DIABETE E TUMORI NELLA PRATICA CLINICA:
RILEVANZA, CRITICITÀ, SOLUZIONI

ROMA, 9 Novembre 2019

UNAHOTELS DECÒ
Via Giovanni Amendola, 57

LA TOSSICITÀ DELLE TERAPIE ANTITUMORALI

Cancer survivors e prevenzione secondaria

Francesco Felicetti, MD

S.S.D. Unità di Transizione
per Neoplasie Curate in Età Pediatrica
A.O.U. Città della Salute e della Scienza di Torino

Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☒ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

☐ Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	**Company/Organization**

The Washington Post
Democracy Dies in Darkness

Health & Science

You survived cancer. Now what?

"We're getting better at catching it earlier and treating it,"

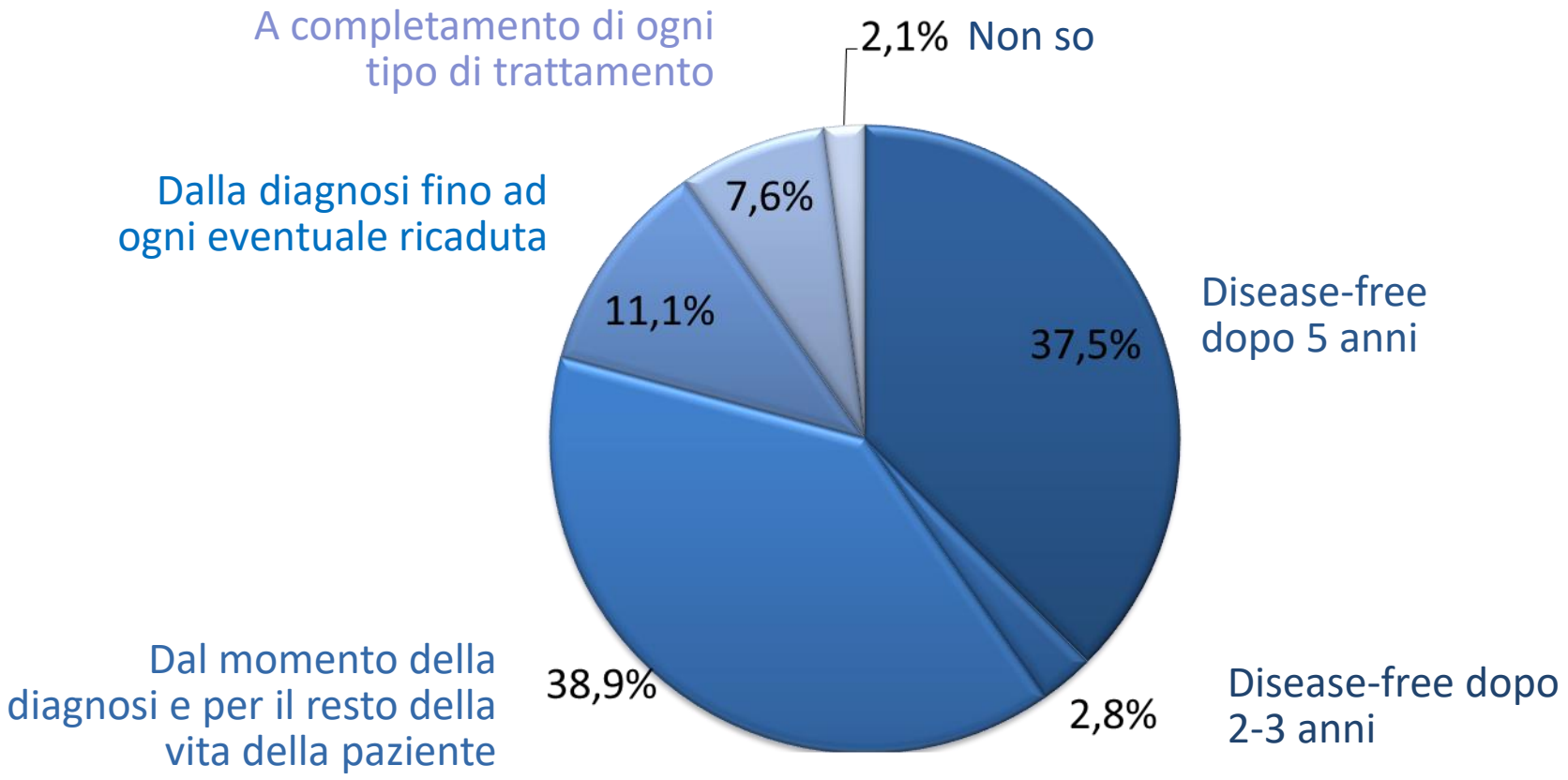
While advances in battling cancer have grabbed the spotlight, ***post-treatment life has gotten much less attention.***

A patient who turns into a survivor faces many challenges*: physical and psychological effects of treatment, including fatigue, numbness, pain and anxiety; and additional disease.*

Some effects can appear ***months or years later****.*

By **Suzanne Allard Levingston**
March 28, 2016

Definizione di *Cancer Survivor*



Breast Cancer Survivorship Alliance. *Health Care Professional Survey: Assessment of Survivorship Awareness and Educational Needs*. Conducted at: 30th Annual San Antonio Breast Cancer Symposium; December 13-17, 2007; San Antonio, TX.

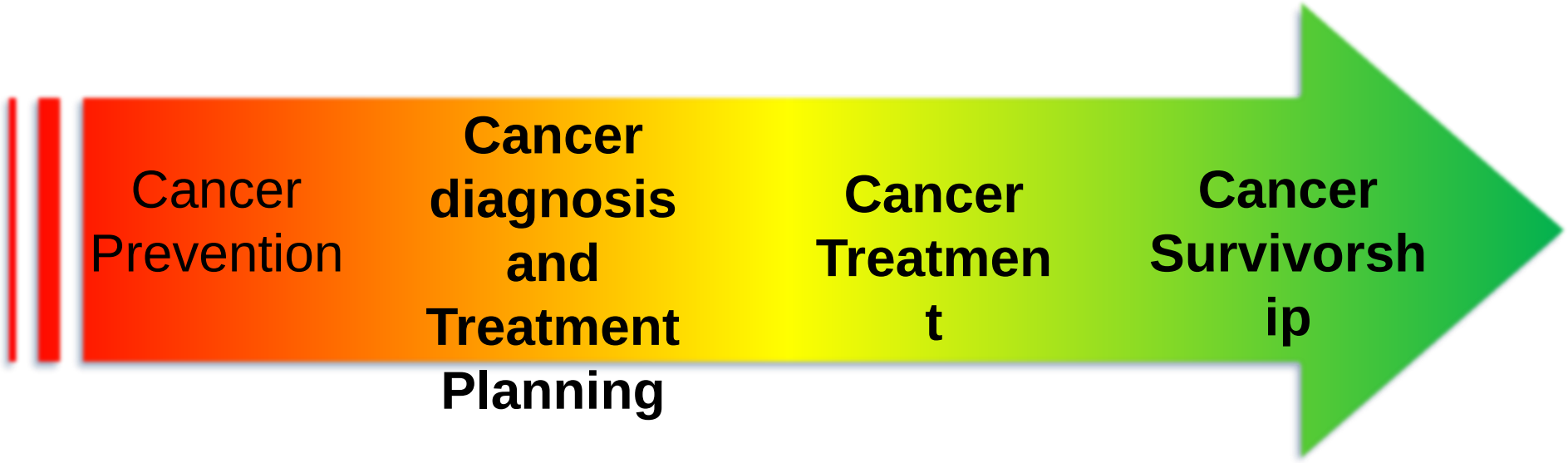
VOLUME 31 · NUMBER 4 · FEBRUARY 1 2013

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

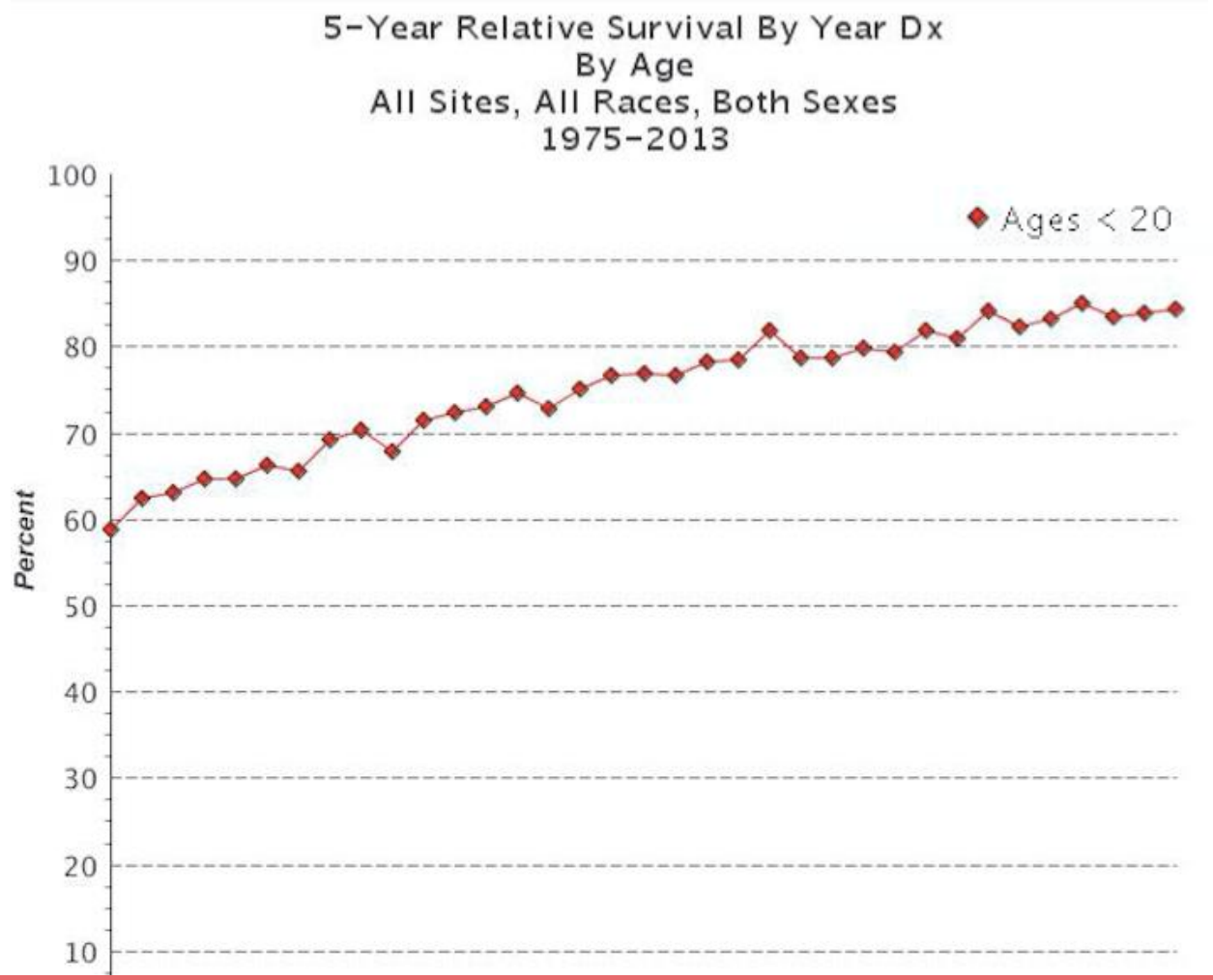
Cancer Survivorship: Why Labels Matter

Kirsten Bell and Svetlana Ristovski-Slijepcevic, *University of British Columbia, Vancouver, British Columbia, Canada*

*The concept of cancer survivorship has been **widely debated** over the past few decades. In biomedical usage, the term survivor has a distinct clinical meaning, referring to **individuals who have had a life-threatening disease but have remained disease free for a minimum of 5 years.***



Il successo dell'Oncologia Pediatrica



La proporzione di CCS è stata stimata fra lo **0,1% e lo 0,15% della popolazione italiana**. Sulla base di una stima conservativa, **ogni anno il numero di CCS nella popolazione italiana cresce di 1.150 unita`**.

