Automatic Airway Analysis on Multidetector Computed Tomography in Cystic Fibrosis

Correlation With Pulmonary Function Testing

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Purpose: To evaluate the fully automatic quantification of airway dimensions on chest multidetector computed tomography (MDCT) performed in cystic fibrosis (CF) patients. Airflow indices including predicted forced expiratory volume in 1 second (FEV1%) were used to study the impact on regional lung function.

Materials and Methods: MDCT data of patients with CF (14 children and 23 adults) and of control patients (11 children and 22 adults) were used to compute total diameter (TD), lumen area (LA), and wall thickness (WT) using dedicated software. Pulmonary function testing including FEV1% was performed in parallel and correlated with MDCT parameters in a generation-based analysis.

Results: TD was largely increased in CF patients (third-generation to fourth-generation airways in children, first to ninth in adults; $P < 0.05$). LA remained unchanged, but WT was also larger in CF compared with controls (third generation to sixth generation in children, first to eleventh in adults; $P < 0.05$). In adult CF patients significant negative correlations for TD, LA, and WT with FEV1% were found for intermediate airways (fifth to seventh generation; $r = -0.7$ to -0.9) but not in pediatric CF patients and controls.

Conclusions: Automatic airway analysis succeeded in quantifying specific pathologies such as airway dilatation and wall thickening in CF patients at different ages. Moreover, our results indicate a shift in main airflow resistance to intermediate airways in cases of chronic CF. The objective computational parameters TD, LA, and WT should be considered for assessment and follow-up of CF airway disease.

Key Words: airway disease, airway dimensions, cystic fibrosis, chronic obstructive pulmonary disease, quantitative computed tomography

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Cystic fibrosis (CF) remains the most lethal autosomal recessive hereditary disease in white populations.[1,2] Multiple mutations of the CF transmembrane conductance regulator (*CFTR*) gene produce defective Cl^- secretion and increased Na^+ absorption through the epithelia of conducting airways.[3] Airway surface dehydration results in highly viscous secretions, thus producing a pulmonary phenotype of impaired mucociliary clearance, chronic mucus obstruction, recurrent or persistent bacterial infection, and high pulmonary mortality.[2,4] Chronic inflammatory processes lead to wall thickening of cartilaginous airways and loss in cartilage volume.[5] Bronchiectasis results from and facilitates chronic bacterial infection. Improvements in clinical management of CF patients have led to a sustained increase in life expectancy to around 40 years, and many CF patients now are of adult age.[6]

In the clinical management of CF lung disease, imaging procedures are frequently and repeatedly performed for a variety of reasons, such as: to assess disease severity and regional distribution; because of complications such as infection, pulmonary embolism, or hemorrhage; or as part of the procedure preceding lung transplantation, bronchoscopy, or therapeutic interventions. Multidetector computed tomography (MDCT) is still considered superior for the depiction of lung changes compared with chest radiographs,[7] and especially for the visualization of distal airways compared with magnetic resonance imaging.[8,9] Importantly, MDCT has been proposed as an outcome measure for therapeutic interventions.[10] Hallmarks of pathologic airway changes in CF lung disease visualized by chest MDCT comprise bronchial wall thickening, mucus plugging, bronchiectasis, and sacculations.[11] Several visual scoring systems have been established to monitor disease severity, along with chest radiographs (eg, Crispin-Norman score[12]), CT (eg, Bhalla score[13,14]), and, recently, magnetic resonance imaging.[15] However, introduction into clinical routine has been hampered by the complexity of the scoring systems. This is underlined by the fact that numerous scores

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have been proposed but are mainly used for research purposes only. Manual and semiautomatic scoring systems show good interreader agreement[7,14,15] but remain a subjective and semiquantitative measure.

Pulmonary function testing (PFT) is frequently used in clinical assessment of CF. So far, the forced expiratory capacity within 1 second (FEV1) remains the most important prognostic factor for disease progression and the most significant predictor of mortality in CF lung disease.[16] It is known that PFT is insensitive to early changes in the lung parenchyma and airways and may remain stable despite obvious regional morphologic changes detected by high-resolution imaging.[17–19] PFT also does not provide any information on regional lung function, which may be subject to specific therapy.

A need for reliable and reproducible, that is, objective and quantitative, parameters for CF lung disease providing surrogate markers for disease severity in the context of patient management and for clinical trials is evident. Therefore, the present study was conducted to evaluate the fully automatic measurement of morphologic airway changes on MDCT in pediatric and adult CF patients compared with a control group using a dedicated postprocessing software tool.[20] In a second step, we correlated the results from airway analysis with paralleled PFT in order to correlate morphologic alterations with lung function. We demonstrated that automatic airway measurements can quantify specific airway pathologies in CF, such as wall thickening and dilatation, and that these alterations correlate with airflow obstruction in PFT in a generation-based analysis.

MATERIALS AND METHODS

Study Population

Data acquisition was performed at our institution from April 2003 to August 2004 (patients up to 18 y of age) and from June 2007 to August 2010 (patients older than 18 y). The study was carried out as a retrospective analysis of clinically indicated MDCT scans, and patients or legal guardians provided informed consent for examination and data processing. Table 1 shows the clinical characteristics of our study population. A total of 37 patients suffering from CF lung disease who received a non–contrast-enhanced chest MDCT (see following subsection) were arbitrarily subdivided into 2 study groups: one consisting of 14 patients comprising children and adolescents less than 18 years of age (CF < 18) and the other comprising 23 adults aged 18 years or above (CF ≥ 18). Indications for diagnostic MDCT were suspected infection, disease severity assessment, or pretransplantation workup. Thus, a wide variety of different stages of CF lung disease were subjected to the automatic software analysis. The selection represents approximately 50% of patients who underwent MDCT during the inclusion periods. All patients showed typical signs of CF lung disease, such as bronchiectasis of at least 1 lobe, bronchial wall thickening, and mucus plugging. In some patients (n = 2) 1 or more collapsed lobes wholly destroyed by cystic bronchiectases were evident.

