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Review article

Global reach of over 20 years of experience in the patient-centered Fabry Registry: Advancement of Fabry disease expertise and dissemination of real-world evidence to the Fabry community

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ABSTRACT

Fabry disease (FD, α-galactosidase A deficiency) is a rare, progressive, complex lysosomal storage disorder affecting multiple organ systems with a diverse spectrum of clinical phenotypes, particularly among female patients. Knowledge of its clinical course was still limited in 2001 when FD-specific therapies first became available and the Fabry Registry (NCT00196742; sponsor: Sanofi) was initiated as a global observational study.

The Fabry Registry has now been operational for over 20 years, overseen by expert Boards of Advisors, and has collected real-world demographic and longitudinal clinical data from more than 8000 individuals with FD. Leveraging the accumulating evidence base, multidisciplinary collaborations have resulted in the creation of 32 peer-reviewed scientific publications, which have contributed to the greatly expanded knowledge on the onset and progression of FD, its clinical management, the role of sex and genetics, the outcomes of enzyme replacement therapy with agalsidase beta, and prognostic factors.

We review how the Fabry Registry has evolved from its inception to become the largest global source of real-world FD patient data, and how the generated scientific evidence has helped to better inform the medical community, individuals living with FD, patient organizations, and other stakeholders.

The patient-centered Fabry Registry fosters collaborative research partnerships with the overarching goal of optimizing the clinical management of patients with FD and is well positioned to add to its past achievements.

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1. Introduction

Fabry disease (FD, OMIM #301500) is a rare, genetic, X-linked, lysosomal storage disorder [1]. The first descriptions of FD as "angiokeratoma corporis diffusum" date back to 1898 [2,3] and, during the ensuing century, many important advances were made in understanding the pathogenesis and genetic basis of the disease. The enzymatic defect (i.e., α-galactosidase A deficiency) which causes progressive accumulation of the toxic metabolite globotriaosylceramide (GL-3, originally described as an "unknown lipid" [4]) was identified in 1967 [5] and deacylated GL-3 (globotriaosylsphingosine, lyso-GL-3) was first reported in 2008 [6]. In the late 1980s, the complete nucleotide sequence of the gene encoding α-galactosidase A (*GLA*) was determined [7,8]. However, at the time FD-specific therapies became available in 2001, there was still a limited understanding of the early clinical manifestations, natural course, and late complications of FD that prompted the creation of FD registries such as the Fabry Registry [9] (2001–ongoing) and the Fabry Outcome Survey [10] (2001−2022).

The scientific interest in FD increased exponentially following the availability of enzyme replacement therapies (ERTs), including agalsidase beta (Fabrazyme®, 1.0 mg/kg every other week [EOW]) [11] and agalsidase alfa (Replagal®, 0.2 mg/kg EOW) [12], first in the European Union in 2001 and subsequently in many other countries around the world. In the United States, agalsidase beta was licensed for use in 2003 and is currently the only approved ERT available [13]. In 2016, migalastat (Galafold®) [14], an oral pharmacological chaperone therapy, became available; however, this treatment is restricted to patients who have amenable pathogenic variants in the *GLA* gene as determined by an in vitro assay [15].

The Fabry Registry (ClinicalTrials.gov Identifier NCT00196742) is a patient-centered, observational study encompassing real-world demographic and clinical data from individuals diagnosed with FD. The Fabry Registry started in July 2001 and, over time, has expanded globally with steadily rising numbers of participating patients and contributing healthcare professionals. Comprising more than 8000 individuals with FD from all over the world, the Fabry Registry has grown to become the largest global source of real-world patient data. Multidisciplinary collaborations between Fabry Registry Advisory Board members and international specialists with expertise in FD, leveraging the accumulating evidence base, have resulted in the creation of 32 peer-reviewed scientific publications [16–47] which have helped to greatly expand our knowledge on the natural history of FD, its clinical characterization, the role of sex and genetics, and outcomes of disease-specific treatment throughout the global community.

The Fabry Registry has now been operational for over 20 years. Here, we review how it has evolved since its inception and how real-world scientific evidence has helped to better inform healthcare professionals and the Fabry community, including individuals living with FD, their families, and caregivers, as well as patient organizations, health authorities and regulatory agencies, on the overarching goal of optimizing the clinical management of patients with FD.

2. The Fabry Registry

The rationale for the Fabry Registry, its design, objectives, governance and operation, and recruitment of participants over time are described in this section.

2.1. The need for a Fabry disease registry

FD is a rare, pan-ethnic, complex disorder affecting multiple organ systems with a wide spectrum of progressive clinical phenotypes, particularly among female patients [40]. To date, more than 1000 *GLA* variants have been reported. The variability in phenotypic expression of a given *GLA* variant exists due to the influence of phenotype-modifying factors such as genetic background, epigenetics, and environmental conditions [48]. A large 2021 European screening study for FD in newborns revealed an overall incidence of α-galactosidase A deficiency of 1 in 7879 (1 in 4068 males), while the frequency of pathogenic *GLA* variants was 1 in 6883 males [49]. No heterozygotes were detected in this study, which used an enzyme-based screening approach that may miss most affected females due to X-chromosome inactivation. Given the X-linked inheritance pattern, the female-to-male ratio of mutant alleles of *GLA* should approach 2:1 [50], assuming equal reproductive fitness of male and female patients with FD, although female heterozygotes may develop only incomplete phenotypes or remain asymptomatic due to predominant expression of the wild-type *GLA* allele in a significant proportion of cells [51]. Thus, FD is much more frequent than previously

