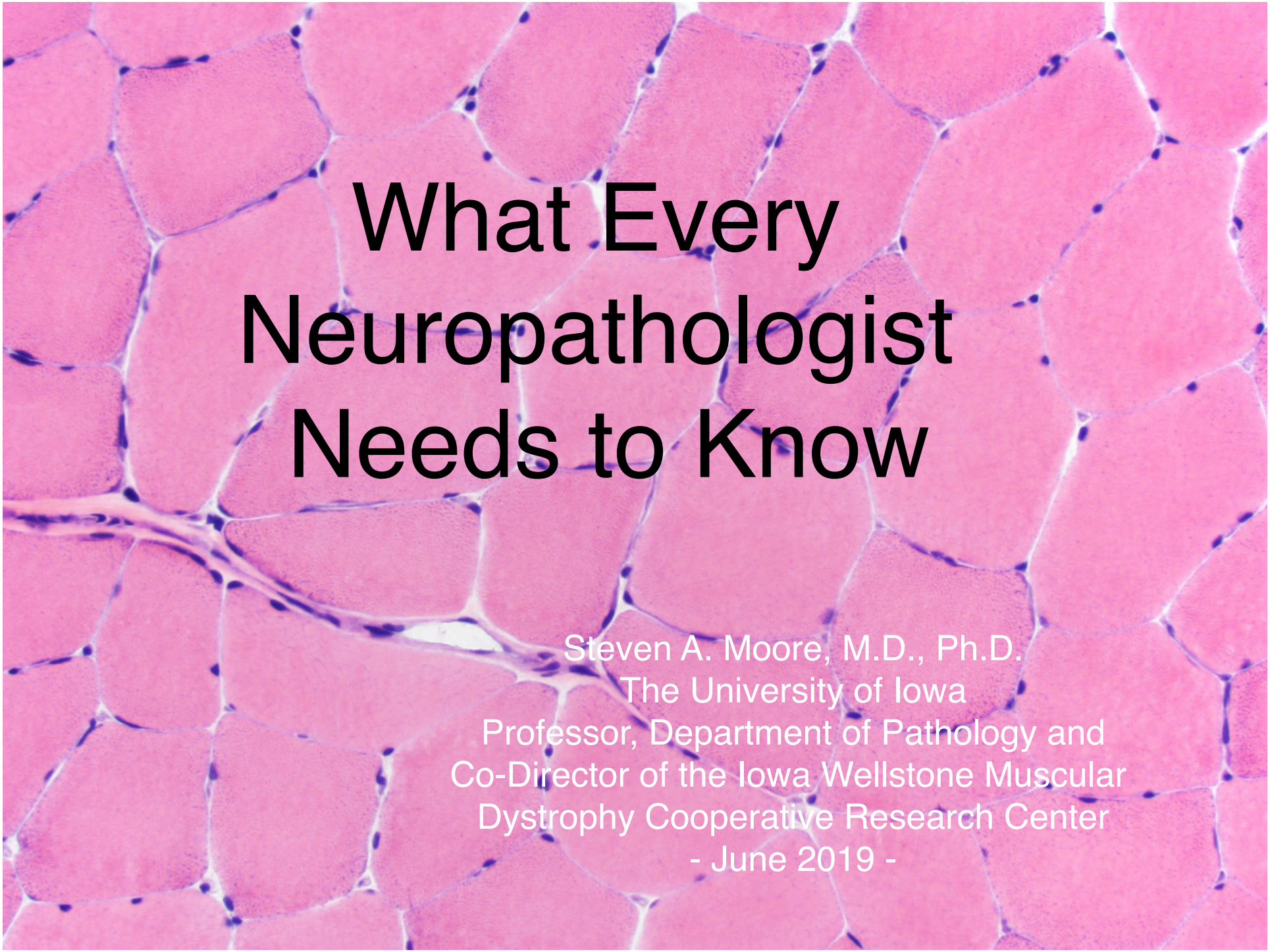
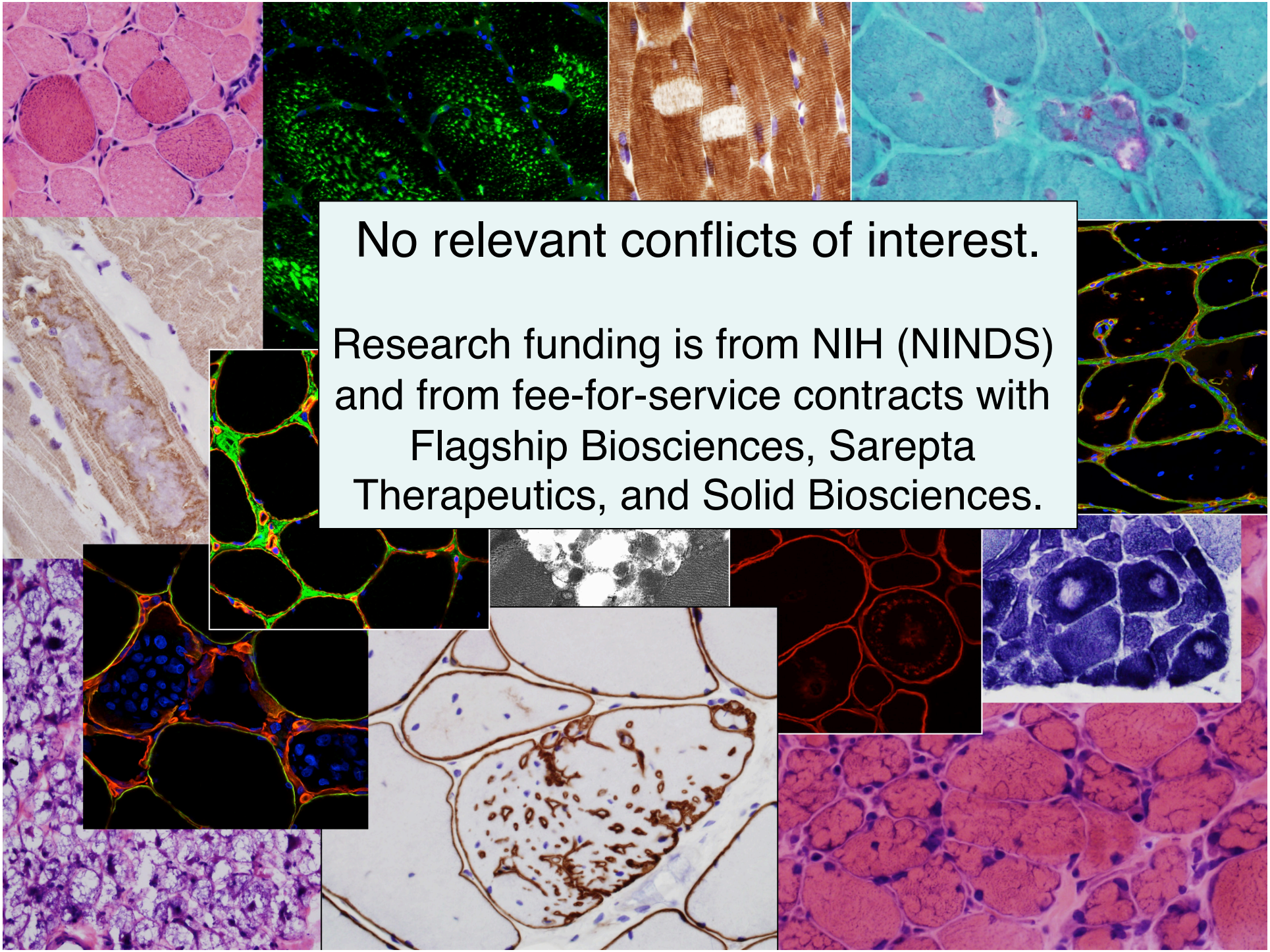


What Every Neuropathologist Needs to Know

Steven A. Moore, M.D., Ph.D.
The University of Iowa
Professor, Department of Pathology and
Co-Director of the Iowa Wellstone Muscular
Dystrophy Cooperative Research Center
- June 2019 -



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- **Neuropathology colleagues – Leslie Bruch, Marco Hefti, Karra Jones**
- **Histology and EM Laboratories, esp. Terese Nelson, Melissa Jans, Amy Trent**
- Molecular diagnostics
  - Univ. of Iowa Molecular Pathology and Cytogenetics Laboratories and Univ. of Utah Genetics - Bob Weiss
- Reagents, mouse models, and basic science - Kevin Campbell
- Research studies in selected clinical cases
  - Moore research laboratory - Mary Cox
  - Wellstone Center Medical Student fellows

UIDL U I Diagnostic Laboratories

NIH National Institute of Neurological Disorders and Stroke

SENATOR PAUL D. WELLSTONE MD COOPERATIVE RESEARCH CENTER

Iowa Wellstone Muscular Dystrophy Cooperative Research Center

Kevin P. Campbell, PhD

- Professor and Chair of Molecular Physiology and Biophysics
- Professor of Neurology and Internal Medicine
- Investigator, Howard Hughes Medical Institute

Katherine D. Mathews, MD

- Professor of Pediatrics and Neurology

Steven A. Moore, MD, PhD

- Professor of Pathology

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Overview

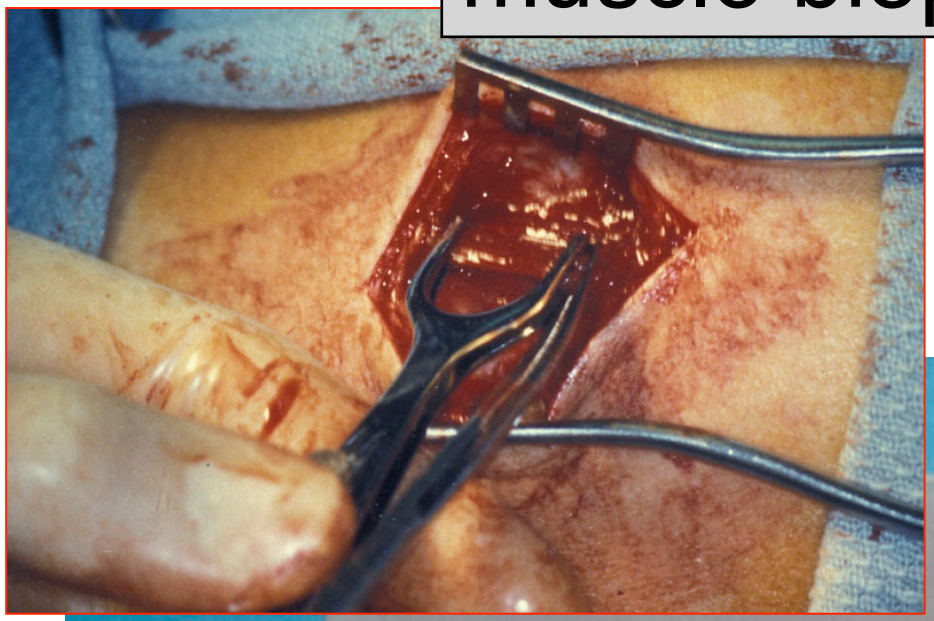
- Optimizing the biopsy
- Approach to evaluation
- Classic biomarkers of disease
- Dystrophinopathy
- Inflammatory myopathies

