European Atherosclerosis Journal
www.eathj.org

EAJ 2024;3:81-86
https://doi.org/10.56095/eaj.v3i3.78

SMASH: An initiative for equitable access to precision medicine for rare or severe lipid disorders

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Keywords
Access;
equity;
rare diseases;
lipid disorders;
SMASH

ABSTRACT

Background: Despite significant improvements in our knowledge of rare or severe dyslipidemias, barriers to access are gradually emerging. SMASH (System and Molecular Approaches of Severe Hyperlipidemia) is a global initiative with the goal of making precision medicine innovations available without discrimination for patients affected by rare or severe dyslipidemias.
Objectives: SMASH main objective is to facilitate access to accurate diagnosis and optimal treatment for patients affected by rare or severe lipid disorders.
Overview: SMASH is an international initiative comprising five interrelated components: SMASH-Access, -Natural History, -Trials, -e-Share, and -Biorepository. SMASH has selected as templates four severe lipid disorders that have in common the accelerated development of precise diagnosis and the emergence of innovative treatments that represent equity challenges. Access issues are broad and not limited to clinical or socio-economic factors.
Summary: SMASH is developed to conceive and support initiatives that might improve our understanding of rare or severe dyslipidemias and facilitate access to innovation.

Received 14 november 2024 accepted 30 december 2024

Introduction

Rare diseases are often ignored, and in different parts of the world many patients have little access to accurate diagnosis or effective treatments. There are 25 dyslipoproteinemias listed in the latest European Atherosclerosis Society (EAS) task force consensus statement on rare dyslipidemias [1] to which other rare or severe disorders can be added including elevated Lipoprotein(a) [Lp(a)], lipid storage diseases, primary lipodystrophies (complete or partial), glycerol kinase deficiency, severe causes of MASLD/MASH (metabolic dysfunction-associated steatotic liver disease/steatohepatitis) and non-monogenic persistent chylomicronemia (**Table 1**).

The last decades have been characterized by the Omics era which has led to a huge improvement in our understanding of the biological basis of diseases, the development of genetic testing, and refinement of disease management, with the emergence of new therapeutic targets, biodrugs, and delivery systems covering a wide range of unmet needs in lipidology. Despite their clinical importance, these improvements could lead to multiple equity concerns and barriers to access globally, particularly in low-middle-income countries or remote regions. The issues are diverse and important, covering (among others) access to a precise diagnosis, the challenge of transport and conservation of biodrugs, and issues of

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Table 1 | Partial List of Rare and Severe Lipid Disorders.

Lipid Disorder	Inheritance	Main Deleterious Consequences	Currently treatable	Emerging Therapies in Development
↑ LDL-cholesterol				
Homozygous familial hypercholesterolemia	ASD	ASCVD	Partly	Yes
Sitosterolemia	AR	ASCVD	Yes	No
Atypical dominant hypercholesterolemia	AD	ASCVD	Yes	Yes
Lysosomal acid lipase deficiency	AR	Multisystemic Liver failure	Partly	Yes
Lysosomal storage diseases (eg. Niemann-Pick)	AR	Multisystemic	Partly	Yes
Extreme Lp(a)	ASD-like	ASCVD Aortic stenosis	No	Yes
↓ LDL-cholesterol or ↓ Triglycerides				
Abetalipoproteinemia	AR	Fat-soluble vitamins deficiency	Yes	No
Homozygous hypobetalipoproteinemia	ASD	None	N/A	No
Chylomicron retention disease (Anderson disease)	AR	Fat-soluble vitamins deficiency	Yes	No
Familial combined hypolipidemia (ANGPTL3 deficiency)	ASD	None	N/A	No Target for drug development
PCSK9 deficiency	ASD	None	N/A	No Target for drug development
Apolipoprotein C-III deficiency	AR	None	N/A	No Target for drug development
↑ Triglycerides				
LPL deficiency	AR	AP Possibly ASCVD	Partly	Yes
Apolipoprotein C-II deficiency	AR	AP Possibly ASCVD	Partly	Yes
Apolipoprotein A-V deficiency	AR	AP Possibly ASCVD	Partly	Yes
Lipase maturation factor 1 deficiency	AR	AP Possibly ASCVD	Partly	Yes
GPIHBP1 deficiency	AR	AP Possibly ASCVD	Partly	Yes
Non-monogenic persistent chylomicronemia	Complex	AP Possibly ASCVD	Partly	Yes
Infantile hypertriglyceridemia, transient	AR	Abdominal pain AP	Yes	No
Dysbetalipoproteinemia	Complex	ASCVD (mainly peripheral)	Yes	Yes
Glycerol kinase deficiency	X-linked	Pseudo-hypertriglyceridemia Glucose intolerance	Comorbidities	No
Primary lipodystrophy (Generalized, partial)	AD or AR	ASCVD AP Multisystemic	Comorbidities	Yes
↓ HDL-cholesterol				
Tangier disease (ABCA1 deficiency)	AR	ASCVD	Partly	No
Apolipoprotein A-I deficiency	AR	ASCVD	Partly	Yes
LCAT deficiency (fish-eye disease)	AR	Multisystemic Corneal opacity	Partly	Yes
Familial LCAT deficiency	AR	Multisystemic Renal disease	Partly	Yes