Patient data for 33 controls were retrieved by an institutional databank search of imaging studies conducted during the same periods as for CF patients. Before inclusion, images were evaluated by a radiologist with > 3 years of experience in chest imaging. Patients without airway disease or major parenchymal changes on the diagnostic MDCT scan were eligible for inclusion into the study and were subdivided into 2 age groups comparable to the CF patient group (11 Normal < 18 and 22 Normal ≥ 18). Solitary pulmonary nodules < 3 cm in diameter within the lung periphery were considered acceptable. Major indications for MDCT in this group were suspected malignancy (primary or secondary; n = 9), suspected infection including tuberculosis (n = 6), chronic cough and dyspnea (n = 4), suspected alveolitis (n = 2), and pectus excavatum (n = 1). Only 5 patients within the Normal ≥ 18 group were active smokers but without meeting clinical, morphologic, or functional criteria for chronic obstructive pulmonary disease (COPD).[21] PFT was successfully performed within 10 days (median delay 0 d) of MDCT in 14 CF < 18 and 16 CF ≥ 18 patients, as well as in 21 Normal ≥ 18 patients. Four Normal < 18 patients were examined by PFT, and thus the Normal < 18 group had to be excluded from correlation analysis (Table 1). All Normal < 18 and Normal ≥ 18 patients showed normal results on PFT (Table 1).

MDCT

Nonenhanced thin-section MDCT in CF and control patients was routinely performed at inspiratory breath-hold in supine position. Before scanning, all patients were trained to achieve a full end-inspiratory breath-hold. All patients aged 18 years or above were examined with a 4-slice Volume Zoom spiral computed tomograph (Siemens AG, Forchheim, Germany) at 120 kV, an effective tube current-time product of 70 mAs, a collimation of 1.25 mm, and a pitch of 2. Patients younger than 18 years were examined either by the system described above or by a 16-slice Aquillion 16 system (Toshiba Corp., Tokyo, Japan) with a dose-modulated protocol at 120 kV and effective mAs adapted to body weight (range, 35 to 80 mAs), 1 mm collimation, and pitch 1.

Reconstruction was performed with a slice thickness of 1.25 and 1 mm increment in a medium-soft B40f algorithm (Siemens scanner) or with a slice thickness of 1.0 and 1 mm increment in an equivalent medium-soft kernel FC05 (Toshiba scanner). Medium-soft kernels are considered more effective for computational airway analysis.[20] The scale of attenuation coefficients with these systems ranges from −1024 to + 3072 Hounsfield Units (HU). The systems were calibrated for water regularly and after major maintenance, as well as for air daily. Scanning and reconstruction protocols were kept constant during the whole inclusion period. Mild respiratory artifacts did not affect the image analysis, and patients with severe respiratory artifacts were not included in this study.

MDCT Airway Analysis Software

Using a custom software (YACTA),[20] the stack of approximately 300 images per patient was analyzed fully automatically in an unattended mode on a standard personal computer (Intel Xeon 2.83 GHz, 4 GB RAM) for approximately 9 minutes per data set. Soft tissues (> −750 HU), lungs (< −500 HU), and the tracheobronchial tree were found fully automatically on the basis of threshold values and an anatomic knowledge-based algorithm, and no manual interaction was carried out. The automatic algorithm initially detects a seeding point within the trachea, and adjacent pixels are defined as belonging to conducting airways using a threshold value by a self-adapting region growing algorithm.[20,22] A centerline is calculated, which represents the course of the related bronchus (Fig. 1). Secondary reconstructions of images that

TABLE 1. Summarized Study Population Characteristics

	Normal < 18	CF < 18	Normal ≥ 18	CF ≥ 18
MDCT/YACTA (n)	11	14	22	23
Age, median (range)	15.2 (4-17)	12.8 (7-16)	42.5 (20-68)	24.3 (18-54)#
Sex	9♂/2♀	7♂/7♀	12♂/10♀	15♂/8♀
Smoker (n)	0	0	5	0
Height, mean (cm)	147 (106-182)	147 (118-168)	172 (158-185)	170 (152–202)
Weight, mean (kg)	45.4 (15.7-84.0)	35.4 (21.5-52.4)	75.8 (55.0-101.0)	56.0 (40.0-86.0)#
BMI, mean (kg/m^2)	19.5 (13-26)	16.1 (12.3-20.7)*	25.6 (20-36)	19.3 (16-24)#
PFT (n)	4	14	21	16
ΔPFT − MDCT median (d)	35 (0-66)	0 (0-6)	0 (0-8)	0 (0-10)
FEV1, mean (L)	2.8 (1.6-4.1)	1.5 (0.7-3.3)	3.6 (2.6-4.9)	1.9 (0.6-6.9)#
FEV1%, median	89 (80-96)	73 (37-108)	105 (80-140)	34 (21-140)#
VC, mean (L)	3.5 (2.2-4.8)	2.0 (0.9-3.7)*	4.3 (3.0-5.8)	2.8 (1.2-7.9)‡
VC%, median	88 (70-94)	74 (45-115)	102 (79-131)	54 (31-127)#
LAB (n)	0	13	15	19
ΔLAB − MDCT, median (d)		0	0	0
CRP, mean (mg/dL)		< 5 (0-20.0)	< 5 (0-18.0)	23.8 (0-187.0)
WBC, mean (10^9/L)		10.5 (5.4-15.4)	6.5 (4.2-12.4)	9.9 (5.4-14.1)#

Descriptive statistics of the pediatric and adult control population (Normal < 18 and Normal ≥ 18, respectively) compared with those of the corresponding CF lung disease patient cohorts (CF < 18 and CF ≥ 18, respectively). Individuals were subjected to MDCT, automatic airway analysis (YACTA), PFT, and blood tests (LAB). ΔPFT − MDCT refers to the delay between PFT and MDCT, ΔLAB − MDCT refers to the delay between LAB and MDCT. Data are presented as mean or median as appropriate; data range is given in brackets.

*P < 0.05; ‡P < 0.01; #P < 0.001. Statistical tests were the Student t test, the Mann-Whitney U test, or the Fisher exact test as appropriate.

are oriented exactly perpendicular to the bronchial axis subsequently allow precise airway wall detection and measurements (Fig. 1). These were carried out using an integral-based method (IBM).[20] Basically, the IBM recognizes the inner and outer borders of an airway wall by calculating the integral value of a density profile starting from the airway center. A total of 128 such density profiles are computed along perpendicular trajectories radiating from the centerline on each secondary reconstruction. For example, measurements on an average of 782 secondary reconstructions of detected airways were taken for an adult CF patient. The parameters of an ideal airway model are changed so that the integral value of a profile across the model fits the integral value of the profile across the real airway. Subsequently, the total diameter (TD) was computed as the mean distance from the outer to outer border of an airway segment (Fig. 1D). The luminal area (LA) is the mean area within the inner border. Wall thickness (WT) is the mean distance between inner and outer borders, and relative WT (WT%) is calculated as WT/TD × 100. The points of maximum density within the inner and outer borders are summed up as mean maximum wall attenuation in HU (HU_{max}). All parameters were calculated for each bronchial generation separately. The final computational results were reviewed by the reader preceding statistical evaluation.

