

Lessons Learned from Carrier Screening: Cystic Fibrosis

The Parent's Perspective

Martin Kharrazi, Ph.D.

Genetic Disease Screening Program
California Department of Public Health

Population-based Carrier Screening for Single Gene Disorders:
Lessons Learned and New Opportunities
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Outline of Talk

1. Results from two California obstetrical provider surveys
 - October 2001 (before ACOG recommendation)
 - August 2003
2. “Parental” perspective on carrier screening for CF

***Cystic Fibrosis Prenatal Screening
in California: Results of a
Statewide Practitioner Survey***

October 2001

Suman M. Paranjape, et al.
Interdisciplinary Masters Program
University of California, Berkeley

Survey Objectives and Methods

- Assess CF prenatal screening practices, attitudes and beliefs prior to ACOG recommendations in October 2001
- 17-item survey mailed to 10% random sample of non-Kaiser obstetrical providers in California

2001 Survey Population

- Response rate - 24% out of N=748
- MDs – 77%
- Patient demographics

<u>Race/Ethnicity</u>	<u>Survey</u>	<u>1999 Births</u>
Caucasian	32%	33%
Hispanic	49%	48%
Black	8%	7%
Other	11%	12%

2001 Survey Results

- Practitioners offering CF screening 41%
- Patients offered CF screening x 42%
- CA patients offered CF screening = 17%
(compared to 96% for XAFP screening
and 39% for 1st trimester Trisomy 21 screening)

Patients to whom providers recommend CF screening

	<u>Respondents</u>
• Family history	44%
• Ethnicity (Caucasian, Jewish, French Canadian)	16%
• At risk	12%

Barriers to CF Screening

	<u>Respondents</u>
• No information for patients/ providers	39%
• Insurance coverage or cost	22%
• Patient demographics	22%
• Other factors/situations	18%

Provider Concerns about CF Screening

Most cited no ethical dilemmas, but some indicated concerns about:

- Genotype/phenotype correlations between CF mutations and disease severity
- Problems identifying mutations in non-Caucasian populations
- Continual improvements in CF treatment

California Prenatal Care Genetic Screening Survey

July 2003

Lisa Feuchtbaum, DrPH, et al.
Genetic Disease Screening Program
California Department of Public Health

Survey Objectives and Methods

- Assess views on, and experiences with, mandatory newborn screening, supplemental newborn screening for metabolic disorders, and **carrier screening for cystic fibrosis in July 2003**
- 12-item survey mailed to prenatal care providers in California (N=6,197)*

