

LES 20 ANS DU CRML

VENDREDI 22 NOVEMBRE 2024



Wladimir Mauhin
Olivier Lidove



20 ANS : LE TEMPS DE PROGRESSER ET DE TRANSMETTRE ...



LES 20 ANS DU CRML – 22 NOVEMBRE 2024

Disclosure

- Travel grants and speaker honoraria from:
 - Amicus
 - Chiesi
 - Genzyme/Sanofi
 - Takeda

Maladie de Fabry

UNIVERSITE PARIS NORD

FACULTE DE MEDECINE DE BOBIGNY

" Léonard de Vinci "

ANNEE 1998

N°

THESE

pour le

DOCTORAT en MEDECINE
Spécialité: MEDECINE INTERNE
(Diplôme d'Etat)

par

OLIVIER LIDOVE,
né le 15 juin 1967 à Le Raincy

Présentée et soutenue publiquement le 20 octobre 1998.

**MALADIE DE FABRY (34 CAS):
MANIFESTATIONS CARDIAQUES,
NEUROLOGIQUES, ET PSYCHIATRIQUES.**

Présidents de thèse : Mr le Professeur Olivier Blétry ;
Mr le Professeur Jean-Pierre Grünfeld .

Directeur de thèse : Mr le Docteur Dominique Joly .

Rapporteur de thèse : Mme le Docteur Dominique Droz .

UNIVERSITÉ PARIS DIDEROT - PARIS 7

FACULTÉ DE MÉDECINE

Année 20 18

n° _____

THÈSE
POUR LE DIPLÔME D'ÉTAT
DE
DOCTEUR EN MÉDECINE

PAR

NOM : MAUHIN Prénoms : Wladimir, Yves, Georges
Date et Lieu de naissance : 27 janvier 1986 à Epinay sur Seine

Présentée et soutenue publiquement le : 25 mai 2018

Elaboration d'un système de classification phénotypique et de
sévérité des patients atteints de maladie de Fabry à partir des
données de la cohorte française FFABRY

Président de thèse : Professeur BENVENISTE Olivier

Directeur de thèse : Docteur LIDOVE Olivier

DES de Médecine Interne

Original Contribution

January 20, 1999

Prevalence of Lysosomal Storage Disorders

Peter J. Meikle, PhD; John J. Hopwood, PhD; Alan E. Clague, FRCPN; [et al](#)

» Author Affiliations

JAMA. 1999;281(3):249-254. doi:10.1001/jama.281.3.249

- LSD 1:7700 naissances
- Fabry: 1:117 000

ARTICLES · Volume 19, 100344, February 2022 · [Open Access](#)

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Prevalence of lysosomal storage disorders in Australia from 2009 to 2020

[Sharon J Chin](#)^a · [Maria Fuller](#)^{a,b}  



LSD 1:4800 naissances

Fabry = 34% of all LSD diagnoses

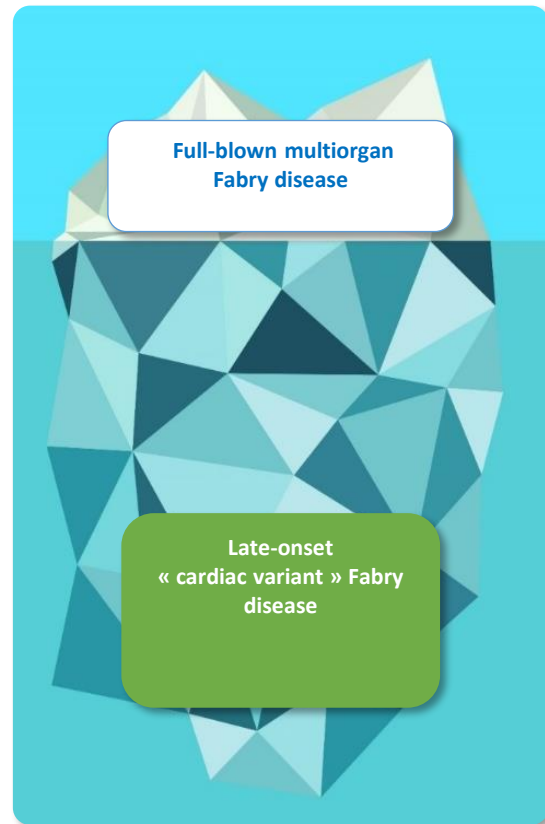
Newborn Screening for Fabry Disease in Northeastern Italy: Results of Five Years of Experience

