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FROM RED FLAGS TO DIAGNOSIS: A HEPATOLOGIST'S GUIDE TO GAUCHER DISEASE AND ACID SPHINGOMYELINASE DEFICIENCY IN ADULTS – INSIGHTS FROM THE ITALIAN "CLOSER TO CARE" INITIATIVE

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ABSTRACT **–** Gaucher disease (GD) and acid sphingomyelinase deficiency (ASMD) are rare lysosomal storage disorders with chronic visceral forms that often present in adulthood with nonspecific hepatic or hematologic signs. Hepatologists are frequently among the first specialists to encounter these patients, particularly when evaluating unexplained hepatosplenomegaly, thrombocytopenia, dyslipidemia, or liver test abnormalities. However, due to clinical overlap with common liver conditions, such as metabolic dysfunction-associated steatotic liver disease and cryptogenic cirrhosis, both GD and ASMD remain significantly underdiagnosed or misdiagnosed. Lack of disease awareness, diagnostic inertia, and the absence of structured pathways contribute to substantial delays in treatment initiation. This review aims to equip hepatologists with practical tools to improve early recognition of GD and ASMD through the application of red flag-based diagnostic flowcharts. Drawing on current literature and field experience, we present an integrated hepatology-focused approach that begins with common clinical triggers and guides enzyme testing and referral decisions. We further describe the development and implementation of the Italian "GD & ASMD – Closer to Care" initiative, which combined field-based training, diagnostic network-building, and pilot screening activities across referral hepatology centers. Finally, we explore emerging perspectives, including the role of newborn and at-risk populations screening and exome sequencing in cryptogenic and multisystemic liver diseases. While advanced diagnostic tools promise future improvements in early detection, actionable awareness, and risk-based screening remain the cornerstone of the current diagnostic strategy. By adopting standardized flowcharts and promoting interdisciplinary collaboration, hepatologists can play a pivotal role in closing the diagnostic gap for GD and ASMD, ensuring earlier diagnosis and access to disease-specific therapies for affected individuals.

Keywords: Gaucher disease, Acid sphingomyelinase deficiency, Lysosomal storage disorders, Hepatology, Splenomegaly, Thrombocytopenia, Red flags, Diagnostic flowcharts, Rare liver diseases, Dried blood spot, Screening.

Abbreviations: Acid sphingomyelinase deficiency (ASMD); body mass index; dried blood spot (DBS); Gaucher disease (GD); Gaucher Earlier Diagnosis Consensus (GED-C); high-density lipoprotein (HDL); low-density lipoprotein (LDL); lysosomal storage disorder (LSD); metabolic dysfunction-associated steatotic liver disease (MASLD); metabolic dysfunction-associated steatohepatitis (MASH); monoclonal gammopathy of undetermined significance (MGUS); newborn screening (NBS); Niemann–Pick disease type A/B (NPD A/B).

INTRODUCTION

Gaucher disease (GD) and acid sphingomyelinase deficiency (ASMD) are rare autosomal recessive lysosomal storage disorders caused by deficient activity of glucocerebrosidase and acid sphingomyelinase, respectively[1,2]. These enzyme deficiencies result in intracellular accumulation of undegraded lipids – glucosylceramide in GD and sphingomyelin in ASMD. While in GD the accumulation is limited to the macrophage lineage, in ASMD it is instead distributed across multiple cell types, leading to multisystem involvement[3,4]. While early-onset neuronopathic forms have dramatic and well-characterized features, the chronic visceral phenotypes – GD type 1 and ASMD type B – are more frequently encountered in adult patients and may be elusive in their presentation, often showing hepatosplenomegaly, cytopenias, dyslipidemia and liver test abnormalities, which may masquerade as common hepatic, hematologic, and metabolic disorders[5,6].

Despite distinct genetic and biochemical bases, GD type 1 and ASMD type B exhibit substantial phenotypic overlap in their adult forms. Common clinical features, such as hepatosplenomegaly, thrombocytopenia and low high-density lipoprotein (HDL) cholesterol, may lead to diagnostic ambiguity, particularly in lean individuals referred for unexplained liver test alterations or cytopenias[7,8]. Nevertheless, differentiating features exist: GD type 1 often presents with skeletal involvement, while ASMD more

frequently progresses to liver fibrosis and cirrhosis, and often shows interstitial lung disease and atherosclerotic cardiovascular disease[9,10]. Differences in biochemical profiles – namely, elevated transaminases and low-density lipoprotein (LDL) cholesterol in ASMD *vs.* hyperferritinemia and hypocholesterolemia in GD – can further support clinical distinction[11].

Liver involvement is a clinically relevant and potentially progressive aspect of both diseases. In GD, hepatic manifestations are commonly limited to hepatomegaly due to Gaucher cell infiltration but may rarely evolve to fibrosis, cirrhosis or hepatocellular carcinoma in selected cases, particularly when concurrent liver diseases are present[12-16]. Splenomegaly is almost invariably present, often massive, with hypersplenism and cytopenias, particularly thrombocytopenia; spleen enlargement always dominates liver enlargement, and is caused primarily by the accumulation of Gaucher cells and a subsequent inflammatory reaction. Other features of GD include biochemical anomalies such as hyperferritinemia without iron overload and polyclonal or monoclonal gammopathies, as well as structural issues like cholelithiasis and focal hepatic and splenic lesions (gaucheromas) that may complicate diagnosis by mimicking other liver conditions[17-23].