The IBM and subsequent measurements were evaluated for accuracy using an anthropomorphic phantom in a previous study and showed a mean error of 5% for airways with 0.3 to 2.5 mm WT and 2.6 to 9.0 mm diameter and proved to be superior over other algorithms such as the full-width at half-maximum method.[20] In a subsequent study, the software has been validated in inflation-fixed porcine lung explants against histologic measurements of TD and WT, with a mean relative error of 5.6% to 11.0% for airways between 0.37 and 1.71 mm WT and 3.17 and 10.74 mm diameter.[23] These validation experiments compare well to the range of WT of 0.3 to 2.4 mm detected in our study population and to the range of TD of 2.7 to 28.2 mm.

PFT and Blood Testing

Postbronchodilator full-body plethysmography PFT (MasterScreen Body; E. Jaeger, Hoechberg, Germany) was performed according to the guidelines of the European Respiratory Society and the standards of the American Thoracic Society.[24] The European Coal and Steel Community–predicted values were selected as our in-house standard[25] and reflect the individually measured value in relation to an age-matched and height-matched control population given in percentage. Therefore, the percentage of predicted values better reflects pathologic changes of a PFT item. The "%" symbol following the PFT parameter indicates the predicted values in percentage. The following lung function parameters were chosen for correlation analysis: the forced expiratory volume in 1 second (FEV1, FEV1%), the peak expiratory flow (PEF, PEF%), the maximum expiratory flow at 50% vital capacity (MEF50, MEF50%), and the maximum expiratory flow at 25% vital capacity (MEF25, MEF25%) are items that measure airflow at different points of a forced expiration maneuvre. A decrease in FEV1% is a diagnostic and prognostic marker of obstructive lung disease. The total airway resistance (R_{tot}) and R_{tot} percent predicted (R_{tot}%) can measure airflow obstruction in conducting airways more directly. The vital capacity (VC, VC%) is the maximum volume of gas that can be actively moved during breathing. The residual volume (RV, RV%) is the volume of gas that remains inside the lungs after thorough expiration and is considered an index of pulmonary gas retention. VC and RV add up to the total lung capacity (TLC, TLC%).

C-reactive protein and white blood cell count were measured in agreement with current guidelines by a certified laboratory.

Statistical Analysis

All data were recorded using a dedicated database (Excel 2008, Miscrosoft Corp., Redmond, WA) and analyzed using Prism (GraphPad Software Inc., La Jolla, CA) and SigmaPlot (Systat Software GmbH, Erkrath, Germany)

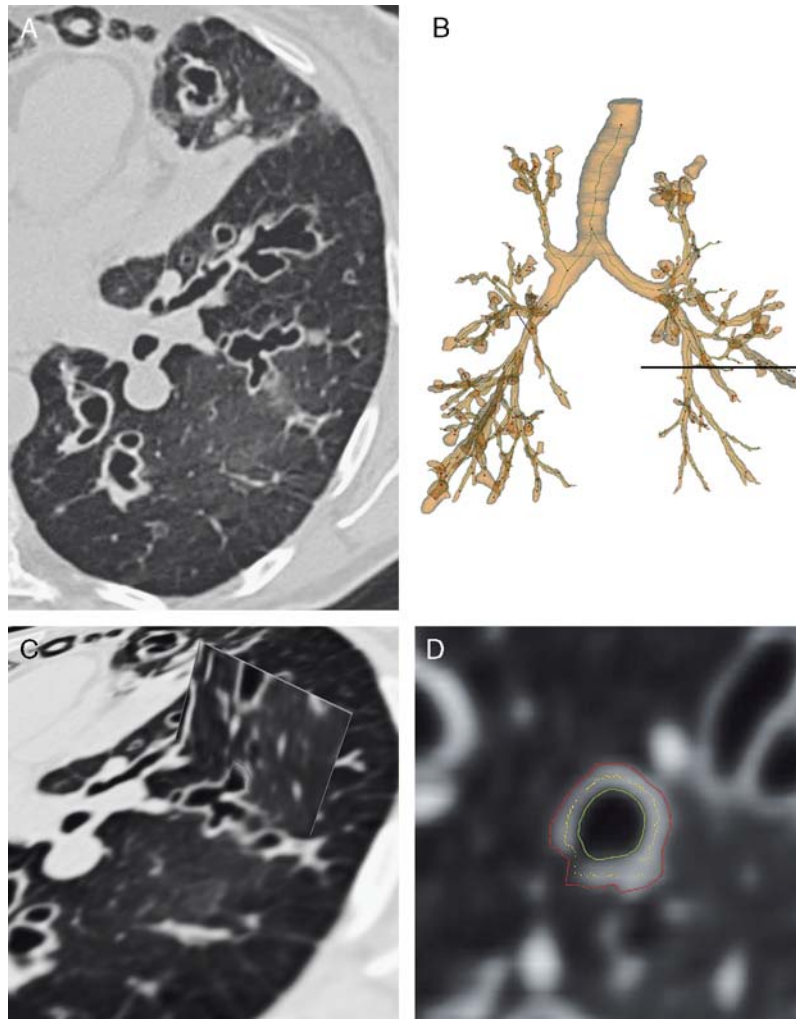

FIGURE 1. Airway registration and analysis algorithm. A, Details from a transversal MDCT slice at the level of the left inferior lobe of a 47-year-old female CF patient with marked varicous bronchiectasis. B, After segmentation of the trachea and bronchi a centerline can be calculated, which represents the long axis of the corresponding bronchial segment. This volume-rendering image of the airway tree depicts bronchiectasis in this patient as buds at the end of plurious bronchi. The level of the MDCT slice (A) is indicated by a black line. C, Secondary reconstructions are possible, which run perpendicular to the long axis of the bronchus. D, On the basis of these secondary images, the bronchial wall is registered by the software's algorithm. The inner (green color) and outer (red color) margins encompass the circumference of the bronchial wall. The intermediate circle (yellow color) represents the points of maximum wall attenuation. full color online

