Past, Present and Future of Clinical Research in Pediatric Rheumatology

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Objectives

1. To describe the evolving nature of clinical research in pediatric rheumatology, using juvenile arthritis as example
2. To highlight the role of collaborative research networks

Today's presentation

- The case:
  - What will happen to my child?
- The past
- The present
- The future
- Back to the case and wrap up

The case

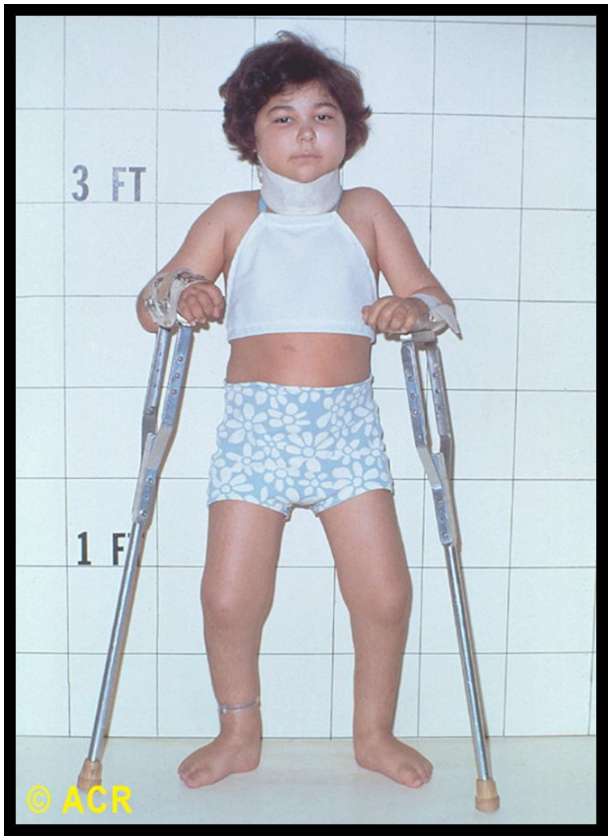
- A.D., a three year old previously healthy girl presents with a right-sided limp for 3 months
- On exam, swelling and limited range in knee, ankle and both wrists.
- X-ray and blood work unremarkable