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thought based on estimates from newborn screening programs, especially the later-onset phenotype [49], and has been described as being the most frequent lysosomal storage disorder [52]. Patients with FD are geographically dispersed and, therefore, the Fabry experience of individual healthcare professionals caring for small numbers of patients, and even that of a country as a whole, may not be sufficient to advance the understanding of important aspects of FD. Clinical trials in FD are essential for drug approval, typically yielding results within a few months or years. However, the overall clinical evidence submitted at the time of marketing authorization application is frequently limited. Trials are often of short duration and, particularly in rare diseases, restricted to a small sample size due to limitations in recruiting patients. Moreover, trials are highly selective, controlling who is included and what is measured. Disease-specific registries, such as the Fabry Registry, can follow large numbers of patients at centers worldwide over a long period of time. They are, therefore, essential in defining the long-term natural history and unmet needs of rare diseases, and in allowing assessments of long-term treatment outcomes in the various clinical phenotypes. Mistry et al. have reviewed the history, processes, and impact of the four large, Sanofi-sponsored lysosomal storage disease registries (for Gaucher disease, Pompe disease, Mucopolysaccharidosis type I, and FD). Over three decades, these registries have generated evidence instrumental in global multistakeholder engagements in an environment of high unmet medical need [53].

2.2. Design of the Fabry Registry and objectives

The Fabry Registry is a multicenter, international, longitudinal, observational study open to all patients with a confirmed diagnosis of FD, irrespective of treatment status or therapy administered. It is designed to collect consistent retrospective and prospective patient data (clinical, demographic, genetic, biochemical, imaging, and therapeutic) with the primary objectives of exploring and defining the variability in the natural history and clinical characteristics across the disease spectrum, and of tracking and characterizing long-term treatment outcomes in a real-world setting. Participation of patients and investigators is voluntary. The Fabry Registry Boards of Advisors (see 2.3) have developed and updated recommended schedules of assessments of key clinical variables for both patients under 18 years of age and adult patients (≥18 years of age) [54] with frequencies of assessments aligned with current knowledge about the courses of disease during these periods of life, including the likelihood of occurrence of clinical events. Although the 18-year age demarcation does not have a clear biological basis, adult and pediatric guidelines are often published separately [37,40].

These schedules of assessment are considered to serve as guidance, not requirements; treating physicians determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up. As a result, data collected in the Fabry Registry, like any other real-world data, represent the variation in medical practice among physicians around the world. The operations and management of the Fabry Registry are supported by an experienced and specialized team from Sanofi, including global operations and monitoring, data management, statistical programing, and epidemiology and biostatistics, in compliance with international standards and regulations and respecting the unique responsibility granted to the Fabry Registry team by participating patients, families, and members of the Advisory Boards.

2.3. Fabry Registry governance

Effective overarching leadership is vital to robust governance of the Fabry Registry. Therefore, the International and Regional Boards of Advisors, comprised of independent physicians with extensive scientific and clinical FD expertise, oversee the direction of the Fabry Registry program. Among other activities, these Boards of Advisors serve as the primary liaisons between the Fabry community and the Fabry Registry team. They ensure that analyses and publications are conducted according to the highest standards of epidemiological and biostatistical methods, scientific interpretation, and peer-review requirements, and that the Fabry Registry activities are conducted according to the principles of inclusion, objectivity, and comprehensiveness. Advisory Board meetings and registry manuscript working groups have been fertile terrain for collegiate interactions among a wide multidisciplinary network of international specialists with expertise in FD, as well as for the establishment of productive research collaborations assisted by the Fabry Registry team. In 2019, the Rare Disease Registries Patient Council, a group of local and global patient-advocacy leaders, was established to engage rare disease community members in how registry data are used and disseminated [53]. Altogether these interactions have contributed to an expanding FD collective in lieu of individual knowledge, and this is ultimately reflected in communications to the FD community which lend a more balanced and comprehensive perspective to support FD patient care.

2.4. Ethics and data privacy

The Fabry Registry adheres to the fundamental principles for the ethical conduct of scientific research involving human subjects. Each Fabry Registry site is independent and responsible for obtaining informed written consent from each patient, their parents, or legal representative before enrollment and submission of demographic and patient data to the Fabry Registry. Patients can also be enrolled into the Fabry Registry posthumously so that their data may contribute to the overall understanding of FD. The Fabry Registry protocol, informed consent form, and any locally required authorization documents needed for entering patient information are reviewed and approved by the local Institutional Review Board or Independent Ethics Committee unless the site provides documentation that approval is not required or has been waived. The Fabry Registry complies with all applicable national privacy regulations and other regional and local laws. Patient confidentiality is strictly maintained by assigning unique patient identification numbers to all enrolled patients and ensuring that all data reported by the Fabry Registry are in de-identified, aggregate format.

2.5. Patient data collection

Fabry Registry operations, monitoring, and data management teams help maintain data collection, quality, quantity, organization, and systematic storage necessary for ensuring analytical requirements to address research questions. The Fabry Registry depends on the participating sites for patient data collection and data entry. During each site's initiation, members of the site are trained on registry operational and regulatory requirements. The Fabry Registry monitoring team supports regulatory and data entry activities at the sites, including patient enrollment, complete data entry for baseline and follow-up assessments, and continuing support, training, and tracking of progress. As the data are being entered, the Fabry Registry team works with the site to resolve any discrepancies or data issues.