(Haupt et al 2013)

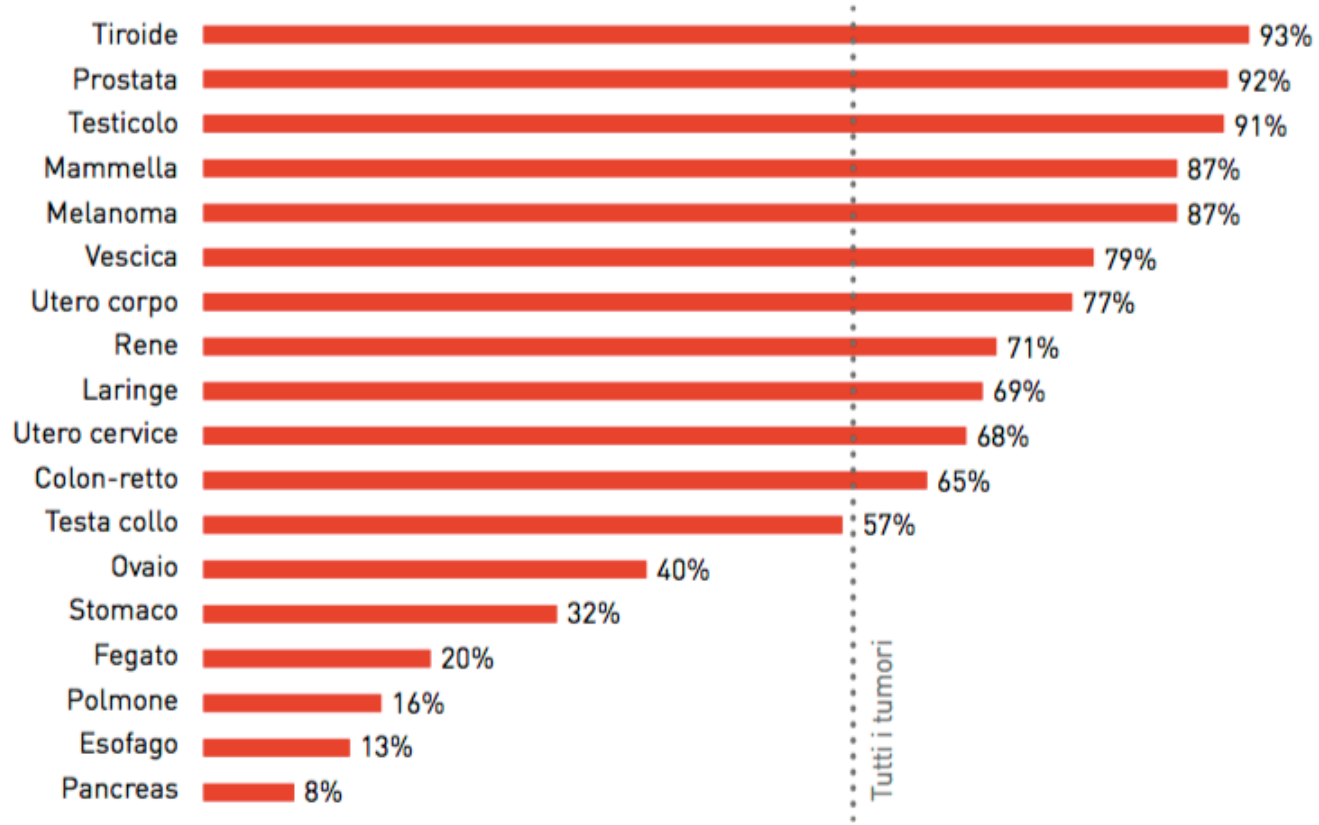


FIGURA 6. **Sopravvivenza netta a 5 anni dalla diagnosi (standardizzata per età) per il periodo di incidenza 2005-2009 (pool AIRTUM), maschi e femmine**

	Maschi				Femmine			
	1990-1994	1995-1999	2000-2004	2005-2009	1990-1994	1995-1999	2000-2004	2005-2009
Tutti i tumori, esclusi carcinomi della cute	39	46	51	54	55	58	60	63

TABELLA 19. **Confronto nel tempo della sopravvivenza netta a 5 anni dalla diagnosi (standardizzata per età) per periodo di incidenza 1990-1994, 1995-1999, 2000-2004 e 2005-2009 (pool AIRTUM). Valori %**

* Comprende lingua, bocca, orofaringe, rinofaringe, ipofaringe, faringe NAS, laringe.
**Comprende sia tumori infiltranti sia non infiltranti.

Tumore	n.	%
Prostata	471.108	30
Colon-retto-ano	250.969	16
Vescica	219.001	14
Rene	84.614	5
Melanomi, cute	77.189	5
Linfomi non-Hodgkin	76.902	5
Polmone	69.508	4
Testicolo	55.591	3
Leucemie	47.486	3
Tiroide	47.205	3
Altri	189.547	12

Tumore	n.	%
Mammella	815.002	44
Colon-retto-ano	230.749	12
Tiroide	158.447	8
Utero, corpo	116.772	6
Melanomi, cute	83.356	4
Linfomi non-Hodgkin	68.895	4
Vescica	58.211	3
Utero cervice	57.000	3
Ovaio	50.032	3
Altri	282.473	15

FIGURA 10. Proporzione di persone che vivono dopo una diagnosi di tumore in Italia nel 2019, per i tipi di tumore più frequenti e sesso

Nel 2019, si stima che gli italiani che vivono dopo una diagnosi di tumore siano circa 3 milioni e mezzo (3.460.025), equivalente al 5,3% dell'intera popolazione (un italiano su 19)

Il prezzo del successo

The NEW ENGLAND JOURNAL of MEDICINE

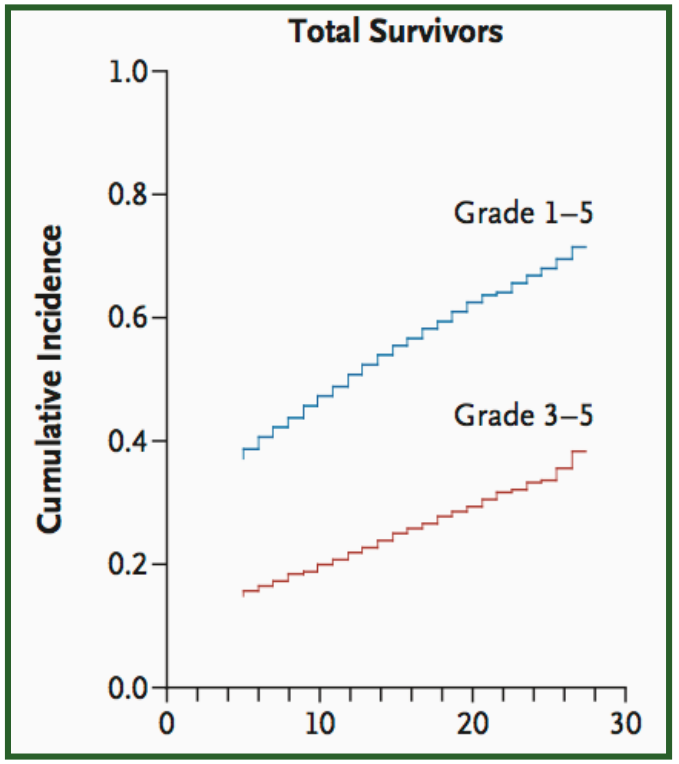
Chronic Health Conditions in Adult Survivors of Childhood Cancer

10,397 survivors and 3034 siblings, with a mean ages of 26.6 years (range, 18.0 to 48.0) and 29.2 years (range, 18.0 to 56.0), respectively.

Among survivors, **62.3% had at least one chronic condition**; **27.5% had a severe or life-threatening condition** (grade 3 or 4).

Health Condition	Survivors (N=10,397)	Siblings (N=3034)
	no. (%)	
Grade 1 (mild)	1931 (18.6)	610 (20.1)
Grade 2 (moderate)	1635 (15.7)	349 (11.5)
Grade 3 (severe)	2128 (20.5)	128 (4.2)
Grade 4 (life-threatening or disabling)	653 (6.3)	30 (1.0)
Grade 5 (fatal)	163 (1.6)	NA†

Oeffinger et al, 2006

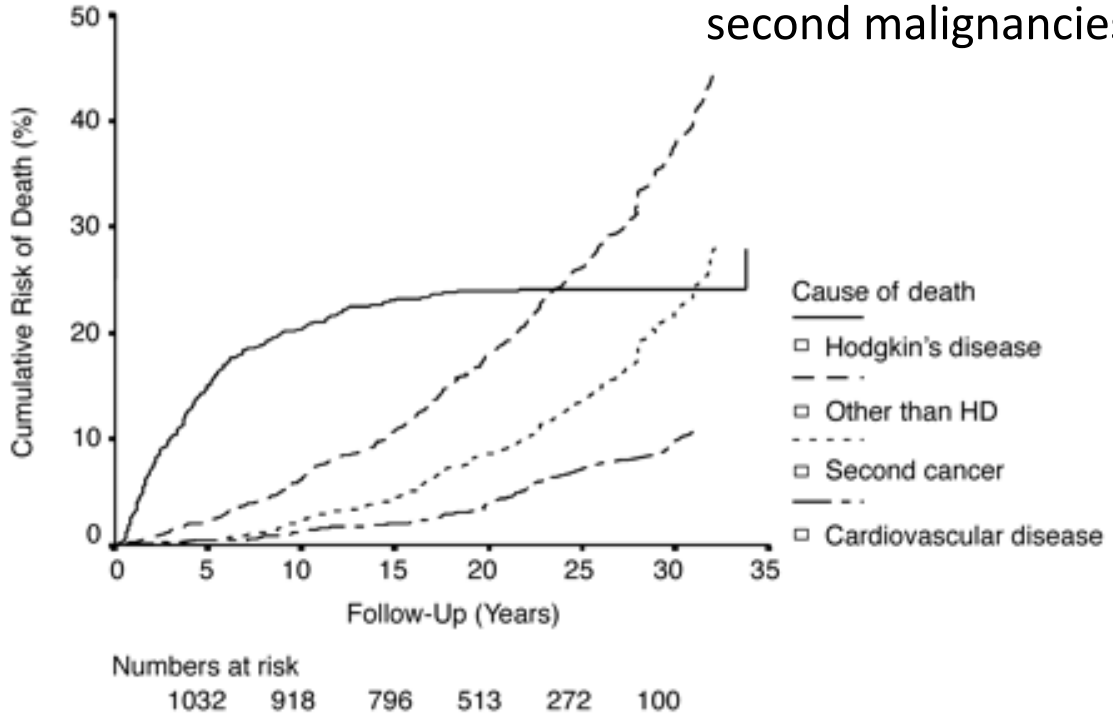


19th Edition

HARRISON'S

PRINCIPLES OF INTERNAL MEDICINE

"Because of the very high cure rate in patients with Hodgkin's lymphoma, **long-term complications have become a major focus for clinical research**. In fact, in some series of patients with early-stage disease, **more patients died from late complications of therapy than from Hodgkin's lymphoma itself.** This is particularly true in patients with localized disease. The most serious late side effects include second malignancies and cardiac injury".



