

Official Title:	Dynamic Airway CT is Diagnostic for Tracheomalacia in Children
NCT Number:	NCT06028646
Study Number:	22-01279
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• August 8, 2023

Dynamic Airway CT is Diagnostic for Tracheomalacia in Children

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NYULMC Study Number:	s22-01279
Funding Sponsor:	KiDS of NYU Foundation
ClinicalTrials.gov Number	N/A

Initial version: August 7, 2023

Amended:

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
DA-CT	Dynamic airway computed tomography

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Protocol Summary

Title	Dynamic Airway CT is Diagnostic for Tracheomalacia in Children
Short Title	Dynamic Airway CT is Diagnostic for Tracheomalacia in Children
Brief Summary	This will be a prospective single-center intervention study of DA-CT performed for evaluation of tracheomalacia in children 0-18 years with respiratory symptoms for whom flexible bronchoscopy has been performed. Participants will receive a low dose DA-CT without sedation for comparison against the gold standard flexible bronchoscopy DA-CT performed on new generation photon-counting CT scanner will be associated with improved image quality and reduced radiation dose. We aim to evaluate the diagnostic accuracy, image quality, and radiation exposure of DA-CT as a potential noninvasive alternative to the gold standard of flexible bronchoscopy in diagnosis of tracheomalacia. A number of 25 participants will allow 95% certainty that our sensitivity and specificity estimates are within 30% of the true values. The results from this pilot study will allow us to estimate sample size for a larger-scale study with more precise estimates of DA-CT diagnostic potential.
Objectives	We aim to evaluate the diagnostic accuracy, image quality, and radiation exposure of DA-CT as a potential noninvasive alternative to the gold standard of flexible bronchoscopy in diagnosis of tracheomalacia.
Methodology	This will be a prospective single-center intervention study of DA-CT is performed for evaluation of tracheomalacia. Subjects will receive a low dose DA-CT without sedation for comparison against the gold standard flexible bronchoscopy.
Endpoint	Use of low dose DA-CT in children with respiratory symptoms to definitively diagnose tracheomalacia will lead to earlier implementation of effective mucociliary clearance techniques, reduce unnecessary sedation and procedures, and reduce overall healthcare costs.
Study Duration	1 Year
Participant Duration	One visit for imaging that may be completed during hospitalization or on the day of another appointment or as a separate visit per family preference and scheduling ability.
Population	Children 0-18 years with respiratory symptoms for whom flexible bronchoscopy has been performed. A sample size of 25 patients will be enrolled.
Study Sites	FINK NYU Langone Pediatrics / NYU Langone Medical Center
Number of participants	25 participants
Key Procedures	DA-CT

