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Propionic Acidemia, Cardiomyopathies, and Arrhythmias

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ABSTRACT

Systemic acid-base imbalances significantly influence the heart, both clinically and experimentally. Extensive knowledge exists regarding the impact of pH on cardiac function, yet the role of organic anions accumulating in acidosis is less explored. In severe metabolic acidosis cases, such as hereditary organic acidemias, these organic compounds can reach millimolar concentrations in blood and other body fluids, exerting significant physiological effects on the heart. Cardiomyopathies and arrhythmias are common in patients with organic acidemia, although the underlying pathophysiological processes remain unclear. Research into organic anion physiology, particularly concerning propionate – which accumulates in propionic acidemia (PA), a form of organic acidemia commonly associated with cardiac illness – has increased substantially in recent years. The purpose of this review is to provide an overview of the cardiac sequelae observed in PA patients who suffer from cardiac diseases.

Keywords: Arrhythmia, cardiomyopathy, hereditary organic acidemia, organic anion, propionic acidemia.

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INTRODUCTION

Propionic acidemia (PA), referenced as Online Mendelian Inheritance in Man number 606054 (OMIM# 606054) and Orphanet number 35 (ORPHA: 35), is a rare autosomal recessive genetic condition. This disorder is characterized by the accumulation of propionyl-Coenzyme A (CoA) and its metabolites due to the poor functioning of the mitochondrial enzyme propionyl-CoA carboxylase (PCC; Enzyme Commission number 6.4.1.3, EC 6.4.1.3). PA was first reported in 1968, identified by metabolic acidosis caused by 5.4 mM plasma propionic acid. The global incidence of PA ranges from 1:50,000 to 1:100,000, with a notably higher rate (1:1,000) in the Greenland Inuit population. Enhanced detection of PA is facilitated by neonatal screening using tandem mass spectrometry. The mitochondrial PCC enzyme, consisting of α and β subunits with a molecular weight of approximately 700,000 Da, catalyzes the conversion of propionyl-CoA to D-methylmalonyl-CoA using Adenosine Triphosphate (ATP). This enzyme operates optimally at a pH of 8.0–8.5 and is potassium-triggered. The α subunit of the PCC enzyme comprises biotin carboxylase, transfer, and carboxyl carrier protein domains. Biotin carboxylase domains A, B, and C carboxylate Mg^{2+}-ATP.[1,2]

Propionyl-CoA, a downstream metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids, and cholesterol side chains, is produced from the fermentation of propionate by gut bacteria, catalyzed by short-chain acetylCoA synthase. Mutations in PCC, reducing enzyme function, lead to the accumulation of propionyl-CoA and its metabolites. The metabolic pathway of propionic acidemia can be summarized as follows: in a typical metabolic process, amino acids and fatty acids are broken down into their respective components and converted into acetyl-CoA, which is used for energy production. In individuals with propionic acidemia, there is a deficiency in the enzyme PCC, which impedes the breakdown of certain amino acids and fatty acids. Consequently, the excess amino acids and fatty acids are converted into propionyl-CoA, which cannot be further broken down in individuals with propionic acidemia. The pathophysiology of PA is not entirely clear; however, several interventions may prevent its development and minimize metabolic decompensations. These treatments include antibiotics, L-carnitine, and protein restriction.[3,4] Mutations in the Propionyl-CoA Carboxylase Alpha Subunit (PCCA) or Propionyl-CoA Carboxylase Beta Subunit (PCCB) genes, which encode the subunits of the PCC enzyme, cause PA. These mutations lead to the accumulation of toxic chemicals, as they encode PCC enzyme subunits. This accumulation results in the storage of toxic metabolites. Consequences include mitochondrial dysfunction, energy starvation, and oxidative cell damage.[5]

PA's systemic and metabolic effects can be detrimental to the heart. There are several ways in which PA may cause cardiac disease. For instance, PA can induce cardiomyopathy (CM), which weakens or enlarges the heart, thereby limiting its ability to pump blood. Metabolic abnormalities and the accumulation of toxic substances in the heart muscle may cause CM. Additionally, PA can lead to cardiac arrhythmias due to metabolic imbalances affecting the heart's electrical signaling, resulting in arrhythmias that impair pumping. Severe PA cases may also affect diastolic heart function, characterized by poor heart muscle relaxation during diastole. This reduces the filling of the heart chambers and impairs blood pumping. PA-related metabolic disorders may lead to imbalances in potassium and calcium levels, potentially causing electrical conduction abnormalities and cardiac arrhythmias. Metabolic decompensation and crises in PA patients may result in oxygen and nutrient deprivation, leading to long-term cardiac malfunction and myocardial damage.[6]