Aleman et al., JCO 2003

GUARIRE
AD OGNI COSTO

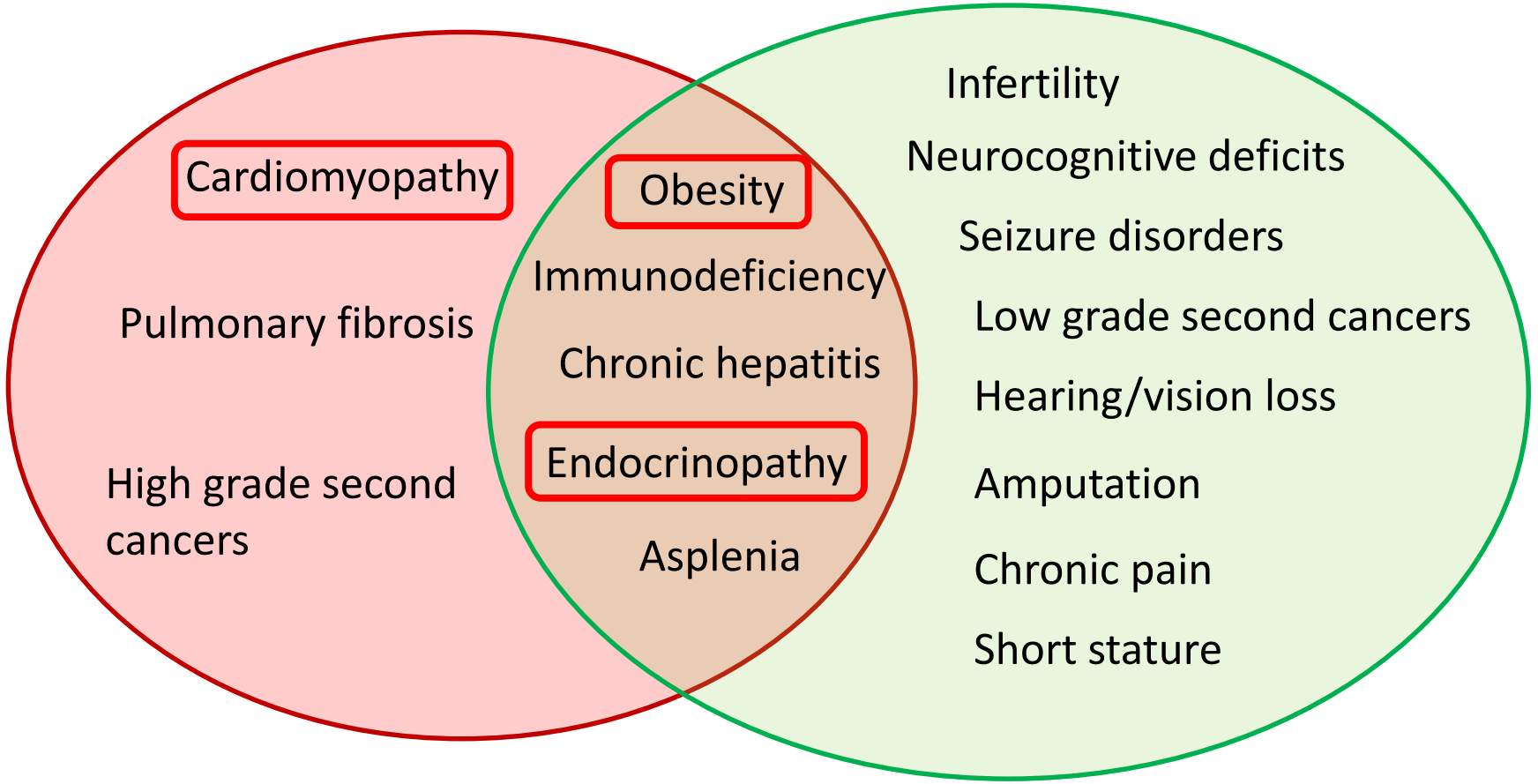
GUARIRE
AL MINOR COSTO
POSSIBILE

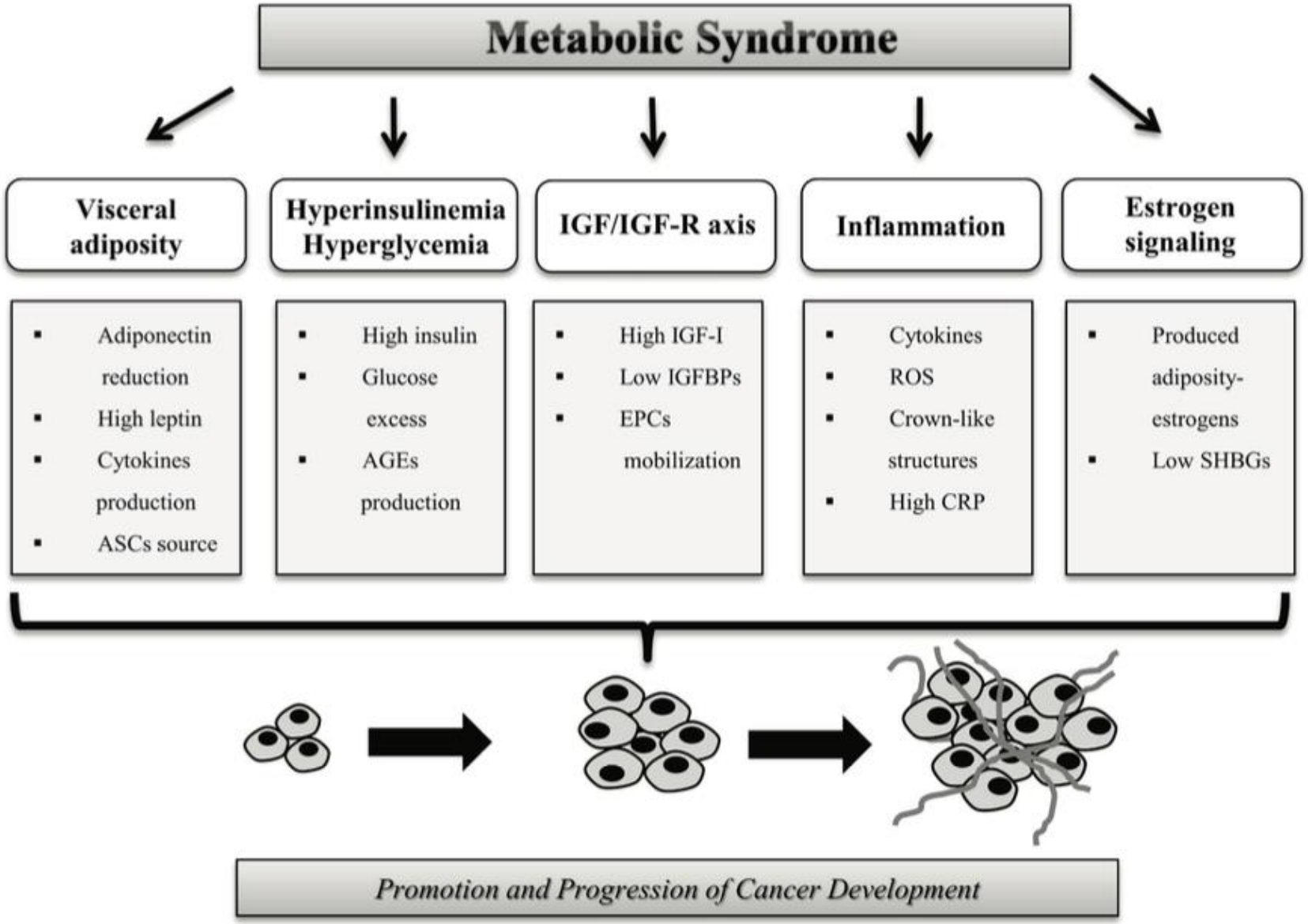
Bisogno sanitario nuovo ed emergente, che pone ai clinici **problematiche inedite** delle quali sempre più i Servizi Sanitari dovranno occuparsi e che per la sua natura e la sua complessità necessita di un approccio multidisciplinare.