by [Vincenza Gagnaniello](#)^{1,†} , [Alessandro P Burlina](#)^{2,†}  , [Giulia Polo](#)¹  , [Antonella Giuliani](#)¹ , [Leonardo Salviati](#)³ , [Giovanni Duro](#)⁴ , [Chiara Cazzorla](#)¹ , [Laura Rubert](#)¹ , [Evelina Maines](#)⁵  , [Dominique P Germain](#)⁶   and [Alberto B Burlina](#)^{1,*}  

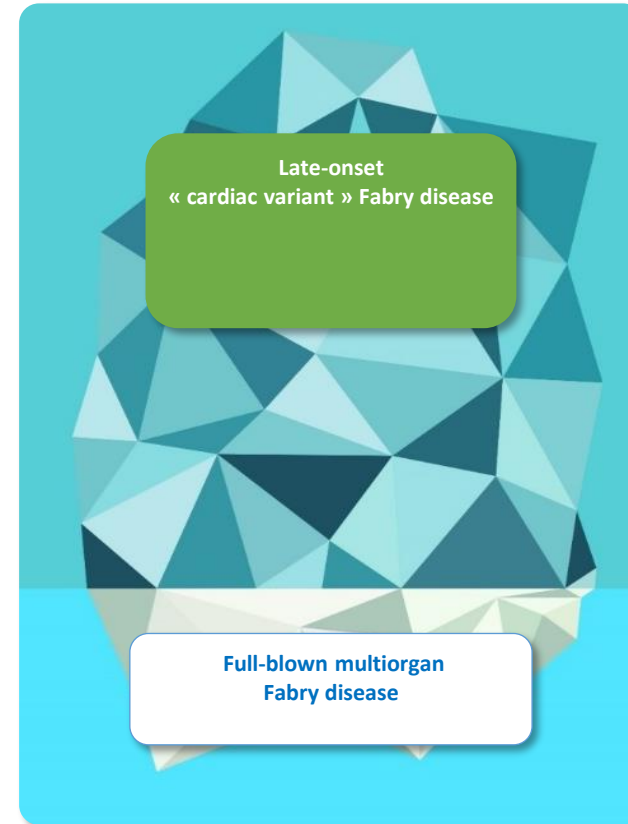
Biomolecules 2021

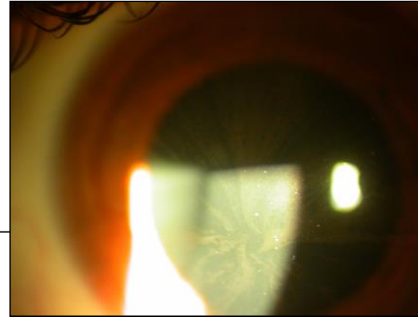
Fabry = 1:6883 naissances chez les garçons

Before



Now





RESEARCH ARTICLE

Cornea verticillata and acroparesthesia efficiently discriminate clusters of severity in Fabry disease

Wladimir Mauhin^{1,2*}, Olivier Benveniste^{2,3}, Damien Amelin², Clémence Montagner¹, Foudil Lamari^{4,5}, Catherine Caillaud^{6,7}, Claire Douillard⁸, Bertrand Dussol^{9,10}, Vanessa Leguy-Seguin¹¹, Pauline D'Halluin¹², Esther Noel¹³, Thierry Zenone¹⁴, Marie Matignon^{15,16}, François Maillot^{17,18}, Kim-Heang Ly¹⁹, Gérard Besson²⁰, Marjolaine Willems²¹, Fabien Labombarda²², Agathe Masseau²³, Christian Lavigne²⁴, Didier Lacombe^{25,26}, Hélène Maillard²⁷, Olivier Lidove^{1,2}

