Supplementary Table T1: Characteristics of the Michigan cohort

Michigan Cohort	Controls	FPLD	Generalized Lipodystrophy	APL
n	70	43	3	2
Gender (M:F)	28M:42F	5M:38F	F, M, F	M, F
Age (years)	52 (33-61)	49 (36-58)	13, 15, 19	24, 40
Race & Ethnicity				
White (W)	55 (78%)	37 (86%)	B, W, W	W, W
Black (B)	9 (13%)	1 (2%)		
Other	6 (9%)	5 (12%)		
Hispanic (Y or N)	0 (0%)	3 (7%)	N, N, N	N, N
Genetic confirmation	NA	19 *LMNA* (44%) 3 *PPARG* (7%) 1 *POLD1* (2%) 20 none identified* (47%)	1 *LMNA* p.T10I 2 none identified*	2 none identified*
BMI (Kg/m^2)	33.3 (31.0-36.7)	30.2 (25.1-33.3)	14.7, 19.2, 21.3	24.0, 29.5
FFMI (Kg/m^2)	19.8 (18.3-21.8)	19.9 (17.9-22.4)	13.5, 13.3, 20.0	20.7, 20.8
FMI (Kg/m^2)	14.0 (11.7-16.5)	9.1 (5.8-12.7)	1.2, 5.9, 1.4	3.4, 8.7
Total Fat Free Mass (Kg)	57.5 (49.8-65.0)	54.2 (46.6-60.7)	37.0, 40.9, 58.9	66.0, 58.4
Arms tissue %fat (%)	38.0 (30.6-42.5)	28.5 (22.0-35.8)	10.2, 6.1, 5.7	5.1, 14.5
Legs tissue %fat (%)	38.8 (30.5-44.5)	22.5 (17.7-28.6)	11.0, 9.1, 6.6	17.9, 35.3
Trunk tissue %fat (%)	47.0 (42.4-50.5)	39.7 (29.7-46.1)	5.4, 6.7, 5.1	4.8, 31.5
Total tissue %fat (%)	42.5 (37.1-46.5)	33.1 (24.8-39.0)	8.8, 8.4, 6.7	14.5, 31.0
Android tissue %fat (%)	50.5 (46.0-54.1)	41.1 (30.3-48.8)	5.3, 7.6, 4.5	17.4, 33.9
Gynoid tissue %fat (%)	41.8 (34.0-48.0)	28.6 (22.4-34.1)	7.9, 5.6, 5.7	17.5, 33.4
FMR	1.24 (1.07-1.47)	1.64 (1.51-1.98)	0.49, 0.74, 0.77	0.83, 0.89
Android / Gynoid Ratio	1.22 (1.07-1.35)	1.33 (1.22-1.51)	0.67, 1.36, 0.79	0.99, 1.01
Arms %fat / Legs %fat	0.98 (0.89-1.07)	1.21 (1.12-1.36)	0.93, 0.67, 0.86	0.28, 0.41

AGL, Acquired Generalized Lipodystrophy; APL, Acquired Partial Lipodystrophy; BMI, Body Mass Index; CGL, Congenital Generalized Lipodystrophy; FFMI, Fat Free Mass Index; FMI, Fat Mass Index; FMR, Fat Mass Ratio (Trunk tissue %fat/Legs tissue %fat); FPLD, Familial Partial Lipodystrophy; *LMNA*, Lamin A/C gene; *POLD1*, Polymerase (DNA-Directed), Δ1, Catalytic Subunit gene; *PPARG;* Peroxisome Proliferator-Activated Receptor-γ. Data presented as *Median (Interquartile range)* or *count (percentage)* if n>3, and individual values separated by commas if n≤3. *: No confirmed pathogenic genes were identified.

Supplementary Table T2: Characteristics of the NIH cohort

NIH Cohort	Controls	FPLD	Generalized Lipodystrophy
n	56	14	13
Gender (M:F)	8M:48F	2M:12F	4M:9F
Age	44 (28-54)	43 (31-50)	20 (18-32)
Race & Ethnicity			
White	51 (91%)	14 (100%)	6 (46%)
Black	0 (0%)	0 (0%)	2 (15%)
Other	5 (9%)	0 (0%)	5 (39%)
Hispanic	4 (7%)	0 (0%)	4 (31%)
Genetic confirmation	NA	3 *LMNA* (21%) 3 *PPARG* (21%) 8 none identified* (57%)	7 *AGPAT2* (54%) 2 *BSCL2* (15%) 1 *PCYT1A* (8%)† 3 none identified*‡ (23%)
BMI (Kg/m^2)	24.9 (22.7-39.2)	26.6 (26.0-30.8)	19.0 (17.6-21.6)
FFMI (Kg/m^2)	17.4 (16.0-19.5)	19.4 (18.3-20.7)	17.2 (16.0-19.2)
FMI (Kg/m^2)	8.4 (6.2-19.7)	6.9 (5.9-11.2)	1.2 (1.1-1.6)
Total Fat Free Mass (Kg)	48.3 (43.7-56.6)	56.8 (50.8-57.6)	50.2 (45.3-56.9)
Arms tissue %fat (%)	36.7 (28.5-49.2)	26.5 (20.0-37.6)	9.4 (7.0-11.5)
Legs tissue %fat (%)	39.5 (31.8-48.4)	19.4 (16.6-23.3)	7.8 (7.4-8.9)
Trunk tissue %fat (%)	36.1 (27.3-54.9)	34.0 (28.2-45.4)	6.0 (4.5-6.8)
Total tissue %fat (%)	37.1 (28.2-51.0)	28.9 (22.8-37.8)	7.5 (7.2-9.0)
Android tissue %fat (%)	39.0 (26.8-57.7)	36.0 (29.3-46.5)	4.7 (4.1-5.3)
Gynoid tissue %fat (%)	42.0 (33.9-52.6)	24.9 (17.6-31.8)	5.7 (4.9-6.6)
FMR (Trunk %fat/Legs %fat)	1.00 (0.83-1.16)	1.83 (1.48-2.10)	0.70 (0.60-0.87)
Android/Gynoid Ratio	0.99 (0.76-1.11)	1.45 (1.35-1.61)	0.84 (0.79-0.85)
Arms %fat/Legs %fat	0.95 (0.90-1.01)	1.35 (1.19-1.45)	1.10 (0.91-1.31)

