



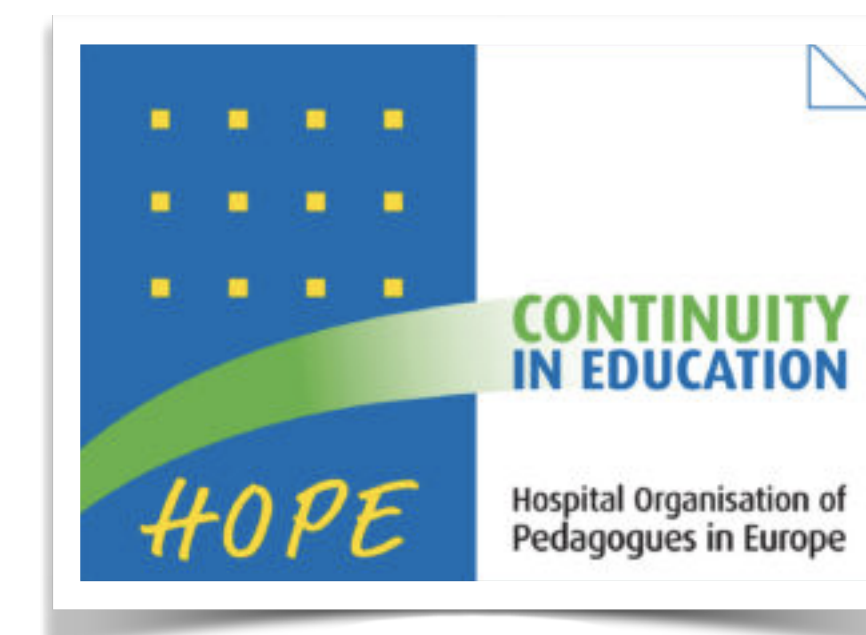
Shaping the future with education

Milano, 8-12 May, 2023

HOPE

Wherever We Go...

**the remarkable journey of a "white coat" treating children
and discovering their resilience, school, families and cultures**



Adriana BALDUZZI, MD

Hematopoietic Stem Cell Transplant Unit, Director

Fondazione IRCCS San Gerardo dei Tintori

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Centro Maria Letizia Verga



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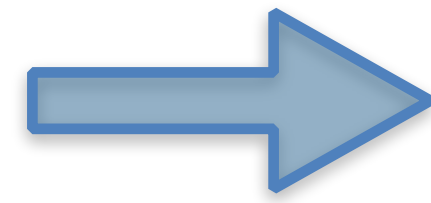
... delighted to be here and join experts in education...

“We are like dwarfs on the shoulders of giants, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size.”

— *Bernard De Chartres*



Presentation Plan



where	affiliation
who	journey as a "white coat"
whom	treating children - life, cure, death
what	patient resilience, school, families and cultures
when	a fulltime work
how	a team dedication
why	common discussion

Delighted to treat and eventually cure them!



il Notiziario

Comitato Maria Letizia Verga
PER LO STUDIO E LA CURA DELLA LEUCEMIA IN FANCIULLINO
ONLUS

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Felici di guarirli

3

CENTRO MARIA LETIZIA VERGA



Entrate nella nostra nuova casa

Una lunga storia che prosegue qui

La racconta la dottoressa Balduzzi da 25 anni con noi



Adriana Balduzzi

E' un po' come quando "metti su casa": i muratori non finiscono mai, ... ma perché non c'è la presa di corrente dove serve? ...vi sono calcinacci e fili ovunque...è tutto da pulire... la consegna dei mobili è in ritardo...ma poi il grande giorno arriva e che emozione stringere tra le mani le chiavi della tua casa nuova...

scorso un periodo di esperienza al Fred Hutchinson Cancer Research Center: il tempio della trapiantologia! Rientro in tempo per partecipare alla inaugurazione del nuovo DHE. Voluta e sostenuto dal Comitato Maria Letizia Verga. Ampi spazi luminosi: come avevamo potuto stare nelle 4 stanze dell'11° piano? 2000: il nuovo Centro Trapianto di Midollo Osseo apre i battenti! 5 moderne stanze ospiteranno i pazienti per il trapianto.

Il primo giorno

1 febbraio 1990: varco la soglia dell'Ospedale San Gerardo di Monza. Mi dirigo all'11° piano. E' il mio primo giorno di lavoro a Monza.
1994: il Centro di Ricerca Tettamanti si insedia nel nuovo Laboratorio: ricercatori brillanti, creativi, efficienti. I picconi che smantellano la parola LEUCEMIA non sono mai stati così ben manovrati.
1995: rientro dagli Stati Uniti d'America, dove ho tra-





Entrate nella nostra nuova casa

Una lunga storia che prosegue qui

La racconta la dottoressa Balduzzi da 25 anni con noi



Adriana Balduzzi

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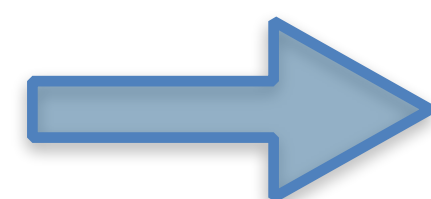
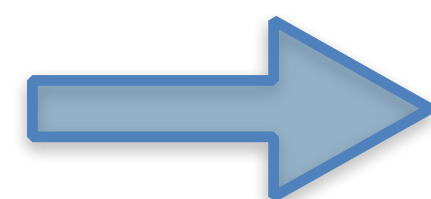




The Future Through Children's Eyes

Centro Maria Letizia Verga

Presentation Plan



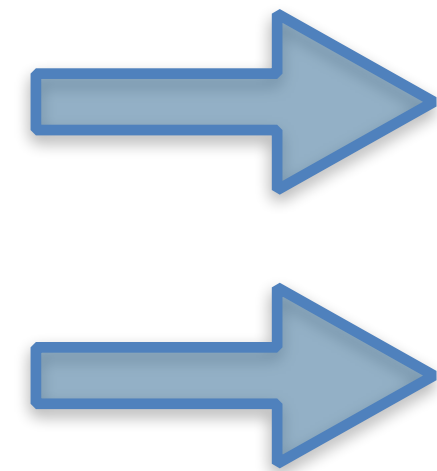
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... my journey as a "white coat": *WHO*