In ASMD, sphingomyelin accumulates in both Kupffer cells and hepatocytes, often leading to progression in steatohepatitis, fibrosis and cirrhosis[24-28]. Advanced cases may present with portal hypertension or variceal bleeding, and end-stage liver disease is among the leading causes of death in patients with ASMD. Initially, splenomegaly is primarily caused by the infiltration of lipid-laden macrophages, whereas an accelerated spleen enlargement may occur secondarily as a result of worsening portal hypertension associated with the progression of fibrotic liver disease[29].

Structured diagnostic flowcharts and educational initiatives have been proposed to raise awareness and streamline the diagnostic approach. In Italy, the national program "GD & ASMD – Closer to Care" has pioneered a hepatology-focused strategy combining field-based education, real-world screening, and collaborative flowchart development. Central to this effort is the identification of red flags that can trigger timely enzymatic testing and early referral.

This review provides hepatologists with a practical and updated overview of GD and ASMD, focusing on adult-onset forms, hepatic manifestations, and diagnostic challenges. It emphasizes the use of structured red flag-based flowcharts. It provides evidence-based insights from the Italian "Closer to Care" initiative, aimed at promoting early detection and the multidisciplinary management of these underrecognized yet treatable disorders.

METHODS

This narrative review combines evidence from the literature and expert experience from the Italian initiative "GD & ASMD – Closer to Care" (October 2023 – October 2024), an accredited continuing medical education training course dedicated to improving the early diagnosis of GD and ASMD in hepatology. A literature search was conducted in PubMed using keywords such as "Gaucher disease", "acid sphingomyelinase deficiency", "lysosomal storage disorders", "hepatology", and "diagnostic algorithms", restricted to English-language publications from the past 20 years.

The diagnostic framework and red flag-based flowchart presented in this review were developed through multidisciplinary discussions during the training initiative. Following the course, participants independently decided to consolidate the insights gained and publish a shared reflection. The resulting flowchart and recommendations reflect both evidence-based practice and consensus formed through real-world experience and educational exchange.

DIAGNOSTIC INERTIA AND DELAY: THE ROLE OF THE HEPATOLOGIST IN DIAGNOSIS, SCREENING, AND MANAGEMENT

Although hepatosplenomegaly, cytopenias, dyslipidemia, and liver test abnormalities are recognized features of both GD and ASMD, these conditions often remain undiagnosed for years[30]. Diagnostic delay is frequently compounded by low clinical suspicion and the rarity of lysosomal storage disorders, especially in adult patients[31,32]. In this context, hepatologists can play a pivotal role, not only in suspecting these conditions during the work-up of unexplained hepatosplenomegaly or liver test abnormalities, but also in initiating appropriate biochemical screening and in longitudinal monitoring of patients with GD and ASMD[33-35].

Diagnostic Inertia

One of the main contributors to delayed diagnosis in lysosomal diseases is diagnostic inertia – the failure to consider rare metabolic disorders, such as GD or ASMD, early in the evaluation of splenomegaly of unknown origin. In a population-based study, 25% of patients presenting with splenomegaly remained without a definitive causal diagnosis despite undergoing extensive diagnostic procedures, including bone marrow biopsy and splenectomy[36]. Notably, only a minority of these patients were ever tested for GD through enzyme activity assays, underscoring a persistent gap in clinical awareness. Hepatologists often contribute to these complex diagnostic pathways through liver imaging, target organ biopsy, or portal hypertension assessment, yet lysosomal storage disorders are rarely considered in the differential diagnoses. This underscores the need for earlier recognition and targeted testing – particularly in patients with unexplained hepatosplenomegaly, cytopenias, dyslipidemia, or liver test abnormalities – before resorting to invasive procedures.

Diagnostic Delay

In both GD and ASMD, patients often experience a prolonged and complex diagnostic journey, during which hepatologists are frequently involved[35]. Many adult patients are initially referred to hepatology services for nonspecific hepatic abnormalities – such as hepatosplenomegaly, thrombocytopenia, transaminase elevation, or hyperferritinemia – before a correct diagnosis is established. In this context, patients are often labeled with alternative hepatic diagnoses, including nonalcoholic fatty liver disease, cryptogenic cirrhosis, or idiopathic portal hypertension. These assumptions may lead to invasive procedures, such as liver biopsy, that yield nonspecific findings and hinder timely lysosomal enzyme testing[31,32].

In ASMD, retrospective data show that more than 85% of patients received an initial incorrect diagnosis, with frequent suspicions of chronic liver or pulmonary disease, hematological malignancies, or metabolic syndromes[32]. The average diagnostic delay ranged from 2 years to 10 years, particularly in adults, where symptoms, such as hepatosplenomegaly or dyslipidemia, may be mistakenly attributed to more common hepatic conditions. Enzyme activity assays – essential for confirming GD or ASMD – were underutilized early in the process, often performed only after a significant accumulation of clinical signs or the involvement of a knowledgeable specialist. Similarly, in GD, liver manifestations often precede diagnosis, but rarely prompt suspicion of a lysosomal storage disorder despite prior evaluations by hepatologists or hematologists[30].

This prolonged diagnostic path underscores the need to raise awareness among hepatologists, who are well-positioned to identify unexplained splenomegaly or chronic liver involvement as potential indicators of an underlying metabolic etiology. Early inclusion of enzyme assays and dried blood spot testing in the diagnostic work-up of hepatosplenomegaly of unclear origin could reduce unnecessary procedures and accelerate appropriate referral and management.

