Pediatric Cardio-Oncology Acute Cardiotoxicity Primary and Secondary Prevention Strategies

Authors of the pathway: Olga H Toro-Salazar MD; Tiffany Berthod BSN, RN, CPN, CCRC; Andrea Orsey MD, MSCE; Ilana Waynik MD

What is a Clinical Pathway?

An evidence-based guideline that decreases unnecessary variation and helps promote safe, effective, and consistent patient care.

Objectives of Pathway

- To develop a comprehensive interdisciplinary pediatric pathway to standardize primary and secondary prevention of a change in systolic performance, also referred to as cancer therapy-related cardiac dysfunction **(CTRCD)**
- To utilize multimodality imaging to assess for change in systolic performance as indicated
- To prevent heart failure and the progression of heart failure
- To ensure appropriate and timely referrals to necessary specialists and ancillary service providers

Why is Pathway Necessary?

- Among the nearly 400,000 long-term childhood cancer survivors in the United States, more than half were treated with cardiotoxic cancer therapy, which results in a 15-fold increased rate of heart failure and an 8-fold increased rate of premature cardiac death.
- No comprehensive pediatric cardio-oncology pathway has been published to guide prevention and management of cardiac effects of cancer treatment.
    - Cardio-oncology is an emerging field
    - Childhood cancer survivors receive numerous cancer treatments that are cardio-toxic
    - We want to preserve heart function throughout cancer therapy so they can get the cancer treatments they need
        - Want to limit dose modifications
        - Want to limit held doses
    - Prevent or limit the long term cardiovascular effects of cancer treatments

- **Appendix A** lists the common effects of cardiotoxic cancer agents
- Targeted Molecular Therapies are growing in the pediatric population & will continue to be used. These also have cardiotoxic effects.

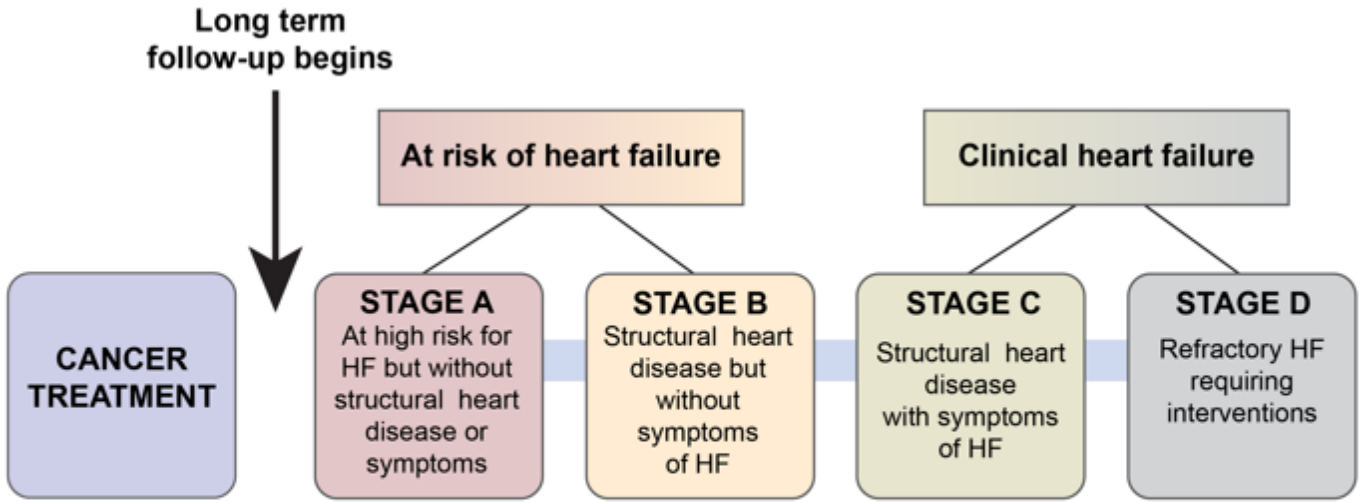
Cardiac effect	LVD/HF	Myocarditis	Arterial Thrombosis	Athero-sclerosis, Coronary Spasm	Pericardial disease	Valve Disease	HTN	Pulmonary HTN or fibrosis
Conventional Therapies								
Anthracyclines	■				■			
Platinum-based Cisplatin			■	■			■	■
Alkylating Agents Cyclophosphamide, Ifosfamide	■		■		■			■
Vinca Alkaloids ^ Vinblastine, Vincristine	■							
Antimetabolites 5-fluorouricil (5-FU), Capecitabine, Cytarabine			■	■	■			
Microtubule Inhibitors (primarily used in adults) Paclitaxel, Docetaxel	■		■					
Targeted Molecular Therapies (primarily used in adults) *								
VEGF Antibodies Bevacizumab	■		■				■	
VEGF TK Inhibitors Sunitinib, Pazopanib	■		■				■	
BCR-ABL TK Inhibtors Imatinib	■	■	■	■	■	■		■
Proteasome Inhibitors Bortezomib, Carfilzomib	■		■				■	■
Radiation	■		■	■	■	■	■	■
Steroids				■			■	
Imaging								
Echo (preferred screening modality)	■	■			■	■	■	■
CMR	■	■	■		■	■	■	
CT			■	■	■			■

^ Vinca Alkaloids only cardiotoxic when used in combination with anthracyclines

** There is continuous introduction of additional target molecular therapies such as BRAF/MEK inhibitors that induce cardiotoxicity. Refer to literature and cancer protocol for additional details.*

Background: Heart Failure

Since outcomes of clinical heart failure (HF) are generally poor, it is vitally important to have a systematic way to both prevent and also provide early intervention.



Outcomes after a diagnosis of clinical HF are generally poor, with 5-year overall survival <50%.

Armenian SH et al. Cardiology research and practice. 2012;2012:713294.

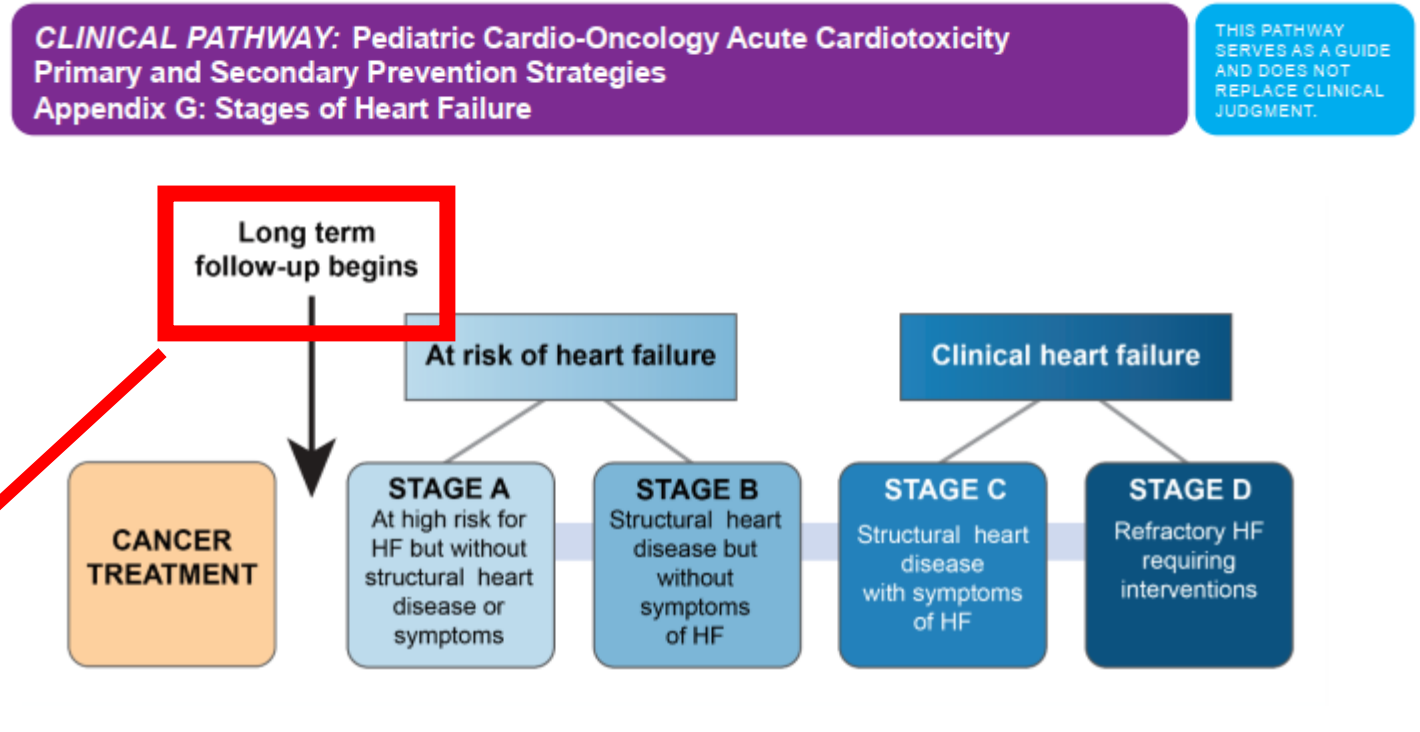
Heart Failure Symptoms

NYHA Class	Symptoms
Class I	No symptoms and can perform ordinary physical activity without limitations
Class II	Mild symptoms and slight limitation of physical activity; No symptoms at rest
Class III	Marked limitation of physical activity (even with less than ordinary activity) due to symptoms; Comfortable at rest
Class IV	Unable to carry out any physical activity; Severe limitations; Symptoms present even at rest

https://www.ezmedlearning.com/blog/congestive-heart-failure-symptoms-stages-treatment

Background: Heart Failure

Appendix G: Stages of Heart Failure



Cardio-oncology prevention begins upon cancer diagnosis not after cancer treatment has finished. Primary and secondary prevention of heart failure (HF) can include the following:

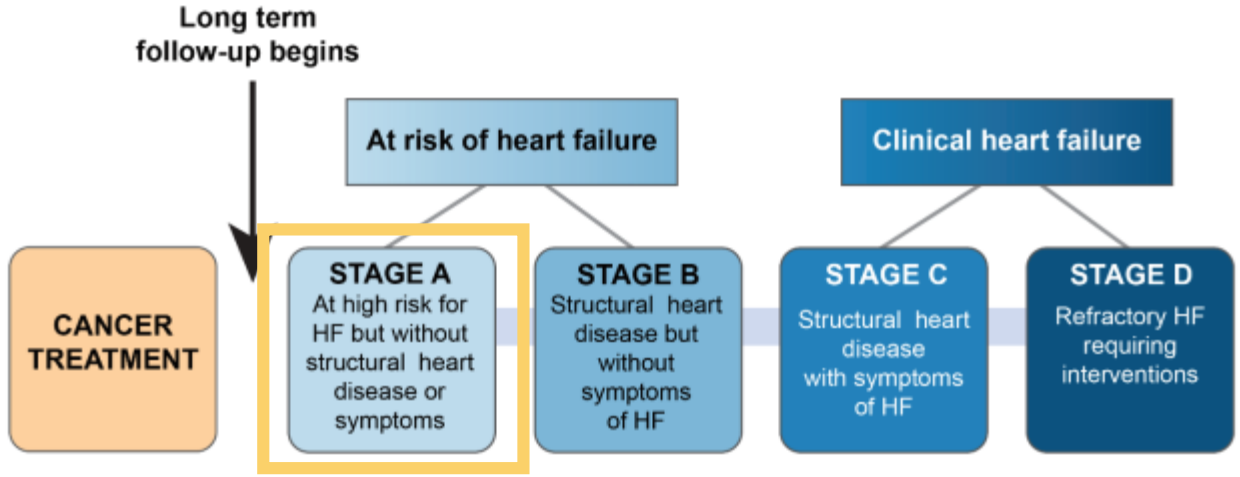
1. Use of Dexrazoxane
2. Monitoring heart function via echos/CMRs
3. Promoting heart healthy diet
4. Promoting physical activity
5. Utilizing cardiac medication(s) to preserve/improve heart function → prevent/reduce the need to dose reduce or skip cancer treatments

Background: Heart Failure

Appendix G: Stages of Heart Failure

CLINICAL PATHWAY: **Pediatric Cardio-Oncology Acute Cardiotoxicity Primary and Secondary Prevention Strategies**
Appendix G: Stages of Heart Failure

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

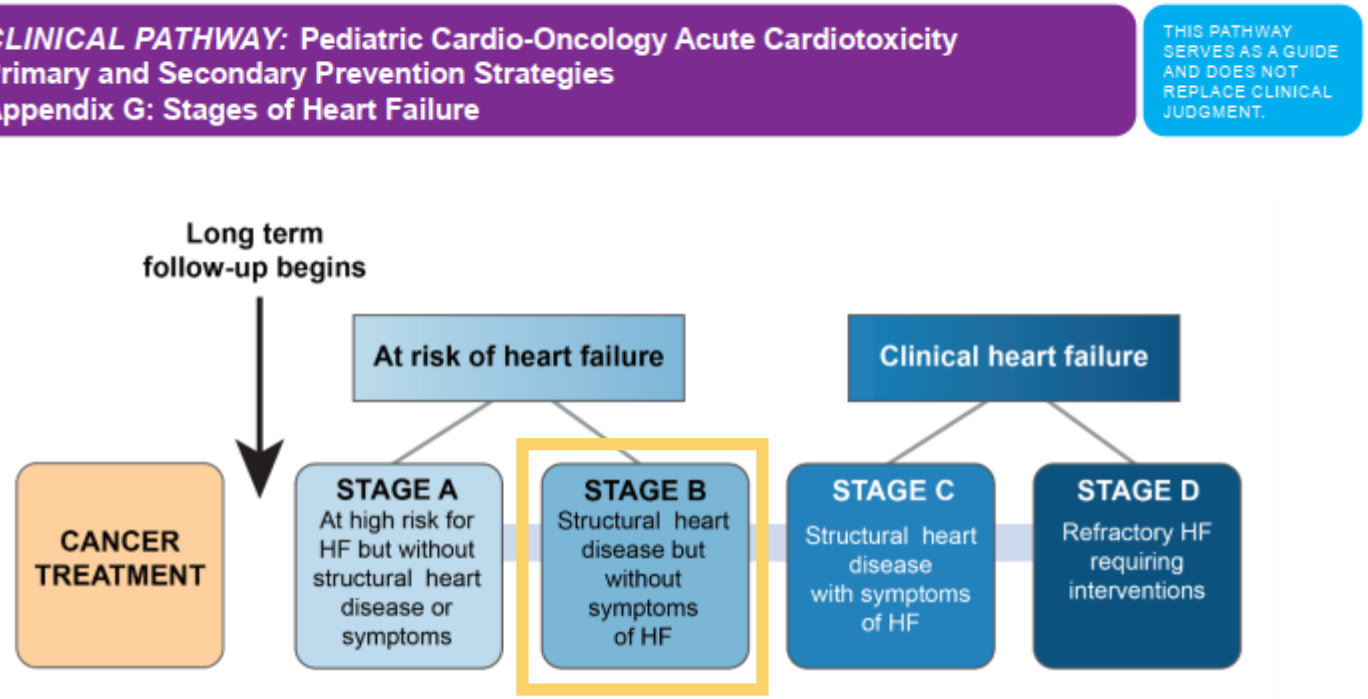


- Heart failure stage A & B are **at risk for heart failure.** All oncology patients that receive cardiotoxic therapy are considered heart failure stage A.

- **Heart failure stage A** means the patient is at high risk for heart failure due to the cardiotoxic cancer therapy, **but do not** have any structural heart disease (as shown via echo or CMR) or symptoms (heart failure symptoms reviewed after heart failure stages reviewed)

Background: Heart Failure

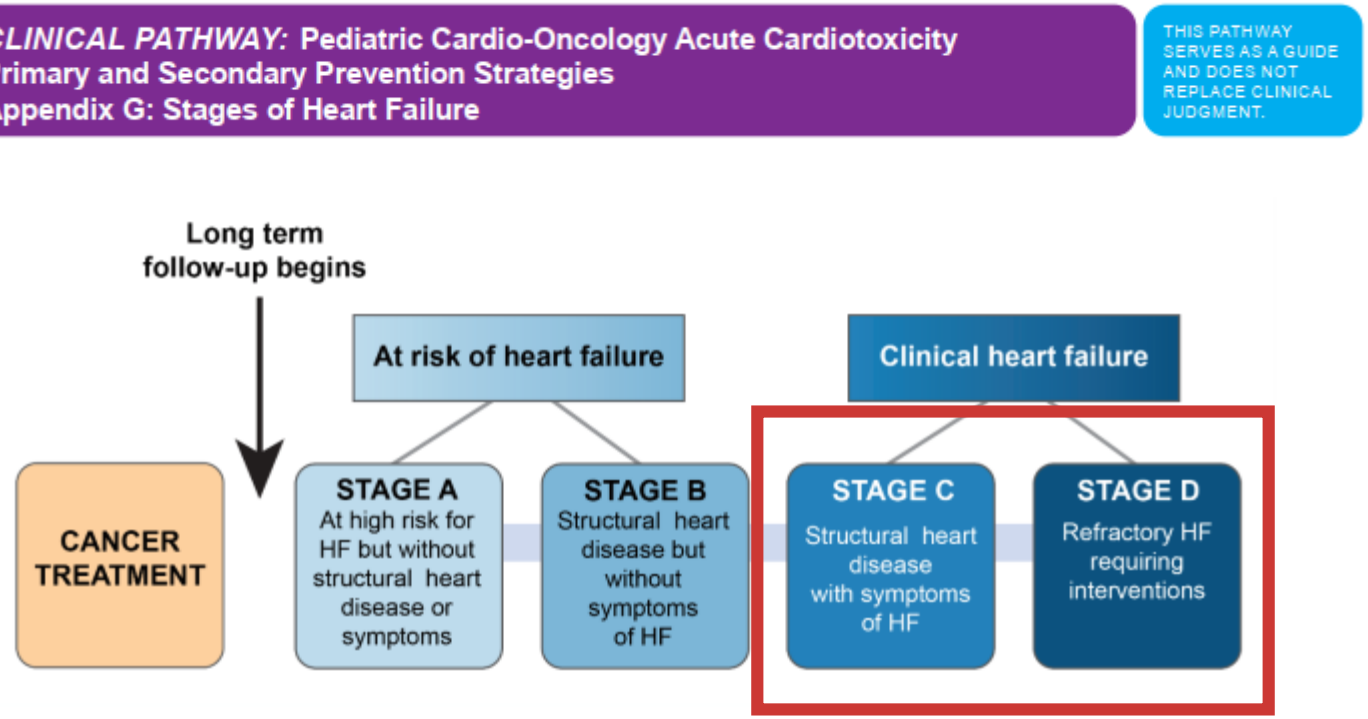
Appendix G: Stages of Heart Failure



Heart failure stage B means the patient is at high risk for heart failure due to the cardiotoxic cancer therapy **and has** structural heart disease (as shown via echo or CMR), but does not have any symptoms. This is the stage where we want to intervene so they do not escalate to stage C or D

Background: Heart Failure

Appendix G: Stages of Heart Failure



- Heart failure stage C & D patients have **clinical heart failure**
- Heart failure stage C patients have **structural heart disease and are experiencing symptoms**
- Heart failure stage D patients have **refractory heart failure, are experiencing symptoms**, and require advance heart failure therapy (i.e. implantable mechanical heart pump, IV medication, etc.) and/or heart transplant