Mucopolysaccharidoses

Relais enfant-adulte

Consultation Jeune adulte - pédiatre – médecin interniste («pédiatre de l'adulte »)

Consultation Jeune adulte - médecin interniste - pédiatre – (« interniste de l'enfant »)

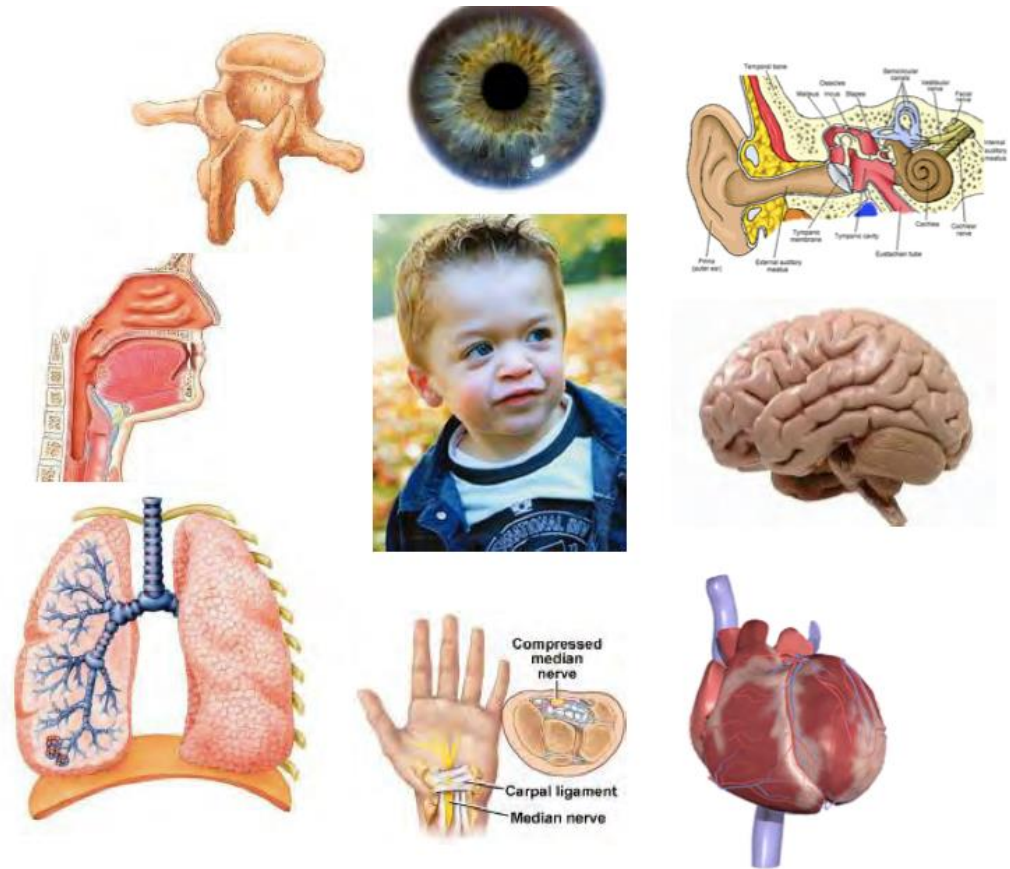
L'interniste observe et écoute le pédiatre :

- Dossier
- Périmètre crânien ...

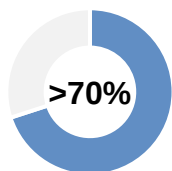
Difficultés

Atteinte systémique :

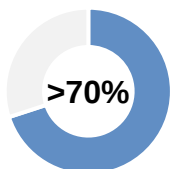
- Prise en charge multidisciplinaire
- Difficulté de trouver des correspondants enfants / adultes



ASMD (Niemann-Pick – majoritairement B)



Hypo-HDLc



Hépatomégalie

CARDIAC DISEASE

- An atherogenic lipid profile is typical of the disease (low HDL: 74%; high total cholesterol: 41%; high triglycerides: 62%; high LDL: 46%; very low-density lipoprotein cholesterol: 62%)
- Cardiac and cardiovascular disturbances manifest at an early age (e.g., elevated coronary artery calcium score)
- Approximately 10% of patients have coronary artery or heart valve disease
- Cardiac disease accounts for >7% of deaths among adults (with chronic visceral or chronic neurovisceral ASMD [NPD B and B variant])

