Clinical reseach in LGMD2A: where are we?

LA DISTROFIA DEI CINGOLI DA DEFICIT DI CALPAINA 3: DAL GENE AL PAZIENTE

Bosisio Parini, 14 Novembre 2015

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Clinical reseach in LGMD2A: where are we?

- Despite improvement of the diagnostics and pathomechanism of LGMD2A, no curative therapies are currently available
- Current medical care consists of symptomatic treatment of the disease and its complications
  - Prevent development of joint contractures
  - Supportive interventions to maintain mobility and independency
  - Respiratory care
- Aim: prolong survival and improve quality of life.

Clinical reseach in LGMD2A: where are we?

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Evaluation of Limb-Girdle Muscular Dystrophy

This study has been completed.

Sponsor:
Cooperative International Neuromuscular Research Group

Collaborator:
Carolinas Medical Center lead study site

Information provided by (Responsible Party):
Cooperative International Neuromuscular Research Group

ClinicalTrials.gov Identifier:
NCT00893334

First received: May 4, 2009
Last updated: March 6, 2014
Last verified: March 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a

Purpose

The purpose of this study is to understand the biochemistry of different types of Limb-Girdle Muscular Dystroph
International Neuromuscular Research Group (CINRG). It involves a one day clinical evaluation at a participatir
by a physician, pulmonary function testing, a complete cardiac evaluation with electrocardiogram (ECG or EKG
participant will be asked to fill out a couple of questionnaires asking questions about quality of life and activity li

Clinical Trial of Coenzyme Q10 and Lisinopril in Muscular Dystrophies

This study is ongoing, but not recruiting participants.

Sponsor:
Cooperative International Neuromuscular Research Group

Collaborator:
Department of Defense

Information provided by (Responsible Party):
Cooperative International Neuromuscular Research Group

ClinicalTrials.gov Identifier:
NCT01126697

First received: May 18, 2010
Last updated: October 10, 2014
Last verified: October 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read

Purpose

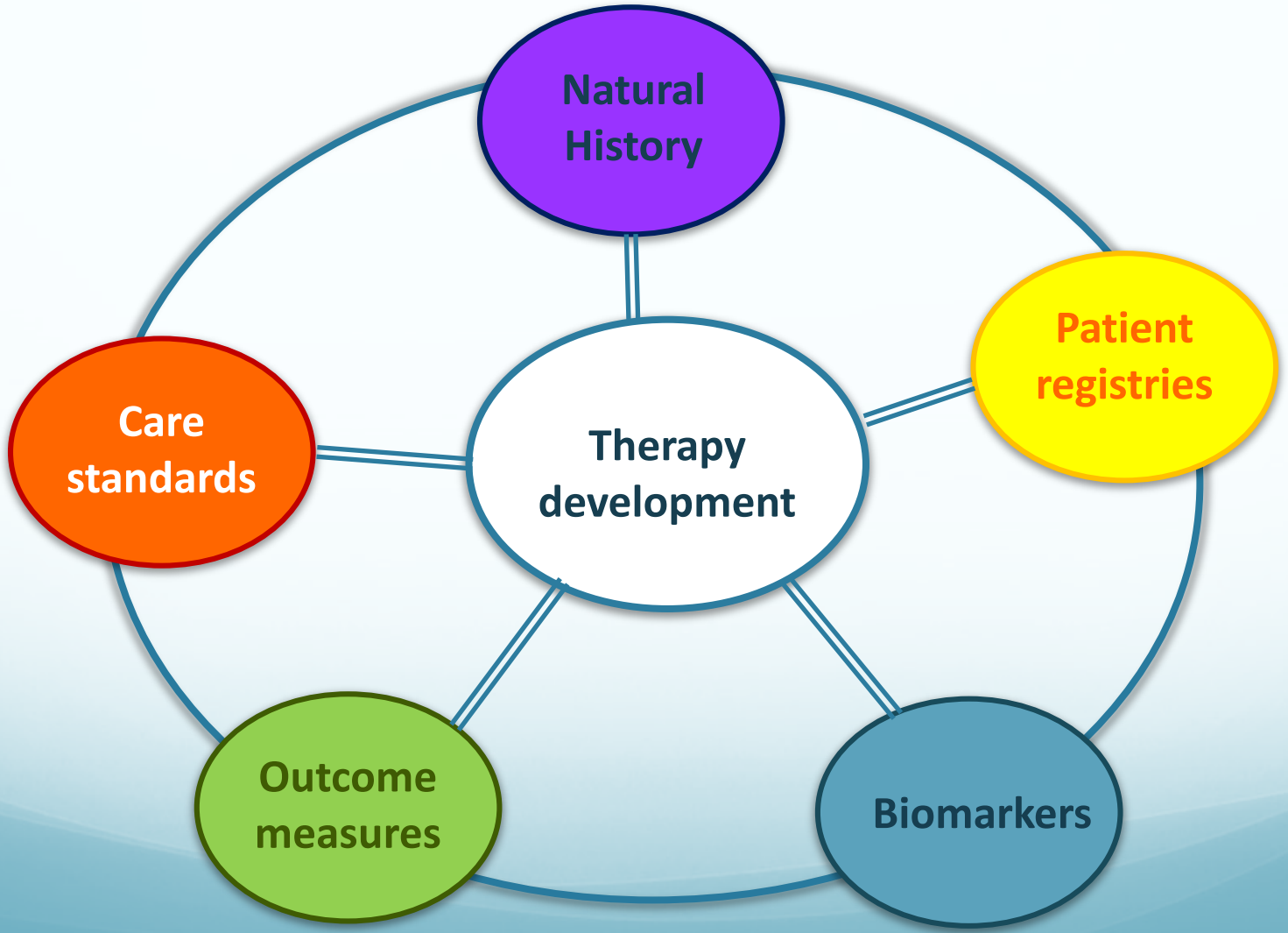
The study will include 120 participants aged 8 and up with Duchenne, Becker, or autosomal recessive limb-g
CoQ10 alone, Arm 2 Lisinopril alone, Arm 3 CoQ10 and Lisinopril or Arm 4 No study medication. Randomiza
standard Doppler echocardiography. The study will last 24 months with visits at Months 0.5,1.5, 6, 12, 18 an