- 1990: a journey starts ... from scratch
- wearing a white coat in front of
 - children and adolescents wearing a pijama
 - life-threatening diseases
 - their parents: the "triangle"
- an unbalanced relationship
 - gaining trust
 - accepting the anger
 - understanding social and cultural diversity



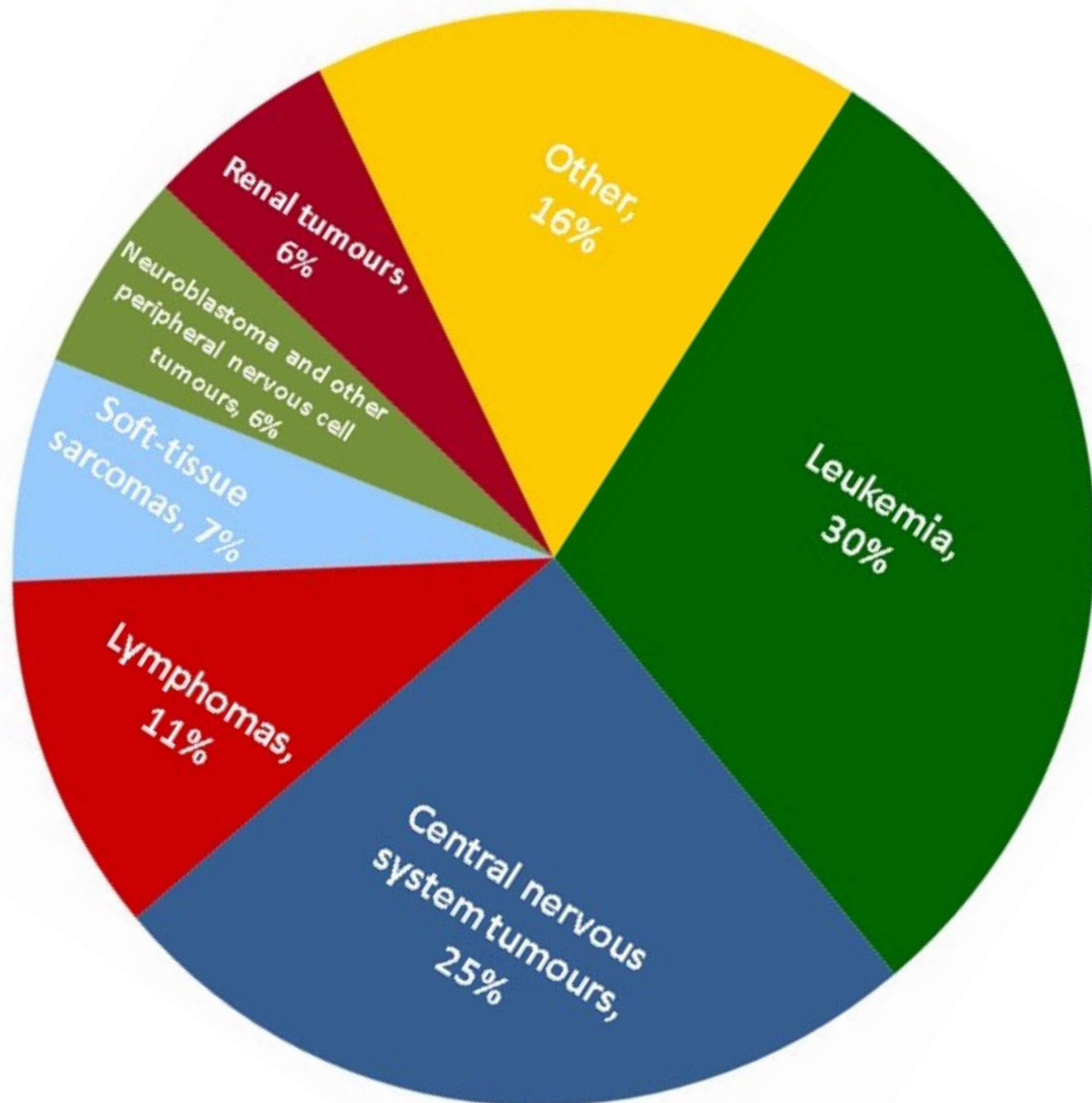
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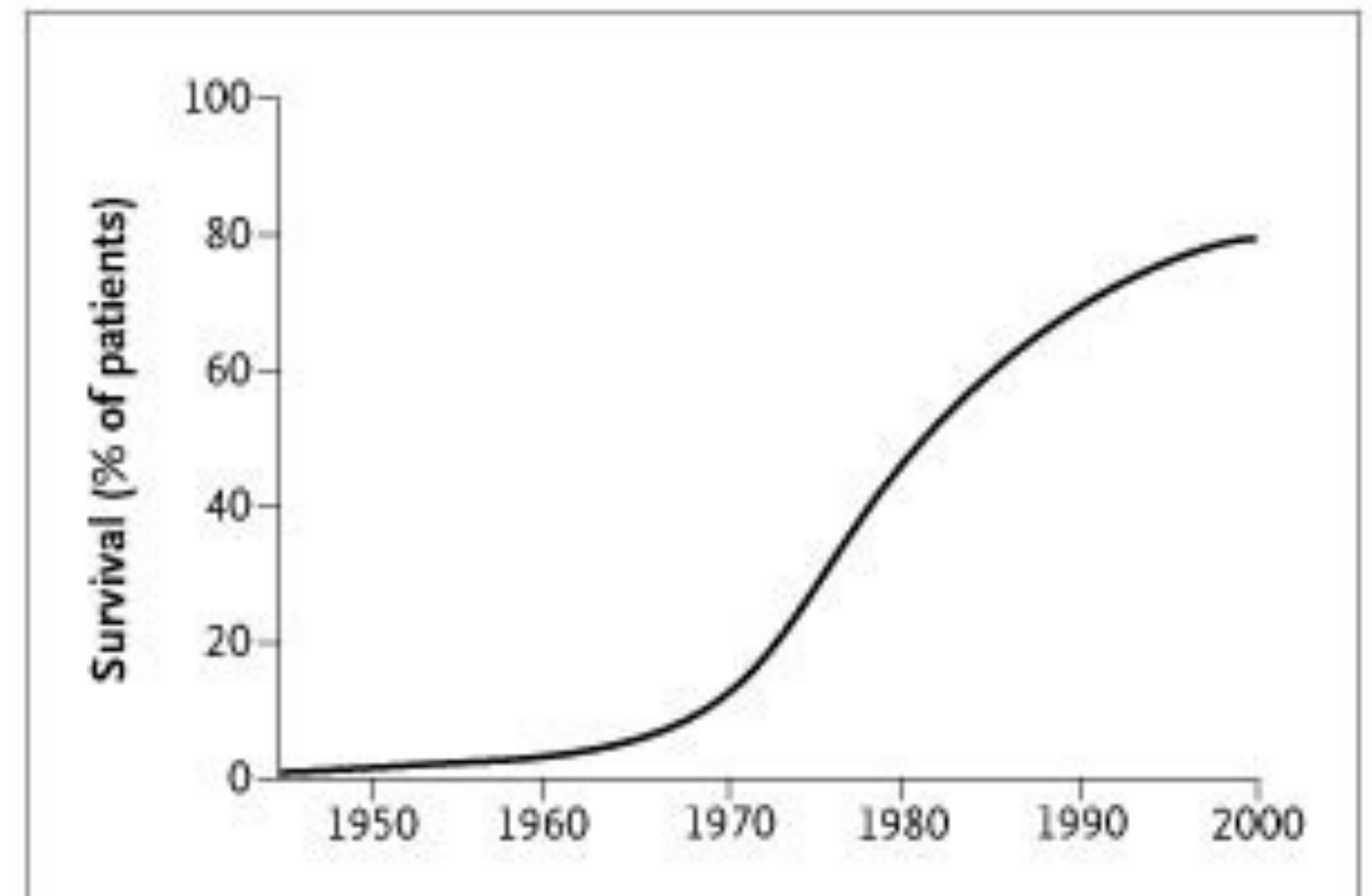
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... my journey as a "white coat": *WHOM*