NEUROLOGICAL MANIFESTATIONS

- Present in approximately 30% of patients with NPD B ("intermediate phenotype")
- Range from mild hypotonia/hyporeflexia to severe progressive abnormalities (e.g. loss of motor function, cognitive impairment)
- Often present in patients with macular cherry-red spots
- Associated with reduced life expectancy

PULMONARY DISEASE

- Interstitial lung disease (based on radiologic findings) present in >80% of patients
- Frequent respiratory infections including pneumonia
- Leading cause of death, due to progressive loss of pulmonary function

LIVER DISEASE

- Liver fibrosis (88%), including minimal, mild, moderate fibrosis and cirrhosis (13% of all fibrosis)
- Liver dysfunction (elevated ALT and AST) is common (50-75% of patients); however in some cases liver function test may be normal despite detected localized or initial signs of liver fibrosis or cirrhosis
- Together with pulmonary disease, liver failure is the most common causes of death

DISEASE OF SPLEEN

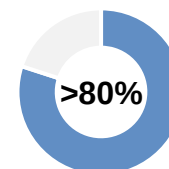
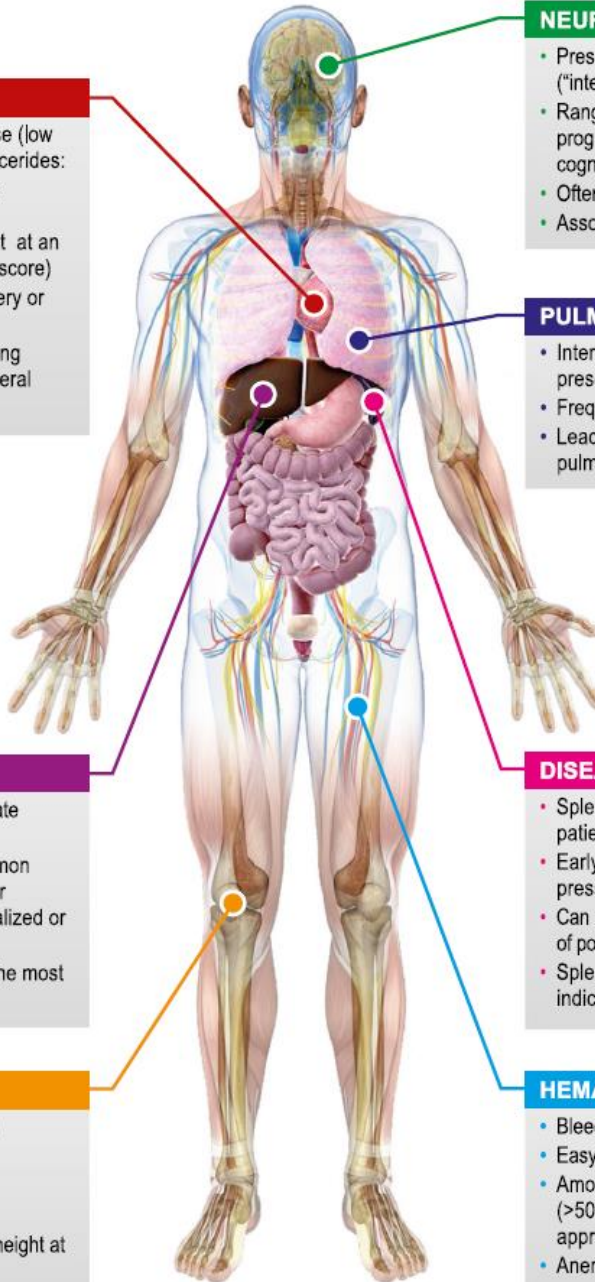
- Splenomegaly is a typical disease manifestation (>90% of patients)
- Early diagnostic sign; symptoms include pain, feeling of pressure and early satiety
- Can be massive (up to 30 multiples of normal); increased risk of potentially fatal bleeding (rupture)
- Splenectomy not associated with better outcomes, but indicated in case of spleen rupture or extensive necrosis