Clinical reseach in LGMD2A: where are we?

	clinicaltrials.gov ID / other	Trial name / Article	Purpose	Interventional drug / Natural history	State (last update on ClinicalTrials.gov)	LGMD2																								
						A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W		
						CAPN3	DYSF	SGCG	SGCA	SGCB	SGCD	TCAP	TRIM32	FKRP	TTN	POMT1	ANO5	FKTN	POMT2	POMGnT1	DAG1	PLEC	DES	TRAPPC11	GMPPB	ISPD	GAA	LIMS2		
clinical trials	NCT00693334	Evaluation of Limb-Girdle Muscular Dystrophy	To understand the biochemistry of different types of LGMD - determine appropriate outcome measures	Natural history	Completed 2014 (Mar 2014)	X	X							X																
	NCT01403402	Congenital Muscle Disease Patient and Proxy Reported Outcome Study (CMDPRO.S)	To describe early sign and symptoms, and adverse events in CMDs	Natural history	Recruiting (Feb 2015)							X		X		X	X	X	X	X										
	NCT01676077	Clinical Outcome Study for Dysferlinopathy	To determine the clinical outcome measures - characterize the disease progression - collect biological samples for the identification of biomarkers	Natural history	Ongoing, recruitment closed March 2014 (Apr 2015)		x																								
	NCT02165358	Muscle MRI in Becker Muscular Dystrophy and in Limb-girdle Muscular Dystrophy Type 2I	To investigate muscle hypertrophy in the calves and tongue seen in patients affected by Becker muscular dystrophy and LGMD2I	Natural history	Recruiting (Jun 2014)									X																
	NCT00313677	Clinical Trial Readiness for the Dystroglycanopathies	To describe the early signs and symptoms of the dystroglycanopathies, and to gather information that will be required for future clinical trials.	Natural history	Recruiting (May 2012)									X		X		X	X											
	NCT01126697	Clinical Trial of Coenzyme Q10 and Lisinopril in Muscular Dystrophies	To compare CoQ10/ Lisinopril CoQ10+Lisinopril for CMP prevention	Interventional drug - Phase II/III	Ongoing, recruitment closed (Oct 2014)			X	X	X	X			X																
	NCT00527228	Deflazacort in Dysferlinopathies	To assess the natural history - evaluate therapeutic efficacy and side effects of Deflazacort in LGMD2B	Interventional drug - Phase II/III	Completed 2008 (Jan 2009) [66]		x																								
	NCT01344798	Clinical Study of AAV1-gamma-sarcoglycan Gene Therapy for LGMD2C	To evaluate of clinical safety and feasibility of gene therapy with LGMD2C	Interventional drug - Phase I	Completed 2010 (Apr 2011) [67]			x																							
	NCT01976091	Gene Transfer Clinical Trial for LGMD2D (Alpha-sarcoglycan Deficiency) Using scAAVrh74.tMCK.hSGCA	To evaluate of clinical safety and efficacy of gene therapy in LGMD2D	Interventional drug - Phase I/IIa	Recruiting (Feb 2015)				X																						
	NCT00494195	Gene Transfer Therapy for Treating Children and Adults With Limb Girdle Muscular Dystrophy Type 2D (LGMD2D)	To evaluate the safety and effectiveness of gene therapy in treating children and adults with LGMD2D	Interventional drug - Phase I	Completed (Feb 2013) [68]				X																						
	NCT00104078	A phase I/II trial of MYO-029 in adult subjects with muscular dystrophy	To evaluate safety of MYO-029 in adult patients with muscular dystrophy.	Interventional drug - Phase I/II	Completed (Dec 2007) [69]	X	X	X	X	X				X																	
	NCT01898364	Safety and Efficacy Evaluation of Repeat neoGAA Dosing in Late Onset Pompe Disease Patients	To evaluate the safety and tolerability of neoGAA in treatment naïve and alglucosidase alfa treated late-onset Pompe disease patients	Interventional drug - Phase I	Completed (March 2015) (extension study NCT02032524 ongoing – Phase 2/3)																						X				
	not registered	1α,25(OH)(2)-Vitamin D3 increases dysferlin expression in vitro and in a human clinical trial.	To evaluate effects of VitD in cell line and carriers subject (15 carriers, 12months – increase in monocyte expression)	VitD	[70]		X																								
	not registered	Effects of rituximab in two patients with dysferlin-deficient muscular dystrophy.	To evaluate effects of rituximab on muscle strength in 2 patients with Myosny myopathy	rituximab	[71]		X																								
	not registered	Homozygous α-sarcoglycan mutation in two siblings: one asymptomatic and one steroid-responsive mild limb–girdle muscular dystrophy patient	To describe of response to treatment with Deflazacort in one patients with LGMD2D	Deflazaoort	[72]				X																						
	not registered	Two siblings with limb-girdle muscular dystrophy type 2E responsive to Deflazacort.	To evaluate response to treatment with Deflazaoort in two patients with LGMD2E	Deflazaoort	[73]					X																					
	not registered	Inflammation and response to steroid treatment in limb-girdle muscular dystrophy 2I.	To evaluate response to treatment with prednisolone in 2 patients with LGMD2I	prednisolone	[74]									X																	
Available outcome measures		Quantitative muscle MRI as an assessment tool for monitoring disease progression in LGMD2I: a multicentre longitudinal study.	To evaluate quantitative muscle MRI as a possible longitudinal outcome measure to assess muscle pathology and monitor therapeutic efficacy		[75]									X																	
		Cardiovascular magnetic resonance of cardiomyopathy in limb girdle muscular dystrophy 2B and 2I.	To evaluate cardiac function by MRI in monitoring cardiac pathology progression		[76]		X							X																	
		http://www.researchrom.com/masterlist	Guidance, information and assistance for choosing the right outcome measures (OMs) for neuromuscular disease trials and studies																												
GMD2 having vailable registries						X	X							X		X		X	X	X							X			

