Survival Inequalities among Children, Adolescents and Young Adults with Acute Leukemia in California

Renata Abrahão, MD MSc PhD

California Cancer Registrars Association
Sacramento – November 3rd, 2016
Objectives

- **To increase awareness** of the burden of cancer among children, adolescents and young adults (AYAs) in California, with specific emphasis on those with acute leukemia.

- **To identify** the main predictors of survival and early death among young patients with acute leukemia.

- **To develop an understanding** of how utilization of cancer registry data may help to identify and decrease health disparities among children and AYAs in California and elsewhere.
Outline

1. Background and Research Questions
2. Materials and Methods
3. Study 1: Acute Lymphoblastic Leukemia (ALL)
4. Study 2: Acute Promyelocytic Leukemia (APL)
5. Study 3: Acute Myeloid Leukemia (AML)
6. Discussion
7. Further Research
8. Conclusions
Background
In 2008, 12.7 million people were diagnosed with cancer
7.6 million died from the disease

In 2030, 21.4 million people will have cancer
13.2 million will die from the disease

Source: IARC GLOBOCAN 2008
Pediatric cancer burden

Current population growth + Decrease in child mortality rates = 30% increase in childhood cancer by 2020

Leading cause of childhood death by disease in the developed world
Leukemia

- Greek: "white" (leukos) and "blood" (haima)
- The most frequent childhood cancer
- Leading cause of cancer death among patients aged $\leq 39$ years in the developed world
- Lymphoid or myeloid
Normal blood cells production in the bone marrow

Multipotent hematopoietic stem cell (Hemocytoblast)

- Common myeloid progenitor
  - Erythrocyte
  - Mast cell
  - Myeloblast
  - Megakaryocyte
    - Thrombocytes
  - Basophil
  - Neutrophil
  - Eosinophil
  - Monocyte
  - Macrophage
  - Plasma cell

- Common lymphoid progenitor
  - Small lymphocyte
    - B lymphocyte
    - T lymphocyte
  - Natural killer cell (Large granular lymphocyte)
Leukemia

- Acute (rapidly progressing) or chronic (slowly progressing) form
- From 100% fatal to potentially curable disease
- However, survival varies widely between and within countries, by disease subtype, by age at diagnosis, race/ethnicity, and socioeconomic status (SES)
International differences in 5-year survival among children with leukemia

Adapted from “Cancer Atlas”: http://canceratlas.cancer.org
Survival variation by age at diagnosis after acute lymphoblastic leukemia

- Survival is worse for adolescents and young adults compared with children.

Adapted from Bleyer et al, *J Adolesc Young Adult Oncol* 2011
Survival variation by SES among children with acute lymphoblastic leukemia (ALL) in the UK (1990–1997)

Source: Lightfoot et al., Eur J Cancer, 2011
Childhood and young adult acute myeloid leukemia

- Substantial survival improvement over the last few decades
- However, long-term survival remains only **60% or less** among young patients
- Improvement mostly due to intensive treatment and optimal supportive care
Evidence from the literature review

1. Few studies have examined survival by race/ethnicity other than black & white race

1. Lack of population-based studies looking at SES and survival among young patients

2. Causes of survival inequalities are not fully understood
Evidence from the literature review

4. Acute promyelocytic leukemia (APL): controversy on whether early death has improved after the US FDA approval of all-trans retinoic acid (ATRA) in 1995

5. Acute myeloid leukemia (AML): lack of population-based studies on early death and survival among children, adolescents and young adults
Racial and Ethnic Disparities in Acute Leukemia

Genetic factors

Environmental Factors

Disease Susceptibility

Racial and Ethnic Disparities in Acute Leukemia

Treatment outcomes

Tumor genomics

Germline genomics

Non-genetic factors

Adapted from Lim et al, Cancer 2014
Research questions
1. How much has survival varied among children, adolescents and young adults with acute leukemia in California in the last few decades?
2. Has **early death** (30-day mortality) decreased among young patients with APL in the ‘ATRA era’?
3. What are the main **predictors** of outcome among young patients with ALL, APL and AML?
Materials and Methods
The California Cancer Registry (CCR)

