Atypical Progeroid Syndrome and Partial Lipodystrophy Due to LMNA Gene p.R349W Mutation

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Atypical progeroid syndrome (APS) comprises heterogeneous disorders characterized by variable degrees of fat loss, metabolic alterations, and comorbidities that affect skeleton, muscles, and/or the heart. We describe 3 patients that were referred to our center for the suspicion of lipodystrophy. They had precocious aging traits such as short stature, mandibular hypoplasia, beaked nose, and partial alopecia manifesting around 10 to 15 years of age recurrently associated with: (1) partial lipodystrophy; (2) proteinuric nephropathy; (3) heart disease (rhythm disorders, valvular abnormalities, and cardiomyopathy); and (4) sensorineural hearing impairment. In all patients, genetic testing revealed a missense heterozygous lamin A/C gene (LMNA) mutation c.1045 C > T (p.Arg349Trp). Ten patients with LMNA p.R349W mutation have been reported so far, all presenting with similar features, which represent the key pathological hallmarks of this subtype of APS. The associated kidney and cardiac complications occurring in the natural history of the disease may reduce life expectancy. Therefore, in these patients a careful and periodic cardiac and kidney function evaluation is required.

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Key Words: atypical progeroid syndrome, lipodystrophy, LMNA mutation

Lamin A/C gene (LMNA) is localized on chromosome 1q21.2 and includes 12 exons; by alternative splicing in exon 10, two main isoforms of proteins (lamins) are produced: lamin A (full form) or C (short form). Lamins A and C polymerize with type B lamin to create the nuclear lamina, a network of proteins placed between chromatin and the inner nuclear membrane, which are involved in nuclear organization and communication [1].
Mutations in *LMNA* can lead to a wide spectrum of tissue-specific disorders, collectively called laminopathies, which include familial partial lipodystrophy type 2, muscular dystrophies, cardiomyopathies, neuropathies, and overlapping phenotypes [1-4]. In addition, laminopathies can cause diseases that share features of accelerated aging, known as progerias (from the Greek words πρό, “Premature” and γήρος, “old”). Progerias associated with *LMNA* mutations are distinguished in typical (Hutchinson-Gilford progeria syndrome [HGPS], type A mandibulo-acral dysplasia [MADA], restrictive dermopathy) and atypical progeroid syndrome (APS), which includes atypical Werner syndrome [5] sometimes used as a synonym of APS. HGPS, MADA, and restrictive dermopathy are all well-characterized syndromes. In contrast, APS comprises heterogeneous disorders characterized by variable degrees of fat loss, metabolic alterations, and comorbidities affecting bone, skeletal muscles, and/or the heart [6, 7]. APS is caused by heterozygous missense *LMNA* mutations. These mutations are highly penetrant, usually de novo, and found throughout the gene (from P4R in exon 1 to R644C in exon 11) without specific hotspots. Very occasionally, homozygous (R435C, R471C, S573L) or compound heterozygous (T528M/M540T) *LMNA* mutations causing APS have also been reported [6-10]. Among APS patients, those presenting the heterozygous *LMNA* mutation c.1045 C > T (p.R349W) have a very peculiar and recurrent phenotype. In this study, we describe 3 patients and review the previously described cases.

**Patients and Methods**

**Patient 1**

A 46-year-old woman was referred to the Obesity and Lipodystrophy Center of the University Hospital of Pisa for suspicion of lipodystrophy. She started losing subcutaneous adipose tissue at age 13 years. She suffered from bilateral hearing loss requiring a hearing aid by the age of 31 years. At 35 years, she was diagnosed with hypertension and dyslipidemia, and, at 44, she developed proteinuria. Her father had a history of cardiomyopathy and died suddenly at the age of 37 years. Her paternal uncle died because of end-stage renal disease occurring at a young age. Their pictures show marked loss of subcutaneous adipose tissue in the face and extremities. Physical examination revealed short stature (height 1.52 m, body mass index 15.1 kg/m²), partial loss of subcutaneous adipose tissue in the face and both upper and lower limbs, and scoliosis (Fig. 1). Skinfold thickness and dual-energy x-ray absorptiometry (DXA) showed a reduction in subcutaneous fat in the upper and lower limbs, but not in the trunk.