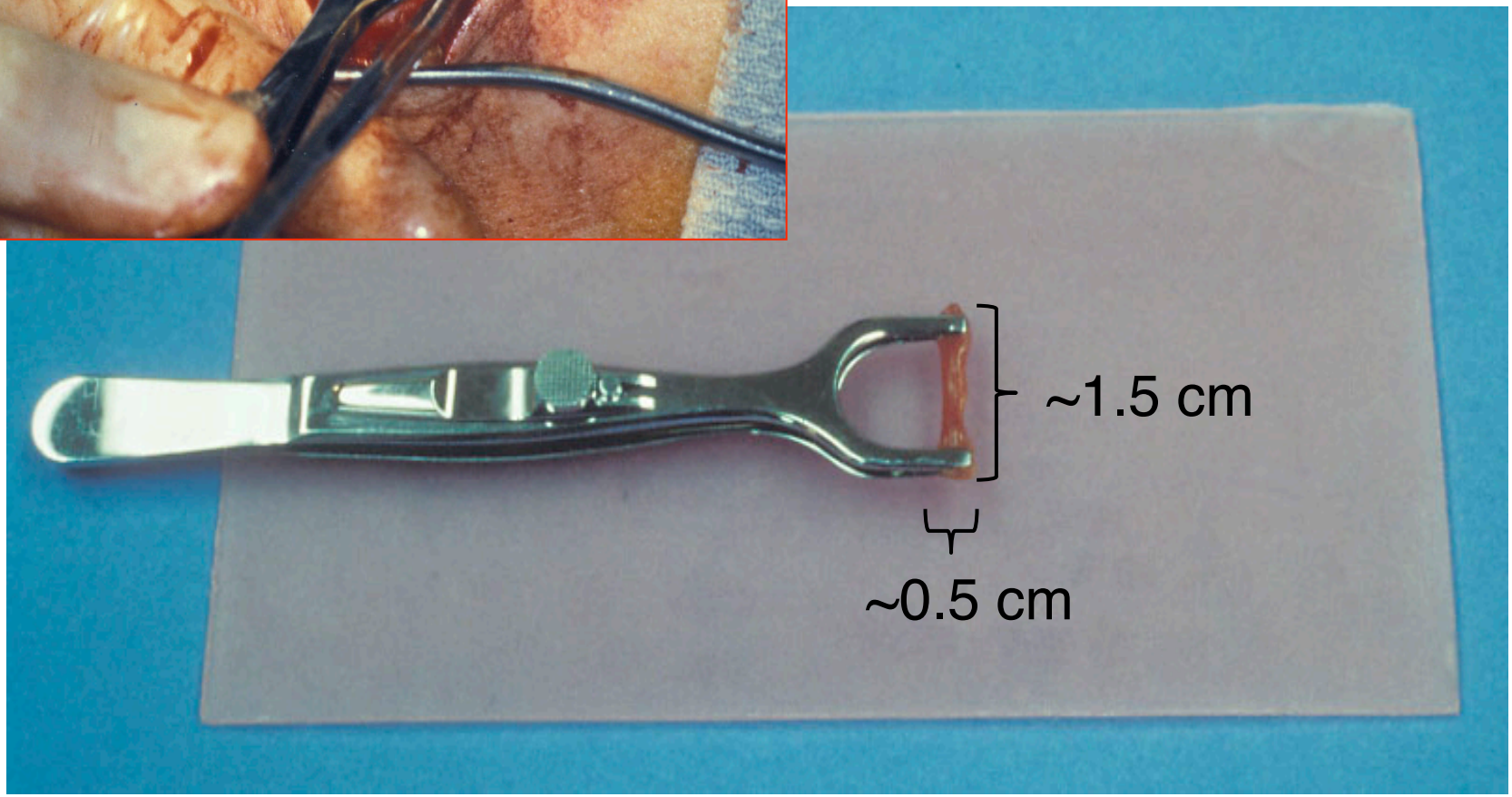

optimizing the biopsy

types of muscle biopsies

- needle biopsy
  - may be less painful
  - may not require general anesthesia
  - smaller amount of muscle may limit testing
  - requires more expertise to obtain good biopsy
- open biopsy
  - may be more painful
  - may require general anesthesia
  - larger amount of muscle allows for broader range of testing
  - muscle clamp technique easy to teach surgeons unfamiliar with muscle biopsy

muscle biopsy using a clamp

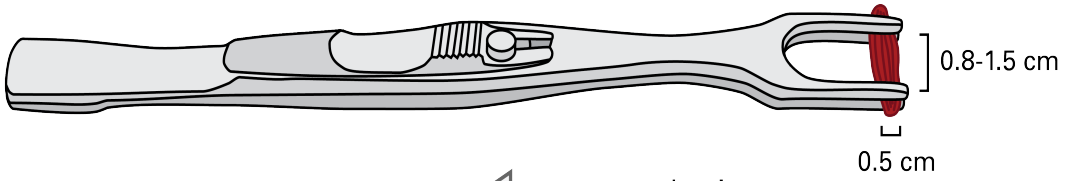




distribute biopsy tissue

- frozen tissue
  - routine histology and enzyme histochemistry
  - immunostains
  - biochemistry (e.g. western blots)
  - DNA or mRNA studies
- formalin-fixed tissue
  - routine histology
  - special stains (e.g. Congo red and IHC)
- glutaraldehyde-fixed tissue
  - plastic section light microscopy (“thicks”)
  - electron microscopy (“thins”)

mount muscle for cross sections and freeze in isopentane at approximately -160° C

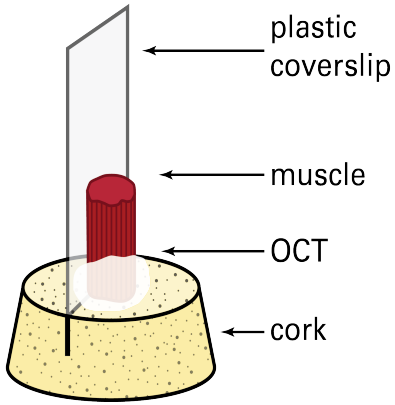


First priority:

1) Cut biopsy from between forks of clamp
2) Trim 0.1 cm diameter strip for glutaraldehyde
3) Mount remainder on cork
4) Freeze in isopentane at -160° C

If there is sufficient tissue:

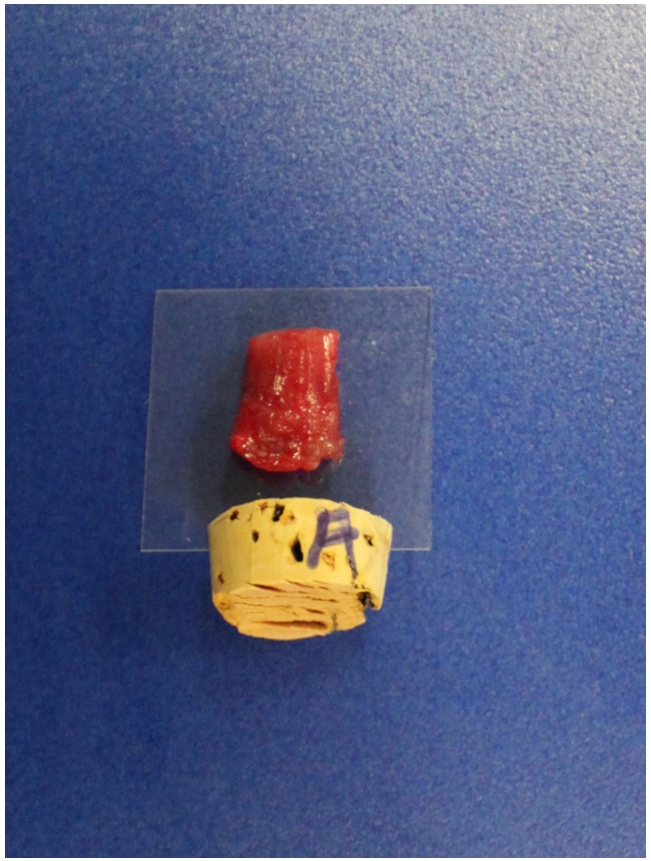
5) Fix a portion in formalin (clamped or unclamped)
6) Freeze a portion in liquid N_2 for biochemical or molecular studies



https://medicine.uiowa.edu/uidl/faculty-services/muscular-dystrophymuscle-biopsy/muscle-biopsy-general-evaluation
UIDL website

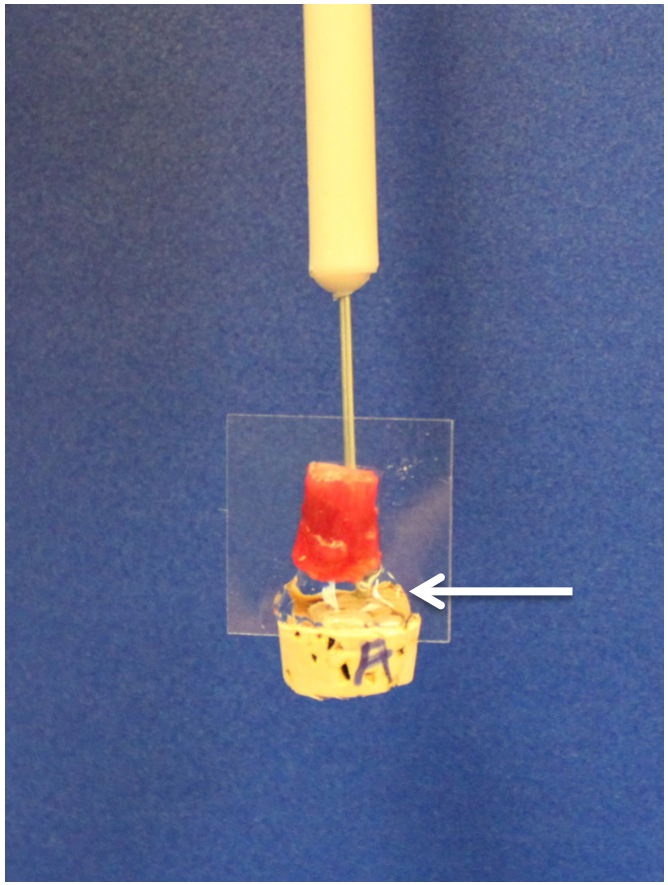
Cut the biopsy from between the forks of the clamp and position on a pre-assembled cork/coverslip.

Trim one or more 0.1 cm diameter strips the entire length of the biopsy to fix in glutaraldehyde.



The tissue to be frozen is positioned on a pre-assembled cork/ coverslip.

A dissecting needle placed into the cork behind the coverslip serves as a handle. Fill the gap with OCT.




Product of
United States
Class IA
4 L
O3551-4
2-Methylbutane
Certified
Maximum Limits of Impurities
ASSAY
COLOR
IDENTIFICATION
C5H12
CAS 78-78-4
LOT
For laboratory and manufacturing use only, not for drug, food or household
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Opened-
UN1265
PENTANES
ChemAlert®
288
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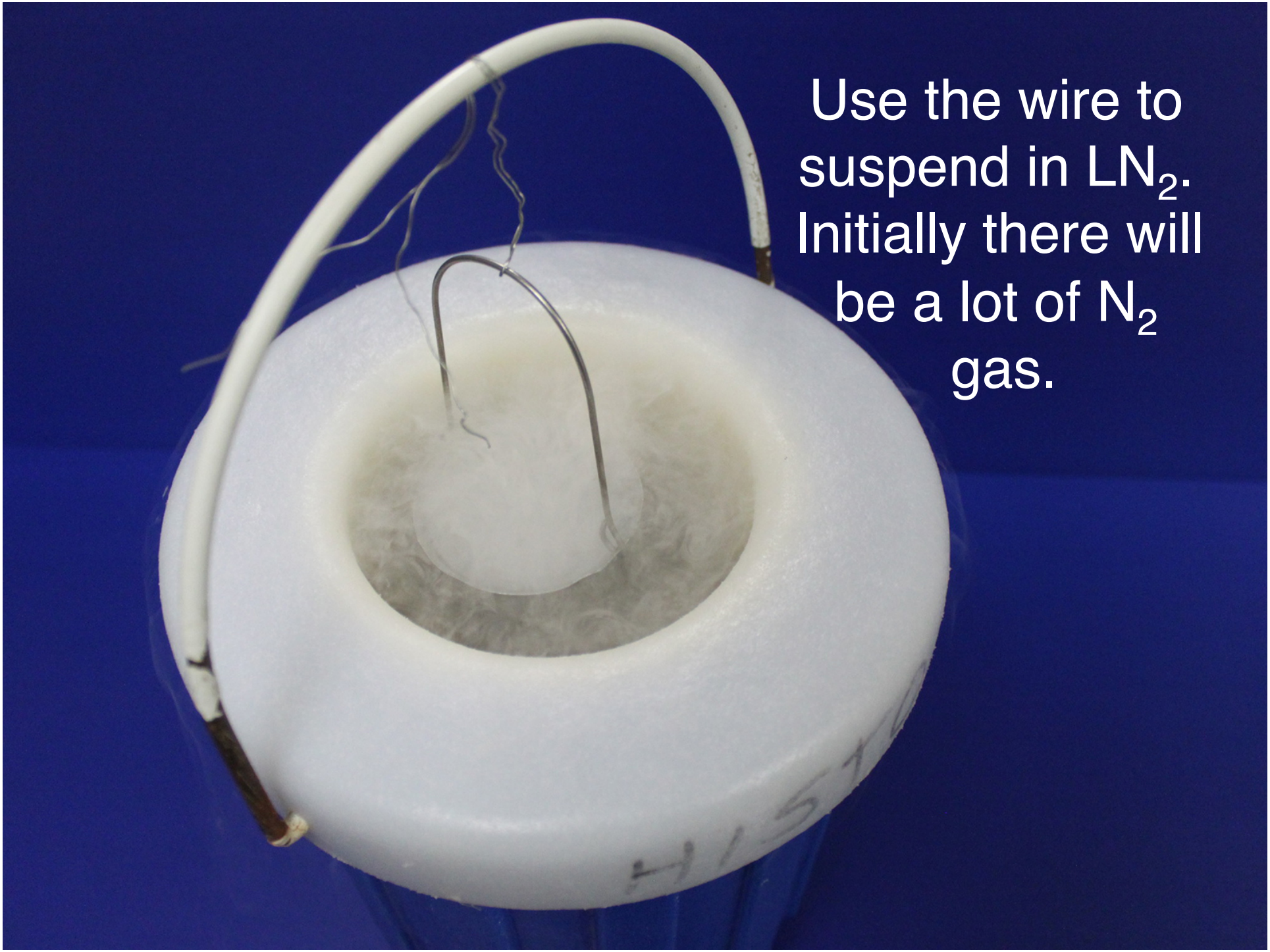
4
1
0
U
R
Storage
Code
Red
isopentane