leukemia and lymphoma:
>40% of childhood cancers



40 years have passed since the first reports that childhood acute lymphoblastic leukemia was no longer incurable



The Progressive Increase in Long-Term Survival among Children with Acute Lymphoblastic Leukemia during the Past Five Decades. J.Simone. NEJM 2003; 349(7): 627-8)¹⁰

... my journey as a "white coat": *WHOM*

...to transplant or not to transplant ... this is the question!

- leukemic patients at dismal prognosis are eligible for transplantation
- definition of eligibility criteria: a dynamic process balancing toxicity sparing to chemotherapy versus efficacy of transplantation
- as the risk profile of the patient worsens, more risky procedures may become acceptable

> efficacy

> toxicity

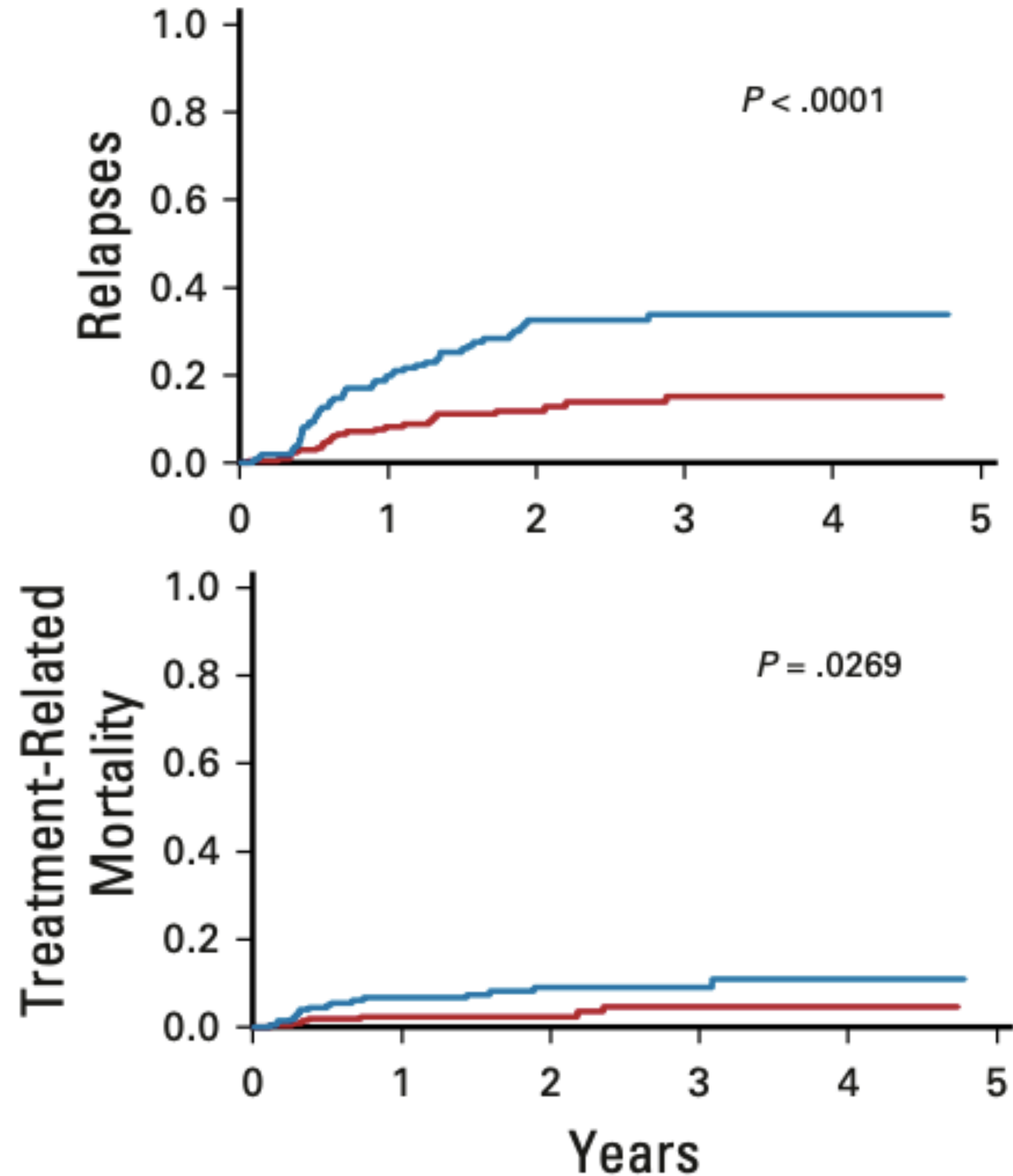
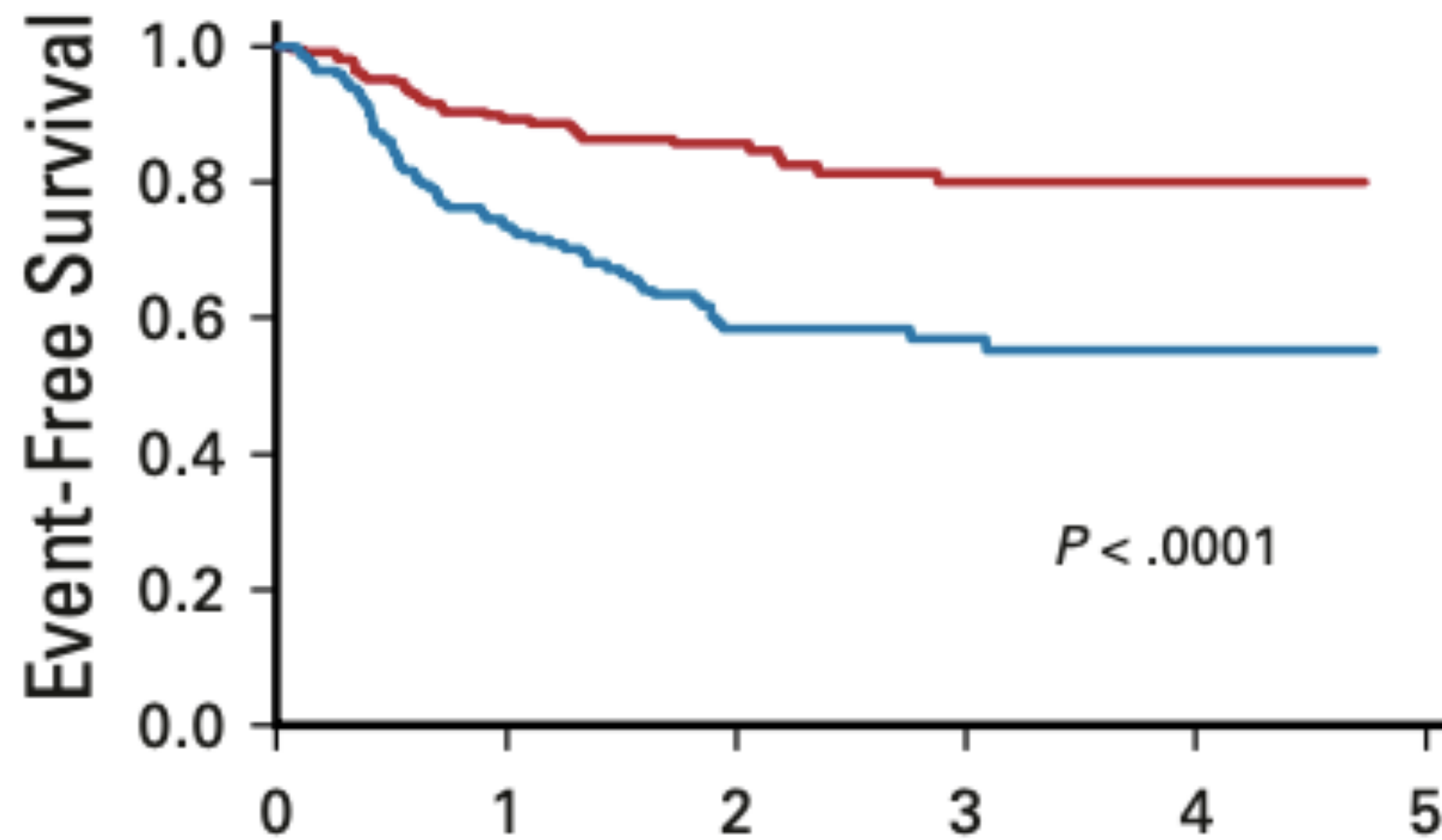
hematopoietic
stem cell
transplantation

chemotherapy

- 6% (vs 15% in the past) of the patients diagnosed with acute lymphoblastic leukemia are considered "at very high risk" —> i.e. eligible for transplantation

... my journey as a "white coat": *WHOM*

...what survival curves do not show...