The Hepatologist's Role in Differential Diagnosis and Multidisciplinary Management of GD and ASMD

Given the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), clinicians, particularly hepatologists, may too readily ascribe liver abnormalities to common metabolic etiologies, overlooking rare monogenic disorders, such as GD or ASMD. However, atypical phenotypes – such as lean phenotypes or persistence of liver abnormalities despite significant improvement of metabolic comorbidities – should prompt consideration of lysosomal storage disorders (LSDs). Indeed, several monogenic causes of steatosis can mimic MASLD and be mistakenly managed as such[33,34]. In these contexts, failure to include LSDs in the differential diagnosis may result in years of misdiagnosis and inappropriate work-up[35].

Importantly, hepatologists are often among the first specialists to evaluate patients with unexplained liver abnormalities and thus play a central role in both suspecting and facilitating early diagnosis of GD or ASMD. Tools such as liver biopsy, though frequently employed, rarely yield specific findings for LSDs and are often unnecessary if enzymatic assays or molecular diagnostics are considered earlier in the evaluation process[34,35].

Beyond diagnosis, hepatologists also contribute significantly to the long-term multidisciplinary care of patients with GD and ASMD. These disorders require integrated follow-up involving monitoring for liver involvement, portal hypertension, liver steatosis, and fibrosis-related complications. International

guidelines support structured hepatic assessment, including regular liver function tests, imaging for hepatosplenomegaly and liver stiffness, and risk stratification for hepatocellular carcinoma in selected patients[13,37,38]. Within multidisciplinary teams, comprising metabolic specialists, hematologists, pulmonologists, radiologists and genetic counsellors, the hepatologist ensures systematic hepatic evaluation both at diagnosis and throughout disease progression. As emphasized in recent expert consensus frameworks, their role includes identifying hepatic red flags, interpreting dynamic changes in liver status, and guiding management decisions related to enzyme replacement or substrate reduction therapy. Such collaborative care models are crucial for ensuring timely intervention, avoiding overtreatment, and preserving hepatic reserve throughout the patient's journey[38-40].

EXPERIENCE WITH SCREENING FOR GD AND ASMD

The expanding availability of disease-specific therapies and growing awareness of the diagnostic odyssey experienced by patients with GD and ASMD have prompted efforts to implement early detection strategies. These include newborn screening (NBS), targeted screening in high-risk populations, and dual enzymatic screening in multispecialty contexts (Table 1)[41-52]. This section summarizes key data from published and pilot experiences.

Table 1. Prevalence of GD and ASMD in targeted screening studies.

Study	Setting/ Population	Country	Sample size	GD incidence/ prevalence	ASMD incidence/ prevalence
Burlina et al[41] 2020	Newborn screening	Italy	127,869	1:12,786	Not tested
Burton et al[42] 2017	Newborn screening	USA (Illinois)	110,000+	1:43,959	Not tested
Gragnaniello et al[43] 2024	Newborn screening	Italy	275,011	Not tested	1:137,506
Hickey and Baker[44] 2024	Newborn screening	USA (Illinois)	93,792	Not tested	~0.79/100,000
Pession et al[45] 2023	Pediatric hematology (splenomegaly/ thrombocytopenia)	Italy	154	9.1%	Not tested
Motta et al[46] 2021	Adult hematology (idiopathic splenomegaly/ thrombocytopenia)	Italy	455	3.3%	Not tested
Giuffrida et al[47] 2023	Adults with MGUS	Italy	600	0.7%	Not tested
Marano et al[48] 2024	Adults with Parkinson disease	Italy	1,344	0.4%	Not tested
Huang et al[49] 2020	Pediatric/adult, splenomegaly and/ or cytopenia	China	787	6.2%	Not tested
Oliva et al[50] 2023	Mixed (suspected GD or LSDs)	Global	31,838	4.4%	1.7%
Giacomarra et al[51] 2024	Mixed (suspected GD)	Italy	627	1.3%	0.5%
Morado Arias et al[52] 2025	Mixed (splenomegaly or splenectomy)	Spain	220	2.7%	0.9%

Acid sphingomyelinase deficiency (ASMD); Gaucher disease (GD); lysosomal storage disorder (LSD); monoclonal gammopathy of undetermined significance (MGUS); newborn screening (NBS).

Newborn Screening

NBS for LSDs has been implemented in various regions to identify patients with GD and ASMD in the pre-symptomatic phase. In northeastern Italy, Burlina et al[53] conducted an extended NBS pilot program including 112,446 newborns screened for Pompe, Fabry, mucopolysaccharidosis type I, and GD. Among these, 28 were recalled for possible GD, and 7 were confirmed to have the disease, yielding a GD incidence of 1 in 16,063 births. In a subsequent report including over 127,000 neonates, the incidence was even higher – one in 12,786 – suggesting a significant underestimation of GD incidence in older datasets[41].

Comparative data from Illinois also underscore geographical differences in GD incidence: while Italian studies report GD rates as high as 1 in 12,786[41], the Illinois program documented a lower incidence of 1 in 43,959[42]. These findings support the feasibility and effectiveness of NBS for GD in Italy, particularly when enhanced by second-tier testing such as LysoGb1 quantification, which increases the diagnostic yield and reduces false positives.

In contrast, NBS for ASMD reveals a considerably lower incidence. A recent study by Gragnaniello et al[43] in Italy screened 275,011 newborns and identified two confirmed cases of ASMD, corresponding to an incidence of 1:137,506 (0.73 per 100,000 births). This is consistent with data from Illinois, USA, reported by Hickey and Baker[44], showing an ASMD incidence of 0.79 per 100,000, based on comprehensive state-level screening.