She had a progeroid face: beaked nose, partial loss of hair from the frontal region, skin atrophy, thin lips, and mandibular hypoplasia. Because of mammary underdevelopment, she had breast implants.

Biochemical blood tests (Table 1), under statin treatment, showed hypertriglyceridemia (208 mg/dL) and normal cholesterol levels. The 2-hour 75-g oral glucose tolerance test showed insulin resistance and impaired glucose tolerance. She had proteinuria (885 mg/24 h). Thyroid, parathyroid, and adrenal tests were normal. Plasma leptin levels were 5.9 ng/mL and adiponectin was 1.1 mcg/mL. Abdominal ultrasound showed mild hepatic steatosis but not hepatomegaly; liver volume was measured by ultrasound using the hepatic left lobe volume as a standardized surrogate of the total liver volume [11]. Liver stiffness, evaluated by FibroScan, was normal (5.4 kPa). Echocardiography revealed mild left ventricular hypertrophy, normal systolic function (ejection fraction 56%), mild mitral and tricuspid regurgitation; Holter 24-hour electrocardiography showed supraventricular tachycardias treated with beta-blockers. Cardiac magnetic resonance imaging (MRI) did not show any abnormalities. Bone radiographs excluded acroosteolysis or clavicular reabsorption. Genetic analysis revealed a missense heterozygous *LMNA* mutation c.1045 C > T (p.R349W).
Patient 2

The second patient was a 14-year-old boy, the second child of the patient 1. His birth weight was 3.750 kg. At a younger age, he was referred to an endocrinologist because of short stature, but no evidence of GH deficiency was found. Physical examination revealed the same key features of the mother (Fig. 1). He was 155 cm tall (on the 5th percentile of the growth charts for his age) and the body mass index was 14.6 kg/m². Biochemical analysis (Table 1) showed normal blood glucose, insulin and glycated hemoglobin, triglycerides, total cholesterol and fractions, and liver function. Creatinine-kinase levels were mildly elevated (300 U/L). The endocrinological evaluation showed normal thyroid, adrenal and pituitary function. The patient had low serum leptin levels (1 ng/mL) and normal adiponectin (8.4 mcg/mL). He had normal hearing sensitivity and no proteinuria. Liver volume was normal without signs of hepatic steatosis. Liver stiffness assessed by FibroScan was normal (6.4 kPa). Electrocardiography showed sinus tachycardia (heart rate 100 beats/min), and echocardiography showed a mild mitral and tricuspid regurgitation. Cardiac MRI did not reveal any pathological findings. Radiograph films excluded acroosteolysis or clavicular resorption. Genetic screening confirmed the missense heterozygous LMNA p.R349W mutation.

Patient 3

The third patient noticed subcutaneous fat tissue loss from the face before 20 years of age. He was then diagnosed with hypertriglyceridemia and hypertension when he was aged 29 and 38, respectively.
At 27, he was diagnosed with a well differentiated serotonin-producing neuroendocrine tumor (NET) of the ileocecal valve treated first with right hemicolectomy and then with liver transplantation because of liver metastases.

At 34, under immunosuppressive therapy, he presented with nephrotic syndrome (9 g/24 h) and progressive kidney failure (estimated glomerular filtration rate 30 mL/min, creatinine 7 mg/dL); kidney biopsy showed focal segmental glomerulosclerosis. He required hemodialysis and then kidney transplantation. There was no family history of NET or kidney disease.

He was referred to our Center at the age of 37 years for the characterization of lipodystrophy. Physical examination (Fig. 1) showed a reduction in subcutaneous fat involving the face and extremities and short stature (he was 1.56 m tall and weighed 44 kg). He had a beaked nose, prominent eyes, loss of hair from the frontal and parietal region, skin atrophy, thin lips and small mandible. Skinfold thickness and DXA measurements showed a reduction of fat mass in the upper, lower limbs and trunk. An audiogram showed reduced sensorineural hearing acuity.

