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FRANK'S SIGN IN CARDIOVASCULAR PRACTICE: FROM CLINICAL VALIDITY TO PROGNOSTIC VALUE

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INTRODUCTION

The Frank's Sign (FS) was formally described in 1973 by Sanders T. Frank, who initially reported the association between the presence of this earlobe crease and conditions such as angina pectoris and coronary artery disease (CAD) (BABOUJIAN *et al.*, 2019). Although its incorporation into modern medicine is relatively recent, historical records suggest its existence since antiquity, with evidence in Roman busts of Emperor Hadrian and in works from the Italian Renaissance. Such evidence indicates that the relationship between external physical characteristics and internal pathologies has sparked interest for centuries (ABRAHIM, 2022; STOYANOV *et al.*, 2022).

Despite growing scientific interest, the pathophysiological basis for using FS as a clinical marker of vascular diseases remains debated. Several hypotheses have been proposed to explain this association, including microvascular changes, loss of tissue elasticity, and degenerative processes associated with aging (WIECKOWSKI *et al.*, 2021).

The clinical relevance of FS in predicting cardiovascular events has been extensively documented, being frequently described as an independent predictor of CAD and myocardial infarction (GAO *et al.*, 2024; GUO *et al.*, 2025). Evidence indicates that specific characteristics of the crease, such as bilaterality, depth, and extent, are positively correlated with the severity of coronary obstruction assessed by angiography (CULEBRAS, 2020; LIU *et al.*, 2020). Furthermore, its association is not restricted to the cardiovascular system; it also extends to the cerebrovascular system, where it has been linked to an increased risk of ischemic and hemorrhagic strokes and to thickening of the carotid artery intima-media layer (NAZZAL *et al.*, 2017).

Despite its clinical potential, the use of FS as an isolated screening tool remains controversial, particularly given its variable diagnostic accuracy across populations (GAKOVIC *et al.*, 2023). On the other hand, it is a simple, non-invasive, and zero-cost semiological finding, making it a relevant resource in the cardiovascular physical examination (ABRAHIM, 2022). Its identification can alert the clinician to the need for a more thorough complementary investigation, favoring the early detection of subclinical atherosclerosis and the implementation of preventive strategies in individuals potentially underdiagnosed by traditional risk stratification models (GAO *et al.*, 2024).

Given this context, the present study aims to investigate the role of FS as an auxiliary tool for the early identification of cardiovascular risk in clinical practice, through an integrated analysis of evidence from scientific literature. It seeks to understand its association with cardiovascular diseases and to discuss the proposed pathophysiological mechanisms that support it. Furthermore, it intends to evaluate its clinical relevance as a simple semiological method with potential application in early detection and the adoption of preventive measures in cardiovascular health.

METHODOLOGY

The present study is an integrative literature review that synthesizes and critically analyzes the scientific evidence on FS as a clinical marker of systemic atherosclerosis and cardiovascular risk. The analysis focused on the association of the sign with coronary artery disease and cerebrovascular events, its potential prognostic relevance, and the underlying pathophysiological mechanisms, including microvascular changes, accelerated vascular aging, and endothelial dysfunction.

The literature search was conducted across electronic databases widely recognized in the health and medical fields, including PubMed, Web of Science, SciELO, Virtual Health Library (VHL/BVS), and the CAPES Journals Portal, alongside consultations of relevant secondary references. Controlled descriptors and free-text terms combined by Boolean operators (AND, OR) were used, such as “Frank's Sign”, “earlobe crease”, “coronary artery disease”, “atherosclerosis”, “cardiovascular risk”, “stroke”, and “endothelial dysfunction”. Search strategies were adapted according to the specificities of each database to increase the sensitivity and comprehensiveness of study retrieval.

Articles published within the last 10 years, available in full text and open access, addressing the relationship between FS and cardiovascular outcomes, pathophysiological aspects, or its diagnostic and prognostic value, were included. Observational, clinical, reviews, and experimental investigations with clinical relevance were considered. Duplicate publications, studies unrelated to the topic, and non-peer-reviewed documents, such as editorials, abstracts, and unpublished academic works, were excluded.