AGL, Acquired Generalized Lipodystrophy; *AGPAT2*, 1-Acylglycerol-3-Phosphate O-Acyltransferase 2; BMI, Body Mass Index; *BSCL2,* Berardinelli-Seip Congenital Lipodystrophy 2 gene; CGL, Congenital Generalized Lipodystrophy; FFMI, Fat Free Mass Index; FMI, Fat Mass Index; FMR, Fat Mass Ratio (Trunk tissue %fat/Legs tissue %fat); FPLD, Familial Partial Lipodystrophy; *LMNA*, Lamin A/C gene; *PCYT1A*, Phosphate Cytidylyltransferase 1, Choline, α-Isoform; *PPARG;* Peroxisome Proliferator-Activated Receptor-γ. Data presented as Median (Interquartile range) or count (percentage) if n>3, and individual values separated by commas if n≤3. *: No confirmed pathogenic mutations were identified. †: Diagnosis is *PCYT1A*-linked lipodystrophy ‡: One patient is thought to be *BSCL2* based on phenotype and lab results, but this has not been confirmed by genetic test yet. The other two are clinically diagnosed with Acquired Generalized Lipodystrophy.

SUPPLEMENTARY DATA

Supplementary Table T3: Frequencies of qualitative features observed in females

Females	All controls	All FPLD	*p*-value	Non-obese controls (BMI<30 kg/m^2)	Generalized Lipodystrophy	*p*-value	FPLDX	FPLD2	*p*-value
n	90	50		32	11		29	21	
Features									
Neck hypertrophy	27 (21-41%)	37 (60-85%)	<0.001	1 (0-16%)	0 (0-28%)	1.00	20 (49-85%)	17 (58-95%)	0.52
Abdominal distention	8 (4-17%)	16 (20-47%)	<0.001	0 (0-11%)	0 (0-28%)	1.00	13 (26-64%)	3 (3-36%)	0.032
Mons pubis fat hypertrophy	0 (0-4%)	31 (47-75%)	<0.001	0 (0-11%)	7 (31-89%)*	<0.001	10 (18-54%)	21 (84-100%)	<0.001
Calf hypertrophy	15 (10-26%)	17 (21-49%)	0.023	2 (1-21%)	0 (0-28%)	1.00	7 (10-44%)	10 (26-70%)	0.13
Local absence or presence of residual fat									
Arms and shoulders	0 (0-4%)	17 (21-49%)	<0.001	0 (0-11%)	11 (72-100%)	<0.001	2 (1-23%)	15 (48-89%)	<0.001
Forearms	15 (10-26%)	43 (73-94%)	<0.001	6 (7-36%)	11 (72-100%)	<0.001	22 (56-90%)	21 (84-100%)	0.017
Flanks (Abdomen)	1 (0-6%)	19 (25-53%)	<0.001	1 (0-16%)	11 (72-100%)	<0.001	0 (0-12%)	19 (70-99%)	<0.001
Hips	0 (0-4%)	25 (36-64%)	<0.001	0 (0-11%)	11 (72-100%)	<0.001	8 (13-47%)	17 (58-95%)	<0.001
Lateral thighs	2 (0-8%)	43 (73-94%)	<0.001	0 (0-11%)	11 (72-100%)	<0.001	22 (56-90%)	21 (84-100%)	0.017
Medial thighs	0 (0-4%)	28 (41-70%)	<0.001	0 (0-11%)	11 (72-100%)	<0.001	8 (13-47%)	20 (76-99%)	<0.001
Calves	2 (0-8%)	41 (69-91%)	<0.001	0 (0-11%)	11 (72-100%)	<0.001	20 (49-85%)	21 (84-100%)	0.006

Fat shadows were visually inspected and grouped according to diagnoses. Absence of subcutaneous fat was assessed in the arms, forearms, flanks (abdomen), hips, lateral thighs, medial thighs, and calves. Hypertrophic fat depots in the neck and mons pubis were assessed. Hypertrophic fat in the mons pubis was defined as presence of high signal corresponding to this area and absence of subcutaneous fat in the medial thighs (historically described as labial hypertrophy or pseudohypertrophy by investigators to describe physical exam findings (1-3)). Certain features outside the fat distribution were also assessed to determine if these features could add to the overall diagnosis, such as abdominal distention and calf muscle hypertrophy. Abdominal distension was assessed based on the rounding of the abdominal wall. Calf muscle hypertrophy was determined indirectly by the shape of the subcutaneous fat outline. Evaluation of the qualitative features in the NIH patients was carried out only after all investigators were unblinded. P-values were calculated with Fisher's exact tes and data is presented as *count (95% CI of percentage)*. FPLD, Familial Partial Lipodystrophy; FPLD2, Familial Partial Lipodystrophy Type 2 (Dunnigan variety); FPLDX, a broad subgroup defined as all FPLD other than FPLD2; BMI, Body Mass Index; *: In FPLD, mons pubis fat hypertrophy was counted, while in Generalized Lipodystrophy patients, visualization of residual fat was counted.