Laboratory tests showed (Table 1) increased glycated hemoglobin (50 mmol/mol), severe hypertriglyceridemia (876 mg/dL), reduced high-density lipoprotein cholesterol (31 mg/dL), and increased liver enzymes (aminotransferase 61 U/L, gamma glutamyl transpeptidase 66 U/L). After kidney transplant, renal function was normal. Abdominal ultrasonography revealed marked liver steatosis; liver stiffness was normal (5.6 kPa). The 24-hour Holter monitoring showed episodes of supraventricular tachycardia (which were treated with beta-blockers) and ectopic atrial and ventricular beats. Transthoracic echocardiography showed mild-to-moderate mitral and tricuspid regurgitation. Cardiac MRI showed normal

### Table 1. Biochemical Tests of the 3 Patients Described

|                    | Patient 1 | Patient 2 | Patient 3 |
|--------------------|-----------|-----------|-----------|
| Glucose Fasting (mg/dL) | 92        | 87        | 89        |
| 1-h OGTT (mg/dL)      | 187       | 146       | -         |
| 2-h OGTT (mg/dL)      | 161       | 103       | -         |
| HbA1c (%)             | 5.5       | 5.4       | 6.7       |
| Insulin Fasting (µUI/mL) | 15.2     | 11.5      | 22.8      |
| 1-h OGTT (µUI/mL)     | 164.3     | 24        | -         |
| 2-h OGTT(µUI/mL)      | 147.7     | 54.7      | -         |
| Lipids Total-C (mg/dL) | 158       | 159       | 208       |
| HDL-C (mg/dL)         | 43        | 67        | 31        |
| LDL-C (mg/dL)         | 94        | 82        | 74        |
| TG (mg/dL)            | 208       | 99        | 876       |
| Liver function AST (U/L) | 19        | 25        | -         |
| ALT (U/L)             | 23        | 29        | 61        |
| γGT(U/L)              | 26        | 14        | 66        |
| Kidney function Creatinine (mg/dL) | 0.62 | 0.49 | 7a |
| eGFR (mL/min)         | 110       | 244       | 30a       |
| Proteinuria (mg/24 h) | 885       | 138       | 9000a     |
| CPK (U/L)             | 149       | 300       | 67        |
| Leptin (ng/mL)        | 5.9       | 1         | 3.5       |
| Adiponectin (mcg/mL)  | 1.1       | 8.4       | 3.1       |

Abbreviations: 1-h OGTT, 1 hour after oral glucose tolerance test; 2-h OGTT, 2 hours after oral glucose tolerance test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; γGT, gamma glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; total-C, total cholesterol; TG, triglycerides. aBefore kidney transplant.
ventricular volumes, mild ventricular systolic dysfunction (left ventricular ejection fraction 49%), with signs of ischemic fibrosis in the left anterior descending and circumflex territories (Fig. 2). The patient had performed a coronary angiography right before kidney transplant, which detected atherosclerotic plaques, although they were not hemodynamically significant. Bone radiographs excluded acroosteolysis or clavicular resorption.

Genetic analysis revealed a missense heterozygous LMNA mutation c.1045 C > T (p.R349W). This mutation was not recorded in either parents indicating that it was a de novo mutation.

Methods

Anthropometric measurements

Height, body weight and circumferences were measured by standard procedures. Skinfold thickness were measured with a Lange caliper (Beta Technology, Santa Cruz, CA) at truncal (abdomen, subscapular, and suprailliac) and peripheral (biceps, triceps, mid thigh, and calf) sites on the right side of the body. The average of 3 repeat measurements at each site was calculated.

DXA (Hologic, Discovery A, S/N 84551) was used to determine whole-body and regional fat in the trunk and upper and lower extremities. The proportion of fat in individual regions as well as the whole body was calculated as percentage of body mass.

Biochemistry and hormones

All determinations were carried out after at least 12 hours of fasting. Leptin and adiponectin were measured by ELISA from Mediagnost, Reutlingen, Germany; free T3 (CLIA), free T4 (CLIA), and TSH (ICMA) from Ortho Clinical Diagnostic, Rochester, NY; FSH (ICMA), prolactin (ICMA), LH (ICMA), and insulin (ICMA) from Beckman Coulter, Inc. Diagnostics, CA; and IGF1 (ICMA) from Immunodiagnostic Systems Holdings, UK. Glucose, cholesterol, triglycerides, creatinine, aspartate aminotransferase, alanine aminotransferase, and GGT were determined using automated equipment at the Laboratories of Clinical Chemistry and Endocrinology of the University Hospital of Cisanello, Italy.