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Late Effects

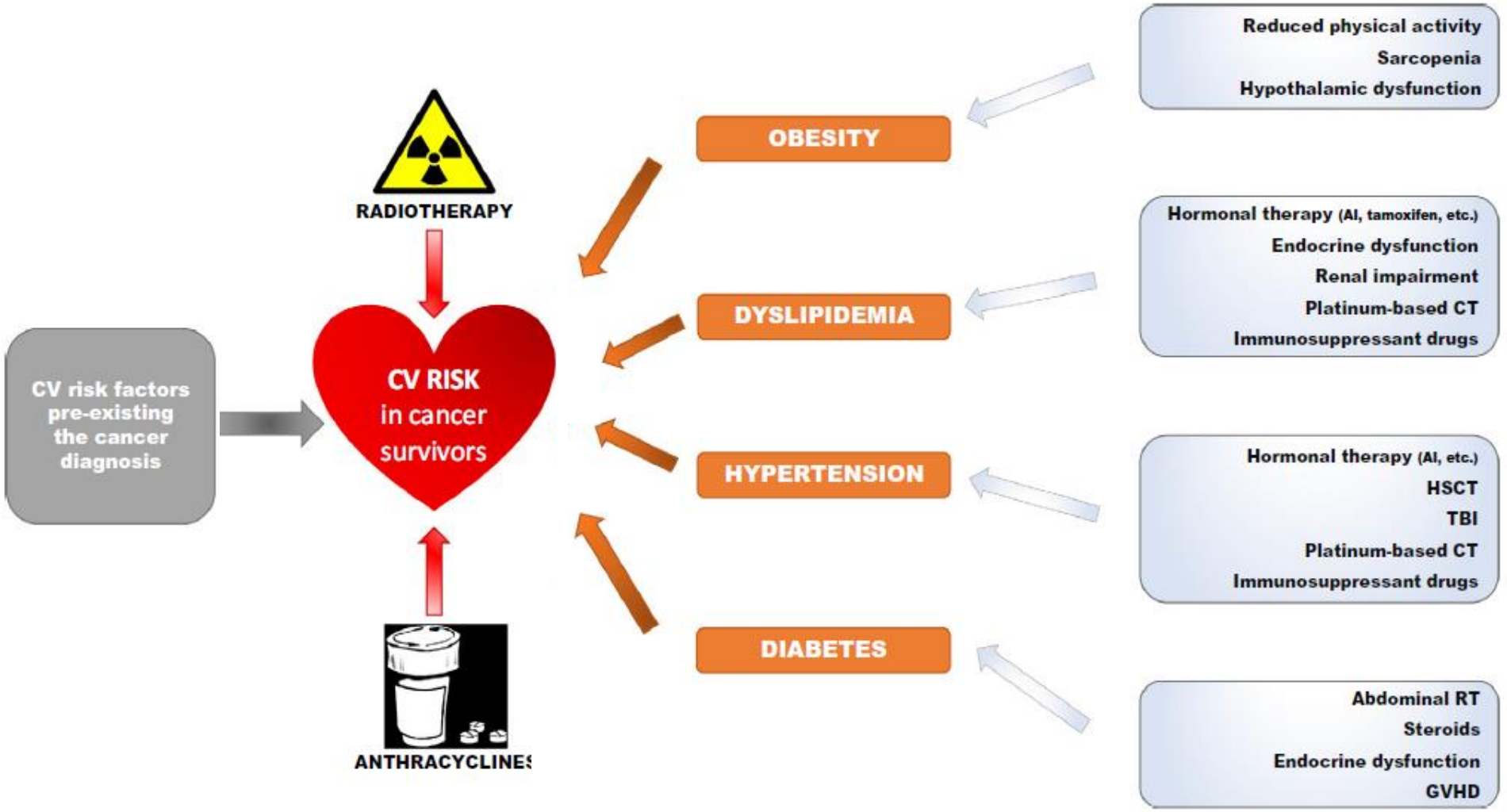
Life Threatening ← Life Altering





Minucci et al, Oncotarget 2016

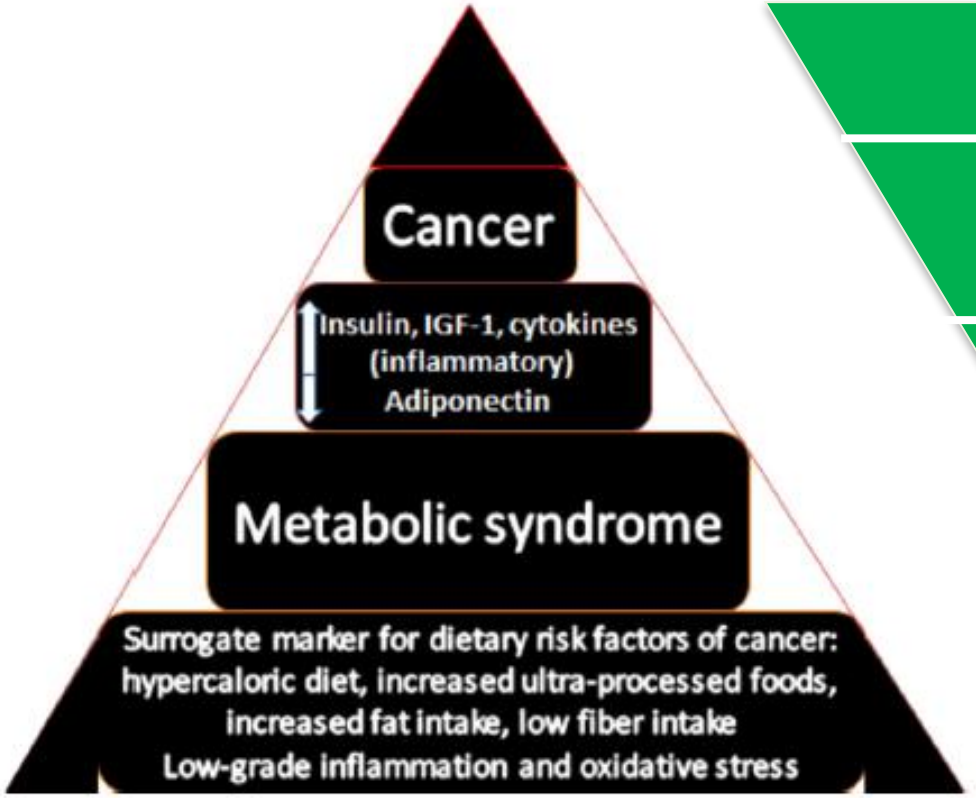
Rischio CV in *cancer survivors*

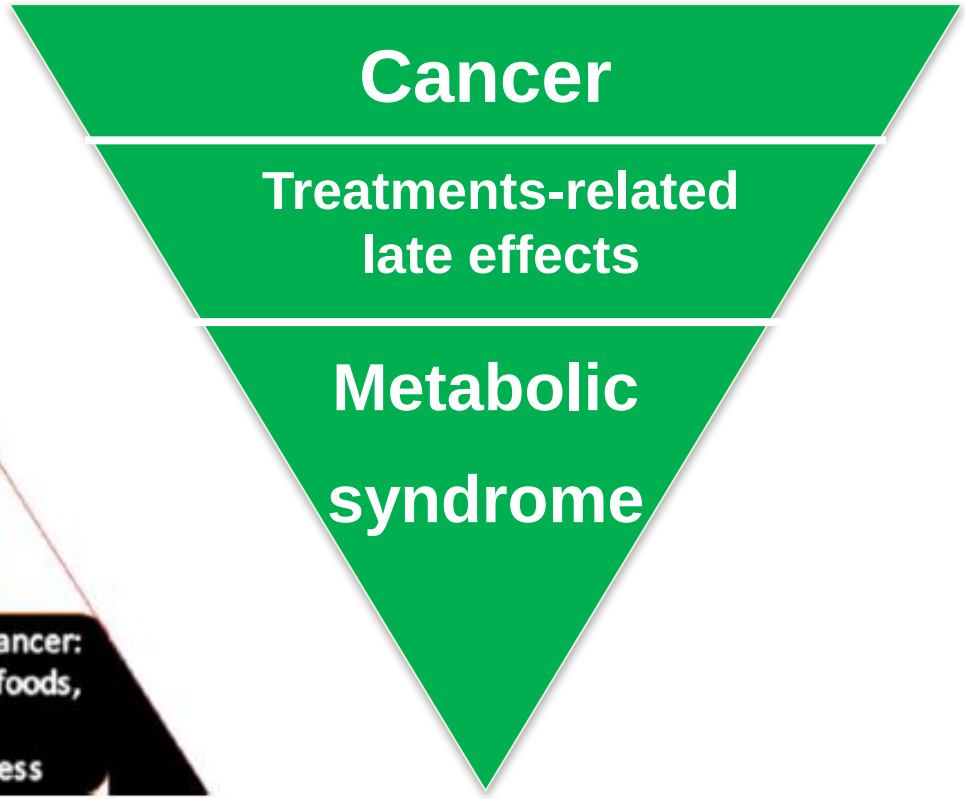


Felicetti […] Brignardello, Diab Res Clin Pract 2018

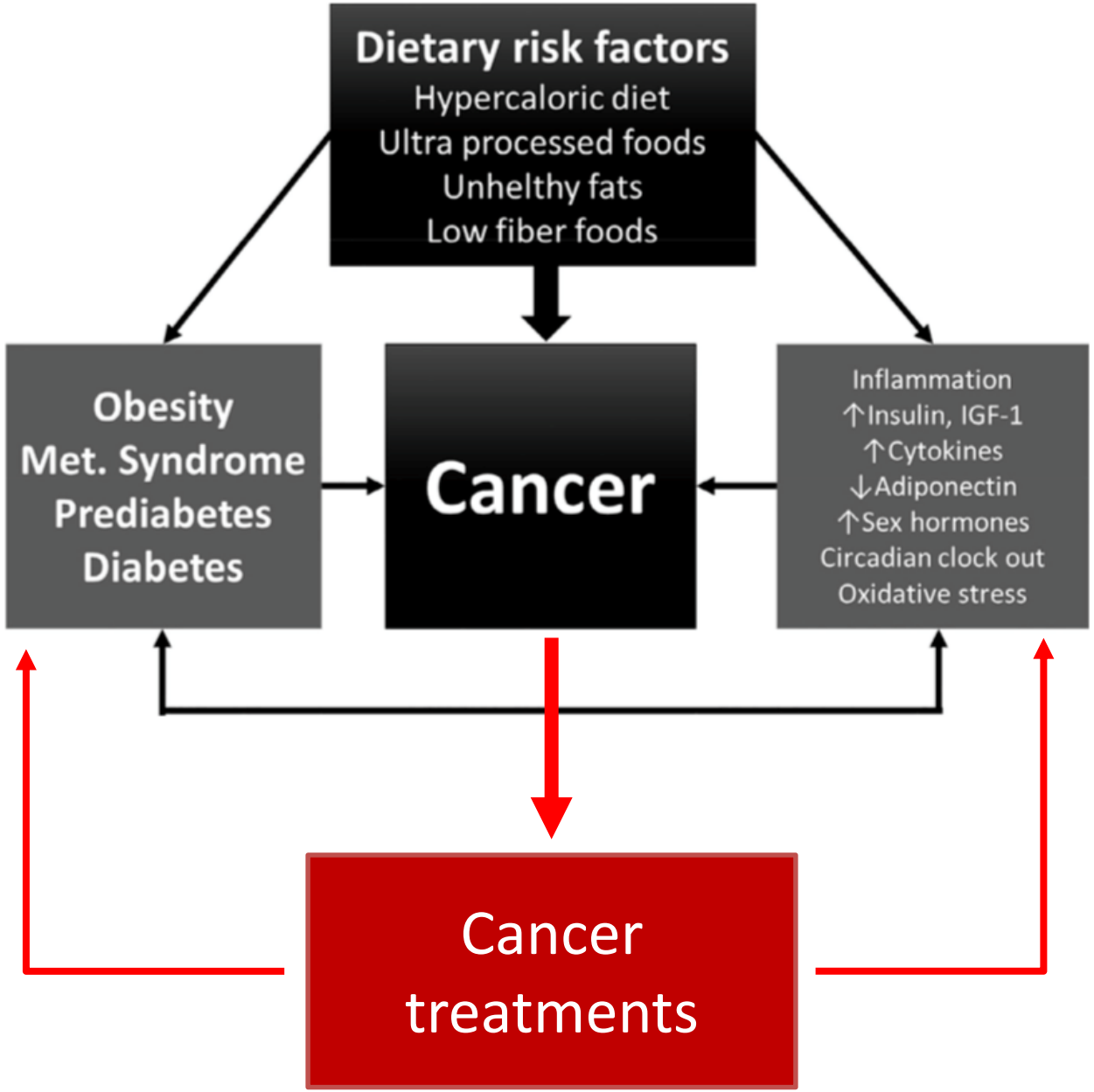
"COMMON SOIL HYPOTHESIS"

Metabolic syndrome and cancer: which direction?