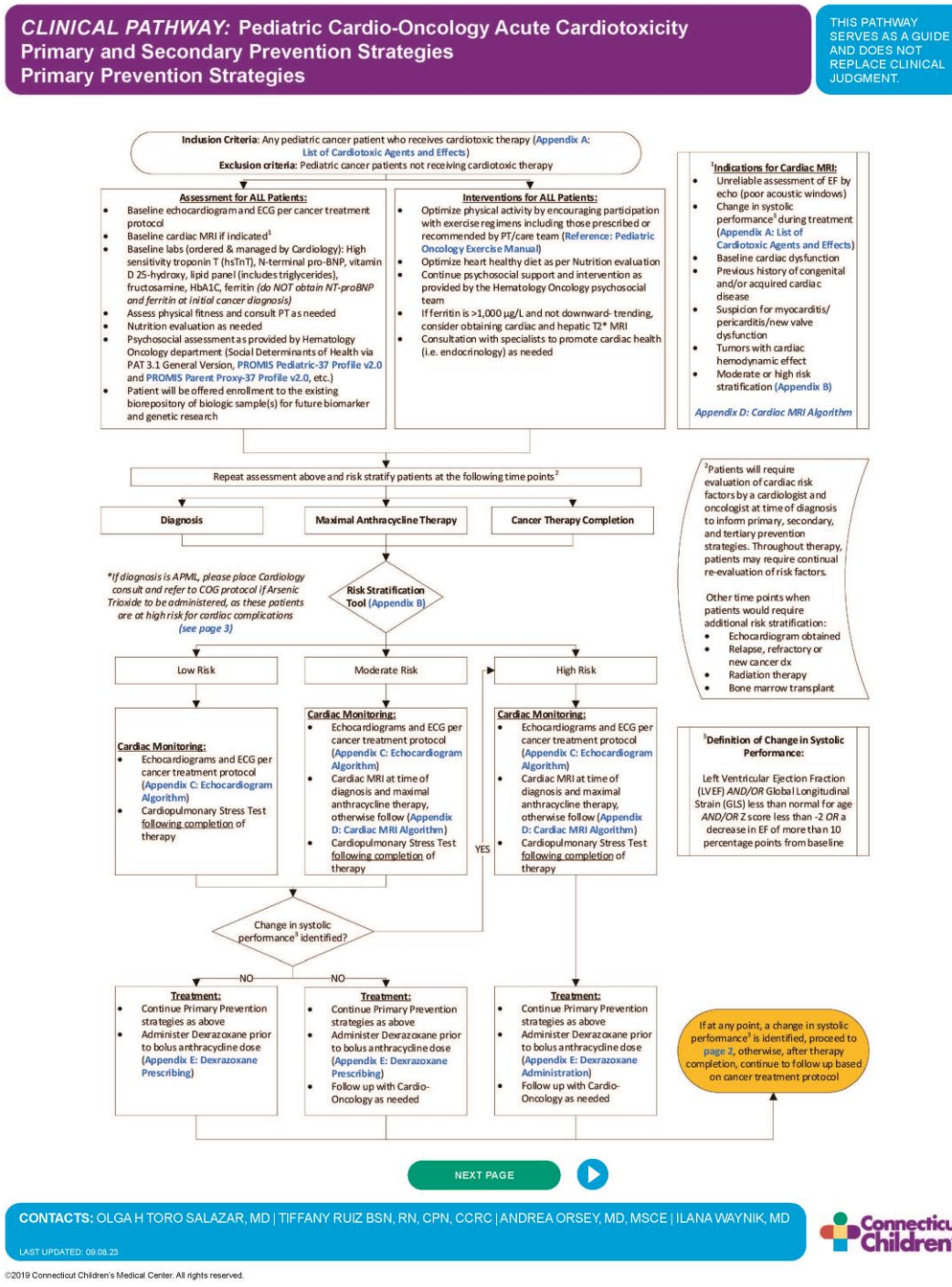
Background

- Children's Oncology Group (COG) define adequate cardiac function for clinical trial enrollment as:
  - Shortening fraction of ≥ 28% by echocardiogram
  - Ejection fraction of ≥ 50% by radionuclide angiogram

- However, our pathway takes a more conservative approach to help prevent progression of heart failure:
  - A change in systolic performance, also known as **CTRCD**, is defined as:
    - EF < 55%
    - SF < 29%
    - GLS < -17% (more negative is good, less negative is bad)
    - Z-scores (located in the table within an echo report)

This is the Pediatric Cardio-Oncology Acute Cardiotoxicity Primary and Secondary Prevention Strategies Clinical Pathway.

We will be reviewing each component in the following slides.



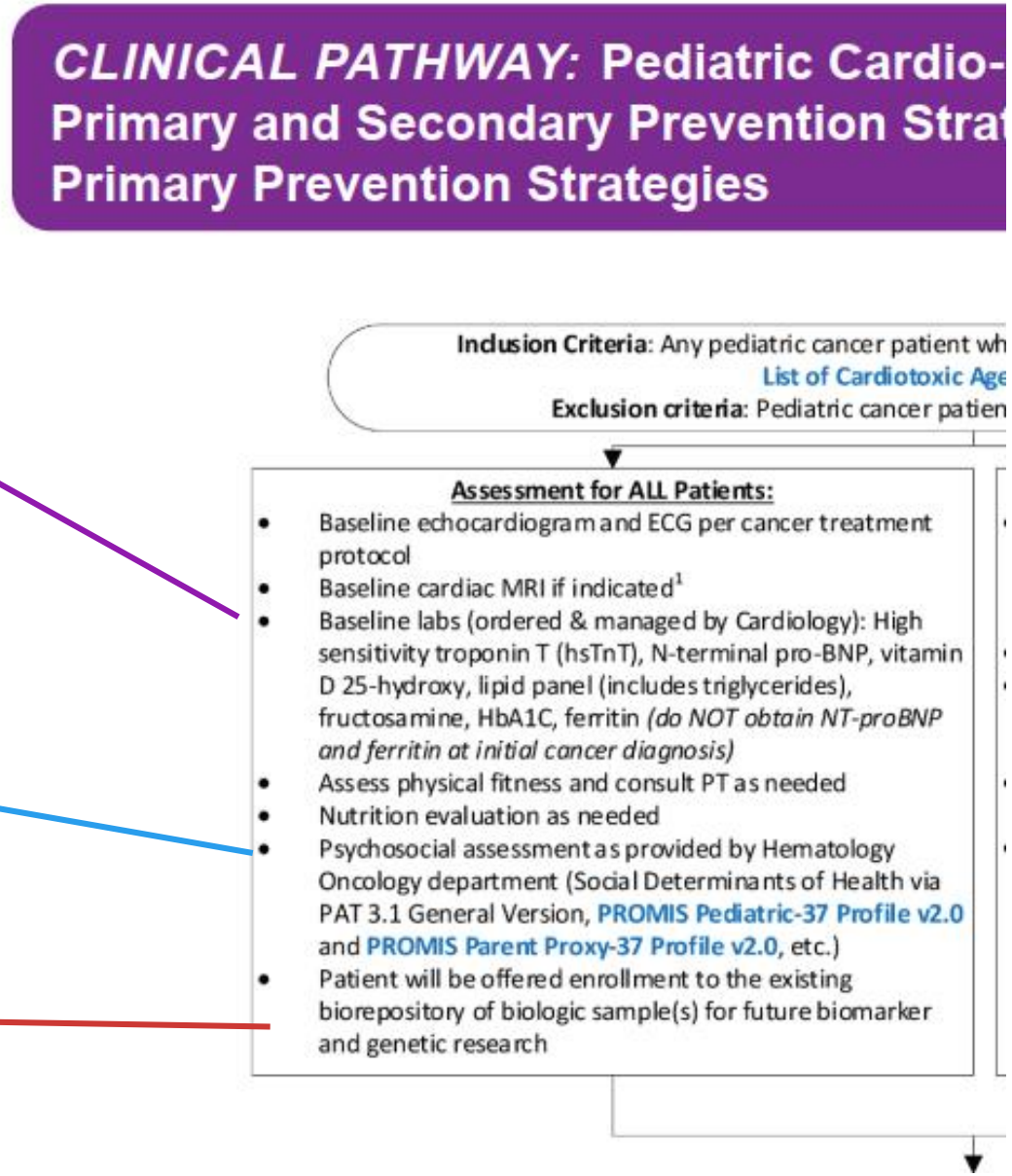
Page 1

The cardio-oncology labs can be ordered by using an order set

All order sets will be reviewed later in this presentation

As per current practice within the hematology/oncology psychosocial team

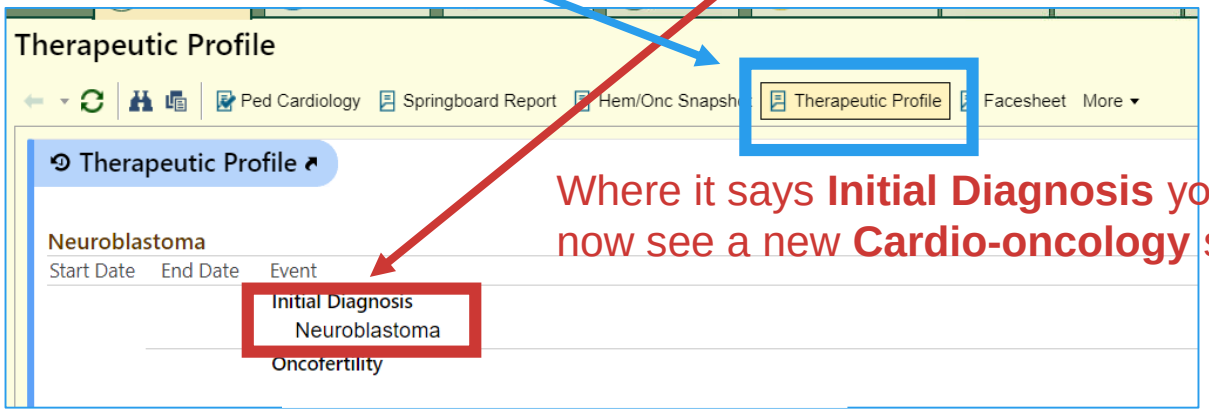
As per current practice within the hematology/oncology department. PI: Dr. Lau



- **Risk stratification** is currently completed by the cardio-oncology department.

The cardio-oncology Epic registry is under development and is designed to auto calculate risk score.

- The Therapeutic profile tab will now have a cardio-oncology section (also referred to as event)



Where it says **Initial Diagnosis** you'll now see a new **Cardio-oncology** section

The cardio-oncology section will be used:

1. Baseline
   - Risk scoring
   - Heart failure stage
   - Baseline cardiac function (via Echo and/or CMR)
2. Any **major** cardio-onc (i.e. +CTRCD)
   - Updated risk scoring
   - Updated heart failure stage
   - Updated cardiac function (via Echo and/or CMR)
   - Cardiac medications

Appendix B: Risk Stratification Tool

Risk Stratification Tool for Patients Receiving Cancer Treatment

Step 1: Score your patient's cardiovascular and cancer related risk categories
Step 2: Total the cardiovascular and cancer related risk categories
Step 3: Determine if patient is at low, moderate, or high risk for developing cardiac toxicity

Cardiovascular Related Risk Categories	
Body Mass Index (BMI) kg/m²	
☐ <85th percentile or BMI 18.5-24.9	0
☐ 85th-95th percentile or BMI 25-29.9	0.5
☐ ≥95th percentile or BMI ≥30	1
☐ ≥120% of 95th % percentile OR BMI ≥35, whichever is lower based on age and sex	1.5
Lipid Panel	
☐ Normal (LDL-c <110 mg/dL, Non HDL-c <120 mg/dL, AND triglycerides <150 mg/dL)	0
☐ Low-Moderate Risk (LDL-c 110-129 mg/dL, OR Non HDL-c 120-144 mg/dL, OR triglycerides 150-199 mg/dL)	0.5
☐ High Risk (LDL-c ≥130 mg/dL, OR Non HDL-c ≥145 mg/dL, OR triglycerides ≥200 mg/dL)	1
Pre-Diabetes/Diabetes	
☐ Normal glucose/A1c (Fasting: <100 mg/dL, 2-hr OGTT: <140 mg/dL, or HbA1c: <5.7%)	0
☐ Prediabetes (Fasting: 100-125 mg/dL, 2hr OGTT: 140-199 mg/dL, or HbA1c: 5.7-6.4%)	0.5
☐ Diabetes (Fasting: ≥126 mg/dL, 2-hr OGTT: ≥200 mg/dL, or HbA1c: ≥6.5%)	1
Ferritin	
☐ <1,000 µg/L	0
☐ >1,000 µg/L	1
Cardiorespiratory Fitness (CRF)	
☐ Good-Superior CRF based on relative VO_2 max for age & sex (> 80% of predicted value)	0
☐ Fair-Very Poor CRF based on relative VO_2 max for age & sex (< 80% of predicted)	1
☐ Less than Very Poor CRF is categorized as functional disability based on relative VO_2 max for age & sex	2
Previous Heart Disease at Diagnosis	
☐ No	0
☐ Yes	2
Hypertension (HTN): per AHA & AAP guidelines	
☐ Normal	0
☐ Elevated/Pre-HTN	0.5
☐ Stage 1	1
☐ Stage 2	3
Change in Systolic Performance*: current or by history	
☐ No	0
☐ Yes	1.5

Cancer Related Risk Categories	
Age at Cancer Diagnosis	
☐ ≥5 years	0
☐ 1-4 years	1
☐ <1 year	2
Gender: at birth	
☐ Male	0
☐ Female	1
Radiation: to heart region only	
☐ None	0
☐ <5 Gy	0.5
☐ 5-14.9 Gy	1
☐ 15-29.9 Gy	3
☐ >30 Gy	5
Vinca alkaloids^	
☐ No	0
☐ Yes	0.5
Alkylating Agents (i.e. CPM, IFOS)	
☐ No	0
☐ Yes	1.5
Anthracycline (AC) Cumulative Dose	
☐ <101 mg/m²	0
☐ 101-200 mg/m²	0.5
☐ >200-250 mg/m²	1
☐ >251-300 mg/m²	2
☐ >300 mg/m²	3
Dexrazoxane Given: applicable only if patient received ≥ 200mg/m² of AC	
☐ No	2
☐ Yes	0
Transplant: Please total scores for ALL transplants patient has undergone (if patient has 2 Tandem transplants patient score would be 2)	
☐ No	0
☐ Autologous/Tandem	1
☐ Allogenic	2

Risk probability for developing cardiac toxicity		
Low Risk	**Moderate Risk**	**High Risk**
0 - <6	6 - <11	≥11
Patient is automatically High Risk if they have a change in systolic performance*		

^ Only when given in combination with AC

*Change in Systolic Performance definition:

1. Left Ventricular Ejection Fraction (LVEF) less than normal for age AND/OR
2. Global Longitudinal Strain (GLS) less than normal for age AND/OR
3. Z score less than -2 OR
4. A decrease in EF of more than 10 percentage points from baseline

Created by: Olga H.Toro-Salazar MD, Tiffany Ruiz BSN, RN, CPN, CCRC, Andrea Orsey MD, MSCE, Eileen Gillan MD, Shailendra Upadhyay MD, Karen Rubin MD

Appendix B: Risk Stratification Tool

- This refers to gender at birth, as in children, females have a higher cardio-oncology risk

- Vinca alkaloids only gets 0.5 points if Anthracyclines were also administered as part of the patient's cancer plan. Vincristine on it's own would score "0"

Patients Receiving Cancer Treatment

ovascular and cancer related risk categories
nd cancer related risk categories
low, moderate, or high risk for developing cardiac toxicity

	0
	0.5
	1
age	1.5
s <150	0
g/dL,	0.5
ides	1
r	0
bA1c:	0.5
.5%)	1
	0
	1

Cancer Related Risk Categories	
Age at Cancer Diagnosis	
☐ ≥5 years	0
☐ 1-4 years	1
☐ <1 year	2
Gender: at birth	
☐ Male	0
☐ Female	1
Radiation: to heart region only	
☐ None	0
☐ <5 Gy	0.5
☐ 5-14.9 Gy	1
☐ 15-29.9 Gy	3
☐ >30 Gy	5
Vinca alkaloids^	
☐ No	0
☐ Yes	0.5
Alkylating Agents (i.e. CPM, IFOS)	
☐ No	0
☐ Yes	1.5
Anthracycline (AC) Cumulative Dose	
☐ <101 mg/m²	0
☐ 101-200 mg/m²	0.5

Appendix B: Risk Stratification Tool

- Dexrazoxane (DRZ) is typically always given prior to anthracycline (AC) doses.
- However, previously DRZ wasn't standard process so there may be patients for whom you will have to check "No"

- In pediatrics use the American Academy of Pediatrics (AAP) guidelines:
  - https://www.mdcalc.com/calc/4052/aap-pediatric-hypertension-guidelines
- For adult patients use the AHA guidelines

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

>300 mg/m²	3
Dexrazoxane Given: applicable only if patient received ≥ 200mg/m² of AC	
No	2
Yes	0
Transplant: Please total scores for ALL transplants patient has undergone (if patient has 2 Tandem transplants patient score would be 2)	
No	0
Autologous/Tandem	1
Allogenic	2

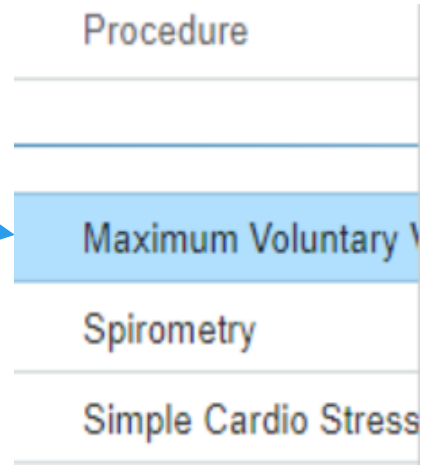
Fair-Very Poor CRF based on relative VO_2 max for age & sex (< 80% of predicted)	1
Less than Very Poor CRF is categorized as functional disability based on relative VO_2 max for age & sex	2
Previous Heart Disease at Diagnosis	
No	0
Yes	2
Hypertension (HTN): per AHA & AAP guidelines	
Normal	0
Elevated/Pre-HTN	0.5
Stage 1	1
Stage 2	3
Change in Systolic Performance[*]**:** current or by history	
No	0
Yes	1.5

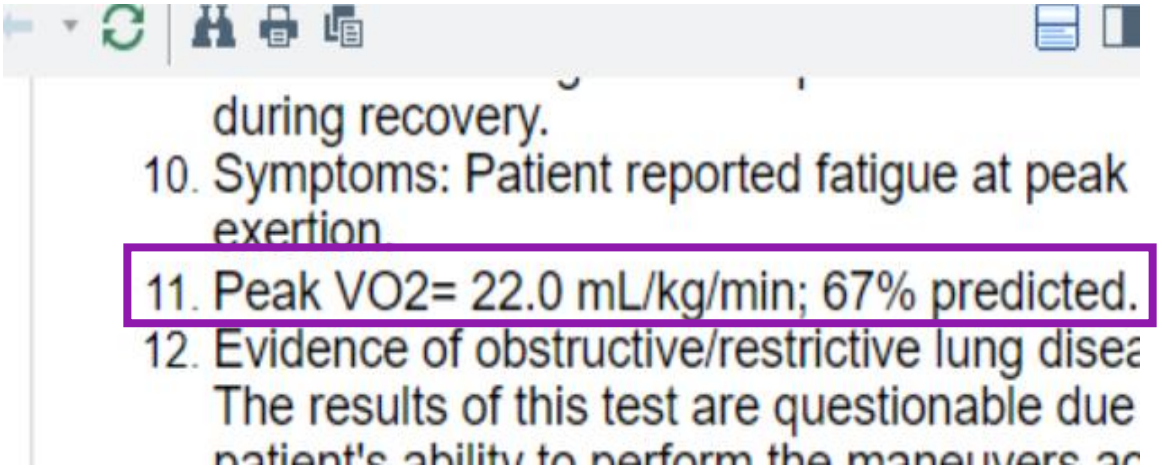
Appendix B: Risk Stratification Tool

	>1,000 µg/L	1
Cardiorespiratory Fitness (CRF)		
☐	Good-Superior CRF based on relative VO_2 max for age & sex (> 80% of predicted value)	0
☐	Fair-Very Poor CRF based on relative VO_2 max for age & sex (< 80% of predicted)	1
☐	Less than Very Poor CRF is categorized as functional disability based on relative VO_2 max for age & sex	2