Genetic testing

LMNA variants were identified by Sanger sequencing and further confirmed on a second DNA sample. Specific primers were designed using Primer 3 (http://primer3.ut.ee/ Primer3web version 4.1.0) to amplify LMNA exons and splice junctions from genomic DNA, isolated from

![Figure 2. Cardiac magnetic resonance imaging of patient 3. At late gadolinium enhancement, the patient presented a subendocardial scar (arrows) involving the (A) basal, (B) mid, and (C) apical segments of the anterior and anterolateral walls of the left ventricle. His previous coronary angiography had shown 3-vessel atherosclerosis, with multiple calcified plaques not hemodynamically significant.](image-url)
whole blood. PCR was performed using PCR Master Mix (Promega Corporation, WI) with an annealing temperature of 55°C. After purification with ExoProStar (GE Healthcare UK Limited, UK), the PCR products were directly sequenced using Applied Biosystems 3130 xl sequencer (Thermo Fisher Scientific, MA).

Informed consent

Data publication was approved by the local institutional review committee; patients and parents gave their informed consent for genetic studies and publication of their clinical details and images.

Discussion

APS is a heterogeneous group of rare disorders caused by LMNA mutations that have in common that they cause an early and accelerated aging process. APS is also characterized by variable degrees of fat loss (partial or generalized) and variable severity of the associated metabolic alterations: a diffuse fat loss is associated more frequently with metabolic complications, as occurs in other forms of congenital and acquired lipodystrophy.

The time of onset of aging symptoms of APS is variable but it is delayed compared to the typical progeroid syndromes (especially HGPS) also caused by LMNA mutations. Despite phenotypic heterogeneity of APS, specific LMNA mutations may result in a peculiar constellation of diseases [12]. We here report 3 patients with LMNA c.1045 C > T (R349W) mutation and compare them with previously described cases. The mutation p.R349W, described so far in only 10 patients worldwide, translates an arginine (polar amino acid) into a tryptophan (apolar amino acid) in position 349. This substitution involves the α-helical domain (rod domain) of the lamin A/C protein. There are several lines of evidence supporting its pathogenicity: Arg349Trp was not observed in the general population databases and systematically cosegregate with the disease in the family pedigrees. Furthermore, alignment of the arginine (R) residue at position 349 is highly conserved among vertebrate lamins, demonstrating its critical role [13]. The primary mechanism causing cellular and organ impairment are different in the different progerias.

In HGPS, the primary mechanism of the disease is an alteration of LMNA splicing and subsequent abnormal post-translational maturation of mutated prelamin A (progerin). Progerin remains permanently farnesylated and its accumulation causes cellular toxicity. Treatment with farnesyltransferase inhibitors reduces nuclear abnormalities of fibroblasts from HGPS patients and ameliorates the phenotype of HGPS mouse models. Yet, this approach does not halt the disease, suggesting that other mechanisms of harmfulness are likely involved [14].

In studies on skin fibroblasts from APS patients, mild to severe nuclear morphological abnormalities have been described. However, accumulation of prelamin A has been reported by some authors but not others [6, 15], and treatment with farnesyltransferase inhibitors did not significantly improve nuclear morphological abnormalities [6]. It is therefore proposed that the primary mechanism of disease in APS is the impairment of mutant lamin A that causes a disruption of chromatin organization and function affecting tissue-specific deregulation of gene expression [14].

Available data from described patients reveal many distinguishing features of LMNA p.R349W mutation (Table 2).

First, all patients presented with short stature and several progeroid features such as partial alopecia, mandibular hypoplasia, beaked nose, thin lips, prominent scalp veins, prominent eyes and atrophic skin.