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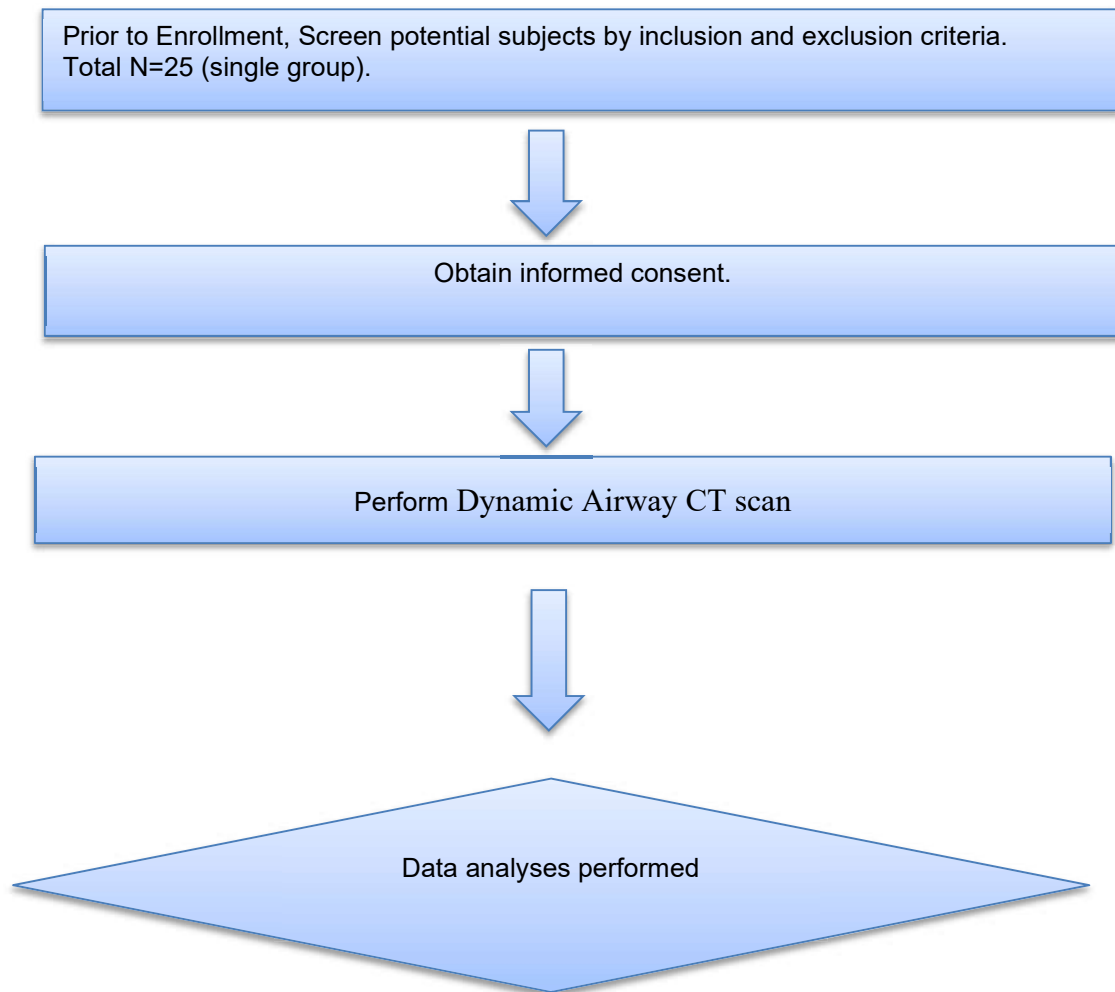
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Statistical Analysis	The primary endpoint for the present study is the sensitivity and specificity of DA-CT as a diagnostic tool in identifying tracheomalacia. The outcome variable of interest, in this case, is the binary result of the DA-CT procedure (tracheomalacia present vs. tracheomalacia absent). These results will be compared in a 2x2 table against the binary result of the “gold standard” procedure in order to calculate sensitivity, specificity, and other parameters of interest such as positive predictive value, negative predictive value, and overall diagnostic accuracy. The methods outlined by Buderer et al. (1996) were used to calculate estimated precision of the 95% confidence intervals of sensitivity and specificity given the pilot sample size of N=25. Assuming that tracheomalacia has a prevalence of 20% in the target population, and that DA-CT sensitivity and specificity are at least 85%, the sample size will yield a 95% CI width of roughly 30%. In other words, the given N will allow us to be 95% certain that our sensitivity and specificity estimates are within 30% of the true values. Radiation exposure as well as the continuous measure of image noise will be compared between photon counting- and traditional- CT images using either paired samples t-tests or Mann-Whitney U tests, depending on distribution of the final data. Image pairs will be matched based on age and diagnosis. Similarly, the ordinal variable for image quality will be compared between traditional and dynamic CT images using the nonparametric Mann-Whitney U test. The per-protocol analysis dataset will be used and incomplete cases will be omitted from the analysis. Results will be presented as mean and standard deviation for continuous, normally distributed data and as median and interquartile range for non-normally distributed continuous data. Image quality results will either be presented as median with interquartile range, or with frequency distributions of the ordinal, Likert-scaled quality ratings.
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Schematic of Study Design