Pediatric Cardiorespiratory Fitness (<20 years old) is based off of peak VO_2 % predicted

- In Epic, Stress Test results are found under "Procedures"
- If you click **Maximum Voluntary Ventilation** once, you'll see the Peak VO_2 located in the **Summary of Findings**

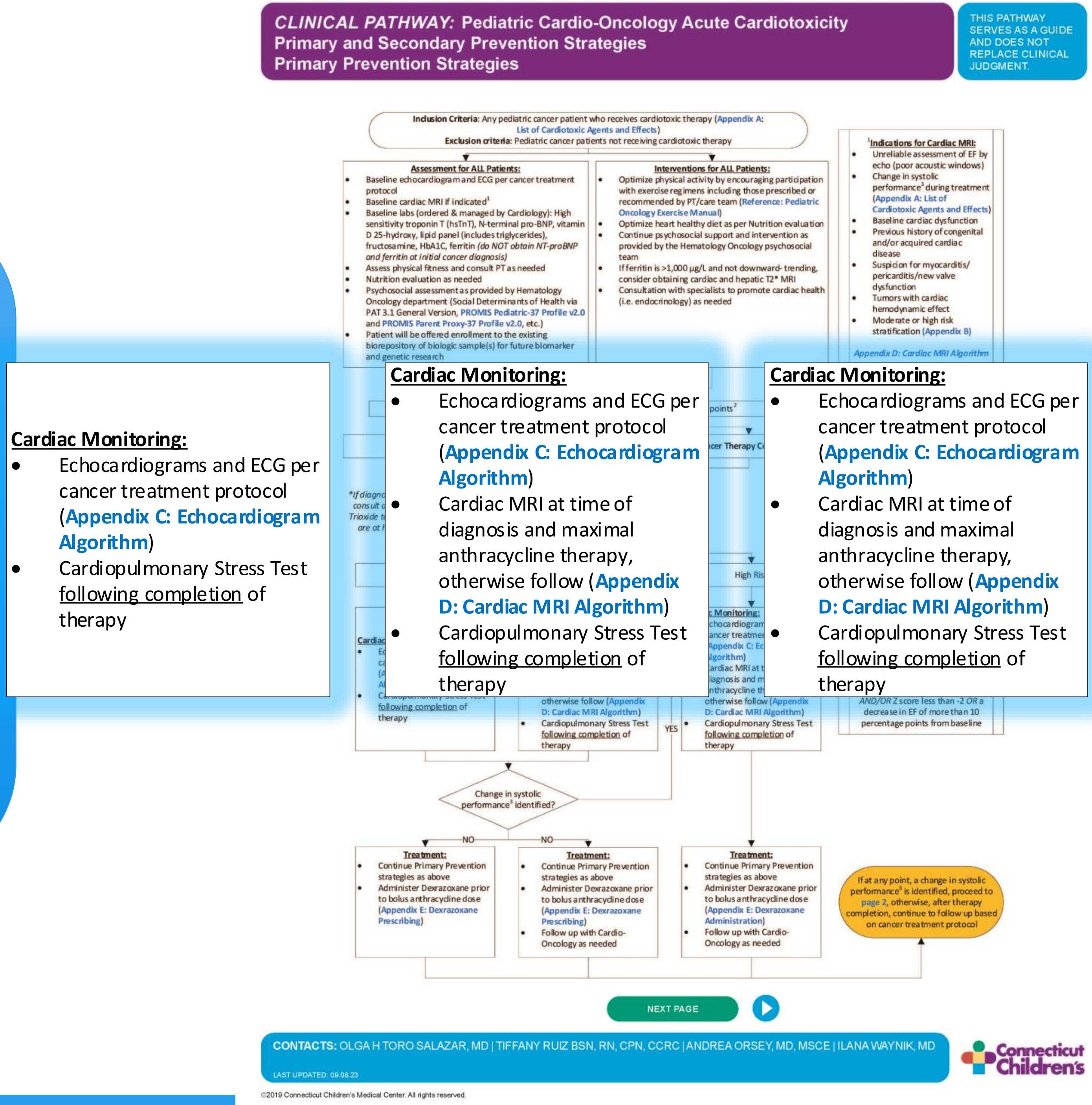



during recovery.
10. Symptoms: Patient reported fatigue at peak exertion.
11. Peak VO2= 22.0 mL/kg/min; 67% predicted.
12. Evidence of obstructive/restrictive lung disea
The results of this test are questionable due

Reminder: The Cardio-oncology dept is responsible for risk scoring. This is for your knowledge.

Appendix B: Risk Stratification Tool

- Cardiopulmonary Stress Test yields a peak VO_2/VO_2 max value
- This indicates a patient's cardiorespiratory fitness and is the most important predictor of morbidity and mortality



Appendix B: Risk Stratification Tool

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Pediatric Cardiorespiratory Fitness (<20 years old) is based off of peak VO_2 % predicted

- Please use the "VO2 Max/Pred (%)" As seen highlighted in red in the PDF report

Exercise

	Rest	AT	VO2 Max	Pred	AT / Pred (%)	VO2 Max/Pred (%)
Time (min)	9:40	15:53	16:29			
Ex Time (min)		6:09	6:45			
---- WORK ----						
Speed (MPH)		3.4	2.5			
Grade (%)		14.0				
---- VENTILATION ----						
Vt BTPS (L)	0.90	1.55	1.84			
RR (br/min)	14	48	46			
VE BTPS (L/min)	12.3	74.3	83.9	116.0	64	72
BR (%)	89.4	35.7	27.4			
SpO2 (%)	93	94	93			
---- O2 CONSUMPTION ----						
VO2 (mL/kg/min)	4.1	19.6	22.0	32.9	60	67
VO2 (L/min)	0.42	1.99	2.23	3.34	60	67
VCO2 (L/min)	0.35	2.24	2.76	4.04	56	68

Appendix B: Risk Stratification Tool

Adult VO_2 max (≥ 20 years) Male Table

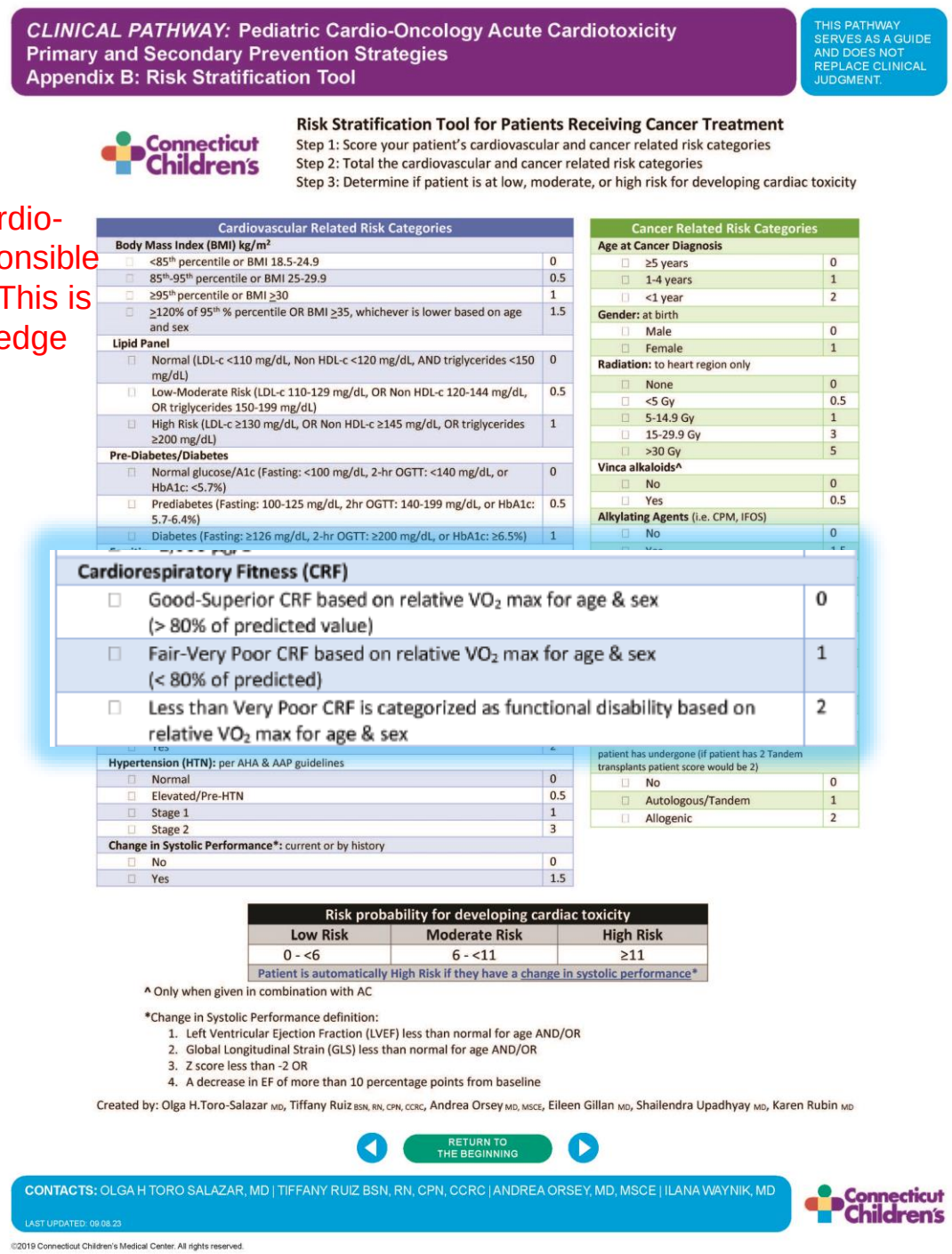
TABLE 3.8 • Treadmill-Based Cardiorespiratory Fitness Classifications ($\dot{V}O_{2max}$) by Age and Sex

$\dot{V}O_{2max}$ (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)

		MEN Age Group (yr)				
Percentile		20–29	30–39	40–49	50–59	60–69
95	Superior	66.3	59.8	55.6	50.7	43.0
90		61.8	56.5	52.1	45.6	40.3
85	Excellent	59.3	54.2	49.3	43.2	38.2
80		57.1	51.6	46.7	41.2	36.1
75		55.2	49.2	45.0	39.7	34.5
70	Good	53.7	48.0	43.9	38.2	32.9
65		52.1	46.6	42.1	36.3	31.6
60		50.2	45.2	40.3	35.1	30.5
55		49.0	43.8	38.9	33.8	29.1
50	Fair	48.0	42.4	37.8	32.6	28.2
45		46.5	41.3	36.7	31.6	27.2
40		44.9	39.6	35.7	30.7	26.6
35		43.5	38.5	34.6	29.5	25.7
30	Poor	41.9	37.4	33.3	28.4	24.6
25		40.1	35.9	31.9	27.1	23.7
20		38.1	34.1	30.5	26.1	22.4
15		35.4	32.7	29.0	24.4	21.2
10	Very poor	32.1	30.2	26.8	22.8	19.8
5		29.0	27.2	24.2	20.9	17.4

Use the VO_2 max obtained, locate their age, determine which category the fall under. Example: 35 year old male with a VO_2 max of 39% would fall under the **poor category** and score a 1 on the risk score.

Reminder: Cardio-oncology is responsible for risk scoring. This is for your knowledge



CLINICAL PATHWAY: Pediatric Cardio-Oncology Acute Cardiotoxicity
Primary and Secondary Prevention Strategies
Appendix B: Risk Stratification Tool

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Connecticut Children's

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85th-95th percentile or BMI 25-29.9	0.5
≥95th percentile or BMI ≥30	1
≥120% of 95th % percentile OR BMI ≥35, whichever is lower based on age and sex	1.5
Lipid Panel	
Normal (LDL-c <110 mg/dL, Non HDL-c <120 mg/dL, AND triglycerides <150 mg/dL)	0
Low-Moderate Risk (LDL-c 110-129 mg/dL, OR Non HDL-c 120-144 mg/dL, OR triglycerides 150-199 mg/dL)	0.5
High Risk (LDL-c ≥130 mg/dL, OR Non HDL-c ≥145 mg/dL, OR triglycerides ≥200 mg/dL)	1
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Normal glucose/A1c (Fasting: <100 mg/dL, 2-hr OGTT: <140 mg/dL, or HbA1c: <5.7%)	0
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Diabetes (Fasting: ≥126 mg/dL, 2-hr OGTT: ≥200 mg/dL, or HbA1c: ≥6.5%)	1
Hypertension (HTN): per AHA & AAP guidelines	
Normal	0
Elevated/Pre-HTN	0.5
Stage 1	1
Stage 2	3
Change in Systolic Performance*: current or by history	
No	0
Yes	1.5

Cancer Related Risk Categories	
Age at Cancer Diagnosis	
≥5 years	0
1-4 years	1
<1 year	2
Gender: at birth	
Male	0
Female	1
Radiation: to heart region only	
None	0
<5 Gy	0.5
5-14.9 Gy	1
15-29.9 Gy	3
>30 Gy	5
Vinca alkaloids^	
No	0
Yes	0.5
Alkylating Agents (i.e. CPM, IFOS)	
No	0

Cardiorespiratory Fitness (CRF)	
Good-Superior CRF based on relative VO_2 max for age & sex (> 80% of predicted value)	0
Fair-Very Poor CRF based on relative VO_2 max for age & sex (< 80% of predicted)	1
Less than Very Poor CRF is categorized as functional disability based on relative VO_2 max for age & sex	2

patient has undergone (if patient has 2 Tandem transplants patient score would be 2)

No	0
Autologous/Tandem	1
Allogenic	2

Risk probability for developing cardiac toxicity		
Low Risk	Moderate Risk	High Risk
0 - <6	6 - <11	≥11
Patient is automatically High Risk if they have a change in systolic performance*		

^ Only when given in combination with AC

*Change in Systolic Performance definition:
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2. Global Longitudinal Strain (GLS) less than normal for age AND/OR
3. Z score less than -2 OR
4. A decrease in EF of more than 10 percentage points from baseline

Created by: Olga H.Toro-Salazar MD, Tiffany Ruiz BSN, RN, CPN, CCRC, Andrea Orsey MD, MSCE, Eileen Gillan MD, Shailendra Upadhyay MD, Karen Rubin MD

RETURN TO THE BEGINNING

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Appendix B: Risk Stratification Tool

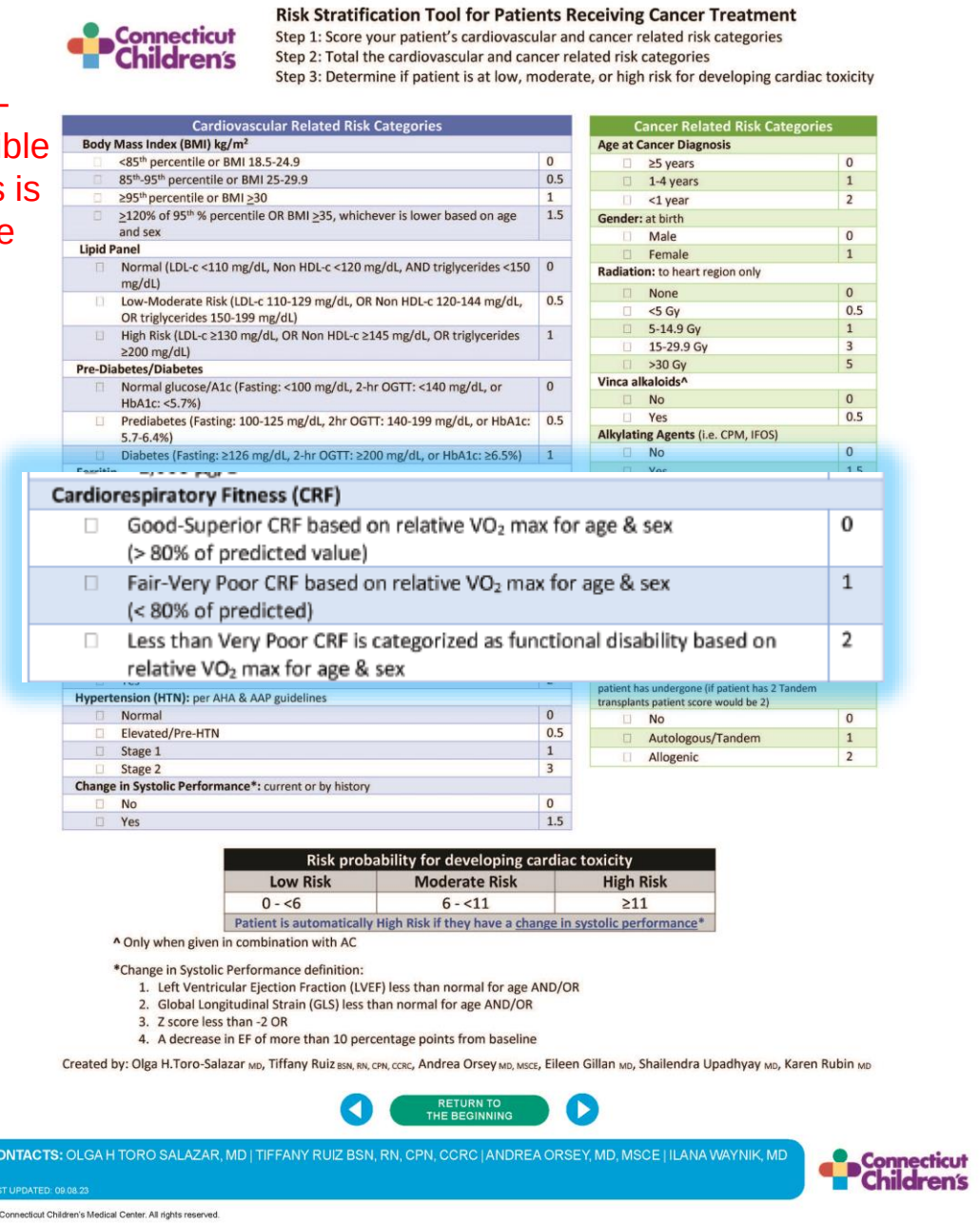
Adult VO_2 max (≥ 20 years) Female Table

Percentile		WOMEN Age Group (yr) 20–29	30–39	40–49	50–59	60–69
95	Superior	56.0	45.8	41.7	35.9	29.4
90		51.3	41.4	38.4	32.0	27.0
85	Excellent	48.3	39.3	36.0	30.2	25.6
80		46.5	37.5	34.0	28.6	24.6
75		44.7	36.1	32.4	27.6	23.8
70	Good	43.2	34.6	31.1	26.8	23.1
65		41.6	33.5	30.0	26.0	22.0
60		40.6	32.2	28.7	25.2	21.2
55		38.9	31.2	27.7	24.4	20.5
50	Fair	37.6	30.2	26.7	23.4	20.0
45		35.9	29.3	25.9	22.7	19.6
40		34.6	28.2	24.9	21.8	18.9
35		33.6	27.4	24.1	21.2	18.4
30	Poor	32.0	26.4	23.3	20.6	17.9
25		30.5	25.3	22.1	19.9	17.2
20		28.6	24.1	21.3	19.1	16.5
15		26.2	22.5	20.0	18.3	15.6
10	Very poor	23.9	20.9	18.8	17.3	14.6
5		21.7	19.0	17.0	16.0	13.4
		(*n* = 410)	(*n* = 608)	(*n* = 843)	(*n* = 805)	(*n* = 408)

Percentiles from cardiopulmonary exercise testing on a treadmill with measured maximal volume of oxygen consumed per unit time ($\dot{V}O_{2max}$) (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$).
Data obtained from the Fitness Registry and the Importance of Exercise National Database (FRIEND) Registry for men and women who were considered free from known cardiovascular disease.