Second, all patients displayed a partial lipodystrophy: skinfold thickness measurements and DXA scans showed a reduction in subcutaneous adipose tissue mainly over the extremities and serum leptin and adiponectin levels were reduced [21]. In line with this, almost all adult patients showed marked metabolic abnormalities. In particular, 70% of the
reported patients had prediabetes or diabetes, 70% hypertriglyceridemia, and 70% hepatic steatosis. Importantly, fat loss pattern is different from familiar partial lipodystrophy type 2 (Dunnigan syndrome), this is the most frequent laminopathy associated with partial lipodystrophy; loss of adipose tissue affects limbs together with an over-accumulation of fat in

Table 2. Clinical Features of Patients With Heterozygous LMNA p.R349W Mutation

| Patient 1 | Patient 2 | Patient 3 | Previously Described Patients with p.R349W Mutation | Mean/Percentage (% of the Described Cases) |
|-----------|-----------|-----------|--------------------------------------------------|------------------------------------------|
| Sex, %    | Current Study | Current Study | Current Study | N = 10a | F; 61% |
| Age at onset (y) | 13 | 14 | 20 | 13; 20 (8 NR) | 16 |
| Age at report (y) | 47 | 14 | 38 | 17; 18; 35; 27; 35; 40; 22; 42; 16; 37 | 29.8 |
| Height (m) | 1.52 | 1.60 | 1.56 | 1.60; 1.58; 1.54 (7 NR) | 1.56 |
| Weight (kg) | 35.5 | 40 | 44 | 50; 63.3 (8 NR) | 46.5 |
| BMI (kg/m²) | 15.4 | 15.6 | 18.1 | 20; 26.4 (8 NR) | 19.1 |
| Lipodystrophy | Partial | Partial | Partial | Partial (2 NR) | 100% partial |
| Loss of hair | + | - | + | 2+/1-/7 NR | 66% |
| Micronodathia | + | + | + | 2+/1-/7 NR | 83% |
| Beaked nose | + | + | + | 1+/1/-8 NR | 80% |
| Acroosteolysis | - | - | - | 1-/9 NR | 0% |
| Atrophic skin | + | - | + | 1+/1/-8 NR | 60% |
| Thin lips | + | + | + | 1-/9 NR | 75% |
| Underdeveloped breasts | + | - | - | 2+/8 NR | 100% |
| Scoliosis | + | - | - | 2+/8 NR | 60% |
| Short height | + | + | + | 3+/7 NR | 100% |
| Hepatic steatosis | + | - | + | 3+/1/-6 NR | 71% |
| Hepatomegaly | - | - | - | 2-/8 NR | 0% |
| Hypertriglyceridemia | + | - | + | 5+/2-/2 NR | 70% |
| Diabetes/IR | IR + IGT | - | DM | 5+/2-/3 NR | 70% |
| Cardiomyopathy | - | - | - | 4+/4-2 NR | 36% |
| Heart valve abnormalities | | | | | |
| Hypertension | + | - | + | 3+/3/-4 NR | 55% |
| Arrhythmia | + | + | + | 6+/2-/2 NR | 81% |
| Myopathy | - | - | - | 4+/4-/2 NR | 36% |
| Proteinuria | + | - | + | 7+/3 NR | 90% |
| (>150 mg/24 h) | | | | | |
| Renal biopsy | - | - | + | 6+/4 NR | 71% FSGS |
| Hearing impairment | + | - | + | 4+/2-/4 NR | 66% |
| Family history of premature sudden death | + | + | - | 6+/1-/3 NR | 80% |
| Whole body fat (%) | 20 | 17.3 | 20.5 | 14.2; 9 NR | 18% |
| Arm fat (%) | 25.1 | 15.5 | 21.4 | 16.7; 9 NR | 19.6% |
| Leg fat (%) | 17.5 | 17.5 | 19.5 | 14.3; 9 NR | 17.2% |
| Truncal fat (%) | 19.5 | 14.6 | 21.4 | 10.9; 9 NR | 16.6% |
| Skinfold thickness | | | | | |
| Abdomen (mm) | 30 | 5 | 24 | 10 NR | 19.6 |
| Suprailiac (mm) | 10 | 3 | 14 | 10 NR | 9 |
| Subscapular (mm) | 21 | 6 | 10 | 10 NR | 12.3 |
| Biceps (mm) | 3 | 2 | 2 | 10 NR | 2.3 |
| Triceps (mm) | 3 | 4 | 4 | 10 NR | 3.6 |
| Midthigh (mm) | 2 | 6 | 2 | 10 NR | 3.3 |
| Calf (mm) | 2 | 5 | 2 | 10 NR | 3 |

Abbreviations: -, absent; +, present; FSGS, focal segmental glomerulosclerosis; IGT, impaired glucose tolerance; IR, insulin resistance; MR, mitral regurgitation; NR, not reported; TR, tricuspid regurgitation.