SKELETAL DISEASE

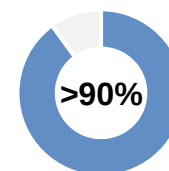
- A majority of patients have back, limb, or joint pain
- Skeletal fractures are common
- Osteopenia and osteoporosis common in adults
- Decreased BMC and BMD in pediatric patients
- Adolescents often experience growth delay; adult height at low normal range

HEMATOLOGIC ABNORMALITIES

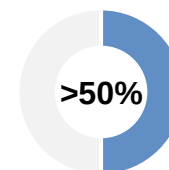
- Bleeding is the third most common cause of death
- Easy bruising and excessive bleeding is common
- Among cytopenias, thrombocytopenia is most common (>50% of patients); anemia and leukemia each affect approximately 20-30% of patients
- Anemia rarely necessitates red blood cell transfusions



Pneumopathie interstitielle



Splénomégalie



Thrombopénie

A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results

[Melissa Wasserstein](#)   • [Robin Lachmann](#) • [Carla Hollak](#) • [Laila Arash-Kaps](#) • [Antonio Barbato](#) •
[Renata C. Gallagher](#) • [Roberto Giugliani](#) • [Norberto Bernardo Guelbert](#) • [Takayuki Ikezoe](#) • [Olivier Lidove](#) •
[Paulina Mabe](#) • [Eugen Mengel](#) • [Maurizio Scarpa](#) • [Eubekir Senates](#) • [Michel Tchan](#) • [Jesus Villarrubia](#) •
[Yixin Chen](#) • [Sandy Furey](#) • [Beth L. Thurberg](#) • [Atef Zaher](#) • [Monica Kumar](#) • [Show less](#)

[Open Access](#) • Published: April 26, 2022 • DOI: <https://doi.org/10.1016/j.gim.2022.03.021> •

Continued improvement in disease manifestations of acid sphingomyelinase deficiency for adults with up to 2 years of olipudase alfa treatment: open-label extension of the ASCEND trial

Melissa P. Wasserstein , Robin Lachmann, Carla Hollak, Antonio Barbato, Renata C. Gallagher, Roberto Giugliani, Norberto Bernardo Guelbert, Julia B. Hennermann, Takayuki Ikezoe, Olivier Lidove, Paulina Mabe, Eugen Mengel, Maurizio Scarpa, Ebubekir Senates, Michel Tchan, Jesus Villarrubia, Beth L. Thurberg, Abhimanyu Yarramaneni, Nicole M. Armstrong, Yong Kim & Monica Kumar

Orphanet Journal of Rare Diseases **18**, Article number: 378 (2023) | [Cite this article](#)



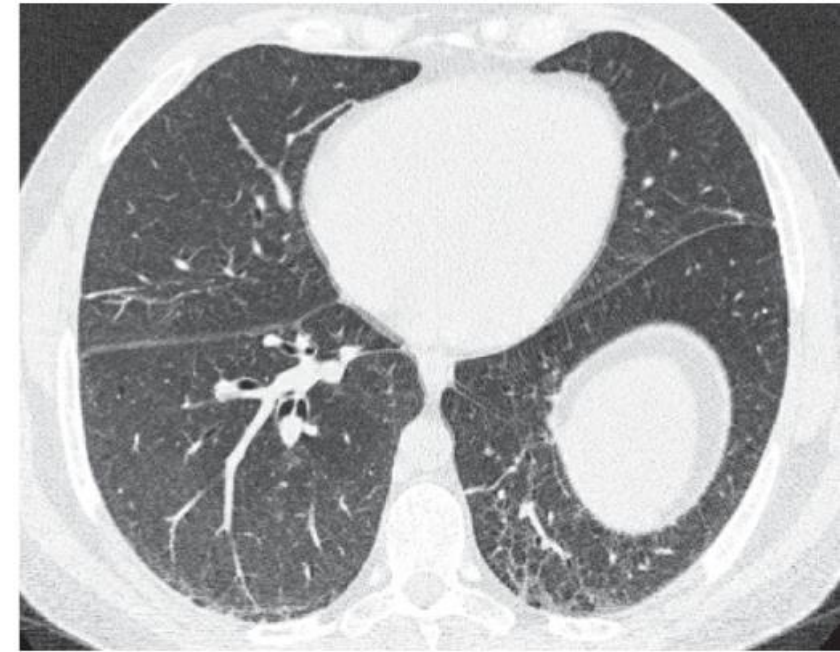
Baseline

Ground glass appearance score: **3**
(Severe, 51-100% of lung volume)