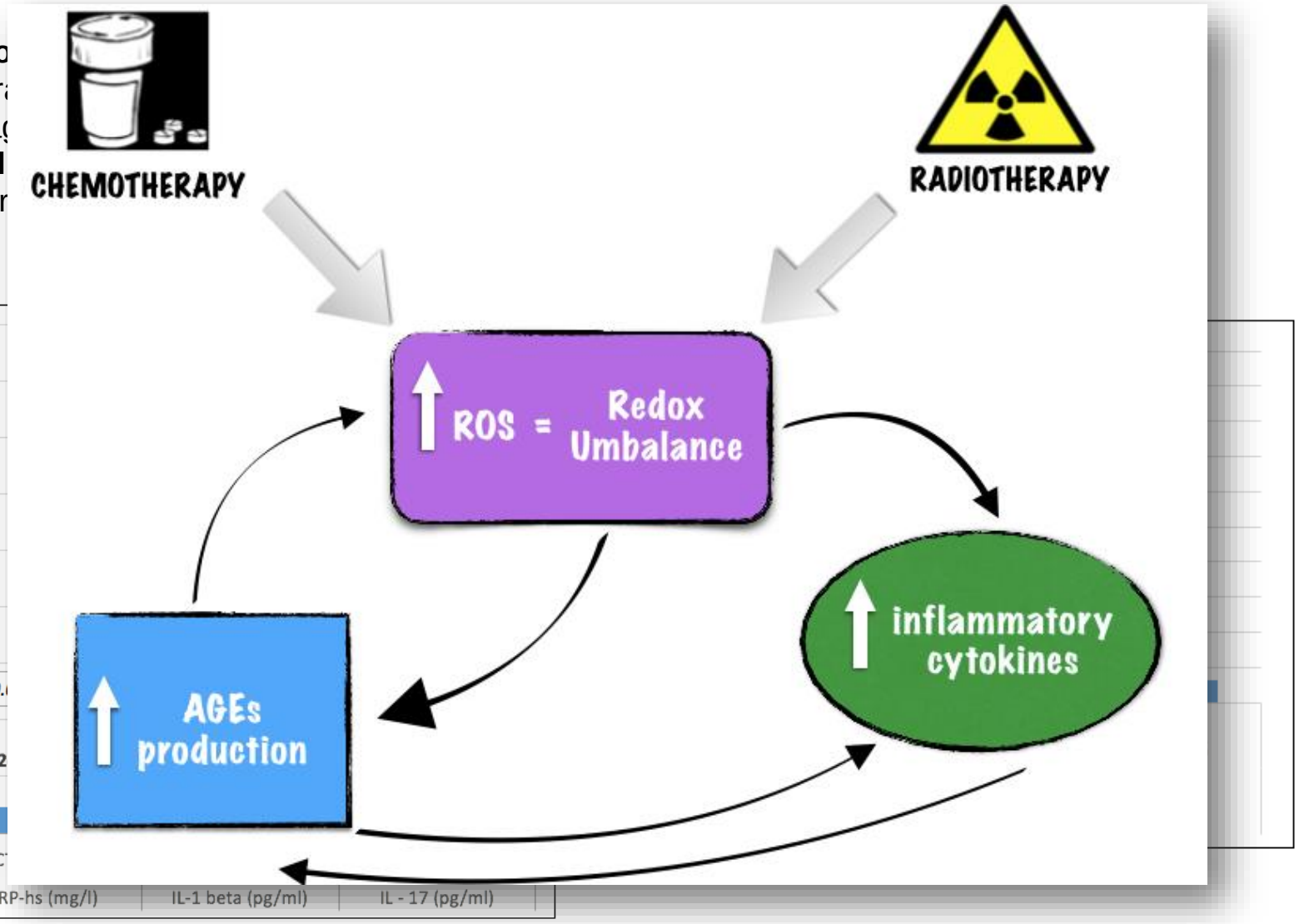
Esposito K et al, Endocrine 2013



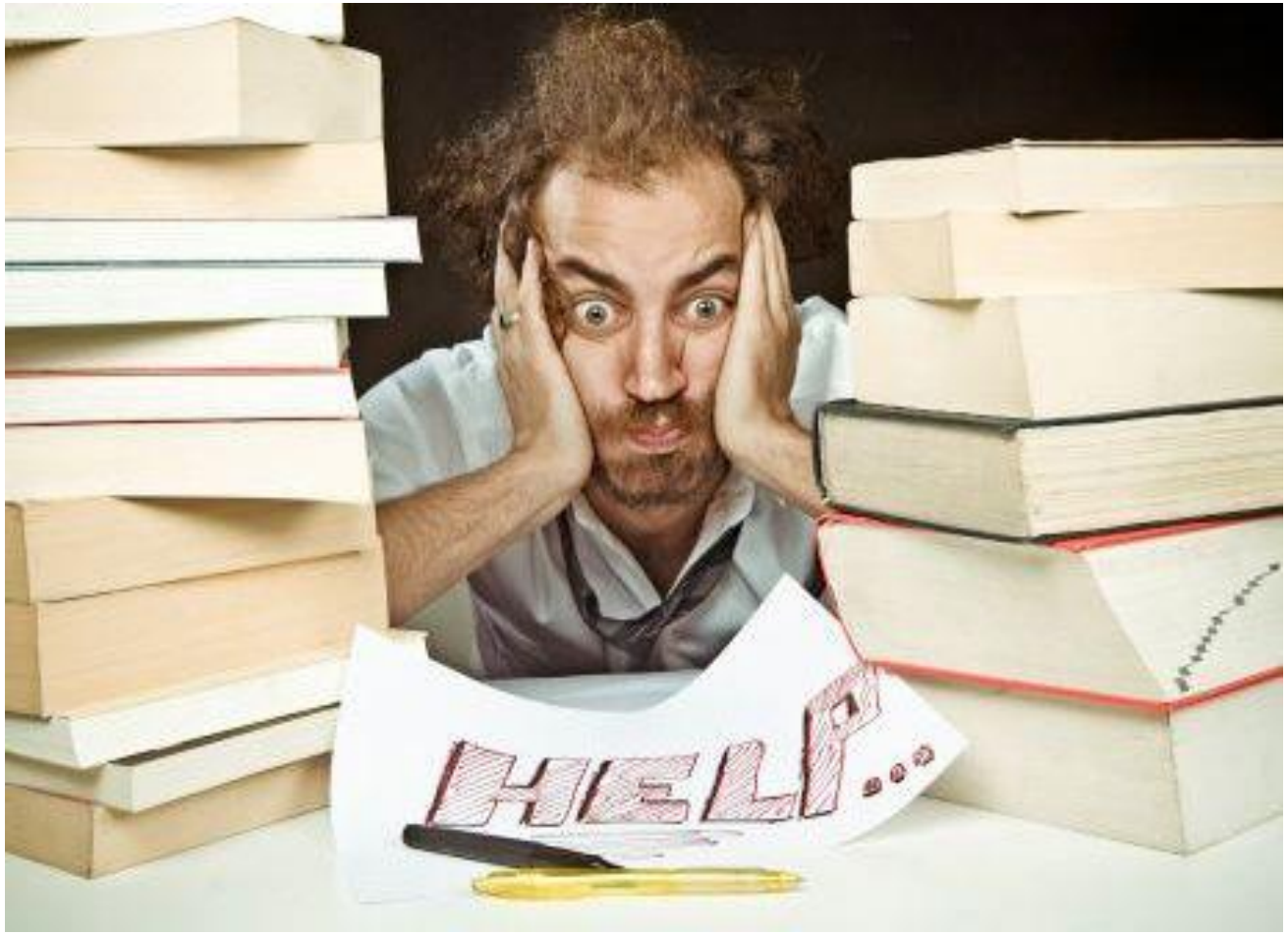
Mod. from Bellastella et al, Diab Res Clin Pract 2018

ADVANCED GLYCATION END PRODUCTS AND CHRONIC INFLAMMATION IN ADULT SURVIVORS OF CHILDHOOD LEUKEMIA TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION.

- **Survivo**
- Off-ther
- Mean ag
- **Normal**
- Compar



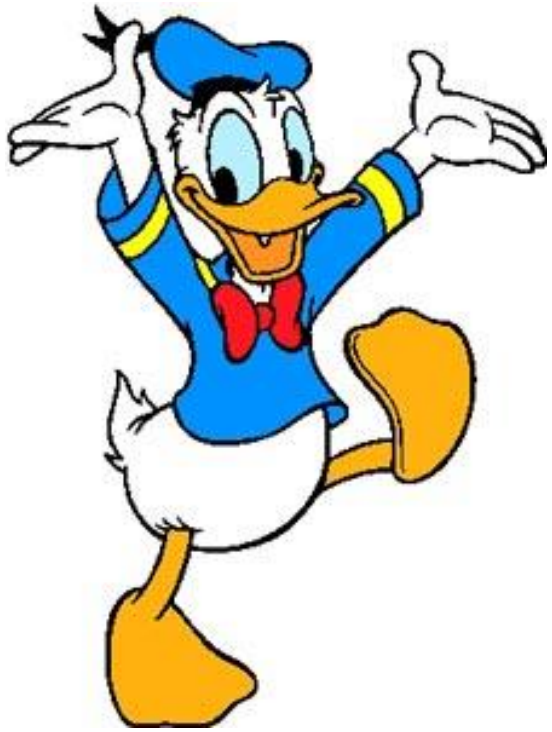
Felicetti […] Brignardello, in press.



OK, MA ALLORA?

Gestione della *survivorship care*

CONSAPEVOLEZZA
(del paziente e del medico)



VOLUME 24 · NUMBER 32 · NOVEMBER 10 2006

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Failing to Plan Is Planning to Fail: Improving the Quality of Care With Survivorship Care Plans

Craig C. Earle

Recommend the creation of **survivorship care plans** for patients as they complete primary therapy for cancer, to ensure clarity for all involved about patients' **diagnoses, treatments received, and surveillance plans**.