Cardiac issues commonly associated with PA include an extended corrected QRS complex to T-wave (QTc) and dilated cardiomyopathy (DCM). Up to 70% of PA patients post-infancy exhibit a prolonged QTc-time, which predisposes them to cardiac arrhythmias. Approximately 23% of PA patients develop DCM. Notably, only three cases have been reported where acute illness onset with DCM was the sole clinical symptom. One of the main manifestations of PA is the accumulation of propionic acid and its derivatives in the body, leading to various symptoms, including cardiac arrhythmias. Sudden cardiac death, although not well-documented in terms of incidence, has been reported in some individuals with PA. Ventricular arrhythmias, such as ventricular tachycardia and ventricular fibrillation, have also been observed in PA patients.[7]

Toxic metabolites accumulate, leading to mitochondrial malfunction, increased generation of reactive oxygen species, and oxidative damage. Clinical signs include cardiac problems, notably cardiac dysfunction and arrhythmias, which are life-threatening. Tamayo et al.[8] employed a hypomorphic mouse model (Pcca-/-(A138T) to study the molecular processes underlying the cardiac phenotype. Pcca-/- (A138T) mice exhibited poorer cardiac function and cell contractility compared to wild-type mice. Pcca-/- (A138T) cardiomyocytes released more Ca^{2+} during diastole when the levels of Ca^{2+} in the sarcoplasmic reticulum (SR-Ca^{2+}) were lower. In Pcca-/-(A138T) cardiomyocytes, Ca^{2+} sparks, waves, and spontaneous [Ca^{2+}] transients can induce ventricular arrhythmias. Decreased Ca^{2+} values are the target of treatment for arrhythmias and cardiac dysfunction in PA.

It is important to remember that not everyone with PA will experience cardiac arrhythmias. The severity and frequency of arrhythmias can also vary among individuals. This review will examine the effects of PA in DCMs and how it might lead to arrhythmias.

DCM

DCM is caused by cardiac inflammation with or without infectious agents, cytotoxic drugs, arrhythmias, and hereditary factors. Multifactorial pathogenesis is observed in certain cases.[9] After rigorous diagnostic tests, 25% of DCM patients are categorized as 'idiopathic'. Between 20–48% of DCM patients have a familial condition, and approximately 50 DCM-related genes have been identified.[10] DCM is primarily autosomal dominant with limited penetrance, though some cases are X-linked, autosomal recessive, or mitochondrial. Mitochondrial proteins and glycosylation genes involved in metabolic activities, such as Tafazzin, succinate dehydrogenase A (SDHA), dolichol kinase deficiency (DOLK), and fukutin, play a role.[11,12] DCM commonly begins in neonates or children with metabolic disorders, and metabolic factors may also contribute to adult-onset DCM.[13]

The pathophysiology of PA-associated DCM is not yet fully understood. One theory is that the accumulation of toxic me-

tabolites, such as 3-hydroxypropionate and 2-methylcitrate, could damage cardiomyocytes. It is also hypothesized that a deficiency of succinyl-CoA or subsequent issues with the respiratory chain could lead to cardiomyopathy by impairing energy utilization.[14] Disruption of the citric acid cycle could result from either an accumulation of toxic metabolites or a deficiency of the precursor succinyl-CoA, the end product of the catabolic pathway involving the PCC complex.[15] Increased PCC activity may heighten the risk of DCM due to repetitive metabolic stresses.[16] This specific mutation may theoretically predispose individuals to the development of DCM. In Japanese PA patients, three common variations in the Propionyl-CoA Carboxylase Beta subunit (PCCB) gene have been associated with an increased risk of developing DCM.[17]

Cases of isolated DCM in 14- and 16-year-old teens have been documented.[17] Unlike neonatal patients, these teenage DCM patients had persistent PCC activity. Both individuals exhibited modest but detectable residual enzymatic activity, indicative of hypomorphic alleles. Additionally, both individuals with PA presented with bundle-branch blocks. Notably, 25–30% of DCM patients have a bundle branch block, so it is not a disease-specific characteristic.