Year 1

Ground glass appearance score: **0**
(None)



Year 2

Ground glass appearance score: **0**
(None)

Décision de traiter = décision partagée

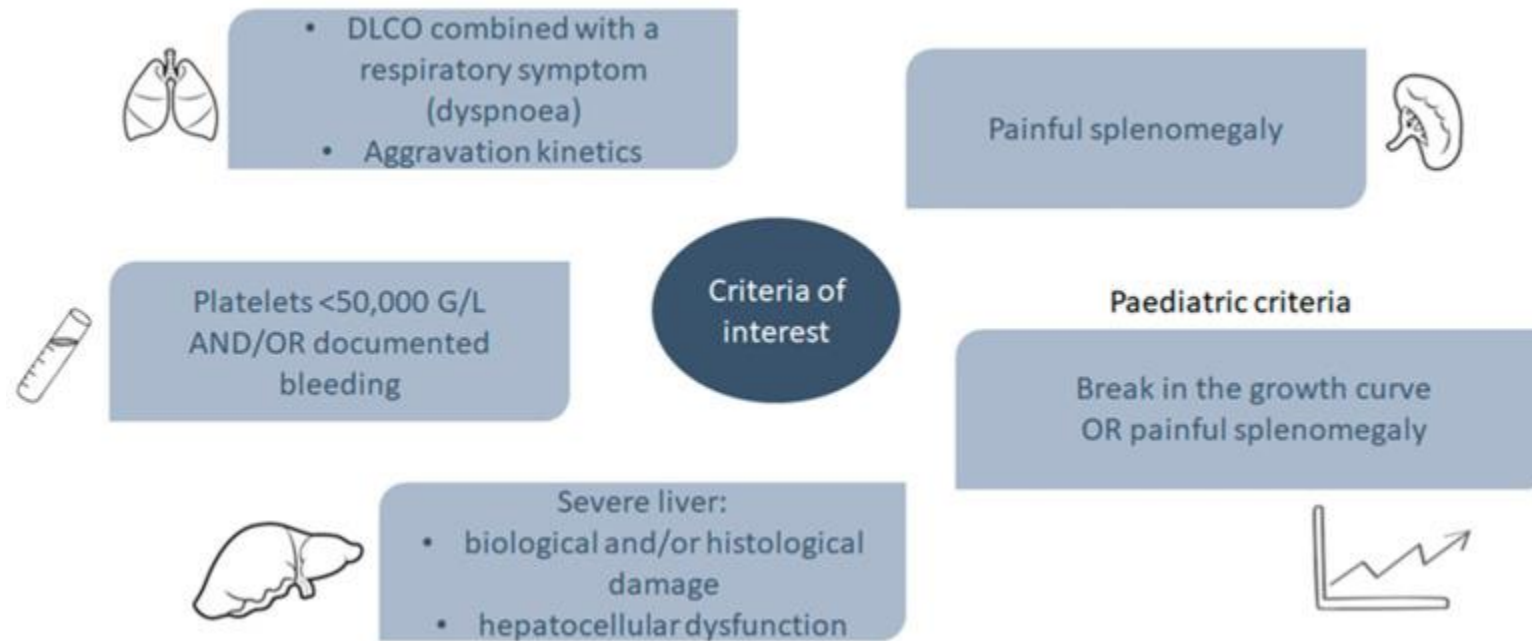


Olipudase alfa

AMM 2024

Indications thérapeutiques retenues

Avis / RCP du CETLipidoses viscérales (www.cetl.net)