Survivorship care plans **must address the chronic effects of cancer, monitoring for and preventing late effects […] and promoting healthy lifestyles.**

It should explicitly **identify the providers responsible** for each aspect of ongoing care and provide information on resources available for psychosocial and other practical issues that may arise as a result of the prior cancer diagnosis.

[…] the creation of **written documents** that may become **part of the medical record.**

Gestione della *survivorship care*

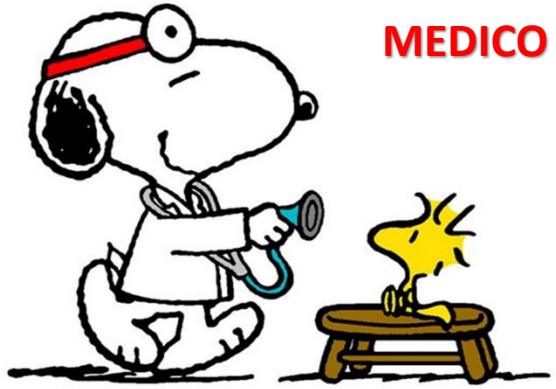
CONSAPEVOLEZZA
(del paziente e del medico)

CONTROLLI CLINICI PERIODICI
(anamnesi, esame obiettivo, …)

LATE EFFECTS PHYSICIAN?

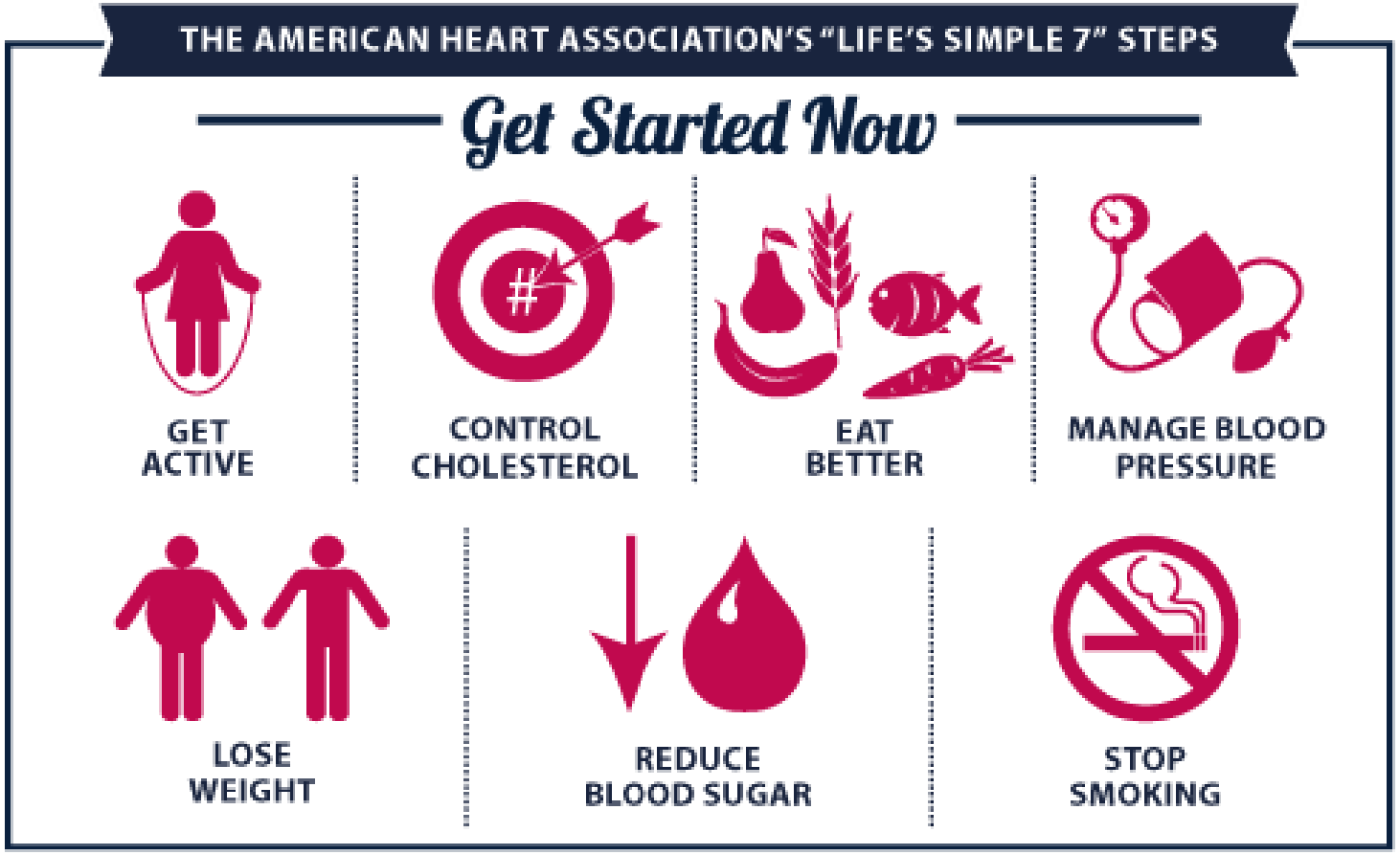
MEDICO DI FAMIGLIA?

INTERNISTA?



ONCOLOGO?

MEDICO DI RIFERIMENTO?



International Guideline Harmonization Group
for Late Effects of Childhood Cancer

Generally, health-care providers **are asked to educate and counsel all survivors** of childhood cancer about the importance of maintaining **a heart-healthy lifestyle** […]. Extensive studies done in non-oncology populations support the benefits of interventions to reduce modifiable risk factors […].

Armenian S et al, Lancet Oncol 2015

Critical Reviews in Oncology / Hematology 123 (2018) 57–73

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Diet and supplements in cancer prevention and treatment: Clinical evidences and future perspectives

Claudio Vernieri[a,b,*], Federico Nichetti[a], Alessandra Raimondi[a], Sara Pusceddu[a], Marco Platania[a], Franco Berrino[c], Filippo de Braud[a,d]

- **discouraging "Western" dietary patterns and promoting "prudent" patterns, such as the Mediterranean pattern**, will result in a significant reduction of cancer incidence.
- In cancer survivors, these recommendations **could reduce primary tumor recurrences, and are undoubtedly protective against CVDs and second tumors**.
- Dietary supplements are generally ineffective to prevent cancer and can even increase cancer incidence or relapses.

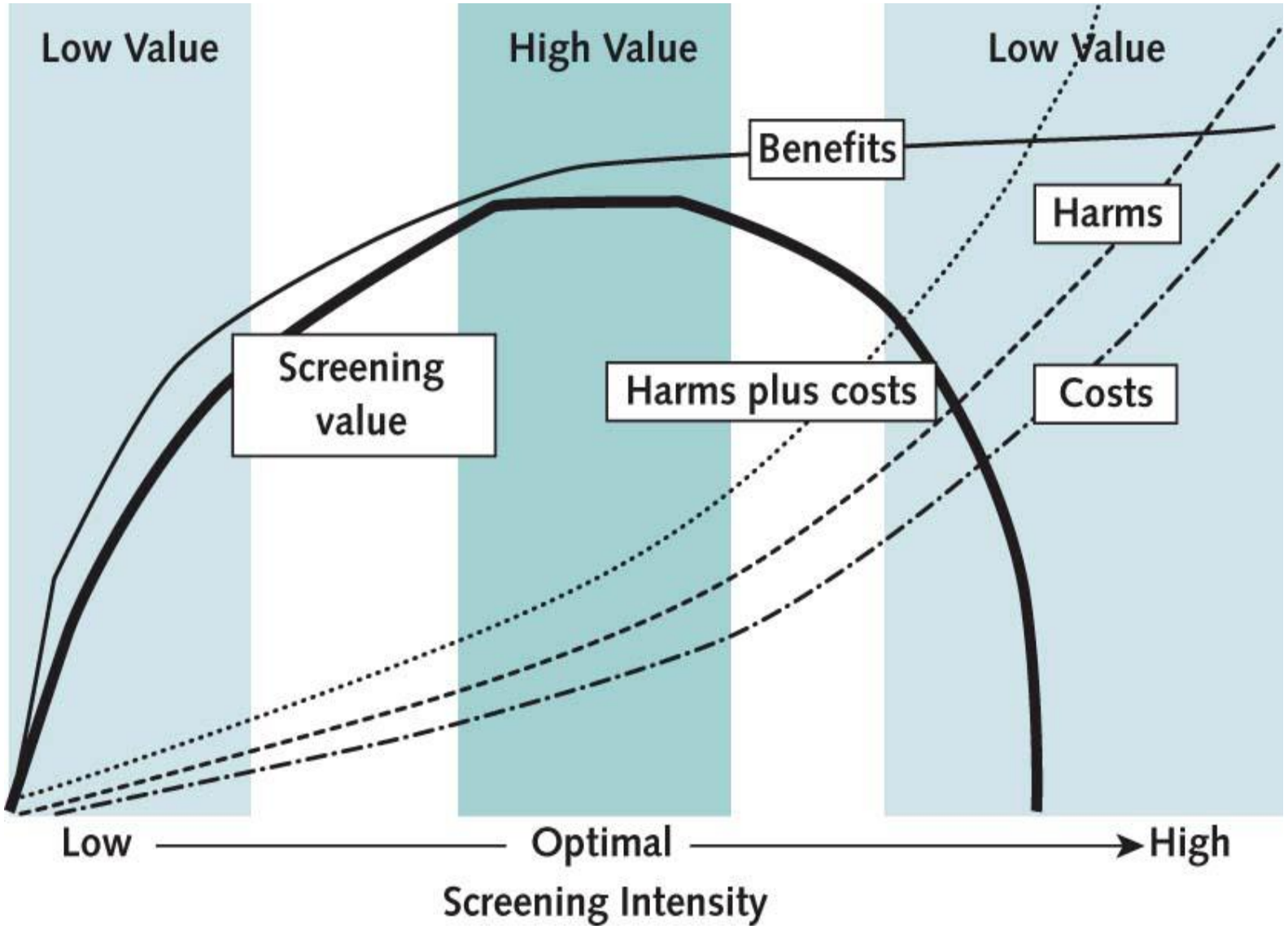
Gestione della *survivorship care*

CONSAPEVOLEZZA
(del paziente e del medico)

CONTROLLI CLINICI PERIODICI
(anamnesi, esame obiettivo, …)

ESAMI STRUMENTALI E LABORATORISTICI
TERAPIE PRECOCI

Lo screening “ideale”



Harris RP et al, Ann Inter Med 2015

Cancer prevention 1

Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms?

