



WHY WE MUST COLLABORATE TO IMPROVE OUTCOMES IN OUR CEREBRAL PALSY PATIENTS

Nigel Paneth MD MPH

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Department of Epidemiology, Michigan State University

ARGUMENTS PROVIDED AGAINST FORMAL ASSESSMENT OF TREATMENTS

- **I know what works.** I have taken care of patients for a long time and I have “clinical experience”.
- **Every patient is different.** There is no way to know out what works overall. I tailor my treatment to the individual.
- **It’s not my job.** My job is to treat patients. I don’t do research. Only basic scientists do research that matters.



CLINICAL EXPERIENCE HAS PROVEN A NOTORIOUSLY BAD GUIDE TO EFFECTIVENESS

Interventions used for decades before proven to be *harmful* by good study designs:

- Diethylstilbestrol for miscarriage
- Irradiation for thymic enlargement
- Sulfa drugs for newborn infections



RESEARCH IS NOT MY JOB

- Can medicine be divorced from research on effectiveness?
- Can medicine be practiced honestly without having a research base as to what works and what does not?
- Sound practice must depend upon research on effectiveness



Paneth's formula for the relationship of practice to research

$$P - R = W$$

Practice without Research equals Witchcraft



MORAL OBLIGATION

- Our patients assume that we provide them only with effective treatments.
- They expect that we have more than our personal prejudice to support the effectiveness of the treatments we provide.
- When we provide a treatment, we are pledging to patients that we have scientific reasons to believe the treatment will be effective.
- If we do not have evidence for that assertion, then we are misleading our patients, which is immoral.





IN SOME CHILDHOOD CONDITIONS,
CLINICIANS AND RESEARCHERS HAVE USED
CAREFUL EVALUATION OF EFFECTIVENESS
TO GREATLY IMPROVE THE HEALTH OF
CHILDREN WITH THESE CONDITIONS



TWO MODELS FOR PROGRESS IN TREATMENT OF RARE CHILDHOOD DISEASES

- ACUTE LYMPHOBLASTIC LEUKEMIA
 - CYSTIC FIBROSIS

The main mode of study of treatments in ALL has been a sequence of **randomized trials**, each building on the preceding trial.

The main approach in cystic fibrosis has been to establish **patient registries**, assembling observations on best practices.