2.6. Data analysis and reporting, and use of data in multistakeholder collaborations

Although the Fabry Registry includes observational data gathered from multiple sites and real-world patient-care experience, the data collection, data management, and statistical analysis are conducted under many of the same strict operating paradigms used for rigorous clinical trials. Moreover, the scientific and clinical questions guiding data analyses focus on generating evidence for unmet medical needs. The outputs from the Fabry Registry are overseen by the expert International Board of Advisors, ensuring that these are conducted according to the highest standards. The evidence resulting from these analyses has contributed important insights and ongoing understanding on the disease onset



Fig. 1. The Fabry Registry: use of real-world data in global multistakeholder collaborations.

and progression, clinical management, and treatment outcomes that are communicated to the Fabry community. The findings are used in multistakeholder engagement between healthcare professionals, patients and patient organizations, payors, and healthcare policy makers, and can support decision making by regulatory agencies (Fig. 1) [53]. For example, in March 2021, the United States Food and Drug Administration granted traditional approval of agalsidase beta for the treatment of adult and pediatric patients 2 years of age and older with confirmed FD [55]. This was based on the totality of evidence on agalsidase beta, where Fabry Registry analyses were a critical part of that evidence.

2.7. Enrollment of patients in the Fabry Registry over time

The Fabry Registry has grown significantly from an initial enrollment of 21 patients with FD at two sites in 2001 to 8098 patients (43.5% male, 56.5% female) as of October 7, 2022 (Fig. 2). Notably, a reversal of the numbers of enrolled male and female patients occurred around the year 2007. This may have been triggered by a data collection effort in which participating physicians were specifically asked to enroll *all* female patients with FD in their practice, regardless of symptom status [20].

The Fabry Registry has a global reach, with a current presence in 44 countries worldwide and 219 participating sites. Enrollment spans the EMEA (45.7%; Europe, Middle East, Eurasia, and Africa), North America (40.3%), JAPAC (8.1%; Japan, Pacific, and Asia), and Latin America (5.9%). As of about 2015, the number of participating sites steadily accelerated patient enrollment (Fig. 2).

Genotype data are available for 7316 of the 8098 (90.3%) patients and, overall, 1039 *GLA* variants are represented in the Fabry Registry. Using available standardized genotype data, classifications of predicted pathogenicity included the classic phenotype (406 variants, 3532 patients), later-onset phenotype (54 variants, 1239 patients), and "other" phenotypes (e.g., [likely] benign, likely classic, likely later-onset, variants of uncertain significance; 70 variants, 762 patients) according to the International Fabry Disease Genotype-Phenotype Database (dbFGP.org, version August 15, 2018; on file). Predictions of phenotypes were not available in this database for 1783 (24.4%) patients with reported genotypes.

Stratification based on age, as used for the available recommended assessment schemes, showed that 19.4% of males and 13.1% of females were younger than 18 years at enrollment regardless of their treatment status.

During the natural history period, patients in the Fabry Registry had a total of 311,137 person-years from birth to last follow-up (122,599 years for males, 188,537 years for females), where last follow-up is the date of treatment initiation (for "ever-treated" patients) or the date of most recent data entry (for "never-treated" patients). Treatment time observed amounts to a total of 40,419 person-years (23,983 years for males, 16,436 years for females) among "ever-treated" patients.

3. Key contributions from 20+ years of the Fabry Registry

Knowledge of the clinical course of FD was limited at the time the Fabry Registry was created in 2001; therefore, analyses of patient data initially focused on delineating the sex- and age-specific clinical characteristics and natural progression of FD, including prognostic indicators. With continued follow-up and collection of longitudinal data from steadily growing numbers of agalsidase beta-treated patients, the focus shifted towards analyzing therapeutic outcomes. In this section, the collective scientific contributions resulting from Fabry Registry-related research in the main areas of study for FD and associated initiatives to develop guidance on clinical management of FD patients are summarized. Moreover, consolidated patient-centered collaborations are discussed, as well as advancements in data collection and statistical methodologies to evaluate the real-world data. Brief narratives on the 32 published peer-reviewed manuscripts (Fig. 3) are provided in the **supplementary file**.

3.1. Fabry disease presentation and natural progression

Prior to the initiation of the Fabry Registry in 2001, FD had long been regarded as an X-linked disorder with constant penetrance in males, with most, if not all, affected males developing the full-blown classic phenotype, and only occasional penetrance in females [1,56]. Indeed, manuscripts and textbooks on FD usually started with the sentence "Fabry disease is an X-linked *recessive* lysosomal storage disorder" [57]. Furthermore, the relatively limited number of published descriptions of FD were primarily based on a small number of patients [58–67] or studies without longitudinal follow-up [68–70]. Hence, there were sizeable gaps in the understanding of the early clinical manifestations, the natural disease course, and the late-occurring complications of untreated FD. A range of Fabry Registry publications have contributed to the reduction in these knowledge gaps.

Hopkin et al. (2008) [18] reported data on disease manifestations in affected children, indicating a pediatric onset of FD that generally clinically emerges earlier in affected boys than in girls, with neuropathic pain often being the first symptom.

Following implementation of concerted efforts to enroll diagnosed female patients with FD independent of symptoms, Wilcox et al.