SUPPLEMENTARY DATA

Supplementary Table T4: Frequencies of qualitative features observed in males

Males	All controls	All FPLD	Non-obese controls (BMI<30 kg/m^2)	Generalized Lipodystrophy	FPLDX	FPLD2
n	36	7	12	5	6	1
Features						
Neck hypertrophy	2 (1-19%)	4 (18-90%)	1 (0-38%)	0 (0-52%)	3 (12-88%)	1 (3-100%)
Abdominal distention	12 (19-51%)	5 (29-96%)	1 (0-38%)	0 (0-52%)	4 (22-96%)	1 (3-100%)
Calf hypertrophy	2 (1-19%)	2 (4-71%)	0 (0-26%)	0 (0-52%)	1 (0-64%)	1 (3-100%)
Local absence or presence of residual fat						
Arms and shoulders	0 (0-10%)	1 (0-58%)	0 (0-26%)	5 (48-100%)	1 (0-64%)	0 (0-98%)
Forearm	7 (8-36%)	5 (29-96%)	2 (2-48%)	5 (48-100%)	4 (22-96%)	1 (3-100%)
Flanks (Abdomen)	0 (0-10%)	1 (0-58%)	0 (0-26%)	5 (48-100%)	0 (0-46%)	1 (3-100%)
Hips	0 (0-10%)	1 (0-58%)	0 (0-26%)	5 (48-100%)	0 (0-46%)	1 (3-100%)
Lateral thigh	1 (0-15%)	2 (4-71%)	1 (0-38%)	5 (48-100%)	1 (0-64%)	1 (3-100%)
Medial thigh	1 (0-15%)	2 (4-71%)	1 (0-38%)	5 (48-100%)	1 (0-64%)	1 (3-100%)
Calves	3 (2-22%)	5 (29-96%)	0 (0-26%)	5 (48-100%)	4 (22-96%)	1 (3-100%)

Fat shadows were visually inspected and grouped according to diagnoses. Absence of subcutaneous fat was assessed in the arms, forearms, flanks (abdomen), hips, lateral thighs, medial thighs, and calves. Hypertrophic fat depots in the neck was assessed. Hypertrophic fat in the mons pubis was defined as presence of high signal corresponding to this area and absence of subcutaneous fat in the medial thighs (historically described as labial hypertrophy or pseudohypertrophy by investigators to describe physical exam findings (1-3)). Certain features outside the fat distribution were also assessed to determine if these features could add to the overall diagnosis, such as abdominal distention and calf muscle hypertrophy. Abdominal distension was assessed based on the rounding of the abdominal wall. Calf muscle hypertrophy was determined indirectly by the shape of the subcutaneous fat outline. Evaluation of the qualitative features in the NIH patients was carried out only after all investigators were unblinded. P-values were calculated with Fisher's exact tes and data is presented as *count (95% CI of percentage)*. FPLD, Familial Partial Lipodystrophy; FPLD2, Familial Partial Lipodystrophy Type 2 (Dunnigan variety); FPLDX, a broad subgroup defined as all FPLD other than FPLD2; BMI, Body Mass Index.

Supplementary Table T5: Diagnostic Accuracy of the Fat Shadow Method in a Stepwise Blinded Evaluation

A. MICHIGAN PREDICTIONS FOR NIH COHORT				
	Actual State			
Predictions	FPLD (+)	Control	Total	
FPLD (+)	12	0	12	Sensitivity: 86% (95%CI: 57-98%)
Control	2	56	58	Specificity: 100% (95%CI: 94-100%)
Total	14	56	70	
B. NIH PREDICTIONS FOR MICHIGAN COHORT				
	Actual State			
Predictions	FPLD (+)	Control	Total	
FPLD (+)	33	5	38	Sensitivity: 85% (95%CI: 69-94)
Control	6	63	69	Specificity: 94% (95%CI: 84-98)
Total	39	68	107	
C. CUMULATIVE FPLD PREDICTIONS				
	Actual State			
Predictions	FPLD (+)	Control	Total	
FPLD (+)	45	5	50	Sensitivity: 85% (95%CI: 72-93)
Control	8	119	127	Specificity: 96% (95%CI: 91-99)
Total	53	124	177	
D. INDEPENDENT INVESTIGATOR FPLD PREDICTIONS				
	Actual State			
Predictions	FPLD (+)	Control	Total	
FPLD (+)	39	2	41	Sensitivity: 75% (95%CI: 61-86)
Control	13	117	130	Specificity: 98% (95%CI: 94-99)
Total	52	119	171	
E. FPLD2 vs FPLDX&Controls				
	Actual State			
Predictions	FPLD2 (+)	Others (FPLDX&Controls)	Total	
FPLD2 (+)	20	8	28	Sensitivity: 100% (95%CI: 83-100)
Others	0	149	149	Specificity: 95% (95%CI: 90-98)
Total	20	157	177	
F. INDEPENDENT INVESTIGATOR GL PREDICTIONS				
	Actual State			
Predictions	GL (+)	Non-obese Control	Total	
GL (+)	16	0	16	Sensitivity: 100% (95%CI: 79-100)
Control	0	44	44	Specificity: 100% (95%CI: 92-100)
Total	16	44	60	

Validation for the fat shadows followed blinded procedures for both Familial Partial Lipodystrophy (FPLD) and for Generalized Lipodystrophy. For FPLD, a three step procedure was followed. **A.** First step of validation: Michigan investigators assessed the scans obtained at the NIH in a blinded fashion. Scan files (*.meb*) were transferred electronically to Michigan after removing all identifiers. Fat shadows were generated from the files at Michigan using the procedure described in Supplemental Figure S2. Two investigators (RM and EAO) evaluated the images independently and reached a consensus in case of disagreement. **B.** Second step of validation: NIH investigators (NM and RJB) assessed the fat shadows from the Michigan cohort. Two investigators (NM and RJB) evaluated the images independently and reached a consensus in case of disagreement. **C.** Cumulative results from A and B. **D.** Third step of validation: an independent investigator (BA) evaluated all cases from both cohorts. **E.** Investigators also identified patients with FPLD2 as an exploratory endpoint during the assessments. Cumulative results from validation steps 1 and 2 are shown. Presence of generalized lipodystophy (GL) was also assessed in a blinded fashion. **F.** The independent investigator (BA) evaluated presence of GL from a blinded compilation of both GL and non-obese control fat shadows. In all cases, the diagnosis of lipodystrophy had been established by specialists with at least 15 years of clinical experience with lipodystrophy (EAO in Michigan, RJB in NIDDK). Confidence intervals for sensitivity and specificity, as well as frequencies were calculated with the exact Clopper-Pearson method (4). FPLD, Familial Partial Lipodystrophy; FPLD2, Familial Partial Lipodystrophy type 2 (Dunnigan variety); FPLDX, a broad subgroup defined as all FPLD other than FPLD2; GL, Generalized Lipodystrophy.