Perspectives

PNDS ASMD finalisé

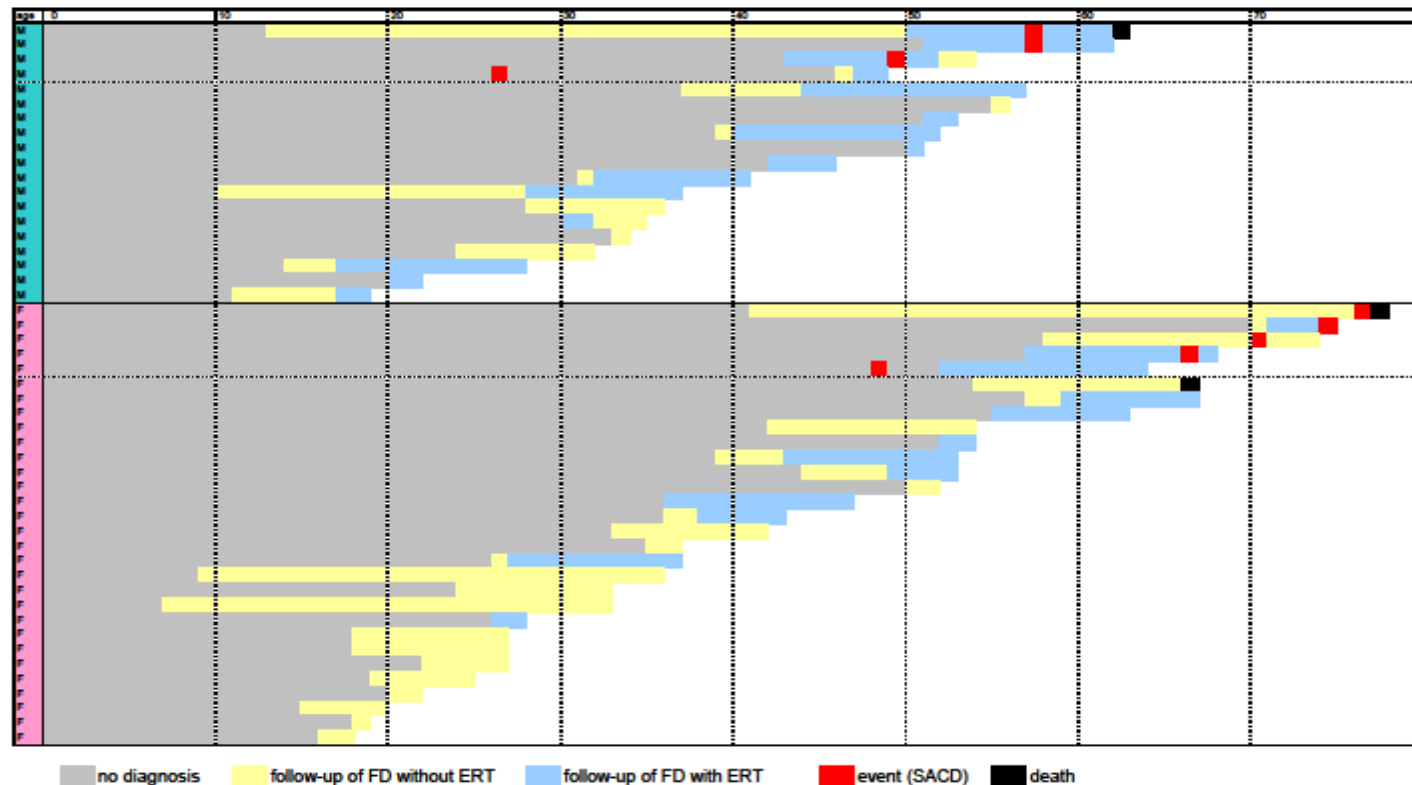


Séminaire Maladies Métaboliques chez l'Adulte

O. Lidove / W. Mauhin

DES MÉDECINE INTERNE – JEUDI 27 JUIN 2024

Cardiac device implantation in Fabry disease



SACD: severe arrhythmia or conduction defect

Sené T, Lidove O *et al.* Medicine (Baltimore). 2016 Oct;95(40):e4996





MERCI

à

SAMIRA ZEBICHE