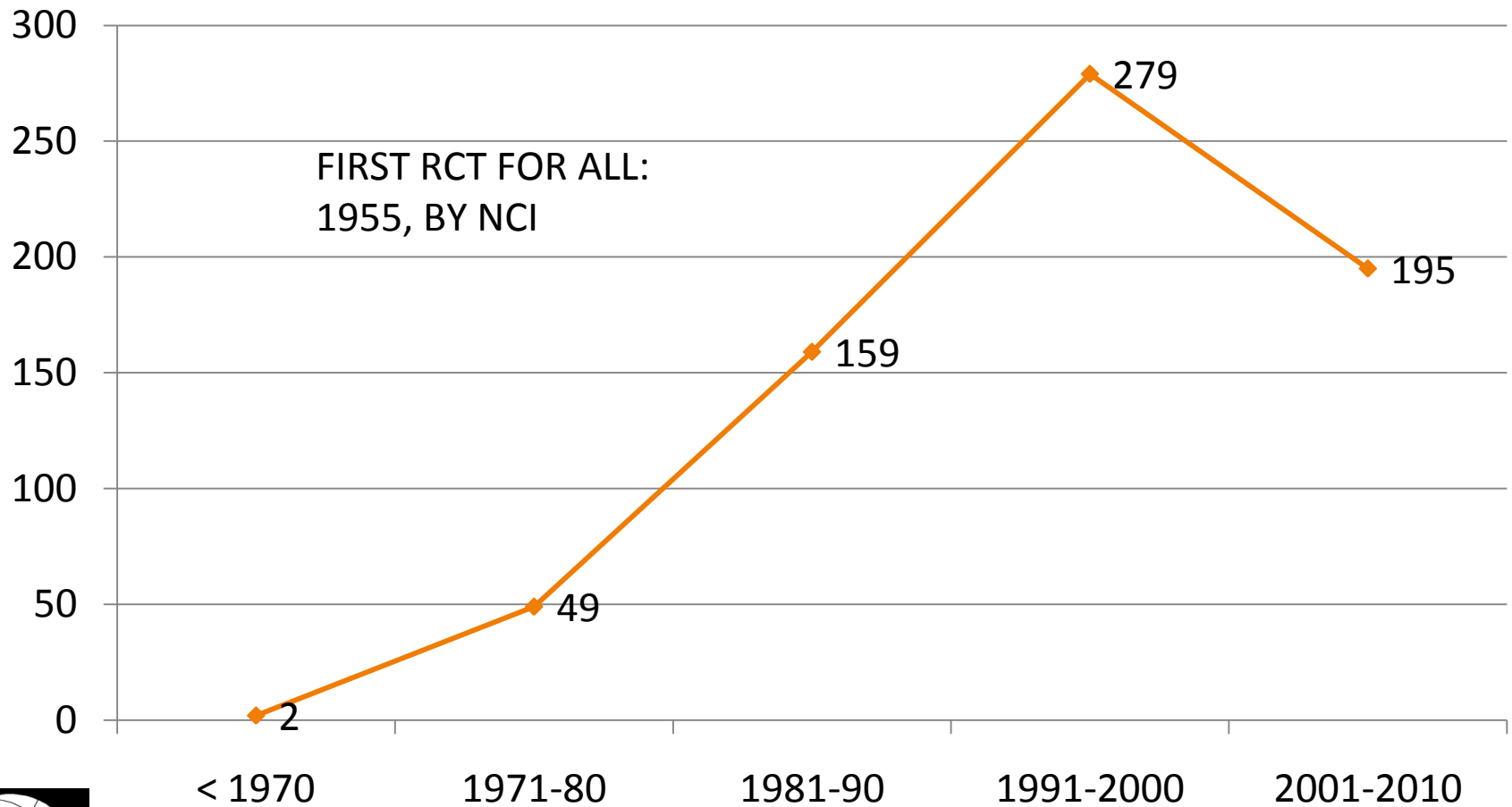


CEREBRAL PALSY IS CONSIDERABLY COMMONER THAN EITHER OF THE OTHER TWO CONDITIONS

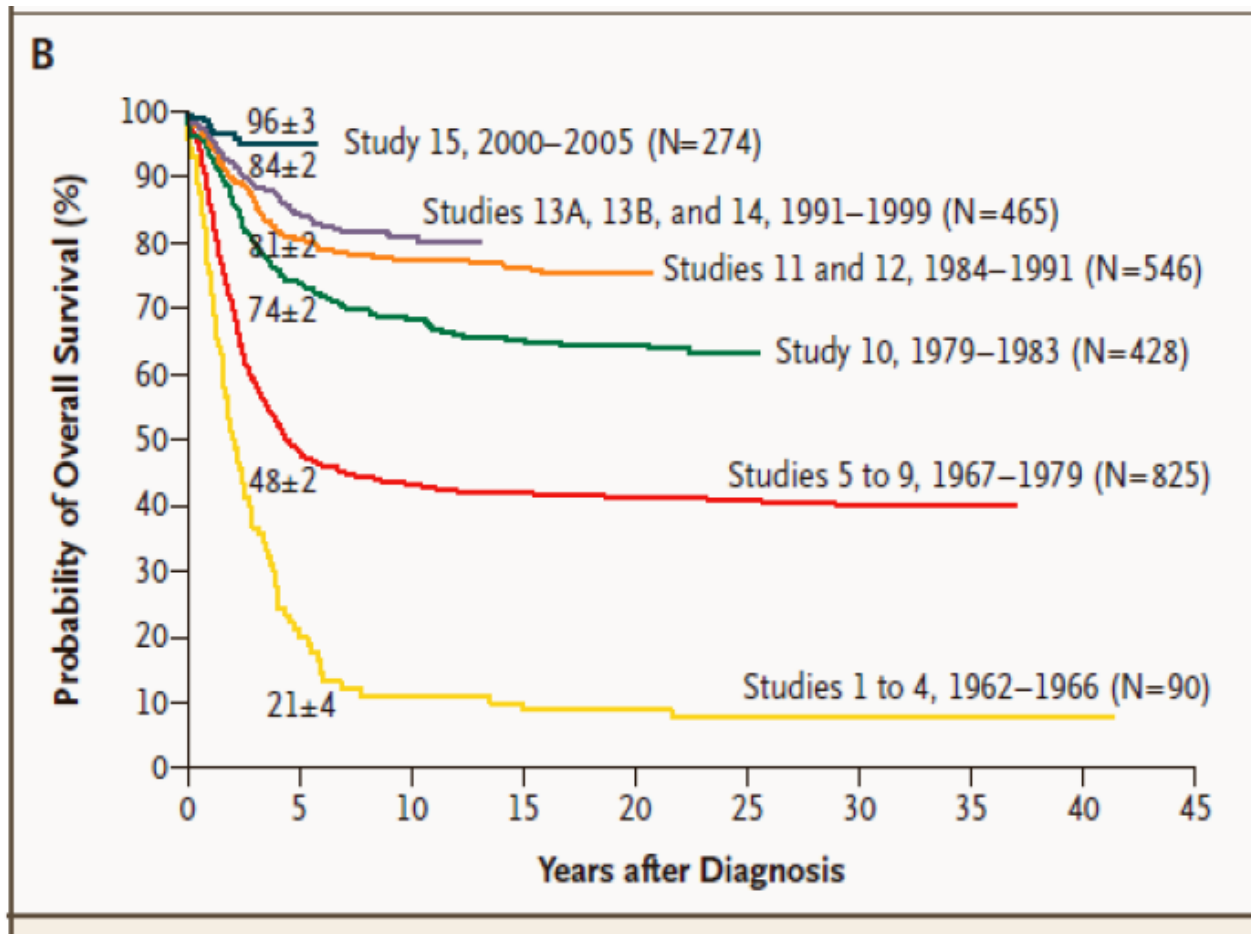
- Cerebral palsy
 - Prevalence: 1 in 500
 - Cystic fibrosis
 - Prevalence: 1 in 3,500
 - Acute lymphoblastic leukemia
 - Incidence: 4-5/100,000/person-years*
- * (if all survived, this would translate to prevalence, by age 15 of 1 per 1,500 children)