References [7, 16-20].
the face, neck and pubis. Only 2 patients who were previously reported presented fat in the neck and dorsocervical pad, respectively [16, 20]. Unfortunately, no measurement of food intake or hunger scales have been performed in this specific group of patients, but increased appetite is expected.

Third, 90% of patients had proteinuria and most of them underwent kidney biopsy, 5 displaying focal segmental glomerulosclerosis (FSGS), 1 focal glomerular mesangioproliferative nephropathy, and 1 thin basement membrane nephropathy. FSGS is a podocyte injury associated with proteinuria and is a major cause of end-stage renal disease. FSGS with proteinuric nephropathy has been frequently described associated with generalized, congenital, or acquired lipodystrophy [22], but rarely in patients with partial lipodystrophy [23-25]. It has been suggested that LMNA mutation may lead to an excess of TGFβ1 production from podocytes, promoting glomerulosclerosis [26].

Fourth, cardiac involvement is very frequent. More than 80% of patients display rhythm disorders, 62% of them cardiac valvular abnormalities including mitral, aortic, or tricuspid regurgitation and 36% a cardiomyopathy. The high prevalence of rhythm disorders can be explained by the fact that arrhythmias have an onset at very young age, whereas the other cardiopathies usually develop later in life. The association between LMNA mutations, lipodystrophy and cardiomyopathy has been amply reported, and the prevalence of all cardiac disorders increases with age [7, 12, 27]. Because the risk of cardiac manifestations and death is increased in patients with R349W, a strict follow-up in this regard is recommended at any age. Indeed, the principal causes of death are due to cardiomyopathy and precocious kidney failure.

The fifth recurring disease is hearing impairment (ranging from reduction or complete sensorineural deafness) occurring in 66% of the patients. However, it is worth mentioning that hearing skills can be compromised in patients with lipodystrophy-related progeroid syndromes resulting from mutations in genes other than LMNA, which include POLD-1, ERCC6/ERCC8, and PIK3R1 [28-31].

Three of 8 post-pubertal females had underdeveloped breasts. Yet, this specific p.R349W mutation does not affect the reproductive axis or cause hypogonadism. Contrary to MADA, LMNA R349W patients did not show signs ofacroosteolysis or clavicular resorption, but some showed scoliosis (Table 2). Some p.R349W patients, including 1 described here, show symptoms of myopathy or elevation of creatinine kinase levels, a feature occurring in other LMNA-related disorders [32]. One of our patients presented a NET of the ileocecal valve. Although progerias may increase cancer incidence, at this time there is no reported association between LMNA mutations and NETs. Nevertheless, because NETs are rare tumors, this possibility should be kept in mind when evaluating LMNA p.R349W patients.

Metreleptin, a recombinant analog of the protein hormone leptin, has been shown to improve metabolic abnormalities in patients with generalized lipodystrophy and selected patients with partial lipodystrophy [4, 33]. Hussinan et al [12] reported on patients affected by APS resulting from an LMNA p.T10I mutation who greatly benefited from leptin treatment; we therefore believe that this option should be considered, whenever indicated.

**Conclusion**

Our current report and the review of the literature demonstrate that patients with heterozygous LMNA gene c.1045 C > T (p.R349W) mutation show a peculiar phenotype characterized by progeroid features manifesting around 15 years of age, recurrently associated with: (1) partial lipodystrophy; (2) proteinuric nephropathy; (3) cardiopathies (rhythm disorders, valvular abnormalities, and cardiomyopathy); and (4) sensorineural hearing impairment that represent the key pathological hallmarks of this subtype of APS. Partial lipodystrophy and rhythm disorders usually manifest at young age and earlier than sensorineural hearing impairment, proteinuric nephropathy or other cardiopathies. The associated kidney and
cardiological complications occurring in the natural history of the disease may reduce life expectancy, requiring a careful cardiac and kidney function in these patients. We remark that, given the phenotype overlapping among progeroid syndromes, genetic analysis and disease registries have an important role in characterizing the disease to guide the screening of comorbidities and personalize therapeutic choices.

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Additional Information

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in the References.

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