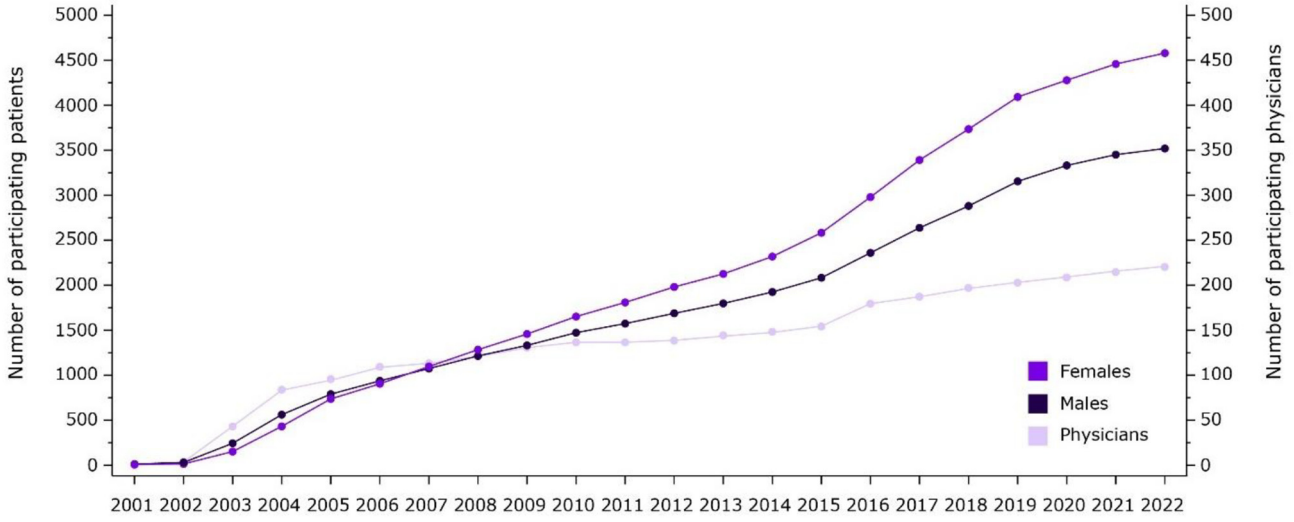

Fig. 2. Cumulative numbers of participating physicians and patients enrolled in the Fabry Registry by year of enrollment.

(2008) [20] clarified the status and need for treatment among female patients who were shown in this study to have a significant risk of major organ involvement and decreased quality of life. Diagnostic delays were considerable, highlighting the need for greater disease awareness and treatment of female patients. Martins et al. (2019) [42] confirmed these findings in a study of female patients from Latin America, where a similar burden of disease was identified in a group of untreated women relative to the burden of disease at baseline of the women who were treated.

The natural history of Fabry nephropathy was unclear and risk factors for chronic kidney disease progression (role of sex, genotype, proteinuria) had not been thoroughly investigated prior to studies by Ortiz et al. (2008 [19], 2010 [25]) and Wanner et al. (2010) [26]. These studies showed that Fabry nephropathy can commence at a very young age and that the spectrum of kidney involvement is broad. Importantly, proteinuria was recognized as a predominant factor in predicting renal disease progression and despite a greater impact of proteinuria on kidney outcomes in male than in female patients, nephrotic range could occasionally be reached in either sex. However, albuminuria may be an even more sensitive marker of kidney injury in Fabry nephropathy than proteinuria [19]. In addition, these studies also showed that in most adult female patients, the rate of estimated glomerular filtration rate (eGFR) decline is similar to the expected age-associated yearly eGFR loss of around 1 mL/min/1.73 m^2. Compared with males, a smaller subset of females develops severe Fabry nephropathy; nevertheless, it progresses to kidney failure in a proportion of this population due to a highly skewed X-chromosome inactivation profile that silences the wild-type *GLA* allele [51]. These studies provided a basis for interpreting the effects of therapeutic interventions on kidney function outcome measures. It should be noted that both male and female FD patients who develop kidney failure do so at a mean age of approximately 40 years [25]. The observation that the natural history of kidney disease is four decades on average is a key piece of information for interpretation of short-term results from clinical trials.

At around the same time period, Waldek et al. (2009) [23] identified cardiovascular events (i.e., sudden cardiac death and heart failure) as being the most common cause of death among untreated patients of both sexes. Patel et al. (2011) [28] also reported occurrence of these events in approximately 5% of untreated adult patients, underscoring the importance of monitoring FD patients for cardiovascular risk factors. Furthermore, Sims et al. (2009) [22] showed that strokes occur in FD patients at markedly higher rates than in the general United States population, even in the absence of other organ-system clinical complications considered key signs of FD. The recognition of early strokes as a manifestation of FD increased the index of suspicion of FD in patients with early stroke of undetermined cause.

Two Fabry Registry publications highlight the importance of registry data for expanding the understanding of genotype–phenotype correlations in FD. The p.N215S (p.Asn215Ser) variant is the most common pathogenic later-onset *GLA* variant in the Fabry Registry (data on file). Given the prevalence of this variant and the limited understanding of its clinical manifestations to support patient care, a detailed study was conducted which led to a publication by Germain et al. (2018) [39]. This work is a model on how to clinically characterize patients with specific genetic variants in numbers that warrant focused evaluation. Moreover, Germain et al. (2020) [43] provided proof of concept for using clinical data from the Fabry Registry to phenotypically characterize patients with genotypes that have not been clearly associated, in publically available databases, with a defined FD phenotype.