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1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Tracheomalacia is a common pediatric condition that is due to the excessive dynamic collapse of the trachea during respiration and flexible bronchoscopy is considered the gold standard for diagnosis. Few retrospective single-institution studies have suggested that low dose dynamic airway multidetector computed tomography (DA-CT) may serve as a useful, complementary tool in the diagnosis of tracheomalacia. Advantages of DA-CT include favorable radiation dose profile, wide availability of multidetector CT scanners, ability to perform quantitative airway assessment, and lack of need for sedation. In contrast, flexible bronchoscopy requires the presence of multiple pediatric subspecialist physicians, including a pulmonologist and anesthesiologist, and must be coordinated in a dedicated procedure or operating room. Symptoms of tracheomalacia are common respiratory complaints in childhood, and include chronic cough, chronic wheeze, expiratory stridor, and respiratory distress. Medical treatment options for tracheomalacia are directed at mitigating effects of chronic inflammation with inhaled corticosteroids and promoting mucociliary clearance. All but the most severe cases of tracheomalacia recover without surgical intervention. Missed, or delayed diagnosis of tracheomalacia can lead to overtreatment. Emerging body of small retrospective studies suggest favorable test characteristics for DA-CT for diagnosis of tracheomalacia in children, however it has not been extensively studied in children and remains infrequently used in clinical practice.

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2.2 Rationale

We hypothesize that DA is equally sensitive and specific as compared to the gold standard flexible bronchoscopy in children with suspected tracheomalacia. DA-CT performed on new generation photon-counting CT (PC-CT) scanner will be associated with improved image quality and reduced radiation dose. We aim to evaluate the diagnostic accuracy, image quality, and radiation exposure of DA-CT as a potential noninvasive alternative to the gold standard of flexible bronchoscopy in diagnosis of tracheomalacia.

2.3 Potential Risks & Benefits

2.3.1 Known Potential Risks

There is exposure to radiation from the DA-CT scan (about 0.5 mSv or less). The risk from this amount of radiation is small, roughly equivalent to several chest radiographs or about 14 transcontinental flights. The risks of receiving very small doses of radiation are thought to be low, but are not actually known.

There is a minor risk of loss of confidentiality in the data collection from the electronic health record and this will be minimized by storing data in accordance with MCIT requirements.

2.3.2 Known Potential Benefits

Potential benefits of this study include data to support use of DA-CT for earlier diagnosis of tracheomalacia in children with easy access to CT but not a pediatric pulmonologist, reduction in the potential overtreatment of children not yet formally diagnosed with tracheomalacia, earlier implementation of effective mucociliary clearance techniques, and reduced subspecialist utilization.

Low dose DA-CT has the advantage of being widely available, directly measures airway dimensions, and can be performed in awake children without sedation.

This study has the potential to significantly reduce overall healthcare costs, improve inefficiencies, and reduce unnecessary procedures highlighting advances in imaging in children.

3 Objectives and Purpose

The purpose of the study is to evaluate the diagnostic accuracy of DA-CT as a potential noninvasive alternative to the gold standard of flexible bronchoscopy by scoring dynamic airway collapse measured with DA-CT compared with visual estimation from intraoperative and video recorded flexible bronchoscopy. DA-CT performed on new generation PC-CT scanner will be associated with improved image quality and reduced radiation dose compared to standard-of-care EID-CT scanners due to the method of photon counting.

4 Study Design and Endpoints

4.1 Description of Study Design

This will be a prospective single-center intervention study of DA-CT performed for evaluation of tracheomalacia in children 0-18 years with respiratory symptoms for whom flexible bronchoscopy is clinically indicated and has been performed.

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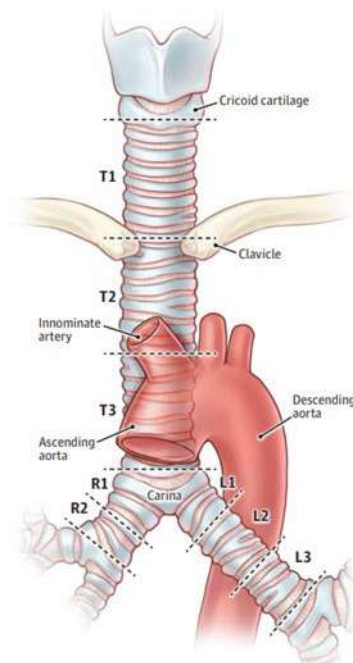
4.2 Study Endpoints

4.2.1 Primary Study Endpoints

We will evaluate the diagnostic accuracy of DA-CT as a potential noninvasive alternative to the gold standard of flexible bronchoscopy by scoring dynamic airway collapse measured with DA-CT compared with visual estimation from intraoperative and video recorded flexible bronchoscopy.