Targeted Screening for GD in High-Risk Populations

In addition to newborn screening, several studies have investigated targeted approaches to identify GD in high-risk populations, particularly those presenting with splenomegaly, cytopenias, monoclonal gammopathy of undetermined significance (MGUS) or neurologic symptoms. These efforts consistently report a significantly higher prevalence of GD compared to general population estimates.

The GAU-PED study, a multicenter Italian initiative in pediatric hematology units, screened 154 children with unexplained splenomegaly and/or cytopenias. Fourteen patients were diagnosed with GD, corresponding to a prevalence of 9.1%, highlighting the importance of systematic GD screening in pediatric hematologic settings[45].

In adult hematology clinics, Motta et al[46] screened 455 patients with idiopathic thrombocytopenia or splenomegaly, showing a GD prevalence of 3.3%. These findings support the need to maintain high diagnostic suspicion in adults, especially when classical features such as cytopenia or organomegaly are present.

Among patients with MGUS, Giuffrida et al[47] reported a GD prevalence of 0.7% in a cohort of 600 adults. Interestingly, 11% were heterozygous carriers of *GBA* gene variants, pointing to a broader spectrum of lysosomal dysfunction in this population.

Beyond hematology, targeted GD screening in neurology clinics has gained relevance. A recent study by Marano et al[48] involving 1,344 patients with Parkinson's disease found a GD prevalence of 0.4%, aligning with the well-established genetic link between *GBA* mutations and synucleinopathies.

Additionally, Huang et al[49] conducted a large-scale screening study in China, enrolling 787 pediatric and adult patients with unexplained splenomegaly and/or thrombocytopenia. GD was confirmed in 6.2% of individuals. All diagnosed patients had splenomegaly, and the vast majority also had thrombocytopenia, reaffirming the diagnostic value of these features as red flags.

Parallel Screening for GD and ASMD

With overlapping clinical features such as hepatosplenomegaly and cytopenias, parallel screening strategies for GD and ASMD have emerged as a pragmatic approach to optimize early diagnosis. Recent prospective and retrospective studies in the literature confirm the value of simultaneous enzymatic testing in patient cohorts presenting with suggestive phenotypes.

In the ARCHIMED multicenter study, Oliva et al[50] reported that among over 31,000 individuals clinically suspected of GD, approximately one in four patients diagnosed with a lysosomal disorder were actually affected by ASMD, not GD. Specifically, 4.4% were confirmed to have GD and 1.7% ASMD, based on enzymatic and genetic testing from dried blood spots (DBS), underscoring the importance of dual diagnostic workflows.

This dual approach was echoed in a large real-world Spanish study by Morado Arias et al[52], in which 2.7% of 220 patients with splenomegaly or history of splenectomy had GD and 0.9% had ASMD, despite prior under-recognition of lysosomal storage disorders in this context.

Similarly, Giacomarra et al[51] reported dual screening outcomes in a mixed cohort of 627 adult-pediatric Italian patients with a clinical suspicion of GD, identifying GD in 1.3% and ASMD in 0.5% of tested individuals. These findings reinforce the practical yield of tandem enzyme testing in real-life diagnostic algorithms.

Importantly, clinical scenarios such as the one presented by Scaramellini et al[54] illustrate how focusing exclusively on GD may lead to misdiagnosis and delay in ASMD detection. In that case, it was only through extended pathological review and subsequent parallel enzymatic testing that ASMD was identified, affirming the need to "think rare" in patients with nonspecific splenomegaly and cytopenias.

RED FLAGS AND DIAGNOSTIC ALGORITHMS TO RAISE AWARENESS FOR GD AND ASMD DIAGNOSIS

Early recognition of GD and ASMD remains a critical unmet need, largely due to their phenotypic overlap with more common hepatic, hematologic, and metabolic disorders. Despite the availability of specific enzymatic and genetic diagnostic tools, these lysosomal storage diseases often go unrecognized for years, resulting in inappropriate investigations and delayed access to treatment. In response, several diagnostic algorithms and consensus recommendations have been developed to help clinicians, including hepatologists, identify key "red flags" that warrant targeted testing. These include core features such as splenomegaly, thrombocytopenia, and low HDL cholesterol, especially in younger patients lacking classic features of metabolic syndrome. The following subsections review disease-specific and combined diagnostic frameworks that can guide early suspicion, streamline diagnostic work-up, and improve timely diagnosis of GD and ASMD in real-world clinical settings.

Diagnostic Algorithms and Red Flags in GD

The clinical heterogeneity of GD, particularly GD type 1, contributes to its frequent underdiagnosis and diagnostic delay. Common early manifestations, such as splenomegaly, thrombocytopenia, or mild hepatomegaly, are nonspecific and often misattributed to more prevalent hepatic or hematologic conditions. To address this, several diagnostic algorithms have been proposed to help clinicians identify individuals who should undergo enzymatic testing. These frameworks are particularly relevant for hepatologists, who frequently encounter liver-related red flags that may be the first or only expression of GD in adult patients.

The presence of splenomegaly of unknown cause, which consistently emerges as the strongest clinical clue for GD, is central to nearly all diagnostic algorithms. This feature is often accompanied by thrombocytopenia or hyperferritinemia, which, while frequently observed in GD, may be misclassified as secondary to portal hypertension, iron overload or inflammation[55,56]. Motta et al[57] validated a simplified algorithm in adult hematologic settings. They demonstrated that by targeting patients with idiopathic splenomegaly or thrombocytopenia and applying a structured pathway including DBS testing, more than 3% were diagnosed with GD.