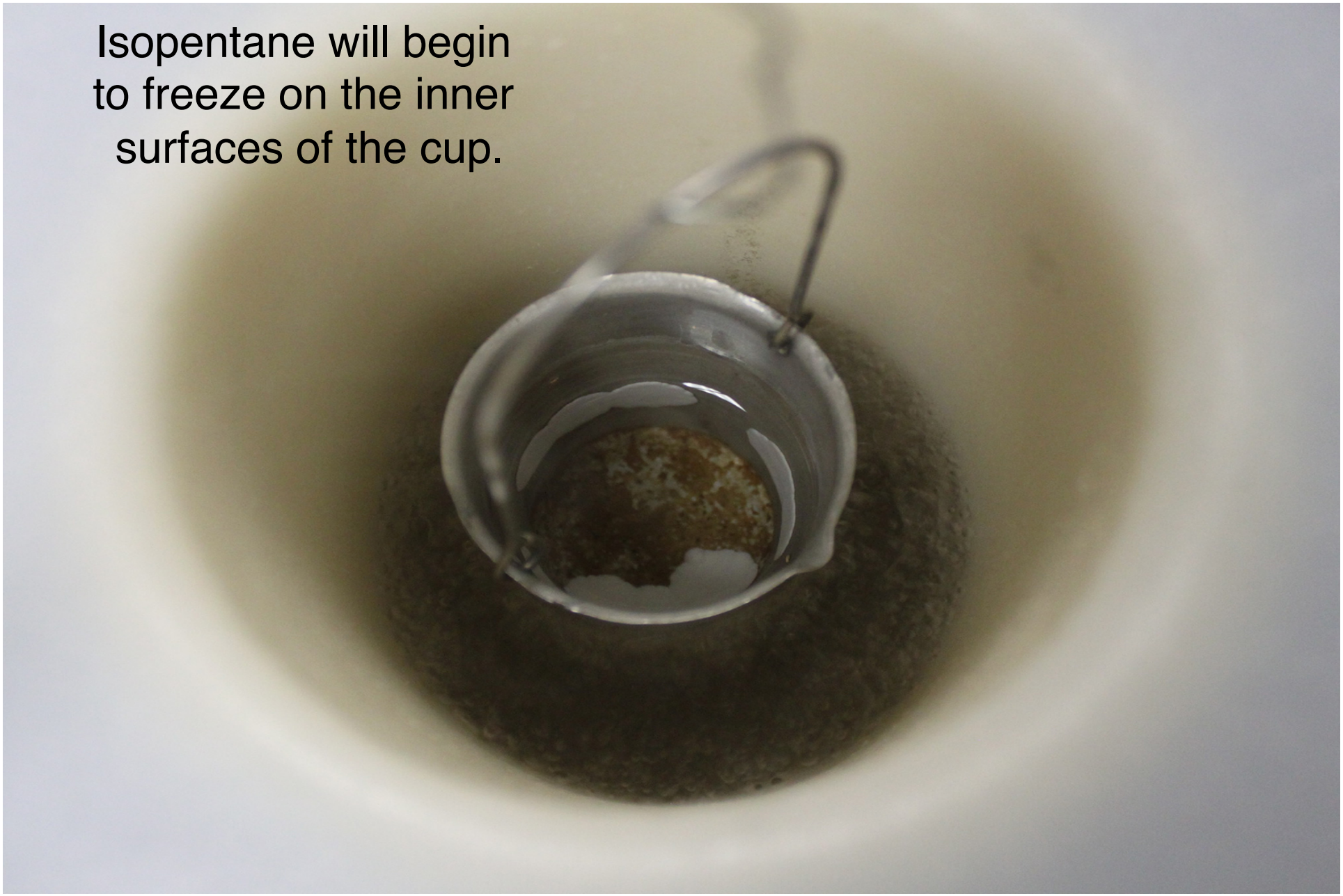
Place isopentane in a metal cup with a flexible wire to suspend in LN_2.

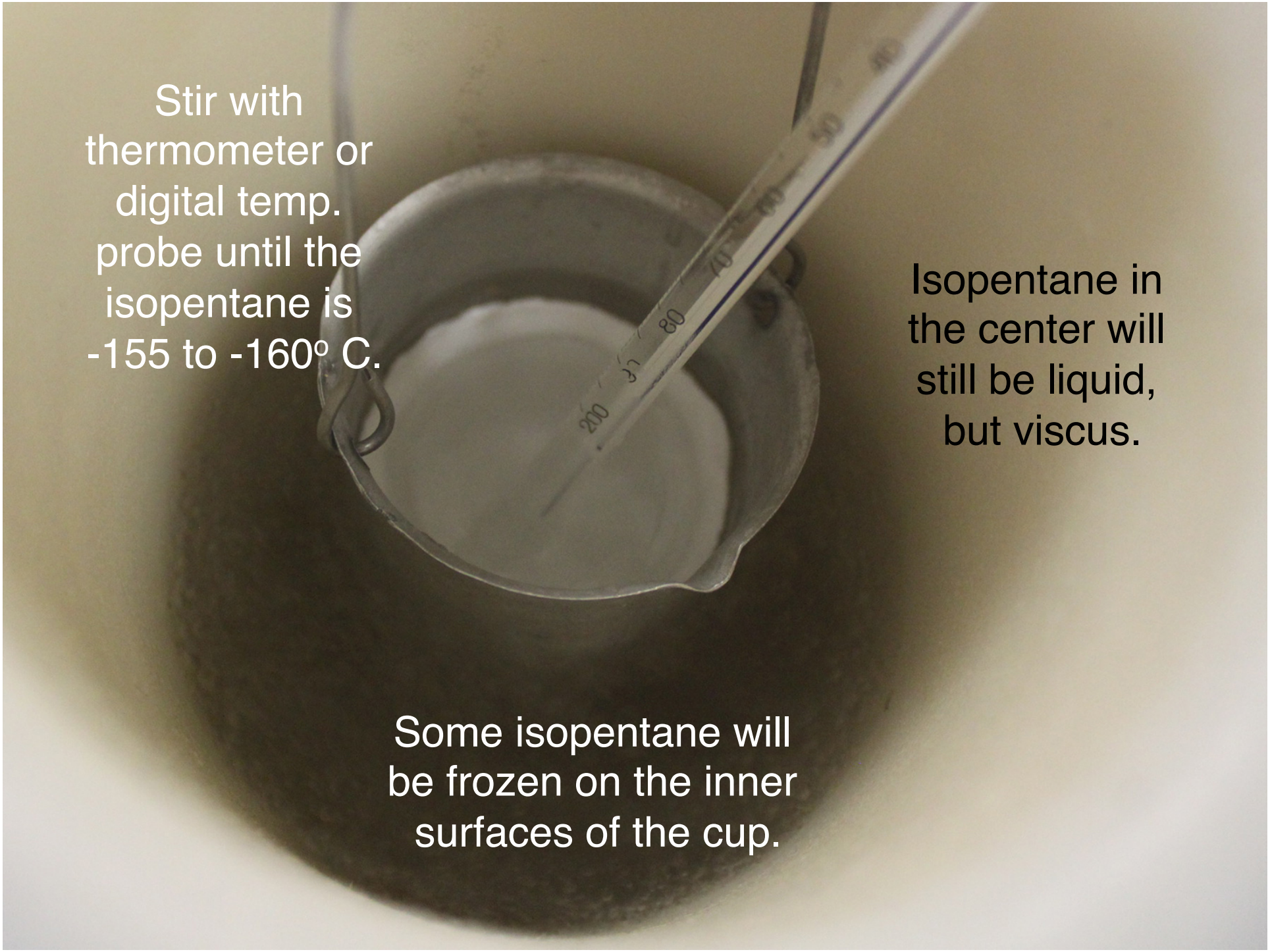
The flexible wire is proprietary. ☺


dewar with
LN_2


Use the wire to suspend in LN_2. Initially there will be a lot of N_2 gas.

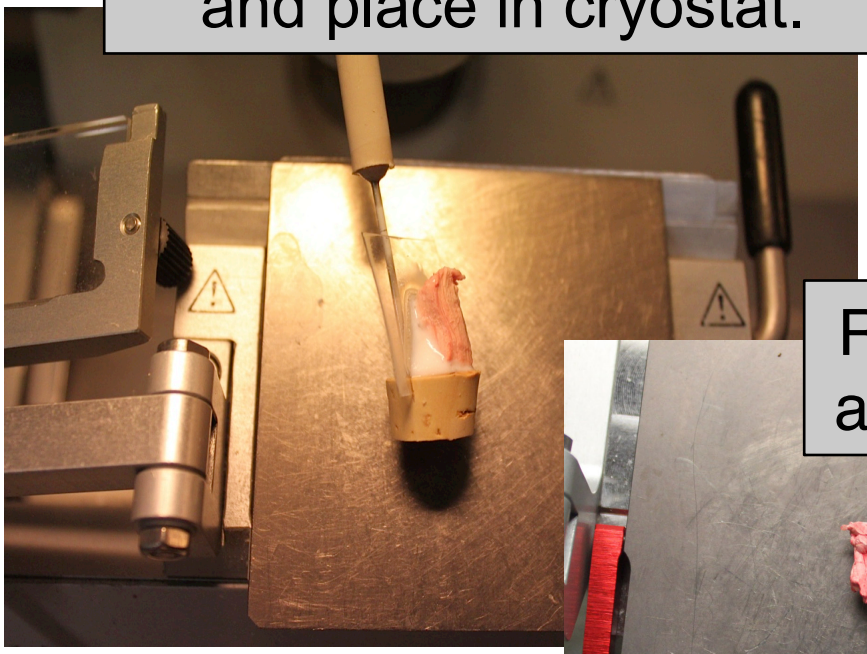

As everything cools, adjust the wire to gradually lower the cup.


Isopentane will begin
to freeze on the inner
surfaces of the cup.


Stir with thermometer or digital temp. probe until the isopentane is -155 to -160º C.
Isopentane in the center will still be liquid, but viscus.
Some isopentane will be frozen on the inner surfaces of the cup.

Plunge muscle biopsy into isopentane.

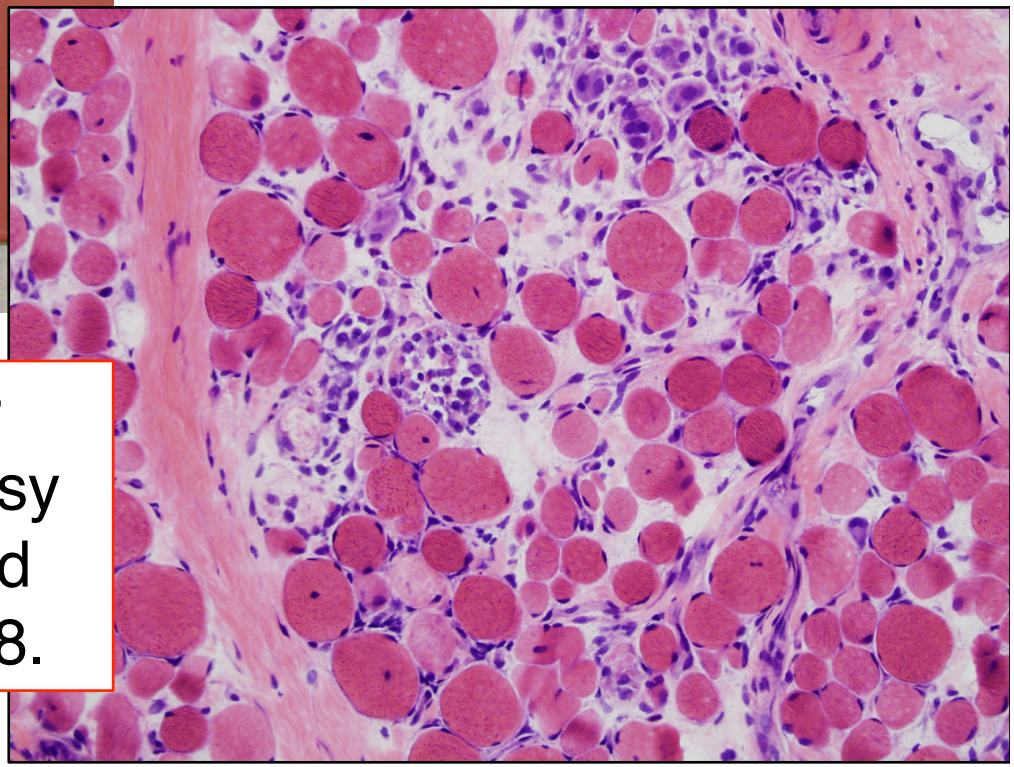
Remove from isopentane and place in cryostat.