The case

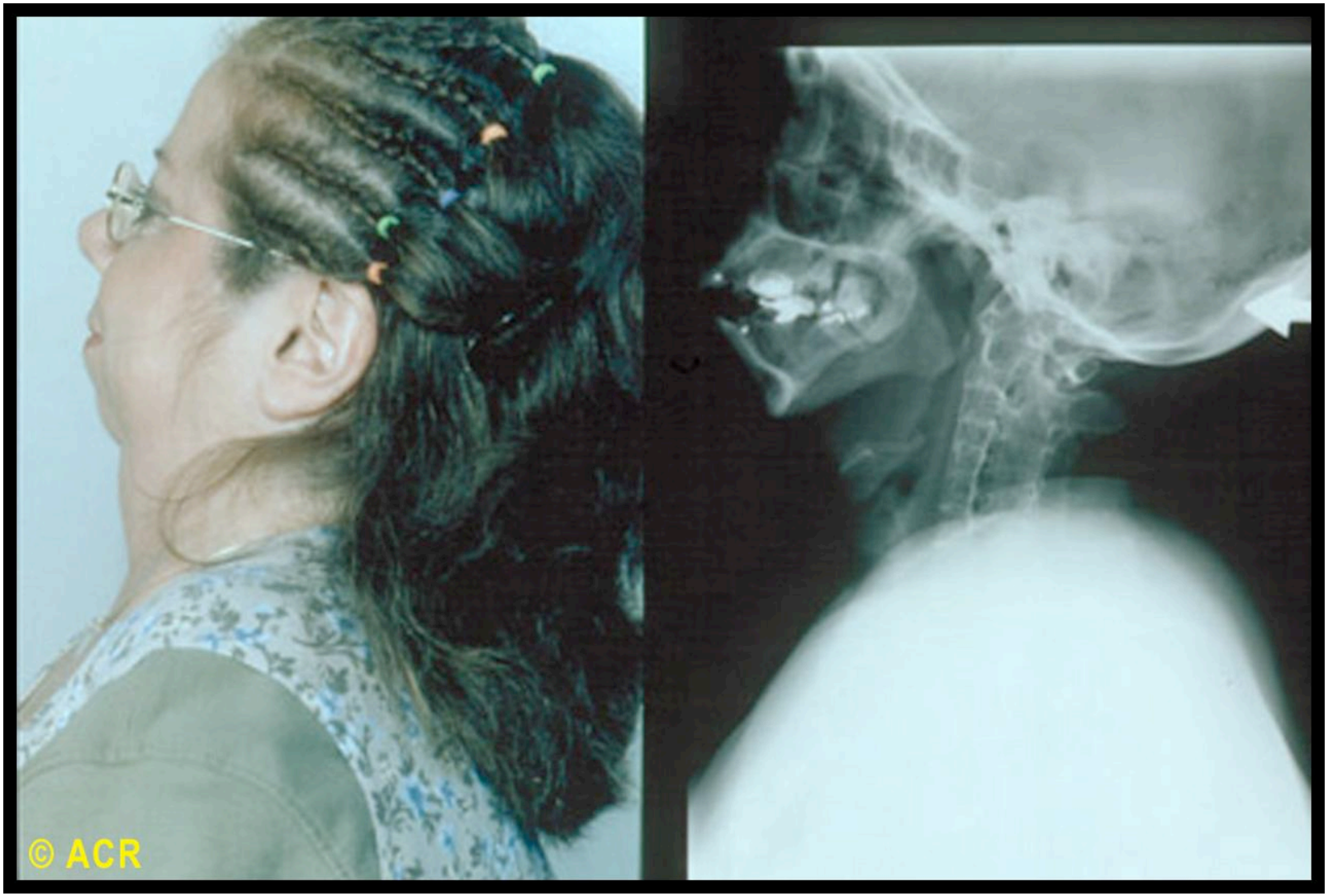
- You give the bad news:
  - Your child has arthritis
- They ask:
  - Doctor, what will happen to my child?
  - What treatment will be needed?
- You scratch your head and reflect:
  - What you said yesterday
  - What can you say today
  - What you might say tomorrow

The past

- Your child has a debilitating disease with no cure
- No medication has ever been properly tested (in a RCT) for this condition
- We can't even agree on how to call this disease
- We will start treatment with high-dose aspirin and see how things go



The past



The past

- Prognosis and treatment based on case series and adult trials
- Disease called juvenile rheumatoid arthritis on this side of the Atlantic and juvenile chronic arthritis on the other side.
- Current criteria for juvenile idiopathic arthritis (JIA) published in 2004
- First properly-sized randomized controlled trials published around 1985

The case – present

- A.D., a three year old girl with newly diagnosed arthritis
- Parents ask:
  - Doctor, what will happen to my child?
  - What treatment will be needed?

The present

- Your child has JIA
- >80 % of children with this JIA subtype (oligoarthritis), are fully controlled with treatment
- Best initial treatment is with NSAIDs and joint injections
- If this doesn't work, DMARDS and biologic agents are effective (RCTs)

The present

- International agreement on JIA definition and subtypes:
  - oligoarthritis (40-60%), polyarthritis RF- (10-25%), polyarthritis RF+ (5-10%), enthesitis-related (3-10%), systemic (5-15%), psoriatic (2-10%), undifferentiated (10-20%)
- Prognosis based on several large inception cohorts
- Treatment informed by > 100 trial reports

Petty et al, J Rheumatol 2004

How did we get here?