original reports

Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study

Christina Peters, MD¹; Jean-Hugues Dalle, MD, PhD²; Franco Locatelli, MD, PhD³; Ulrike Poetschger, PhD⁴; Petr Sedlacek, MD⁵; Jochen Buechner, MD, PhD⁶; Peter J. Shaw, MD⁷; Raquel Staciuk, MD⁸; Marianne Iversen, MD, PhD⁹; Herbert Pichler, MD¹; Kim Vetterranta, MD, PhD¹⁰; Peter Svec, MD, PhD¹¹; Olga Aleinikova, MD, PhD¹²; Jerry Stein, MD¹³; Tayfun Güngör, MD¹⁴; Jacek Toporski, MD¹⁵; Tony H. Truong, MD, MPH¹⁶; Cristina Diaz-de-Heredia, MD¹⁷; Marc Bierings, MD, PhD¹⁸; Hany Ariffin, MD, PhD¹⁹; Mohammed Essa, MD²⁰; Birgit Burkhardt, MD, PhD²¹; Kirk Schultz, MD²²; Roland Meisel, MD²³; Arjan Lankester, MD, PhD²⁴; Marc Ansari, MD²⁵; and Martin Schrappe, MD, PhD²⁶ on behalf of the IBFM Study Group; Arend von Stackelberg, MD²⁷ on behalf of the IntReALL Study Group; Adriana Balduzzi, MD²⁸ on behalf of the I-BFM SCT Study Group; Selim Corbacioglu, MD²⁹ on behalf of the EBMT Paediatric Diseases Working Party; and Peter Bader, MD³⁰

... my journey as a "white coat": *WHOM*

...early & late toxicity after transplantation...

acute toxicity

- organ toxicity
- infection (sometimes fatal)
- immunological toxicity

chronic toxicity and sequelae

- sterility
- failure to thrive
- endocrinology and pubertal development
- cataract
- osteonecrosis
- pneumopathy, cardiopatie, nephropaty, neuropatia, ecc
- secondary neoplasia

... my journey as a "white coat": *WHOM*

...early & late toxicity after transplantation...

innovative treatments: targeted therapy

- **blinatumomab**
- **CAR-T cell therapy**
- **inotuzunab...**

...lower toxicity and mortality?



How many kids are "cured"?

- 1 subject over 750 young adults in the US general population is a survivor of childhood cancer (Meadows, 2003)
- 1 subject over 1,000 (0.1%) of the Nordic countries population is a childhood cancer survivor (Olsen, 2009)



	Population	Survivors
U.S. *	250 M	328,000
E.U.	488 M	~300 – 500,000?

* Mariotto AB. et al. Cancer Epidemiol Biomarkers Prev, 2009

Numbers in Europe and in Italy

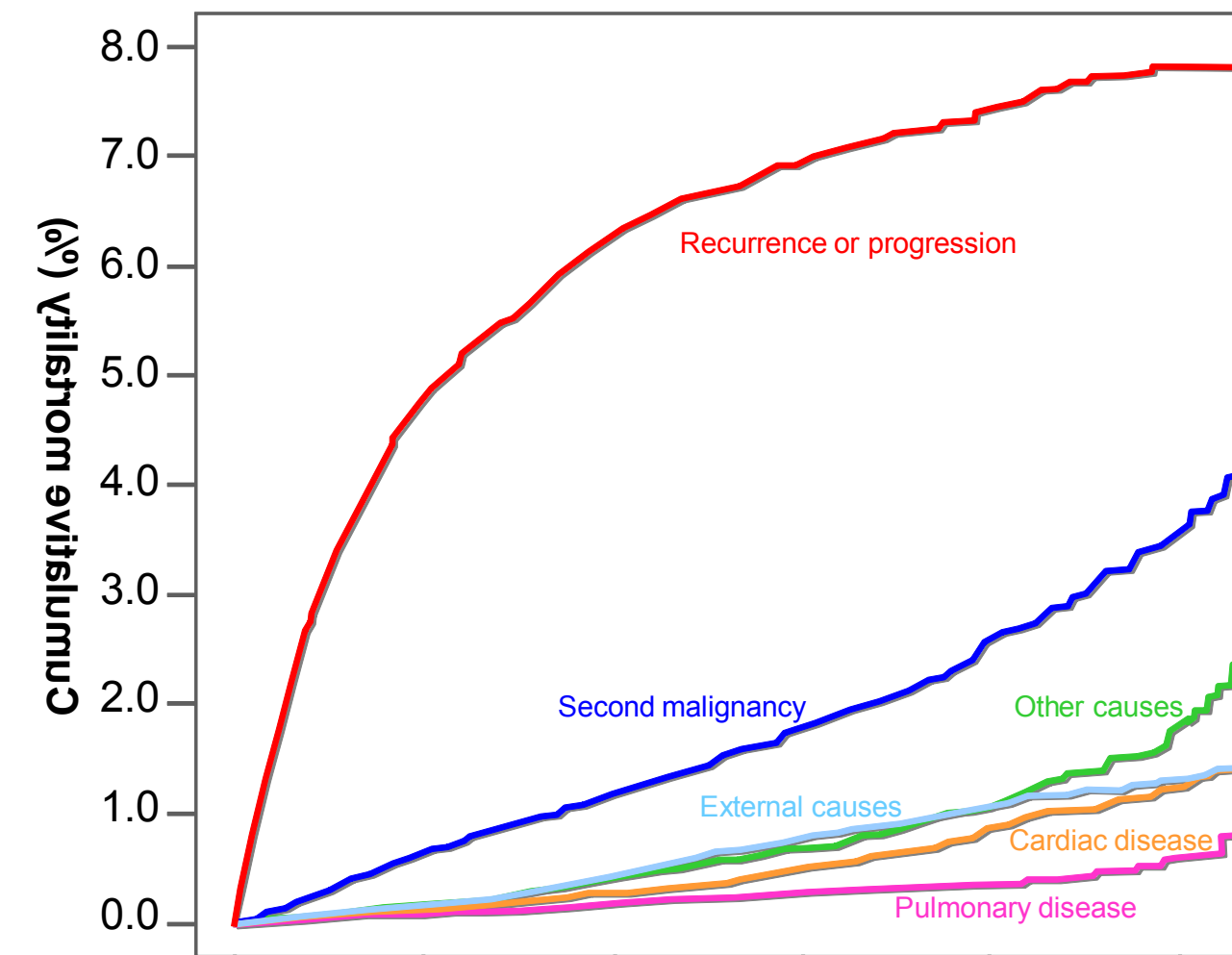
Total population of the 27 EU countries	~ 488,5 million
Percentage of the population 0-14 years	~ 16%
Population aged 0-14 years	~ 78,2 million
New cases of cancer aged 0-14 years	~ 11,000/year
Overall conservative 5-year survival	75%
Increase of the population of long-term survivors	~ 8,250/yr
New yearly cases In Italy	~ 1500/yr
New cases who discontinued treatment	~ 1100/yr