Data analysis was conducted using a qualitative, descriptive approach through a full reading of the selected studies and the organization of findings into thematic axes, including associations with coronary artery disease and cardiovascular events, morphological characteristics of the sign, and the biological mechanisms involved. Since this is a narrative review, a formal methodological quality assessment or meta-analysis was not performed. The synthesis of results prioritized a critical, integrative, and theoretically grounded interpretation, seeking to understand the role of FS as a complementary clinical tool in cardiovascular risk stratification.

RESULTS AND DISCUSSION

Concept and characterization of Frank's Sign

The FS, technically termed the diagonal earlobe crease, constitutes an acquired physical feature of high semiological value (STOYANOV *et al.*, 2022). It is based on the premise that easily observable external findings can reflect internal vascular changes and act as potential clinical markers for systemic diseases (PACEI *et al.*, 2020; ABRAHIM, 2022).

From a semiological perspective, the sign manifests as a groove or wrinkle originating in the tragus region and extending obliquely in a posteroinferior direction, forming an approximate 45-degree angle along the earlobe to its posterior border (**Figure 13.1**) (BAZOUKIS *et al.*, 2022; STOYANOV *et al.*, 2022). It can present unilaterally or bilaterally and, in terms of extent, can be classified as complete, when it runs across the entire lobe, or incomplete (VELÁZQUEZ-SOTELO *et al.*, 2023). Additionally, various grading systems have been proposed to assess its severity, ranging from superficial creases (Grade 1) to deep, complete grooves in which the base is not visible (Grades 3-4) (PRANGENBERG *et al.*, 2022).

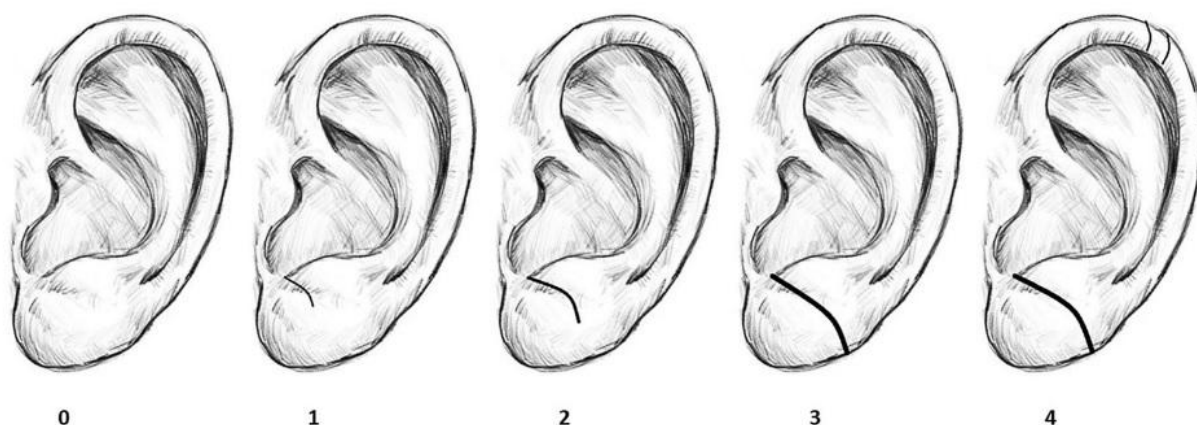
From a histological perspective, the characteristic crease of FS is associated with relevant microvascular changes, including elastic fiber degeneration, arterial myoelastofibrosis, deep tissue fibrosis, and peripheral nerve degeneration (JO *et al.*, 2025). These modifications reflect structural changes in tissues supplied by end-arteries, such as the earlobe, and appear to replicate, on a smaller scale, the atherosclerotic processes and morphological changes observed in the coronary arteries and myocardium (BABOUJIAN *et al.*, 2019). Furthermore, the prevalence of the sign progressively increases with

age, showing a positive correlation with the extent and severity of CAD, as well as cardiometabolic disorders, including arterial hypertension, type 2 diabetes mellitus, stroke, and facial visceral obesity (ABRAHIM, 2022).

From a clinical perspective, FS has greater prognostic value in younger individuals, partic-

ularly those under 60 years of age. In this population, its presence is less expected and may indicate early biological or vascular aging, serving as an important marker of subclinical atherosclerosis that is undetected by traditional risk stratification models (PASTERNAK; SAMI, 1982; PRANGENBERG *et al.*, 2022).