- Two major clinical research advances:
  - Multicentre longitudinal inception cohorts
  - Multicentre randomized clinical trials
- In essence: collaborative clinical research networks
- Similar to networks in other areas of pediatrics, but mostly investigator driven
- Basic research advances, biologic agents

Collaborative networks

- Pioneers: The U.S.A.—U.S.S.R. collaborative clinics
- Pediatric Rheumatology Collaborative Study Group (PRCSG)
- Pediatric Rheumatology International Trials Organization (PRINTO)
- Canadian Association of Pediatric Rheumatology Investigators (CAPRI)

Ruperto N, Martini A. Arch Dis Child. 2011

Multicentre cohorts vs. case series

Cohorts:

- Many centres, generalisable
- Defined data collection
- Prospective data entered in database
- Few years to collect enough sample
- Standard self-report measures

Case series:

- One centre, limited generalisability
- Usual charting
- Retrospective extraction of data
- Many years to collect enough sample
- No self-report available

ReACCh-Out

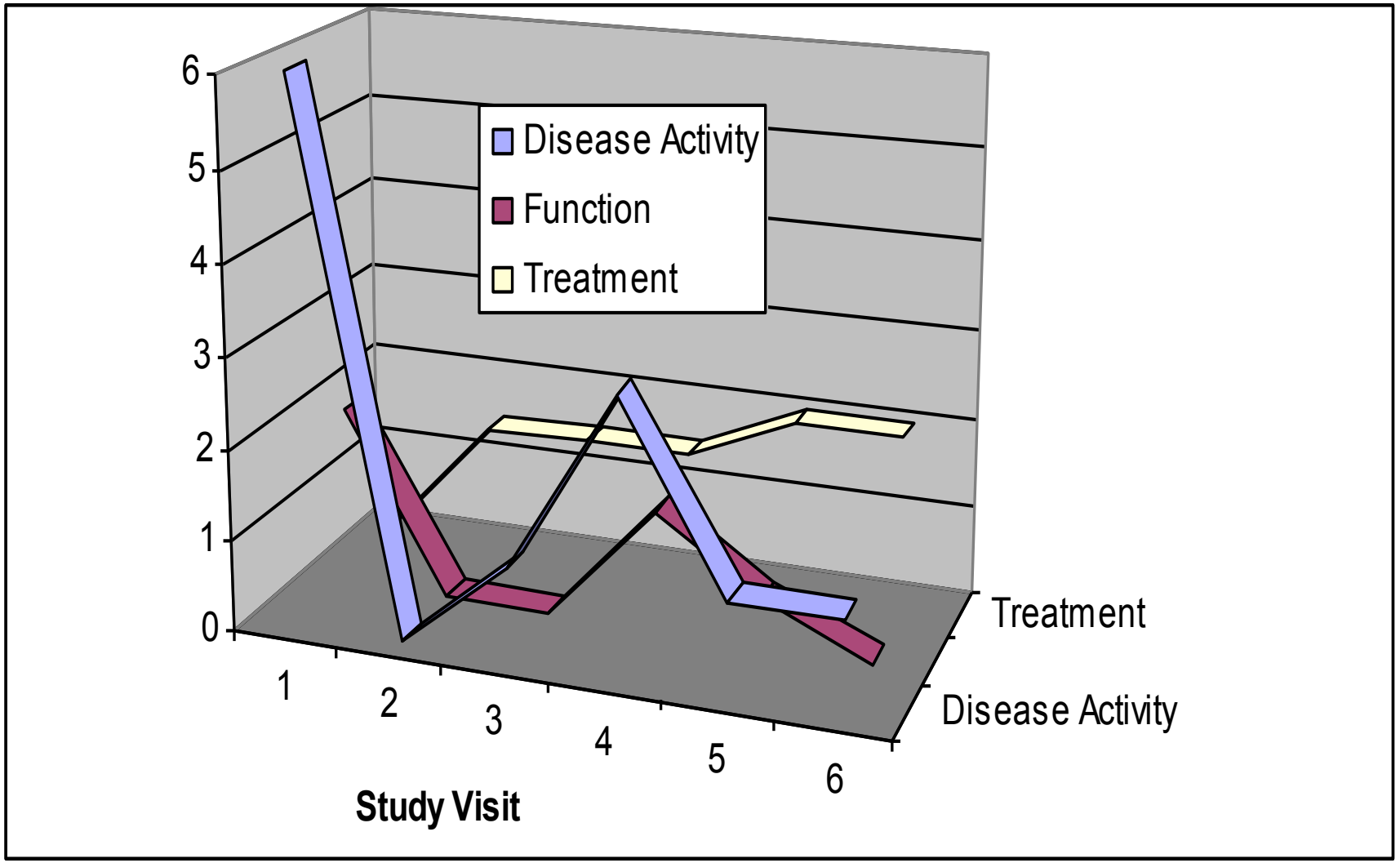
- Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out).
- Pan-Canadian project of pediatric rheumatology centres (CAPRI) funded by CIHR
- Follows course and outcomes of >1500 children with JIA
- Every 6 months core data set:
  - joint counts, functioning, parent and physician global assessment, quality of life, inflammatory markers, disease features, treatment requirements