Free carnitine and biotin insufficiency are risk factors for DCM in PA patients.[18] The normal blood carnitine levels in our patients rule out deficiency. *In vitro* biotin supplementation did not affect PCC activity, ruling out biotin insufficiency. Although methylphenidate probably did not cause DCM, its use was discontinued due to recorded instances of adverse effects.[18] There is no established link between DCM and metabolic decompensation in PA. Kovacevic et al.[19] reported a 39% incidence of CMs among early-onset PA patients. Two-thirds of these patients demonstrated diastolic left ventricular (LV) dysfunction, which often preceded systolic LV failure. Standard treatments with angiotensin-converting enzyme inhibitors (ACE-I) did not improve LV systolic function, suggesting that tailored therapies or early liver transplantation are necessary. PA patients with advanced DCM may benefit from liver transplantation. However, there is a report of a PA patient developing severe DCM following liver transplantation.[20]

Long QT Syndrome (LQTS)

Several recent studies have demonstrated a connection between PA and LQTS, which can be fatal.[21] Duras et al.[22] described two sisters with PA who had prolonged QT intervals. An electrocardiogram (ECG), exercise stress test, and 24-hour Holter monitoring confirmed LQTS. This paper emphasizes the importance of early detection of LQTS in asymptomatic PA patients to prevent its fatal consequences. Kakavand et al.[23] reported a case where a patient initially diagnosed with PA was later found to have LQTS on an ECG, confirmed by an exercise stress test and an epinephrine challenge. Despite the woman being asymptomatic and having no arrhythmias, atenolol was prescribed for her.

Even in clinically stable individuals with PA, cardiac electrophysiological abnormalities might cause cardiac issues. Toxic metabolites or substrate depletion are possible mechanisms. Baumgartner et al.[24] recommended frequent cardiac examinations for this population to prevent life-threatening complications. PA metabolites have been demonstrated to acutely reduce the slow delayed rectifier potassium current (Iks), thereby prolonging the action potential duration and causing LQTS.[25]

Screening for Arrhythmias and DCM

It is crucial for individuals with PA, as they may be at increased risk for these complications. The screening recommendations may vary depending on the specific guidelines of the treating institution and the individual's clinical presentation. Generally, it is advised that all individuals with PA undergo an ECG performed at diagnosis and then at regular intervals, such as every 6 to 12 months. An echocardiogram should also be conducted at diagnosis and then at regular intervals, such as every one to two years, or more frequently if there are any indications of cardiac dysfunction.

Additionally, regular monitoring of metabolic control is recommended for patients with PA, including checking blood propionate levels, and managing the metabolic abnormalities with diet and/or medications. It is important to note that these are general recommendations, and the best course of action will depend on the individual's specific needs. This should be discussed with a healthcare provider who is familiar with the management of PA.

For individuals with PA, the use of an implantable cardioverter-defibrillator (ICD) may be indicated to prevent sudden cardiac death. The decision to implant an ICD is usually based on several factors, including the individual's history of cardiac arrhythmias, the presence of structural cardiac disease, and the results of non-invasive cardiac testing. The most common indication for ICD implantation in PA patients is the presence of symptomatic ventricular arrhythmias, such as ventricular tachycardia or ventricular fibrillation. Individuals who have a history of cardiac arrest or near-arrest or who have previously received an ICD may also be considered for ICD implantation. Additionally, if an individual with PA is found to have DCM on echocardiography and the ejection fraction is lower than 35%, ICD implantation should be considered. It is crucial to understand that the decision to implant an ICD should be made on a case-by-case basis, in consultation with a healthcare provider who is familiar with the management of PA and the individual's specific cardiac history and risk factors.