3.2. Clinical outcomes of treatment with agalsidase beta

Prior to the inception of the Fabry Registry and availability of ERTs in 2001, the care of patients with FD consisted of symptomatic treatments and nonspecific measures, such as the use of analgesics to relieve agonizing pain, chronic dialysis or kidney transplantation and cardiac surgery as life-saving procedures, as well as pharmacological prophylaxis for stroke [71]. Consequently, the clinical prospects for modification of disease progression in affected patients were poor. Over time, the Fabry Registry has increased the number of participating patients treated with agalsidase beta who have longitudinal follow-up. Data analyses from these patient cohorts over extended periods of time have contributed to clinical insights into the outcomes of agalsidase beta treatment, including prognostic factors. The following studies highlight Fabry Registry contributions to the understanding of patient-treatment-specific outcomes.

Warnock et al. (2012) [29] showed that agalsidase beta-treated males who had low levels of proteinuria, higher baseline eGFR, and who began treatment at a younger age had stable eGFR over time. Higher proteinuria levels, poorer initial kidney function, and delayed initiation of treatment were associated with more rapid kidney disease progression. Generally, kidney function among treated females appeared to remain normal over time.

Germain et al. (2015) [35] reported clinical outcomes in primarily male patients with classic FD who had participated in the extended Phase 3 study of agalsidase beta and were followed in the Fabry Registry

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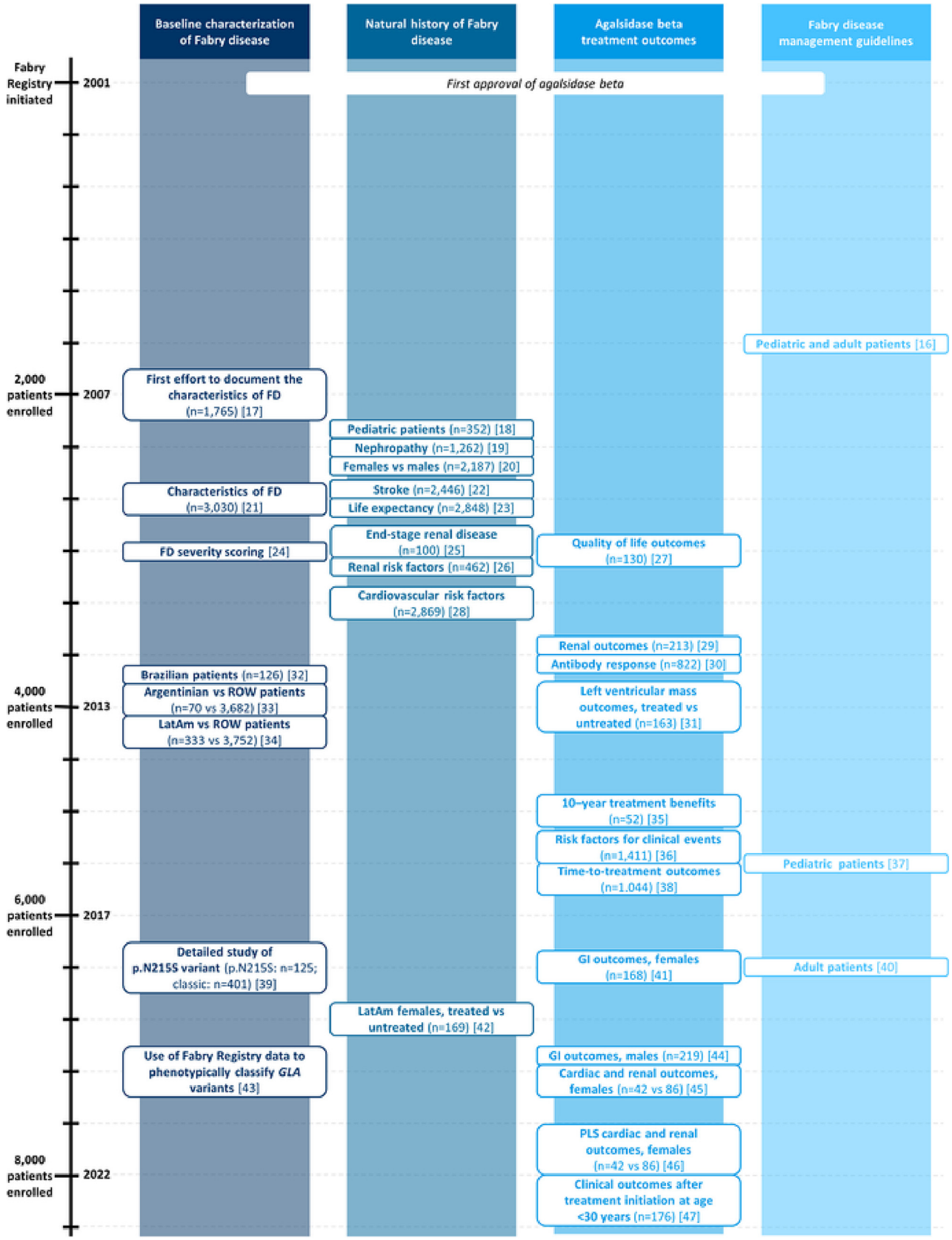

Fig. 3. Topics covered by Fabry Registry publications.
Abbreviations: FD, Fabry disease; GI, gastrointestinal; LatAm, Latin America; PLS, plain language summary publication; ROW, rest of the world

for a total median duration of 10 years. At the end of the follow-up period, 81% of the patients had remained free of clinical events and 95% were alive. The most favorable treatment responses measured by eGFR and echocardiographic parameters were observed among young patients who exhibited little organ damage during the pre-treatment period. However, even in patients with advanced FD, initiation of treatment may have slowed the progression of kidney disease and cardiomyopathy.