N OF PUBLISHED RANDOMIZED TRIALS IN PUBMED FOR ACUTE LYMPHOBLASTIC/LYMPHOCYTIC LEUKEMIA



IMPROVEMENT IN CHILDHOOD LEUKEMIA SURVIVAL 1962-66 TO 2000-05

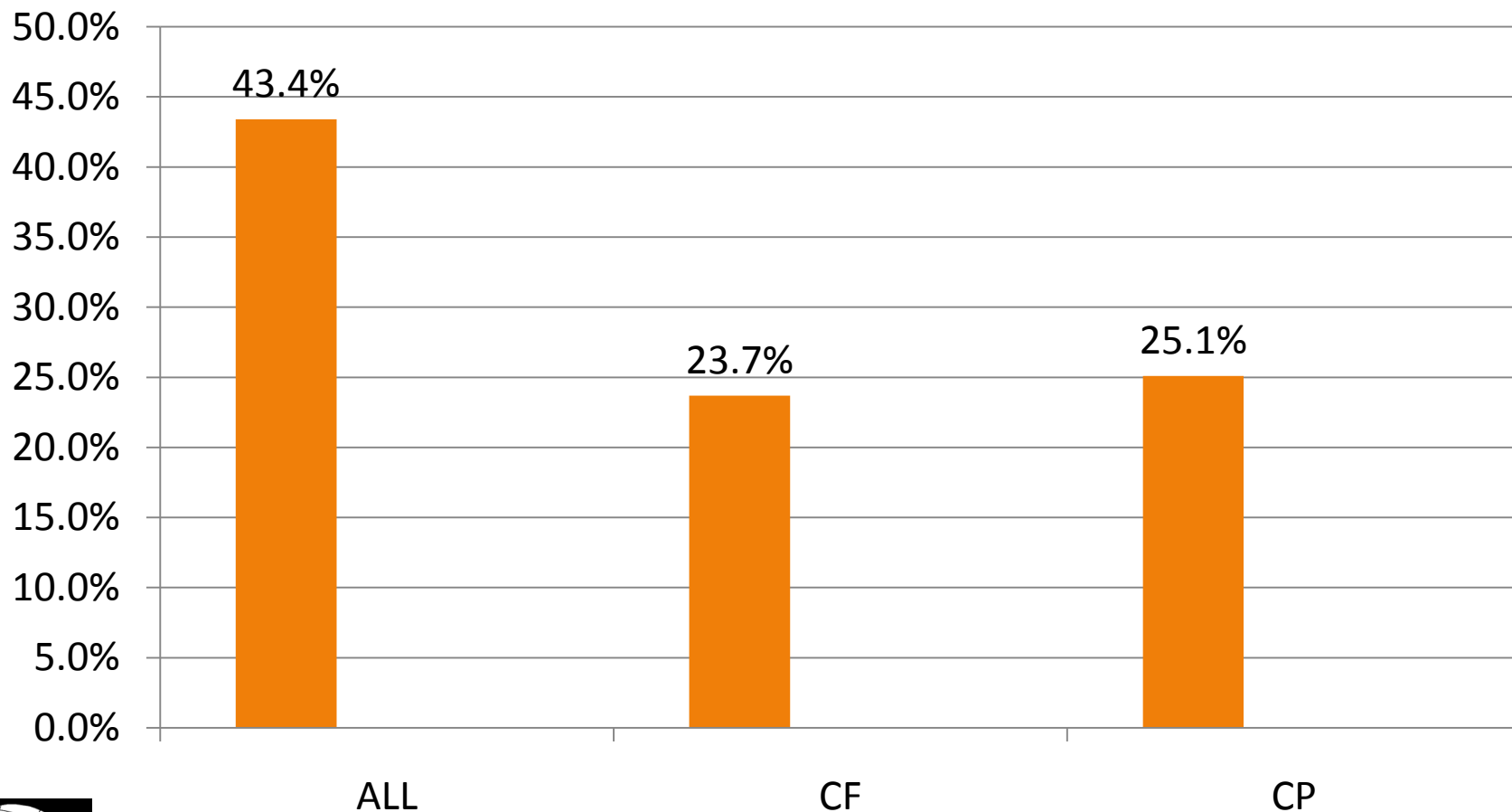


KEY ELEMENTS IN THE SUCCESS OF LEUKEMIA TREATMENT

- Death was a clear cut endpoint with high frequency.
- Effective treatments became available from intensive laboratory work – the NCI clinical trials program was an offspring of their drug screening program.
- Strong financial support from the National Cancer Institute
- Willingness of clinician-scientists to work together to perform multicenter trials



PERCENT OF ALL, CF AND CP TRIALS SINCE 2001 THAT WERE MULTICENTER



CYSTIC FIBROSIS FOUNDATION MISSION

Until we conquer this disease, our team will work tirelessly to extend and enhance life for those with cystic fibrosis by functioning as:

Scientific pioneers, blazing new trails in CF research

Fund-raisers, securing the money needed to support our efforts

Advocates, keeping CF a top priority in government, industry and research

Investors, funding drug discovery and development

Caregivers, linking patients and families to specialized CF care

Family, offering support, information and resources



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THE APPROACH TO CYSTIC FIBROSIS CARE IN THE US

1. Cystic Fibrosis foundation founded in 1955
2. Foundation decided to accredit centers providing CF care.
3. Accredited centers (n = 110) receive
 1. Care guidelines
 2. Training in quality improvement
 3. Financial support in the form of grants