Flexible Bronchoscopy Dynamic Collapse

Flexible bronchoscopy has been performed as clinically indicated. Scoring of the degree of airway collapse will be determined by one of two fellowship-trained pediatric pulmonologists with 30 and 2 years of post-fellowship experience. All bronchoscopies are video recorded and stored in a secure data file. The trachea is anatomically divided into T1 (upper third), T2 (middle third), and T3 (lower third) regions, as well as right main stem bronchus, and left main stem bronchus (**Figure**) [5]. Prior studies have indicated subsegments of each mainstem bronchus (R1, R2, L1, L2, L3), however this goes beyond the scope. Video recordings and images will be deidentified and reviewed by both pediatric pulmonologists and scores averaged. Bronchoscopic appearance will be graded in percent dynamic narrowing classified as follows: mild: 50%–74%, moderate: 75%–89%, severe: >90%. If there is a greater than 10% difference between our measurements, we will review the video together, and if there remains a discrepancy in interpretation, Dr. Kazachkov, as the expert, will determine the degree of tracheomalacia. Videos will be evaluated for quality of visual field to be able to evaluate full cross-sectional area and cases excluded on the basis of inadequate visualization. The shape of anterior cartilage will be described as C-shaped, U-shaped, or bow-shaped at each anatomic region. Additional bronchoscopic findings will be recorded.



DA-CT Tracheomalacia Analysis

Airway collapse assessment on DA-CT will follow the method described by Koenigs et al [14]. Two readers blinded to the clinical data and to the bronchoscopy findings will review each case on the clinical picture archiving and communication system (PACS), Visage Imaging GmbH, Berlin, Germany. Peak

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inspiratory and end-expiratory phases will be identified based on lung and thoracic motion. Static or fixed narrowing, termed Maximal Airway Change (MAC) at any location will be determined in inspiration and quantified using tracheal cross-sectional area (CSA) compared to a normal segment of the trachea as follows: $MAC = CSA \text{ at narrowed segment in inspiration} / CSA \text{ of trachea at thoracic inlet in inspiration}$. Severity of MAC will be classified as follows: mild: 33%–49%, moderate: 50%–66%, severe: >67%.

Dynamic narrowing, termed excessive dynamic airway collapse (EDAC), will be defined as >50% reduction in CSA in expiration at any given location as follows: $(EDAC = CSA \text{ at airway segment in expiration} / CSA \text{ at same location in inspiration})$. Severity of EDAC will be classified as follows: mild: 50%–74%, moderate: 75%–89%, severe: >90%. If tracheomalacia was identified, it was characterized as purely dynamic narrowing or combined static and dynamic narrowing, since secondary tracheomalacia is frequently characterized by the latter.

The primary endpoint for the present study is the sensitivity and specificity of DA-CT as a diagnostic tool in identifying tracheomalacia. The outcome variable of interest, in this case, is the binary result of the DA-CT procedure (tracheomalacia present vs. tracheomalacia absent). These results will be compared in a 2x2 table against the binary result of the “gold standard” procedure in order to calculate sensitivity, specificity, and other parameters of interest such as positive predictive value, negative predictive value, and overall diagnostic accuracy. The methods outlined by Buderer et al. (1996) were used to calculate estimated precision of the 95% confidence intervals of sensitivity and specificity given the pilot sample size of N=25. Assuming that tracheomalacia has a prevalence of 20% in the target population, and that DA-CT sensitivity and specificity are at least 85%, the sample size will yield a 95% CI width of roughly 30%. In other words, the given N will allow us to be 95% certain that our sensitivity and specificity estimates are within 30% of the true values. The results from this pilot study will allow us to estimate sample size for a larger-scale study with more precise estimates of DA-CT diagnostic potential.

4.2.2 Secondary Study Endpoints

We will compare the image quality and radiation exposure of DA-CT performed on new generation PC-CT scanners compared to standard-of-care EID-CT scanners.