The published evidence available for evaluating various clinical outcomes among young patients with FD was still relatively limited due to the scarcity of data in young age groups when Hopkin et al. (2023) [47] analyzed data from patients with classic or unclassified *GLA* variants (with similar characteristics) who initiated agalsidase beta treatment before 30 years of age. Factors that had contributed to dataset maturity included a focused data collection effort (2015–2016), continued enrollment of young patients in the Fabry Registry, and sustained follow-up of the patients eligible for inclusion in the analyses. The results were suggestive of an overall stability or improvement after sustained treatment. Kidney function (median follow-up ≥5 years) modestly decreased among younger patients with low renal involvement (determined based on proteinuria/albuminuria levels), while the decrease was greater in older males with proteinuria, which may suggest a benefit of early treatment. Echocardiographic variables (i.e., end-diastolic interventricular septal thickness and left ventricular posterior wall thickness; median follow-up ≥4 years) were stable among males and younger females, and reports of FD symptoms significantly reduced, particularly among males during long-term follow-up.

To better understand patient treatment outcomes, ideally an untreated control cohort arm should be included in a study. Over the years this has been challenging due to the scarcity of untreated patients with similar characteristics to the treated group (especially regarding disease severity), which is necessary to form an unbiased comparator group. To overcome this challenge, Wanner et al. (2020) [45] reported findings from a self-controlled study by using a pre- versus post-treatment comparison of data from female patients suggesting a beneficial effect of agalsidase beta treatment on cardiac hypertrophy (pre-treatment progressive hypertrophy stabilized). The overall eGFR decline remained stable and within the normal range of a healthy population both before and after initiation of therapy.

Regarding severe clinical events, Ortiz et al. (2016) [38] documented the progression and modified history of advanced FD by agalsidase beta. The incidence rate for combined clinical events decreased after the first 6 months of agalsidase beta treatment in adult patients, with stabilization during sustained treatment, contrary to the expected increase in incidence of events over time in patients who remain untreated. Patients at highest risk for events (those aged ≥40 years and patients of male sex) displayed the greatest absolute reduction in event rate over time. However, a reduction of event incidence rate was observed for all subgroups analyzed (among them females and younger patients), including patients with severe events prior to starting ERT. Hopkin et al. (2016) [36] also determined the incidence and type of severe events prior to and following initiation of agalsidase beta. Among the male patients without pre-treatment events, 84% did not develop any on-treatment events after sustained treatment, compared with 64% of males who had a pre-treatment event. The findings among female patients were similar. Patients with on-treatment events were older and had significantly more advanced cardiac and kidney disease at treatment baseline.

Wilcox et al. (2018) [41] and Hopkin et al. (2020) [44] reported the first evidence of agalsidase beta treatment having a positive impact on gastrointestinal symptoms of female and male patients with FD, respectively.

Watt et al. (2010) [27] exploring health-related quality of life (HRQoL) outcomes found that agalsidase beta treatment substantially improved HRQoL in both male and female patients. A lower HRQoL prior to commencing treatment was associated with greater improvement in response to agalsidase beta.

Wilcox et al. (2012) [30] analyzed anti-agalsidase beta antibody formation and infusion reactions. The majority of treated male patients developed antibodies and those with nonsense *GLA* variants were generally more likely to develop antibodies than were males with missense variants. Most females remained seronegative. Patients who tolerized (two consecutive negative antibody test results) had lower median peak antibody titers than patients who remained seropositive. Most infusion-associated reactions occurred during the first 6–12 months of treatment and decreased over time.

Further valuable contributions to unmet needs include publications examining Fabry Registry data on arrhythmias in pediatric patients [72] and lymphedema [73].

3.3. Guidance on clinical management of patients with Fabry disease

The Fabry Registry studies delineating the natural history of FD defined an era of increasing understanding and recognition of several underappreciated aspects of FD, particularly the heterogeneity of FD manifestations requiring multiorgan comprehensive assessments. Prior to the establishment of the Fabry Registry, available evidence and/or clinical knowledge to guide approaches for disease management, or even recommended schedule of assessments for patients with FD, was scarce. The body of real-world evidence on the disease course and clinical insights into the outcomes of treatment have steadily grown and have informed the development and subsequent updates of guidelines for monitoring and treatment of pediatric and adult patients with FD [16,37,40] through multidisciplinary collaborations between Fabry Registry Advisory Board members and international specialists with expertise in FD. Key pillars of the guidelines include comprehensive and regular assessment of each organ system and initiation of FD-specific treatment early in the disease process. The most recent updated recommendations specify that the long-term management of adult patients with FD by an experienced multidisciplinary team depends on an individualized approach to care, reflecting the genotype, sex, family history, phenotype, and specific clinical symptom severity of a given patient [40].

3.4. Patient-centered Fabry Registry and the patient perspective

The Fabry Registry is a worldwide community collaboration including patients with FD as research partners to empower them to become active participants. This reflects the shifting role of the patient in healthcare from that of a passive recipient of medical care to an active contributor in clinical decision-making. Fabry Registry publications, in addition to the medical community, also inform patients and patient organizations on the importance of education, thus raising awareness about FD and diagnosis, aiding patients, and advocating for FD issues.

To ensure a greater understanding of the Fabry Registry research for the entire FD community, the first plain language summary publication on FD was published in 2022 by Wanner et al. [46]. This is a visually enriched open-access summary and reports on the previously published manuscript which focused on the effects of agalsidase beta treatment on heart-muscle thickening and renal function in females with FD [45].