software. Numerical results from YACTA airway analysis (TD, LA, WT, HU_{max}) (see Table, Supplemental Digital Content 1, http://links.lww.com/JTI/A35) were normalized to the body mass index, which was calculated as weight/height^2, for further analysis. For quantitative data, normality testing was performed to assess whether parametric or non-parametric tests should be used. Multiple comparisons within the same observational group (ie, CF or Normal) were performed using 1-way analysis of variance with post hoc tests as appropriate. Statistical comparisons between groups were performed using the Student t test or the Mann-Whitney U test, and multiple comparisons were compensated for by using the Bonferroni method. A P-value < 0.05 or $P < 0.05/m$ (number of tests) with the Bonferroni method was considered statistically significant.

Because the data encompass parametric and non-parametric variables, the Spearman rank order correlation coefficient (r_s) was calculated for selected parameters from MDCT, PFT, and patient age, each separately for different bronchial generations in pediatric and adult Normal and CF subjects. It is to be noted that, for the correlation analysis for patient age, non-normalized values of airway parameters TD, LA, WT, and HU_{max} were used.

RESULTS

Airway Segmentation

Because the assignment of generations by the segmentation algorithm of YACTA is based on bifurcations, the number of potentially detectable bronchi within 1 generation can be predicted as $n = 2^{(generation-1)}$, with the first generation being the trachea. Severe respiratory artifacts in 1 pediatric and 1 adult CF patient and destroyed parenchyma in 2 adult CF patients led to an early halt of the segmentation

TABLE 2. Airways Detected Per Generation in Comparison With the Number Predicted

		Mean (n)			
Generation	**Predicted**	**Normal < 18**	**CF < 18**	**Normal ≥ 18**	**CF ≥ 18**
1	1	1.0 (11)	1.0 (14)	1.0 (22)	1.0 (23)
2	2	2.0 (11)	1.9 (14)	2.0 (22)	2.0 (23)
3	4	3.7 (11)	3.9 (14)	4.0 (22)	3.9 (23)
4	8	7.0 (11)	7.1 (14)	7.9 (22)	7.3 (23)
5	16	7.2 (11)*	11.4 (14)*	13.4 (22)*	14.1 (23)
6	32	8.1 (7)*	13.5 (14)*	13.6 (20)*	17.4 (22)*
7	64	3.3 (6)*	12.4 (14)*	7.3 (20)*	16.7 (22)*
8	128	2.5 (2)*	9.9 (8)*	4.7 (19)*	11.5 (22)*
9	256	2.0 (1)*	8.3 (12)*	3.6 (14)*	9.4 (20)*
10	512	—	3.8 (10)*	3.5 (10)*	7.1 (18)*
11	1024	—	4.0 (7)*	2.3 (4)*	5.8 (13)*

Data are presented as mean number of airways detected by YACTA software in pediatric and adult control groups (Normal < 18 and Normal ≥ 18, respectively) and in the corresponding CF lung disease patient cohorts (CF < 18 and CF ≥ 18). The number of remaining patient data sets is given in brackets.
*$P < 0.001$ versus predicted (1-sample t test).

process with a detection of half or less of the expected number of airways of the fourth and fifth generation. Until the fourth generation, on average all bronchial segments could be registered for each group by YACTA as predicted (Table 2). For the fifth generation, significantly fewer, yet representative, number of bronchi were detected (Table 2). For the following generations, few airway segments could be measured. Interestingly, a significantly larger absolute number of distal airways were recognized by YACTA in both CF < 18 and CF ≥ 18 groups as compared with the corresponding control groups (Fig. 2).

TD and LA

A significantly increased TD of multiple airway generations is evident in both CF < 18 and CF ≥ 18 patients as compared with each corresponding control. However, the gap is more pronounced in the CF ≥ 18 group, whereas TD of the Normal ≥ 18 group does not differ from that of the Normal < 18 group (Fig. 2). This mean increase in the bronchial transverse diameter in CF is not accompanied by an increase in LA, which does not change between CF patients and controls for either age group (Fig. 2).

Airway WT and Attenuation

Significant wall thickening was found in CF < 18 patients and was more pronounced in CF ≥ 18 patients for the trachea (ie, first generation), proximal (second to fourth generation), and intermediate airways (fifth to seventh generation) (Fig. 3). Moreover, an increased WT to TD ratio (WT%), especially in CF ≥ 18 patients, was evident. Corresponding with TD, HU_{max} was increased in the CF groups compared with each control (Fig. 3).

Correlation of Airway Morphology With PFT

To validate the computational airway measurements, all parameters computed were correlated with clinical markers of airflow obstruction and hyperinflation in PFT. In the Normal ≥ 18 group, FEV1% moderately correlates with the TD of second to third generation airways (Table 3). A slightly stronger correlation was found for LA of the same generations (Table 4). VC and TLC correlate similarly with TD and LA of second to third generation airways. Importantly, no systematic correlation was found for WT (Table 5) with airflow indices in the Normal ≥ 18 group.

In CF < 18 patients TD and LA showed moderate but negative correlations with FEV1% for second-generation and third-generation airways, which appear inverted compared with that in the Normal ≥ 18 group (Tables 3, 4). Correlations of VC and TLC with TD and LA for the same generations are also moderate (Tables 3, 4). For CF < 18 patients also, no relevant correlation between WT (Table 5) and airflow indices was found.

In CF ≥ 18 patients, however, a strong negative correlation was detected between TD and LA of fifth-generation to seventh-generation airways and FEV1% (Tables 3, 4). Of all parameters analyzed, WT of the fifth generation correlates best with FEV1% and MEF50% in CF ≥ 18 patients but not in CF < 18 and Normal ≥ 18 patients (Table 5). Increased WT is associated with reduced airflow (Fig. 4). In contrast, R_{tot} increases with WT (Table 5). Similar, yet less intense, correlations with FEV1% were calculated for WT% and HU_{max} (Fig. 4). Detailed tables of the correlation analysis are provided with the online supplement (see Tables, Supplemental Digital Content 3, 4, and 5, http://links.lww.com/JTI/A36, http://links.lww.com/JTI/A37, and http://links.lww.com/JTI/A38). In all groups analyzed, CF patients and controls, no correlation existed between airway parameters and blood markers of inflammation, namely, C-reactive protein and white blood cell count.