ReACCh-Out findings

- With current treatments, the percentage of children with inactive JIA (all subtypes) increases from 5% at enrollment to 33% at 6 months, and 49% at 24 months
- >50% of children with oligoarthritis were fully functional and had no detectable disease within 6 months

Oen et al, Arthritis Care & Res 2010. Tse et al, 2011

Analysis challenges



Trials in JIA

- > 14 trials of anti-inflammatories
- > 14 trials of non-biologic DMARDS
- > 5 trials of biologic agents
- 3 trials of corticosteroid injections

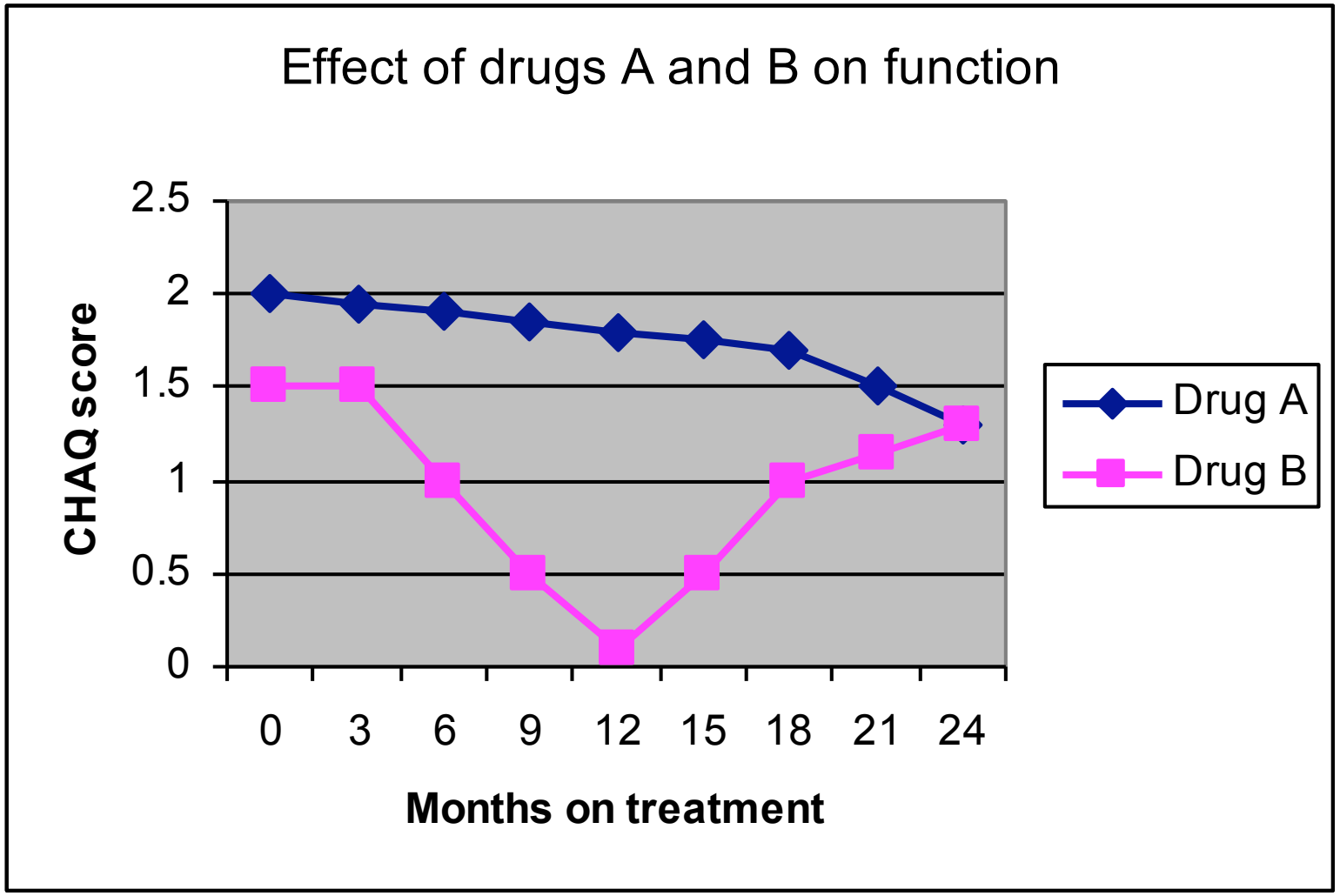
- Challenges in data analysis
- Unique randomized withdrawal trials