The Gaucher Earlier Diagnosis Consensus (GED-C) scoring system, developed through a Delphi process among international experts, provides a more quantitative tool to guide suspicion. It assigns weighted values to clinical signs such as splenomegaly, thrombocytopenia, hepatomegaly, bone pain, anemia, hyperferritinemia, and monoclonal gammopathy. In a large real-world validation study using health records of over 3,700 patients, a GED-C score ≥6 was found to effectively discriminate between patients with GD and controls[58]. The utility of this tool lies not only in specialist centers but also in non-specialist settings where early recognition is critical.

From a hepatology standpoint, several features embedded in these diagnostic frameworks hold specific relevance. Hepatologists frequently encounter patients with modest hepatomegaly, unexplained cytopenias, gammopathies, or elevated ferritin levels in the absence of true iron overload. Low HDL cholesterol, recurrent gallstone disease at a young age, and metabolic phenotypes that do not align with classical MASLD profiles may further strengthen the suspicion of GD[14,35,59]. Moreover, splenic or hepatic nodular lesions, sometimes misinterpreted as neoplasms, may represent Gaucheromas and warrant further evaluation.

Despite the availability of reliable diagnostic tests, such as enzymatic assays and Lyso-Gb1 quantification, diagnostic inertia persists. In many cases, invasive procedures such as liver or bone marrow biopsy are performed before or in place of appropriate biochemical testing, prolonging the diagnostic delay[30]. Mehta et al[31] highlighted this issue in their retrospective analysis of the diagnostic journey in GD, demonstrating that enzyme testing was often performed late, after years of symptom progression and multiple specialist evaluations.

Diagnostic algorithms specifically designed for hepatologists have been proposed to address these challenges. Carubbi et al[14], Nascimbeni et al[35] and Marchi et al[23] suggested targeted GD testing in patients with unexplained hepatosplenomegaly, thrombocytopenia, or hyperferritinemia with preserved transferrin saturation. Their approach emphasizes the role of the hepatologist not only in identifying red flags but also in initiating diagnostic work-up and facilitating referral to metabolic specialists[14,23,35].

Collectively, these algorithmic approaches help ensure that GD is considered in the differential diagnosis of patients with unexplained liver and hematologic abnormalities. Their use may prevent unnecessary invasive investigations, reduce diagnostic delays, and enable timely access to disease-specific therapies.

Diagnostic Algorithms and Red Flags in ASMD

ASMD, particularly the chronic visceral (type B) and attenuated chronic neurovisceral (type A/B) forms, is an underrecognized lysosomal storage disorder that commonly presents with hepatosplenomegaly and may mimic more frequent hepatic and metabolic conditions. Like GD, ASMD has a highly variable phenotype, but its association with a distinct cluster of red flags – some of which are of direct hepatologic interest – offers an opportunity to improve case detection through targeted diagnostic algorithms.

The starting point in most algorithmic frameworks is the presence of unexplained splenomegaly or hepatosplenomegaly. In a large natural history study, these features were observed in over 90% of patients with ASMD type B[5]. Mild thrombocytopenia, typically less severe than in GD, is also frequently present. From a hepatology standpoint, additional red flags that may help differentiate ASMD from other causes of organomegaly include persistently elevated transaminases, steatosis/steatohepatitis with atypical metabolic features (e.g., normal body mass index and no insulin resistance) and atherogenic dyslipidemia, often characterized by a high total to HDL cholesterol ratio with strikingly low HDL cholesterol levels[7,9,35], and high LDL cholesterol and triglycerides levels. Importantly, these metabolic abnormalities may be detected years before a formal diagnosis is reached and are not typically associated with insulin resistance, obesity, or other metabolic syndrome components.

Interstitial lung disease, especially with radiographic findings such as ground-glass opacities, is another major clue and, in some cases, may be the first manifestation that triggers evaluation. In this context, the study by Villeneuve et al[60] is particularly informative. Their real-world screening program used a combination of biological and clinical criteria (e.g., low platelets, hepatosplenomegaly, elevated total to HDL cholesterol ratio, and lung imaging features) to flag patients for ASMD testing. This hybrid data-extraction and expert review model enabled the identification of previously undiagnosed ASMD cases, illustrating how algorithmic approaches can be adapted to real-life hepatology or pulmonology practice[60].

In addition to the hepatic red flags, systemic features such as chronic fatigue, growth delay, and – in chronic neurovisceral forms – atypical neurocognitive symptoms may also be present. However, unlike neuronopathic forms, chronic visceral ASMD may be missed entirely unless these subtle indicators are correctly interpreted. McGovern et al[25] proposed a consensus-based diagnostic approach incorporating both visceral and metabolic clues, emphasizing the role of splenomegaly, low HDL cholesterol, and pulmonary involvement as key triggers for enzyme testing.

Despite the availability of enzyme replacement therapy (ERT) with olipudase alfa, which has shown sustained benefit in organ volume reduction and lung function improvement, the diagnosis of ASMD still occurs late in the disease course[25,60]. This delay may be mitigated by wider dissemination of simplified diagnostic pathways among hepatologists and internal medicine specialists, particularly in patients with organomegaly and dyslipidemia who do not fit conventional MASLD or hematologic frameworks[7,9,35].