Bennett E Levis, Phillip F Binkley, Charles L Shapiro

Although the cardiotoxic effects of anthracyclines have been known for at least 40 years, **no evidence-based guidelines exist for post-treatment monitoring and prevention of treatment-related cardiotoxicity** in clinically asymptomatic adult survivors of breast cancer. Hence, the recommendations of various national and international policy-making institutions vary greatly and are inconsistent, leaving clinicians and breast cancer survivors in a quandary about what approach is best […]

Lancet Oncol 2017; 18: e445–56

Canadian Journal of Cardiology 32 (2016) 831–841

Society Guidelines

Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy

Detection and Prevention of Cardiotoxicity

There are currently no consistent recommendations on the frequency and modality with which cardiac imaging should be performed in patients at risk of LV dysfunction related to cancer therapy. **Existing surveillance protocols are on the basis of methodology from clinical trials and expert opinion**.

Reco
surv
Inter
Harr

Saro H Arn
Sadhna Sh
Leontien C

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordance/ discordance
Who needs cardiomyopathy surveillance?					
Treatments that increase risk					
Anthracyclines	Yes	Yes	Yes	Yes	Concordance
Mitoxantrone	Yes	Yes	Yes	Yes	Concordance
Differing risk by anthracycline analogues	Yes	Not stated	Not stated	Not stated	Discordance
Chest radiation	Yes	Yes	Yes	Yes	Concordance
Cardiovascular risk factors	Yes	Yes	Yes	Yes	Concordance
Highest risk factors	≥300 mg/m² anthracyclines ≥30 Gy RT involving heart* Anthracyclines + chest RT Younger age at treatment Pregnancy	≥300 mg/m² anthracyclines ≥30 Gy RT involving heart* Anthracyclines + chest RT Pregnancy	>250 mg/m² anthracyclines Anthracyclines + chest RT History of transient cardiomyopathy during treatment Pregnancy	>250 mg/m² anthracyclines ≥30 Gy RT involving heart* Anthracyclines + chest RT	Discordance
What surveillance modality should be used?					
Screening for cardiomyopathy					
Echocardiography	Yes	Yes	Yes	Yes	Concordance
Radionuclide angiography	Yes	Yes	No	No	Discordance
At what frequency and for how long should cardiomyopathy surveillance be performed?					
Screening begins	≥2 years after treatment or ≥5 years after diagnosis (whichever is first)	≥5 years after diagnosis	1–3 months after treatment	≥5 years after completion of treatment	Discordance
Screening frequency	Every 1–5 years	Every 2–5 years	Every 3–5 years	Every 2–5 years	Discordance
Duration of screening	Lifelong	Lifelong	Not stated	Not stated	Discordance
Closer monitoring during pregnancy	Yes	Yes	Yes	Yes	Concordance
What should be done when abnormalities are identified?					
Refer to cardiologist	Yes	Yes	Yes	Yes	Concordance
Consider ACE inhibitors	Not stated	Yes	Not stated	Yes	Discordance

RT=radiotherapy. ACE=angiotensin converting enzyme. *RT involving the heart: mediastinal, thoracic, spinal, left or whole upper abdominal or total body irradiation.

Table 1: **Concordances and discordances in cardiomyopathy surveillance recommendations**

Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

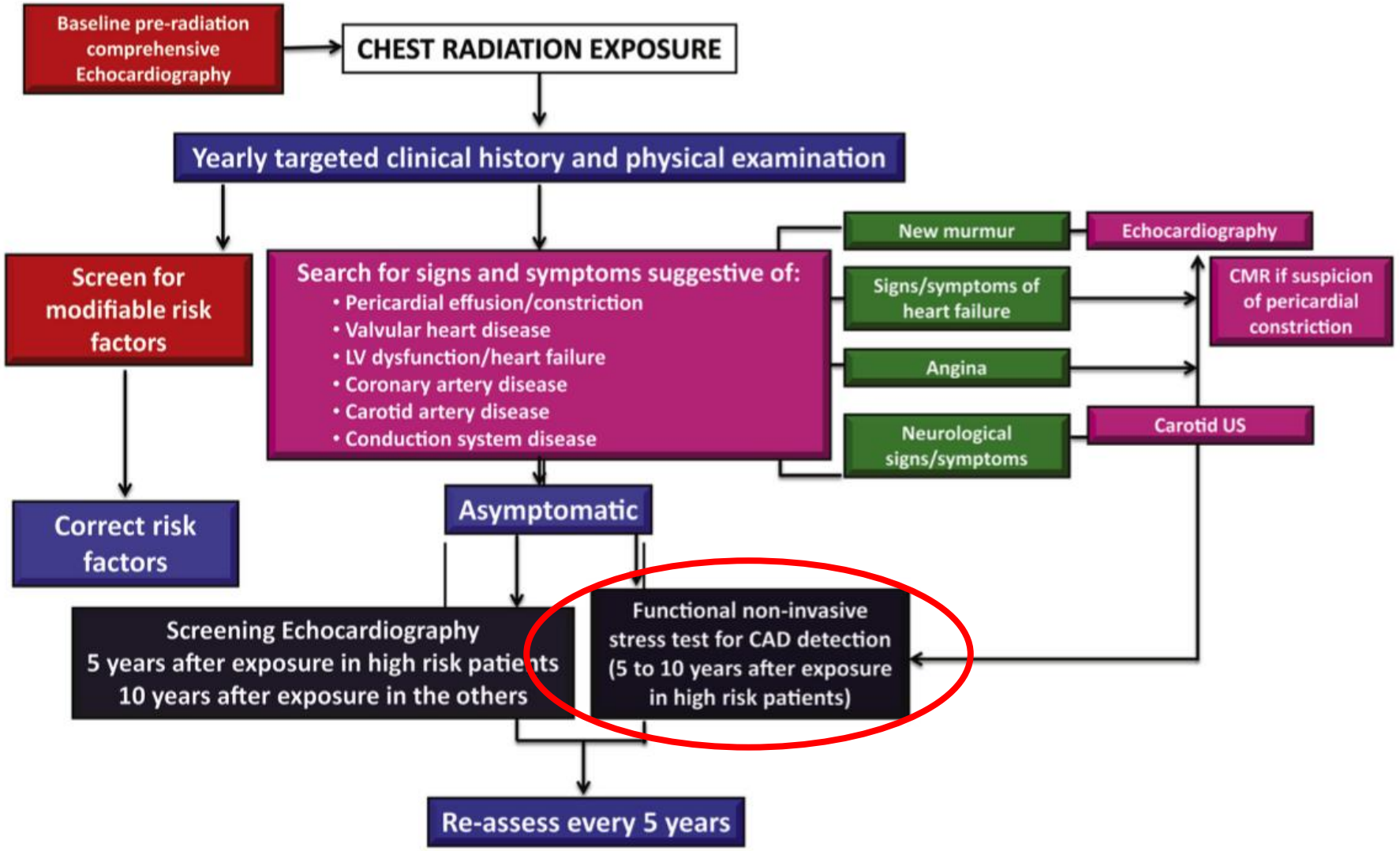
Saro H Armenian, Melissa M Hudson, Renee L Mulder, Ming Hui Chen, Louis S Constine, Mary Dwyer, Paul C Nathan, Wim J E Tissing, Sadhna Shankar, Elske Sieswerda, Rod Skinner, Julia Steinberger, Elvira C van Dalen, Helena van der Pal, W Hamish Wallace, Gill Levitt, Leontien C M Kremer

Owing to the absence of data, **recommendations** for initiation and frequency of surveillance **are largely consensus based.**

There was a consensus **that surveillance should begin no later than 2 years after completion of cardiotoxic therapy and continue for a minimum of every 5 years thereafter**, as pharmacological interventions in individuals with asymptomatic cardiomyopathy can delay the onset of congestive heart failure and decrease mortality.

Lancet Oncol 2015; 16: e123–36

Algorithm for patient management after chest radiotherapy



Lancellotti et al., J Am Soc Echocardiogr. 2013

- Current **expert opinion** by the European Association of Cardiovascular Imaging and the American Society of Echocardiography **recommend screening with a functional noninvasive stress test in asymptomatic individuals for CAD detection 5–10 years after exposure in high-risk patients, with reassessment every 5 years**

- Current expert opinion by the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend screening with a functional noninvasive stress test in asymptomatic individuals for CAD detection 5–10 years after exposure in high-risk patients, with reassessment every 5 years

- **While these are opinions, and not guidelines, the true impact of screening asymptomatic patients is unclear and consideration should be given to whether this is the best practice.**

Cardiac follow-up of cancer survivors

Eiman Jahangir, MD MPH, Nichole Polin, MD

European Heart Journal, Volume 37, Issue 36, 21 September 2016, Pages 2745–2747,
https://doi.org/10.1093/eurheartj/ehw362

Issues with stress testing in asymptomatic individuals, that may derive no symptomatic improvement or mortality benefit, range from **false positive tests** to increased radiation exposure in an already exposed group. False-positive test results **may lead to unnecessary anxiety** **and may have adverse consequences related to work**, **insurance, etc**. while typically leading to further testing

QUANTIFICARE IL RISCHIO CV NEI *CS*

Heart Failure Risk Prediction in Childhood Cancer Survivors: Where Is Our Crystal Ball?

Elizabeth C. Bluhm, *MedStar Washington Hospital Center, Washington, DC*
Ana Barac, *MedStar Washington Hospital Center; and MedStar Heart Institute, Washington, DC*

- 40 anni,
- [redacted]

Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

Rischio di CVD (a 10 anni): 2,3-4,1 %

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Individual Prediction of Heart Failure Among Childhood Cancer Survivors

Rischio di CHF: 9,1-16 %

Bluhm et al, J Clin Oncol 2014

Editorial

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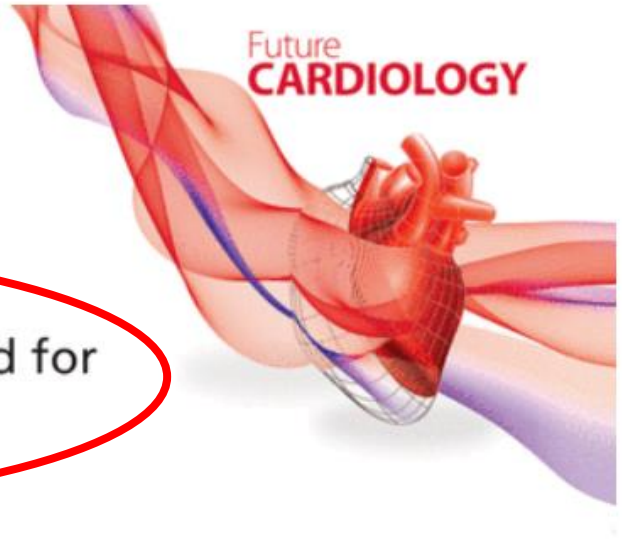


Statins and cancer survivors: the need for structured guidelines

Zakaria Almahmeed[1,2], Olivia Hung[3] & Susmita Parashar*[,3]

[1]Department of Medicine, Emory School of Medicine, Atlanta, GA 30322, USA
[2]Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA
[3]Division of Cardiology, Department of Medicine, Emory School of Medicine, Atlanta, GA 30322, USA
* Author for correspondence: smalik@emory.edu

"The discussion of CVD risk prevention should be integrated into the discussion of curative treatments among cancer survivors and oncology populations in general."