Adapted with permission from (124).

Reminder: Cardio-oncology is responsible for risk scoring. This is for your knowledge



CLINICAL PATHWAY: Pediatric Cardio-Oncology Acute Cardiotoxicity
Primary and Secondary Prevention Strategies
Appendix B: Risk Stratification Tool

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

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Risk Stratification Tool for Patients Receiving Cancer Treatment
Step 1: Score your patient's cardiovascular and cancer related risk categories
Step 2: Total the cardiovascular and cancer related risk categories
Step 3: Determine if patient is at low, moderate, or high risk for developing cardiac toxicity

Cardiovascular Related Risk Categories

Body Mass Index (BMI) kg/m²	
<85th percentile or BMI 18.5-24.9	0
85th-95th percentile or BMI 25-29.9	0.5
≥95th percentile or BMI ≥30	1
≥120% of 95th % percentile OR BMI ≥35, whichever is lower based on age and sex	1.5
Lipid Panel	
Normal (LDL-c <110 mg/dL, Non HDL-c <120 mg/dL, AND triglycerides <150 mg/dL)	0
Low-Moderate Risk (LDL-c 110-129 mg/dL, OR Non HDL-c 120-144 mg/dL, OR triglycerides 150-199 mg/dL)	0.5
High Risk (LDL-c ≥130 mg/dL, OR Non HDL-c ≥145 mg/dL, OR triglycerides ≥200 mg/dL)	1
Pre-Diabetes/Diabetes	
Normal glucose/A1c (Fasting: <100 mg/dL, 2-hr OGTT: <140 mg/dL, or HbA1c: <5.7%)	0
Prediabetes (Fasting: 100-125 mg/dL, 2hr OGTT: 140-199 mg/dL, or HbA1c: 5.7-6.4%)	0.5
Diabetes (Fasting: ≥126 mg/dL, 2-hr OGTT: ≥200 mg/dL, or HbA1c: ≥6.5%)	1
Hypertension (HTN): per AHA & AAP guidelines	
Normal	0
Elevated/Pre-HTN	0.5
Stage 1	1
Stage 2	3
Change in Systolic Performance*: current or by history	
No	0
Yes	1.5

Cancer Related Risk Categories

Age at Cancer Diagnosis	
≥5 years	0
1-4 years	1
<1 year	2
Gender: at birth	
Male	0
Female	1
Radiation: to heart region only	
None	0
<5 Gy	0.5
5-14.9 Gy	1
15-29.9 Gy	3
>30 Gy	5
Vinca alkaloids^	
No	0
Yes	0.5
Alkylating Agents (i.e. CPM, IFOS)	
No	0

Cardiorespiratory Fitness (CRF)

Good-Superior CRF based on relative VO_2 max for age & sex (> 80% of predicted value)	0
Fair-Very Poor CRF based on relative VO_2 max for age & sex (< 80% of predicted)	1
Less than Very Poor CRF is categorized as functional disability based on relative VO_2 max for age & sex	2

patient has undergone (if patient has 2 Tandem transplants patient score would be 2)

No	0
Autologous/Tandem	1
Allogenic	2

Risk probability for developing cardiac toxicity

Low Risk	Moderate Risk	High Risk
0 - <6	6 - <11	≥11

Patient is automatically High Risk if they have a change in systolic performance*

^ Only when given in combination with AC

*Change in Systolic Performance definition:
1. Left Ventricular Ejection Fraction (LVEF) less than normal for age AND/OR
2. Global Longitudinal Strain (GLS) less than normal for age AND/OR
3. Z score less than -2 OR
4. A decrease in EF of more than 10 percentage points from baseline

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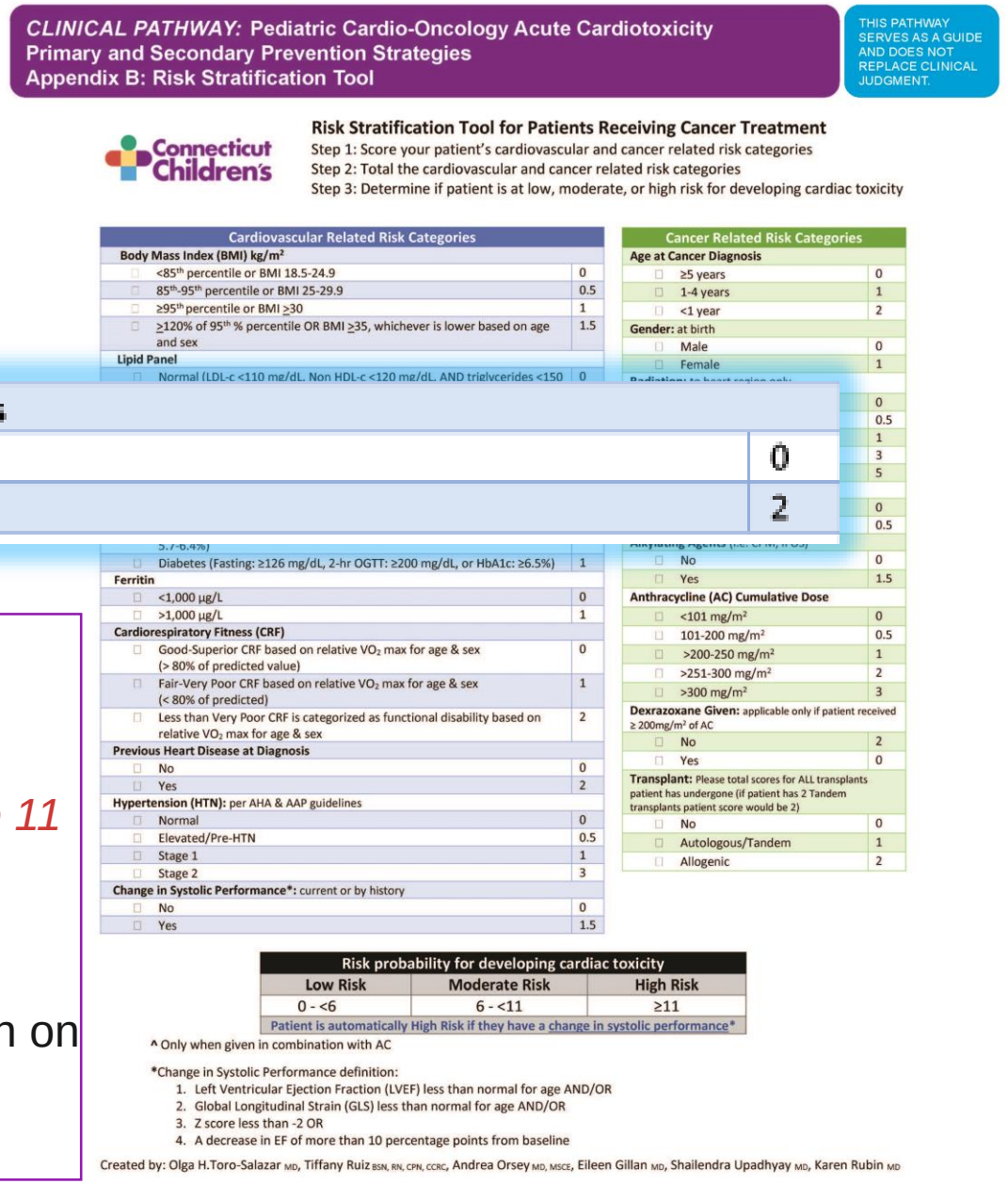
Appendix B: Risk Stratification Tool



CLINICAL PATHWAY: Pediatric Cardio-Oncology Acute Cardiotoxicity
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85th-95th percentile or BMI 25-29.9	0.5
≥95th percentile or BMI ≥30	1
≥120% of 95th % percentile OR BMI ≥35, whichever is lower based on age and sex	1.5
Lipid Panel	
Normal (LDL-c <110 mg/dL, Non HDL-c <120 mg/dL, AND triglycerides <150	0
Diabetes (Fasting: ≥126 mg/dL, 2-hr OGTT: ≥200 mg/dL, or HbA1c: ≥6.5%)	1
Ferritin	
<1,000 µg/L	0
>1,000 µg/L	1
Cardiorespiratory Fitness (CRF)	
Good-Superior CRF based on relative VO_2 max for age & sex (> 80% of predicted value)	0
Fair-Very Poor CRF based on relative VO_2 max for age & sex (< 80% of predicted)	1
Less than Very Poor CRF is categorized as functional disability based on relative VO_2 max for age & sex	2
Previous Heart Disease at Diagnosis	
No	0
Yes	2
Hypertension (HTN): per AHA & AAP guidelines	
Normal	0
Elevated/Pre-HTN	0.5
Stage 1	1
Stage 2	3
Change in Systolic Performance*: current or by history	
No	0
Yes	1.5

Cancer Related Risk Categories	
Age at Cancer Diagnosis	
≥5 years	0
1-4 years	1
<1 year	2
Gender: at birth	
Male	0
Female	1
No	0
Yes	1.5
Anthracycline (AC) Cumulative Dose	
<101 mg/m²	0
101-200 mg/m²	0.5
>200-250 mg/m²	1
>251-300 mg/m²	2
>300 mg/m²	3
Dexrazoxane Given: applicable only if patient received ≥ 200mg/m² of AC	
No	2
Yes	0
Transplant: Please total scores for ALL transplants patient has undergone (if patient has 2 Tandem transplants patient score would be 2)	
No	0
Autologous/Tandem	1
Allogenic	2

Previous Heart Disease at Diagnosis

No	0
Yes	2

Risk probability for developing cardiac toxicity		
Low Risk	**Moderate Risk**	**High Risk**
0 - <6	6 - <11	≥11
Patient is automatically High Risk if they have a change in systolic performance*		

^ Only when given in combination with AC

*Change in Systolic Performance definition:
1. Left Ventricular Ejection Fraction (LVEF) less than normal for age AND/OR
2. Global Longitudinal Strain (GLS) less than normal for age AND/OR
3. Z score less than -2 OR
4. A decrease in EF of more than 10 percentage points from baseline

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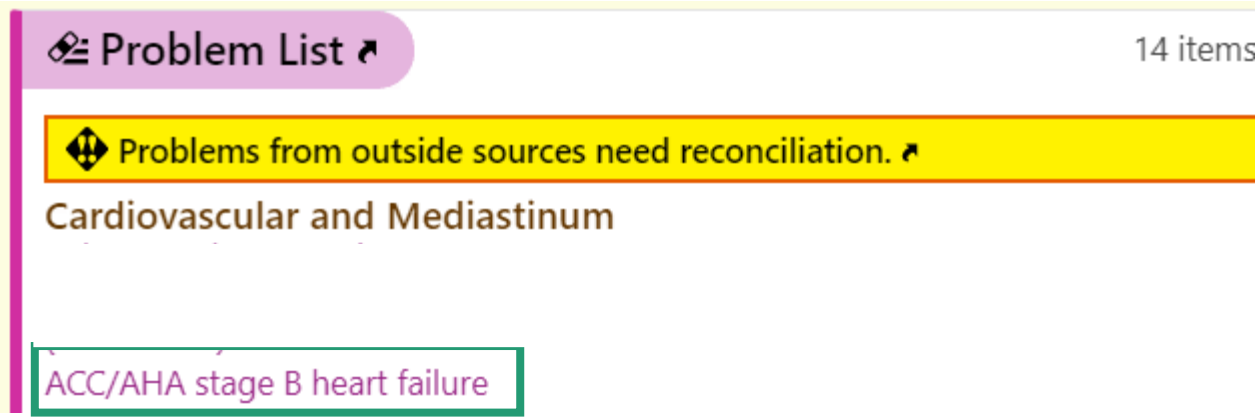
The following constitute as previous heart disease at diagnosis:

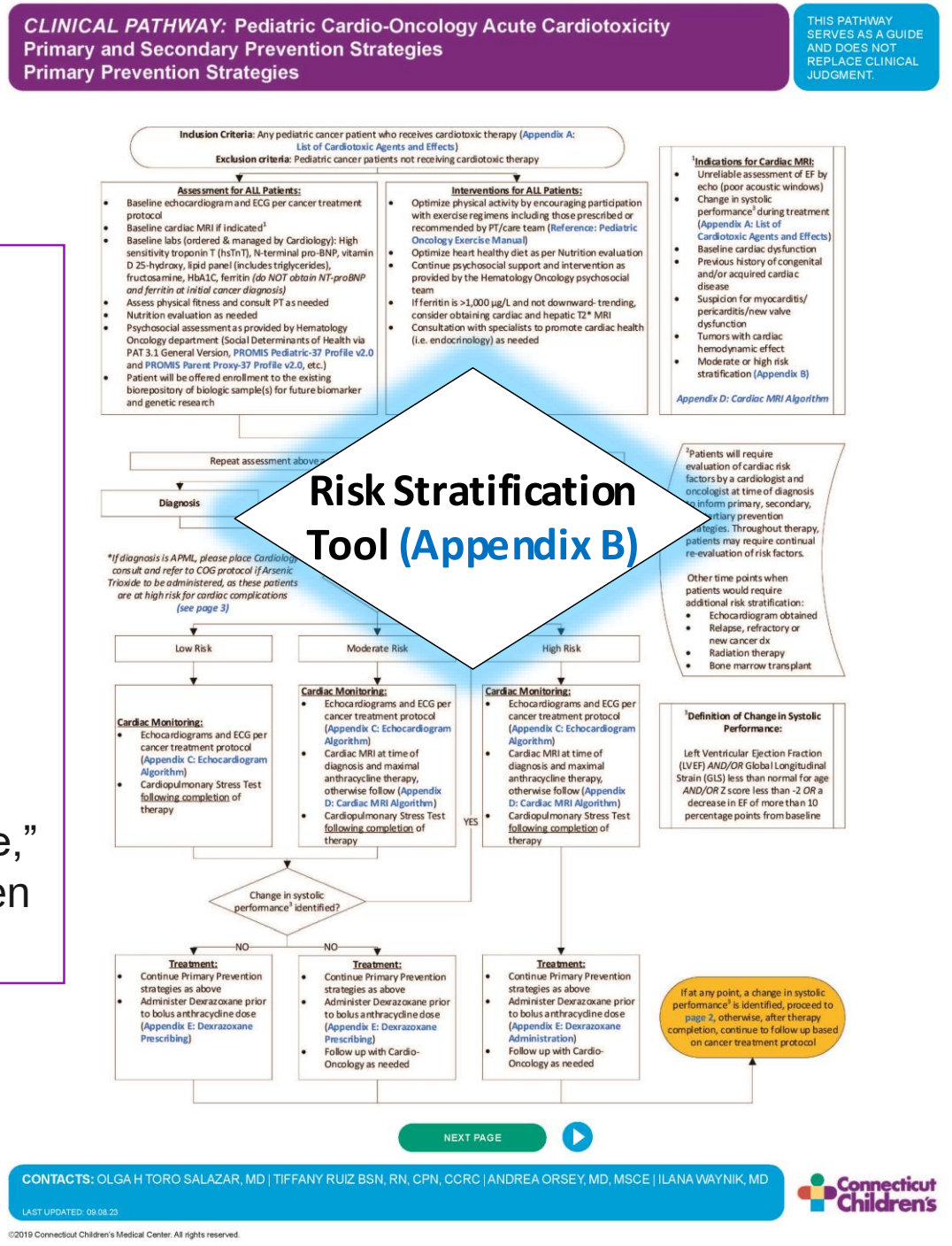
- Baseline **change in systolic performance** (also known as myocardial dysfunction or CTRCD) *previously explained on slide 11*
- Pericardial effusion
- Pericardial tamponade
- Previous history of congenital and/or acquired heart disease
- Tumor with cardiac hemodynamic effects (i.e. tumor compression on the heart or blood vessels – reported at the top of echo reports)
- Myocarditis

View Heart Failure Risk Details on Problem List

Under the Problem List the team will place a **Cardiovascular and Mediastinum** diagnosis for cardio-oncology patients.



An Epic user can click on the problem “ACC/AHA heart failure stage,” and details of this conditions can be seen. An example of this is seen on the next slide.



View Heart Failure Risk Details on Problem List

Problem Detail

Noted: 1/29/2019

Overview: Addendum 10/30/2023 11:22 AM by Tiffany L Ruiz, RN

Time stamp will show last time it was updated

Cardio-oncology history

1. **Cancer Diagnosis:** B-lymphoblastic lymphoma
2. **Age at Diagnosis:** 15 years
3. **Cancer Protocol:** AALL0932
4. **Anthracyclines received**: Please see life time dosing section below
5. **Radiation Therapy**: No
6. **Previous heart disease at diagnosis:** Congenital anomaly of heart
7. **Transplant**: No
8. **Other chemotherapies given:** Vincristine, Cyclophosphamide, Cytarabine, Methotrexate, Etoposide, 6MP, 6TG, steroids
9. **Risk factors for CTRCD**: Low risk
10. **Cardiovascular History**: None during cancer therapy.
11. **Heart failure medications:** None indicated

Lifetime Dose Tracking

- doxorubicin: 76.366 mg/m2 (126 mg) = 16.97 % of the maximum lifetime dose of 450 mg/m2
- cyclophosphamide: 1,050.955 mg/m2 (1,650 mg) = 14.01 % of the maximum lifetime dose of 7,500 mg/m2
- Total Anthracycline: 76.366 mg/m2 (126 mg) = 16.97 % of the maximum lifetime dose of 450 mg/m2

Previously conducted echos:

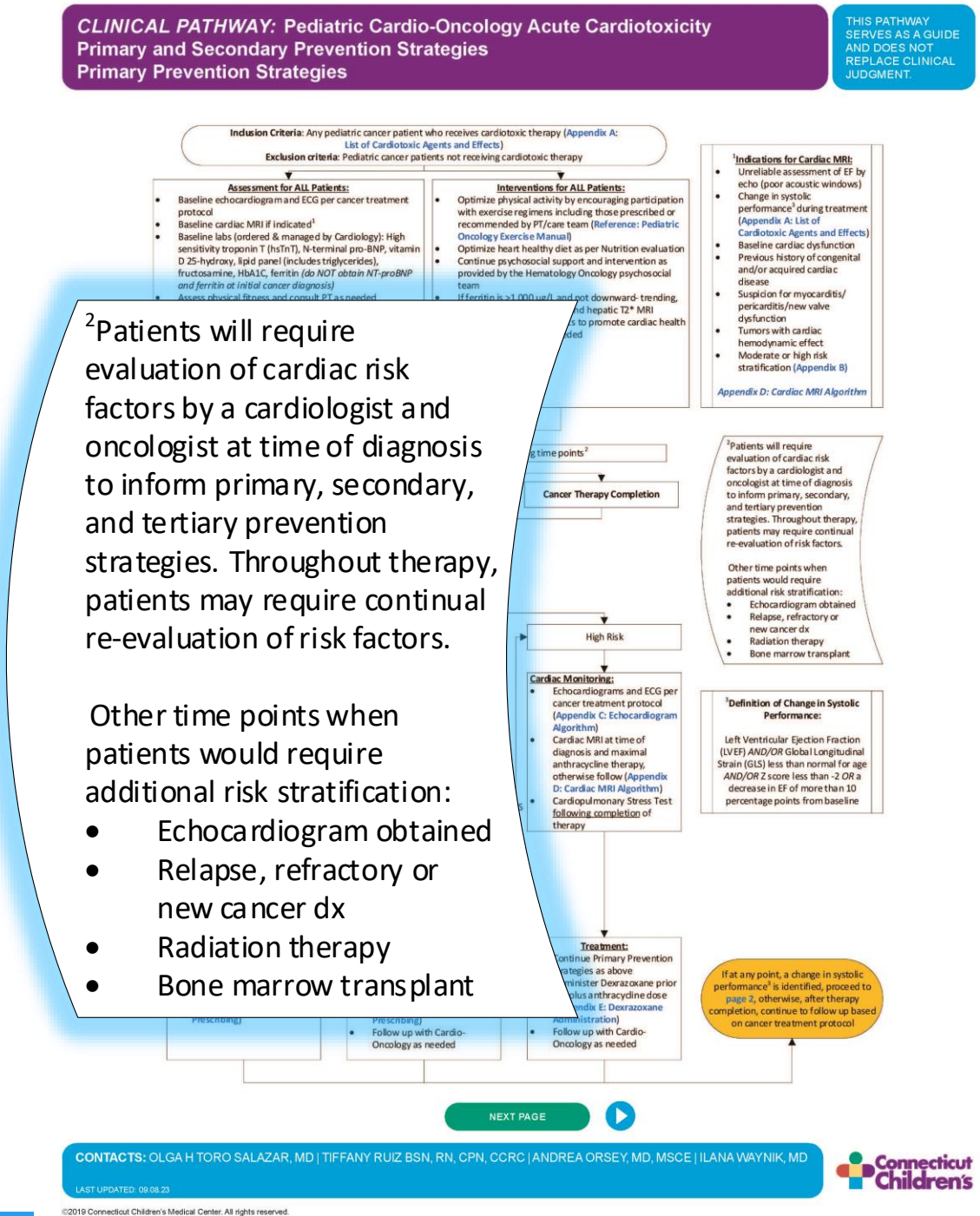
Date	EF% (3D)	GLS %	FS %	Med E' Peak cm/sec	Notes/Comments
	60		41.2	9.5	Mild aortic valve insufficiency
	63.4		41.9	9.5	Poor acoustic window. Buckling of the mitral valve leaflets to the plane of the annulus without prolapse. Trivial mitral valve insufficiency
	57		29	11.1	
	58	-	31		Limited acoustic windows, limited imaging.