**American Journal of Obstetrics & Gynecology* 194:131-137, January 2006.

2003 Survey Population

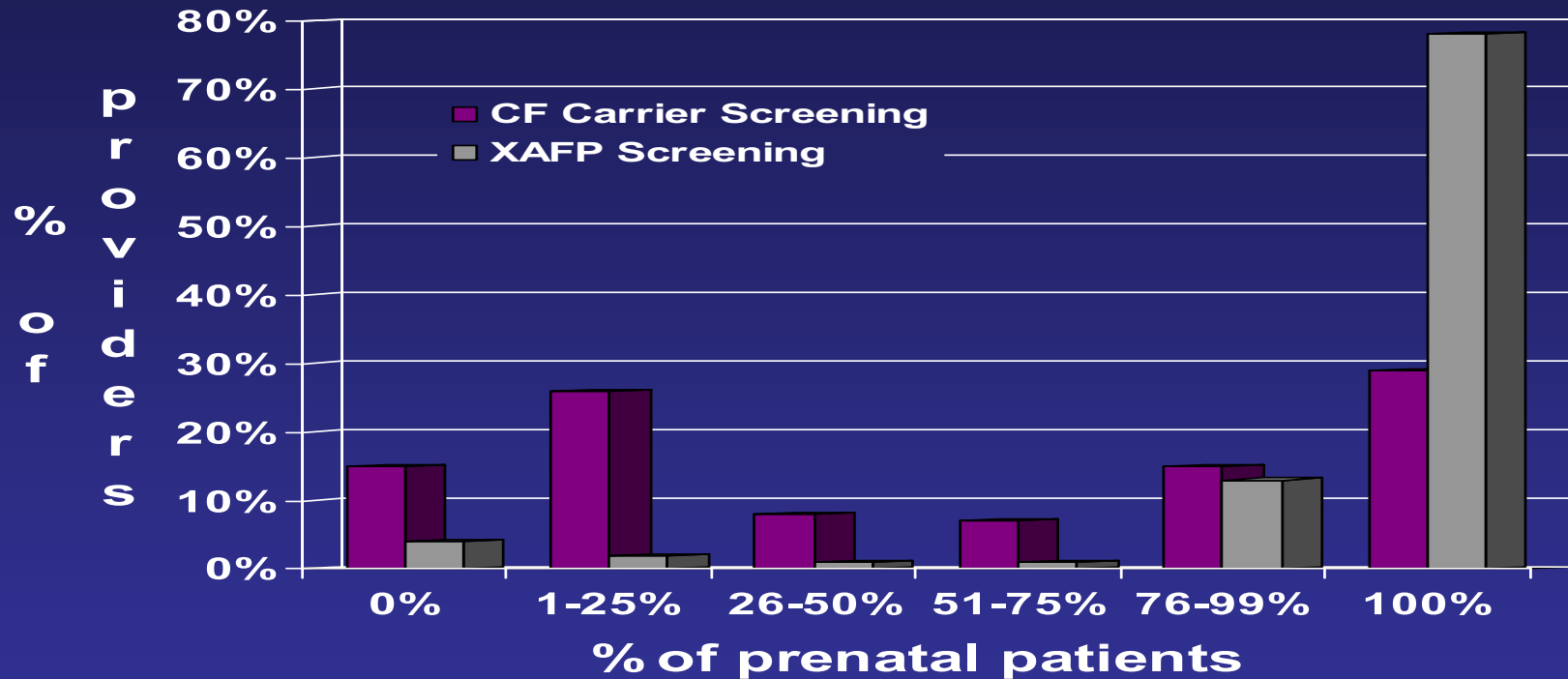
Type of Providers

	<u>Response Rate</u>	<u>Respondents</u>
Overall	11%	669 (100%)
MD/DO	9%	470 (70%)
Nurses/Midwives/ Others	18%	199 (30%)

Prenatal Patients

	<u>% on Medicaid</u>
Patients of respondents	39% (min, max = 31%, 47%)
CA Live Births	42%

Q: Please estimate the percentage of prenatal patients with whom you and your staff discussed each of these screening services. (Please select only one for each)