Correlation With Patient Age

To further evaluate the influence of patient age on bronchial dimensions, measurement data from Normal and CF patients were pooled across age groups and correlated with patient age (Table 6). Non-normalized TD is positively correlated with age for the second and third generations in both groups but for fifth-generation airways in the CF group only. The LA of even more distal airways, that is, seventh and ninth generation, seems to increase with age also. Interestingly, WT is associated with age only for the proximal airways in CF patients, and WT% seems to even decline with age in both groups. The latter may also be observed as a trend in Figures 3C, D.

DISCUSSION

Its capability for continuous volumetric data acquisition within a single breath-hold at submillimeter isotropic resolution and the high inherent tissue contrast of the lungs and airways render MDCT the gold standard modality for airway

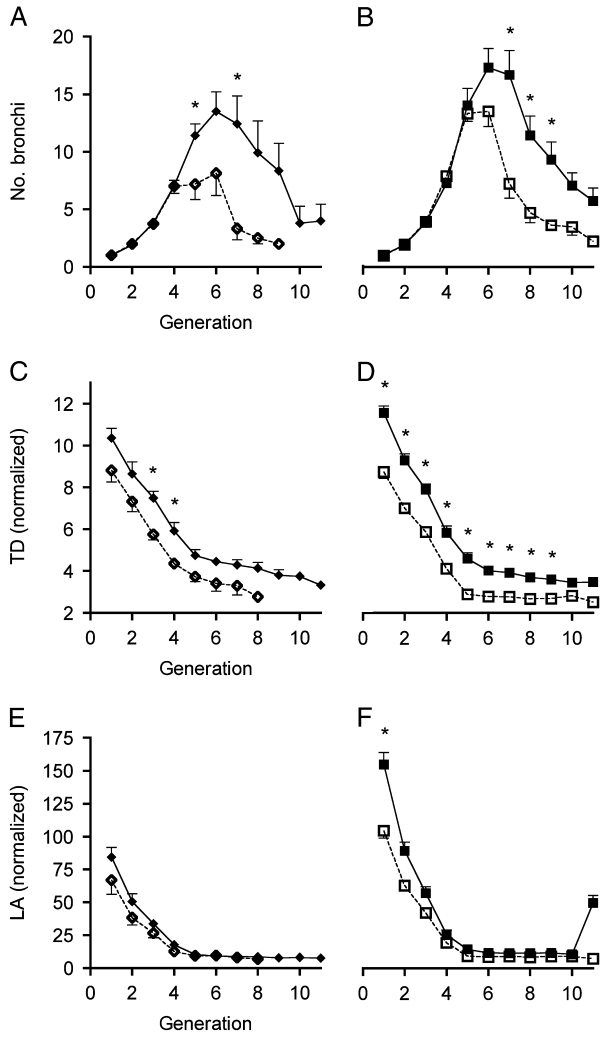

FIGURE 2. A and B, In pediatric and adult CF patients, a significantly larger number of airway segments per generation could be detected by the software. C–F, The mean TD and mean LA were calculated for each bronchial generation separately and corrected for body mass index. Interestingly, normalized TD did not differ significantly from childhood to adult ages in controls (Normal < 18 and Normal ≥ 18) and CF (CF < 18 and CF ≥ 18) groups, but the gap between Normal and CF is slightly larger in adults (D). Also in both, pediatric and adult patients, LA did not differ between Normal and CF except from the trachea (E, F). All data are presented as mean ± SEM. Symbol legends are Normal < 18 (◇), CF < 18 (◆), Normal ≥ 18 (□), and CF ≥ 18 (■). *P < 0.05/8 = 0.00625 for <18 and *P < 0.05/11 = 0.004545 for ≥ 18 groups (Bonferroni correction for the Student t test).

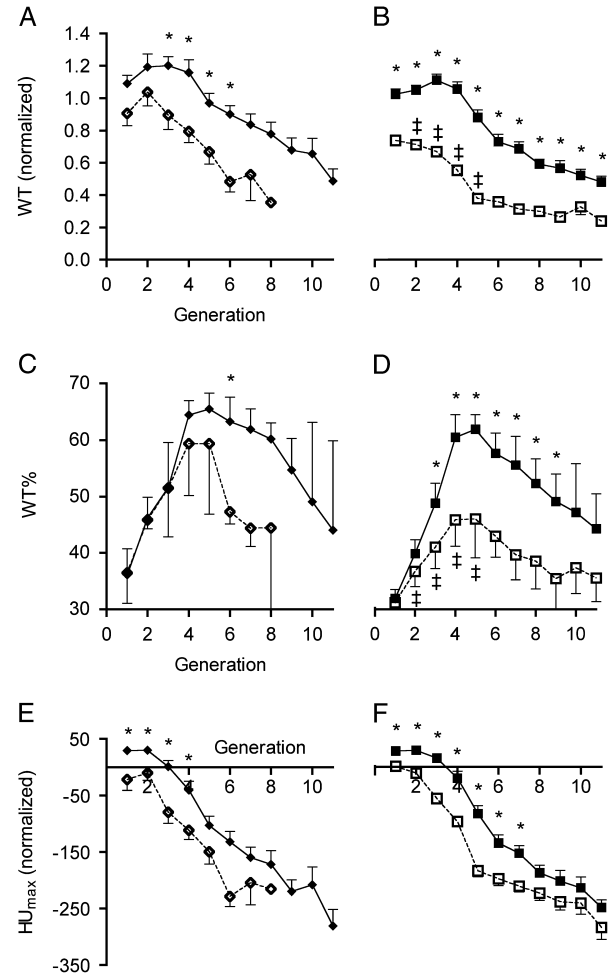

FIGURE 3. A and B, Mean WT was calculated for each bronchial generation separately and corrected for body mass index. WT was similar between pediatric and adult CF patients (CF < 18 and CF ≥ 18, respectively). Nevertheless, a significant increase in WT in comparison with corresponding controls (Normal < 18 and Normal ≥ 18) was more pronounced in CF ≥ 18 patients, because WT was lower in Normal ≥ 18 patients than in Normal < 18 patients for proximal and intermediate bronchi. C and D, WT was also calculated as a percentage of the TD (WT%). E and F, Mean maximum wall attenuation in HU (HU_{max}) was calculated for each bronchial generation separately and also normalized to body mass index. WT and HU_{max} are presented as mean ± SEM; WT% data are presented as median ± interquartile range. Symbol legends are Normal < 18 (◇), CF < 18 (◆), Normal ≥ 18 (□), and CF ≥ 18 (■). *P < 0.05/8 = 0.00625 for <18 and *P < 0.05/11 = 0.004545 for ≥ 18 groups, ‡P < 0.05/8 = 0.00625 vs. Normal < 18 (Bonferroni correction for the Student t test for WT and HU_{max} and for the Mann-Whitney test for WT%).