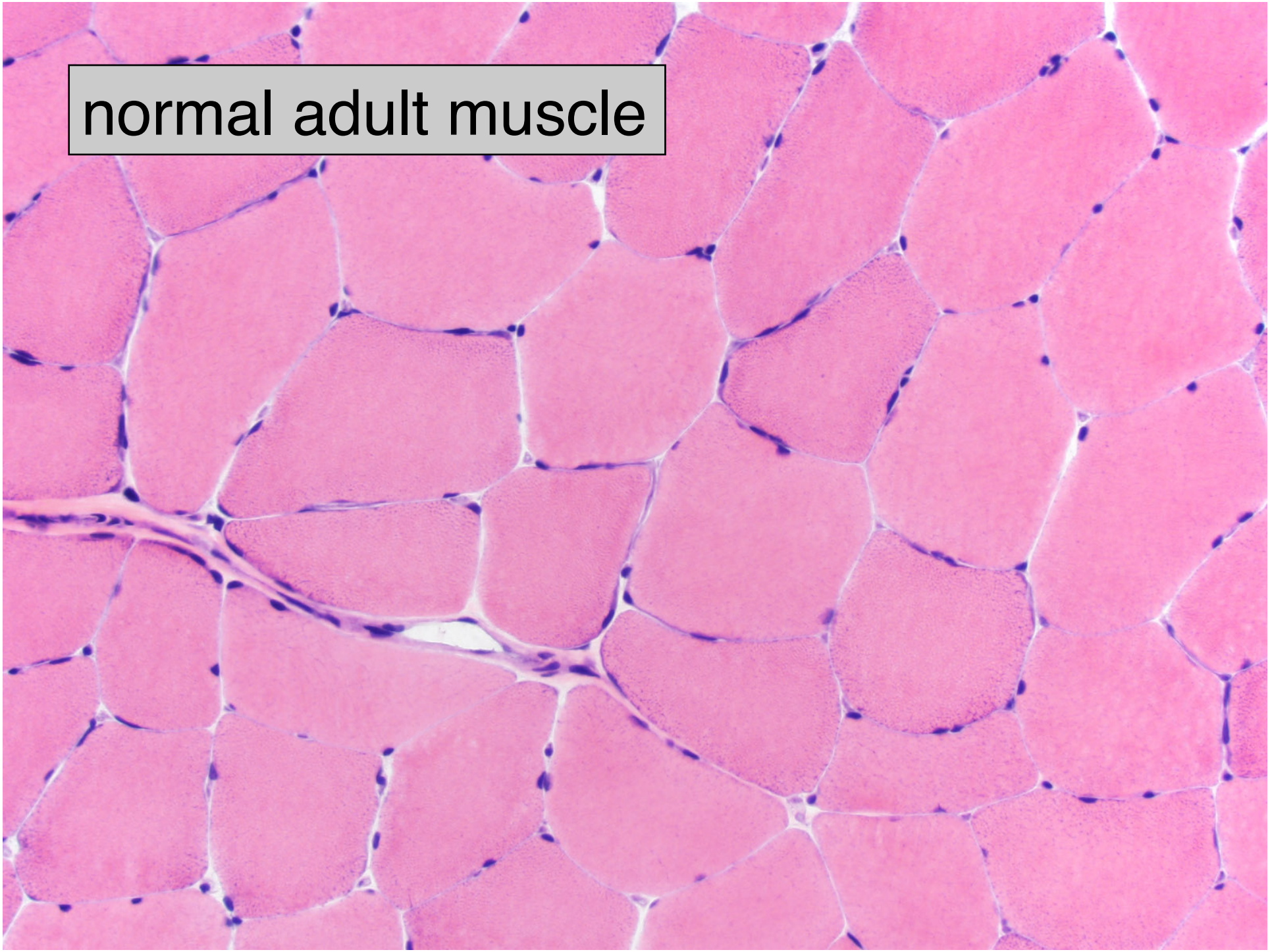
Remove coverslip and cut away cork.

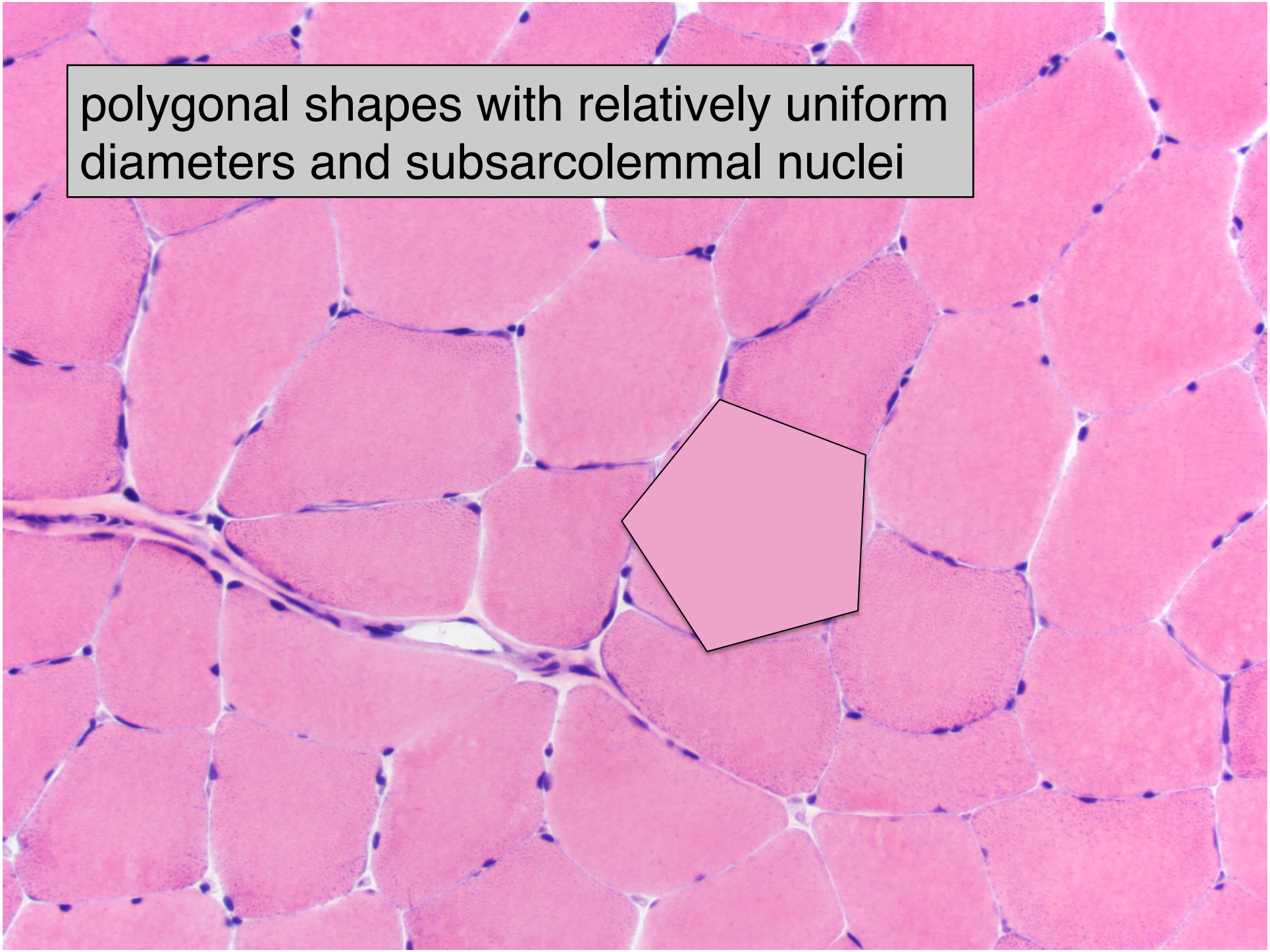
Wrap in precooled foil.

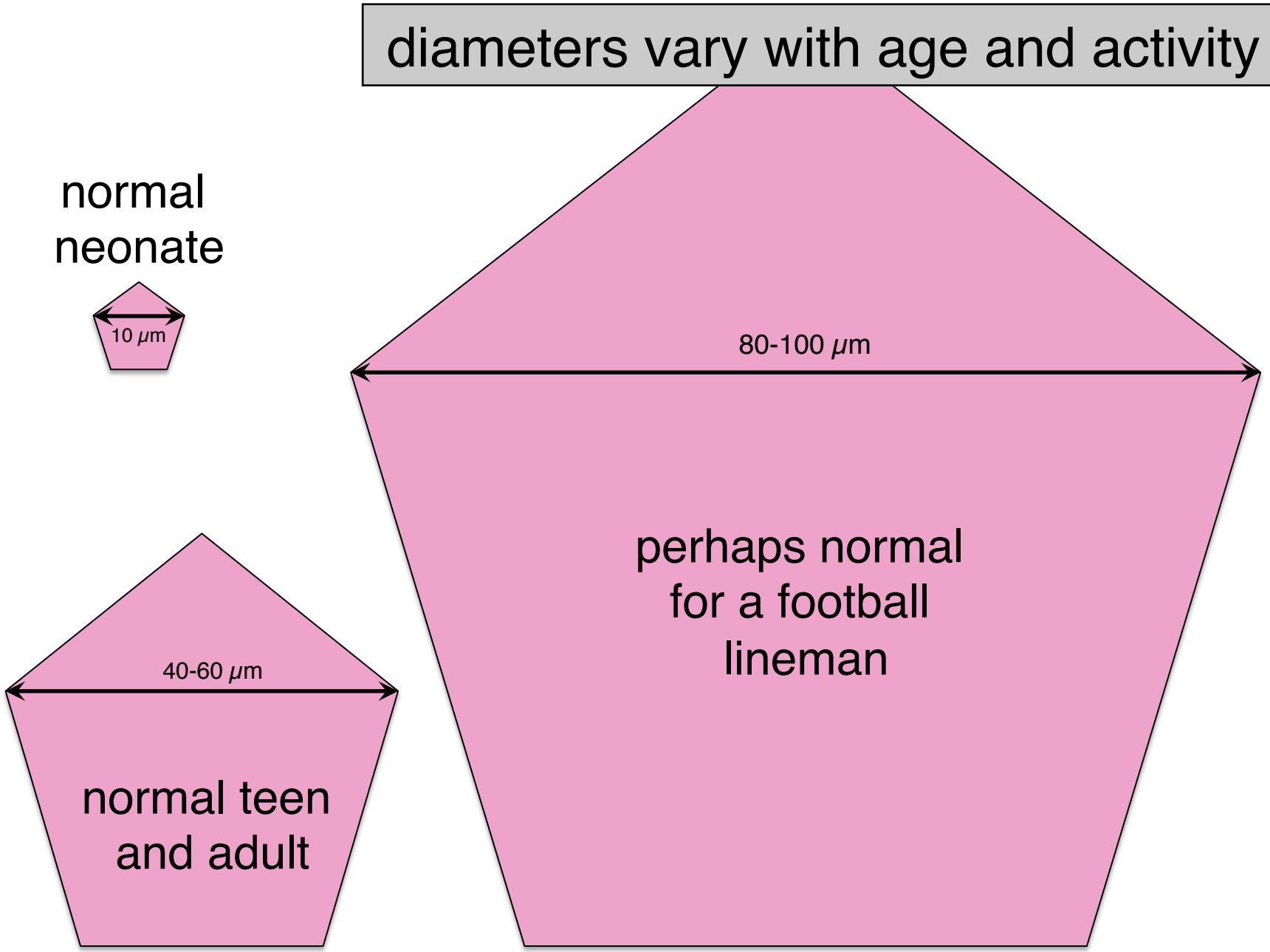
Place in prelabeled, precooled polycon and store at -80^{o} C .