Lipid Disorder	Inheritance	Main Deleterious Consequences	Currently treatable	Emerging Therapies in Development
↑ HDL-cholesterol				
Genetic cholesteryl ester transfer protein deficiency	ASD	Age-related macular degeneration	Comorbidities	No Target for drug development
Scavenger receptor B1 deficiency	ASD	ASCVD? Female fertility issues?	Comorbidities	Yes
Hepatic lipase deficiency	AR	ASCVD	Partly	No
Others				
Lipid storage diseases (several)	Variable	Multisystemic	Partly	Yes
Metabolic dysfunction-associated steatohepatitis (MASH)	Complex	ASCVD Cirrhosis – hepatocellular carcinoma	Yes Comorbidities	Yes

ABCA1: ATP-binding cassette A1, AD: Autosomal dominant, ANGPTL3: Angiopoietin-like protein 3, AP: Acute pancreatitis, AR: Autosomal recessive, ASCVD: Atherosclerotic cardiovascular disease, ASD: Autosomal semi-dominant, GPIHBP1: Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1, HDL: High density lipoprotein, LCAT: Lecithin-cholesterol acyltransferase, LDL: Low-density lipoprotein, Lp(a): Lipoprotein (a) LPL: Lipoprotein lipase, PCSK9: Proprotein convertase subtilisin/kexin type 9.

reimbursement or insurability [2]. Once approved, novel precision therapies developed through clinical trials are often expensive, and their use is regularly restricted. It is therefore necessary to network efforts to document the clinical expression of rare or severe lipid diseases and facilitate access to accurate diagnosis and effective, safe, and affordable therapies.

SMASH (System and Molecular Approaches of Severe Hyperlipidemia) is a global initiative with the goal of making health and precision medicine innovations available without discrimination for patients affected by rare or severe lipid disorders.

SMASH objectives

Access is the priority of the SMASH initiative, and all activities are patient-centered and community-centered. The main objective is to facilitate access to accurate diagnosis and optimal treatment for patients affected by rare or severe lipid disorders regardless of where they live, their gender, ethnicity, or socioeconomic status by supporting networks, associations, organizations, patients, clinicians, researchers, and other stakeholders concerned by access issues.

Overview of the smash initiative

SMASH is an international philanthropic initiative comprising five interrelated components described below: SMASH-Access, SMASH-Natural History, SMASH-Trials, SMASH e-Share, and SMASH-Biorepository (**Figure 1**).

SMASH-Access

SMASH-Access aims to globally map hurdles to access to diagnosis and treatment of rare or severe lipid disorders including reimbursement, geographical or geopolitical issues, socioeconomic status, mobility difficulties, lack of specialized clinics, etc. Such mapping will facilitate the identification of countries and collectivities where access is an important issue as well as supporting the networking of clinicians, patients, stakeholders and resources regarding access. SMASH will facilitate the development of initiatives favoring access through the principle of equity and will disseminate information through the SMASH website (e-Share component).