imaging.[26] Hence, mostly CT scores have been used to conduct clinical studies and have proven to be more sensitive in detecting subtle and/or regional changes in the CF lung compared with paralleled PFT.[27] Our approach was to quantify bronchial wall thickening and bronchial dilatation user-independently by means of fully automatic airway segmentation using a novel custom software tool, which can generate objective results that may contribute to assessment and reporting in different stages of CF lung disease.

Quantitative automatic analyses of the airway dimensions on thin-section MDCT pose some advantages over visual perception in the assessment of diffuse airway disease. Qualitative airway morphology assessment is highly subjective, reader dependent, and associated with a high interobserver variability.[28,29] Dedicated software tools now allow semiautomatic or fully automatic measurements of the bronchial tree down to the subsegmental level.[28] Quantitative indices of airway morphology comprise the LA, inner and outer airway diameters, WT, wall area, wall attenuation values, airway segment lengths, airway taper

TABLE 3. Generation-based Correlation Analysis of TD With PFT

	2			5			7		
Generation	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**
TD vs.									
FEV1%	**0.38**	**−0.53**	−0.11	0.10	−0.05	**−0.86***	0.12	0.31	**−0.74***
PEF%	**0.66***	**−0.50**	−0.14	0.38	−0.02	**−0.61**	0.54	0.14	**−0.70***
MEF50%	**0.34**	**−0.51**	−0.14	0.21	−0.04	**−0.87***	0.06	0.35	**−0.72***
MEF25%	**0.25**	**−0.48**	−0.12	0.11	−0.10	**−0.78***	0.04	0.34	**−0.70***
R_{tot}%	**−0.52**	—	−0.05	−0.33	—	**0.74***	−0.51	—	**0.77***
VC%	**0.45**	**−0.48**	−0.22	0.17	−0.17	**−0.71***	0.29	0.22	**−0.68***
RV%	**−0.06**	**0.48**	0.21	−0.17	0.04	**0.43**	−0.04	−0.38	**0.56**
TLC%	**0.27**	**0.21**	0.21	−0.15	−0.11	**0.04**	0.13	−0.31	**0.12**
n	18-22	12	12-16	18-22	14	12-16	16-20	13	12-16

Correlation of normalized TD with results from PFT in the adult control group (Normal ≥ 18) and CF lung disease patient cohorts (CF < 18 and CF ≥ 18). The table shows a summary of calculated Spearman rank order coefficients (r_s) for selected airway generations, that is, second, fifth, and seventh, with indices of PFT in the control group Normal ≥ 18, as well as in CF < 18 and CF ≥ 18 groups. Columns with relevant correlations are highlighted in bold letters. Full correlation data are provided as an online supplement.

*$P < 0.05/5 = 0.01$ (Bonferroni correction with 5 generations tested for each parameter).

TABLE 4. Generation-based Correlation Analysis of LA With PFT

	2			3			7		
Generation	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**
LA vs.									
FEV1%	**0.60***	**−0.64**	0.06	**0.44**	**−0.49**	0.08	0.11	0.16	**−0.70***
PEF%	**0.67***	**−0.64**	−0.04	**0.49**	**−0.38**	0.07	0.42	0.18	**−0.70***
MEF50%	**0.46**	**−0.66**	−0.02	**0.31**	**−0.56**	0.12	0.08	0.22	**−0.74***
MEF25%	**0.34**	**−0.57**	−0.06	**0.22**	**−0.69***	−0.02	0.09	0.17	**−0.75***
R_{tot}%	**−0.68***	—	−0.26	**−0.53**	—	−0.17	−0.42	—	**0.68**
VC%	**0.58***	**−0.59**	0.00	**0.53**	**−0.33**	0.02	0.22	0.09	**−0.62***
RV%	**−0.19**	**0.61**	0.11	**−0.06**	**0.53**	0.14	−0.23	−0.19	**0.54**
TLC%	**0.34**	**0.36**	0.22	**0.37**	**0.37**	0.14	−0.03	−0.30	**0.22**
n	18-22	12	12-16	18-22	14	12-16	16-20	13	12-16

Correlation of normalized LA with results from PFT in the adult control group (Normal ≥ 18) and CF lung disease patient cohorts (CF < 18 and CF ≥ 18). The table shows a summary of calculated Spearman rank order coefficients (r_s) for selected airway generations, that is, second, third, and seventh, with indices of PFT in the control group Normal ≥ 18, as well as in CF < 18 and CF ≥ 18 patients. Columns with relevant correlations are highlighted in bold letters. Full correlation data are provided as an online supplement.

*$P < 0.05/5 = 0.01$ (Bonferroni correction with 5 generations tested for each parameter).