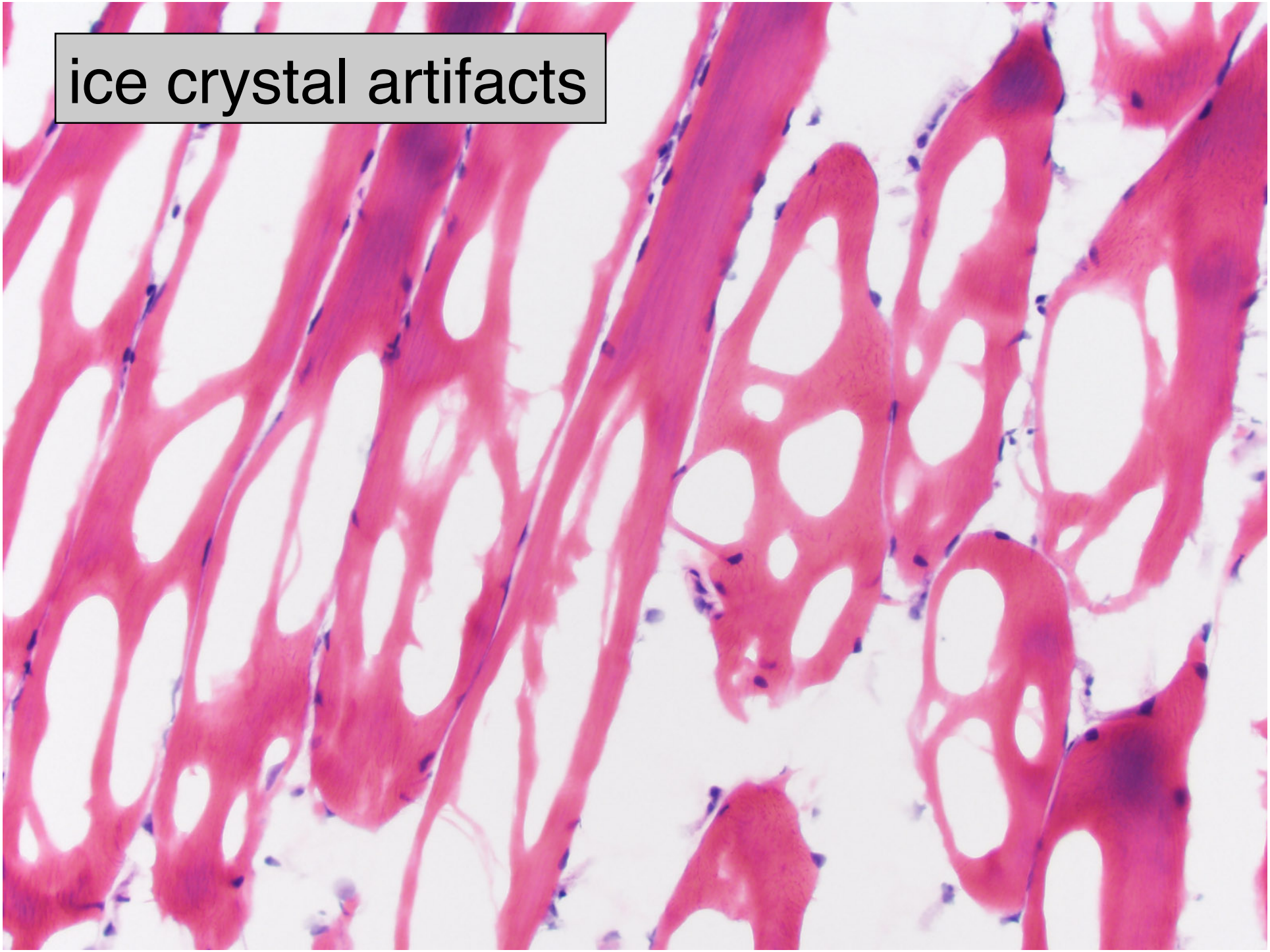


Duchenne muscular dystrophy (DMD) biopsy stored since 1995 and cryosectioned in 2018.


normal adult muscle

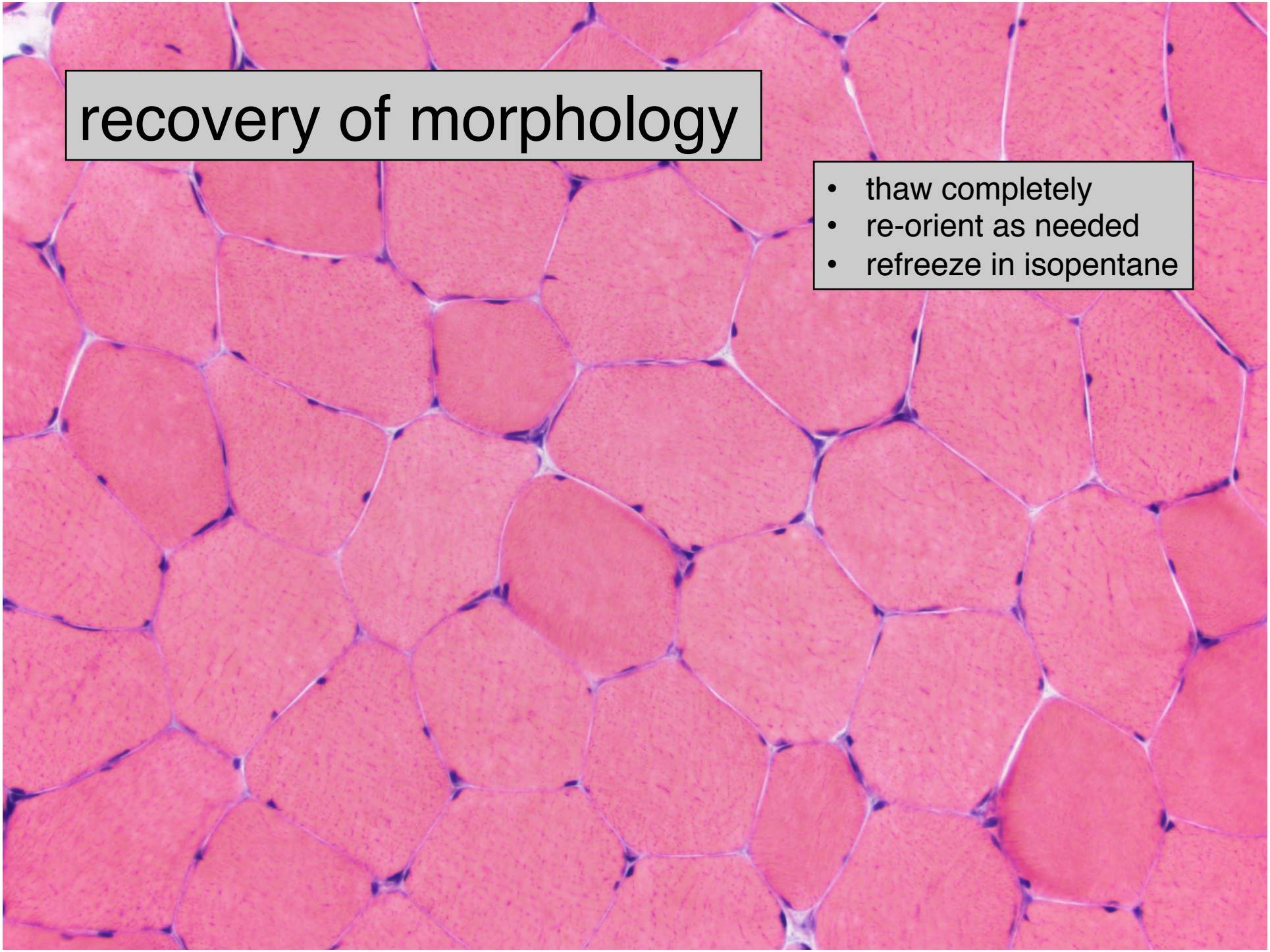

polygonal shapes with relatively uniform diameters and subsarcolemmal nuclei


diameters vary with age and activity
normal neonate
10 μm
80-100 μm
perhaps normal for a football lineman
40-60 μm
normal teen and adult