SUPPLEMENTARY DATA

Supplementary Table T6: Inter-observer and inter-site agreement rates

A. Inter-observer agreement rate		
Kappa (95% CI)	FPLD Predictions	FPLD2 Predictions
Michigan (RM&EAO), predicting NIH (n=70)	0.96 (0.87-1.00) 14 FPLD, 56 Control	0.90 (0.71-1.00) 3 FPLD2, 67 Others*
NIH (NM and RB), predicting Michigan (n=107)	0.80 (0.69-0.92) 39 FPLD, 68 Control	0.76 (0.64-0.87) 17 FPLD2, 90 Others*
B. Agreement rates of independent investigator with individual sites		
Kappa (95% CI)	FPLD Predictions	FPLD2 Predictions
Michigan (consensus), predicting NIH (n=70)	0.83 (0.65-1.00) 13† FPLD, 51† Control	0.73 (0.39-1.00) 3 FPLD2, 61† Others*
NIH (consensus), predicting Michigan (n=107)	0.79 (0.66-0.91) 39 FPLD, 68 Control	0.75 (0.63-0.88) 17 FPLD2, 90 Others*

A. Inter-observer agreement rates for FPLD and subtype predictions. **B.** Each site's agreement rate with the independent investigator (Inter-site agreement rate). Inter-observer and inter-site agreement rates were calculated using Cohen's Kappa (5). All analyses were done using R v3.4.4 (Vienna, Austria) (6). FPLD, Familial Partial Lipodystrophy; FPLD2, Familial Partial Lipodystrophy type 2 (Dunnigan variety); RM, NM, RJB and EAO are author name abbreviations. *: Others include FPLDX and Controls. †: The independent investigator saw less cases than Michigan investigators, as some were included in the training set.

SUPPLEMENTARY DATA

Supplementary Table T7: Exploratory subtype predictions

A. Distinction of FPLD2 subtype from other FPLD

	Actual		
Predicted	FPLD2	FPLDX	Total
FPLD2	20	6	26
FPLDX	0	28	28
Total	20	34	54

Sensitivity: 100% (95% CI: 83-100)
Specificity: 82% (95% CI: 65-93)

B. Generalized Lipodystrophy subtypes

	Actual				
	AGL	CGL1	CGL2	Other	
AGL		1			
CGL1	1	**5**		1	71%
CGL2	2	1	**3**	1	43%
Other	1				
		71%	100%		

A. FPLD2 subtype is recognizable by the unique fat distribution pattern associated with LMNA mutations (Figure 1C, Supplemental Figure S4). Investigators were able to recognize FPLD2 among other FPLD quite succesfully. False positives did exist, and most were confused due to the presence of fat hypertrophy around the pubic region. **B.** An attempt was made to identify individual subtypes of GL. For this, the independent investigator was asked to determine any subtype of generalized lipodystrophy if possible. Although no statistically significant conclusions could be derived, a tendency for correct identification of CGL1 more frequently was noted. These patients were recognizable by residual fat seen in the soles (observed in 5 out of 7 patients, with the remaining 2 having poor visualization of the soles), periauricular area (observed in 3 out of 7 patients) and mons pubis (observed in 4 out of 6 females). AGL, CGL2 and other rare subtypes (Lamin A/C p.T10I-linked, Phosphate Cytidylyltransferase 1, Choline, Alpha Isoform-linked) did not appear to be distinguishable from one another by this method. These findings were consistent with what is repored by previous MRI studies (7-9). Probability of the distribution was calculated as p=0.18 (Fisher's exact test). See Supplemental Fat Shadow Atlas for each image used in these assessments. AGL, Acquired Generalized Lipodystrophy; CGL1, Congenital Generalized Lipodystrophy type 1; CGL2, Congenital Generalized Lipodystrophy type 2; FPLD, Familial Partial Lipodystrophy; FPLD2, Familial Partial Lipodystrophy type 2 (Dunnigan variety); FPLDX, a broad subgroup defined as all FPLD other than FPLD2; GL, Generalized Lipodystrophy.

SUPPLEMENTARY DATA

Supplementary Table T8: Advantages and Limitations of the Fat Shadow Method

A. Advantages compared to alternative methods

Advantages of Fat Shadow	**Alternative Method**	**References for the Use of Alternate Method in the Context of Lipodystrophy**
Objective doucmenatation, can be easily adjudicated without worry of patient privacy	Skinfold measurements	Guillin-Amarelle et al. (10)
Not expensive and very quick	Magnetic Resonance Imaging	Garg et al. (7) Garg et al. (11) Altay et al. (9)
Low dose radiation	Computed Tomography	Huang et al. (12)

