowing the components of the model to have variability and showing a range of outcome values. Overall, results from the simulations demonstrated that the IRT/IRT system offers substantial cost savings as compared with IRT/DNA but has the potential to miss or delay diagnosis for up to 50% of all infants given a diagnosis of CF

TABLE 3 Summary of Costs by Category

Cost Type	IRT/IRT		IRT/DNA	
	Average	Interquartile range	Average	Interquartile range
Total	457	443–471	678	660–696
State laboratory	364	352–375	585	568–601
Insurance	57	50–63	73.0	67–79
Family	36	34–38	20	19–21
Undiagnosed ^a	28	21–33	8	5–10

^a Undiagnosed includes some insurance costs and some family costs.

through screening annually as compared with 15% for the IRT/DNA system. As such, the IRT/DNA system cost per diagnosis is 14% lower than the IRT/IRT cost per diagnosis. Thus, the decision trees provide a visual process to examine costs at each stage of the screening program and could be used to help in a systematic evaluation of the effectiveness of laboratory costs.

Because early diagnosis of CF, before 1 to 2 months of age,^{14,39} is the key reason for screening, it is crucially important for NBS programs to consider both expected outcomes^{40–46} and costs. Three publications from the United States have assessed the costs of the IRT/DNA method and the individual cost of IRT,^{10,11,16} but none of these studies included the cost of health effects or offered a comparison with other screening methods. The authors of another publication from the United Kingdom assessed the cost-effectiveness of IRT/DNA compared with no screening but did not offer a comparison with other screening methodologies.¹⁴ Finally, the authors of 1 comprehensive study from the Netherlands conducted a thorough assessment of the cost-effectiveness of 4 screening methodologies but did not account for problems with loss to follow-up in either system, nor did they offer a critique of the overall system designs with a discussion of possible solutions to correct flaws in each system.¹² In addition, the Netherlands study did not take into account the possible cost consequences of lowering the initial IRT cutoff levels in the IRT/IRT system to avoid false negatives.^{6,26}

There are some limitations to our study and also some other “hidden” costs in both screening methods that are currently difficult to define with precision. It should be pointed out that some sweat tests need to be repeated because of insufficient quantities of sweat; in fact, up to 10% can be assumed,⁴⁷ which adds \$4029 (at \$237 per sweat test) plus

\$1700 (at \$103 per sweat test) for family travel and work costs assuming a cohort of 100 000 newborns. In addition, many states that employ IRT/IRT screening are now using expanded genetic analysis either as part of the screening process for evaluating premature infants or in conjunction with the diagnostic sweat test. A survey of 4 commercial laboratories revealed that charges for *CFTR* multmutation analyses range from \$550 to \$800, and gene sequencing is \$2485 to \$3546 per test.

Another limitation is that we relied heavily on Wisconsin data to have completely accessible costs and outcomes for the models, but their general applicability in the United States has been described⁴⁸ recently. On the other hand, certain expenses such as salaries for personnel will vary in other regions and thus the simulations described herein may require revisions (eg, in the United Kingdom where the newborn blood specimens are obtained at home, which causes greater health care personnel costs but lower family expenses).

Two major system failures were identified as contributors to missed and delayed diagnoses: (1) protocol definition failures and (2) follow-up system failures. Protocol definition failures, the first type of system failure accounting for the largest proportions of potential missed diagnoses, resulted most commonly from the definitions of an abnormal IRT screen in each protocol. In the design of our IRT/IRT assessment, standard cutoffs of 105 ng/mL and 70 ng/mL were set as the abnormal values for the first and second screen, respectively, but data suggest that this can lead to a potential missed diagnosis rate estimated as high as ~30% of the total number of newborns with CF given a diagnosis annually through screening.⁶ Thus IRT cutoff values have been lowered continuously during the past decade and have varied among the states from 58 to 130 ng/mL for the first IRT and 50 to 90

ng/mL for the second IRT. The IRT/DNA system uses a much lower cutoff level for identifying abnormal IRT screens, thereby lowering the percentage of infants with CF with a missed diagnosis. Therefore, lowering the cutoff level of the abnormal IRT screens in the IRT/IRT system may offer 1 solution to this prominent system failure but will also lead to an unintended consequence of increasing costs. If the IRT/IRT system were to adopt the same cutoff levels as the IRT/DNA system, 4000 infants out of the 100 000 fictional screened newborns would require a second blood specimen.