Haskes & Laxer, JAMA 2008

Analysis of RCT's

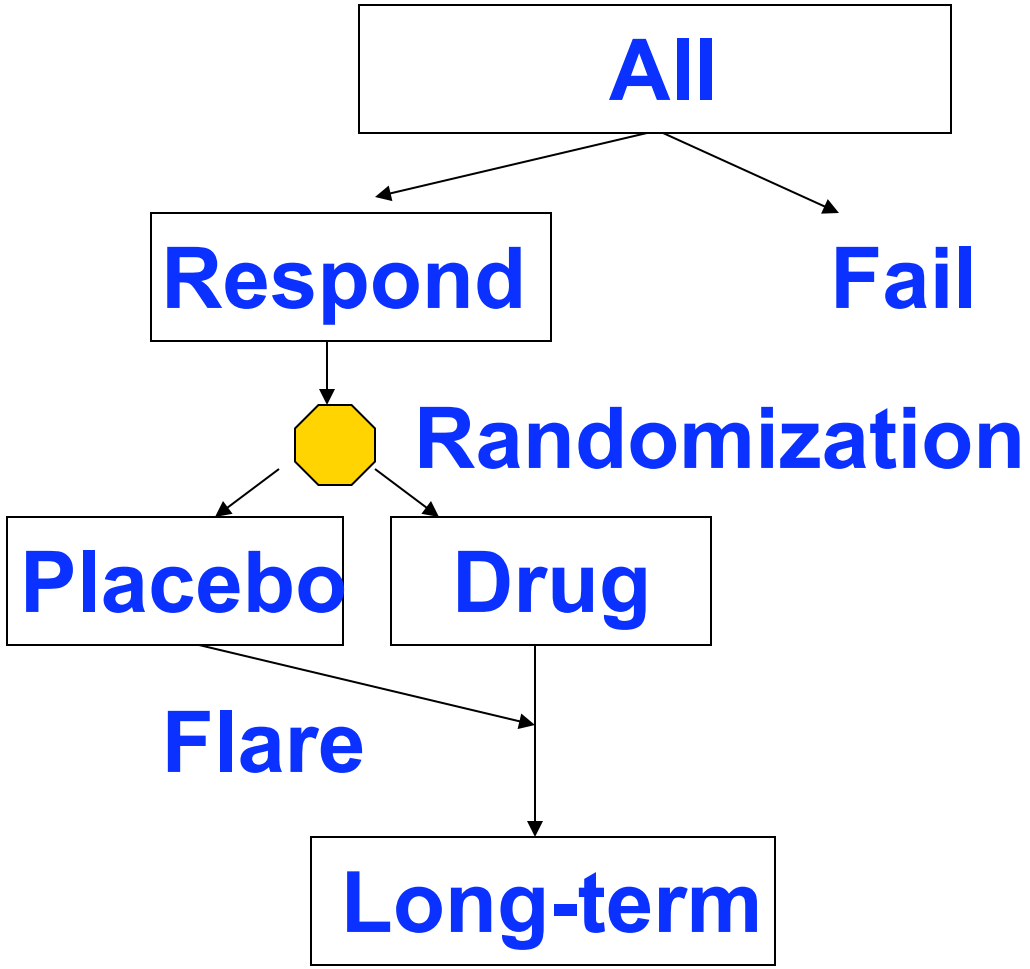
- Follow subjects on treatment A or treatment B for two years
  - See how they end
  - See how they change from baseline to end
  - See how they do during the full study