Cancer Prevention Institute of California
<table>
<thead>
<tr>
<th>Variables available in CCR dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>Age at diagnosis</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Neighborhood SES</td>
</tr>
<tr>
<td>Race/ethnicity</td>
</tr>
<tr>
<td>Date of birth</td>
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<tr>
<td>Patient ID</td>
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</table>
## Variables available in CCR dataset

<table>
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<tr>
<th>Patient</th>
<th>Tumor</th>
<th>Clinical</th>
<th>Follow-up</th>
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<tr>
<td>Age at diagnosis</td>
<td>Morphology code</td>
<td>Chemotherapy</td>
<td>Date of Last vital status</td>
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<tr>
<td>Sex</td>
<td>Behavior</td>
<td>Radiotherapy</td>
<td>Vital status</td>
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<tr>
<td>Neighborhood SES</td>
<td>Diagnostic confirmation</td>
<td>HSCT (2003 onwards)</td>
<td>Cause of death</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Immunophenotype (ALL)</td>
<td>Treatment facility</td>
<td></td>
</tr>
<tr>
<td>Date of birth</td>
<td>Date of diagnosis</td>
<td>Health insurance (1996 onwards)</td>
<td></td>
</tr>
<tr>
<td>Patient ID</td>
<td>Tumor ID</td>
<td>Period of diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary malignancy (ALL)</td>
<td></td>
</tr>
</tbody>
</table>
Materials and Methods

• Study design: population-based cohort studies
• Period of diagnosis: 1988–2011
• Follow-up until December 2012
• Age range: 0–19y (ALL)
  0–39y (APL and AML)
Materials and Methods

Survival analysis

- Kaplan-Meier method: overall survival

- Cox proportional hazards models
  - Measure the association between the hazard of death and sociodemographic and clinical variables
Materials and Methods

Early death

- Proportion of patients with APL and AML who died within 30 days after diagnosis
- 7-day mortality also investigated for APL

Logistic regression

- Measure the association between early death and sociodemographic and clinical variables
Results
Study 1

Acute Lymphoblastic Leukemia (ALL)

Racial/Ethnic and Socioeconomic Disparities in Survival Among Children With Acute Lymphoblastic Leukemia in California, 1988–2011: A Population-Based Observational Study

Renata Abrahão, MD, MSC,1,2* Daphne Y. Lichtensztajn, MD, MPH,2 Raul C. Ribeiro, MD,3 Neyssa M. Marina, MD,4 Ruth H. Keogh, PhD,5 Rafael Marcos-Gragera, MD, MSC, PhD,6 Sally L. Glaser, PhD,2,7 and Theresa H.M. Keegan, PhD, MSC2,7

Study 1: Acute Lymphoblastic Leukemia

- Out of 9,295 patients, 21% died during follow-up

Adjusted hazard ratios of death

<table>
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<tr>
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<tbody>
<tr>
<td><strong>Race/ethnicity</strong></td>
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<td></td>
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<tr>
<td>White</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
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<tr>
<td>Black</td>
<td>1.57 (1.26–1.96)</td>
<td>1.74 (1.31–2.31)</td>
<td>1.72 (1.29–2.28)</td>
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<tr>
<td>Hispanic</td>
<td>1.38 (1.23–1.55)</td>
<td>1.43 (1.22–1.68)</td>
<td>1.37 (1.17–1.62)</td>
</tr>
<tr>
<td>Asian</td>
<td>1.33 (1.12–1.59)</td>
<td>1.42 (1.13–1.79)</td>
<td>1.40 (1.11–1.76)</td>
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<tr>
<td><strong>Neighbourhood socioeconomic status</strong></td>
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<td></td>
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<tr>
<td>1. Lowest 20%</td>
<td>1.39 (1.18–1.64)</td>
<td>1.40 (1.12–1.75)</td>
<td>1.30 (1.04–2.27)</td>
</tr>
<tr>
<td>2.</td>
<td>1.15 (0.97–1.35)</td>
<td>1.20 (0.95–1.51)</td>
<td>1.15 (0.91–1.44)</td>
</tr>
<tr>
<td>3. Middle 20%</td>
<td>1.13 (0.95–1.33)</td>
<td>1.10 (0.87–1.38)</td>
<td>1.06 (0.84–1.34)</td>
</tr>
<tr>
<td>4.</td>
<td>1.17 (0.99–1.39)</td>
<td>1.22 (0.97–1.54)</td>
<td>1.20 (0.95–1.51)</td>
</tr>
<tr>
<td>5. Highest 20%</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
</tbody>
</table>
ALL: 10-year survival by race/ethnicity