Image quality will be measured in two ways:

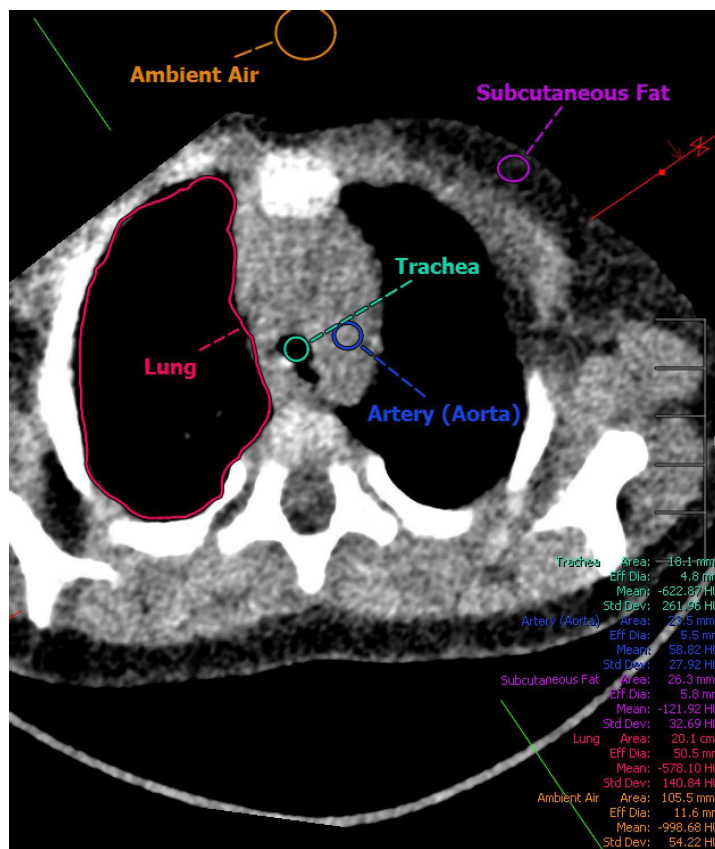
Quantitative Image Quality Analysis

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First, image noise will be represented as the standard deviation of attenuation values (measured in Hounsfield Units (HU)) of several different 2-dimensional regions of interest (ROI). The ROI measurements will be placed in the (1) tracheal air column (2) largest imaged mediastinal artery (such as the aorta or major branch vessel) (3) entire two dimensional right lung measurement (4) subcutaneous fat and (5) ambient air (**Figure**). Tracheal ROI will be placed within the tracheal air column at the level of most normal caliber; the largest possible continuous ROI will be placed within the mediastinal artery, avoiding calcification, surgical material or obvious thrombus; contoured ROI of the entire right lung area will be obtained at the level of the maximal imaged area; oval ROI will be placed within the subcutaneous fat of the anterior chest wall approximately at the level of the sternum; an approximately 0.1 cm² ROI within ambient air anterior to the sternum.

Contrast-to-noise-ratio (CNR) was calculated as $CNR = (\text{mean HU in the artery ROI} - \text{mean HU in the tracheal air column ROI}) / \text{image noise inside the trachea}$.



Qualitative Image Quality Analysis

Second, images will be reviewed on the picture archiving and communication system (PACS) by two fellowship-trained radiologists with 20 and 2 years of post-fellowship experience. Scan labels and markings will be removed to blind readers to CT scan type. Readers will qualitatively assess the following on a 5-point Likert scale: overall image quality, image noise, delineation of large airways, delineation of small airways, noise texture. If artifacts are present they will be graded on a 5-point scale and the type of artifact will be indicated by free text response.

Radiation Dose Assessment

Anonymous DA-CT data will be transferred to commercial dose management software (Radimetrics, Version 3.4.0-B, Bayer Healthcare, Leverkusen, Germany) to retrieve the CT scanner model, scan region, age, sex, weight, peak kilo-voltage (kVp), effective diameter, and diagnostic reference level (DRL) quantities, including volume CT dose index (CTDI_{vol}) and dose-length product (DLP). The effective dose (in mSv) will be automatically calculated with Radimetrics software, with tissue weighting factors from ICRP publication 103 [Protection, Radiological. "ICRP publication 103." *Ann ICRP* 37.2.4 (2007): 2.] In our study, the reference phantom size of DRL quantities for the DA-CT examinations was 32 cm.