Traditional RCT

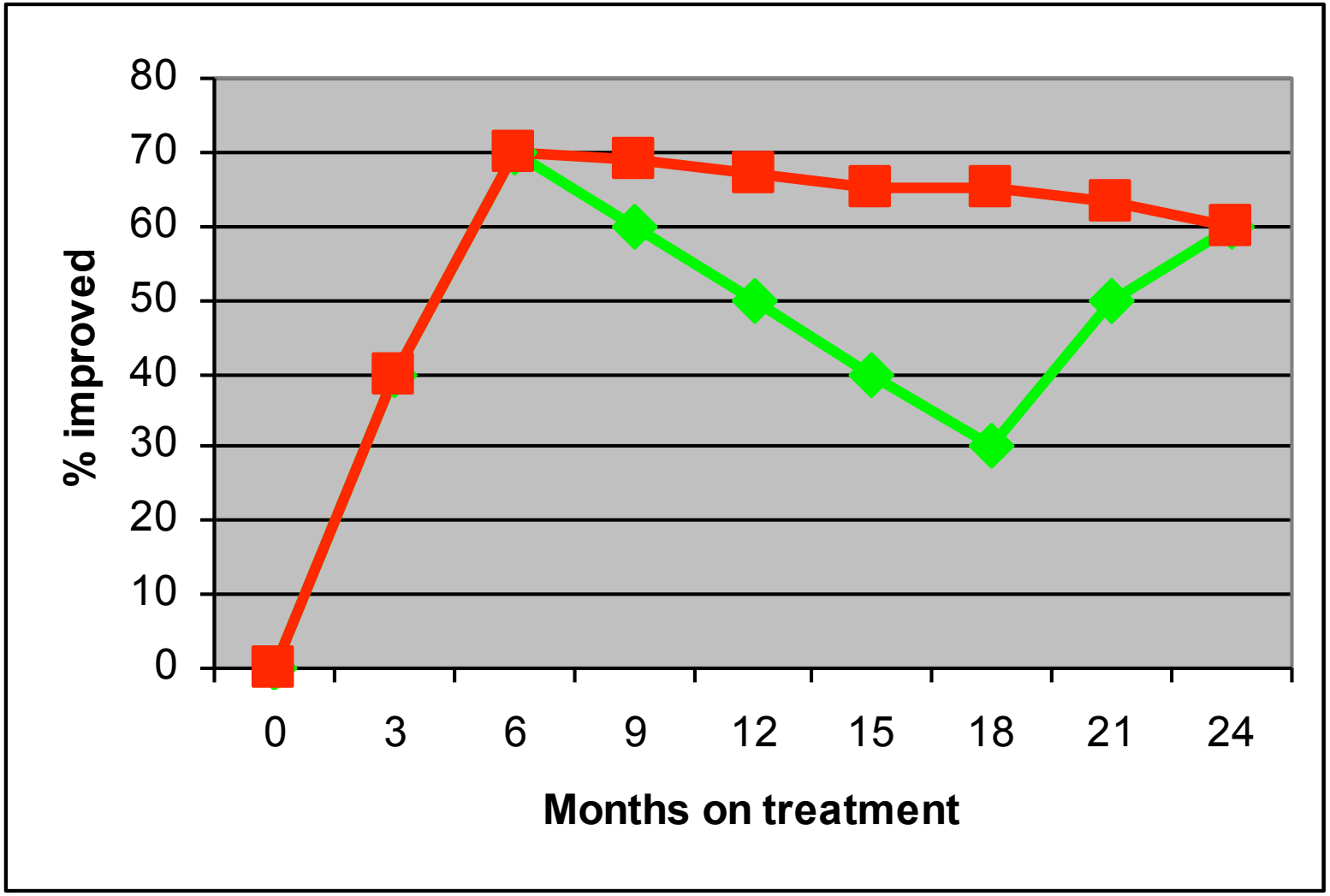


Randomized withdrawal trial

- All children start on active drug
- Responders are randomized to continue drug or switch to placebo
- Children who flare on placebo go back on drug
- Open long-term follow-up