Survival probabilities (%)

Years after diagnosis of ALL

P < 0.0001

82% (80%-83%)
77% (74%-84%)
74% (73%-76%)
71% (65%-75%)

Whites
Asians
Hispanics
Blacks
ALL: 10-year survival by neighborhood SES
Original Article

Disparities in Early Death and Survival in Children, Adolescents, and Young Adults with Acute Promyelocytic Leukemia in California

Renata Abrahão, MD, MSc1,2; Raul C. Ribeiro, MD3; Bruno C. Medeiros, MD4; Ruth H. Keogh, DPhil5; and Theresa H.M. Keegan, PhD, MSc2,6

BACKGROUND: Findings from clinical trials and population-based studies have differed with regard to whether mortality within 30 days of diagnosis (early death) of acute promyelocytic leukemia (APL) has decreased in the era of all-trans retinoic acid and

Abrahão et al., Cancer, 2015
Study 2: Acute Promyelocytic Leukemia

- 30-day mortality decreased from 26% (pre ATRA era) to 14% (later ATRA era)

- Despite improvement, this result is higher than that reported in clinical trials (3%–8%)

- When excluded 7-day mortality patients, 30-day mortality decreased from 15% (pre-ATRA era) to 3%–8% (ATRA era)
## The odds ratio of early death

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio 1 (95% CI, 1988–2011)</th>
<th>Odds ratio 2 (95% CI, 1996–2011)</th>
<th>Odds ratio 3 (95% CI, 1996–2011)</th>
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<tbody>
<tr>
<td><strong>Calendar period</strong></td>
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<td></td>
<td></td>
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<tr>
<td>1988–1995 (pre-ATRA)</td>
<td>3.01 (1.66–5.46)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>1996–2003 (earlier ATRA era)</td>
<td>1.39 (0.80–2.43)</td>
<td>1.41 (0.81–2.46)</td>
<td>1.30 (0.74–2.30)</td>
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<tr>
<td>2004–2011 (later ATRA era)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
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<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>Black</td>
<td>1.82 (0.63–5.20)</td>
<td>2.48 (0.72–8.51)</td>
<td>2.37 (0.68–8.31)</td>
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<tr>
<td>Hispanic</td>
<td>2.13 (1.16–3.89)</td>
<td>2.20 (1.04–4.63)</td>
<td>2.23 (1.01–4.92)</td>
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<tr>
<td>Asian</td>
<td>1.35 (0.56–3.26)</td>
<td>1.11 (0.36–3.51)</td>
<td>1.24 (0.39–3.87)</td>
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<td><strong>Health insurance (limited to patients diagnosed in 1996–2011; n = 609)</strong></td>
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<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td><strong>2.67 (1.10–6.52)</strong></td>
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<td>Public</td>
<td>N/A</td>
<td>N/A</td>
<td>0.66 (0.32–1.33)</td>
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<td>Private</td>
<td>N/A</td>
<td>N/A</td>
<td>1 (base)</td>
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<tr>
<td>Unknown/NOS</td>
<td>N/A</td>
<td>N/A</td>
<td>0.22 (0.06–0.79)</td>
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</table>
Study 3

Acute Myeloid Leukemia (AML)

Predictors of early death and survival among children, adolescents and young adults with acute myeloid leukaemia in California, 1988–2011: a population-based study

Renata Abrahão, Ruth H. Keogh, Daphne Y. Lichtensztajn, Rafael Marcos-Graga, Bruno C. Medeiros, Michel P. Coleman, Raul C. Ribeiro and Theresa H. M. Keegan

Summary

A better understanding of factors associated with early death and survival among children, adolescents and young adults with acute myeloid leukaemia (AML) may guide health policy aimed at improving outcomes in these populations.