Previously conducted cardiac MRI (CMR): None previously performed

Previously conducted stress tests (CPET): None previously performed

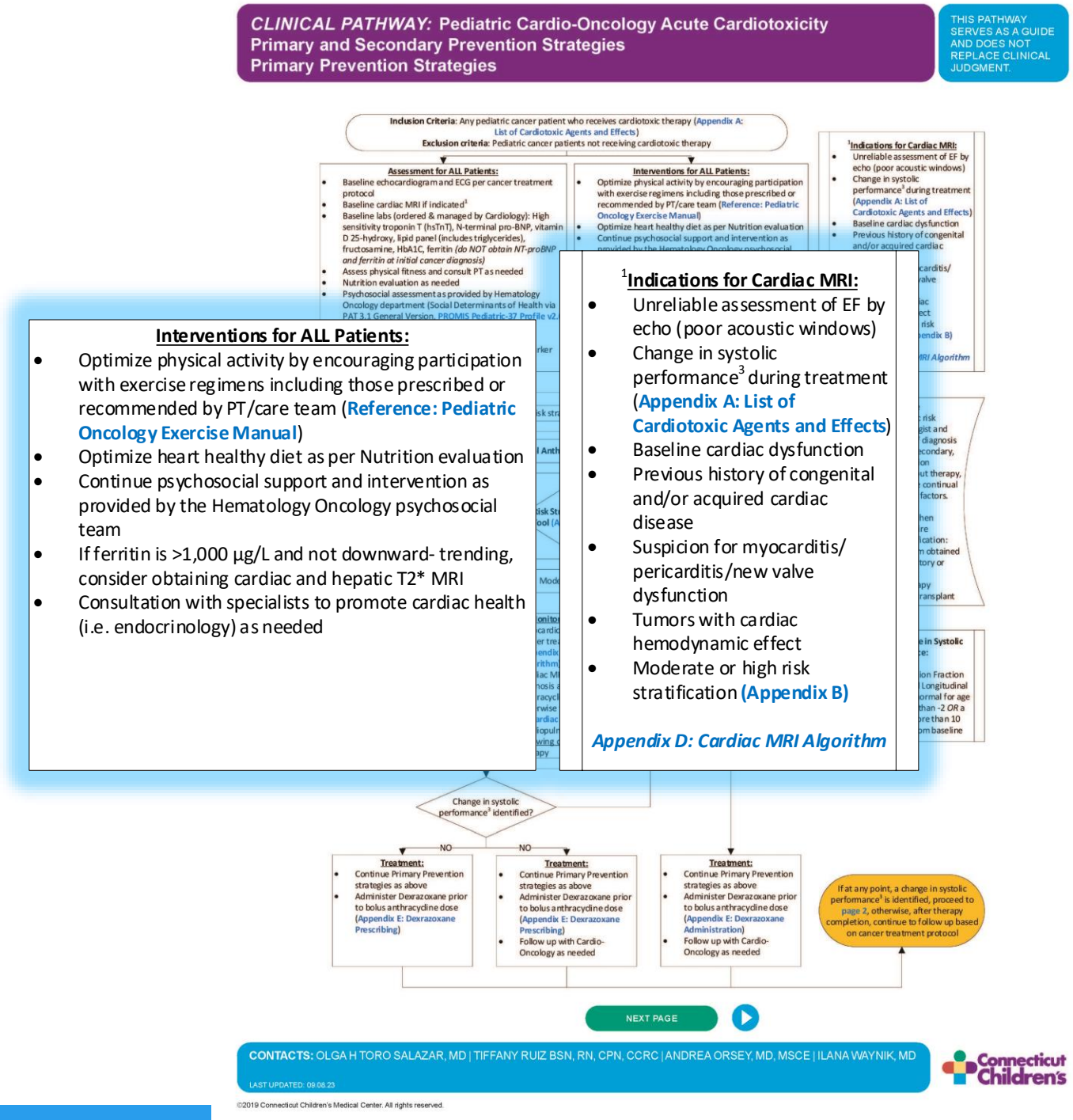
Risk Stratification Tool Use

Of note, risk scoring also takes place at other time periods during the patients cancer treatment, not just at diagnosis, max anthracycline therapy, and therapy completion



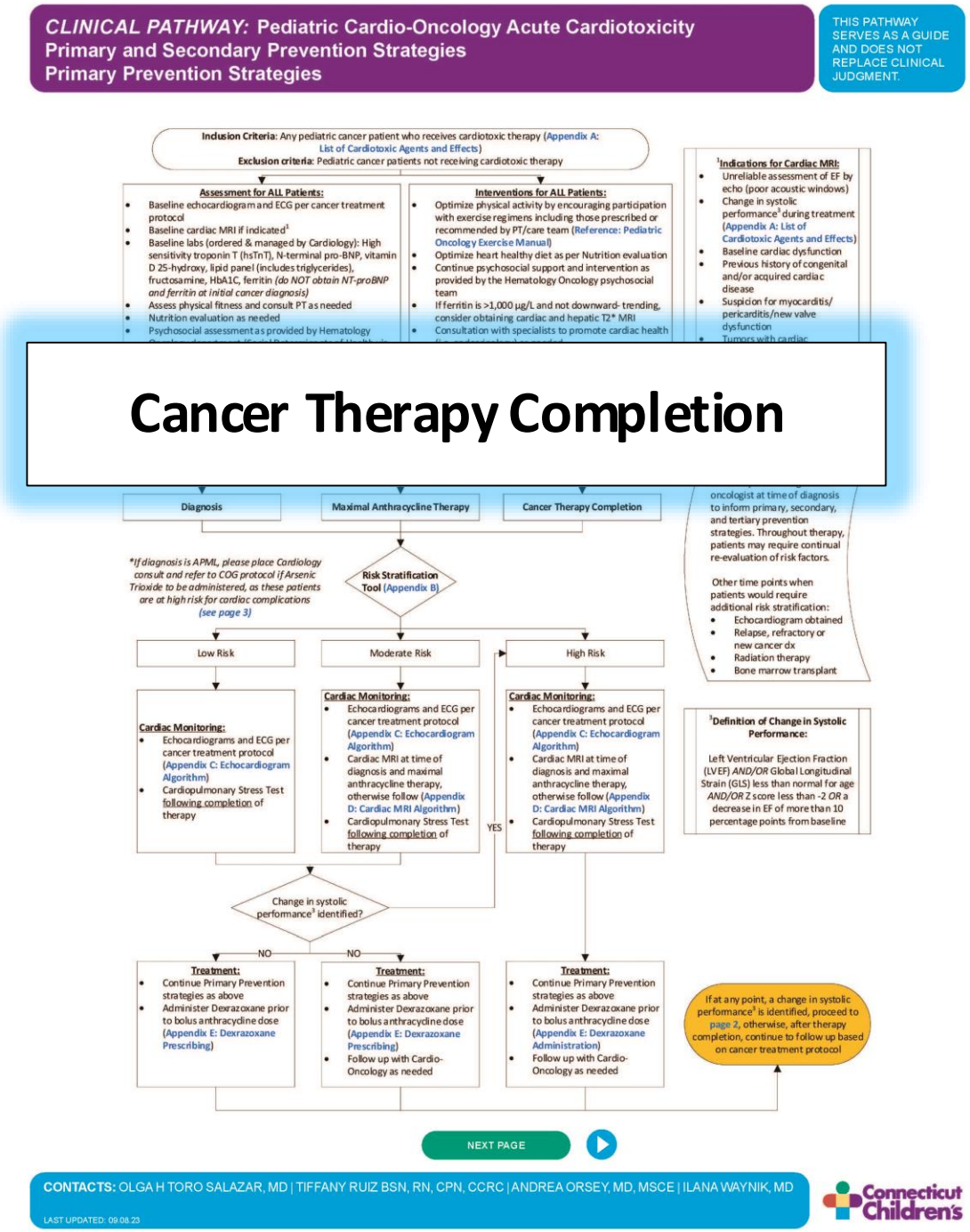
Page 1: Primary Prevention Other Tips on Management

- Please note that “Interventions for ALL Patients” serves as a guide for clinicians
- A box on the right lists the indications for obtaining a cardiac MRI (CMR)



Page 1: Primary Prevention

Cancer therapy completion/End of Treatment (EOT) = from the time the patient completes their cancer therapy up until 2 years post completion

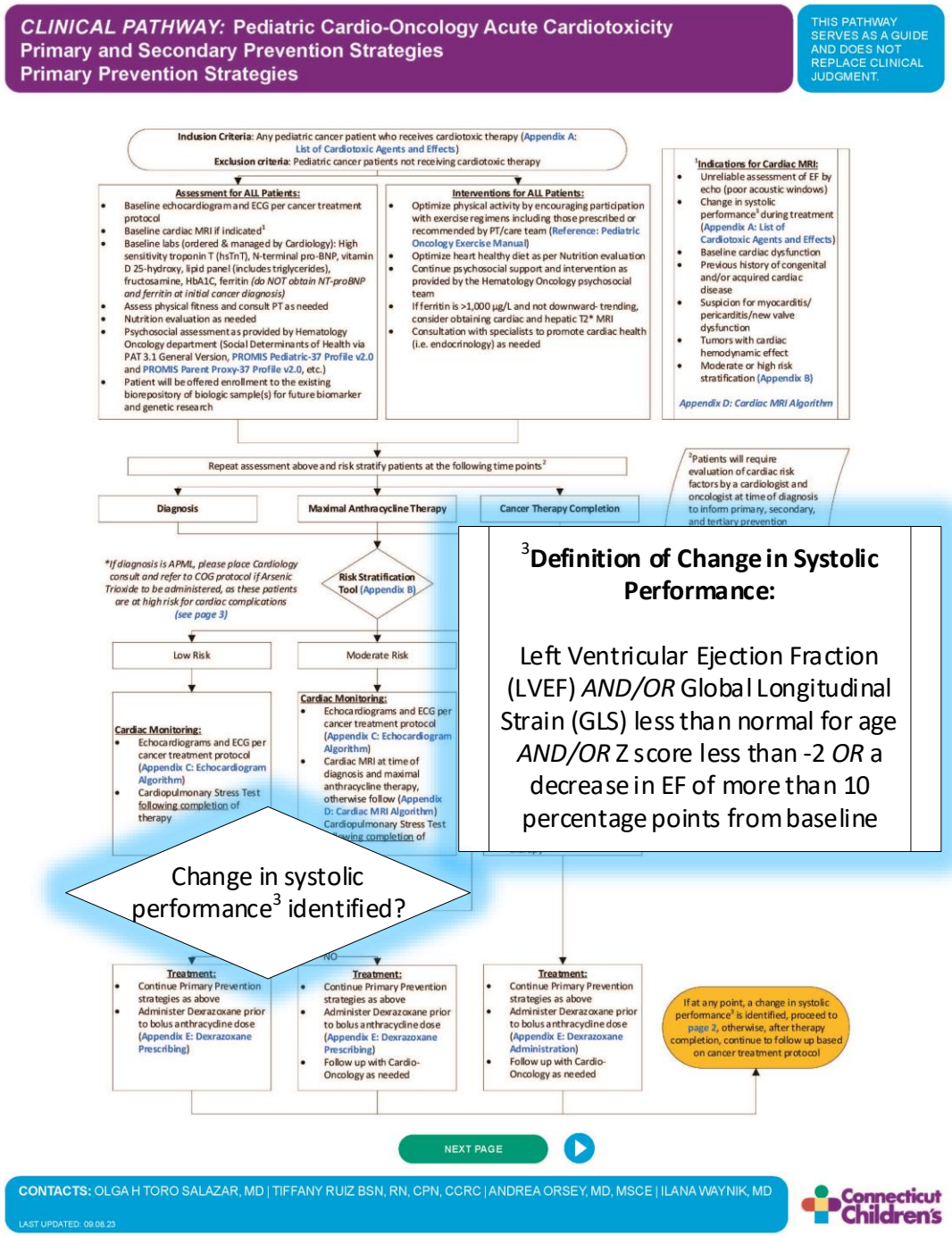


Page 1: Primary Prevention

- A change in systolic performance, also known as CTRCD, is defined as the following:
  - EF < 55%
  - SF < 29%
  - GLS < -17% (more negative is good, less negative is bad)
  - Z-scores are located in the table within an echo report. Outliers are marked in red
- A decrease in EF of more than 10 percentage points from baseline
  - Example patient had a EF of 66% at one point. Then had a repeat echo which showed an EF of 56%.
- Global longitudinal strain (GLS) is not always reported. If it is, it will be noted at the top part of the echo report under **Interpretation Summary**.

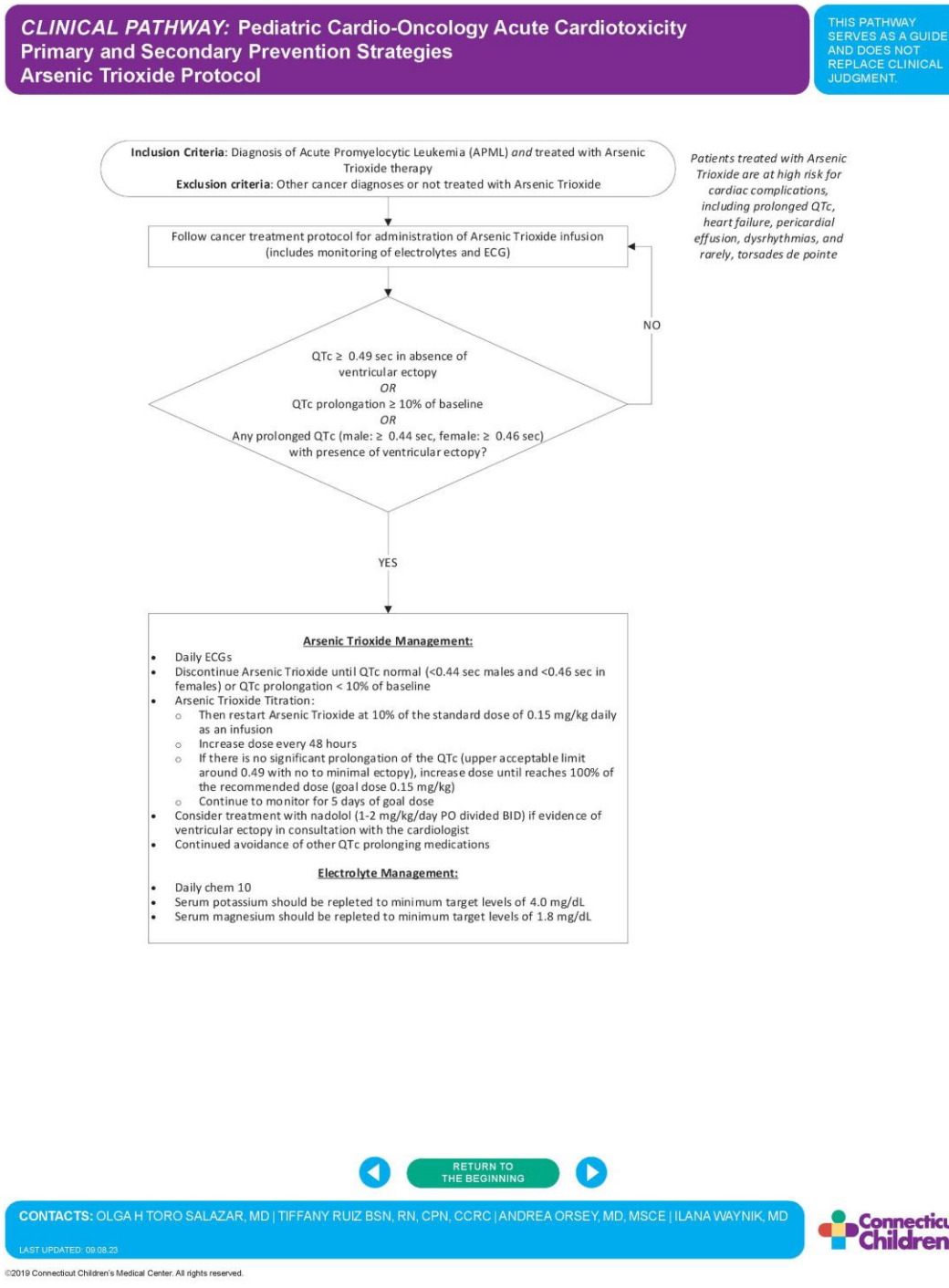
Interpretation Summary

1) Normal left ventricular size, well preserved global left ventricular systolic function estimated ejection fraction 58% by area length, 65.2% by 3D, shortening fraction 34%
2) Normal myocardial deformation parameters, GLS -19.9%, GCS -33.1%
3) Normal diastolic function, medial peak E velocity of 12.2 cm/s, lateral peak E velocity 18.2 cm/s
4) Thickness dimension ratio: 0.24
5) Normal end systolic wall stress estimated at 39.5 g/cm².