The follow-up component is the second type of system where failures can occur. Among the 2 screening methods compared in this study, IRT/IRT clearly experiences the greatest number of potential missed diagnoses in the follow-up system and the largest proportion of these were lost at the point of obtaining the second dried blood specimen. In the IRT/DNA method, very few newborns with CF are categorized as a loss to follow-up because replacing the second dried blood specimen with a mutation analysis conducted on the initial dried blood specimen does not allow for loss to follow-up at this stage.

Therefore, the results from this study have demonstrated that the system design of the IRT/IRT and IRT/DNA screening programs offer different sets of advantages and disadvantages. The design of the IRT/DNA screening protocol minimizes system failures and out-of-pocket costs to families. The IRT/IRT screening protocol minimizes costs to state laboratories and insurance but is associated with more potential system failures. Redesigning the IRT/IRT system by increasing the sensitivity of the initial IRT test (ie, lowering the initial cutoff for abnormal) and decreasing loss to follow-up will improve early detection and treatment of infants with CF but will substantially increase the societal cost of the screening program.

ACKNOWLEDGMENTS

This research was supported by National Institutes of Health grant R01DK34108. Professor Rosenberg was partially supported by grant 1UL1RR025011 from the Clinical and Translational Science Award

(CTSA) program of the National Center for Research Resources, National Institutes of Health.

We thank the other investigators who have participated in the Wisconsin Cystic Fibrosis Neonatal Screening Project,

especially the Madison CF Center Director, Dr Michael Rock, and its longtime coordinator, Anita Laxova. We also thank W. H. Hannon, PhD (former director of the Newborn Screening Branch at the Centers for Disease Control and Prevention).