Figure 13.1 Frank's Sign and grades of variation



Source: STOYANOV *et al.*, 2022.

On the other hand, aging constitutes a limiting factor for the diagnostic accuracy of the sign, as its frequency naturally increases with age. This aspect poses a significant clinical challenge, making it difficult to distinguish changes resulting from physiological skin aging from those associated with vascular pathological processes (CULEBRAS, 2020; MOLINA-GALLARDO *et al.*, 2024).

In summary, although FS is considered an independent marker of cardiovascular risk, its specificity tends to decrease in elderly populations. Thus, its clinical applicability proves particularly useful as a screening and early prevention tool in young and middle-aged adults, in whom it can contribute more significantly to identifying underlying cardiovascular risk (PRANGENBERG *et al.*, 2022; VELÁZQUEZ-SOTELO *et al.*, 2023).

Pathophysiological mechanisms of Frank's Sign

The formation of FS (diagonal earlobe crease) is not limited to a superficial skin alteration; it results from complex histological and pathophysiological processes that reflect systemic vascular and neurological status. Histopathological evidence demonstrates that the base of the crease presents big structural changes, including arterial myoelastofibrosis, characterized by the thickening of vascular walls and degeneration of elastic fibers in local arterioles, a process analogous to the arteriosclerosis observed in small vessel diseases of the brain and coronary arteries (WIECKOWSKI *et al.*, 2021; STOYANOV *et al.*, 2022). Additionally, Wallerian-type nerve degeneration is observed in peripheral nerves within the groove, associated with eosinophilic inclusions and deep tissue fibrosis not exclusively related to sun exposure (SÁNCHEZ-CIRERA *et al.*,

2021; STOYANOV *et al.*, 2022). Additional vascular changes, such as the tortuous "corkscrew" appearance of arterioles, reinforce the hypothesis of local chronic ischemia (STOYANOV *et al.*, 2022).

From a pathophysiological standpoint, the formation of the sign can be understood through the interaction of multiple mechanisms. The vulnerability of end arteries is central, as both the earlobe and the myocardium depend on terminal circulation with a limited collateral network, rendering them susceptible to hypoperfusion and hypoxia resulting from systemic atherosclerosis (JO *et al.*, 2025). Additionally, endothelial dysfunction, evidenced by reduced flow-mediated dilation, has been associated with the presence of the sign, indicating early vascular impairment (PACEI *et al.*, 2020). Another relevant mechanism involves connective tissue degeneration, with loss of collagen and elastin integrity, possibly related to inflammatory and metabolic dysfunctions similar to those observed in atherogenesis (ABRAHIM, 2022).

In parallel, mechanical theories have also been proposed, such as the influence of facial visceral adiposity. In this model, an increase in Bichat's fat pad (buccal fat pad) could exert chronic traction on facial ligamentous structures, contributing to the formation of the crease over time (ABRAHIM, 2022). Together, these findings support the interpretation of FS as a peripheral manifestation of systemic processes, including chronic ischemia, neural degeneration, and fibrotic remodeling, acting as an external indicator of internal vascular changes.

Genetic bases and associated molecular markers

The association of FS with molecular markers of vascular aging has been extensively investigated, highlighting the relationship between FS and telomere shortening. Studies

demonstrate that individuals with the crease exhibit significantly shorter leukocyte telomeres, indicating accelerated cellular senescence and reinforcing the association between the crease and early biological aging (ABRAHIM, 2022). In addition, reduced levels of the Klotho hormone, known for its vascular-protective and anti-aging properties, have been observed in these patients, suggesting a relevant role in the pathophysiology of systemic vascular damage (JO *et al.*, 2025).

In the genetic domain, several associations have been described. FS has been correlated with immunogenetic markers, such as the human leukocyte antigen HLA-B27, as well as localized alterations on chromosome 11 and possible associations with the atherosclerosis-related gene CF-3 (PACEI *et al.*, 2020; SÁNCHEZ-CIRERA *et al.*, 2021). Furthermore, genetic variants of the LPA gene, responsible for regulating lipoprotein(a) levels, have been implicated in amplifying cardiovascular risk in individuals with the sign, especially in carriers of risk genotypes, such as LPAKIV-2/rs10455872 (GUO *et al.*, 2025).