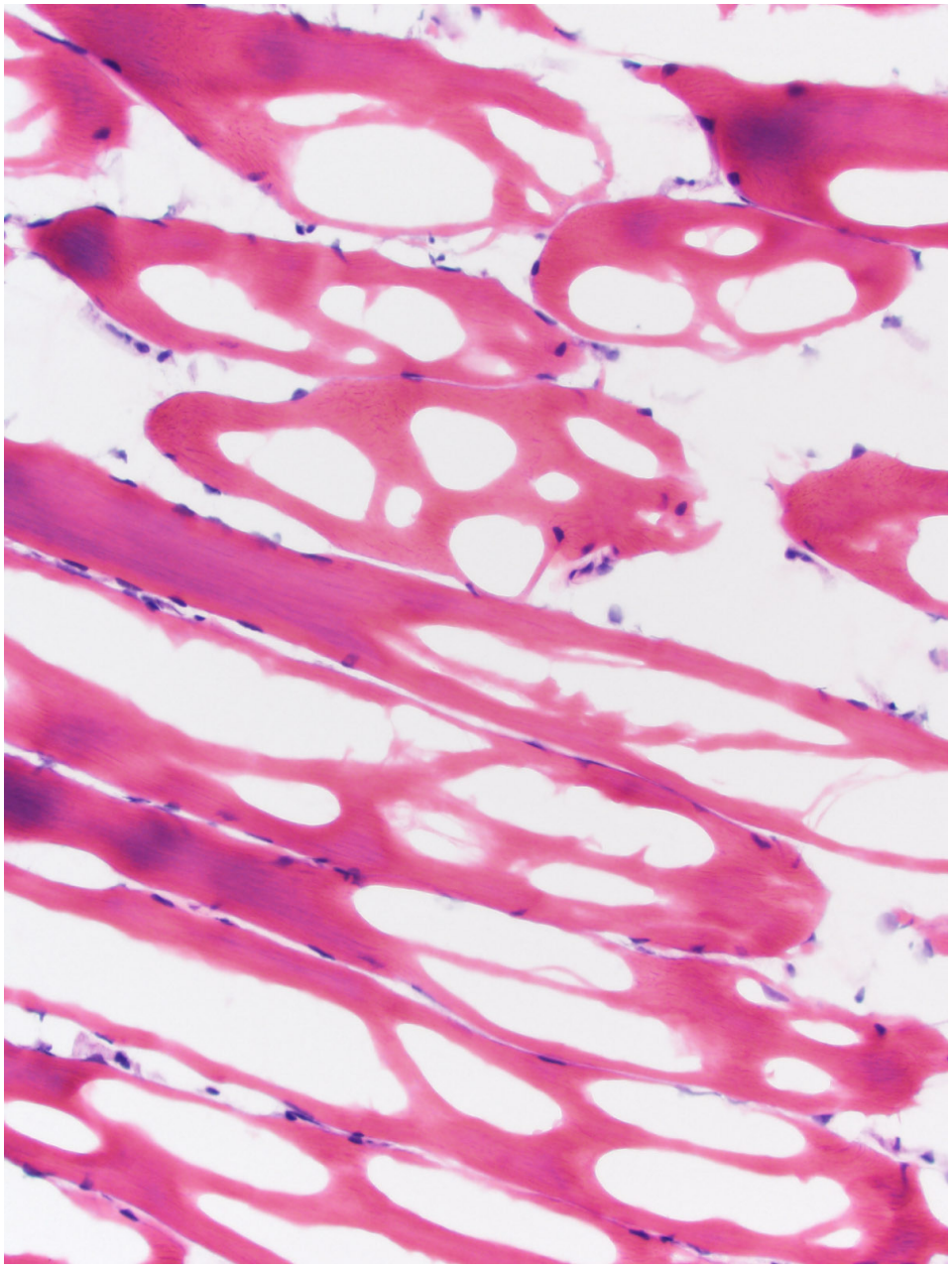

ice crystal artifacts

recovery of morphology

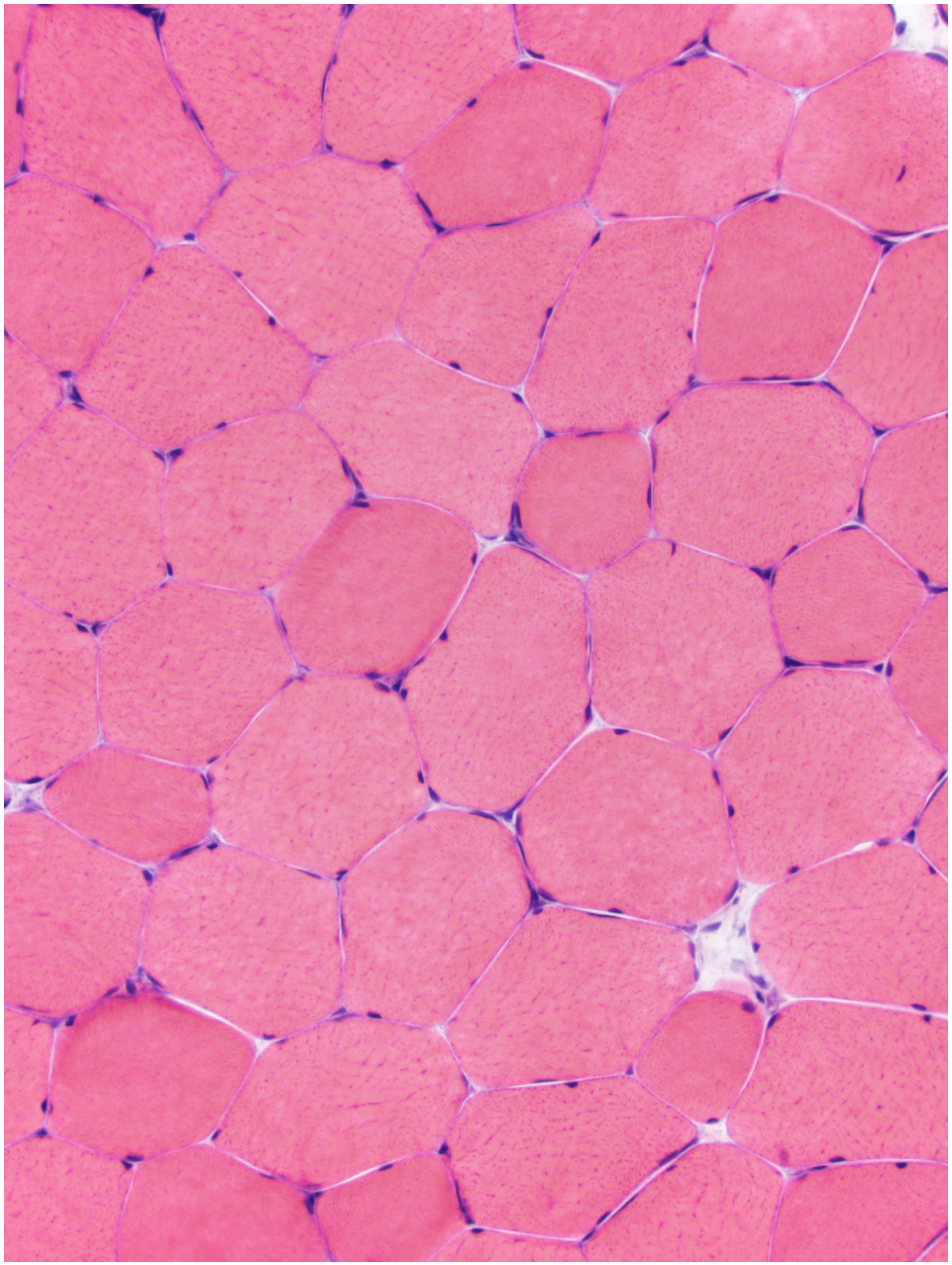
- thaw completely
- re-orient as needed
- refreeze in isopentane

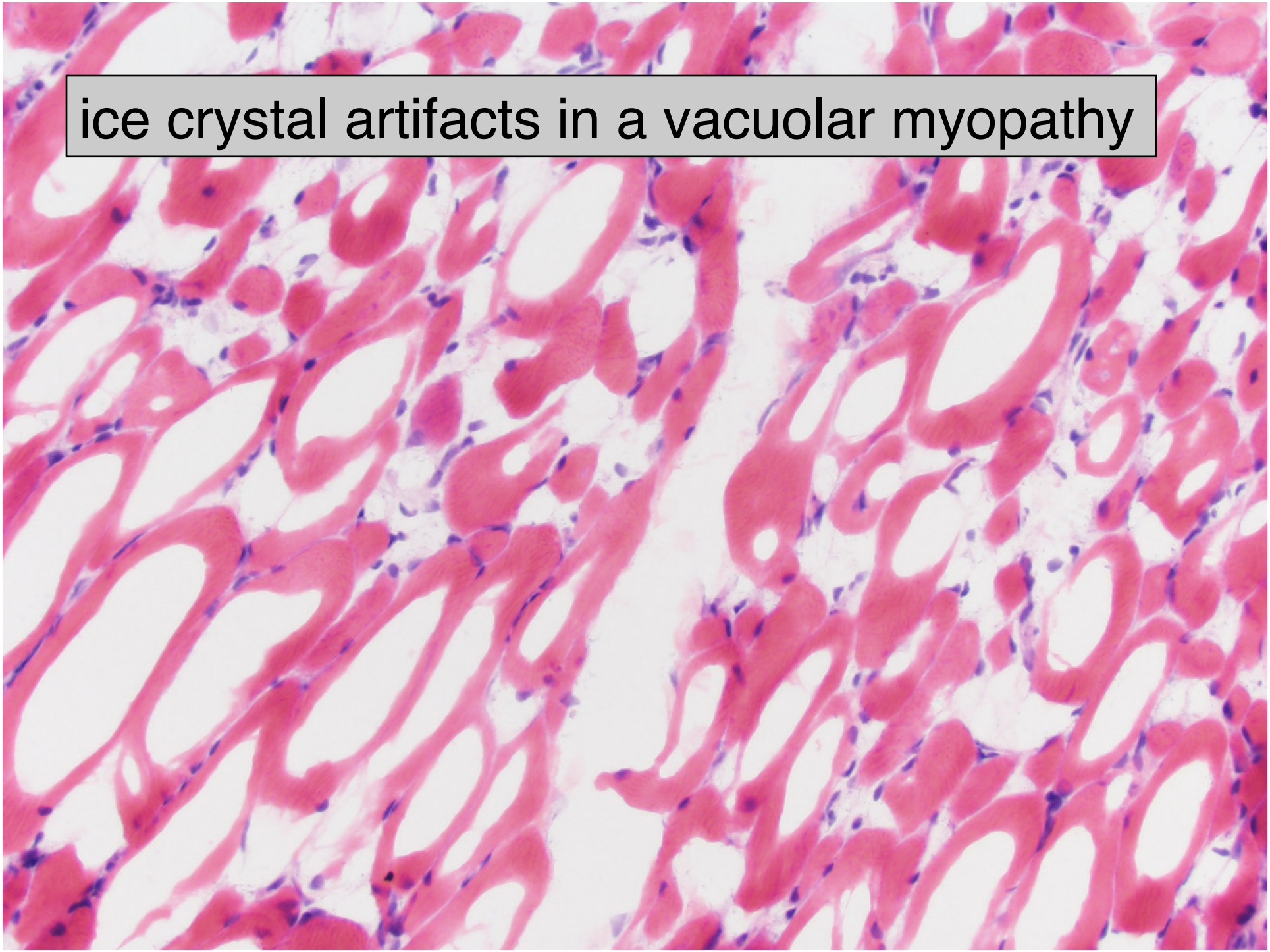


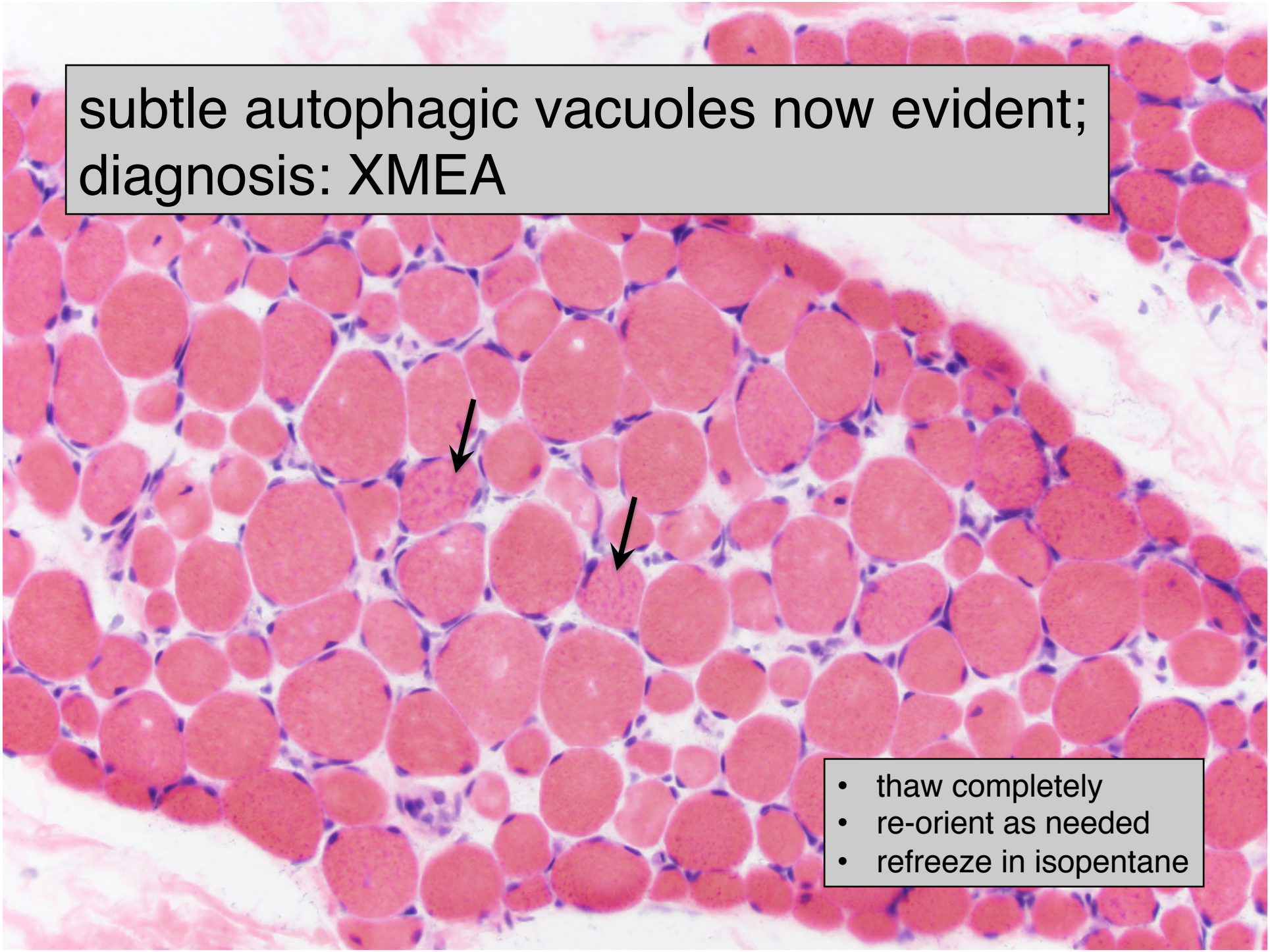
original H&E



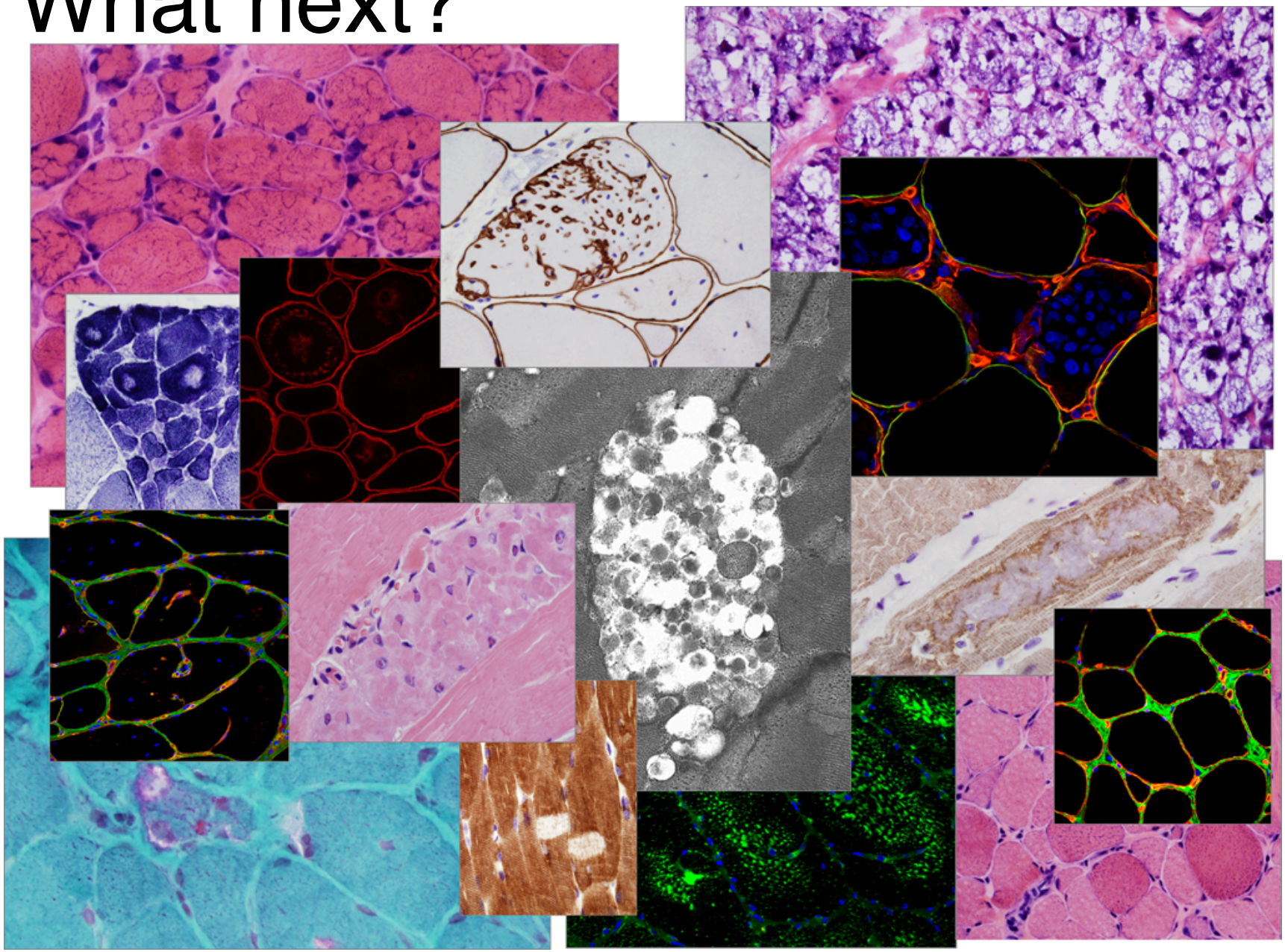
thaw, re-orient, refreeze




ice crystal artifacts in a vacuolar myopathy


subtle autophagic vacuoles now evident;
diagnosis: XMEA
• thaw completely
• re-orient as needed
• refreeze in isopentane

