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Appendix E1

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Table E1. Number of subjects according to scanner make and convolution kernels.

	Number of subjects		Number of subjects
Filtered back projection		Iterative reconstruction	
General Electric STANDARD	441	General Electric STANDARD + ASIR100	438
Siemens B31f	493	Siemens I31f	202
Siemens Bf40d	235		
Philips B	36		

Table E2. Number of scans by manufacturer and model.

GE	441/1205 (37%)
Discovery CT750 HD	209
LightSpeed VCT	135
LightSpeed VCT64	44
Revolution CT	53
Siemens	728/1205 (60%)
Definition	28
Definition AS	154
Definition AS+	167
Definition Edge	2
Force	235
Sensation 64	142
Philips	36/1205 (3%)
Brilliance64	35
iCT 256	1

Appendix E2

Volume Adjustment

The volume adjustment model assumed spatially uniform volume changes and thus spatially uniform density changes in the lungs (ie, mass-preserving).

Application of the volume adjustment model to a CT scan is performed using the equation below:

$$CT_{VA}(i) = \left(\frac{V_{actual}}{V_{predicted}} CT_{original}(i) + 1000\,HU \right) - 1000\,HU$$

,

where $CT_{original}(i)$ is the HU value at voxel i in the nonadjusted CT scan, $CT_{VA}(i)$ is the HU value at voxel i in the volume adjusted CT scan, V_{actual} is the lung volume obtained from the CT scan, and $V_{predicted}$ is the predicted volume. The equation used to calculate patient specific predicted lung volume was developed from the Multi-Ethnic Study of Atherosclerosis (MESA) in Hoffman et al (18, Table 4). It depends on age, height, sex, race/ethnicity, and body mass index. Pompe et al (1) validated the MESA equation for COPDGene and found that it was suitable.

Reproducibility Coefficient

The reproducibility coefficients for Perc15 and LAA-950 were computed using two different methods, which are outlined in Obuchowski et al. Perc15 uses within-subject variance (wSD) method

$$wSD^2 = \frac{\sum_n^N \left(x_n^{FD} - x_n^{RD}\right)^2}{2N},$$

where n is an individual subject and N is the total number of subjects.

Because differences in LAA-950 vary as a function of the average LAA-950 value (see Fig E1), a significant ratio between measurements is calculated using the within-subject coefficient of variation (wCV) rather than the wSD

$$wCV^2 = \frac{\sum_n^N \frac{\left(x_n^{FD} - x_n^{RD}\right)^2}{2\mu_n^2}}{N}, \mu_n = \frac{x_n^{FD} + x_n^{RD}}{2},$$

where n is an individual subject and N is the total number of subjects.

The reproducibility coefficients (RDC) are computed using the following equations

$$RDC_{perc15} = 2.77\sqrt{wSD^2}$$

$$RDC_{LAA-950} = 2.77\sqrt{wCV^2}.$$

Thus, the RDCs should be interpreted as follows

$$-RDC_{perc15} < Perc15_{follow-up} - Perc15_{baseline} < RDC_{perc15}: \text{No change}$$

$$-RDC_{perc15} > Perc15_{follow-up} - Perc15_{baseline}: \text{True regression}$$

$$Perc15_{follow-up} - Perc15_{baseline} > RDC_{perc15}: \text{True progression}$$

$$-RDC_{LAA-950} < \frac{LAA_{baseline} - LAA_{follow-up}}{0.5*(LAA_{baseline} + LAA_{follow-up})} < -RDC_{LAA-950}: \text{No change}$$

$$-RDC_{LAA-950} > \frac{LAA_{baseline} - LAA_{follow-up}}{0.5*(LAA_{baseline} + LAA_{follow-up})}: \text{True regression}$$

$$\frac{LAA_{baseline} - LAA_{follow-up}}{0.5*(LAA_{baseline} + LAA_{follow-up})} :> RDC_{LAA-950} : \text{True progression}$$

Python code for computing the reproducibility coefficients is shown below:

```
#x_fd is a numpy.ndarray containing full-dose measurements
#x_rd is a numpy.ndarray containing reduced-dose measurements
import numpy as np
def compute_within_subject_variance_RDC (x_fd, x_rd):
n = len (x_fd)
difference = x_fd-x_rd
dsum = (difference * difference).sum ()
dsum = dsum/(2*N)
return 2.77*np.sqrt (dsum)
def compute_within_subject_coef_var_RDC (x_fd, x_rd):
n = len (x_fd)
difference = x_fd-x_rd
mean = 0.5 * (x_fd + x_rd)
dsum = ((difference * difference)/(2*mean*mean)).sum ()
dsum = dsum/N
return 2.77*np.sqrt (dsum)
```

Table E3. LAA-950 reproducibility coefficients, limits of agreement, and biases for each comparison between FD and RD scans.