Atrial Fibrillation (AF)

There is limited scientific evidence linking propionic acidemia with AF, a type of irregular heartbeat that can lead to blood clots, strokes, and other complications. However, some studies have suggested that individuals with propionic acidemia may be at increased risk for cardiovascular problems, including cardiac arrhythmias like AF. The exact mechanism by which propionic acidemia may lead to AF is not well understood, but it is thought that the accumulation of toxic byproducts in the blood and tissues of individuals with this condition may contribute to inflammation and oxidative stress, potentially damaging the heart and other organs over time. If you or someone you know has propionic acidemia and is experiencing symptoms of AF or other cardiovascular issues, it is crucial to seek medical attention immediately. Treatment may involve medications to control heart rate and rhythm, as well as lifestyle modifications to reduce the risk of complications.

PA Patient's Treatment

The management of propionic acidemia involves dietary restrictions, medications, and supportive interventions. The primary goals of treatment are to prevent toxic buildup and alleviate symptoms. Common treatments for propionic acidemia include:

- A low-protein diet to reduce propionic acid synthesis. This diet may also involve low-protein, high-carbohydrate formulations.
- Carnitine supplementation: Carnitine naturally converts fat into energy. Carnitine supplementation enhances energy metabolism and reduces toxicity.
- Biotin supplementation: Biotin breaks down amino acids and lipids. Patients with propionic acidemia and a deficiency in the PCC enzyme might benefit from biotin supplementation.
- Antibiotics: Bacterial infections can exacerbate symptoms of propionic acidemia, so antibiotics may be recommended.
- Emergency treatment: Metabolic crises require intravenous fluids, glucose, and medications to reduce toxic substances.

A coordinated approach involving a metabolic geneticist, dietician, and other healthcare professionals is essential for the complex treatment of propionic acidemia. Regular monitoring and care can help patients with propionic acidemia avoid complications and improve outcomes.[26]

Dual messenger Ribonucleic Acid (mRNA) therapy is an innovative approach to treating genetic disorders, involving the delivery of two different mRNA molecules to cells in the body. One mRNA molecule codes for a protein that is missing or defective in the patient's cells, while the other codes for a protein that aids the functioning of the first protein. Dual mRNA therapy could be applied to address the metabolic issue causing propionic acidemia. For example, one mRNA molecule could be used to increase levels of a key enzyme that is deficient in patients with propionic acidemia, while the other mRNA molecule could be used to support the function of this enzyme. However, it is important to note that dual mRNA therapy is still an experimental approach and has not yet been tested in clinical trials for propionic acidemia. Further research is needed to determine if this treatment method is safe and effective for this disorder.[27] The main points of recent studies are summarized in Table 1.

PA Patients with Cardiac Involvement Benefit from Early Strain Echocardiography or Cardiac Magnetic Resonance Imaging (MRI) Diagnosis

Detecting and monitoring cardiac involvement in patients suspected of having PA is crucial for optimal management. Strain echocardiography (strain echo) and cardiac magnetic resonance (CMR) imaging may reveal detailed heart function in these individuals. Strain echo is a non-invasive imaging method that measures heart muscle tension throughout each cardiac cycle, providing comprehensive myocardial function data. It can identify subtle changes in heart function before ejection fraction issues become apparent. Strain echo is useful for determining cardiac involvement and changes in patients suspected of having PA. Advanced CMR imaging provides in-depth views of the heart's anatomy and function. It can visualize cardiac structure and function more clearly than echocardiography.[28]

CMR may offer detailed information about heart shape, tissue properties, and function, making it valuable for determining cardiac involvement in suspected PA cases. Patients with suspected PA who need cardiac involvement tests include:

1. Patients with proven PA: A complete monitoring regimen may include strain echo or CMR cardiac assessments.[29]
2. Patients with symptoms or clinical indicators: Those with suspected or confirmed PA should be evaluated for cardiac involvement if they exhibit heart murmurs, arrhythmias, or unexplained lethargy.
3. Newly diagnosed patients: Cardiac screening may be used to assess systemic involvement.
4. Patients with metabolic decompensation: Metabolic abnormalities can damage the heart; therefore, cardiac function should be monitored during crises.[30]