V Straub, M Beroli, submitted

LGMD2A: Trial Readiness

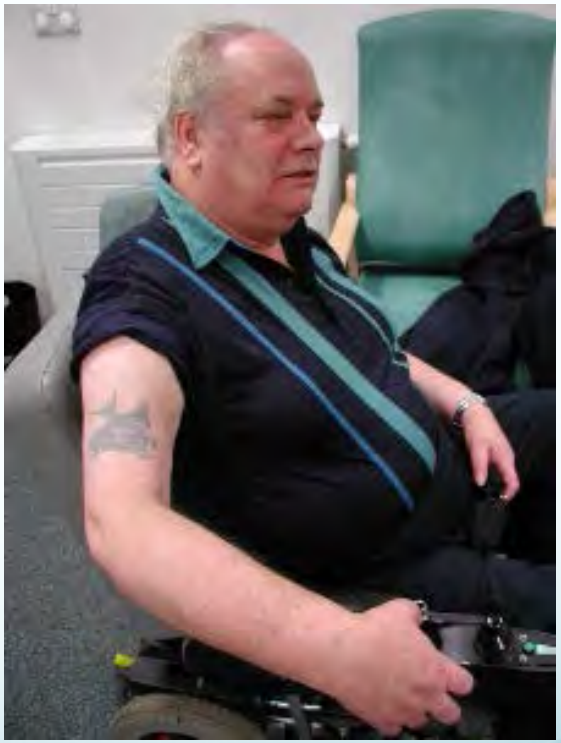


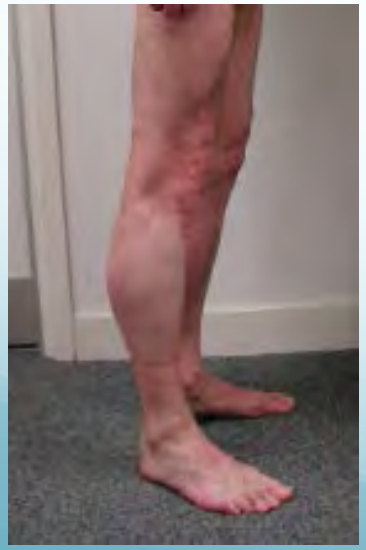
LGMD 2A: Natural History

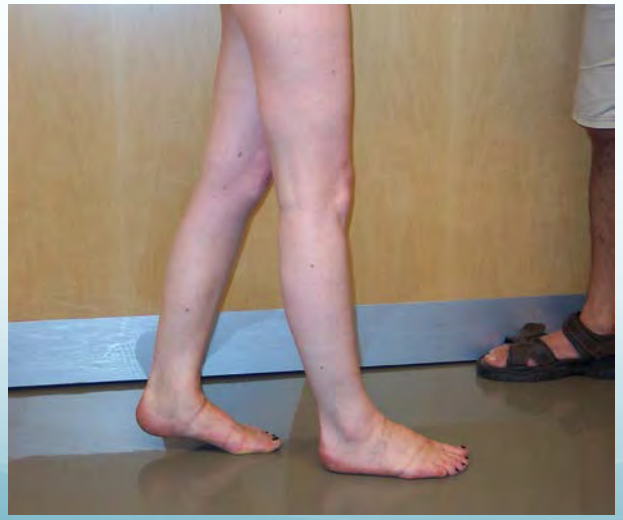
- Mean age of onset: 8-15 years (range 2-40 years)
- CK: 5-80X
- Progression: moderate
- Loss of ambulation: 11-28 years from onset
- Contractures: common
- Respiratory impairment: uncommon
- Cardiomyopathy: rare

LGMD 2A: Natural History

- Inter- and intra familiar variability
- Childhood versus adult onset
- Rate of progression





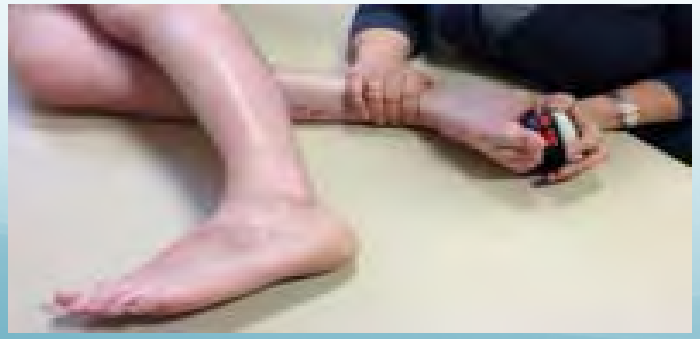


LGMD2A: Natural History

- Clinical study design
  - Duration of the study
  - Monitoring
- Outcome measures
  - Clinically meaningful
  - Sensitive to change
- Therapeutic effect
  - Against natural course of the disease