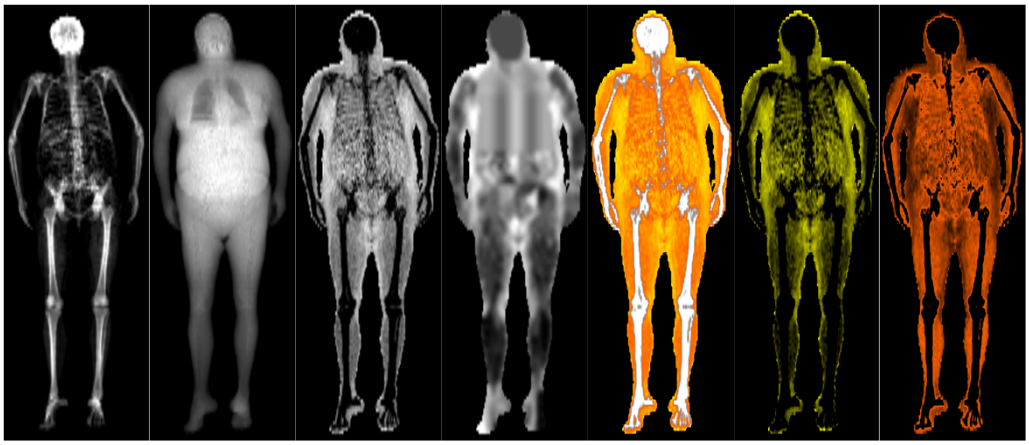
B. Limitations of the method and the study design

Limitation Category	**Description of Limitation**	**Solution**
Technique	Lack of standardization of patient position	Standard operation procedures for patient positioning should be developed
	Inability to evlaute the dorsocervical and gluteal fat depots	Lateral scans can be obtained (as shown in Supplemental Figure S6)
Study Design	Retrospective evaluation of data collected from predominantly Caucasian population	Prospective validation studies should be performed taking into account ethnic differences
	Inconsistent matching parameters used across cohorts (BMI used in NIH, FFMI used in Michigan)	Both BMI and FFMI (and thus FMI) can be used as matching parameters in future studies
	Potentially limited training for the investigators outside UM (did not include any males at all)	Standard training deck developed and can be enhanced for the future
	Pediatric age not studied	Separate pediatric study should be performed
	Lack of comparison of GL patients to other patients with low adiposity	Future studies should be performed

BMI, Body Mass Index; FFMI, Fat Free Mass Index, FMI, Fat Mass Index (difference between BMI and FFMI).

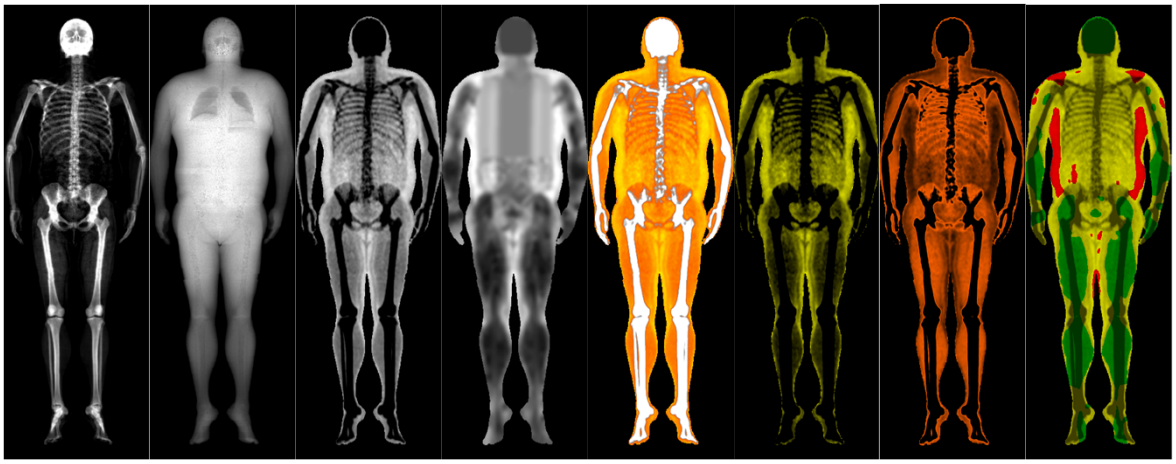
Supplementary Figure S1: Alternative visualization options in enCore v14.10

Prodigy



Enhanced bone | Tissue | Composition | Tissue composition | Color coding | Custom color coding (Fat shadow) | Custom color coding (Muscle shadow)

iDXA



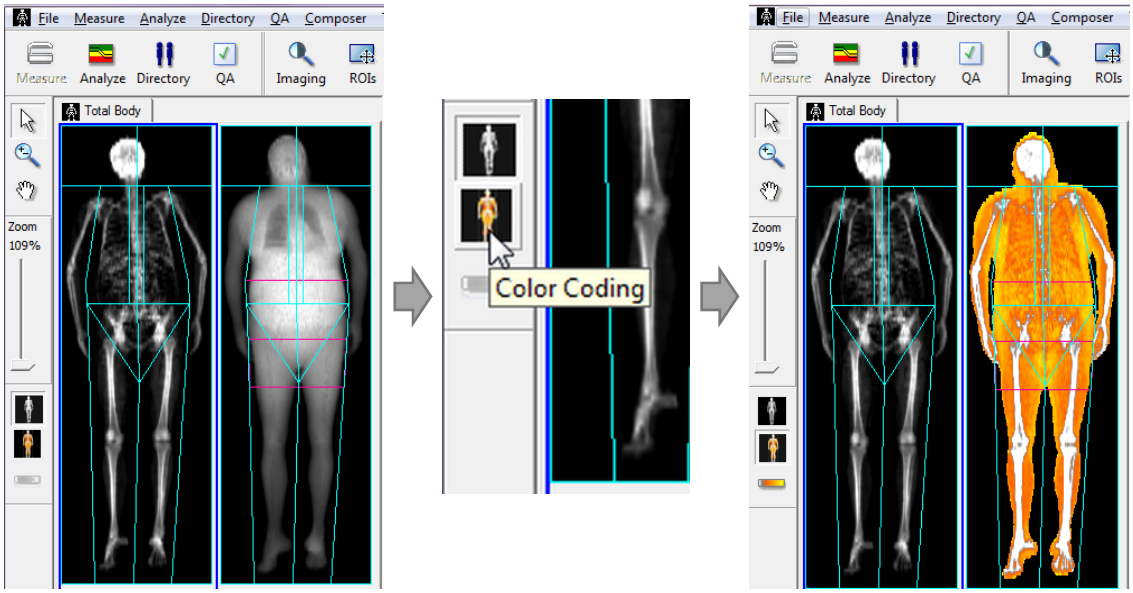
Enhanced bone | Tissue | Composition | Tissue composition | Color coding | Custom color coding (Fat shadow) | Custom color coding (Muscle shadow) | Color mapping