Randomized withdrawal trial



The case – future

- A.D., a three year old girl with newly diagnosed arthritis
- Parents ask:
  - Doctor, what will happen to my child?
  - What treatment will be needed?

The future

- Based on her genetic, biological and clinical markers, your child has a 90% chance of full remission within 2 years and 60% chance that it will never come back (cured?).
- The best initial treatment for her is A, followed by B+C.
- We will avoid D since it has a high risk of side effects in your child.

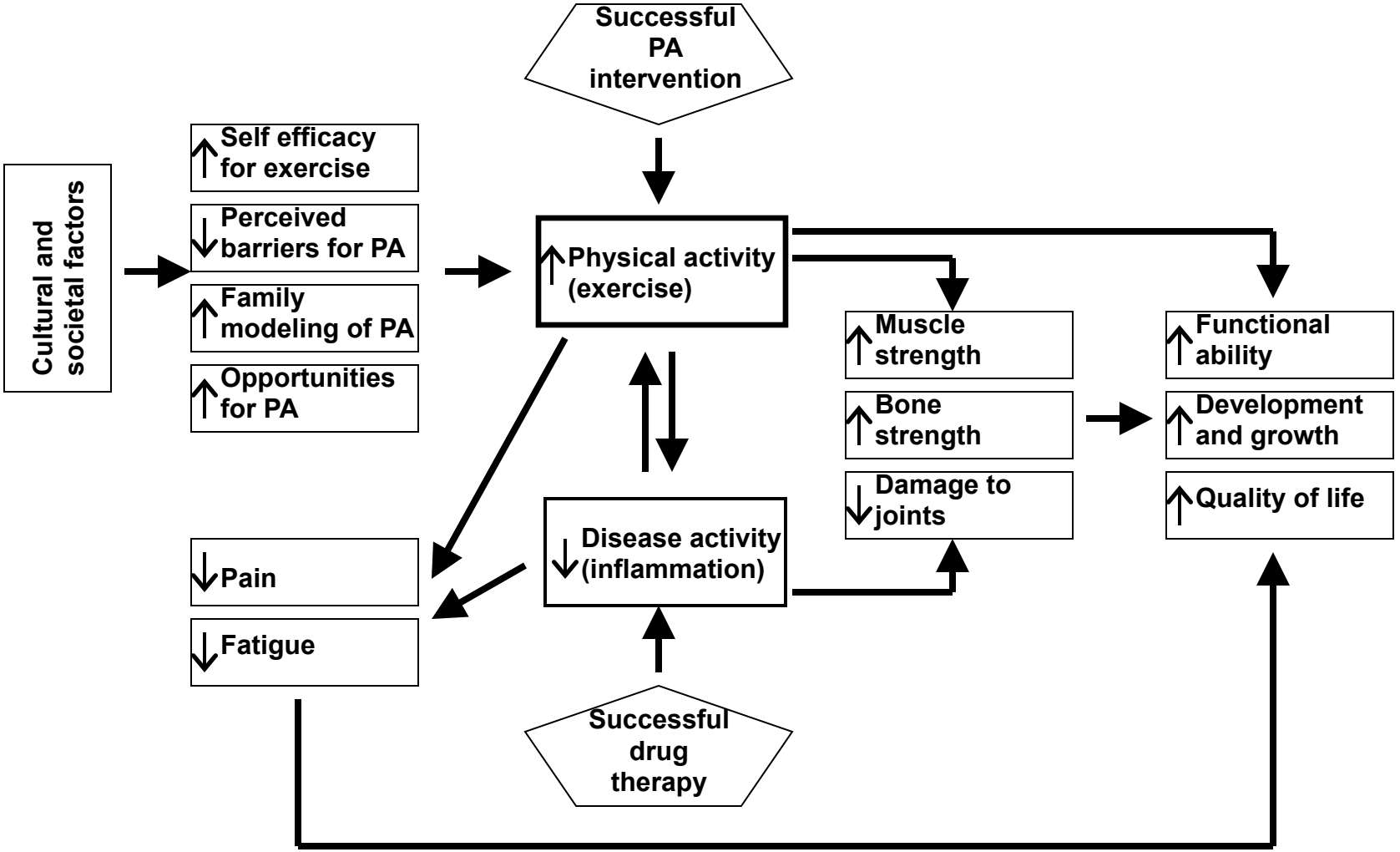
The future

- Genetic markers
- Biological markers
- Clinical prediction
- Collaborative trials of treatment paths instead of single drugs
- Real-time monitoring of function
- Oral “biologic” agents targeted to mediator signal transduction

The LEAP project

- Linking Exercise, Activity and Pathophysiology in JIA (LEAP)
- Team grant funded by CIHR (about half a million per year)
- Collaboration of researchers in rheumatology (CAPRI), physical activity and rehabilitation, biomarkers, bone and muscle development
- Longitudinal measurement of physical activity, disease activity, biomarkers, bone structure and muscle strength in JIA cohorts