Outcome measures

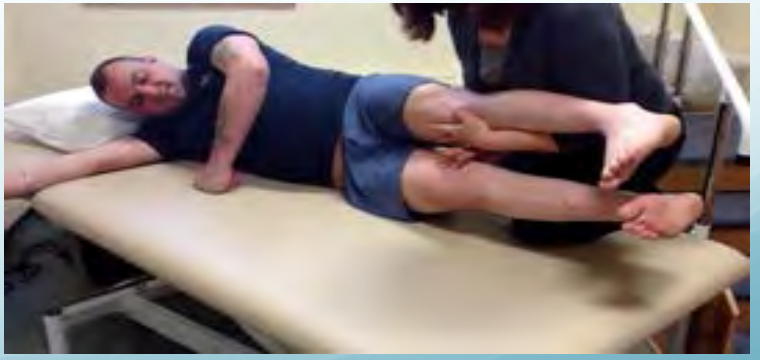
- A measure of the quality of medical care (including pharmacological and non-pharmacological interventions)
  - Feasible
  - Reliable
  - Reproducible
  - Sensitive
- Measure of functional abilities according to the severity or the stage of the diseases



LGMD2A: Outcome measures

- Manual muscle testing (MRC)

- North Star Ambulatory Assessment
- Time functional tests
  - Time to rise form the floor
  - Time to run/walk 10 meters
  - Time to climb 4 steps
- Time up and go
- 6Minute walking test (6MWT)



Patient registry

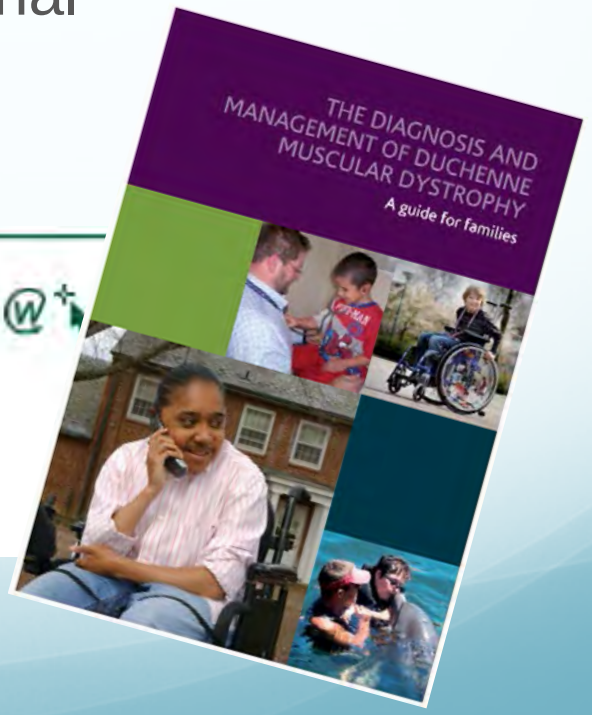
- Database to collect information about people affected by a particular condition
- Genetic and Medical information
- LGMD is a rare condition - without a patient registry finding enough patients for a trial can take a long time
- Keep patients informed about research, clinical trials and outcomes

Care standards

- Homogeneous population for clinical trial
- Studies in DMD with investigational drugs have underlined the impact of care standards in clinical trial

Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management

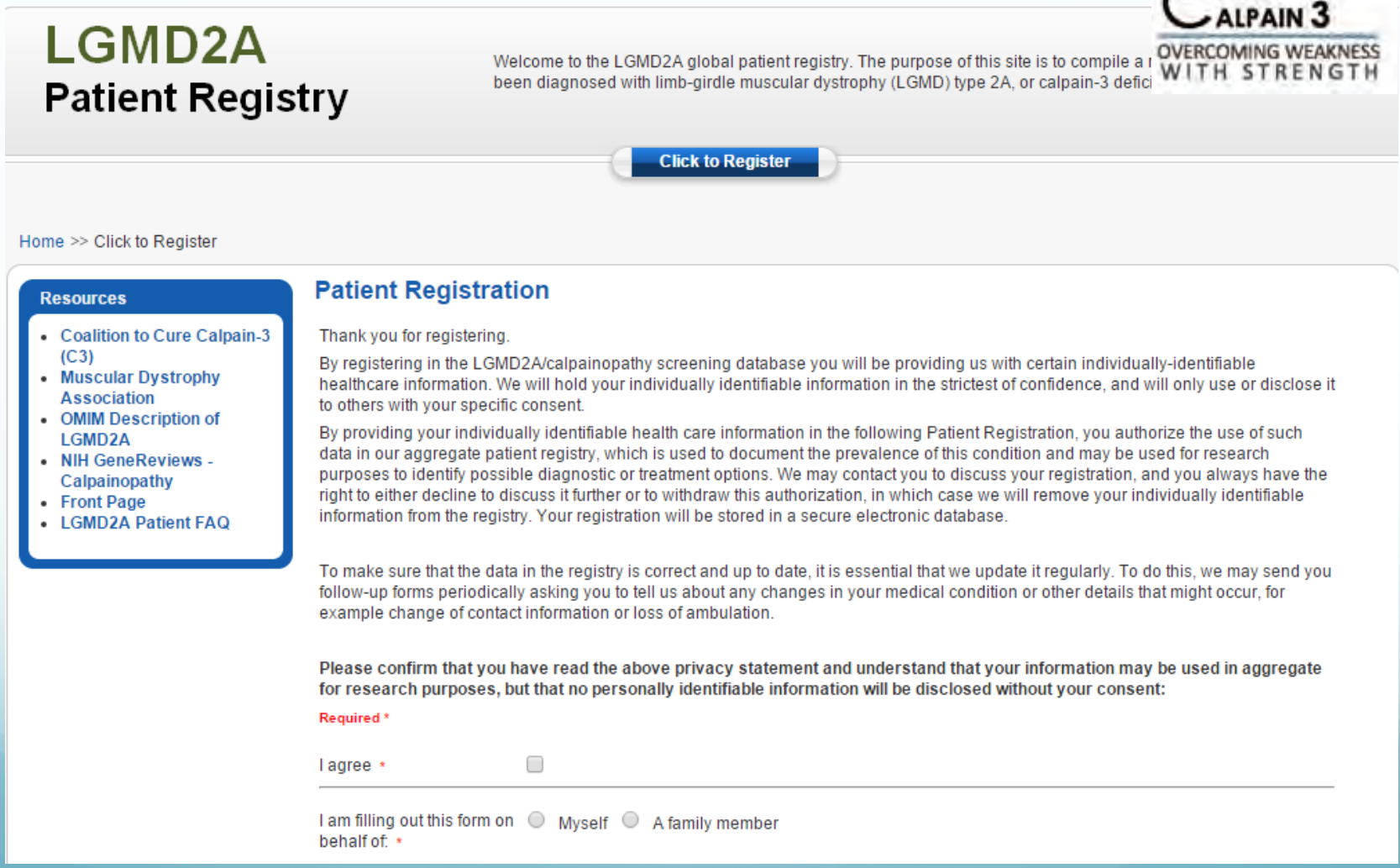
*Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula R Clemens, Linda Cripe, Ajay Kaul, Kathi Kinnett, Craig McDonald, Shree Pandya, James Poysky, Frederic Shapiro, Jean Tomezsko, Carolyn Constantin, for the DMD Care Considerations Working Group**



Patient registry

- Identification of subjects suitable for clinical trials
- Patient registries allow people to who may be eligible for certain trials to be contacted quickly and easily
- Geographically locate subjects with specific characteristic (site selection)
- Doctors and researcher can also access the medical data to learn more about the condition

LGMD 2A: Patient registry



LGMD2A
Patient Registry

Welcome to the LGMD2A global patient registry. The purpose of this site is to compile a r
been diagnosed with limb-girdle muscular dystrophy (LGMD) type 2A, or calpain-3 defici

COALITION TO CURE CALPAIN 3
OVERCOMING WEAKNESS WITH STRENGTH

Click to Register

Home >> Click to Register

Resources

- Coalition to Cure Calpain-3 (C3)
- Muscular Dystrophy Association
- OMIM Description of LGMD2A
- NIH GeneReviews - Calpainopathy
- Front Page
- LGMD2A Patient FAQ

Patient Registration

Thank you for registering.

By registering in the LGMD2A/calpainopathy screening database you will be providing us with certain individually-identifiable healthcare information. We will hold your individually identifiable information in the strictest of confidence, and will only use or disclose it to others with your specific consent.

By providing your individually identifiable health care information in the following Patient Registration, you authorize the use of such data in our aggregate patient registry, which is used to document the prevalence of this condition and may be used for research purposes to identify possible diagnostic or treatment options. We may contact you to discuss your registration, and you always have the right to either decline to discuss it further or to withdraw this authorization, in which case we will remove your individually identifiable information from the registry. Your registration will be stored in a secure electronic database.

To make sure that the data in the registry is correct and up to date, it is essential that we update it regularly. To do this, we may send you follow-up forms periodically asking you to tell us about any changes in your medical condition or other details that might occur, for example change of contact information or loss of ambulation.