Late mortality

- Cumulative death rate is 11 x higher
- Due to recurrence of cancer (66%)
- BUT**
- toxicity related to treatment (20%) SMN > cardiac disease and > pulmonary

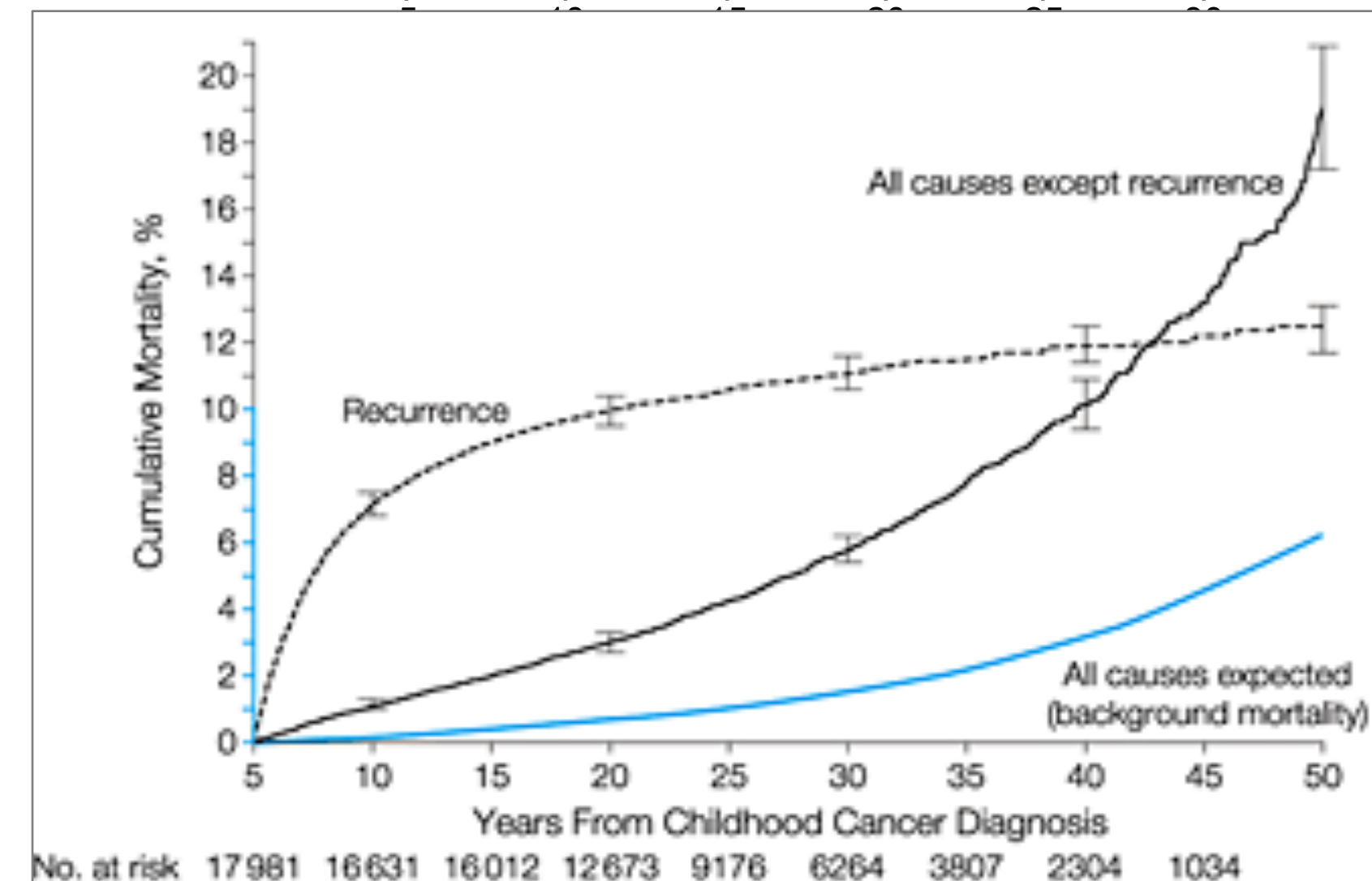
CCSS cohort Mertens et al 2001/2008 JCO

Cumulative mortality due to recurrence of cancer, second malignancy, cardiac disease, external causes, and all other causes

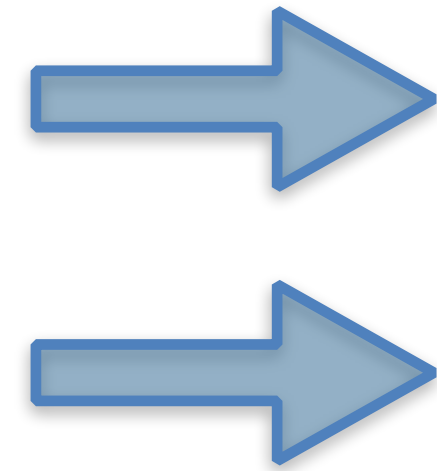


It increases even 40 years after diagnosis

BCSS cohort Reulen et al 2010 JAMA



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... my journey as a "white coat": *WHAT*