SMASH-Natural History

In order to facilitate access, it is essential to improve our understanding of the natural history of rare and severe lipid disorders. The list of rare lipid disorders and subtypes will be dynamically updated, and those requiring efforts in terms of diagnosis or treatment will be highlighted. SMASH-Natural History will map, support, or launch in-

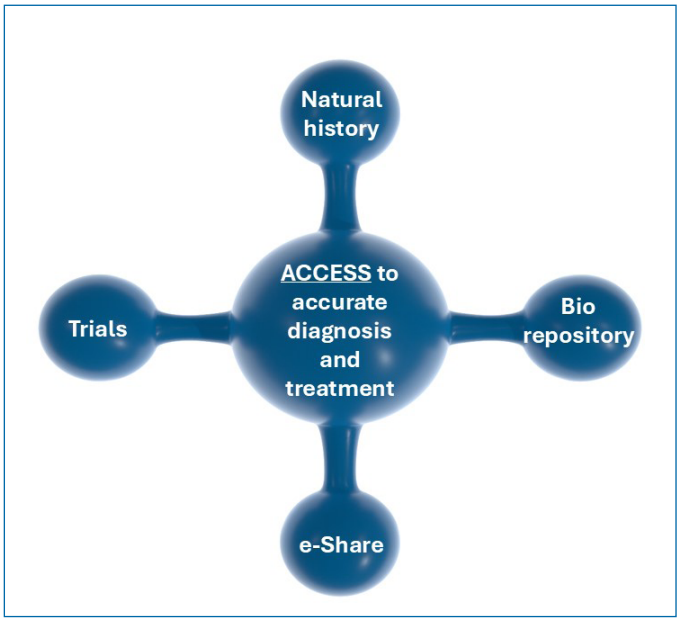

Figure 1 | Description of the components of the SMASH initiative. *SMASH has five components all dedicated to facilitating equitable access to accurate diagnosis and optimal treatment for patients affected by rare or severe lipid disorders. These components are interrelated and cover the needs of better documenting the natural history of lipid disorders, provide access to standardized and decentralized repositories of biosamples, support ongoing initiatives or the conception of investigator initiated clinical studies and disseminate educational material.*

itiatives documenting or targeting the natural history of rare lipid disorders using persistent chylomicronemia, homozygous familial hypercholesterolemia (HoFH), lecithin-cholesterol acyltransferase (LCAT) deficiency and elevated Lp(a) as templates before extending to other diseases. This component also aims to facilitate the acquisition and dissemination of new knowledge acquired via academic research or clinical trials by networking with patients, experts, associations and stakeholders involved in managing rare lipid disorders. Data collected will vary from one disease to another, according to the needs and access issues.

SMASH-Trials

The Trials component conceives, supports, executes, or monitors proof-of-concept, investigator-initiated trials or sub-studies promoting access to innovation and documenting the natural history of diseases or the impacts of interventions. SMASH has the willingness to support inexperienced sites or clinicians in order to manage all aspects of clinical trials, including GCP training, regulatory issues, data management, and remote monitoring. Partnerships with pharma, biotechs, and academic experts will be maintained with the vision of facilitating access to precision treatments where and when needed, based on the principle of equity.

SMASH e-Share

E-Share is a pillar of the SMASH initiative, a virtual platform where all stakeholders can connect. It aims at developing a patient-centered interactive platform connecting key players involved in rare or severe lipid disorders including patients, healthcare providers, researchers, industrial partners, health decision-makers, etc. The platform will also facilitate disseminating existing information and educational material across international networks. SMASH will support the development of new educational material to complement those already available. In order to raise awareness around access to accurate diagnosis and treatments for rare or severe lipid disorders, partners are invited to sign the SMASH declaration (manifesto) on access at www.smash-access.org. Signatures from around the world will be collected and mapped. The declaration will be the voice of patients affected by rare or severe lipid disorders and their relatives, clinicians, researchers, and other stakeholders concerned by access issues. Patients will have the opportunity to participate actively in the SMASH initiative through the e-Share platform which will offer multiple possibilities for patients-driven initiatives. Advocacy groups and patients' associations will also have the opportunity to contribute to a connected knowledge network supporting their efforts in disseminating disease information and awareness.

SMASH Biorepository

SMASH intends to enhance the ability to generate and share new knowledge on rare or severe lipid diseases by supporting national registries and researchers in the development of decentralized biobanking capacities, allowing the standardization and optimization of biosamples storage globally, including in low-middle-income countries and remote regions. The monitoring of storage units and of the samples themselves should be supervised anonymously with high quality standards. A decentralized biobanking approach will foster collaborations between research teams and will help to nurture knowledge acquisition on the natural history and risk trajectory of rare and severe lipid disorders.