Analysis of Secondary Endpoint(s)

Radiation exposure as well as the continuous measure of image noise will be compared between dynamic- and traditional- CT images using either paired samples t-tests or Mann-Whitney U tests, depending on distribution of the final data. Image pairs will be matched based on age and diagnosis. Similarly, the ordinal variable for image quality will be compared between traditional and dynamic CT images using the nonparametric Mann-Whitney U test. The per-protocol analysis dataset will be used and incomplete cases will be omitted from the analysis. Results will be presented as mean and standard deviation for continuous, normally distributed data and as median and interquartile range for non-normally

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distributed continuous data. Image quality results will either be presented as median with interquartile range, or with frequency distributions of the ordinal, Likert-scaled quality ratings.

5 Study Enrollment and Withdrawal

This is a prospective pilot cohort selection design study to determine the effectiveness of DA-CT to diagnose tracheomalacia.

The study population will consist of 25 participants, age 0-18 years old, with respiratory symptoms for whom flexible bronchoscopy has been performed as clinically indicated.

Participants will be recruited from inpatient pulmonary consult service and outpatient pulmonary clinic. Patients will be excluded if they are unable to undergo CT scanning without sedation and if they have a tracheostomy.

Participants will have the study described to them and need to sign a consent form.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Participants 0-18 years old, with
2. Clinically indicated flexible bronchoscopy has been performed.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy or breastfeeding
2. Unable to undergo CT scanning without sedation
3. Patients with tracheostomy

5.3 Vulnerable Subjects

Children 7-17 will need to sign a separate assent form.

There is a “minor increase over minimal risk” means that the increase in the probability and magnitude of harm is only slightly more than minimal risk, any potential harms associated with the procedure will be transient and reversible in consideration of the nature of the harm, and there is no or an extremely small probability that subjects will experience significant pain, discomfort, stress or harm.

Effective dose (measured in millisievert, mSv) is a number that is sometimes used to compare the relative amount of radiation from various radiological procedures. Based on our institutional experience, estimated effective dose from DA-CT is 0.5 mSv or less, and is usually much lower. By comparison, effective dose from several chest radiographs is approximately 0.5 mSv (approximately 2 to 5 radiographs, depending on technique). This amount is less than the annual radiation exposure that you receive from the natural environment, which is 3.1 mSv in the U.S. It is also much less than the annual limit set by the FDA for individuals participating in basic research studies, which is 50mSv. According to the International Commission on Radiological Protection (ICRP), the increased risk of health effects, such as cancer, from the radiation exposure you will receive in this study is too small to be easily measured.

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5.4 Strategies for Recruitment and Retention

All subjects will be recruited from the PI and sub-investigators' practices. Potential subjects will be approached at one of their standard clinic visits or during hospitalization by the PI, sub-investigators, or research coordinators. If patients have already undergone clinically indicated bronchoscopy previously, initial recruitment may occur over the telephone to discuss the study with the patient and their parents/guardians. Patients who express interest in participating will be scheduled to be consented and subsequently complete the DA-CT in the same day. Telephone recruitment script will be submitted via modification following initial IRB approval.

The PI/sub-investigator will screen for inclusion/exclusion criteria. If enrollment criteria are met and the patient/parent(s) are interested, the PI will obtain informed consent/assent and enroll the participant in the study.

Participants will be asked to schedule DA-CT.

Our target sample size is 25 participants.

5.5 Duration of Study Participation

Participants will be consented during routine clinic visits or hospitalization. Enrolled participants will need to do DA- CT scan at a separate visit or during hospitalization per family preference and scheduling ability. No other study visit is required.

Recruitment will end when 25 participants are enrolled and complete the study imaging.

5.6 Participant Withdrawal or Termination

5.6.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request.

5.6.2 Handling of Participant Withdrawals or Termination

Subjects that withdraw from the study will continue to receive usual care from their Center team. Every effort will be made to capture the reason for subject withdrawal and to ascertain if any adverse events or serious adverse events occurred, which would be immediately reported to the IRB and study sponsor. Participants will be recruited to replace to a full cohort of 25 in any case of subject withdrawal or termination.

6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

DA-CT has the advantage of being widely available, directly measures airway dimensions, and can be performed in awake children without sedation.