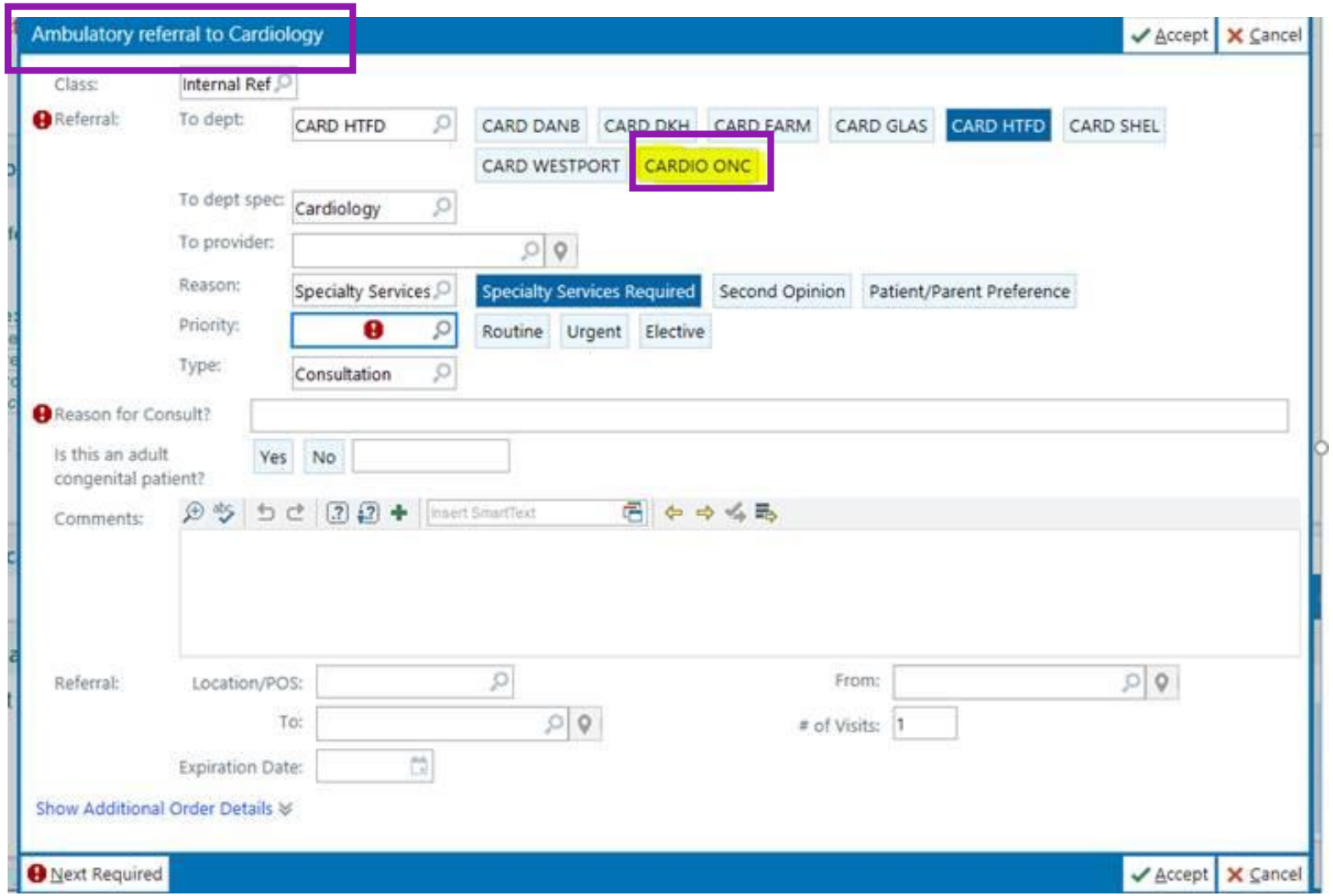


Page 3: Arsenic Trioxide Protocol

- Page 3 of the clinical pathway
- Patients diagnosed with APML require arsenic trioxide for their cancer treatment and should be followed accordingly
- For additional guidance from cardiology, please order a cardiology consult in Epic
- *At this time the cardio-oncology department does not have an inpatient component.*



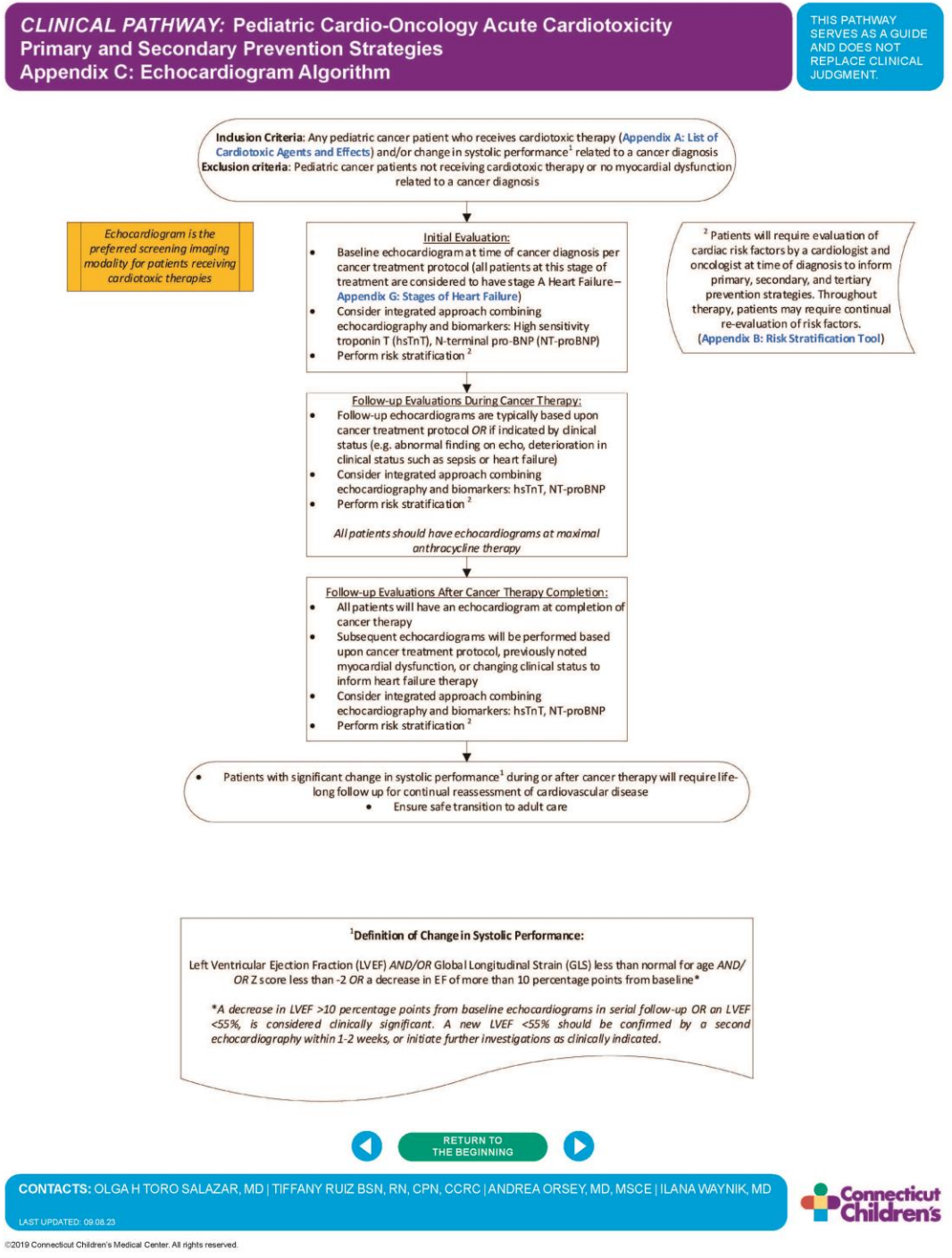
How to place an ambulatory referral to Cardio-Oncology



Please make sure to select the Cardio Onc radio button under the department section, so the correct cardiologist receives the consult.

Appendix C: Echocardiogram Algorithm

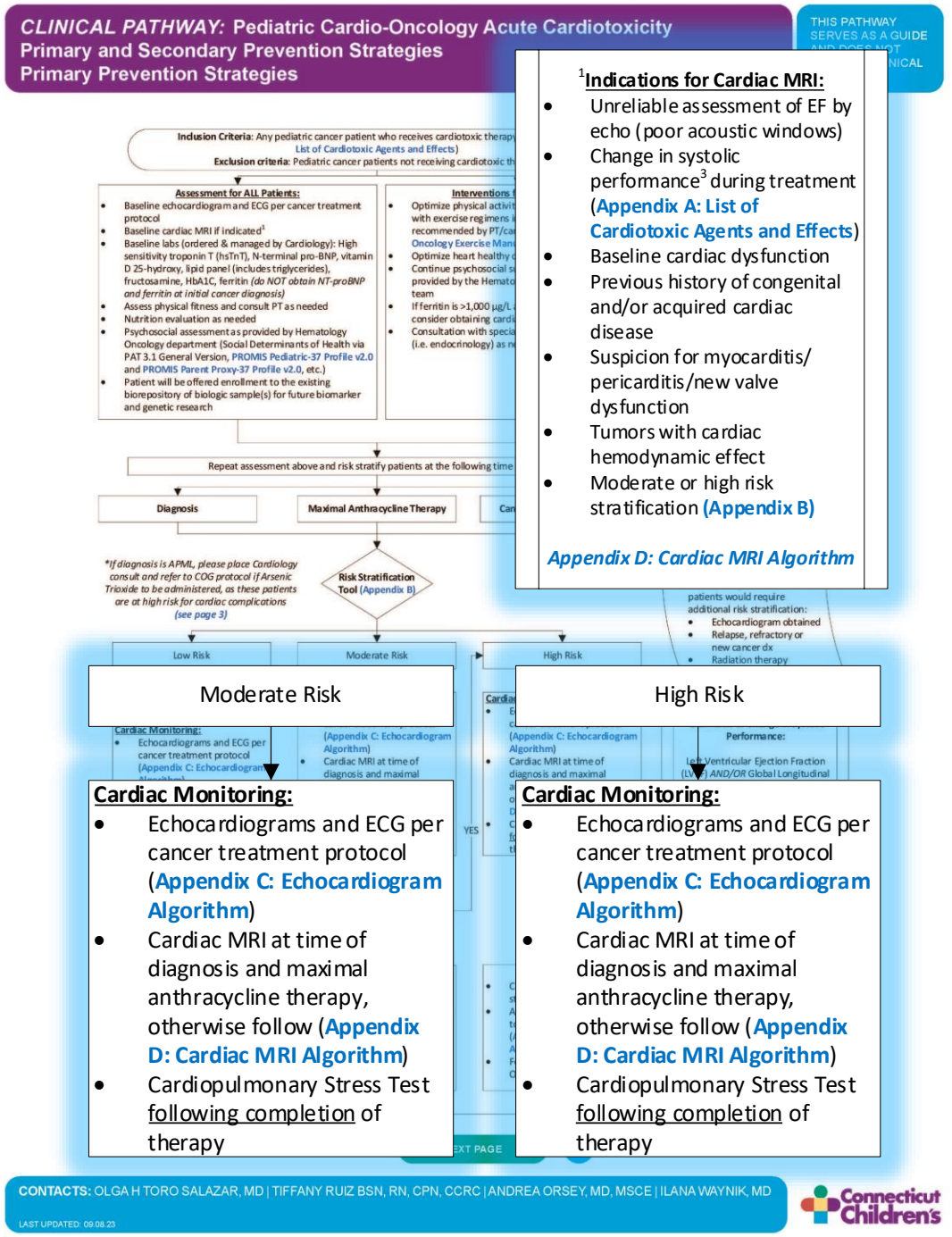
- Page 1 of pathway indicates at which times to perform echocardiogram and links to this appendix
- Recalculate risk score stratification at time of every echocardiogram evaluation, which will include the trends of systolic performance (also referred to as CTRCD)



Appendix D: Cardiac MRI (CMR) Algorithm

- CMR indicated in certain clinical scenarios that are outlined on page 1 of the clinical pathway
- For patients for whom CMR is indicated, appendix D outlines our CMR protocol, including how to obtain and when to repeat imaging

Note: At this time CMRs are only scheduled on Wednesdays and Fridays



Appendix E: Dexrazoxane Dosing

CHEMOTHERAPY

Sec #	Therapeutic Exposure	Potential Late Effects
34	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** Use the following formulas to convert to doxorubicin isotoxic equivalents prior calculating total cumulat anthracycline dose.	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular

To estimate cumulative anthracycline dose in doxorubicin isotoxic equivalents

1.0 x (doxorubicin total dose) +
0.5 x (daunorubicin total dose) +
0.67 x (epirubicin total dose) +
5.0 x (idarubicin total dose) +
10.0 x (mitoxantrone total dose)

- Dexrazoxane dose is a 10:1 ratio per the doxorubicin isotoxic equivalents
- *mitoXANtrne dose is the exception to this rule (see Appendix E)*

Appendix E: Dexrazoxane Administration

Dexrazoxane used only with bolus dosing of anthracycline (NOT continuous infusion)

Dosing:

- Dexrazoxane dose is 5 times the DAUNOrubicin dose
- Dexrazoxane dose is 10 times the DOXOrubicin
- Dexrazoxane dose is 6.7 times the epiRUBicin dose
- Dexrazoxane dose is 50 times the IDArubicin dose
- Dexrazoxane dose is 40 times the mitoXANtrone dose

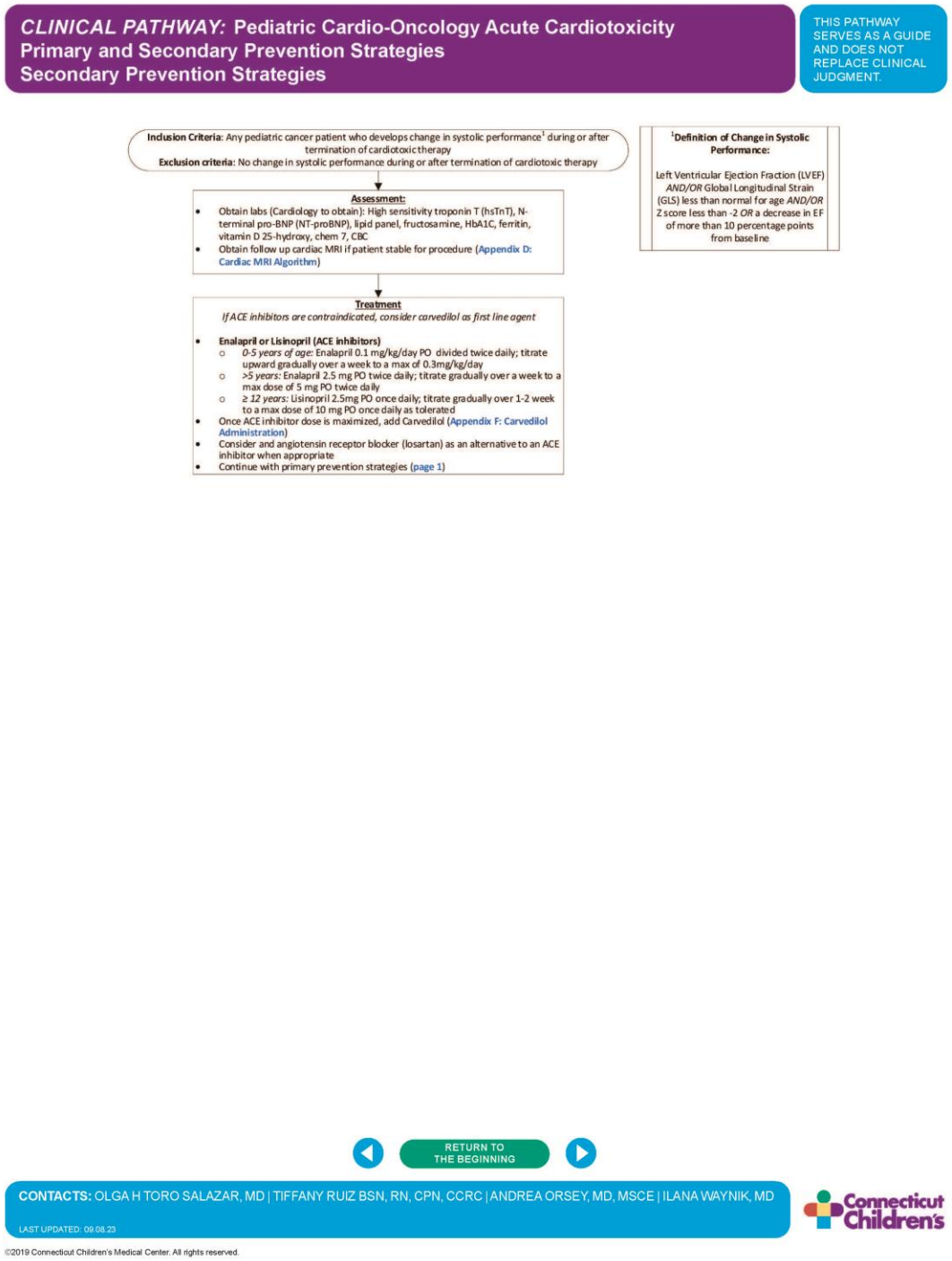
Administration:

- Administer immediately prior to anthracycline (AC)
  - Must be within 30 minutes of beginning the AC infusion
- Administer IV over 15 minutes

- Dexrazoxane is a cardioprotectant drug that Connecticut Children's administers prior to every bolus **anthracycline dose.** ***This is not standard process world-wide***
- Per the current COG Long-Term Follow-Up Guidelines version 6, the Doxorubicin conversions are indicated here.

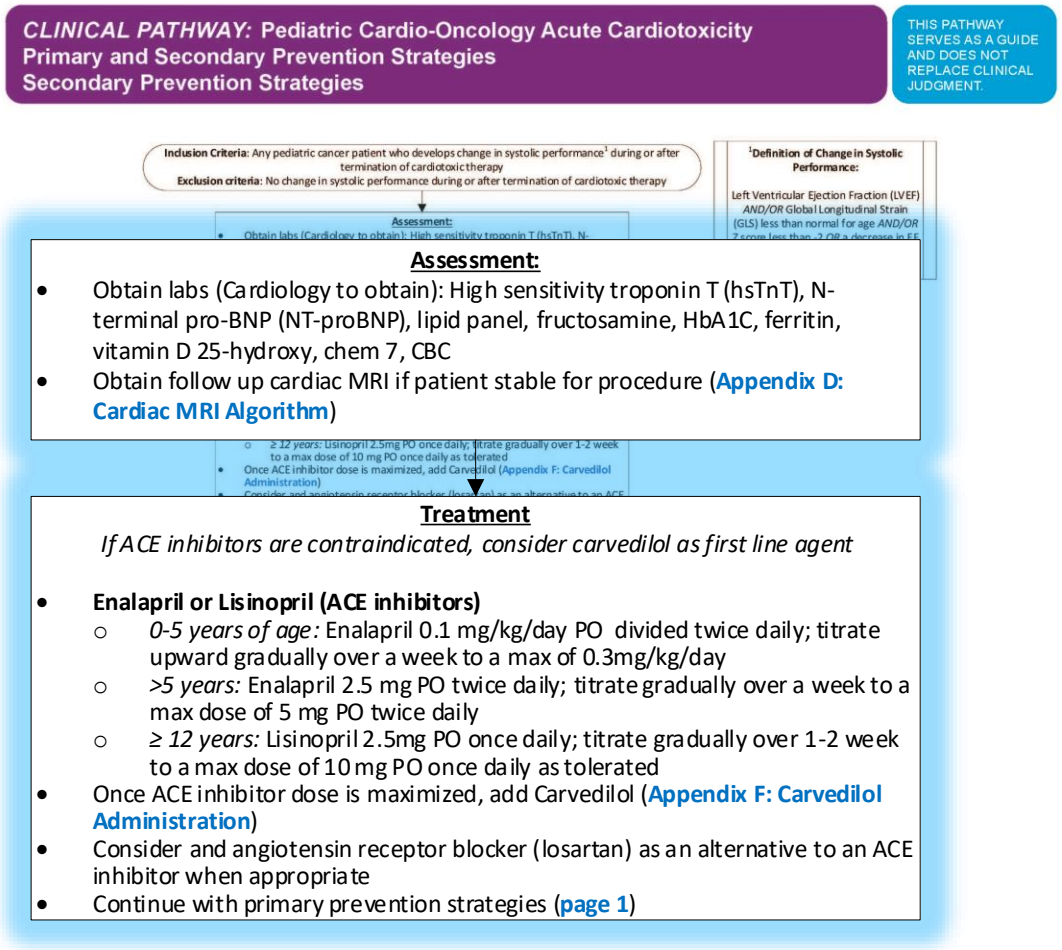
Page 2: Secondary Prevention Strategies

- For patients that have a change in systolic performance pathway users will be directed to page 2 of the clinical pathway



