Phase	Milestones/important points/ …

Pre-diagnosis	Medical
	• Age of onset may vary considerably, from childhood to 40+ years of age. It is more common in adults. Children tend to progress more quickly than adults do.
	• Age of onset may vary even within one family.
	• When there are no other known patients in the family, one or more inaccurate diagnoses are often set before the correct one. Result: long time between first symptoms and the final diagnosis.
	• Red flags that may point towards MFM: when patients experience a lack of strength in the hands or feet, frequent falls or tripping, difficulties in running, climbing stairs or walking long distances, difficulties in cutting food or handling tools, a physician should be consulted. In children and young adults a cervical weakness with head lag, neck stiffness or scoliosis may develop in addition to hand and feet extension weakness (steppage). These symptoms are not specific for MFM, but may point into that direction (in particular if an EMG is not suspect of neurogenic disease such as Charcot- Marie Tooth neuropathy, and it is rather normal or myogenic)
	• In children and young adults a cervical weakness with head lag, neck stiffness or scoliosis may develop in addition to hand and feet extension weakness (steppage).
	• Some cases present with heart involvement. Unexplained dilated or hypertrophic cardiomyopathy could be a sign of MFM and neurological consultation could be useful. (short explanation: dilated cardiomyopathy: the heart chambers enlarge and lose their ability to contract; hypertrophic cardiomyopathy: the walls of the left ventricle become thick and stiff).
	• Some cases may present with respiratory involvement. When respiratory symptoms cannot be explained by other causes and there is no family history, MFM could be considered, but it is not an isolated or predominant complication in MFM patients.
	• Mutations in certain MFM subtypes can be associated to specific symptoms such as (see also the table below):
	  ○ aB-crystalline: ocular involvement (cataract)
	  Titin may present with spinal stiffness and significant respiratory involvement (especially if onset in early childhood and non-acquisition of walking ability).
	  ○ When it runs in the family, people often know what they have before going to the physician for confirming the diagnosis.
	• People who have it in their family are often aware of their condition before visiting a doctor to confirm the diagnosis.
	• A list of experts can be found at the ERN web page: Healthcare Providers – European Reference Network – EURO-NMD (ern-euro-nmd.eu).
	Social
	• People may see you as clumsy or lazy.
	• Feeling / knowing that there is something wrong, not knowing what, makes you feel uncertain, looking for explanations.

Diagnosis	• MFM is a group of diseases causing muscle weakness. Mutations can be found in different proteins (see Table below). Symptoms may vary depending on the affected protein. • The results of the following tests can point in the direction of MFM: Blood samples, including determination of CK (creatine phosphokinase) levels, EMG (electromyogram), muscle magnetic resonance (MRI) and muscle biopsy. A muscle biopsy can confirm a MFM.