What next?



approach to evaluation

Iowa routine

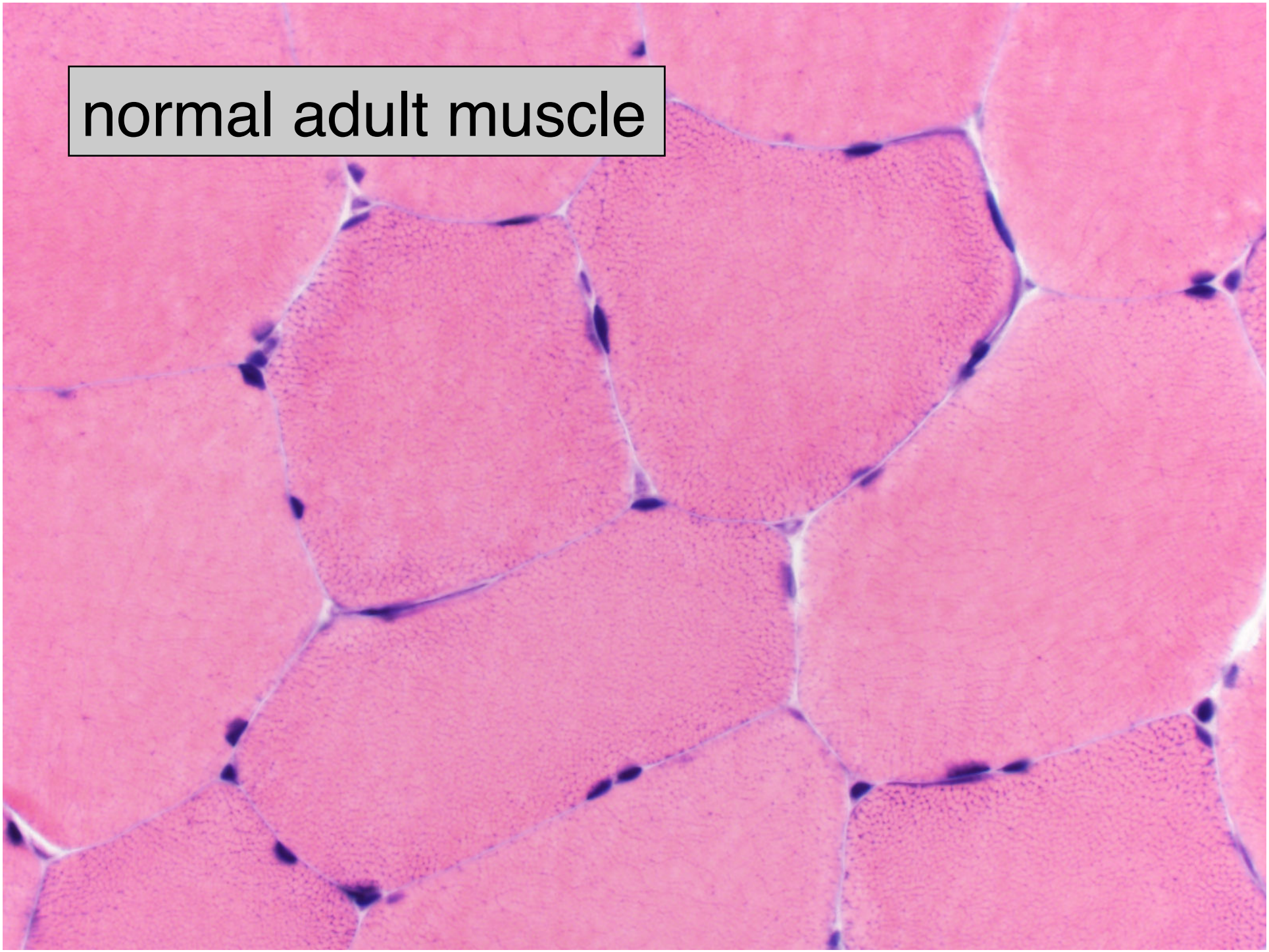
- H&E
- fiber typing
  - slow myosin IHC
  - fast myosin IHC
- NADH-TR
- SDH
- COX-SDH
- Gomori trichrome
- tailor the remainder to best fit each biopsy

shot gun (partial list)

- H&E
- fiber typing
  - ATPase at pH 4.2, 4.6, and 9.4
  - slow and fast myosin IHC
- NADH-TR
- SDH
- COX or COX-SDH
- Gomori trichrome
- acid and alkaline phosphatase
- esterase
- phosphorylase
- PAS and PASD
- ORO
- VVG
- MHC class I immunostaining
- lymphocyte and macrophage marker IHC
- Congo red

H&E is your best friend!

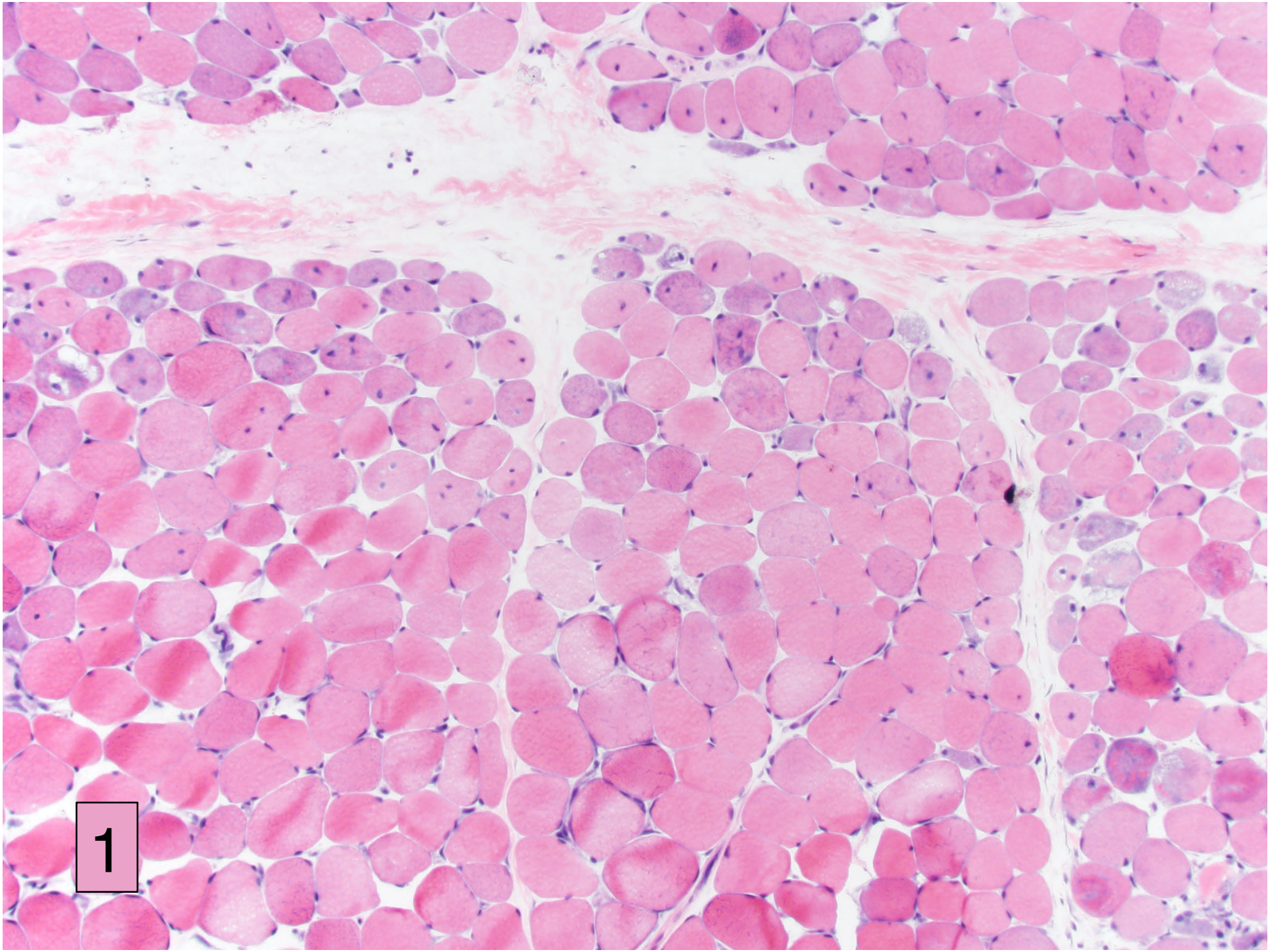
- H&E, not h&**E**
- Reliable for most critically important histologic/histopathologic features
  - main exceptions are fiber typing and most nemaline rods


normal adult muscle

H&E is your best friend!

- H&E, not h&E
- Reliable for most critically important histologic/histopathologic features except fiber typing and most nemaline rods