Little attention has been paid to using DXA as a tool for visualization. Recent advancements in technology and resolution remain mostly underutilized. Fat shadows were found to be quite informative about the overall distribution of subcutaneous fat depots. Even though we did not attempt to adapt the “shadowing” method to study unique muscle tissue or bone characteristics, it is also possible that the method may prove useful for this group of disorders. Although there is a significant improvement in resolution with the iDXA system, images produced by Prodigy also seem adequate. Color mapping is only possible in scans acquired with iDXA. The proposed method can be applied retrospectively to already existing total body composition scans. Patients shown in this figure are Familial Partial Lipodystrophy Type 1 (Köbbering variety).

Supplementary Figure S2: Steps to create a fat shadow in enCore v14.10

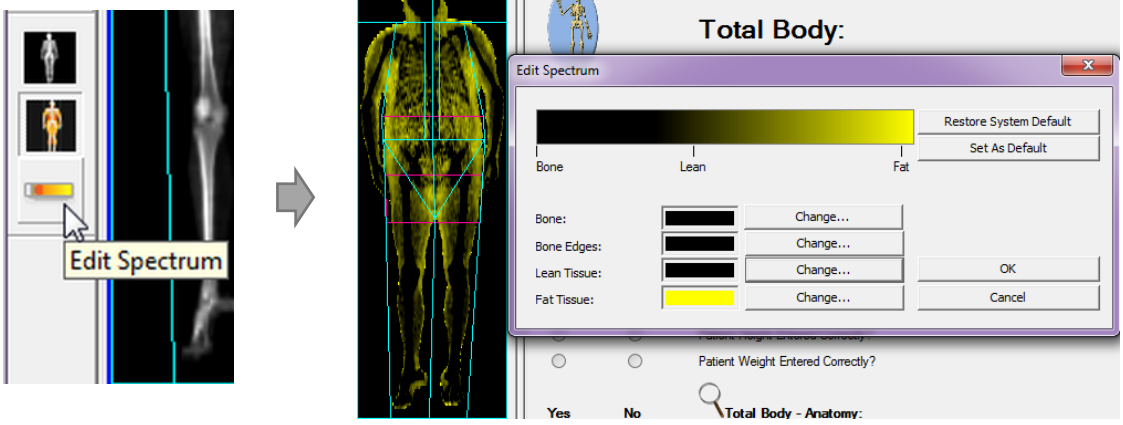
Step 1: Navigate to the analysis page of the DEXA

Step 2: Enable “color coding”