	• Genetic testing with characterisation of the mutation is necessary to confirm the diagnosis. Many patients are not (yet) genetically typed. • When a new mutation is found, extended family genetic examination and clinical examination may be necessary to clarify its pathological role. • As it is a rare disease, diagnosis is often set in a referral/expert centre (university or academic centre). • The diagnosis can be set by a neurologist or genetic counsellor often specialized in neuro-muscular disorders. • Getting a second opinion might help to be more certain about the diagnosis (especially if no genetic confirmation is available). • Patients should be made aware that their diagnosis may have consequences for other family members. Family members may have the disease while not knowing this. Most variants of MFM are inherited in autosomal dominant way (the condition is caused by one faulty copy of the gene). Whereas most mutations are autosomal dominant, Titin and Desmin, can be autosomal recessive (two faulty copies of the gene will need to be inherited), or autosomal dominant. The autosomal recessive variant is found mostly in children, whereas the autosomal dominant variant is mostly found in adult onset. Social • It may be a relief to finally get the correct diagnosis • For affected parents: It can be difficult to see that you passed the disease on to your child • Having a close relative or friend to accompany you when getting the diagnosis can be helpful. • Your partner or other significant persons may need time to accept the disease as well. • Those who are the first in the family with this diagnosis usually experience problems in finding information about this rare disease. • Uncertainty about the impact of the disease, what to expect on what time frame and what to arrange, e.g. regarding supporting aids • Since it is a rare disease: o There are very few communities of persons with the same diagnosis o Your social environment might have difficulties to estimate the severity of the disease, because it is unknown.
First years after diagnosis	Medical • Although symptoms may be mild, it is recommended to have regular consultations with medical specialists. Patients should be regularly followed up by the relevant specialties. At least by the neurologist or cardiologist, preferably by both. Follow-up may address cardiac problems, muscle skeletal evaluation, rehabilitation, respiratory function and swallowing problems. • Some mutations come with cardiac problems. In that case a specialized cardiologist should be consulted regularly. • Some mutations affect the heart in such a way that a heart transplant may be needed (this is rare but should be considered). • Doing exercise is important. Today still some patients are advised not to exercise as would worsen the condition. The idea that you should not move is not true. Under medical or specialist supervision, proper exercise is good. However, there is no information available on what is the proper type of exercise. Most recommendations regarding exercise come from other diseases that have similar symptoms, since the disease is commonly rare and some mutations (like those in BAG3) are ultrarare. Proper exercise and mobilisation of joints is important to

	avoid contractures and pain. Stretching is good. Moving the muscles that are still in good condition. Keeping breathing muscles in condition is useful to remain having an effective cough. Children should not be pushed to do the same level of exercise as their peers. However, immobilization will worsen muscle waist and will cause pain. So, exercise is not going to the gym, but going for instance to the pool and splash around. The problem is often how to motivate the kid to move. This is also the case for, for instance, the BAG3 mutation, that affects initially the muscles that are the most used in daily activities, such as walking. • Recommendations concerning the **diet** are the following: patients should avoid getting overweight or underweight. The diet should be varied. Supplementation of vitamins could be useful, for instance for bone health, such as vitamin D (the blood levels can be checked for this vitamin to monitor intake). Swallowing problems do not become very severe, but if there are swallowing problems, patients should ask advice from a dietician and a physician to assess swallowing function, in particular in the case of sudden weight gain or weight loss. When the patient gets tired when eating (or it takes too long or it is not comfortable in the sight of others) or has problems with choking, he/she should be referred to the physician. Social • Some patients or their parents start seeking actively for a cure via fundraising and awareness raising. • This may be a good time to reconsider your professional ambitions to find a job that is possibly less strenuous and/or can be continued when the body weakens (for instance when a wheelchair becomes necessary). • Having a job can contribute significantly to the feeling of having a meaningful live. • In the early stage, the disease often is “invisible” for others. For others it may be difficult to understand what it does to you. • Doing mild exercises seems to help slowing down progression. Examples are swimming, aquarobics, cycling with power support.
When symptoms get more serious	Medical • A rehabilitation physician or neurologist (depending on the country where you live) may help to prevent overburdening or under use of muscles. • Some mutations affect breathing muscles. Be aware of symptoms such as daytime sleepiness, nightmares, morning headaches, waking up very tired after having slept all night. An evaluation of the respiratory function should be done regularly from day one. Respiratory function tests (for adults) or an evaluation CO2 levels in the blood (for children) may be wise. • A regular cardiac evaluation is recommended. • Physical therapy may be helpful, especially to help prevent overburdening of healthy muscles, but this needs to be a person that knows about muscle diseases or is willing to learn. • Pain management may be necessary as a result of overburdening (healthy) muscles or contractures • Healthcare is not only about medical care, but also about knowing your rights and how to obtain access to help. Some patients are not aware of what is possible in their healthcare system and should be pointed to options for assistance at in employment matters and social support. • It can be useful / necessary to have an easy accessible instruction (e.g. in your phone or written on a card) for emergency workers in case of an accident or other emergency: what to do or not to do (e.g. respiratory support or anaesthetics that may be avoided, your physician can provide information on this) Social