First draft submitted: 5 September 2017; Accepted for publication: 17 October 2017; Published online: 23 November 2017

Keywords: atherosclerosis • atherosclerotic cardiovascular disease • cancer survivors • guidelines • statins

The population of children and adult cancer survivors in the USA is estimated to grow to more than 19 million in 2024 according to the American Cancer Society [1,2]. This rapidly growing population has been exposed to various diagnostic and therapeutic modalities that may impact cardiovascular health [3]. In addition, cancer survivors have a higher prevalence of traditional cardiovascular disease (CVD) risk factors compared with age-matched populations [4]. Moreover, there is evidence that the 10-year predicted risk of developing a myocardial infarction or stroke is at least comparable to breast cancer recurrence risk among breast cancer survivors [5]. Thus, pursuing CVD risk prevention in survivorship care through appropriate and structured guidelines is of utmost importance. However, despite having a higher prevalence of CVD risk factors, a significant proportion of cancer survivors do

TERAPIA IPOLIPEMIZZANTE IN CS

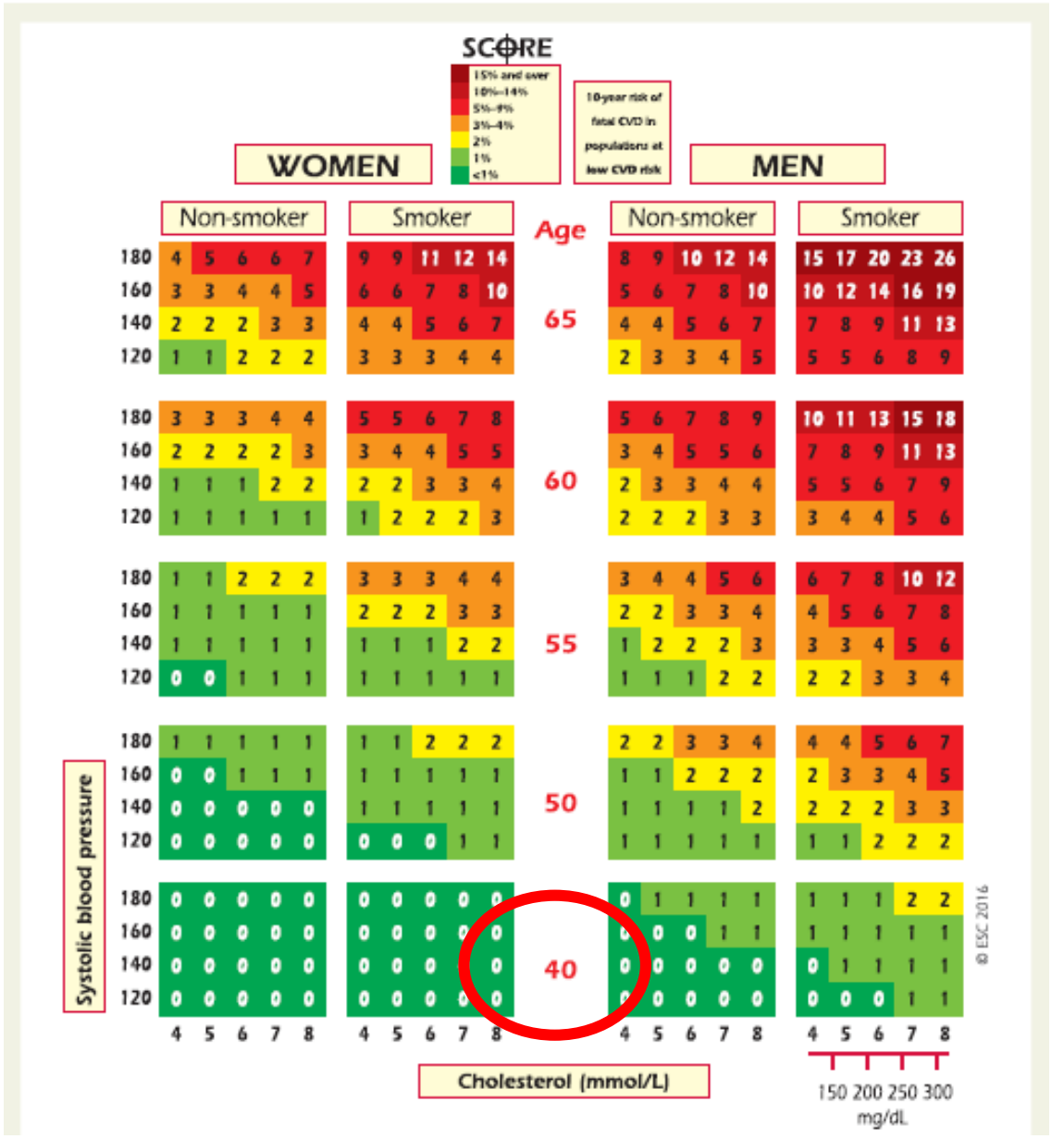
• Tutte le raccomandazioni disponibili consigliano di **monitorare periodicamente il rischio cardiovascolare dei *cancer survivors*, ma non vi sono indicazioni univoche sulla cadenza degli esami**

• Molte raccomandazioni **raccomandano di trattare in maniera aggressiva** i *cancer survivors* con livelli **elevati di colesterolo LDL, ma non sono disponibili target terapeutici per queste popolazioni**.

NOTA 13 Allegato 1

Classificazione in base al livello di rischio

… *"Sono da considerare pazienti a rischio alto, oltre a coloro che presentano un risk score ≥5% e < 10% per CVD fatale a 10 anni, i pazienti con dislipidemie familiari o con ipertensione severa, i pazienti diabetici senza fattori di rischio CV e senza danno d'organo"*, ***i pazienti con pregressa esposizione a trattamenti oncologici potenzialmente cardiotossici*** *"e i pazienti con IRC moderata (FG 30-59 ml/min/1.73m^2.)"…*


SCORE
≥5% and over
4%–4%
2%
1%
<1%
10-year risk of fatal CVD in populations at low CVD risk
WOMEN
MEN
Non-smoker
Smoker
Age
65
60
55
50
40
Systolic blood pressure
Cholesterol (mmol/L)
150 200 250 300
mg/dL
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RACCOMANDAZIONI PER IL MONITORAGGIO A LUNGO TERMINE DEI PAZIENTI PRECEDENTEMENTE CURATI PER LINFOMA DI HODGKIN, LINFOMA PRIMITIVO DEL MEDIASTINO E LINFOMI NON- HODGKIN AGGRESSIVI TRATTATI CON INTENTO CURATIVO

Nei pazienti sottoposti a irradiazione mediastinica è stato proposto come ragionevole lo screening lipidologico **(determinazione di colesterolo totale + HDL e trigliceridi) a cadenza triennale, iniziando nel 5° anno** dopo il completamento delle terapie e con durata indefinita.

La terapia farmacologica di elezione per il trattamento delle dislipidemie è rappresentata dalle statine. In assenza di indicazioni specifiche, per i pazienti sottoposti a terapie potenzialmente cardiotossiche, è ragionevole l'utilizzo dei target proposti per pazienti a medio e alto rischio CV. La

	Senza FRCV	Con uno o più FRCV
Colesterolo LDL	< 115 mg/d	< 100 mg/dl

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Table 5 Intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle intervention, consider drug[f]	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

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Lipids LDL-C is the primary target[a]	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[b] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

RACCOMANDAZIONI PER IL MONITORAGGIO A LUNGO TERMINE DEI PAZIENTI PRECEDE…URATI PER LINFOMA DI HODGKIN, LIN…EDIASTINO E LINFOMI NON- HODGKIN A…ON INTENTO CURATIVO

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www.thelancet.com/oncology Vol 18 January 2017

Looking back, moving forward: the evolution of cancer survivorship care

[…] an inherent challenge in survivorship care is **the absence of a one size fits all solution to the diverse needs of survivors, providers, and health-care systems**. A consensus exists surrounding **the need for more research, increased collaboration**, renewed **attention to the needs of survivors** that are too frequently overlooked, and a push for improvements in how we **implement models of care and interventions**, with **incorporation of robust evaluations to measure programme effectiveness**. As we reflect on the progress made in cancer survivorship, we must remain **aware of the gaps in knowledge and care, unmet needs, and systematic and individual level challenges.**

It doesn't stop at cure: monitoring childhood cancer survivors

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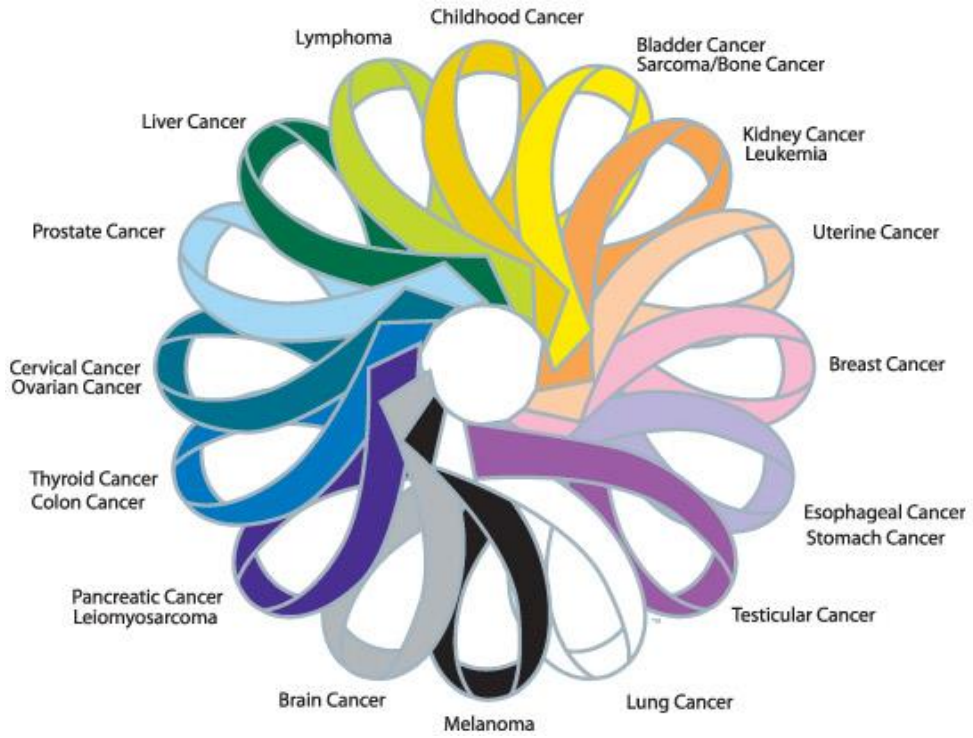
Treating the patient doesn't stop with their last cycle of therapy.

Care



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