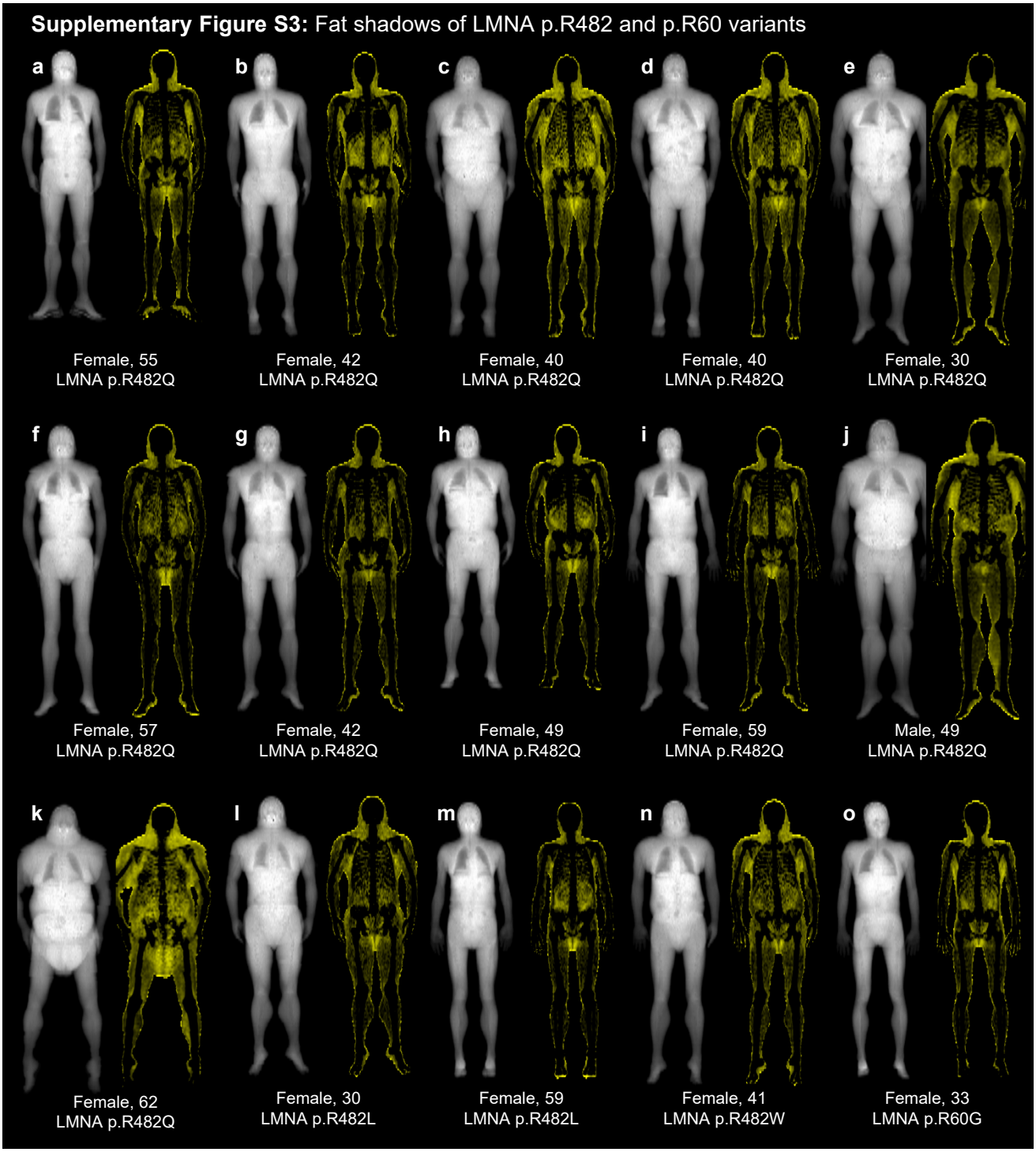


Step 3: Open the “edit spectrum” dialogue

Step 4: Highlight fat signal by setting everything other than fat to the background color, enabling easier visualization of subcutaneous fat in lipoatrophic areas.



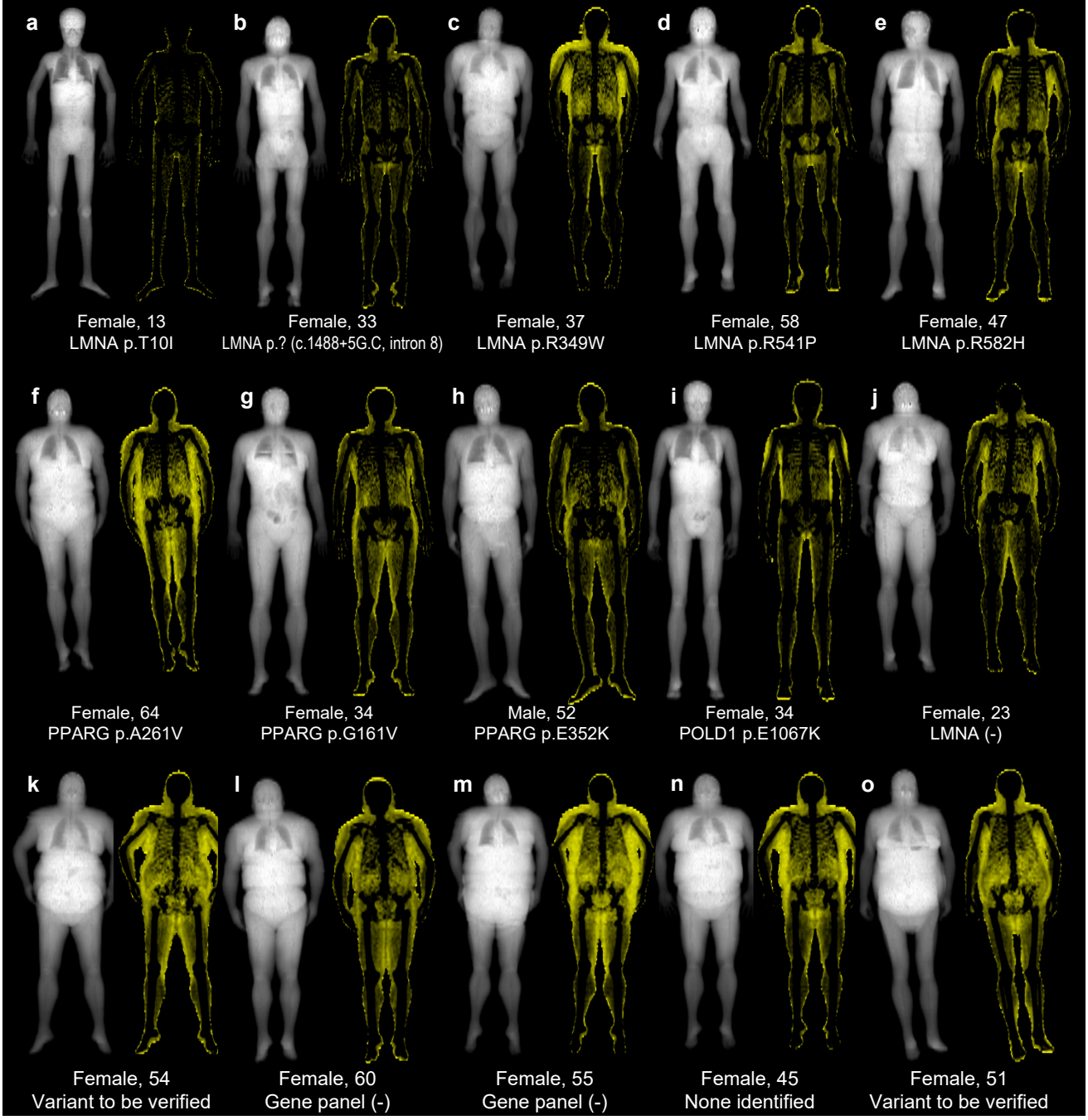
Export is only possible through screen capture.



a-k: *LMNA (*lamin A/C gene*)* p.R482Q variants **l-n:** *LMNA* p.R482L and p.R482W variants **o:** *LMNA* p.R60G variant. The same signature fat distribution pattern was consistently observed in all patients, with the exception for **k**, who had exceptionally increased fat deposition. The increased fat signal in the mons pubis region includes hypertrophic labia majora and mons pubis fat.