Ultimately, the development and implementation of practical diagnostic algorithms tailored to hepatology and respiratory medicine may help integrate ASMD into routine differential diagnoses, enabling earlier recognition and treatment.

Combined Diagnostic Algorithms for GD and ASMD

Given the phenotypic overlap between GD type 1 and chronic visceral ASMD, combined diagnostic approaches have been increasingly advocated. These disorders share key clinical features, including hepatosplenomegaly, thrombocytopenia, and low HDL cholesterol, that may present in young patients without other common risk factors, such as obesity, diabetes, or metabolic syndrome. In this context, clinical algorithms that consider both diseases simultaneously can support earlier recognition and facilitate appropriate enzymatic testing.

A central concept in combined algorithms is the recognition that splenomegaly of unknown origin, often accompanied by mild thrombocytopenia, should prompt a structured diagnostic work-up, even in the absence of overt systemic illness. As highlighted by Cappellini et al[7], both GD and ASMD are present in significant proportions of patients with unexplained visceromegaly. However, ASMD is often underdiagnosed, as clinicians tend to prioritize GD in their differential diagnosis due to its relatively higher prevalence[7].

The proposed dual-pathway diagnostic algorithm published by the same group delineates two parallel routes depending on the presence of multisystem features. For GD, associated signs include hyperferritinemia, low HDL cholesterol, gammopathy, anemia, osteopenia or bone pain, and bleeding tendencies. For ASMD, key indicators include dyslipidemia with an atherogenic profile, persistent elevation of liver enzymes, interstitial lung disease, and recurrent respiratory infections. Importantly, these algorithms recommend simultaneous testing of glucocerebrosidase and sphingomyelinase activities from a single DBS sample to avoid misdiagnosis and streamline workflow[7].

Mistry et al[9] have similarly emphasized the importance of structured case identification in patients with multisystem phenotypes and have advocated for broader implementation of GD and ASMD screening in internal medicine and hepatology clinics. According to their work, the diagnostic yield of this approach may be particularly high in populations with atypical presentations or metabolic profiles that do not conform to standard diagnostic categories; in particular, their findings underscore the value of combined suspicion, particularly in young patients with hepato-splenomegaly, low HDL, and absence of features consistent with MASLD or other metabolic conditions[9].

Ultimately, combined diagnostic algorithms are not only clinically effective but also cost-efficient, particularly when integrated into diagnostic flows in hepatology, hematology, or pulmonology. Their broader adoption may significantly reduce diagnostic delays and improve access to disease-specific therapies for both GD and ASMD. A practical summary of these features – categorized by disease specificity and diagnostic level – is presented in Table 2 and Table 3, providing a quick-reference tool to support structured clinical reasoning.

FIELD-BASED TRAINING AND THE HEPATOLOGY WORKING GROUP: A NATIONAL STRATEGY TO RAISE AWARENESS OF GD AND ASMD

Within the broader framework of the “GD & ASMD – Closer to Care” initiative – a national educational and diagnostic program developed to improve early identification and management of lysosomal storage disorders – a dedicated training strategy was implemented to engage hepatologists in the early recognition of GD and ASMD. The overarching goal of the initiative is to bring specialist care “closer to the patient” by fostering awareness, building local diagnostic capacity, and promoting the timely initiation of disease-specific therapies. This is achieved through education, multidisciplinary networking, and implementation of targeted screening protocols in real-world clinical settings.

As a key pillar of this effort, a structured field-based training program was launched to address the historical under-recognition of GD and ASMD in hepatology. Even though many patients present with hepatologic manifestations, such as splenomegaly, hepatomegaly, thrombocytopenia, or unexplained liver enzyme elevations, these conditions often remain undiagnosed for years. The field-training program was specifically designed to empower hepatologists to identify disease-specific red flags and apply structured diagnostic reasoning.

Conducted between October 2023 and October 2024, the program included four national educational meetings that blended in-person workshops, case-based learning, and asynchronous e-learning modules. The curriculum focused on diagnostic algorithms, imaging interpretation, metabolic clues, and practical screening techniques, including DBS testing. These educational tools were contextualized within daily hepatology practice, emphasizing integration rather than specialization.

Table 2. Hepatic red flags.

	Gaucher disease	Acid sphingomyelinase deficiency
Splenomegaly	Always present, often massive; usually not related to portal hypertension or chronic liver disease with cirrhotic progression	Always present, often massive; may also be worsened by chronic liver disease with cirrhotic progression and portal hypertension
Liver disease	Hepatomegaly is less significant than splenomegaly, often not associated with hepatic dysfunction	Frequent progression to chronic liver disease with fibrosis/cirrhosis and liver failure
Liver histology	Hypertrophy of Kupffer cells/macrophages, foamy appearance, with/without iron deposits. Steatosis is NOT characteristic	Differential diagnosis with MASLD/MASH. Steatotic necro-inflammatory and fibrosing liver disease due to sphingomyelin accumulation in both the reticuloendothelial system (hypertrophic and foamy Kupffer cells/macrophages) and hepatocytes
Other relevant hepatological features	Hepatic and splenic focal lesions (Gaucheromas) in up to 1/3 of cases	Hepatic and splenic focal lesions may be present
	Hyperferritinemia without iron overload in 60-80% of cases	Hyperferritinemia may be present
	Polyclonal hypergammaglobulinemia in >50% of cases and monoclonal gammopathy (MGUS/myeloma); frequent nonspecific autoimmune positivity	Hypergammaglobulinemia may be present
	Increased frequency of cholelithiasis	No reported association with cholelithiasis
	Hypolipidemia with low HDL cholesterol	Atherogenic dyslipidemia with hypercholesterolemia, hypertriglyceridemia, and low HDL cholesterol

Acid sphingomyelinase deficiency (ASMD); Gaucher disease (GD); high-density lipoprotein (HDL); metabolic dysfunction-associated steatotic liver disease (MASLD); metabolic dysfunction-associated steatohepatitis (MASH); monoclonal gammopathy of undetermined significance (MGUS).