Abrahão et al., Br J Haematol, 2016
AML: survival by period of diagnosis
AML: 10-year survival by age at diagnosis

Survival probabilities (%)

Years from diagnosis

P value < 0.0001

- 0–9 years: 50% (46%–53%), N=964
- 10–19 years: 41% (38%–45%), N=733
- 20–29 years: 38% (35%–41%), N=951
- 30–39 years: 33% (30%–35%), N=1,287
AML: survival by race/ethnicity

Survival probabilities (%) vs Years from diagnosis of AML

Whites, Hispanics and Asians vs Blacks

Log-rank P=0.0087
AML: survival by treatment facility

- Affiliated-NCI hospitals
- Non-affiliated NCI hospitals

Survival probabilities (%)

Years from diagnosis of AML

P<0.0001
AML: survival by health insurance status (1996–2011)

Survival probabilities (%)

Years from diagnosis of AML

Log rank P = 0.0045
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Odds ratios for early death (95% CI)</th>
<th>Hazards ratios for death (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
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<tr>
<td>0–9</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>10–19</td>
<td>1.21 (0.82–1.40)</td>
<td>1.23 (1.07–1.40)</td>
</tr>
<tr>
<td>20–29</td>
<td>1.64 (1.16–2.34)</td>
<td>1.34 (1.18–1.52)</td>
</tr>
<tr>
<td>30–39</td>
<td>1.70 (1.22–2.38)</td>
<td>1.55 (1.38–1.74)</td>
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<tr>
<td><strong>Race/ethnicity</strong></td>
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<tr>
<td>Non-Hispanic white</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<tr>
<td>Non-Hispanic black</td>
<td>1.15 (0.74–1.79)</td>
<td>1.27 (1.08–1.49)</td>
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<tr>
<td>Hispanic</td>
<td>1.14 (0.86–1.49)</td>
<td>1.05 (0.95–1.16)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.65 (0.42–0.99)</td>
<td>0.98 (0.86–1.13)</td>
</tr>
<tr>
<td><strong>Neighbourhood socioeconomic status (quintiles)</strong></td>
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</tr>
<tr>
<td>1. Lowest 20%</td>
<td>1.57 (1.05–2.34)</td>
<td>1.14 (0.99–1.31)</td>
</tr>
<tr>
<td>2.</td>
<td>1.04 (0.68–1.57)</td>
<td>1.10 (0.95–1.27)</td>
</tr>
<tr>
<td>3. Middle 20%</td>
<td>1.18 (0.78–1.77)</td>
<td>1.13 (0.98–1.30)</td>
</tr>
<tr>
<td>4.</td>
<td>1.19 (0.78–1.81)</td>
<td>1.01 (0.87–1.15)</td>
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<td>5. Highest 20%</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td><strong>Initial care at hospitals affiliated with NCI-designated cancer centres</strong></td>
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<td>Yes</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<tr>
<td>No</td>
<td>1.75 (1.28–2.39)</td>
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<td>Private</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<tr>
<td>Unknown/NOS</td>
<td>1.04 (0.01–0.43)</td>
<td>1.27 (1.07–1.51)</td>
</tr>
</tbody>
</table>
Discussion
Drawing comparisons between studies

1. Calendar period: overall survival have improved over time for all leukemias (less for AML)

2. Age at diagnosis: survival was lower for patients aged $\geq 10$ years compared with younger children

3. Racial/ethnic disparities:
   - Lower survival for black patients in all studies
   - Lower survival for Hispanics for ALL and APL but not AML
Drawing comparisons between studies