In an effort to hear the patient voice while identifying gaps, selecting research projects, or evaluating data at the Registry Advisory Boards, patient representation has been included in Advisory Board Meetings, and in 2019, the Rare Diseases Registries Patient Council was established with representation of patient-advocacy leaders, including those from local and global FD patient-advocacy organizations. Similarly, in highly interactive and collaborative engagements, Sanofi Registry and Public Affairs associates meet periodically with representatives of the global patient-advocacy leaders to better understand their perspectives and what matters most to patients with FD. Valuing the direct contributions of patients to their own care, and to complement this patient-centered approach geared towards long-term patient involvement, in 2022, the Fabry Registry implemented ePRO, the electronic collection of patient-

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reported outcomes, to capture the experience of patients with FD on quality of life and general health status.

3.5. Continued evolution of data collection

Over time, the Fabry Registry has evolved from the early days of paper case-report forms to a state-of-the-art, interactive, mobile-friendly, web-based collection and reporting technology platform, RegistryNXT! [54]. This platform promotes ease of data submission and can be used as a tool for disease management. Through their providers, patients are able to serially monitor organ involvement and changes in symptoms corresponding to their treatment modalities. This may help them understand the disease process and the impact of therapy, and reassure them about the care they receive.

The Fabry Registry has been evolving and adapting appropriately, and relevant changes have been implemented as deemed necessary over the years. As such, the content of the Fabry Registry case-report forms represents a guidance to physicians concerning relevant parameters required for the follow-up of patients, including complex patients. With the advancement of imaging technology, new cardiac magnetic resonance imaging and other cardiovascular and cerebrovascular parameters have been included. As of 2017, plasma lyso-GL-3 concentration is included in the Recommended Schedule of Assessments and data are collected through the Fabry Registry as the body of evidence supporting its potential value as a biomarker for disease staging and treatment response has grown [74]. Moreover, following the outbreak of the COVID-19 pandemic, questions emerged about the potential susceptibility of FD patients and impact of this viral infection on disease outcomes [75]. These scientific questions prompted the development of the COVID-19 case-report form, and COVID-19-related data have been collected since 2020. Strategies for analyses of these data will depend on the maturity of the data sets.

Newborn screening will provide opportunities and challenges which are difficult to gauge at this time [49]. However, there is little doubt that the potential benefit of newborn screening to the understanding of FD would be greatly limited without focused registry involvement in this rapidly emerging area. While the Fabry Registry currently collects whether a patient was identified via newborn screening, future needs may include additional assessments and data collection tools for these patients.

3.6. Advancing statistical methodology

Continued collection of longitudinal data expands opportunities to apply advanced statistical methodologic approaches that are commonly used for analysis of more prevalent diseases. The initial Fabry Registry analyses were mainly descriptive and cross-sectional but, with more data becoming available, the Registry has had increasing potential to conduct more complex analyses (e.g., linear mixed models) with stratification and/or subgrouping of patients based on important patient demographics (e.g., sex and age), genotype, and baseline disease severity (e.g., renal risk based on proteinuria/albuminuria levels, and clinical events) to evaluate and control for confounding. FD has a wide spectrum of heterogeneously progressive clinical phenotypes among patients of both sexes, and therapeutic outcomes largely depend on disease severity at the start of treatment. Thus, separating samples into subgroups according to FD phenotype or other potential confounders is of critical importance to discerning differences in treatment outcomes between subpopulations of patients [31,38,39,44,45,47]. In addition, to overcome the lack of appropriate untreated comparison groups, the innovative self-controlled pre- versus post-treatment comparison approach to the analysis of clinical outcome data from patients with FD was implemented [45].

Since its initiation, the Fabry Registry has received and processed hundreds of FD-related, hypothesis-driven analysis requests from Fabry healthcare professionals for research or patient-care purposes covering diverse topics. All requests were considered according to their scientific and clinical merits.

4. Limitations of the Fabry Registry

Several limitations of the Fabry Registry need to be acknowledged. Fabry Registry data are observational in nature and submitted voluntarily and therefore measurements are not evenly distributed across the different patients. However, the Fabry Registry team uses specific modeling techniques in analyses to account for this limitation, such as the use of linear mixed models [26,35,45,47]. The lack of an appropriate untreated comparison group of patients may limit data interpretation; however, the use of untreated comparators is sometimes possible [31], as is the self-controlled study design approach which compares pre- versus post-treatment data to evaluate the outcomes. While eliminating all time-invariant confounding and providing an alternative study design when an appropriate comparator group is difficult to identify [45], the self-controlled study design has notable limitations in its assumptions and interpretation [76]. Selection bias and confounding by severity arising from the inclusion of more severely affected patients are inevitable and cannot be excluded. Not all FD patients have been diagnosed and subsequently enrolled. This may be particularly applicable to heterozygous females. The possible under-enrollment of asymptomatic or minimally affected females may influence Fabry Registry-based depictions of the female phenotype to the more severe end of the phenotypic spectrum. Indeed, asymptomatic patients in general are less likely to be captured in the Fabry Registry before seeking medical care unless another family member has been diagnosed and has consented to disclose their diagnosis to their family.

Data completeness is a further limitation. Despite regular site follow-up, not all patients have complete sets of reported clinical data, thus reducing the numbers of patients with repeated assessments required for longitudinal analysis. Certain inclusion/exclusion criteria have been set in all studies utilizing the Fabry Registry data, and some statistical modeling techniques have been used to reduce this bias. Finally, the Fabry Registry does not include biobanking of patient samples or central reading of imaging. Despite these collective limitations, the Fabry Registry offers the largest and most comprehensive ongoing source of long-term, real-world data on patients with FD which have been key in understanding the epidemiology and natural history of FD and the clinical course while on agalsidase beta therapy, along with several other important contributions made by the observational Fabry Outcome Survey [77] and studies of migalastat [78–80]. A comparison of data from all these sources would be informative; however, well-designed comparative studies of the different Fabry-specific therapies are lacking, and such a comparison is beyond the scope of the present review.