6.1.2 Standard of Care Study Procedures

Flexible bronchoscopy is completed as clinically indicated and standard of care.

6.2 Study Schedule

Subjects with respiratory symptoms for whom flexible bronchoscopy has been performed will be asked to participate in the study.

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- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- A Dynamic airway computed tomography (DA-CT) test will be scheduled.

Timeline

		Year 1			
		Q1	Q2	Q3	Q4
	Bronchoscopy	13	12		
Aim 1	Bronchoscopy Scoring	13	12		
	Resolve Pulm Discrepancies				
	DA-CT Scan	13	12		
	DA-CT Scoring	13	12		
	Resolve Rads Discrepancies				
Aim 2	PC-CT Radiation Scoring				
	EID-CT Radiation Scoring				
	CT Radiation Data Analysis				
	Resolve Rads Discrepancies				
Project Goals	Data Safety Review				
	Prepare Abstract to ATS				
	Prepare & Submit Manuscript				

6.3 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events to the IRB.

7 Clinical Monitoring

The PI is responsible for data safety monitoring reviews. This includes conducting systematic and periodic reviews of aggregate data and adverse events. These specific data and events include: reports

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of subject complaints, discomfort, and breaches of confidentiality. These data and events will be reviewed quarterly.

No predefined stopping rules will be used.

A summary of the outcomes of these safety reviews along with accumulated adverse events and deviations will be submitted to the IRB as part of an annual progress report at the time of the Continuing Review submission.

8 Statistical Considerations

8.1 Statistical and Analytical Plans (SAP)

Statistical analyses will be conducted using Stata version 17. The result of the DA-CT procedure (tracheomalacia present vs. tracheomalacia absent), the primary outcome, will be compared in a 2x2 table against the binary result of the “gold standard” procedure in order to calculate sensitivity, specificity, and other parameters of interest such as positive predictive value, negative predictive value, and overall diagnostic accuracy. Radiation exposure and the continuous measure of image noise will be compared between dynamic- and traditional- CT images using either paired samples t-tests or Mann-Whitney U tests, depending on distribution of the final data. Image pairs will be matched based on age and diagnosis. Similarly, the ordinal variable for image quality will be compared between traditional and dynamic CT images using the nonparametric Mann-Whitney U test

8.2 Statistical Hypotheses

The main hypothesis is that DA-CT is an equally sensitive and specific alternative to the gold standard flexible bronchoscopy in children with tracheomalacia. Specifically, when assessing this hypothesis, the minimally acceptable criteria for sensitivity and specificity for DA-CT will be set to 85% and 90%, respectively. Therefore, the following null hypothesis (H0) will be tested: Sensitivity <0.85 and specificity<0.90. The alternative hypothesis (HA) is: Sensitivity $\geq$ 0.85 and specificity $\geq$ 0.90.

The secondary hypotheses posit that DA-CT performed on new generation photon-counting CT (PC-CT) scanner will be associated with (1a & 1b) improved image quality and (2) reduced radiation dose. In this case, the null hypotheses (H0) are: (1a) image noise: mean/median(PC-CT)< mean/median(EID-CT) (1b) image quality: median(PC-CT)< median(EID-CT) (2) radiation exposure: mean/median(PC-CT)> mean/median(EID-CT). Furthermore, the alternative hypotheses for the secondary outcomes (HA) are: (1a) image noise: mean/median(PC-CT) $\geq$ mean/median(EID-CT) (1b) image quality: median(PC-CT) $\geq$ median(EID-CT) (2) radiation exposure: mean/median(PC-CT) $\leq$ mean/median(EID-CT). All endpoints will be analyzed once data collection is complete.

8.3 Analysis Datasets

All participants' data will be maintained in a comprehensive REDCap database. A per-protocol analysis dataset, containing only subjects who completed both flexible bronchoscopy and DA-CT imaging (as planned) will be used for final analysis.

8.4 Description of Statistical Methods

8.4.1 General Approach

This is a cohort selection design study to investigate the diagnostic accuracy of DA-CT in children 0-18 years with respiratory symptoms for whom flexible bronchoscopy has been performed. For the purpose of this study, the type I error rate (α) is set to 5%. Therefore, all statistical tests with p values less than 0.05

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will be considered significant. Type II error rate (β) is 20%, due to the desired power of 80%. A 95% confidence interval will be included with relevant parameter estimates.