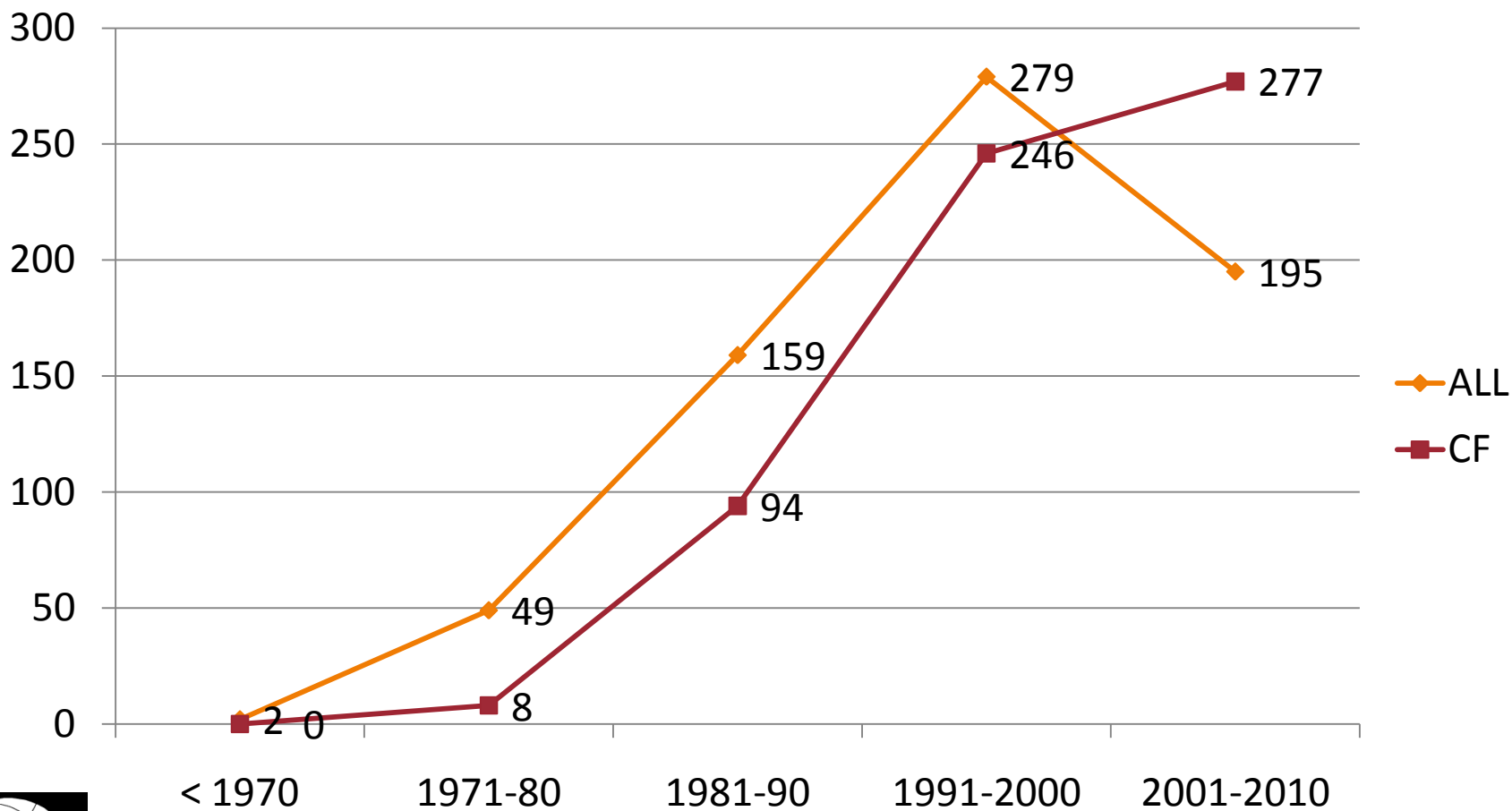


THE APPROACH TO CYSTIC FIBROSIS CARE IN THE US

1. Accredited centers must
 1. Pool their data into the CF patient **registry**
 2. Provide information on **growth, pulmonary function and survival** to the foundation
2. A subset of 77 centers constitutes a clinical trial group