REFERENCES

1. Crossley JR, Elliott RB, Smith PA. Dried-blood spot screening for cystic fibrosis in the newborn. *Lancet*. 1979;1(8114):472–474
2. Grosse SD, Boyle CA, Botkin JR, et al; CDC. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep*. 2004; 53(RR-13):1–36
3. Campbell PW, III, White TB. Newborn screening for cystic fibrosis: an opportunity to improve care and outcomes. *J Pediatr*. 2005; 147(suppl 3):S2–S5
4. Department of Health and Human Services. Newborn screening: toward a uniform screening panel and system. 70 Federal Register 11247 (2005)
5. Gregg RG, Wilfond BS, Farrell PM, Laxova A, Hassemer D, Mischler EH. Application of DNA analysis in a population-screening program for neonatal diagnosis of cystic fibrosis (CF): comparison of screening protocols. *Am J Hum Genet*. 1993;52(3):616–626
6. Kloosterboer M, Hoffman G, Rock MJ, et al. Clarification of laboratory and clinical variables that influence cystic fibrosis newborn screening with initial analysis of immunoreactive trypsinogen. *Pediatrics*. 2009;123(2). Available at: www.pediatrics.org/cgi/content/full/123/2/e338
7. Ross LF. Newborn screening for cystic fibrosis: a lesson in public health disparities. *J Pediatr*. 2008;153(3):308–313
8. Castellani C, Southern KW, Brownlee K, et al. European best practice guidelines for cystic fibrosis neonatal screening. *J Cyst Fibros*. 2009;8(3):153–173
9. Kerem B, Rommens JM, Buchanan JA, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science*. 1989;245(4922): 1073–1080
10. Lee DS, Rosenberg MA, Peterson A, et al. Analysis of the costs of diagnosing cystic fibrosis with a newborn screening program. *J Pediatr*. 2003;142(6):617–623
11. Rosenberg MA, Farrell PM. Assessing the cost of cystic fibrosis diagnosis and treatment. *J Pediatr*. 2005;147(suppl 3):S101–S105
12. van den Akker-van Marle ME, Dankert HM, Verkerk PH, Dankert-Roelse JE. Cost-effectiveness of 4 neonatal screening strategies for cystic fibrosis. *Pediatrics*. 2006;118 (3):896–905
13. Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A; United Kingdom Cystic Fibrosis Database Steering Committee. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics*. 2007;119(1):19–28
14. Sims EJ, Mugford M, Clark A, et al; UK Cystic Fibrosis Database Steering Committee. Economic implications of newborn screening for cystic fibrosis: a cost of illness retrospective cohort study. *Lancet*. 2007; 369(9568):1187–1195
15. Sekhar DL, Wang L, Hollenbeck CS, Widome MD, Paul IM. A cost-effectiveness analysis of screening urine dipsticks in well-child care. *Pediatrics*. 2010;125(4):660–663
16. Simpson N, Anderson R, Sassi F, et al. The cost-effectiveness of neonatal screening for cystic fibrosis: an analysis of alternative scenarios using a decision model. *Cost Eff Resour Alloc*. 2005;3:8
17. Mandelblatt J, Freeman H, Winczewski D, et al. The costs and effects of cervical and breast cancer screening in a public hospital emergency room. The Cancer Control Center of Harlem. *Am J Public Health*. 1997;87(7): 1182–1189
18. Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. *Stat Med*. 1996;15 (5):449–462
19. Hale JE, Parad RB, Comeau AM. Newborn screening showing decreasing incidence of cystic fibrosis. *N Engl J Med*. 2008;358(9): 973–974
20. Castellani C, Picci L, Tamanini A, Girardi P, Rizzotti P, Assael BM. Association between carrier screening and incidence of cystic fibrosis. *JAMA*. 2009;302(23):2573–2579
21. Massie J, Curnow L, Gaffney L, Carlin J, Francis I. Declining prevalence of cystic fibrosis since the introduction of newborn screening. *Arch Dis Child*. 2010;95(7):531–533
22. Grody WW, Cutting GR, Klinger KW, Richards CS, Watson MS, Desnick RJ; Subcommittee on Cystic Fibrosis Screening, Accreditation of Genetic Services Committee, ACMG. American College of Medical Genetics. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genet Med*. 2001;3(2):149–154
23. Comeau AM, Parad RB, Dorkin HL, et al. Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections. *Pediatrics*. 2004;113(6):1573–1581
24. Southern KW, Munck A, Pollitt R, et al; ECFS CF Neonatal Screening Working Group. A survey of newborn screening for cystic fibrosis in Europe. *J Cyst Fibros*. 2007;6(1): 57–65
25. Farrell PM, Joffe S, Foley L, Canny GJ, Mayne P, Rosenberg M. Diagnosis of cystic fibrosis in the Republic of Ireland: epidemiology and costs. *Ir Med J*. 2007;100(8):557–560
26. Sontag MK, Hammond KB, Zielinski J, Wagener JS, Accurso FJ. Two-tiered immunoreactive trypsinogen-based newborn screening for cystic fibrosis in Colorado: screening efficacy and diagnostic outcomes. *J Pediatr*. 2005;147(suppl 3):S83–S88
27. Hammond KB, Abman SH, Sokol RJ, Accurso FJ. Efficacy of statewide neonatal screening for cystic fibrosis by assay of trypsinogen concentrations. *N Engl J Med*. 1991;325(11): 769–774
28. Henry RL, Boulton TJ, Roddick LG. False negative results on newborn screening for cystic fibrosis. *J Paediatr Child Health*. 1990;26(3):150–151
29. Hassemer DJ, Laessig RH, Hoffman GL, Farrell PM. Laboratory quality control issues related