Type of screening

CF Carrier

XAFP

% of prenatal patients

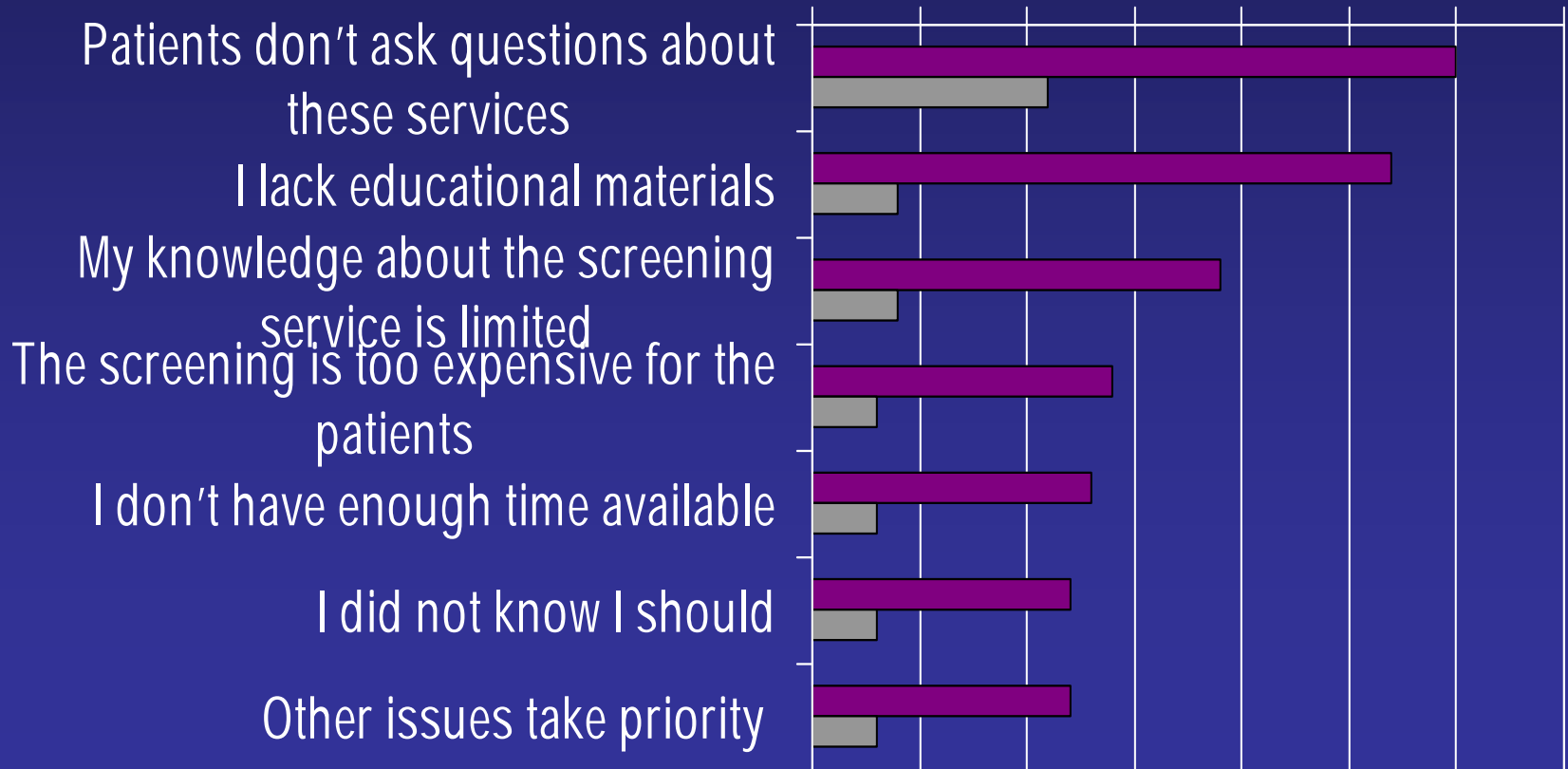
53% (min 46%, max 60%)

91% (min 89%, max 93%)