4. Lack of health insurance: associated with outcomes for APL and AML, but not for ALL

5. Treatment at specialized cancer centers: relevant for AML only

6. Lower neighborhood SES: associated with outcomes for ALL and AML, but not APL
Studies main contributions to the field of Hematology

1. Reinforces the persistence of survival inequalities by age at diagnosis, race/ethnicity and SES among young patients with acute leukemia

2. Contributes to the debate over whether early death from APL has decreased in the ‘ATRA era’
Studies main contributions to the field of Hematology

3. Calls attention to the association of lack of health insurance with lower survival after AML and APL

4. Provides baseline data to further comparisons of survival after the implementation of the Affordable Care Act (“Obamacare”)
Studies main contributions to the field of Hematology

5. Emphasises the need of new drugs development for the treatment of AML and high-risk ALL

6. Highlights the importance of treatment of patients with AML at specialized cancer centers

7. Reinforces the fundamental need for linking population-based data with clinical / hospital data
Strengths
Studies strengths

1. Population-based studies
2. High-quality data
3. Large sample sizes
4. Long period of observation
Studies strengths

5. Racial/ethnic diverse population
6. Information on neighborhood SES
7. Information on access to care
8. Some data on treatment
9. Full dates (day, month, year)
Limitations
Limitations

Adapted from California HealthCare Foundation & Hiatt et al., J Natl Cancer Inst 2015
Lack of information on:

1. Disease biology
2. Performance status & risk stratification
3. Laboratory chemistry
4. Detailed information on treatment
5. Treatment adherence (mainly ALL)
6. Relapse
Further Research
Questions for future research

1. Are the findings of my studies representative of the United States population?

2. Have adolescents and young adults with ALL been treated on pediatric protocols by adult oncologists in California?
Are the findings of my studies representative of the United States population?

Original Article

Racial Disparities in the Survival of American Children, Adolescents, and Young Adults With Acute Lymphoblastic Leukemia, Acute Myelogenous Leukemia, and Hodgkin Lymphoma

Justine M. Kahn, MD; Theresa H.M. Keegan, PhD, MS; Li Tao, MD, PhD; Renata Abrahão, MD, MSC, PhD; Archie Bleyer, MD; and Aaron D. Viny, MD, MS

Kahn et al., Cancer, 2016
2. Have adolescents and young adults with ALL been treated on pediatric protocols by adult oncologists in California?

Original Article

Adoption of Pediatric-Inspired Acute Lymphoblastic Leukemia Regimens by Adult Oncologists Treating Adolescents and Young Adults: A Population-Based Study

Lori Muffy, MD, MS; Daphne Lichtensztajn, MD, MPH; Parveen Shiraz, MD; Renata Abrahão, MD, MSc; Jennifer McNeer, MD, MS; Wendy Stock, MD; Theresa Keegan, PhD; and Scarlett Lin Gomez, PhD

BACKGROUND: Studies have demonstrated superior outcomes for adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL) who are treated using pediatric versus adult therapeutic regimens. To the best of our knowledge, whether adult oncologists in the United States have adopted this approach to ALL in AYA patients is currently unknown. The objective of the

Muffy et al., Cancer, 2016
Conclusions
Conclusions

• My studies showed that survival improved over time for all leukemias

• However, survival varied widely in the most populous state of the United States, lower for vulnerable patients

• Survival inequalities are secondary to multiple factors
Racial and Ethnic Disparities in Acute Leukemia

Genetic factors

Environmental Factors

Disease Susceptibility

Treatment outcomes

Tumor genomics

Germline genomics

Non-genetic factors

Adapted from Lim et al, Cancer 2014
POVERTY

Inadequate diet
Poor education
Environmental risks

POOR HEALTH

Unemployment
Loss of income
Health care costs
“If we are to preserve civilization, we must make certain its benefits are available to the many, not reserved for the few.”

Dr Raul Ribeiro, N Engl J Med 2005
Acknowledgement
Thank you for your attention!

Q & A

Source: https://www.stjude.org