- to screening newborns for cystic fibrosis using immunoreactive trypsin. *Pediatr Pulmonol Suppl.* 1991;7:76–83
30. Wilcken B, Wiley V, Sherry G, Bayliss U. Neonatal screening for cystic fibrosis: a comparison of two strategies for case detection in 1.2 million babies. *J Pediatr.* 1995;127(6):965–970
 31. Rock MJ, Mischler EH, Farrell PM, et al. Newborn screening for cystic fibrosis is complicated by age-related decline in immunoreactive trypsinogen levels. *Pediatrics.* 1990;85(6):1001–1007
 32. Padoan R, Genoni S, Moretti E, Seia M, Giunta A, Corbetta C. Genetic and clinical features of false-negative infants in a neonatal screening programme for cystic fibrosis. *Acta Paediatr.* 2002;91(1):82–87
 33. Comeau AM, Parad RB, Dorkin HL, et al. Population-based newborn screening for genetic disorders when multiple mutation DNA testing is incorporated: a cystic fibrosis newborn screening model demonstrating increased sensitivity but more carrier detections. *Pediatrics.* 2004;113(6):1573–1581
 34. Gregg RG, Simantel A, Farrell PM, et al. Newborn screening for cystic fibrosis in Wisconsin: comparison of biochemical and molecular methods. *Pediatrics.* 1997;99(6):819–824
 35. Collaco JM, Panny SR, Hamosh A, Mogayzel PJ Jr. False negative cystic fibrosis newborn screen. *Clin Pediatr (Phila).* 2010;49(3):214–216
 36. Comeau AM, Parad R, Gerstle R, et al. Communications systems and their models: Massachusetts parent compliance with recommended specialty care after positive cystic fibrosis newborn screening result. *J Pediatr.* 2005;147(suppl 3):S98–S100
 37. Farrell PM. Improving the health of patients with cystic fibrosis through newborn screening. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *Adv Pediatr.* 2000;47:79–115
 38. Rock MJ, Hoffman G, Laessig RH, Kopish GJ, Litsheim TJ, Farrell PM. Newborn screening for cystic fibrosis in Wisconsin: nine-year experience with routine trypsinogen/DNA testing. *J Pediatr.* 2005;147(suppl 3):S73–S77
 39. Farrell PM. The meaning of “early” diagnosis in a new era of cystic fibrosis care. *Pediatrics.* 2007;119(1):156–157
 40. Chatfield S, Owen G, Ryley HC, et al. Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessment after five years of screening. *Arch Dis Child.* 1991;66(1 Spec No):29–33
 41. Farrell PM, Kosorok MR, Rock MJ, et al; Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics.* 2001;107(1):1–13
 42. Rosenfeld M. Overview of published evidence on outcomes with early diagnosis from large US observational studies. *J Pediatr.* 2005;147(suppl 3):S11–S14
 43. Kosciuk RL, Lai HJ, Laxova A, et al. Preventing early, prolonged vitamin E deficiency: an opportunity for better cognitive outcomes via early diagnosis through neonatal screening. *J Pediatr.* 2005;147(suppl 3):S51–S56
 44. Lai HJ, Cheng Y, Farrell PM. The survival advantage of patients with cystic fibrosis diagnosed through neonatal screening: evidence from the United States Cystic Fibrosis Foundation registry data. *J Pediatr.* 2005;147(suppl 3):S57–S63
 45. Farrell PM, Lai HJ, Li Z, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough! *J Pediatr.* 2005;147(suppl 3):S30–S36
 46. Grosse SD, Rosenfeld M, Devine OJ, Lai HJ, Farrell PM. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. *J Pediatr.* 2006;149(3):362–366
 47. Legrys VA, McColley SA, Li Z, Farrell PM. The need for quality improvement in sweat testing infants after newborn screening for cystic fibrosis. *J Pediatr.* 2010;157(6):1035–1037
 48. Baker MW, Groose M, Hoffman G, Rock M, Levy H, Farrell PM. Optimal DNA tier for the IRT/DNA algorithm determined by CFTR mutation results over 14 years of newborn screening. *J Cyst Fibros.* 2011;10(4):278–281
 49. Fost N, Farrell PM. A prospective randomized trial of early diagnosis and treatment of cystic fibrosis: a unique ethical dilemma. *Clin Res.* 1989;37(3):495–500