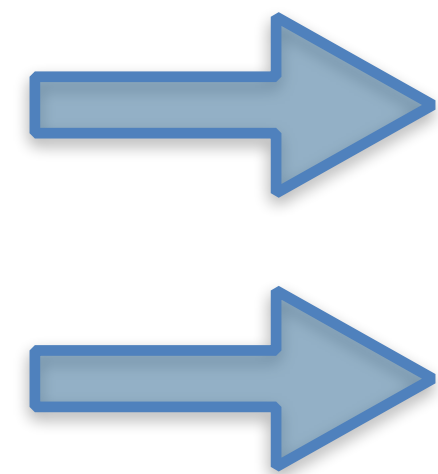
- overwhelming resilience
- patients from all over the world
- cultural mediators

- the first son in a Muslim family: the father's child
- impact on fertility
- Chinese families: little participation vs you as technician

- specific death rituals



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When each of us decided to wear a white coat daily, as a doctor, we all made a clear choice. Our beloveds usually did not; nevertheless, they had to endure it. Sometimes, when they pretend to show some interest in our activities, they are actually trying to estimate how much of our time, potentially shared with them, will be taken away in the near future.

So happened when I started investigating the impact of minimal residual disease (MRD) and chimerism on outcome in the transplantation setting of pediatric acute lymphoblastic leukemia (ALL). When my husband cautiously asked me what I was dealing with, my answer was, "It's like when you gave me the engagement ring, you wondered 'How could such a small thing being so expensive?' [By the way: most of the magic vanished upon that statement!] It is basically the same



The Value of Minimal Residual Disease (and Diamonds)

Adriana Balduzzi *

Clinica Pediatrica Università degli Studi di Milano Bicocca Hospital, Fondazione Monza e Brianza per il Bambino e la sua Mamma, Ospedale San Gerardo di Monza, Monza, MB, Italy



bjh research paper

Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: is there any room for intervention?

British Journal of Haematology, 2014: 164, 396–408

Adriana Balduzzi,¹ Lucia Di Maio,¹ Daniela Silvestri,^{1,2} Simona Songia,³ Sonia Bonanomi,¹ Attilio Rovelli,¹ Valentino Conter,¹ Andrea Biondi,^{1,3} Giovanni Cazzaniga^{3*} and Maria G. Valsecchi^{2*}

¹Clinica Pediatrica, Università degli Studi di Milano-Bicocca, Ospedale San Gerardo, ²Dipartimento di Scienze della Salute, Centro di Ricerca in Ematologia e Trapianti, Ospedale San Gerardo di Monza, ³Fondazione Monza e Brianza per il Bambino e la sua Mamma

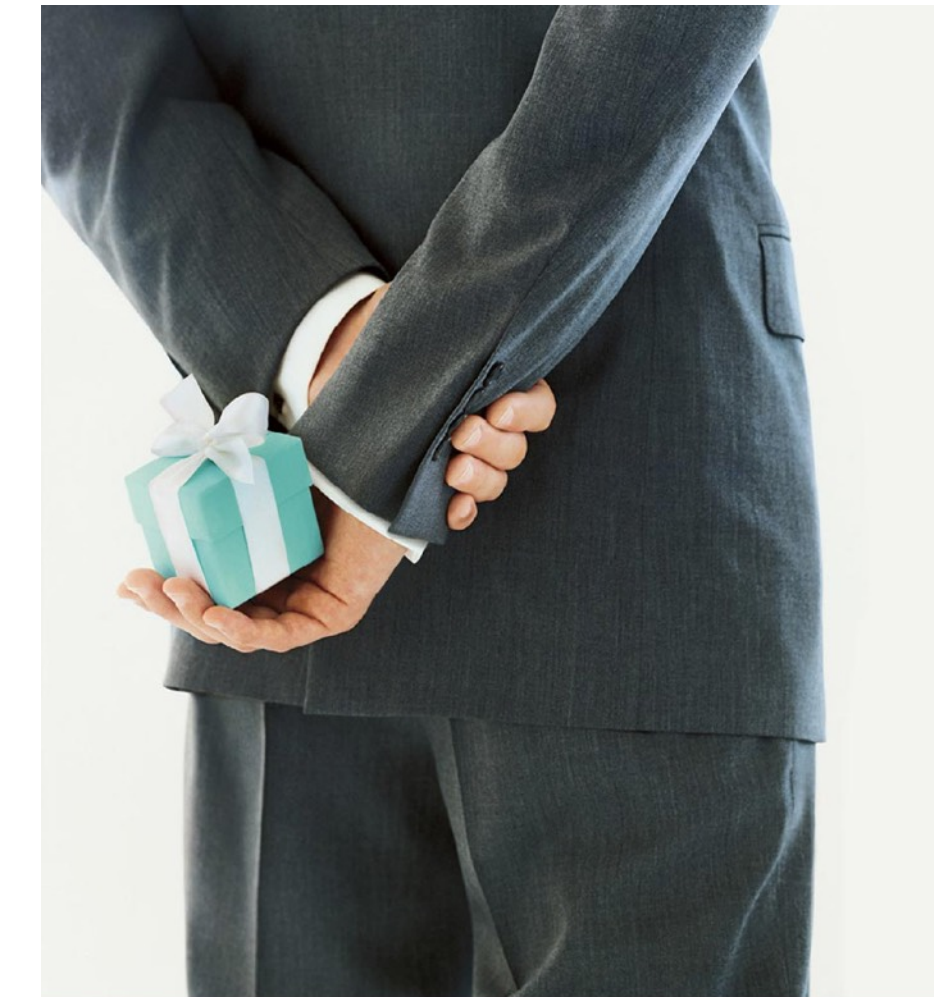
Summary

Eighty-two children and adolescents who underwent allogeneic transplantation for acute lymphoblastic leukaemia in remission (period 2001–2011, median follow-up 4.9 years) had been assessed for minimal residual disease (MRD) by real-time quantitative polymerase chain reaction before and at 1, 3, 6, 9 and 12 months after transplantation. Five-year event-free survival (EFS) and cumulative incidence of relapse were 77.7% [standard error (SE) 5.7] and 11.4% (SE 4.4), respectively, for patients with pre-transplant MRD at 10⁻⁴ (SE 0.1) and 10⁻⁵ (SE 0.1) (P = 0.001).