Dose Comparison	LAA-950 reproducibility coefficient	LAA-950 limits of agreement	LAA-950 bias	*P* value
No volume adjustment				
FD vs RD	242.19 ± 4.40	6.09 ± 0.23	4.84% ± 0.17%	0.001
FD vs RD-MF	106.40 ± 4.68	2.60 ± 0.25	0.59% ± 0.08%	0.001
FD vs RD-IR	91.53 ± 6.31	2.16 ± 0.28	0.19% ± 0.09%	0.001
Volume Adjustment Applied				
FD vs RD	248.84 ± 4.06	5.37 ± 0.22	4.76% ± 0.15%	0.001
FD vs RD-MF	99.91 ± 4.30	1.99 ± 0.14	0.52% ± 0.06%	0.001
FD vs RD-IR	79.77 ± 4.94	1.81 ± 0.20	0.19% ± 0.07%	0.001

FD vs RD comparisons were between 1205 subjects, while FD vs RD-IR were between 640 subjects. Note that the repeatability coefficient for LAA-950 is expressed as a percentage increase rather than measurement difference (see Appendix E3 for details).

Table E4. Perc15 reproducibility coefficients, limits of agreement, and biases for comparisons between FD and RD scans for the subset of subjects that had iterative reconstructions available (*n* = 640).

Dose Comparison	Perc15 reproducibility coefficient (HU)	Perc15 limits of agreement (HU)	Perc15 bias (HU)	*P* value
No volume adjustment				
FD vs RD	34.37 ± 2.18	22.33 ± 3.69	13.32 ± 0.89	<0.001
FD vs RD-MF	22.16 ± 3.82	22.10 ± 3.89	0.82 ± 0.87	0.073
FD vs RD-IR	22.48 ± 3.92 HU	21.89 ± 3.83	−2.63 ± 0.87	<0.001
Volume Adjustment Applied				
FD vs RD	30.61 ± 0.83	10.48 ± 0.63	14.68 ± 0.42	<0.001
FD vs RD-MF	8.31 ± 0.52	7.15 ± 0.48	2.16 ± 0.28	<0.001
FD vs RD-IR	7.10 ± 0.52 HU	6.49 ± 0.56	−1.47 ± 0.26	<0.001

Table E5. LAA-950 reproducibility coefficients, limits of agreement, and biases for comparisons between FD and RD scans for the subset of subjects that had iterative reconstructions available (*n* = 640).

Dose Comparison	LAA-950 reproducibility coefficient (%)	LAA-950 limits of agreement (%)	LAA-950 bias (%)	*P* value
No volume adjustment				
FD vs RD	256.56 ± 5.62	6.32 ± 0.33	−4.57 ± 0.25	<0.01
FD vs RD-MF	120.31 ± 6.24	2.65 ± 0.25	−0.79 ± 0.10	0.07
FD vs RD-IR	91.53 ± 6.31	2.16 ± 0.28	0.19 ± 0.09	<0.01
Volume Adjustment Applied				
FD vs RD	263.19 ± 5.32	5.30 ± 0.29	−4.50 ± 0.20	<0.01
FD vs RD-MF	114.51 ± 6.13	2.00 ± 0.17	−0.69 ± 0.08	<0.01
FD vs RD-IR	79.77 ± 4.94	1.81 ± 0.20	0.19 ± 0.07	<0.01

Note that the repeatability coefficient for LAA-950 is expressed as a percentage increase rather than measurement difference (see Appendix E3 for details).

Table E6. Differences of longitudinal changes (baseline to five-year follow-up) in Perc15 between FD and RD protocols.