A particularly relevant model is observed in the genetic small vessel disease known as CADASIL, in which mutations in the NOTCH3 gene lead to the accumulation of abnormal proteins (Notch3ECD) in the vascular wall. This process triggers cellular stress and smooth muscle cell degeneration, affecting both cerebral circulation and peripheral vascularization, including the earlobe. This pathophysiological overlap explains the high prevalence of FS in patients with this condition (JO *et al.*, 2025).

Together, these findings indicate that FS is not merely a morphological marker but also a possible reflection of genetic and molecular changes associated with accelerated vascular aging and predisposition to atherosclerotic diseases.

Diagnostic and prognostic value

The diagnostic and prognostic value of FS, also termed diagonal earlobe crease (DELC), has been widely investigated as a clinical marker of systemic atherosclerosis. Despite the significant volume of studies, accuracy varies considerably, depending on both the characteristics of the analyzed population and the methodological rigor and diagnostic criteria adopted (BABOUJIAN *et al.*, 2019).

In this context, the available scientific evidence indicates substantial heterogeneity in the accuracy of predicting coronary artery disease (CAD), as summarized in **Chart 13.1**. This variability reinforces the need for a careful interpretation of the sign in the clinical context, considering individual factors and its association with other cardiovascular risk markers.

Chart 13.1 Diagnostic accuracy of FS (sensitivity and specificity)

Study / Source	Sensitivity	Specificity	Notes and context
Pasternac; Sami (1982)	59,5%	81,9%	A study with 340 patients undergoing arteriography showed a Positive Predictive Value (PPV) of 91.1% for predicting the presence of CAD.
Gakovic <i>et al.</i> (2023)	55,0%	53,0%	Evaluation of Bilateral FS in 1,377 patients to detect obstructive coronary artery disease (CAD).
Bazoukis <i>et al.</i> (2022)	80,65%	44,15%	Specific accuracy observed in patients with Chronic Obstructive Pulmonary Disease (COPD).
Velázquez-Sotelo <i>et al.</i> (2023)	68,0%	77,0%	A study in a Mexican population confirmed the sign as useful for identifying CAD, with a PPV of 94%.

FS is not limited to indicating the presence of atherosclerotic disease but also shows a significant association with the extent and severity of vascular impairment (BAZOUKIS *et al.*, 2022). In this context, a positive correlation is observed between the grade of the sign and the complexity of coronary lesions, as measured by the SYNTAX Score, such that individuals with bilateral and deep creases tend to have a higher probability of severe obstruction and multivessel involvement (VELÁZQUEZ-SOTELO *et al.*, 2023). Furthermore, its presence has been associated with worse clinical outcomes, including an increased risk of cardiovascular morbidity and mortality, a higher incidence of myocardial infarction, and lower long-term survival among previously affected patients (PRANGENBERG *et al.*, 2022). Within the cerebrovascular scope, the sign also stands out as an independent predictor of ischemic stroke

and is associated with more unfavorable functional outcomes 90 days after the event (OR = 1.87) (JO *et al.*, 2025).

Although aging is a major confounding factor, there is consistent evidence supporting FS's independence as a clinical marker. Multivariate regression models demonstrate that its association with cardiovascular events remains statistically significant even after adjusting for traditional risk factors such as age, diabetes mellitus, arterial hypertension, and smoking (GAO *et al.*, 2024). Furthermore, histopathological findings reinforce its biological plausibility, showing arterial myoelastofibrosis and deep tissue fibrosis at the base of the crease, alterations that reflect systemic vascular damage (BAZOUKIS *et al.*, 2022; STOYANOV *et al.*, 2022). From a molecular standpoint, the sign has also been associated with telomere shortening and reduced levels of Klotho, an anti-aging hormone, which corroborates its link to accelerated vascular aging (JO *et al.*, 2025; ABRAHIM, 2022).

Despite its isolated diagnostic accuracy being considered moderate, FS remains clinically relevant due to its simplicity, non-invasive nature, and zero cost. Thus, its inclusion in the physical examination can help identify individuals who require a more thorough evaluation and more rigorous cardiovascular risk stratification, especially when used in conjunction with other clinical and laboratory markers (GAKOVIC *et al.*, 2023).