Simple univariate statistics will be calculated to describe the final sample and to summarize key variables of interest. Continuous and discrete data will be summarized using mean and standard deviation if they are normally distributed, and using median and interquartile range if they are not. Categorical data will be summarized in terms of frequency and percent. All continuous data will be assessed for normality using skewness and kurtosis parameters as well as histograms. In the event that data do not sufficiently meet the assumption of normality, nonparametric methods will be utilized.

8.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint for the present study is the sensitivity and specificity of DA-CT as a diagnostic tool in identifying tracheomalacia. The outcome variable of interest, in this case, is the binary result of the DA-CT procedure (tracheomalacia present vs. tracheomalacia absent). These results will be compared in a 2x2 table against the binary result of the “gold standard” procedure in order to calculate sensitivity, specificity, and other parameters of interest such as positive predictive value, negative predictive value, and overall diagnostic accuracy.

8.4.3 Analysis of the Secondary Endpoint(s)

Radiation exposure as well as the continuous measure of image noise will be compared between dynamic- and traditional- CT images using either paired samples t-tests or Mann-Whitney U tests, depending on distribution of the final data. Image pairs will be matched based on age and diagnosis. Similarly, the ordinal variable for image quality will be compared between traditional and dynamic CT images using the nonparametric Mann-Whitney U test. The per-protocol analysis dataset will be used and incomplete cases will be omitted from the analysis. Results will be presented as mean and standard deviation for continuous, normally distributed data and as median and interquartile range for non-normally distributed continuous data. Image quality results will either be presented as median with interquartile range, or with frequency distributions of the ordinal, Likert-scaled quality ratings.

8.5 Sample Size

The methods outlined by Buderer et al. (1996) were used to calculate estimated precision of the 95% confidence intervals of sensitivity and specificity given the pilot sample size of N=25. Assuming that tracheomalacia has a prevalence of 20% in the target population, and that DA-CT sensitivity and specificity are at least 85%, the sample size will yield a 95% CI width of roughly 30%. In other words, the given N will allow us to be 95% certain that our sensitivity and specificity estimates are within 30% of the true values. The results from this pilot study will allow us to estimate sample size for a larger-scale study with more precise estimates of DA-CT diagnostic potential.

9 Ethics/Protection of Human Subjects

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, and/or the ICH E6.

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9.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented/assented.

9.3 Informed Consent Process

During regularly scheduled appointments at the NYU Medical Center, the PI or IRB approved study member will obtain the written consent/assent of the patient and parents for participation in the study.

Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant's parents/guardians will be asked to read and review the document. Consent will be obtained by the pediatric pulmonologist, PI Dr. Eleanor Muise, pediatric Co-I, Dr. Mikhail Kazachkov, or pediatric nurse practitioners Ms. Bernstein or Ms. Erkman who have pediatric specific expertise, full understanding of this study, and knowledge of the informed consent process. The investigator will explain the research study to the participant and their parents/guardians and answer any questions that may arise. All participants and their parents/guardians will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Discussion and language will be age-appropriate for the age and developmental stage of each participant who will be asked to give verbal assent. Children ages 7-17 will be asked to sign an assent form. Participants and their parents/guardians will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their parents/guardians or think about it prior to agreeing to participate. The participant's parent/guardian will sign the informed consent document prior to any procedures being done specifically for the study. The participants and their parent/guardian may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants/parents/guardians for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

9.4 Participant and Data Confidentiality

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NYU Langone medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU center.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

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10 Data Handling and Record Keeping

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported

10.1 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting / publication.

10.2 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

11 Study Finances

11.1 Funding Source

KIDS of NYU Foundation.

11.2 Costs to the Participant

No charge to the participant is done for the study.

11.3 Participant Reimbursements or Payments

There are no participant reimbursements or payments.

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13 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Consent Form
- Assent Forms
- Key-information Form
- Appendix children Form

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14 Schedule of Events

Activity	Visit 1	Visit 2
Study team procedures		
Consent	X	
AD-CT scan		X

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Interventional Template Version: 18 July 2022