LEAP conceptual model



Measuring What Counts

- 20 children with JIA monitored one week before and one week after joint injection
- Electronic tracking of physical activity and community participation via iPhone and accelerometer
- To test feasibility of monitoring in cohorts and as outcome measure in trials

UCAN

- Understanding Childhood Arthritis Network
- International collaboration of cohorts of children with JIA (Meta-Cohorts)
- To elucidate genetic markers explaining disease phenotype heterogeneity

From: bluegiant.com

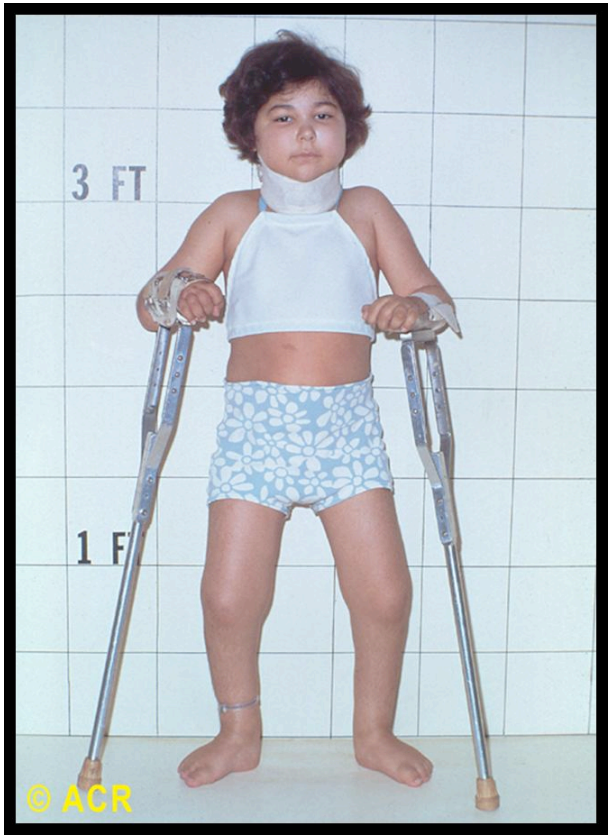
Back to the case – wrap up

- A.D., a three year old girl with newly diagnosed JIA
- Parents ask:
  - Doctor, what will happen to my child?
  - What treatment will be needed?

In summary

- Pediatric rheumatology has seen major changes in how clinical research is done
- Multicenter inception cohorts and randomized withdrawal trials have advanced prognosis and treatment of JIA
- How do we answer parents' questions is changing and the future is bright
- Clinical epidemiology challenges remain in deciding how best to analyze information

Past, present, future



Thank you. Any questions?

From: estabrook.ci.lexington.ma.us