To sustain impact beyond the training sessions, a dedicated hepatology working group was established, bringing together clinicians from referral centers across Italy. This group facilitated peer exchange, promoted the use of shared diagnostic pathways, and initiated local pilot screening programs in high-risk populations. Through collaborative work and experience-sharing, the group has contributed to the emergence of a national diagnostic network for hepatic presentations of lysosomal disorders.

By embedding education within clinical practice and supporting the development of a hepatologist-led community of interest, the "Closer to Care" initiative has helped catalyze earlier diagnosis, interdisciplinary collaboration, and improved patient care pathways for GD and ASMD across the Italian healthcare system.

TOWARD A HEPATOLOGIST-ORIENTED DIAGNOSTIC FLOWCHART

A key output of the "GD & ASMD – Closer to Care" initiative was the development of a hepatologist-oriented diagnostic flowchart, designed to streamline the identification of patients at risk for GD and ASMD (Figure 1). This initiative promotes a proximity-based model of care, aiming to equip frontline specialists, such as hepatologists, with the knowledge and practical tools needed to recognize rare diseases in their early stages and initiate appropriate diagnostic pathways.

Table 3. Systemic red flags.

Gaucher disease	Acid sphingomyelinase deficiency
Thrombocytopenia; anemia; leukopenia; bleeding diathesis; chronic fatigue/fatigability; growth retardation/ delayed puberty	
Acute and/or chronic bone pain. Bone disease is always present, often severe, though variable: includes marrow infiltration, osteopenia/osteoporosis, pathological fractures, skeletal deformities (Erlenmeyer flask), osteonecrosis.	**Chronic bone pain.** Bone disease is common with osteopenia/osteoporosis, pathological fractures.
Rare cardiopulmonary involvement. Pulmonary hypertension and valvular calcifications in severe cases or specific mutations.	**Interstitial lung disease** is present in >80% of cases often severe and progressive, up to severe respiratory failure. **Early and accelerated atherosclerotic cardiovascular disease.** **Cardiomyopathies and valvular heart diseases.**
Adult neurological involvement is variable: – In the chronic neuronopathic form (Gaucher type 3): oculomotor apraxia, epilepsy, ataxia – In all cases: increased risk of Parkinsonism (also in unaffected family members)	**Adult neurological involvement is frequent and variable:** – In the chronic neurovisceral form (NPD A/B): severe impairment with cognitive decline, ataxia, progressive loss of motor and mental skills; cherry-red spot in retina; – In the chronic visceral form: peripheral neuropathy, dysautonomia with abdominal pain/diarrhoea, headache
Family history of GD or ASMD/consanguinity.	

Acid sphingomyelinase deficiency (ASMD); Gaucher disease (GD); Niemann–Pick disease type A/B (NPD A/B).

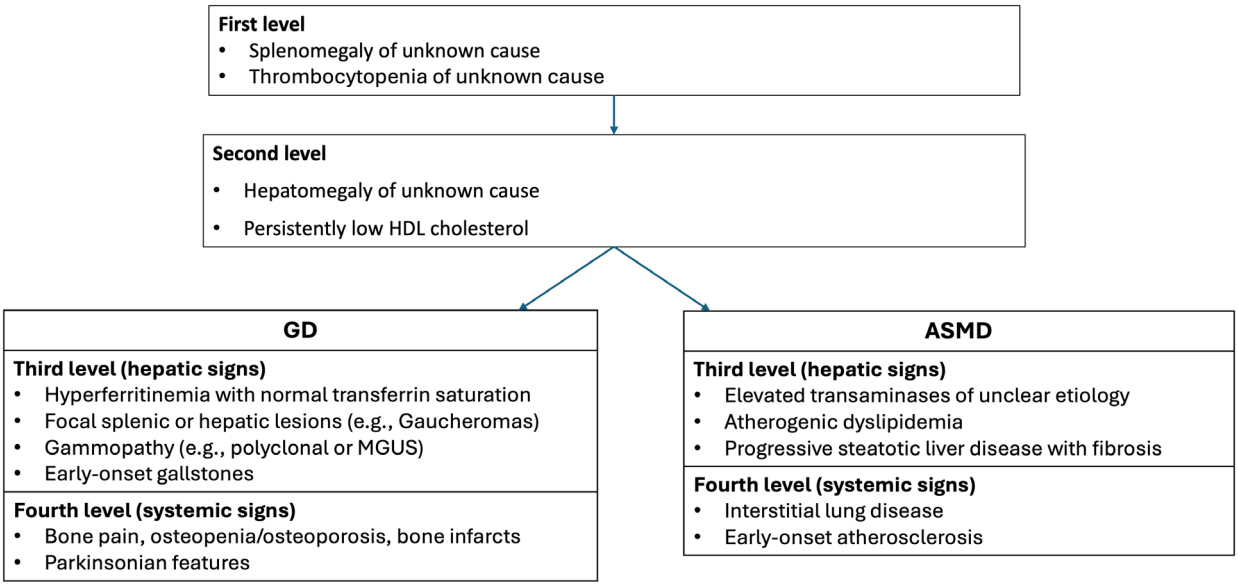

Figure 1. Hepatologist-oriented diagnostic flowchart for GD and ASMD.