ΔPerc15	Mean	Standard Deviation	Standard Error
$(FD_{follow\text{-}up}\text{-}FD_{baseline})$ - $(RD_{follow\text{-}up}\text{-}\ FD_{baseline})$	15.0 HU	5.4 HU	0.22
$(FD_{follow\text{-}up}\text{-}FD_{baseline})$ - $(RD\text{-}MF_{follow\text{-}up}\text{-}\ FD_{baseline})$	2.2 HU	3.7 HU	0.16
$(FD_{follow\text{-}up}\text{-}FD_{baseline})$ - $(RD\text{-}IR_{follow\text{-}up}\text{-}\ FD_{baseline})$	1.5 HU	3.4 HU	0.14

Table E7. Receiver operating curve characteristic AUCs with *P* values in comparison to the FD scan, J-statistic values, and optimal prediction thresholds (±95CI) for LAA-950 based prediction of spirometrically defined COPD diagnosis and at least one annual exacerbation using different dose and noise filtering methods.

Dose Comparison	Volume adjustment applied			No volume adjustment		
	ROC-AUC (*P* value vs FD scan)	J-statistic	Optimal threshold (%)	ROC-AUC	J-statistic	Optimal threshold (%)
COPD Diagnosis						

FD	0.796 ± 0.043 (*P* = NA)	0.516 ± 0.071	1.44 ± 0.60	0.821 ± 0.040 (*P* = NA)	0.553 ± 0.070	1.94 ± 0.79
RD	0.771 ± 0.042 (*P* = .02)	0.465 ± 0.075	8.36 ± 1.13	0.787 ± 0.042 (*P* < .001)	0.507 ± 0.074	8.84 ± 1.24
RD-MF	0.784 ± 0.042 (*P* = .13)	0.492 ± 0.074	3.05 ± 0.69	0.801 ± 0.041 (*P* = .001)	0.529 ± 0.073	3.41 ± 0.82
RD-IR	0.754 ± 0.046 (*P* < .001)	0.445 ± 0.074	1.68 ± 0.81	0.790 ± 0.043 (*P* < .001)	0.517 ± 0.074	2.06 ± 0.54
At least one annual exacerbation						
FD	0.647 ± 0.064 (*P* = NA)	0.323 ± 0.100	1.44 ± 0.53	0.643 ± 0.066 (*P* = NA)	0.299 ± 0.097	1.72 ± 1.44
RD	0.618 ± 0.063 (*P* = .08)	0.231 ± 0.093	7.97 ± 4.15	0.611 ± 0.063 (*P* = .04)	0.220 ± 0.092	9.67 ± 6.57
RD-MF	0.618 ± 0.065 (*P* = .01)	0.239 ± 0.096	3.22 ± 3.05	0.613 ± 0.066 (*P* = .01)	0.234 ± 0.096	4.08 ± 4.56
RD-IR	0.615 ± 0.066 (*P* = .03)	0.261 ± 0.100	1.95 ± 1.34	0.618 ± 0.066 (*P* = .03)	0.244 ± 0.097	2.26 ± 3.20

Due to this being a direct comparison between RD scan noise reduction techniques, only scans that had IR were included in the analysis.

Table E8. Spearman correlations between CTD measurements and GOLD stage using different dose and noise filtering methods.

Dose Comparison	**Volume adjustment applied**		**No volume adjustment**	
	r	***P* value**	**r**	***P* value**
Perc15				
FD	−0.41 ± 0.06	<0.001	−0.43 ± 0.06	<0.001
RD	−0.41 ± 0.06	<0.001	−0.41 ± 0.06	<0.001
RD-MF	−0.40 ± 0.06	<0.001	−0.41 ± 0.06	<0.001
RD-IR	−0.40 ± 0.08	<0.001	−0.43 ± 0.08	<0.001
LAA-950				
FD	0.50 ± 0.05	<0.001	0.49 ± 0.05	<0.001
RD	0.45 ± 0.06	<0.001	0.44 ± 0.06	<0.001
RD-MF	0.49 ± 0.05	<0.001	0.47 ± 0.06	<0.001
RD-IR	0.45 ± 0.08	<0.001	0.48 ± 0.08	<0.001

Only subjects with GOLD stage 0–4 were used for this analysis, resulting in 913 total subjects for FD, RD, and RD-MF scans and 497 subjects for RD-IR scans.