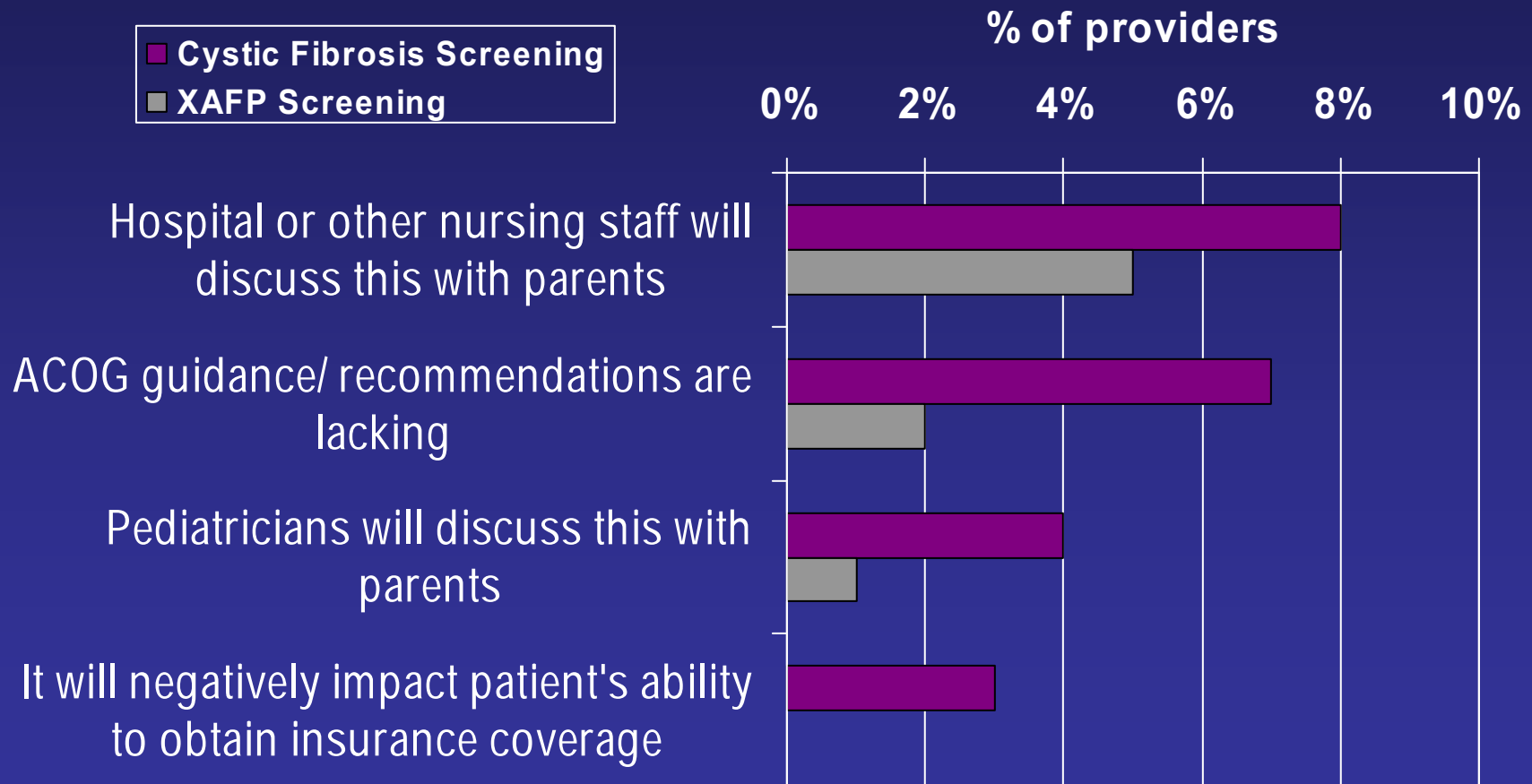
Q: Which of the following 11 factors, if any, limit your ability or willingness to discuss screening with your prenatal patients? (Please select all that apply) – top seven factors (>10%)

■ Cystic Fibrosis Screening
 ■ XAFP Screening

% of providers
 0% 5% 10% 15% 20% 25% 30% 35%



Q: Which of the following 11 factors, if any, limit your ability or willingness to discuss screening with your prenatal patients? (Please select all that apply) – bottom four factors (<10%)



Conclusions: 2001 & 2003 Surveys

- Penetration of prenatal CF carrier screening increased from ~17% in 2001 to ~53% in 2003
- In 2003, barriers included:
 - Inadequate provider knowledge and time
 - Lack of patient knowledge to ask
 - Lack of CF screening educational materials
 - Screening test costs too high for some patients

Other Changes since October 2001

- Availability of CF newborn screening has increased dramatically from 8 state programs in 2001 to over 40 currently
- CF clinical care has improved and predicted median age of survival has risen from 32 years in 2001 to 37 years in 2006
- Knowledge about CFTR mutation frequencies and genotype-phenotype correlations has improved
- Over one dozen different commercial CFTR multiple mutation panel tests available (ACMG-23 or more)
- Six years of experience gained conducting CF carrier screening