The proposed flowchart is tailored to the clinical scenarios commonly encountered in hepatology and builds on validated diagnostic elements and shared red flags. Inspired by previous models, particularly the structured approach by Cappellini et al[7], this version introduces modifications that prioritize hepatologic entry points. At the first level, which applies to both GD and ASMD, the flowchart identifies splenomegaly of unknown origin and thrombocytopenia of unknown origin as principal warning signs. In the absence of other evident causes, these findings are sufficient to warrant first-line DBS-based enzymatic screening.

The second level reinforces this suspicion by integrating additional hepatologic indicators such as unexplained hepatomegaly and low HDL-cholesterol, both frequently observed in these conditions but rarely linked to lysosomal etiology in routine practice. These features are especially relevant when occurring in young or nonmetabolic patients without obesity, diabetes/insulin resistance, or alcohol-related liver disease.

From this shared pathway, the flowchart bifurcates into two disease-specific diagnostic branches. For GD, third-tier hepatic signs include hyperferritinemia, focal liver or splenic lesions, polyclonal or monoclonal gammopathy, and early-onset cholelithiasis. For ASMD, the corresponding hepatic markers include unexplained transaminase elevation, steatotic liver disease with fibrotic evolution, and atherogenic lipid profile.

Finally, systemic features such as bone disease and Parkinsonism for GD or interstitial lung involvement and early atherosclerosis for ASMD form the fourth diagnostic tier, further guiding differential work-up. The flowchart is supported by a standardized clinical history form, designed to capture relevant hepatic and systemic clues.

Together, these tools represent a practical and structured aid for hepatologists to suspect GD and ASMD in appropriate clinical contexts, aligning with the broader goals of the Closer to Care program: early recognition, community building, and timely patient access to specialized care.

CLOSING THE DIAGNOSTIC GAP: FROM TARGETED SCREENING TO FUTURE-READY HEPATOLOGY

The educational and clinical framework developed through the “GD & ASMD – Closer to Care” initiative has underscored the importance of proactive hepatologist engagement in the diagnosis of GD and ASMD. These lysosomal storage disorders often present with hepatic or hematologic manifestations – hepatosplenomegaly, thrombocytopenia, dyslipidemia, or unexplained liver abnormalities – that fall within the hepatologist’s diagnostic domain. Through field-based training, flowchart development, and inter-specialty dialogue, a shared diagnostic culture is beginning to emerge, aiming to reduce diagnostic delays and facilitate the timely initiation of disease-modifying treatments.

Looking to the future, two promising directions offer the potential to further revolutionize diagnostic strategies. First, NBS programs for GD and ASMD may enable diagnosis within the first weeks of life, long before clinical symptoms appear. Pilot programs in Italy and internationally have already demonstrated the feasibility and diagnostic yield of NBS for lysosomal diseases. A broader adoption of such programs would support earlier access to treatment and the prevention of irreversible organ damage, particularly in chronic progressive forms of these disorders.

Second, the incorporation of exome sequencing into the diagnostic work-up of cryptogenic and complex liver diseases is poised to transform rare liver disease diagnostics. Several studies have demonstrated the utility of next-generation sequencing in uncovering monogenic etiologies in patients with unexplained steatosis, liver fibrosis/cirrhosis, or multisystemic phenotypes[61-66]. In this context, lysosomal storage disorders, such as GD and ASMD, represent an important, and potentially actionable, subset of genetic liver diseases.

However, while awaiting broader implementation of genome-wide diagnostics and universal screening programs, immediate efforts must focus on awareness and targeted screening of at-risk populations. Individuals with unexplained hepatosplenomegaly, cytopenias, dyslipidemia, or liver abnormalities – especially when present since a young age, occurring with multisystemic phenotypes and in the absence of classical metabolic syndrome components or other common etiologies – should be evaluated through structured diagnostic algorithms. The adoption of simple, noninvasive screening methods such as dried blood spot enzymatic testing remains a practical and effective approach for frontline hepatologists.

Bridging current practice with emerging diagnostic technologies will require continuous education, interdisciplinary collaboration, and systematic integration of red flag-based flowcharts. Through these combined efforts, the diagnostic landscape for GD and ASMD can shift from delayed recognition to early intervention, ultimately improving outcomes for affected individuals.

CONCLUSIONS

In conclusion, GD and ASMD should be systematically considered in adult patients presenting with unexplained hepatosplenomegaly, cytopenias, dyslipidemia, or atypical liver disease. Their frequent overlap with common hepatic conditions continues to cause diagnostic inertia and delay, despite the availability of reliable enzymatic testing and disease-modifying therapies. The hepatologist-oriented flowchart developed within the Italian "GD & ASMD – Closer to Care" initiative shows how structured recognition of red flags, combined with accessible dried blood spot screening and multidisciplinary collaboration, can facilitate earlier diagnosis and more appropriate referral. While newborn screening and genomic sequencing are likely to expand future diagnostic horizons, embedding awareness-driven, risk-based screening strategies into routine hepatology practice plays also a crucial role. By integrating standardized flowcharts into daily clinical decision-making, hepatologists can play a decisive role in transforming rare lysosomal disorders from missed diagnoses into timely, treatable conditions.

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