The expected fat distribution pattern associated with a common pathogenic variant in the *LMNA* gene is as follows: near total absence of subcutaneous fat in the extremities and abdomen. Hypertrophic fat depots in the supraclavicular (neck) and dorsocervical (buffalo hump) area. Patients may have have increased fat under the axillae as well. In both genders, hypertrophic mons pubis fat (including the labia majora fat in women) can be seen, which stands out due to complete absence of fat in the entire lower half of the body. This pattern can be termed Dunnigan sign on the fat shadow.

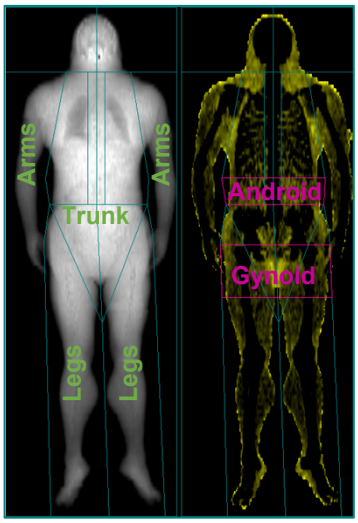
Supplementary Figure S4: Fat shadows of rare *LMNA* variants and other FPLDX



a-e: Rare *LMNA* variants. **a** is a patient that was diagnosed originally with Acquired Generalized Lipodystrophy and Juvenile Dermatomyositis. Upon whole exome sequencing, she was found to have *LMNA* p.T10I (13, 14). **b** is a patient with an intronic mutation in the *LMNA* gene, who presented with fat loss in the generalized end of the spectrum, with respect to other *LMNA* variants. **c** is a patient with *LMNA* p.R349W, a variant known to be associated with cardiomyopathy and focal segmental glomerulosclerosis (15, 16). She had both non-ischemic and ischemic cardiomyopathy and conduction abnormalities and passed away due to sudden cardiac death at the age of 40. **c** and **e** are the only *LMNA* variants that are observed to have abdominal fat in the subcutaneous compartment, and are the only patients with pathologic *LMNA* variants that do not fit our definition of the Dunnigan sign. **c** also has subcutaneous fat observed in the medial thigh. **f-h:** Confirmed pathogenic *PPARG* variants. **i:** A mother with *POLD1* variant. Her daughter (age 17, not shown) carries the same mutation and developed a similar phenotype (17). **j** This patient got frequently identified as FPLD2 in the validation studies. A pathogenic variant had not been found in the *LMNA* p.482 and p.10 sites (Amplicon), but the entire gene was not sequenced. **k-o:** A selection of Familial Partial Lipodystrophy type 1 (Köbberling variety) patients. Note the heterogeneity of fat distribution patterns among FPLD1.

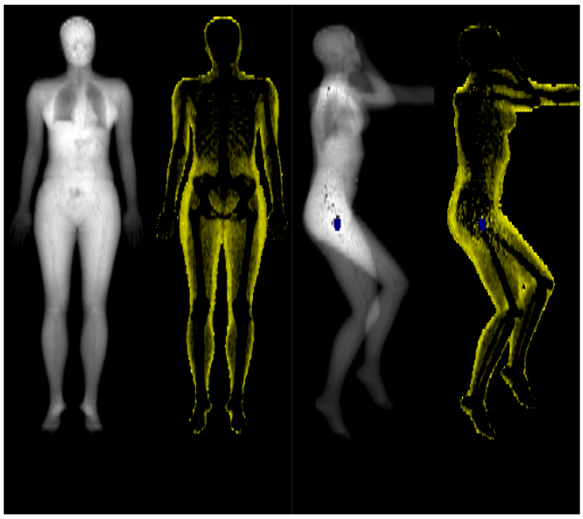
SupplementaryFigure S5

A.

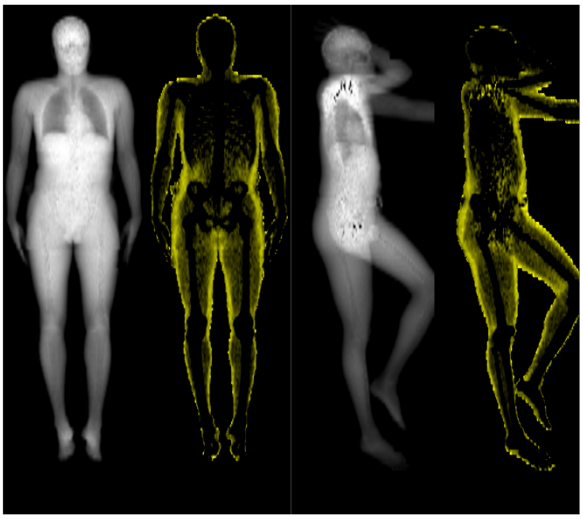


Standard regions of interest (ROI) as defined by the enCore software. While the use of DXA is a clinically relevant test for the diagnosis of bone loss, its capability of determining whole-body composition has found place only in research studies, predominantly in the metabolism field. Quantitative results, from 3 compartments (bone, lean, fat), divided into broad regions of interest (arms, legs, trunk) are typically reported as an outcome in studies with total body composition scans. There are no ROI's designed to focus on clinically relevant areas for lipodystrophy, such as the neck, which is included in the very broad trunk ROI; or the genital region, which is included in the gynoid and trunk ROI's. Proximal and distal extremities are included in the same ROI, which is another limitation.

B.



Female control



Male control

A limitation of the fat shadow method is the poor visualization of the dorsocervical fat pads (the so called "buffalo hump") and the gluteal fat. Acquiring an additional scan with the patient positioned laterally may overcome this issue. Here, volunteers are lying on the table in the recovery position, supported by pillows, and a default total body composition scan is acquired.

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