N OF PUBLISHED RANDOMIZED TRIALS IN PUBMED FOR ALL and CF BY DECADE



GOALS OF THE CF FOUNDATION FOR ITS CENTERS

People with CF:

- are full members of the care team
- will have normal growth and nutrition
- will receive the right therapies to keep lung function steady and reduce infections
- Will be screened for complications
- Will receive care as needed regardless of insurance
- Will be supported in transplantation and end-of-life decisions
- Will have reduced exposure to germs of other CF patients



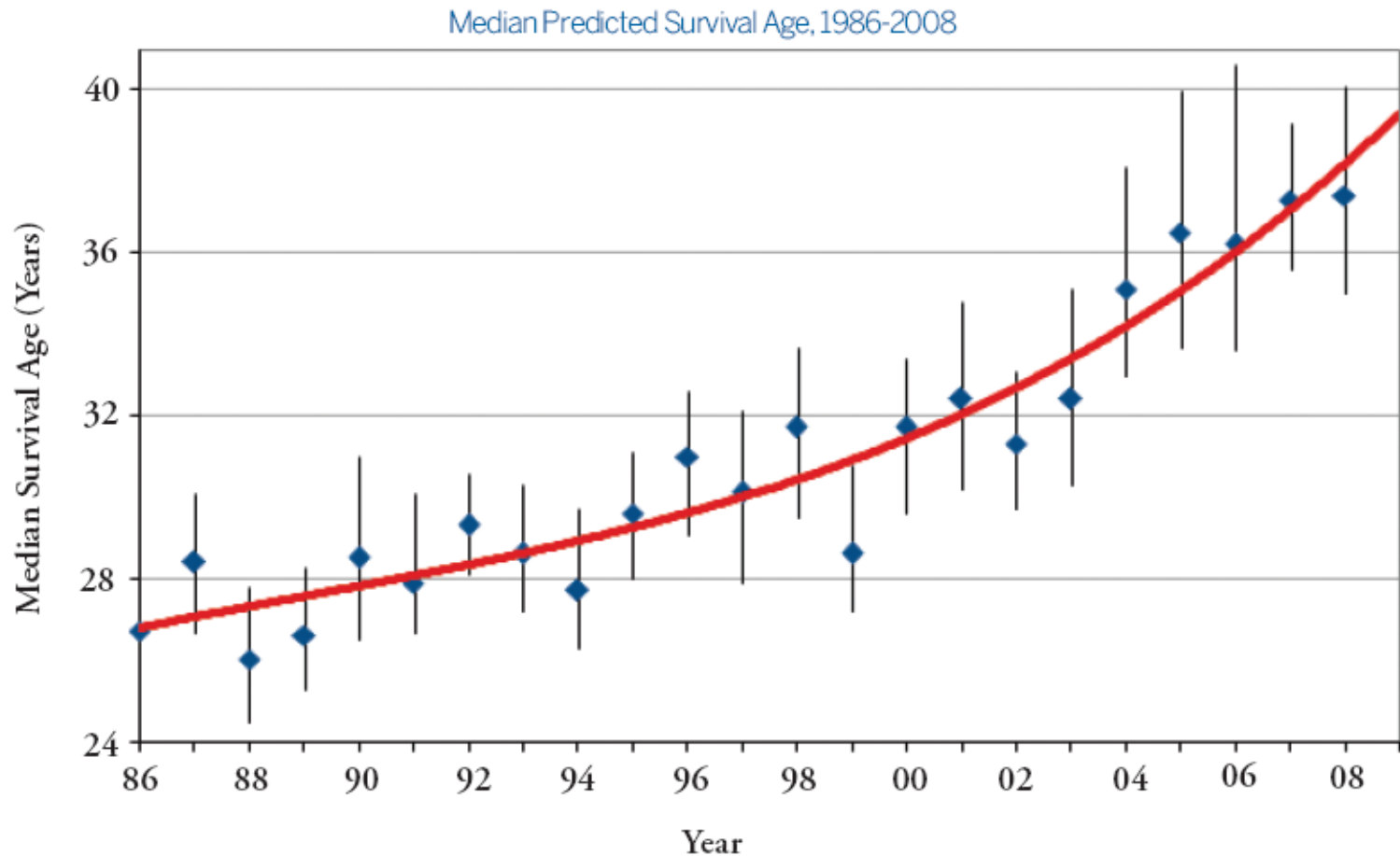
DATA COLLECTED IN THE CF REGISTRY

The registry anonymously reports patient data from more than 25,000 CF patients who receive care at 110 accredited centers. The information collected includes:

- Height, weight
- genotype
- lung function test results
- pancreatic enzyme use
- length of hospitalizations
- home IV use
- complications related to CF



MEDIAN SURVIVAL OF CF PATIENTS CARED FOR IN CF CENTERS IN US, 1986 - 2008



KEY ELEMENTS IN THE SUCCESS OF CF TREATMENT

- Defining measurable objective end-points
- Agreeing to monitor those end-points collaboratively
- Strong scientific interest in the disease
- Mission-based foundation with considerable resources:
 - CF Foundation annual expenditures for research \$85 M
 - CPI REF annual expenditures for research \$1.5 M





THE ONE FEATURE COMMON TO
PROGRESS IN BOTH ALL AND CF
COLLABORATION ACROSS TREATMENT
CENTERS



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THE SITUATION FOR CP

- Many treatments, most without strong evidence of effectiveness
- End-points may be difficult to define
- No strong history of collaboration across centers
- No strong supporting institution with a sense of mission
- Lack of financial support for research



TREATMENTS IN USE FOR CP

- Pharmacologic agents for spasticity

1. **Botulinum toxin type A***

2. Botulinum toxin type B

3. Intrathecal baclofen

4. Oral baclofen

5. Valium

6. Tizanidine

7. Dantrolene

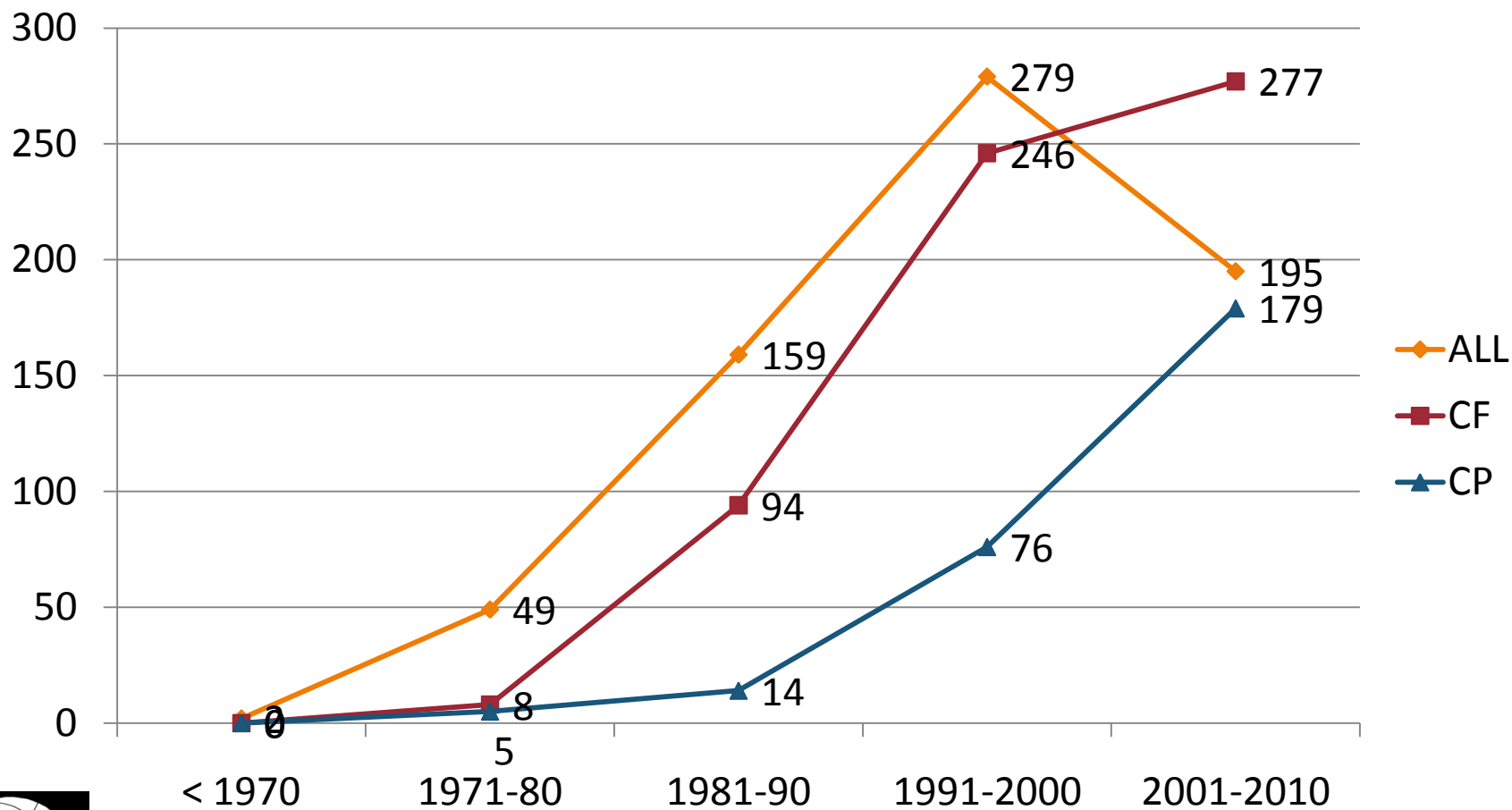
8. Phenol

9. Alcohol

*only agent considered clearly effective by AAN and CNS- Delgado et al *Neurology* 2010;74:336



N OF PUBLISHED RANDOMIZED TRIALS IN PUBMED FOR ALL, CF AND CP BY DECADE



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THE KEY TO PROGRESS IN CEREBRAL PALSY TREATMENT

COLLABORATION ACROSS TREATMENT CENTERS



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FIVE DEGREES OF COLLABORATION

1. Informal collaboration for one study
2. Collaboration for one study, but sufficiently well established to provide group name
3. Collaboration organized for several studies of the same type (e.g. RCT's)
4. Collaboration organized for several studies of different types
5. Collaboration encompassing studies and also ongoing reporting of clinical outcomes