Rare disease templates in SMASH

Over the past few decades, the diagnostic and therapeutic offer for rare lipid disorders has evolved rapidly and demand for services has hardly kept pace, which is even more true in remote regions and lower-income economies. Although the issue of equity is becoming increasingly important and central, clinical research has not evolved at the same pace for all diseases, and thus, access issues are not the same for all rare or severe lipid disorders. This is why SMASH has selected as templates four lipid disorders for which there are immediate challenges in terms of access to accurate diagnosis and effective treatments and which also globally represent important equity challenges: HoFH, persistent chylomicronemia, LCAT deficiency, and severely elevated Lp(a). All these severe diseases have in common the accelerated development of precise diagnosis or screening tools and the emergence of innovative treatments. HoFH is a rare condition characterized by the presence of bi-allelic variants in four genes that cause absent or extremely reduced LDL receptor activity (*LDLR, APOB, PCSK9 and LDLRAP1*) and extremely elevated LDL cholesterol (LDL-C) levels, premature atherosclerotic cardiovascular disease (ASCVD), aortic or supra-aortic valve disease, and risk of early death [3]. Persistent chylomicronemia is caused by sustained lipoprotein lipase deficiency (LPLD) or lack of LPL bioavailability. LPLD is associated with the familial chylomicronemia syndrome (FCS), a term that is usually used to describe the monogenic (autosomal recessive) form of LPLD, but this rare disease also has multifactorial causes and is associated with an increased risk of recurrent acute pancreatitis and other morbidities [4]. LCAT deficiency is a rare disease characterized by partial or complete absence of LCAT enzyme activity. LCAT deficiency hampers the maturation of HDL particles and reverse cholesterol transport, thus potentially increasing the risk of ASCVD and can lead to corneal opacification and chronic kidney disease (CKD) in the most severe cases [5]. Elevated Lp(a) is associated with increased risk of ASCVD (including stroke) and aortic valvular disease [6-8]. Many efforts are currently being made to improve the diagnosis and management of these rare and severe diseases.

HoFH. The HoFH International Clinical Collaboration (HICC) is a registry launched in 2016 aiming at creating a formal network of healthcare professionals managing HoFH in order to describe and follow the clinical characteristics of affected patients from around the world. So far, the HICC registry includes nearly 1000 patients from several tens of countries on all continents [9]. LDL receptor independent treatments such as lipoprotein apheresis, evinacumab (ANGPTL3 monoclonal antibody) and lomitapide (MTP inhibitor) have demonstrated great efficacy in reducing LDL-cholesterol in HoFH [10-12]. However, these treatments are expensive and are not available everywhere, and reimbursement can be an issue even in high-income countries. Access to lipoprotein apheresis is often very limited, and many countries do not have the equipment needed [13]. Although genetic testing is still recommended when available and reimbursed, a clinical diagnosis of HoFH is widely accepted and sufficient to prescribe these advanced treatment options, making access to genetic testing a less critical barrier.

Persistent chylomicronemia. Access to accurate diagnosis and effective treatments is also an issue for patients affected by persistent chylomicronemia. All affected patients present sustained lack of LPL bioavailability. However, not all of them carry bi-allelic combination of pathogenic variants in the LPL gene machinery [4]. Since a genetic diagnosis is often required in clinical trials targeting LPLD and FCS, this leads to an equity issue and a dilemma concerning the access to treatment for those with persistent chylomicronemia not carrying bi-allelic combination of pathogenic variants but presenting clinical characteristics of FCS, a term having been specifically used to date to describe patients having a proven pathogenic genetic defect. Clinical diagnosis scoring systems and other strategies can accurately support persistent chylomicronemia diagnosis even in the absence of knowl-

edge of the genetic background [14, 15]. Among emerging or new therapies developed for severe hypertriglyceridemia, apolipoprotein C3 (APOC3) inhibitors (APOC3i) are the most advanced. APOC3i efficiently decreases TG levels even in the absence of available LPL (LPL-independent mechanism). Most APOC3i are sophisticated biodrugs interfering with the APOC3 gene translation, specifically single-stranded antisense oligonucleotides (ASO) or double-stranded small interfering RNA (siRNA) [16, 17]. When approved, these agents might not be easily available or affordable everywhere, particularly in low-middle-income countries [2]. Access might also be initially limited to patients presenting a genetic diagnosis of FCS, although some recent trials include patients presenting clinical features of FCS without carrying bi-allelic pathogenic variants [16]. Access to genetic testing is not evenly distributed across the world and may be limited in many countries. As in the case of HoFH, molecular diagnosis should not be mandatory to make a diagnosis of persistent chylomicronemia or clinical FCS and allow equitable access to treatments for this severe unmet medical need.