	• Aids, such as a wheelchair, crutches, walking stick or mobility scooter may help to manage fatigue and keep doing things that make you happy (and thus provide energy). Try to plan availability of aids in advance, since the application process may take time and aids may not be available in time. • The disease will become more visible. Think ahead what you will say when people (sometimes complete strangers) ask what is wrong with you. • Adaptations may be necessary to continue driving a car safely. • Fatigue may affect your ability to keep positive. Learning to manage your energy levels is important. • Those with a paid job may need to adapt their working hours or adjust their tasks to less strenuous activities
When severe disability is the case	Medical • Not all mutations result in very severe disability, which is rare and usually occurring in late-disease stages. • See a physician regularly to prevent problems such as pressure sores, contractures, loosing energy due to insufficient body support/inadequate seating. • Correcting or preventing contractures can be done by stretching and wearing (night)splints. • Aids may be needed to help: hoist, hospital bed, arm support to keep moving your arms, power wheelchair, high toilet, shower commode. • Home care may help with dressing, showering and other activities of daily living. • Breathing support may be indicated. This may be non-invasive via a mask during the night or via a tracheostoma (tube in the throat) in more severe cases (very rare) • Be aware that inactivity may also affect bone health, possibly resulting in osteoporosis, making falls having severe consequences. • Prevention and the need for management of pressure sores and contractures should be monitored Social • Don't get tired of visiting all different medical specialists. Healthcare is typically not yet organized around the patient, but being followed up medically is important. • It is important to keep socially active and to somehow have a meaningful life. Make good use of your better days. • In some cases it is possible to keep driving a car, although (expensive) adaptations may be necessary. • Using a power chair may limit you in social contacts as friends' houses may be not accessible • Having a (suprapubic) catheter or belly button stoma may be supportive in toilet issues (as transfers may become difficult or there is a lack of accessible toilets). • Make sure you know the way to obtain the necessary aids. Sometimes the administrative burden to get them reimbursed may be considerable. • Participation in social live may become difficult due to accessibility problems • Work: a paid job may become too strenuous and an application for disability pension may be required. • Holidays and events: important to keep doing, but you will have to prepare more regarding accessibility and availability of supporting aids (toilet access, bed facilities, breathing aids, transport and transfers). It will be more complex and sometimes more expensive to realize.

Table of protein that may cause MFM when there is a mutation present

Protein	**Gene**	**Class**	**Expression**
Desmin	DES	Intermediate filament	Skeletal, Cardiac, smooth muscles
aB-crystalline	CRYAB	Small heat-shock protein	Skeletal, Cardiac, lens, kidney, lung
Myotilin	MYOT	Sarcomere protein	Skeletal, Cardiac
Protein cypher	ZASP	Sarcomere protein	Skeletal, Cardiac
BAG3	BAG3	BAG family	Skeletal, Cardiac, smooth muscles
Filamin C	FLNC	Filamin family	Skeletal, Cardiac
FHL1	FHL1	FHL family	Skeletal, Cardiac
Titin	TTN	Third filament system	Skeletal, Cardiac
Plectin	PLEC *	Intermediate filament	Skeletal, Skin
DNAJB6	DNAJB6 *	DNAJ family	Skeletal, Brain
α-actin	ACTA1 *	thin filament	Skeletal, Cardiac
HSPB8	HSPB8 *	Small heat-shock protein	Skeletal muscle, heart, placenta

There are specific symptoms for some of the specific mutations:

- aB-crystalline: ocular involvement (cataract)
- Desmin: whereas most mutations are autosomal dominant, Desmin can be autosomal recessive (mostly in children) or autosomal dominant (mostly in adults)
- Titin may present with spinal stiffness and significant respiratory involvement (especially if onset in early childhood and non-acquisition of walking ability).