PHYSICAL THERAPY CLINICAL RESEARCH NETWORK

<http://pt.usc.edu/clinresnet/about.html>

- PTClinResNet is a multisite clinical research network that links together five premier centers of physical therapy research and practice
 - USC
 - UCLA
 - Northwestern
 - Rancho Los Amigos National Rehabilitation Center
 - Southwest Missouri State University, and the University of California at Los Angeles.



COLLABORATION IN CP

- Need centers that treat children with CP and are willing to record and share data
- Need work to standardize which elements are commonly recorded and how to record them
- Need a willingness both to participate in trials and to share clinical data
- Need a source of funds to support this work
- Need a sense of mission



SOME NEW TOOLS TO MAKE COMPARISONS EASIER

- The five-item **Gross Motor Function Classification System (GMFCS)** has been in place for some time
- Recently two more functional assessments have been developed, both also with five categories
 - **MACS** – Manual Activity Classification System (Eliasson – Stockholm)
 - **CFCS** – Communication Function Classification System (Hidecker – East Lansing, Arkansas)



CONCLUSIONS 1

- Great progress has been made in severe childhood conditions by a combination of:
 - Multicenter randomized trials.
 - Regular monitoring of specific end-points and adopting best practices from a network of centers.
- Cerebral palsy, and perhaps other developmental disorders, can learn from these experiences



CONCLUSIONS 2

The health and wellbeing of children with CP is likely to be improved if we take advantage of

- A plethora of treatments badly in need of assessment
- Strong commitment to RCT's since 2000
- Excellent registry system in Europe that has helped standardize diagnosis and foster epidemiologic collaboration
- New tools to assess functionality that will make assessment better





THANK YOU FOR YOUR
ATTENTION

I AM HAPPY TO TAKE QUESTIONS



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