Please confirm that you have read the above privacy statement and understand that your information may be used in aggregate for research purposes, but that no personally identifiable information will be disclosed without your consent:

Required *

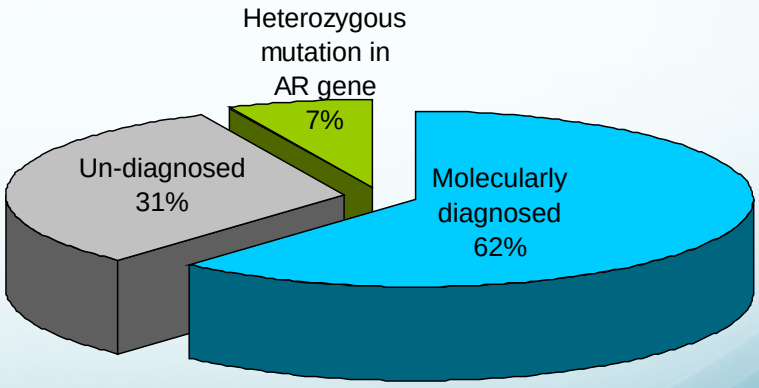
I agree * ☐

I am filling out this form on behalf of: * ○ Myself ○ A family member

The Italian Registry

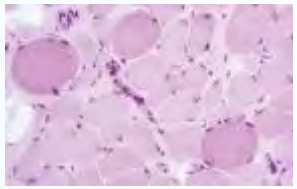
Clinical and laboratory network for LGMD diagnosis, in view of a national registry Telethon UILDM GUP10006

599 LGMD patients



Data collection

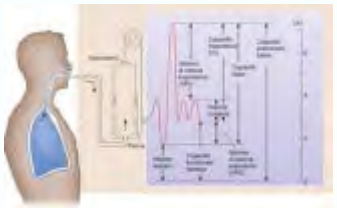
ANAMNESTIC DATA
Familiarity
Onset
CK values
Muscular involvement (distribution)
Tendon retraction
Scoliosis



MUSCLE BIOPSY
Morphology
IHC analysis
WB analysis

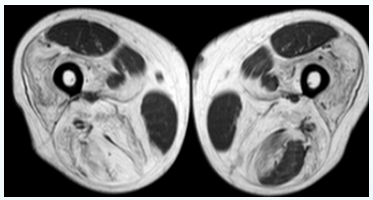
MOLECULAR ANALYSIS

CARDIAC FUNCTION
ECG
Holter ECG
Echocardiogram



RESPIRATORY FUNCTION
Spirometry
Nocturnal saturimetry
NIV

FUNCTIONAL EVALUATIONS
MRC
Walton
MFM
6MWT



MAGNETIC RESONANCE
Muscular MRI
Brain MRI

DATABASE containing retrospective and prospective data

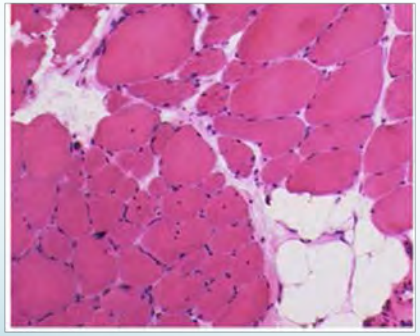
Biomarkers

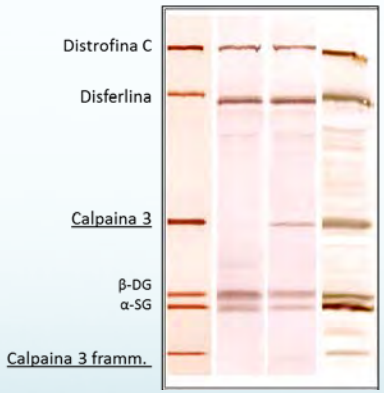
- Objective measures (blood not subject to placebo effect)
- Possibly an acute read out (changes in blood seen before clinical changes)
- Should support and extend clinical outcomes
- Should help build ‘compelling case’ for regulators: accelerated approval
- Could allow clinical trials in populations where there are no strong clinical outcomes (young boys and older, non-ambulant subjects)