TABLE 5. Generation-based Correlation Analysis of WT With PFT

	2			5			7		
Generation	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**	**Normal ≥ 18**	**CF < 18**	**CF ≥ 18**
WT vs.									
FEV1%	−0.12	−0.17	−0.31	−0.12	0.12	**−0.90***	−0.03	0.36	−0.57
PEF%	0.25	−0.28	−0.33	0.05	0.05	**−0.72***	0.23	0.11	−0.58
MEF50%	0.06	−0.29	−0.31	−0.06	0.11	**−0.90***	−0.05	0.36	−0.44
MEF25%	0.00	−0.20	−0.39	−0.20	0.09	**−0.83***	−0.05	0.42	−0.31
R_{tot}%	−0.13	—	0.33	−0.01	—	**0.84***	−0.19	—	0.74*
VC%	0.02	0.01	−0.31	0.00	−0.06	**−0.74***	0.17	0.31	−0.59
RV%	−0.20	0.25	0.06	0.08	−0.12	**0.51**	0.09	−0.45	0.54
TLC%	−0.09	0.34	−0.15	−0.13	−0.15	**−0.02**	0.19	−0.30	0.08
n	18-22	12	12-16	18-22	14	12-16	16-20	13	12-16

Correlation of normalized WT with results from PFT in the adult control group (Normal ≥ 18) and CF lung disease patient cohorts (CF < 18 and CF ≥ 18). The table shows a summary of calculated Spearman rank order coefficients (r_s) for selected airway generations, that is, second, fifth, and seventh, with indices of PFT in the control group Normal ≥ 18, as well as in CF < 18 and CF ≥ 18 patients. Columns with relevant correlations are highlighted in bold letters. Full correlation data are provided as an online supplement.

*$P < 0.05/5 = 0.01$ (Bonferroni correction with 5 generations tested for each parameter).

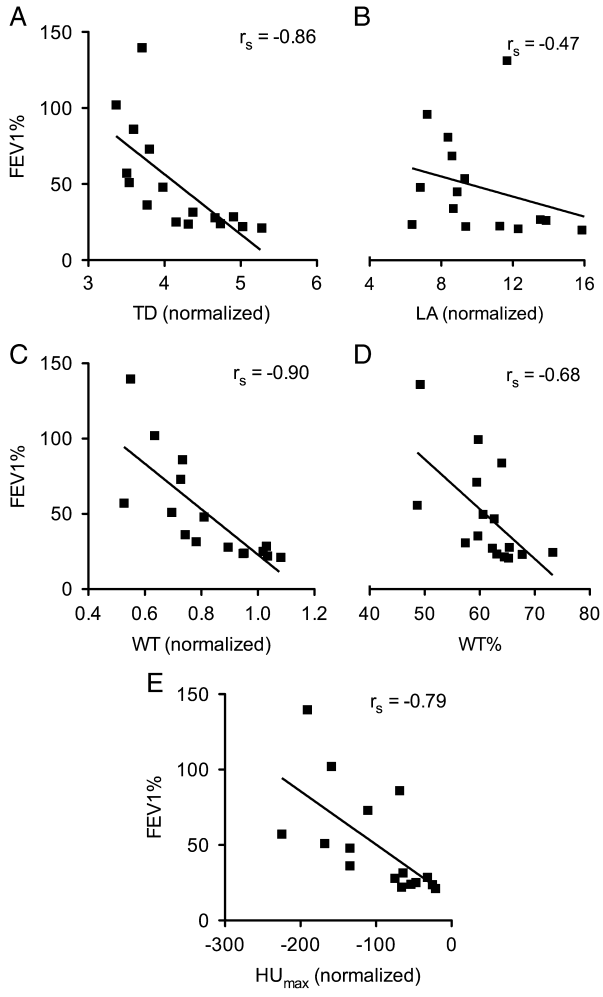

FIGURE 4. A–E, Selected results from the correlation analysis are displayed for fifth-generation airways in adult CF patients (CF ≥ 18) only. The Spearman rank order coefficient (r_s) is given for each parameter: TD, LA, WT, WT as a percentage of TD (WT%), and mean maximum wall attenuation (HU_{max}).

indices, and airway branching patterns. Nevertheless, a consensus on which airway parameter should be measured best in any airway disease is pending.[28]

Limitations of computational airway analysis are mainly inherent to CT. Small differences in attenuation values and only discrete alterations of the lumen configuration complicate the differentiation of wall thickening and mucus obstruction and render automatic and manual measurements imprecise. Currently, MDCT resolution precludes anatomic visualization of bronchi smaller than 200 to 300 μm. These are usually distal to the seventh to ninth generation.[29] In our study the IBM was used, which proved to show more precise results for airways smaller than 1 mm compared with the traditional full-width at half-maximum method.[20] Despite the advanced registration algorithm, the analysis of distal bronchi is still biased, because dilated airways are detected preferentially. This is also demonstrated by our results, as we could analyze more airways distal to the fifth generation in CF patients than in controls, likely because of a lack of bronchial tapering, that is, bronchiectasis. This systematic bias applies to both CF patients and controls, and TD in CF patients may even be underestimated because it will be compared only against the largest airways of the controls. This is supported by the comparison with published normal values for TD and WT. Lobar and segmental airways should be 5 to 8 mm wide with a WT of 1.5 mm. This compares well to our results (see Table, Supplemental Digital Content 1, http://links.lww.com/JTI/A35). Subsegmental bronchi and bronchioles have a diameter of 1 mm and a WT of 0.2 to 0.3 mm.[30] Thus, airways after the fifth generation in adult controls had a larger diameter and WT than expected. However, no in vivo validation studies including MDCT-derived normal values are available for comparison yet.

How far airways detected after the fifth generation are representative of their generation is not clear. One must keep in mind that we analyzed averaged parameters from multiple measurements of multiple airways per generation; hence, the contribution of an individual airway segment to the results is relatively low. Even for generations 7 to 11 the software could analyze a sizeable number of airway segments (Table 2). Previously published work often used single slice measurements on only few or even single airways in similar correlation analyses,[28,31] and hence the added value of automated measurements is to provide data that are potentially more representative. Airways detected distal to the 11th generation have been excluded from the analysis in the present study because too few airway segments were detected.

For other chronic obstructive lung diseases such as COPD and asthma, studies have already been conducted to manually and automatically assess airway dimensions with MDCT. Wall thickening in MDCT directly correlated with the severity of airflow obstruction measured with PFT[31–33] and

TABLE 6. Generation-based Correlation Analysis of Airway Dimensions With Patient Age

	2		3		5		7		9	
Generation	**Normal**	**CF**	**Normal**	**CF**	**Normal**	**CF**	**Normal**	**CF**	**Normal**	**CF**
TD	**0.57***	**0.67***	**0.63***	**0.67***	−0.02	**0.46***	0.29	0.36	−0.34	0.32
LA	**0.62***	**0.63***	**0.56***	**0.63***	0.27	**0.52***	0.28	**0.67***	−0.29	**0.60***
WT	−0.08	**0.49***	0.12	**0.51***	−0.42	0.26	0.01	−0.14	−0.18	−0.16
WT%	−0.59*	**−0.51***	−0.31	−0.26	−0.45*	−0.31	−0.21	**−0.50***	−0.01	**−0.49***
HU_{max}	0.00	0.18	−0.20	0.27	**−0.71***	0.06	−0.40	−0.35	−0.23	−0.28

Correlation of non-normalized values of TD, LA, WT, relative WT (WT%), and mean maximum wall attenuation (HU_{max}) with patient age across both age groups (ie, < 18 and ≥ 18) in the control group Normal, as well as in CF lung disease patients (CF). The table shows a summary of calculated Spearman rank order coefficients (r_s) for selected airway generations, that is, second, third, fifth, seventh, and ninth. Cells with relevant correlations are highlighted in bold letters.