Prenatal Couples Need:

- Clear education about CF prior to testing
- Safe & accurate screening test
- Low cost test, couple covered by insurance
- Safe & accurate fetal diagnostic testing
- Interpretable test results
- Available and clear genetic counseling
- All follow up options available

Problems with Education

- Medical providers educate parents differently about CF depending on their specialty area
 - Obstetrical providers: CF = fatal childhood disease
 - Pediatric providers: CF = treatable, chronic disorder
- Lack of clear educational message leads to parental confusion and distrust of medical profession

- **Possible Solutions:**

Medical providers should give parents a similar message about CF across specialty areas. Education should start early and enlist the assistance of other preconception educators.

Problems with Mutation Panel

- ACMG-23 CFTR mutation testing panel is:
 - based largely on carrier mutation frequencies, not case frequencies
 - includes mutations with varying degrees of severity
 - not equitable across geographic subgroups
 - not comprehensive for the non-White population

Challenges posed by presence of CF Newborn Screening

- CF case detection rates are lower for prenatal carrier screening than for newborn screening

% of California cases detectable

	<u>Prenatal Screening</u>	<u>Newborn Screening</u>
Whites	88%	95%
Blacks	64%	88%
Hispanics	57%	84%

- Parental confusion occurs when prenatal screen negative goes on to have a newborn screen positive test result

Possible Solutions to Mutation Panel Problems

- Continue to strive for a more sensitive and specific CFTR mutation panel
 - add mutations to improve sensitivity and equity across race/ethnic and geographic subgroups
 - remove mutations that are not severe yet prevalent to improve specificity
 - screen for variant combinations that result in severe disease, eg, R117H and (TG12-5T or TG13-5T)
 - consider using a more comprehensive mutation panel for male partner when sequential screening is used

Conclusions about CF Carrier Screening

- Needs to be seen in a new context
 - Improved care for persons with CF
 - Earlier detection of CF with near universal newborn screening
- Need for earlier, more consistent, and clearer patient education about CF
- Need for a less costly yet more simple, sensitive, specific and equitable screening test
- Needs to be offered to more patients

Thank you!

CA Panel Selection Process

Mutations were selected to achieve an overall case detection rate of 90% or more in each race group

Race	Min. mutation frequency to detect 78% of all chromosomes	# mutations selected
White	1.0%	8
Black	1.9%	6
Hispanic	0.5%	23
Total		38*

*CFTRdele2,3(21kb) was also added to the panel

California 38 Panel vs. ACMG 23

- | | | |
|--------------------|-----------------------------|--------------------------------|
| 1. delF508 * | 16. delF311 ^ | 31. 3272-26A>G ^ |
| 2. delI507 * | 17. A559T ^ | 32. 663delT ^ |
| 3. G542X * | 18. R75X ^ | 33. H199Y ^ |
| 4. G551D * | 19. R1066C ^ | 34. P205S ^ |
| 5. G85E * | 20. S549N ^ | 35. Q98R ^ |
| 6. N1303K * | 21. W1089X ^ | 36. S492F ^ |
| 7. R1162X * | 22. 1812-1G>A ^ | 37. W1204X ^ |
| 8. R334W * | 23. 2055del9>A ^ | 38. <u>CFTRdele2,3(21kb)</u> ^ |
| 9. R553X * | 24. 2307insA ^ | 39. A455E ** |
| 10. W1282X * | 25. 3876delA ^ | 40. R117H ** |
| 11. 1717-1G>A * | 26. 935delA ^ | 41. R347P ** |
| 12. 3120+1G>A * | 27. 406-1G>A ^ | 42. R560T ** |
| 13. 3849+10kbC>T * | 28. 1288insTA ^ | 43. 1898+1G>A ** |
| 14. 621+1G>T * | 29. 2105-2117del13insAGAAA^ | 44. 2184delA ** |
| 15. 711+1G>T * | 30. 296+2T>A ^ | 45. 2789+5G>A ** |
| | | 46. 3659delC ** |

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