LGMD2A: Trial Readiness

Disease

Pre-clinical





Pathogenesis

Pre-clinical models

Diagnosis

Natural history

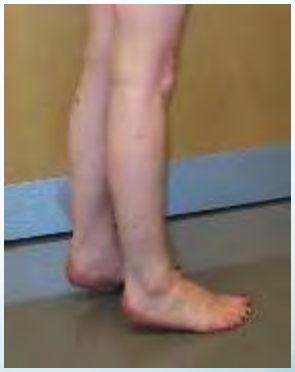
Care standards

Outcome measure

Registry

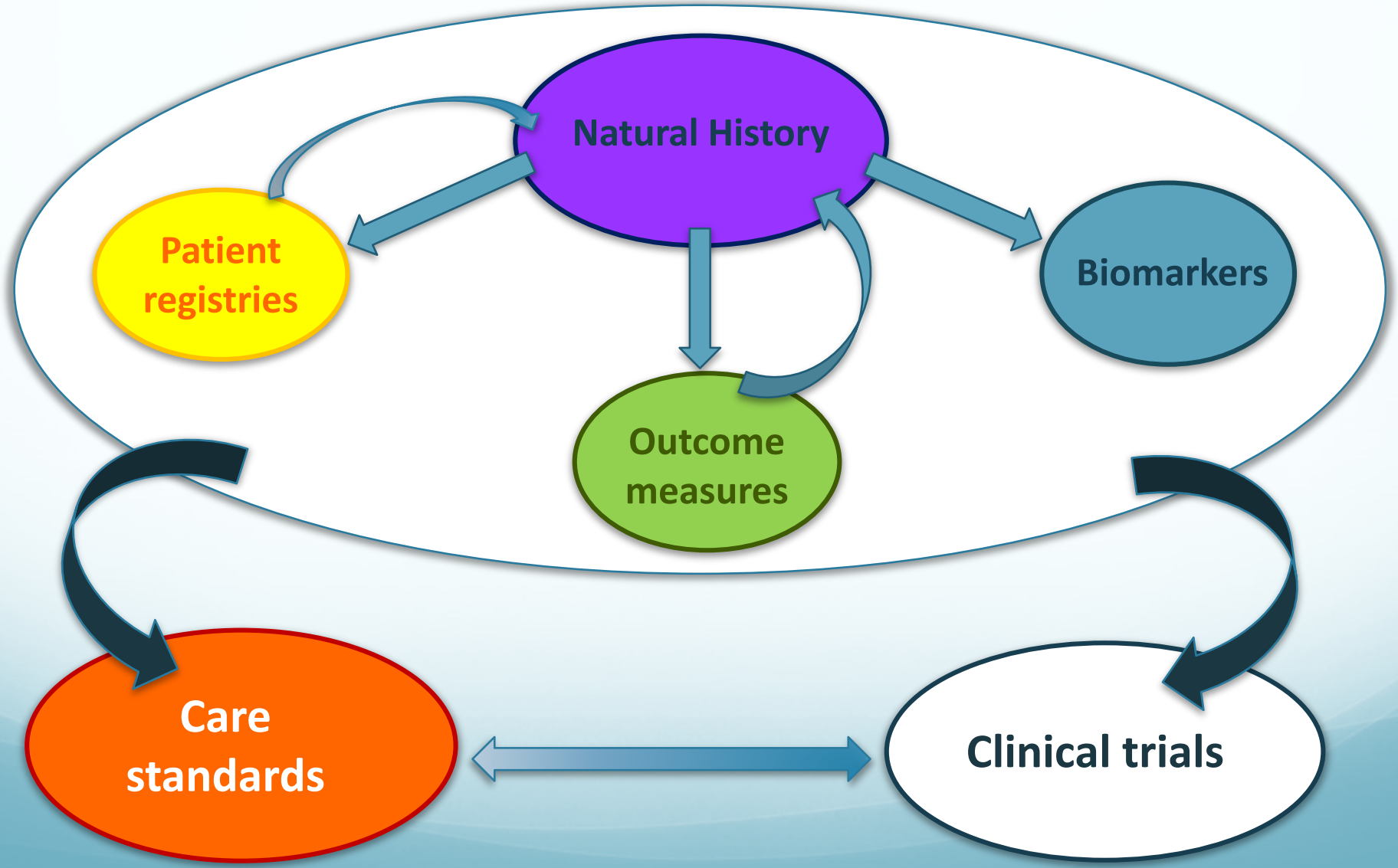
Biomarkers

Clinical



Therapies

LGMD2A: Therapy delivery



THE John Walton MUSCULAR DYSTROPHY RESEARCH CENTRE

Newcastle University

Thank You