Page 2: Secondary Prevention Strategies

- Some patients with CTRCD will qualify for heart failure treatment with an ACE inhibitor to restore their heart function
- *Patients with abnormal renal function cannot receive an ACE inhibitor. Please check renal function PRIOR to starting this medication.*
- Once ACE inhibitor dose is maximized add carvedilol (on next slide, we'll review carvedilol administration appendix)
- CMR is recommended for patients on this page of the pathway



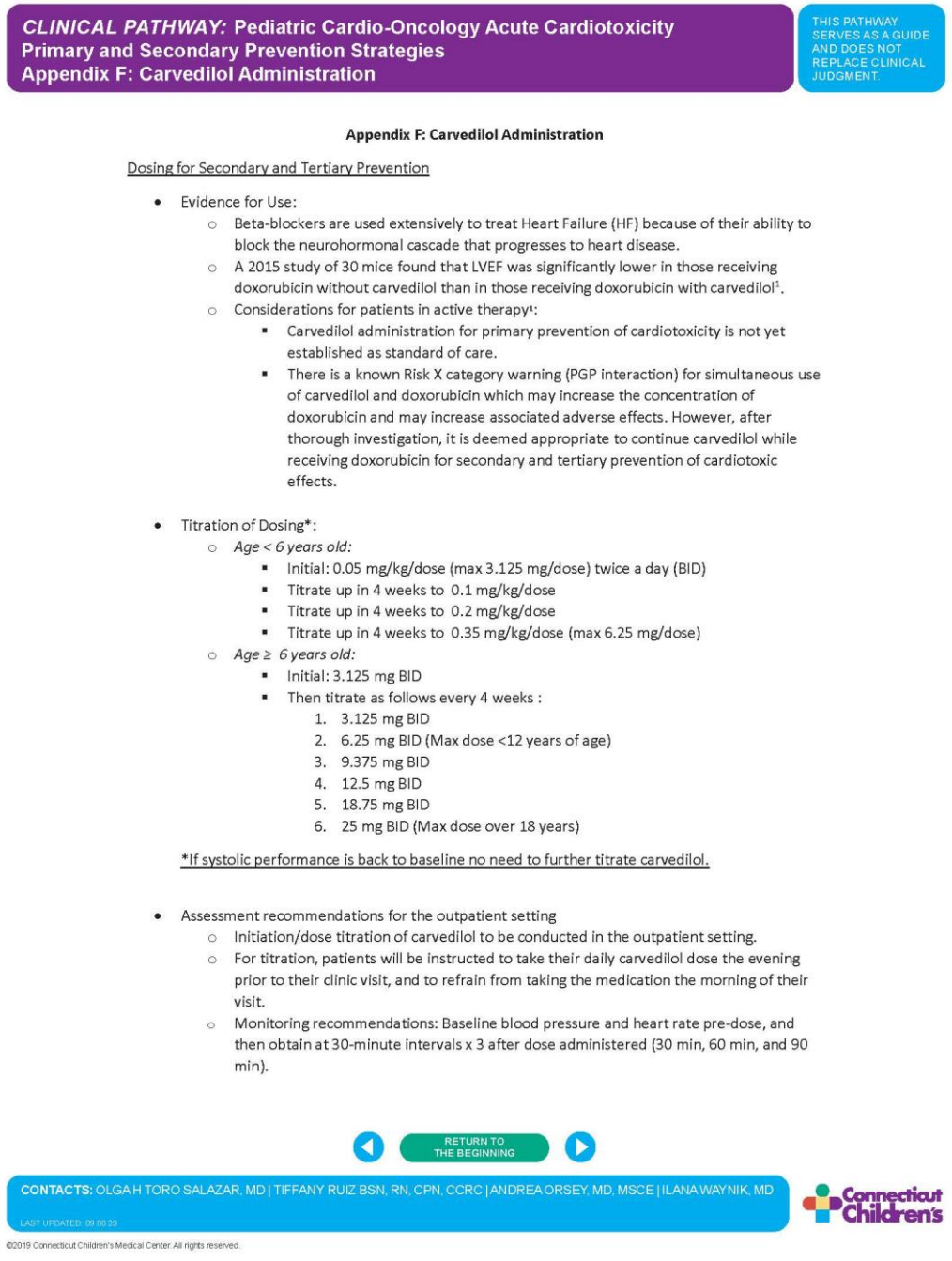
Appendix F: Carvedilol Administration

Background for the use of carvedilol

Dosing assistance

*Note: Carvedilol **can** be administered on days when Doxorubicin is administered*

Initiation and titration monitoring **.carvedilol** SmartPhrase is available for all to utilize



CLINICAL PATHWAY: **Pediatric Cardio-Oncology Acute Cardiotoxicity Primary and Secondary Prevention Strategies Appendix F: Carvedilol Administration**

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

Appendix F: Carvedilol Administration

Dosing for Secondary and Tertiary Prevention

- Evidence for Use:
  - Beta-blockers are used extensively to treat Heart Failure (HF) because of their ability to block the neurohormonal cascade that progresses to heart disease.
  - A 2015 study of 30 mice found that LVEF was significantly lower in those receiving doxorubicin without carvedilol than in those receiving doxorubicin with carvedilol[3].
  - Considerations for patients in active therapy[1]:
    - Carvedilol administration for primary prevention of cardiotoxicity is not yet established as standard of care.
    - There is a known Risk X category warning (PGP interaction) for simultaneous use of carvedilol and doxorubicin which may increase the concentration of doxorubicin and may increase associated adverse effects. However, after thorough investigation, it is deemed appropriate to continue carvedilol while receiving doxorubicin for secondary and tertiary prevention of cardiotoxic effects.
- Titration of Dosing*:
  - *Age < 6 years old:*
    - Initial: 0.05 mg/kg/dose (max 3.125 mg/dose) twice a day (BID)
    - Titrate up in 4 weeks to 0.1 mg/kg/dose
    - Titrate up in 4 weeks to 0.2 mg/kg/dose
    - Titrate up in 4 weeks to 0.35 mg/kg/dose (max 6.25 mg/dose)
  - *Age ≥ 6 years old:*
    - Initial: 3.125 mg BID
    - Then titrate as follows every 4 weeks :
      1. 3.125 mg BID
      2. 6.25 mg BID (Max dose <12 years of age)
      3. 9.375 mg BID
      4. 12.5 mg BID
      5. 18.75 mg BID
      6. 25 mg BID (Max dose over 18 years)

*If systolic performance is back to baseline no need to further titrate carvedilol.

- Assessment recommendations for the outpatient setting
  - Initiation/dose titration of carvedilol to be conducted in the outpatient setting.
  - For titration, patients will be instructed to take their daily carvedilol dose the evening prior to their clinic visit, and to refrain from taking the medication the morning of their visit.
  - Monitoring recommendations: Baseline blood pressure and heart rate pre-dose, and then obtain at 30-minute intervals x 3 after dose administered (30 min, 60 min, and 90 min).

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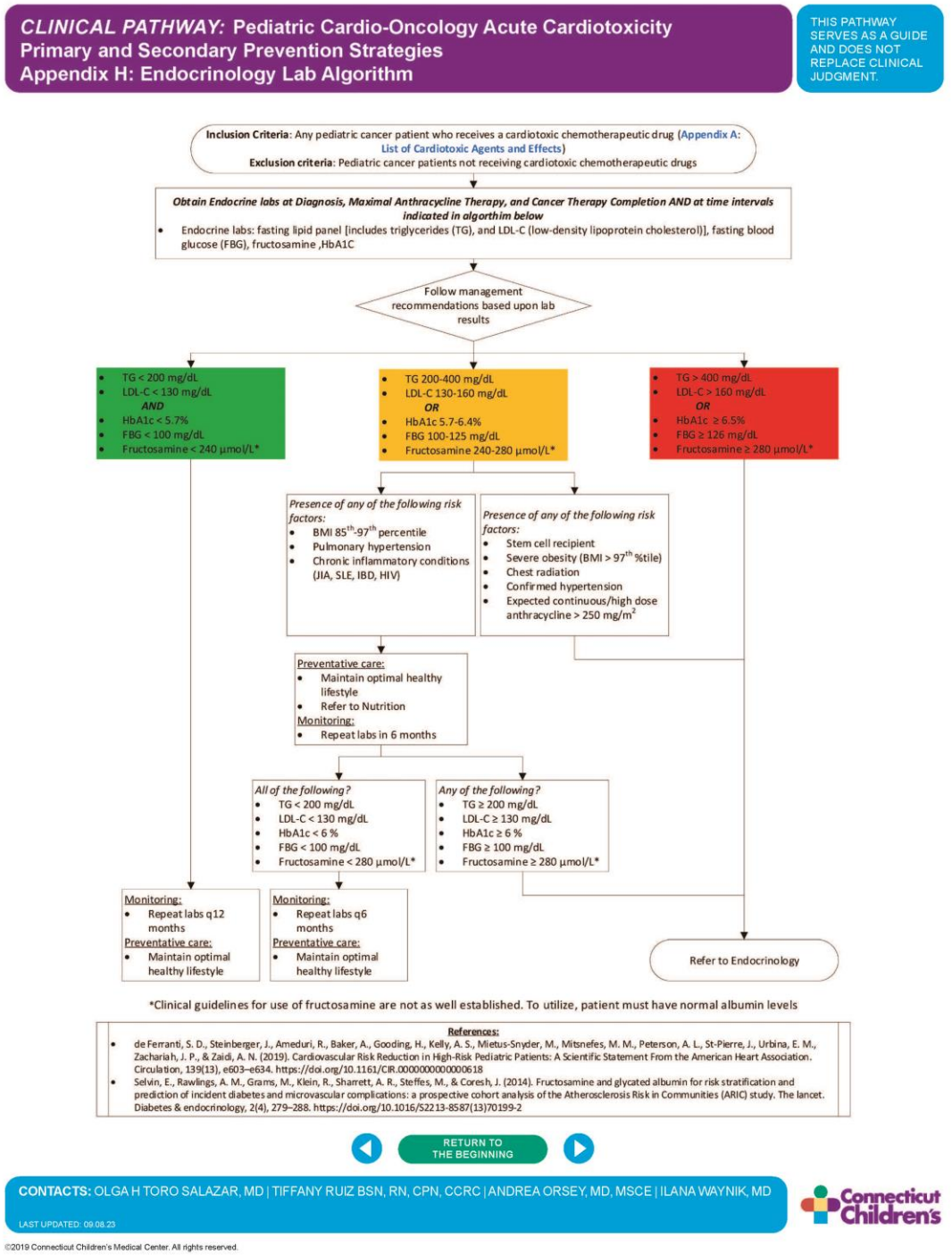
Appendix H: Endocrinology Lab Algorithm

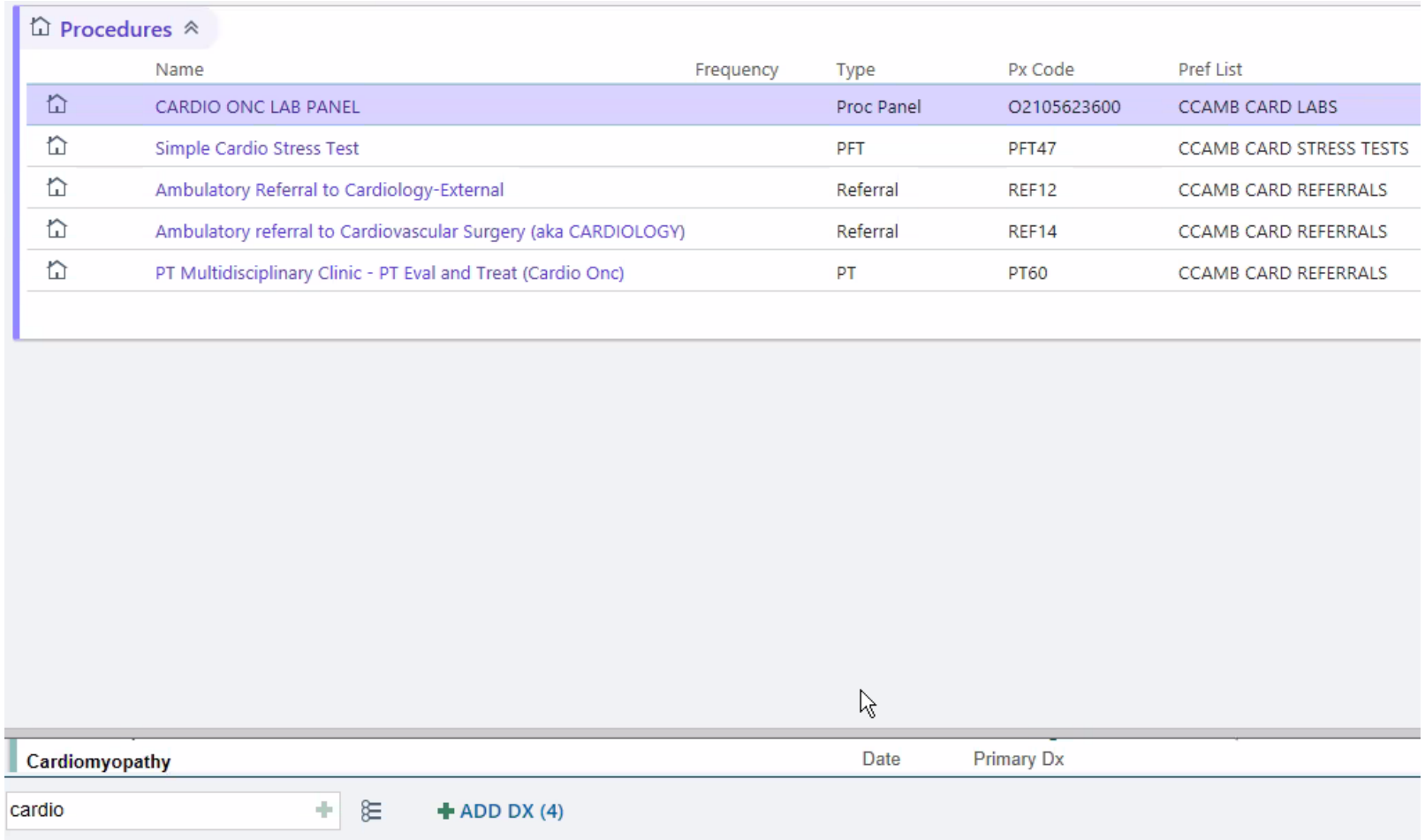
- As part of primary prevention, endocrine labs are obtained throughout treatment as indicated on page 1
- The algorithm on appendix H outlines the actions that need to take place based upon these lab results

Green = Endocrinology labs within normal range
Yellow = Endocrinology labs slightly elevated → suggested diet modification and monitoring
Red = Endocrinology labs very elevated → refer to endocrinology



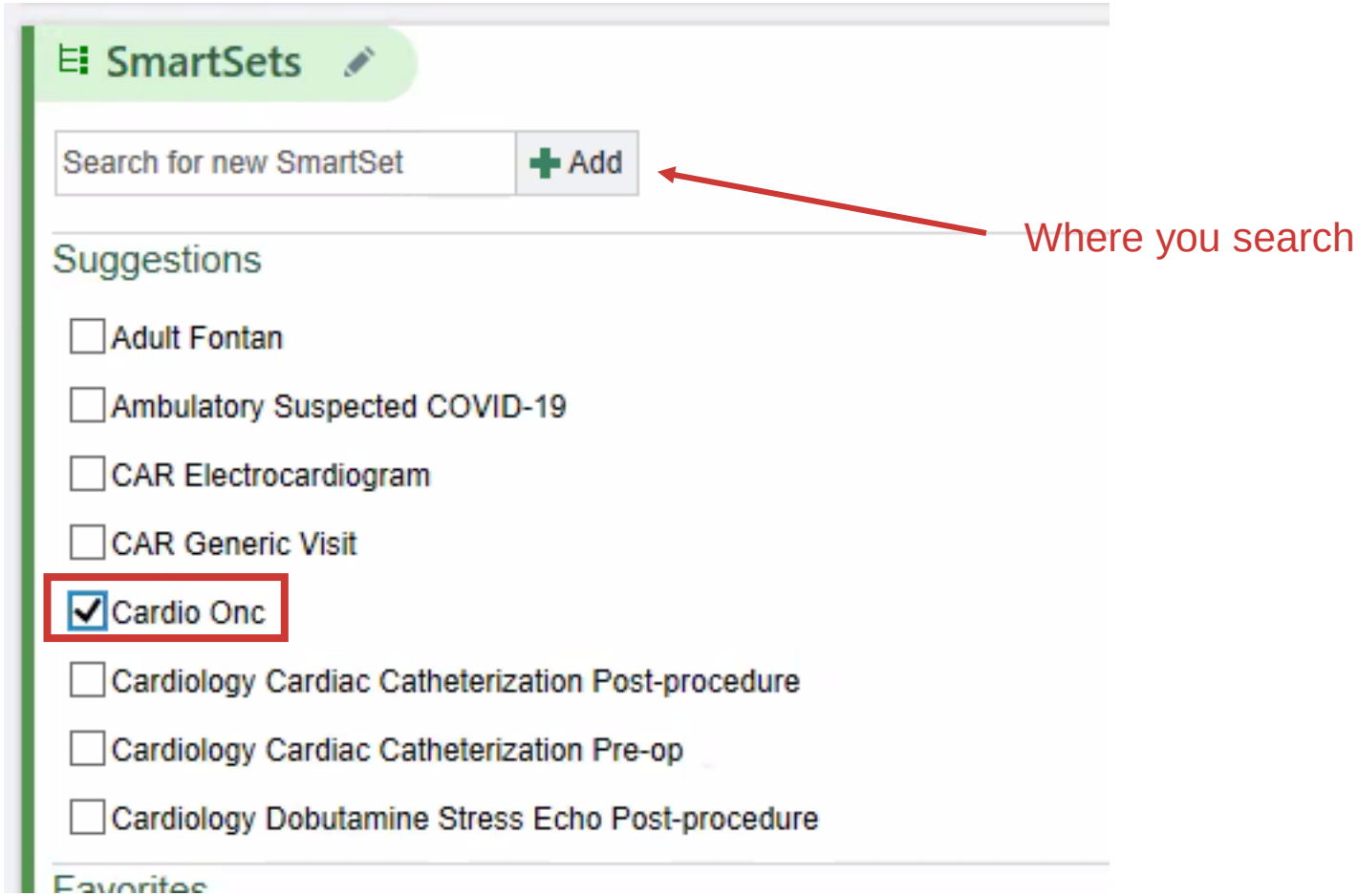
Use of Order Panel

- This **order panel** is intended for ordering the cardio-oncology labs
- Available in Epic and can be accessed by Cardiology and Cardio-Oncology *only* in ambulatory settings



Use of Smart Set

- This **SmartSet** is intended for cardiology provider use when managing a patient during an office visit
- This can be accessed by Cardiology and Cardio-Oncology by **selecting** the **SmartSet** or **searching** for it
- **SmartSet** includes templates for provider notes, orders, visit diagnoses, NYHA symptoms, commonly prescribed medications, etc.



Quality Metrics

- Percentage of eligible patients managed appropriately per pathway
- Percentage of patients that have labs ordered as indicated per pathway
  - If abnormal endocrine labs, percentage of patients with endocrine referral
- Percentage of patients that have physical therapy assessments performed
- Percentage of patients that have nutrition assessments performed
- Percentage of patients that have psychosocial assessment performed
- Percentage of patients with new cancer diagnosis that receive transitional education
- Percentage of patients that have risk scores performed as indicated per pathway
- Percentage of patients that have CTRCD identified via echo or CMR within a week of time indicated per pathway
  - If abnormal heart function:
    - Percentage of patients with CTRCD initiated on heart failure treatment
    - Average time to initiation of heart failure treatment

Pathway Contacts

- Tiffany Berthod, BSN, RN, CPN, CCRC
  - Cardio-Oncology
- Olga Salazar, MD
  - Cardiology
- Andrea Orsey, MD, MSCE
  - Hematology/Oncology
- Ilana Waynik, MD
  - Pediatric Hospital Medicine
  - Clinical Effectiveness

Cardio-oncology team members we'd like to recognize that assisted with the pathway!