*$P < 0.05/5 = 0.01$ (Bonferroni correction with 5 generations tested for each parameter).

with the WT measured in biopsy samples.[34] Subsequently, the group of Montaudon et al[35] measured bronchial wall area and LA on MDCT of 16 patients suffering from CF and correlated these results with PFT. They used a Laplacian of Gaussian algorithm that required semiautomatic editing and performed 1 measurement per bronchus.[35,36] Considering the complexity of the airways, the heterogenous distribution of CF lung disease, and the applicability in clinical routine, a need for automatic segmentation and measurements of the whole lung is evident. All data from airway measurements presented in this study were acquired in a user-independent manner by simply subjecting routine reconstructions of CT images to the dedicated postprocessing software. One drawback of this method is that airway generations based on bifurcations are not exactly equal to the anatomic generations, especially in the right lung.

Montaudon et al[35] found no difference in correlations with PFT when airway parameters were compared between selected dilated and nondilated bronchi, which required user interaction. Therefore, our approach was to analyze averaged airway parameters for each generation separately. The latter approach also resembles physiology, as pulmonary function is also a result of the ensemble of multiple functional units—that is, conducting airways and alveoli. Importantly, mucus did not impair automatic bronchial registration algorithms for airways proximal to the fifth generation in a relevant manner, thus allowing representative quantifications throughout many generations. Mild respiratory artifacts did not interrupt the segmentation process either.

Our study demonstrates that TD was largely increased for third and fourth airway generations in pediatric and for first to ninth in adult CF patients. This is consistent with bronchiectasis. We also found significantly more airways distal to the fifth generation in pediatric and adult CF patients compared with controls, which indicates a lack of bronchial tapering and therefore bronchiectasis. We speculate that bronchial dilatation may commence in third-generation and fourth-generation airways, progressing to more distal airways during aging. However, the average LA of each airway generation remained unchanged. This may be explained by significant wall thickening in pediatric and adult CF patients and by an increased WT to TD ratio. Previous reports have shown comparable[37] but also conflicting results[35,38,39] likely depending on the patient cohort composition. These data may also be reconciled by the fact that bronchiectasis usually affects airway segments in a discontinuous manner. Peripheral dilatation of airway segments cannot be subject to automatic detection if the connection to the more proximal airways is not visualized by MDCT or is obstructed by mucus. Interestingly, our data indicate that increased LA of the intermediate airways is associated with older patient age and a deterioration of FEV1%.

The major physiological airway resistance in healthy individuals is located between the mouth and segmental bronchi, that is, the third generation in this study, when breathing orally, which renders PFT insensitive for early pathologic changes of more distal airways.[40] This is likely to be reflected by moderate correlations for TD and LA of proximal airways with FEV1% and R_{tot} in the adult control group, whereas in pediatric CF patients already moderate negative correlations with FEV1% were found. In adult CF patients, FEV1% as a marker of global lung function showed strong negative correlations with regional TD, LA, and WT of the intermediate airways. In contrast, total airway resistance is also strongly associated with the TD, LA, and WT of the same generations in adult CF patients. The data are consistent with the previous report by Montaudon et al.[35] However, this publication did not compare correlations among different airway generations. These findings may indicate that the major site of airflow obstruction in chronic CF is concentrated to the intermediate and distal conducting airways and that with increasing WT of these airways pulmonary function declines. Correspondingly, correlation coefficients for TD and WT were best with MEF50% when compared with PEF% and MEF25%. MEF50% is considered to reflect airflow in the intermediate conducting airways, supporting the above-mentioned interpretation. The RV also seems to increase together with TD, LA, and WT of the intermediate airways only in adult CF patients. However, we are aware that the software cannot measure the gross number of small airways distal to the seventh to ninth generation, which comprise a major part of airflow obstruction in patients with CF or COPD.[41] Nevertheless, the intermediate airways as discussed above are affected by similar pathophysiological processes and may serve as a surrogate for more distal airways.[42] In COPD, for example, it has also been demonstrated that therapeutic interventions lead to a detectable increase in caliber mainly of the bronchi from the fourth to sixth generations as measured on MDCT.[43]

Patient growth will on average lead to a redistribution of mucus to the more distal airways and may in part explain the shift in airway resistance in adult CF patients. It is noteworthy that similar results were recently derived from a mouse model of CF lung disease.[44] We speculate that this is represented by the high correlations between FEV1% and TD in intermediate airways of CF $\geq$ 18 patients. One limitation of our study in this respect are the limited data available for pediatric CF patients and controls and that these groups comprise a broad age range. Thus, we performed additional correlation analyses for patient age. In our population, an increase in TD of the intermediate airways and in LA of the intermediate to distal airways is associated with age in CF patients but not in controls. At the same time WT of the proximal airways seems to increase with age in CF patients. These results indicate disease progression with bronchiectasis in CF, too.

Because of the stable clinical course of our patient population, no data are available to date to correlate the results from airway analysis with patient survival. As we have shown good correlations of TD, LA, and WT with FEV1 and FEV1%, with the latter still being the most important prognostic marker,[16] we speculate that airway dimensions will also have prognostic significance.

In summary, our results demonstrate that fully automatic airway analysis in CF lung disease is feasible and generates reliable data for regional bronchial dilatation and wall thickening, which correlate with impairment in pulmonary function. We suggest that TD, LA, and WT are the most suitable parameters for assessing CF airway disease. Consecutively, these parameters for intermediate airways should be further evaluated for their applicability as surrogates in disease progression, patient outcome, and therapy response.

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