5. Conclusions

The Fabry Registry activities have greatly contributed to transforming our understanding of FD over the last 20 years and to better clinical prospects of individuals with this complex disorder. The Fabry Registry has provided the local, national, and global research infrastructures to aggregate longitudinal real-world data from large numbers of patients with FD. Multidisciplinary collaborations between Fabry Registry Advisory Board members and international specialists with expertise in FD have facilitated publication of 32 articles to date in peer-reviewed journals, sharing of data at important national and international scientific meetings, and advising clinicians on patient-specific characteristics and clinical outcomes. However, we are still learning about the clinical issues that were the key focus when the Fabry Registry started (e.g., best management of kidney involvement and cardiac hypertrophy) and the scope of investigations will continue to expand. New clinical investigators will become more involved in this field, with the Fabry Registry serving as a catalyst for their interest and participation.

The Fabry Registry is an industry-supported community partnership with the contribution of both patients and healthcare professionals throughout the world and is well positioned to add to its past achievements. Enrollment of patients in the largest disease registry for FD will

continue for the foreseeable future, demonstrating an ongoing commitment to the Fabry community.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

C.W. has received honoraria for board meetings and lecturing from Amicus Therapeutics, Chiesi Pharmaceuticals, Idorsia Pharmaceuticals, Sanofi, and Takeda.

A.O. has received grants from Sanofi and consultancy, speaker fees or travel support from Advicenne, Alexion, Amgen, Amicus Therapeutics, Astellas, AstraZeneca, Bayer, Chiesi Pharmaceuticals, Fresenius Medical Care, GlaxoSmithKline, Idorsia Pharmaceuticals, Kyowa Kirin, Menarini, Novo-Nordisk, Otsuka, and Vifor Fresenius Medical Care Renal Pharma, and is Director of the Cátedra Mundipharma-UAM of diabetic kidney disease and the Cátedra AstraZeneca-UAM of chronic kidney disease and electrolytes.

W.R.W. is a member of the Fabry Registry Board of Advisors, has consulted for Amicus Therapeutics, Sanofi, Spark, Takeda, and UniQure, and has been an investigator in clinical studies for Fabry disease sponsored by Amicus Therapeutics, Chiesi Pharmaceuticals, Freeline Therapeutics, Idorsia Pharmaceuticals, 4D Molecular Therapeutics, Protalix Biotherapeutics, Sangamo Therapeutics, and Sanofi. These activities are monitored and are in compliance with the conflict-of-interest policies at Emory University School of Medicine.

R.J.H. is a member of the Fabry Registry Advisory Board, consults with Amicus Therapeutics and Sanofi, and has been an investigator in clinical trials sponsored by Amicus Therapeutics, Idorsia Pharmaceuticals, Protalix Biotherapeutics, Sangamo Therapeutics, Sanofi, and Takeda. These activities have been monitored and found to be in compliance with the conflict-of-interest policies at Cincinnati Children's Hospital Medical Center.

J.J. has received honoraria from Sanofi, and travel support from Amicus Therapeutics and Sanofi.

E.P., J.T.E., J.L.B., and Ma.M. are full-time employees of Sanofi and may hold/have held stock and/or stock options in that company.

J.M.P. has received honoraria from Amicus Therapeutics, Sanofi, and Takeda, and consulting fees from Sanofi and Takeda.

A.M.M. has received Advisory Board honoraria from Astra Zeneca-Alexion Pharmaceuticals, BioMarin Pharmaceutical, JCR Pharmaceuticals, and Sanofi, and speaker honoraria and travel support from Astra Zeneca-Alexion Pharmaceuticals, BioMarin Pharmaceutical, Chiesi Pharmaceuticals, JCR Pharmaceuticals, and Sanofi.

M.B. is a member of the Fabry Registry Advisory Board and has received honoraria for consultancies, honoraria for disease registry advisory board meetngs, honoraria for lecturing and support for research from Sanofi. She also has received consulting and/or lecturing honoraria from Amicus Therapeutics and Chiesi Pharmaceuticals.

A.L. has received consulting honoraria from Amicus Therapeutics, Sanofi Genzyme, and Takeda, and speaker honoraria and travel support from Sanofi Genzyme and Takeda.

Mi.M. is a member of the Fabry Registry Board, has an investigator-initiated research grant from Sanofi, performs laboratory work and is a consultant to Sanofi for clinical trial design, received speaker fees and travel support from Sanofi for non-promotional presentations (these interests have been reviewed and managed by the University of Minnesota in accordance with its conflict-of-interest policies), is a consultant and performs laboratory work for Amicus Therapeutics, and is a consultant to Acelink Therapeutics, Avrobio, Freeline Therapeutics, and Sangamo Therapeutics.

J.P.O. is member of the European Advisory Board of the Fabry Registry and has received honoraria for consultancies, honoraria for disease registry advisory board, honoraria for lecturing and support for research from Sanofi. He also has received consulting and/or lecturing honoraria from Amicus Therapeutics, Chiesi Pharmaceuticals and Takeda, and support for travel and accommodation from Amicus Therapeutics, Sanofi, and Takeda.

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Appendix A. Supplementary data

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