- Lauren Ayr-Volta, Hematology/Oncology
- Cem Demirci, Endocrinology
- Karina Engelke, Hematology/Oncology
- Michael Isakoff, Hematology/Oncology
- Mary Keller, Hematology/Oncology
- Raymond Lorenzoni, Cardiology
- Andrea Orsey, Hematology/Oncology
- Victoria Pohl, Hematology/Oncology
- Karen Rubin, Chief Clinical Transformation Officer
- Tiffany Ruiz, Cardio-Oncology
- Olga Salazar, Cardiology
- Sunitha Sura, Endocrinology
- Shailendra Upadhyay, Cardiology
- Irfan Warsy, Cardiology
- Ilana Waynik, Director Clinical Effectiveness

We couldn't have done this without you all!

References

Armenian, S. H., Gelehrter, S. K., & Chow, E. J. (2012). Strategies to prevent anthracycline-related congestive heart failure in survivors of childhood cancer. *Cardiol Res Pract*, *2012*, 713294. https://doi.org/10.1155/2012/713294

Beavers, C. J., Rodgers, J. E., Bagnola, A. J., Beckie, T. M., Campia, U., Di Palo, K. E., Okwuosa, T. M., Przespolewski, E. R., & Dent, S. (2022). Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association. *Circulation*, *145*(15), e811-e838. https://doi.org/10.1161/cir.0000000000001056

Beck, T. C., Arhontoulis, D. C., Morningstar, J. E., Hyams, N., Stoddard, A., Springs, K., Mukherjee, R., Helke, K., Guo, L., Moore, K., Gensemer, C., Biggs, R., Petrucci, T., Kwon, J., Stayer, K., Koren, N., Harvey, A., Holman, H., Dunne, J., . . . Norris, R. A. (2022). Cellular and Molecular Mechanisms of MEK1 Inhibitor-Induced Cardiotoxicity. *JACC CardioOncol*, *4*(4), 535-548. https://doi.org/10.1016/j.jaccao.2022.07.009

Blair, S. N., Kohl, H. W., 3rd, Paffenbarger, R. S., Jr., Clark, D. G., Cooper, K. H., & Gibbons, L. W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women. *Jama*, *262*(17), 2395-2401. https://doi.org/10.1001/jama.262.17.2395

Bosch, X., Rovira, M., Sitges, M., Domènech, A., Ortiz-Pérez, J. T., de Caralt, T. M., Morales-Ruiz, M., Perea, R. J., Monzó, M., & Esteve, J. (2013). Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol*, *61*(23), 2355-2362. https://doi.org/10.1016/j.jacc.2013.02.072

Butel-Simoes, L. E., Haw, T. J., Williams, T., Sritharan, S., Gadre, P., Herrmann, S. M., Herrmann, J., Ngo, D. T. M., & Sverdlov, A. L. (2023). Established and Emerging Cancer Therapies and Cardiovascular System: Focus on Hypertension-Mechanisms and Mitigation. *Hypertension*, *80*(4), 685-710. https://doi.org/10.1161/hypertensionaha.122.17947

Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., Zucker, D. S., Matthews, C. E., Ligibel, J. A., Gerber, L. H., Morris, G. S., Patel, A. V., Hue, T. F., Perna, F. M., & Schmitz, K. H. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*, *51*(11), 2375-2390. https://doi.org/10.1249/mss.0000000000002116

Cardinale, D., Colombo, A., Lamantia, G., Colombo, N., Civelli, M., De Giacomi, G., Rubino, M., Veglia, F., Fiorentini, C., & Cipolla, C. M. (2010). Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*, *55*(3), 213-220. https://doi.org/10.1016/j.jacc.2009.03.095

Chaput, J. P., Willumsen, J., Bull, F., Chou, R., Ekelund, U., Firth, J., Jago, R., Ortega, F. B., & Katzmarzyk, P. T. (2020). 2020 WHO guidelines on physical activity and sedentary behaviour for children and adolescents aged 5-17 years: summary of the evidence. *Int J Behav Nutr Phys Act*, *17*(1), 141. https://doi.org/10.1186/s12966-020-01037-z

References

Chen, Y. L., Chung, S. Y., Chai, H. T., Chen, C. H., Liu, C. F., Chen, Y. L., Huang, T. H., Zhen, Y. Y., Sung, P. H., Sun, C. K., Chua, S., Lu, H. I., Lee, F. Y., Sheu, J. J., & Yip, H. K. (2015). Early Administration of Carvedilol Protected against Doxorubicin-Induced Cardiomyopathy. *J Pharmacol Exp Ther*, *355*(3), 516-527. https://doi.org/10.1124/jpet.115.225375

Cheung, A. T., Li, W. H. C., Ho, L. L. K., Ho, K. Y., Chan, G. C. F., & Chung, J. O. K. (2021). Physical activity for pediatric cancer survivors: a systematic review of randomized controlled trials. *J Cancer Surviv*, *15*(6), 876-889. https://doi.org/10.1007/s11764-020-00981-w

Chovanec, J., Chovanec, M., & Mego, M. (2020). Levels of NT-proBNP and Troponin T in Cancer Patients - Mini-Review. *Klin Onkol*, *33*(3), 171-176. https://doi.org/10.14735/amko2020171 (Hladiny NT-proBNP a troponínu T u onkologických pacientov - stručný prehľad.)

de Baat, E. C., Feijen, E. A. M., Reulen, R. C., Allodji, R. S., Bagnasco, F., Bardi, E., Belle, F. N., Byrne, J., van Dalen, E. C., Debiche, G., Diallo, I., Grabow, D., Hjorth, L., Jankovic, M., Kuehni, C. E., Levitt, G., Llanas, D., Loonen, J., Zaletel, L. Z., . . . Kremer, L. C. M. (2023). Risk Factors for Heart Failure Among Pan-European Childhood Cancer Survivors: A PanCareSurFup and ProCardio Cohort and Nested Case-Control Study. *J Clin Oncol*, *41*(1), 96-106. https://doi.org/10.1200/jco.21.02944

de Ferranti, S. D., Steinberger, J., Ameduri, R., Baker, A., Gooding, H., Kelly, A. S., Mietus-Snyder, M., Mitsnefes, M. M., Peterson, A. L., St-Pierre, J., Urbina, E. M., Zachariah, J. P., & Zaidi, A. N. (2019). Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association. *Circulation*, *139*(13), e603-e634. https://doi.org/10.1161/cir.0000000000000618

Fernandes, T., Baraúna, V. G., Negrão, C. E., Phillips, M. I., & Oliveira, E. M. (2015). Aerobic exercise training promotes physiological cardiac remodeling involving a set of microRNAs. *Am J Physiol Heart Circ Physiol*, *309*(4), H543-552. https://doi.org/10.1152/ajpheart.00899.2014

Foulkes, S. J., Howden, E. J., Haykowsky, M. J., Antill, Y., Salim, A., Nightingale, S. S., Loi, S., Claus, P., Janssens, K., Mitchell, A. M., Wright, L., Costello, B. T., Lindqvist, A., Burnham, L., Wallace, I., Daly, R. M., Fraser, S. F., & La Gerche, A. (2023). Exercise for the Prevention of Anthracycline-Induced Functional Disability and Cardiac Dysfunction: The BREXIT Study. *Circulation*, *147*(7), 532-545. https://doi.org/10.1161/circulationaha.122.062814

Glen, C., Tan, Y. Y., Waterston, A., Evans, T. R. J., Jones, R. J., Petrie, M. C., & Lang, N. N. (2022). Mechanistic and Clinical Overview Cardiovascular Toxicity of BRAF and MEK Inhibitors: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol*, *4*(1), 1-18. https://doi.org/10.1016/j.jaccao.2022.01.096

References

Groarke, J. D., Nguyen, P. L., Nohria, A., Ferrari, R., Cheng, S., & Moslehi, J. (2014). Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. *Eur Heart J, 35*(10), 612-623. https://doi.org/10.1093/eurheartj/eht114

Groarke, J. D., Payne, D. L., Claggett, B., Mehra, M. R., Gong, J., Caron, J., Mahmood, S. S., Hainer, J., Neilan, T. G., Partridge, A. H., Di Carli, M., Jones, L. W., & Nohria, A. (2020). Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. *Eur Heart J Qual Care Clin Outcomes*, *6*(4), 315-322. https://doi.org/10.1093/ehjqcco/qcaa015

Gupta, V., Kumar Singh, S., Agrawal, V., & Bali Singh, T. (2018). Role of ACE inhibitors in anthracycline-induced cardiotoxicity: A randomized, double-blind, placebo-controlled trial. *Pediatr Blood Cancer*, *65*(11), e27308. https://doi.org/10.1002/pbc.27308

Hamer, M., Ingle, L., Carroll, S., & Stamatakis, E. (2012). Physical activity and cardiovascular mortality risk: possible protective mechanisms? *Med Sci Sports Exerc*, *44*(1), 84-88. https://doi.org/10.1249/MSS.0b013e3182251077

Harries, I., Liang, K., Williams, M., Berlot, B., Biglino, G., Lancellotti, P., Plana, J. C., & Bucciarelli-Ducci, C. (2020). Magnetic Resonance Imaging to Detect Cardiovascular Effects of Cancer Therapy: JACC CardioOncology State-of-the-Art Review. *JACC CardioOncol*, *2*(2), 270-292. https://doi.org/10.1016/j.jaccao.2020.04.011

Herrmann, J. (2020). Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol*, *17*(8), 474-502. https://doi.org/10.1038/s41569-020-0348-1

Hoffmann, T. C., Maher, C. G., Briffa, T., Sherrington, C., Bennell, K., Alison, J., Singh, M. F., & Glasziou, P. P. (2016). Prescribing exercise interventions for patients with chronic conditions. *Cmaj*, *188*(7), 510-518. https://doi.org/10.1503/cmaj.150684

Jeong, S. W., Kim, S. H., Kang, S. H., Kim, H. J., Yoon, C. H., Youn, T. J., & Chae, I. H. (2019). Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J*, *40*(43), 3547-3555. https://doi.org/10.1093/eurheartj/ehz564

References

Kavanagh, T., Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., & Shephard, R. J. (2003). Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol*, *42*(12), 2139-2143. https://doi.org/10.1016/j.jacc.2003.07.028

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., Sugawara, A., Totsuka, K., Shimano, H., Ohashi, Y., Yamada, N., & Sone, H. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *Jama*, *301*(19), 2024-2035. https://doi.org/10.1001/jama.2009.681

Korosoglou, G., Giusca, S., Montenbruck, M., Patel, A. R., Lapinskas, T., Götze, C., Zieschang, V., Al-Tabatabaee, S., Pieske, B., Florian, A., Erley, J., Katus, H. A., Kelle, S., & Steen, H. (2021). Fast Strain-Encoded Cardiac Magnetic Resonance for Diagnostic Classification and Risk Stratification of Heart Failure Patients. *JACC Cardiovasc Imaging*, *14*(6), 1177-1188. https://doi.org/10.1016/j.jcmg.2020.10.024

Lipshultz, S. E., Rifai, N., Dalton, V. M., Levy, D. E., Silverman, L. B., Lipsitz, S. R., Colan, S. D., Asselin, B. L., Barr, R. D., Clavell, L. A., Hurwitz, C. A., Moghrabi, A., Samson, Y., Schorin, M. A., Gelber, R. D., & Sallan, S. E. (2004). The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med*, *351*(2), 145-153. https://doi.org/10.1056/NEJMoa035153

Lyon, A. R., López-Fernández, T., Couch, L. S., Asteggiano, R., Aznar, M. C., Bergler-Klein, J., Boriani, G., Cardinale, D., Cordoba, R., Cosyns, B., Cutter, D. J., de Azambuja, E., de Boer, R. A., Dent, S. F., Farmakis, D., Gevaert, S. A., Gorog, D. A., Herrmann, J., Lenihan, D., . . . van der Pal, H. J. H. (2022). 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*, *43*(41), 4229-4361. https://doi.org/10.1093/eurheartj/ehac244

Patel, A. V., Friedenreich, C. M., Moore, S. C., Hayes, S. C., Silver, J. K., Campbell, K. L., Winters-Stone, K., Gerber, L. H., George, S. M., Fulton, J. E., Denlinger, C., Morris, G. S., Hue, T., Schmitz, K. H., & Matthews, C. E. (2019). American College of Sports Medicine Roundtable Report on Physical Activity, Sedentary Behavior, and Cancer Prevention and Control. *Med Sci Sports Exerc*, *51*(11), 2391-2402. https://doi.org/10.1249/mss.0000000000002117

References

Piña, I. L., Apstein, C. S., Balady, G. J., Belardinelli, R., Chaitman, B. R., Duscha, B. D., Fletcher, B. J., Fleg, J. L., Myers, J. N., & Sullivan, M. J. (2003). Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*, *107*(8), 1210-1225. https://doi.org/10.1161/01.cir.0000055013.92097.40

Plana, J. C., Thavendiranathan, P., Bucciarelli-Ducci, C., & Lancellotti, P. (2018). Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient. *JACC Cardiovasc Imaging*, *11*(8), 1173-1186. https://doi.org/10.1016/j.jcmg.2018.06.003

Ross, R., Blair, S. N., Arena, R., Church, T. S., Després, J. P., Franklin, B. A., Haskell, W. L., Kaminsky, L. A., Levine, B. D., Lavie, C. J., Myers, J., Niebauer, J., Sallis, R., Sawada, S. S., Sui, X., & Wisløff, U. (2016). Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation*, *134*(24), e653-e699. https://doi.org/10.1161/cir.0000000000000461

Scott, J. M., Lakoski, S., Mackey, J. R., Douglas, P. S., Haykowsky, M. J., & Jones, L. W. (2013). The potential role of aerobic exercise to modulate cardiotoxicity of molecularly targeted cancer therapeutics. *Oncologist*, *18*(2), 221-231. https://doi.org/10.1634/theoncologist.2012-0226

Selvin, E., Rawlings, A. M., Grams, M., Klein, R., Sharrett, A. R., Steffes, M., & Coresh, J. (2014). Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol*, *2*(4), 279-288. https://doi.org/10.1016/s2213-8587(13)70199-2

Sepe, D. M., Ginsberg, J. P., & Balis, F. M. (2010). Dexrazoxane as a cardioprotectant in children receiving anthracyclines. *Oncologist*, *15*(11), 1220-1226. https://doi.org/10.1634/theoncologist.2010-0162

Testi, A. M., Pession, A., Diverio, D., Grimwade, D., Gibson, B., de Azevedo, A. C., Moran, L., Leverger, G., Elitzur, S., Hasle, H., van der Werff ten Bosch, J., Smith, O., De Rosa, M., Piciocchi, A., Lo Coco, F., Foà, R., Locatelli, F., & Kaspers, G. J. L. (2018). Risk-adapted treatment of acute promyelocytic leukemia: results from the International Consortium for Childhood APL. *Blood*, *132*(4), 405-412. https://doi.org/10.1182/blood-2018-03-836528

Tonorezos, E. S., Snell, P. G., Moskowitz, C. S., Eshelman-Kent, D. A., Liu, J. E., Chou, J. F., Smith, S. M., Dunn, A. L., Church, T. S., & Oeffinger, K. C. (2013). Reduced cardiorespiratory fitness in adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*, *60*(8), 1358-1364. https://doi.org/10.1002/pbc.24492

References

Toro-Salazar, O. H., Ferranti, J., Lorenzoni, R., Walling, S., Mazur, W., Raman, S. V., Davey, B. T., Gillan, E., O'Loughlin, M., Klas, B., & Hor, K. N. (2016). Feasibility of Echocardiographic Techniques to Detect Subclinical Cancer Therapeutics-Related Cardiac Dysfunction among High-Dose Patients When Compared with Cardiac Magnetic Resonance Imaging. *J Am Soc Echocardiogr*, *29*(2), 119-131. https://doi.org/10.1016/j.echo.2015.10.008

Toro-Salazar, O. H., Gillan, E., Ferranti, J., Orsey, A., Rubin, K., Upadhyay, S., Mazur, W., & Hor, K. N. (2015). Effect of myocardial dysfunction in cardiac morbidity and all cause mortality in childhood cancer subjects treated with anthracycline therapy. *Cardiooncology*, *1*(1), 1. https://doi.org/10.1186/s40959-015-0005-8

Tukenova, M., Guibout, C., Oberlin, O., Doyon, F., Mousannif, A., Haddy, N., Guérin, S., Pacquement, H., Aouba, A., Hawkins, M., Winter, D., Bourhis, J., Lefkopoulos, D., Diallo, I., & de Vathaire, F. (2010). Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol*, *28*(8), 1308-1315. https://doi.org/10.1200/jco.2008.20.2267

Unnikrishnan, D., Dutcher, J. P., Varshneya, N., Lucariello, R., Api, M., Garl, S., Wiernik, P. H., & Chiaramida, S. (2001). Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. *Blood*, *97*(5), 1514-1516. https://doi.org/10.1182/blood.v97.5.1514

van der Schoot, G. G. F., Ormel, H. L., Westerink, N. L., May, A. M., Elias, S. G., Hummel, Y. M., Lefrandt, J. D., van der Meer, P., van Melle, J. P., Poppema, B. J., Stel, J. M. A., van der Velden, A. W. G., Vrieling, A. H., Wempe, J. B., Ten Wolde, M. G., Nijland, M., de Vries, E. G. E., Gietema, J. A., & Walenkamp, A. M. E. (2022). Optimal Timing of a Physical Exercise Intervention to Improve Cardiorespiratory Fitness: During or After Chemotherapy. *JACC CardioOncol*, *4*(4), 491-503. https://doi.org/10.1016/j.jaccao.2022.07.006

Wanderley, M. R. B., Jr., Ávila, M. S., Fernandes-Silva, M. M., Cruz, F. D. D., Brandão, S. M. G., Rigaud, V. O. C., Hajjar, L. A., Filho, R. K., Cunha-Neto, E., Bocchi, E. A., & Ayub-Ferreira, S. M. (2022). Plasma biomarkers reflecting high oxidative stress in the prediction of myocardial injury due to anthracycline chemotherapy and the effect of carvedilol: insights from the CECCY Trial. *Oncotarget*, *13*, 214-223. https://doi.org/10.18632/oncotarget.28182

Wenningmann, N., Knapp, M., Ande, A., Vaidya, T. R., & Ait-Oudhia, S. (2019). Insights into Doxorubicin-induced Cardiotoxicity: Molecular Mechanisms, Preventive Strategies, and Early Monitoring. *Mol Pharmacol*, *96*(2), 219-232. https://doi.org/10.1124/mol.119.115725

Winter, C., Müller, C., Hoffmann, C., Boos, J., & Rosenbaum, D. (2010). Physical activity and childhood cancer. *Pediatr Blood Cancer*, *54*(4), 501-510. https://doi.org/10.1002/pbc.22271

Zukkoor Zorn, S., & Thohan, V. (2018). *Drug-Drug Interactions of Common Cardiac Medications and Chemotherapeutic Agents*. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2018/12/21/09/52/drug-drug-interactions-of-common-cardiac-medications-and-chemotherapeutic-agents

Thank You!

About Connecticut Children's Pathways Program

Clinical pathways guide the management of patients to optimize consistent use of evidence-based practice. Clinical pathways have been shown to improve guideline adherence and quality outcomes, while decreasing length of stay and cost. Here at Connecticut Children's, our Clinical Pathways Program aims to deliver evidence-based, high value care to the greatest number of children in a diversity of patient settings. These pathways serve as a guide for providers and do not replace clinical judgment.