Clinical applicability, controversies, and perspectives

The FS stands out as a relevant component of physical inspection in cardiology, as a non-invasive, low-cost, and easily identifiable visual marker (BABOUJIAN *et al.*, 2019). Its clinical applicability spans different contexts, especially in cardiovascular risk assessment. In this sense, its primary utility lies in predicting coronary artery disease (CAD), since its presence has been positively correlated with the prevalence, extent, and severity of the disease, independently of traditional risk factors such as hypertension and diabetes mellitus (PACEI *et al.*, 2020). Evidence indicates that bilateral, deep, and complete creases are associated with more severe coronary obstructions, frequently confirmed by angiography (STOYANOV *et al.*, 2022).

In addition, FS has also been described as a potential marker of cerebrovascular risk. Studies demonstrate its association with a higher risk of ischemic brain events and structural changes, including an increased burden of white matter lesions and thickening of the carotid artery intima-media layer. In stroke patients, the prevalence is higher in ischemic than in hemorrhagic cases (NAZZAL *et al.*, 2017; SÁNCHEZ-CIRERA *et al.*, 2021). Furthermore, it has particular utility in specific populations, such as young individuals, in whom its

presence is less expected and may indicate early vascular aging or subclinical atherosclerosis (ABRAHIM, 2022). When combined with other biomarkers, such as lipoprotein(a), the sign can further refine risk stratification models, increasing accuracy in predicting coronary disease (GUO *et al.*, 2025).

Despite this evidence, controversies persist regarding its true independence as a clinical marker. While some in the literature recognize it as an independent predictor of cardiovascular risk, others argue that its association with vascular diseases may be spurious, largely reflecting the effects of chronological aging (WIECKOWSKI *et al.*, 2021). Compounding this is the uncertainty regarding its etiology, with hypotheses ranging from chronic hypoperfusion mechanisms in end-arteries to mechanical factors, such as sleeping position or traction exerted by facial adiposity (Bichat's fat pad) (ABRAHIM, 2022). Additionally, its predictive value is limited in populations with specific comorbidities, as demonstrated by studies that found no significant independent association in patients with type 2 diabetes mellitus (STOYANOV *et al.*, 2022).

Given this scenario, future perspectives on the use of FS in clinical practice involve methodological and technological advancements to increase its reliability and applicability. The incorporation of AI-based tools, such as facial image analysis or three-dimensional reconstructions from magnetic resonance imaging (MRI), can reduce the subjectivity of clinical assessment and promote greater diagnostic standardization (JO *et al.*, 2025). Furthermore, the sign can serve as an initial screening tool for genetic small-vessel diseases, especially in resource-limited settings (JO *et al.*, 2025). Conducting large-scale prospective studies is also essential to clarify the temporal relationship between the appearance of the crease and the progression of

vascular disease, thereby determining its true predictive value (PRANGENBERG *et al.*, 2022). Finally, international standardization of its nomenclature and classification is fundamental to ensuring greater comparability across studies and to enabling its consistent integration into formal cardiovascular risk assessment models (WIECKOWSKI *et al.*, 2021).

CONCLUSION

FS is considered a semiological finding of great interest in clinical practice, primarily due to its simplicity, non-invasive nature, and low cost. From a pathophysiological standpoint, FS reveals itself as a peripheral manifestation of complex systemic processes, including endothelial dysfunction, chronic ischemia, connective tissue degeneration, and accelerated vascular aging. The association with molecular markers, such as telomere shortening and reduced Klotho levels, as well as specific genetic factors, reinforces its biological plausibility and

broadens the understanding of its relationship with cardiovascular diseases.

Despite this evidence, the variability in its diagnostic accuracy and the influence of aging as a confounding factor limit its use as an isolated marker. In this context, FS must be interpreted in an integrated manner with other clinical, laboratory, and imaging factors, contributing as a complementary tool in cardiovascular risk stratification, especially in younger individuals, in whom its predictive value tends to be more significant.

Finally, the need for large-scale prospective studies with greater methodological standardization is highlighted to consolidate its role in clinical practice. Advances in technology offer a promising avenue for increasing diagnostic precision and reducing subjectivity in identification. Thus, FS remains a relevant clinical marker, with applicability in the early detection and prevention of cardiovascular diseases.