Table 1. Main topic points of recent studies

Ref. no.	Authors	Subjects	Main theme
Ref (21)	Rodriguez-Gonzalez et al.	Patients with propionic acidemia	Propionic acidemia increases the risk of Long QT Syndrome (LQTS) and sudden cardiac death in children. Therefore, 12-lead electrocardiograms (ECGs), echocardiograms, Holter monitoring, and activity tests are recommended. Diagnosis of LQTS necessitates beta-blockers, lifestyle modifications, and avoidance of QTc prolongation.
Ref (5)	Haijes et al.	Patients	The overall outcome remains poor in the majority of patients, who suffer from various progression-related consequences, including cardiac changes (arrhythmias, dilated cardiomyopathy (DCM), or hypertrophic cardiomyopathy), a major cause of morbidity and death in propionic acidemia (PA).
Ref (8)	Tamayo et al.	Mouse model of propionic acidemia	PA patients with cardiac dysfunction and ventricular arrhythmias may benefit from targeting redox-modified Ca^{2+} handling.
Ref (14)	Riemersma et al.	Adult-onset dilated cardiomyopathy	The HOSPITAL score and LACE index predicted 30-day and 1-year mortality in older multimorbid polypharmacy patients. These simple parameters may predict post-hospitalization mortality in older multimorbid individuals.
Ref (16)	Baruteau et al.	Cardiomyopathy patients	DCM commonly begins in neonates or children with metabolic disorders. Metabolism may contribute to adult-onset DCM.
Ref (17)	Laemmle et al.	Adolescent with acute onset of dilated cardiomyopathy	Increased propionyl-CoA carboxylase (PCC) activity may heighten the risk of DCM due to repetitive metabolic stresses.
Ref (19)	Kovacevic et al.	Patients with propionic acidemia	A 39% incidence of cardiomyopathies (CMs) among early-onset PA patients. Two-thirds of these individuals demonstrated diastolic left ventricular (LV) dysfunction, which often preceded systolic LV failure.
Ref (20)	Arrizza et al.	Liver transplantation patients	Routine angiotensin-converting enzyme inhibitor (ACE-I) medication did not enhance LV systolic function, indicating the necessity for tailored therapies or early liver transplantation. PA patients with advanced DCM may benefit from a liver transplant. However, following liver transplantation, a patient with PA may develop severe DCM.
Ref (21)	Rodríguez-González et al.	A 9-year-old boy diagnosed with propionic acidemia	Several recent articles have established the link between PA and LQTS, which can be fatal.
Ref (22)	Duras et al.	Two sisters with propionic acidemia	Two sisters with PA had prolonged QT lengths. An ECG, stress test, and 24-hour Holter monitoring confirmed LQTS. This paper emphasizes the importance of early detection of LQTS in asymptomatic PA patients to prevent its fatal consequences.
Ref (25)	Bodi et al.	Patients with propionic acidemia	PA metabolites have been shown to acutely reduce IKs, thereby prolonging action potential duration and causing LQTS.
Ref (26)	Baumgartner et al.	Neonatal patients	Methylmalonic acidemia (MMA) leads to chronic renal failure and PA cardiomyopathy. The mental prognosis for PA is worse. Apart from vitamin B12-responsive forms, outcomes for MMA are generally poor.

PA particularly impacts cardiac diastolic function in several ways:

1. PA may induce cardiomyopathy, which impairs both systolic (contractile) and diastolic (relaxation) heart functions. Changes in myocardial tissue associated with cardiomyopathy can lead to diastolic dysfunction, preventing the heart from relaxing and filling properly.
2. High blood acid: Patients with PA often develop metabolic acidosis. This direct myocardial metabolic acidosis can reduce diastolic function. Acidosis may also affect the handling of calcium in cardiac muscle cells, impacting heart relaxation.
3. Electrolytes: Metabolic abnormalities related to PA can cause imbalances in potassium and calcium, affecting heart muscle function. Such electrolyte imbalances might impair cardiac relaxation.
4. Arrhythmia risk: PA increases the risk of arrhythmias, which can disrupt diastole and impair diastolic filling.
5. Myocardial damage: In severe metabolic crises, PA patients may experience myocardial damage, affecting heart function for years. A deficiency of oxygen and nutrients during these crises can damage the heart muscle and induce diastolic dysfunction.[31]