**Gianni Cazzaniga
Simona Songia**

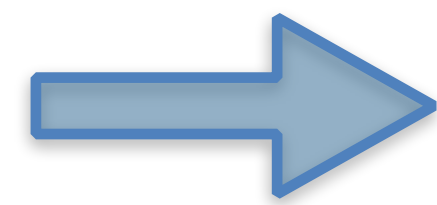
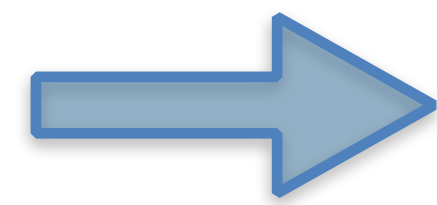


**Maria Grazia Valsecchi
Daniela Silvestri**



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... my journey as a "white coat": *HOW*

- **teachers**

- **pillars of their future**
- **back to "normal" life**

- **alliance amongst:**

- **physicians**
- **nurses**
- **psychologist**
- **social worker**
- **educators**
- **child life specialists**
 - **professionals**
 - **volunteers**
- **families**



**GUARDA IL FUTURO
NEGLI OCCHI**

... my journey as a "white coat": *HOW*

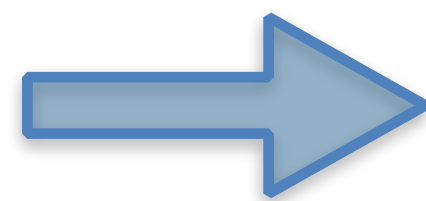
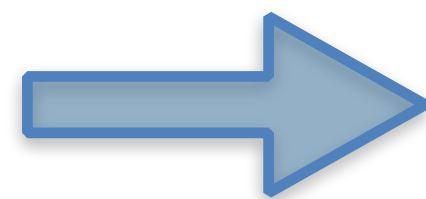
- in case of failure
 - disease refractoriness
 - complications



- you need to build their resilience:
 - facing sequelae
 - quality of life
 - back to normal (?)
 - isolation
 - unemployment
 - economical issues
 - sexuality issues
 - partner
 - offspring
 - degenerative diseases
 - bedrest
- risk/fear of death

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I-BFM SCT Committee @ SIOPe Annual Meeting 23-25 March 2022



Teachers & Educators @CMLV



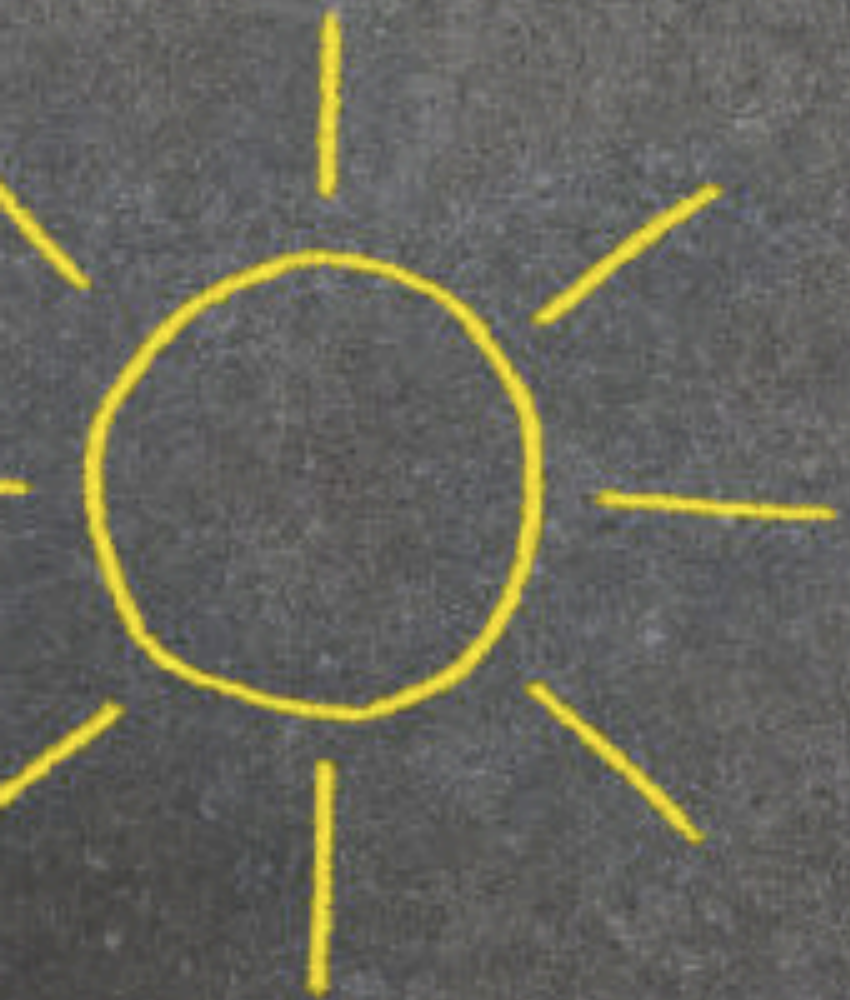
...



**Michele Capurso
and Committee**



Thank you for your attention!



Comitato
Maria Letizia Verga
PER LO STUDIO E LA CURA DELLA LEUCEMIA DEL BAMBINO

ONLUS

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