REFERENCES

- ABRAHIM, M. Unified anatomical explanation of diagonal earlobe creases, preauricular creases, and paired creases of the helix. *Cureus*, v. 14, e27929, 2022. doi: 10.7759/cureus.27929.
- BABOUJIAN, A. *et al.* Diagonal earlobe crease, a marker of coronary artery disease: a case report on Frank's sign. *Cureus*, v. 11, 2019. doi: 10.7759/cureus.4219.
- BAZOUKIS, G. *et al.* The importance of inspection in clinical cardiology: Frank's sign. *Clinical Case Reports*, v. 10, e06150, 2022. doi: 10.1002/ccr3.6150.
- CULEBRAS, A.C. Bilateral earlobe creases and subsequent malignant cerebral infarction: a patient with diffuse endothelial dysfunction. *Cureus*, v. 12, e9308, 2020. doi: 10.7759/cureus.9329.
- GAKOVIC, B. *et al.* The relationship of diagonal earlobe crease (Frank's sign) and obstructive coronary artery disease in patients undergoing coronary angiography. *Wiener klinische Wochenschrift*, v. 135, p. 667, 2023. doi: 10.1007/s00508-023-02297-y.
- GAO, J. *et al.* Clinical value of the diagonal earlobe crease in patients with chest pain for diagnosing coronary heart disease. *International Journal of General Medicine*, v. 17, p. 1557, 2024. doi: 10.2147/IJGM.S454888.
- GUO, R. *et al.* Diagnostic value of the diagonal earlobe crease in combination with lipoprotein(a) in coronary heart disease. *Scientific Reports*, v. 15, 2025. doi: 10.1038/s41598-025-06464-1.
- JO, S. *et al.* Frank's sign as a dose-dependent marker of white matter burden in cadasil: a brain MRI study. *Journal of Clinical Medicine*, v. 14, 2025. doi: 10.3390/jcm14196865.
- LIU, Z. *et al.* Ear crease features are associated with complexity of coronary lesions. *Medical Science Monitor*, v. 26, 2020. doi: 10.12659/MSM.923343
- MOLINA-GALLARDO, R. *et al.* Traditional Cardiovascular risk factors associated with diagonal earlobe crease (Frank Sign) in mexican adults: aging, obesity, arterial hypertension, and being male are the most important. *International Journal of Hypertension*, v. 2024, 2024. doi: 10.1155/2024/5598134.
- NAZZAL, S. *et al.* Diagonal earlobe crease (Frank's sign): a predictor of cerebral vascular events. *The American Journal of Medicine*, v. 130, 2017. doi: 10.1016/j.amjmed.2017.03.059.
- PACEI, F. *et al.* Diagonal earlobe crease (Frank's sign) and increased risk of cerebrovascular diseases: review of the literature and implications for clinical practice. *Neurological Sciences*, v. 41, p. 257, 2020. doi: 10.1007/s10072-019-04080-2.
- PASTERNAK, A.; SAMI, M. Predictive value of the ear-crease sign in coronary artery disease. *Canadian Medical Association Journal*, v. 126, p. 645, 1982.
- PRANGENBERG, J. *et al.* The prognostic value of the Frank sign. *Forensic Science, Medicine and Pathology*, v. 18, p. 149, 2022. doi: 10.1007/s12024-022-00463-8.
- SÁNCHEZ-CIRERA, L. *et al.* Prevalence of the Frank's sign by aetiopathogenic stroke subtype: a prospective analysis. *PLoS ONE*, v. 16, 2021. doi: 10.1371/journal.pone.0261080.
- STOYANOV, G.S. *et al.* Frank's sign and paired ear creases of the helix: current concepts of significance for morbidity. *Wiener Klinische Wochenschrift*, v. 134, p. 237, 2022. doi: 10.1007/s00508-021-01969-x.
- VELÁZQUEZ-SOTELO, C.E. *et al.* Frank's sign associated with the severity of ischemic heart disease in patients under 65 years old. *Medicina Clínica*, v. 161, p. 509, 2023. doi: 10.1016/j.medcli.2023.07.003.
- WIECKOWSKI, K. *et al.* Diagonal earlobe crease (Frank's Sign) for diagnosis of coronary artery disease: a systematic review of diagnostic test accuracy studies. *Journal of Clinical Medicine*, v. 10, 2021. doi: 10.3390/jcm10132799.