Reversible DCM in Patients with Medicinal Therapy

Hypocalcemia lowers cardiac function because contraction coupling requires calcium. Rarely, hypocalcemia can lead to cardiomyopathy (CM) and congestive heart failure (HF).[32] Complete recovery from DCM caused by hypocalcemia is possible with the normalization of serum calcium levels. Most newborns and older children experience vitamin D insufficiency and hypocalcemia. In breastfed children, vitamin D deficiency can lead to nutritional rickets.[33] Cardiac contraction requires calcium ions. During cardiac action potentials, ionized calcium enters cells through depolarization-activated calcium channels. This ionized calcium releases calcium from the sarcoplasmic reticulum (SR). Ca^{2+} from troponin C on myofilaments contracts the heart. Mainly, two mechanisms impact cardiac contractility: changes in the amplitude or duration of the Ca^{2+} transient, and alterations in myofilament Ca^{2+} sensitivity.[34] Hypocalcemia-induced dilated cardiomyopathy (DCMP) is often the result of changes in Ca^{2+} transient amplitude or duration.[35]

In the Middle East, vitamin D insufficiency is a significant public health concern, particularly for exclusively breastfed infants born to mothers with low vitamin D stores, dark complexions, and/or sedentary lifestyles that limit UV radiation exposure.[36] Hypocalcemia in vitamin D-deficient mothers may cause early and severe sequelae.[37] For newborns with vitamin D-deficient mothers or limited sun exposure, the American Academy of Pediatrics (AAP) and the Canadian Paediatric Society (CPS) recommend 400 IU/day of vitamin D immediately after birth, an increase from the previous recommendation of 200 IU/day in the first two months. This supplementation should continue until the child can consume one liter of vitamin D-fortified formula daily. A balanced diet and 2,000 IU/day of maternal vitamin D supplementation are also recommended.[38]

All pregnant and lactating women, especially those at risk of vitamin D deficiency, should be aware of this updated advice.[39] One study reviewed hospital records of vitamin D-deficient DCM from 1997 to 2007, finding four exclusively breastfed African American infants. These infants, suffering from DCM-related congestive heart failure, presented with hypocalcemic rickets. Heart function improved with vitamin D and calcium supplementation over months.[37] In another study, 15 Indian children aged 45 days to five months with acute left ventricular failure had hypocalcemia and hypomagnesemia. Most cases of hypocalcemia were due to vitamin D insufficiency. Vitamin D and calcium supplementation benefited these children.[40]

PA Impact on Cardiac Markers and Monitoring Recommendations

Since metabolic issues in PA are systemic, PA may indirectly impair heart function, though it is not known to directly alter cardiac disease or injury-related symptoms. Cardiac markers in blood tests are used to identify heart disease. These markers indicate heart muscle or cardiac disease. Troponin, found in heart muscle, can elevate during a cardiac attack, indicating heart muscle injury. However, troponin levels are not directly increased by propionic acidemia. Creatine Kinase-MB (CK-MB), a cardiac muscle enzyme, signifies myocardial damage when elevated, but PA does not affect CK-MB levels. N-terminal pro b-type natriuretic peptide (NT-proBNP) is produced by the heart in response to cardiac stress. Both brain natriuretic peptide (BNP) and NT-proBNP may increase in heart failure and other cardiac diseases. However, PA seldom raises BNP or NT-proBNP levels. Myoglobin, present in both heart and skeletal muscles, may indicate heart muscle damage when elevated. PA does not affect myoglobin levels. While PA does not directly influence cardiac markers, metabolic crises can be widespread. Such a crisis may cause metabolic acidosis, electrolyte abnormalities, and cardiac damage. Secondary metabolic diseases may alter cardiac parameters.[28]

CONCLUSION

Organic acidemias are considered "simple" enzymatic lesions, yet their phenotypes can be complex due to the wide range of metabolites involved. PA, for instance, is prone to cardiac dysfunction. Given the complexity and rarity of these disorders, the molecular basis of their dysfunction remains largely

unexplored. Over the past decade, there has been increasing interest in propionate biology and research to understand gross organ failure in PA. PA individuals may have congenital deficiencies in PCC and proteins that are mutated in DCM or LQTS, although this is unlikely. Current information suggests that harmful metabolites such as propionate, propionyl-CoA, and 2-methylcitrate contribute to these cardiac diseases. Mitochondrial dysfunction, oxidative stress, and alterations in gene expression have been observed. It is implausible that a single mechanism is solely responsible. Understanding these mechanisms and identifying molecular targets in the hearts of PA patients can aid in developing more effective therapy options.

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