LCAT Deficiency. LCAT deficiency is a rare and complex lipid disorder characterized in the most severe cases by chronic kidney disease that progresses to end stage renal disease by the 4th decade of life. Currently, there is no curative treatment, and the management of these patients focuses on controlling the renal symptomatology, with limited success. Some novel agents such as recombinant human LCAT gene, gene therapy and LCAT activators are in development [18, 19]. The biggest regulatory obstacle to the development of novel therapeutic approaches is the poor understanding of the natural history of this condition, that hinders our ability to identify patients that will progress towards CKD or other complications. Access to accurate LCAT deficiency diagnosis and emerging therapies is thus an issue.

Elevated Lp(a). Another SMASH template is severely elevated Lp(a). Strongly genetically determined apo(a) production and plasma concentration of Lp(a) are affected by several factors. The prevalence of elevated Lp(a) (approximately 1 in 5 individuals) varies worldwide and by ethnicity but does not meet rare disease criteria [6]. Patients with elevated Lp(a) values have an increased risk of ASCVD, including coronary artery disease, stroke, and aortic valvular disease [20]. Individuals with Lp(a) levels ≥125 nmol/L are considered at high risk [6], although there is no definite risk threshold or clear cut-off. Extreme values (estimated ≥430 nmol/L) are rarer and have been associated with a 2.5x increased risk of ASCVD independently of LDL-cholesterol in a cross-sectional study [21]. Historically, few agents were effective in decreasing Lp(a), and their efficacy was limited (≤ 25%). This includes niacin, PCSK9, and ANGPTL3 inhibitors among others [22]. Lipoprotein apheresis effectively decreases Lp(a) particle number but is not available everywhere. The emergence of potent apo(a) inhibitors reducing Lp(a) by up to 90% [23-27] will most likely influence medical practice. Although most current guidelines suggest determining Lp(a) at least once in a lifetime, there is a large discrepancy in Lp(a) testing worldwide, and the availability of the test can be an issue in several countries. A recent survey conducted among members of the EAS Lipid Clinic Network in different continents illustrates the lack of consistency in using Lp(a) to assess cardiovascular risk (unpublished data).

Access issues are not limited to clinical or socio-economic factors. Several environmental variables are also contributory. For example, the capacity to optimally store or deliver drugs can be affected by the stability of electricity supply in several low-middle-income countries, as illustrated by the situation in South Africa or in countries at war or armed conflicts. Access to healthcare services is more difficult in remote regions or in some parts of countries that have large sparsely populated territories, for displaced populations or for patients with disabilities.

Conclusion

Identifying and mapping all hurdles to access is only a first step. The second step is to join efforts to facilitate equitable access to accurate diagnosis and optimal treatment for all patients affected by rare or severe lipid disorders. SMASH is developed to conceive, support, or catalyze initiatives that might improve our understanding of rare or severe dyslipidemias and cover the needs of affected patients and healthcare providers from around the world. SMASH will not duplicate ongoing initiatives but will support them when feasible, and promote networking of patients, organizations, healthcare providers, and stakeholders. A system approach and a structured collaborative effort is mandatory to provide fair access to emerging treatments to patients in both developed countries and emerging economies [28].

Acknowledgements

SMASH initiative is dedicated to all patients affected by rare or severe lipid disorders.

Source of funding

SMASH is made possible by logistical and financial support of ECOGENE-21, a non-for-profit organization dedicated to access to health innovations in precision medicine. ECOGENE-21 has received unrestricted contributions from Amgen Canada, Amryt/ Chiesi, Eder Therapeutics, Merck Canada, Novartis Canada, Sanofi Canada and Ultragenyx to develop SMASH.

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