- Live test - audience participation required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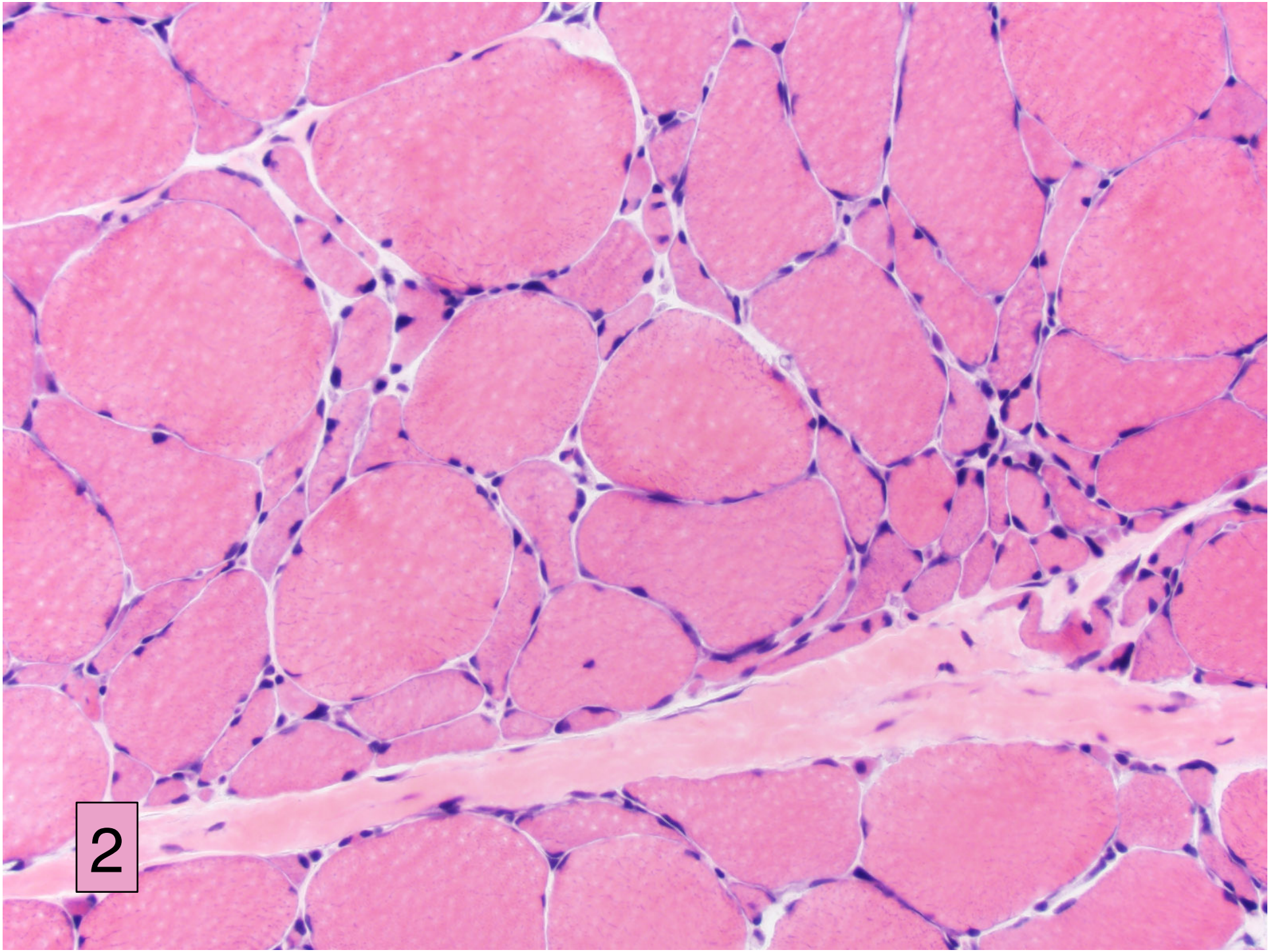
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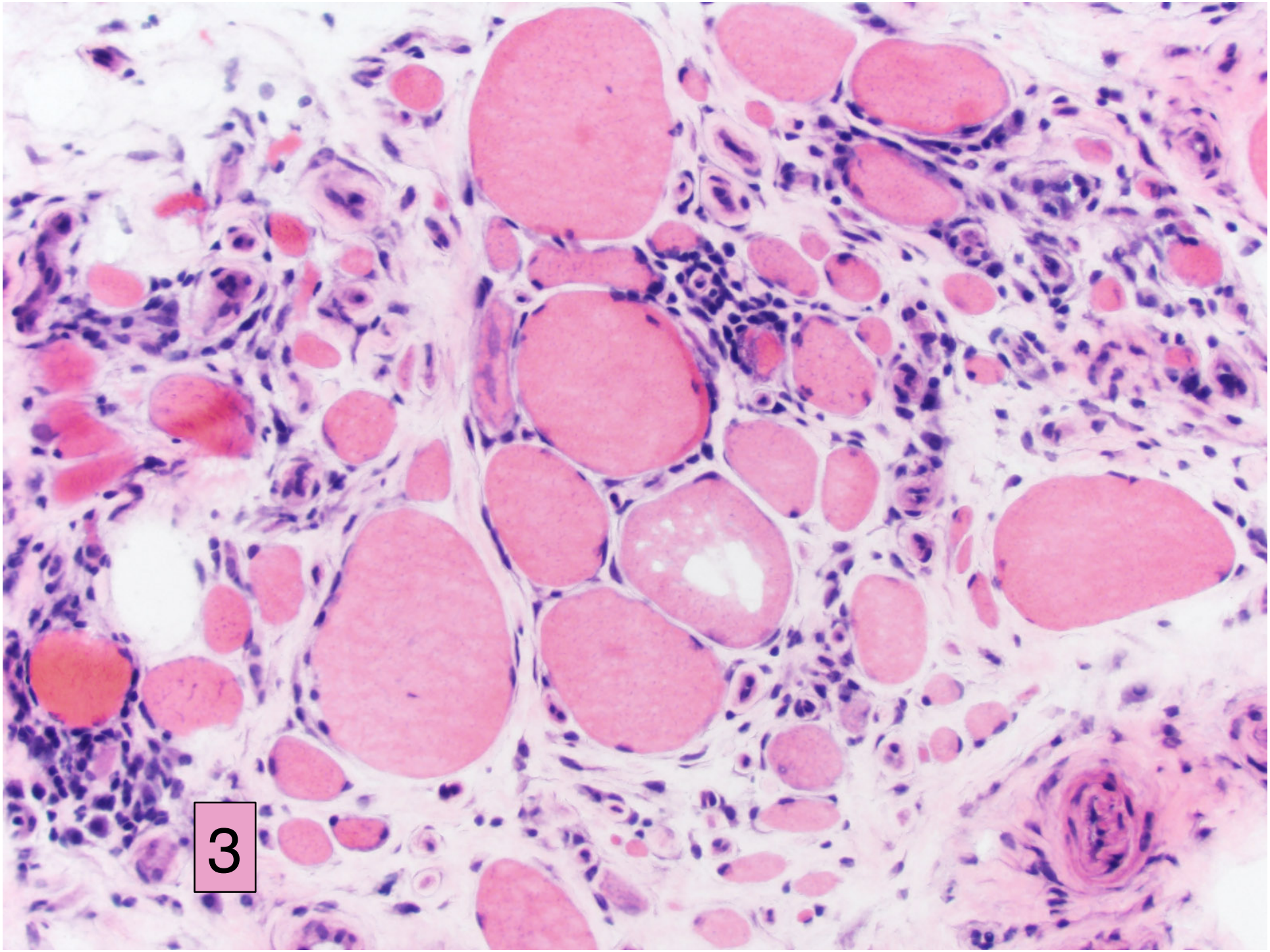
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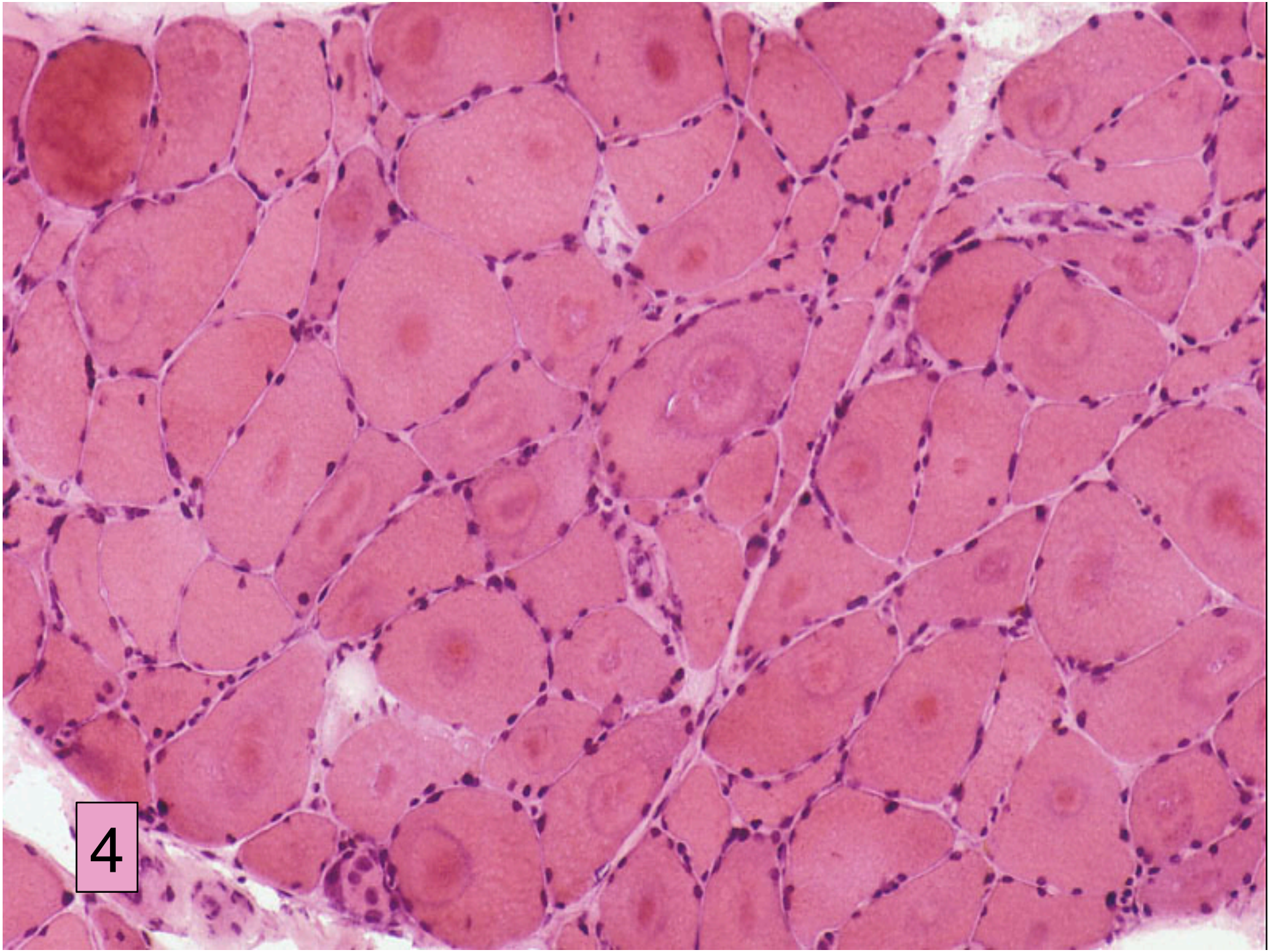
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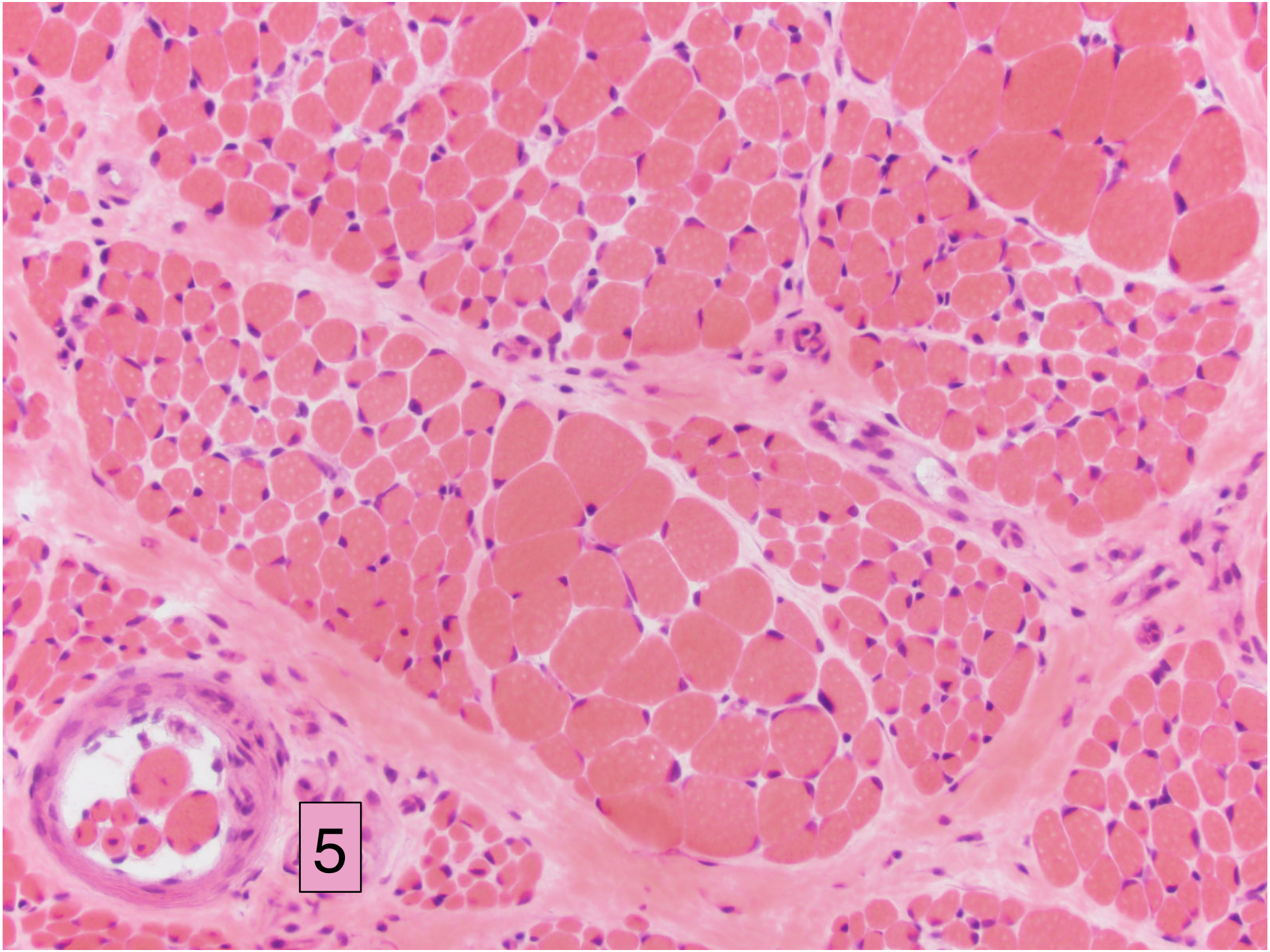
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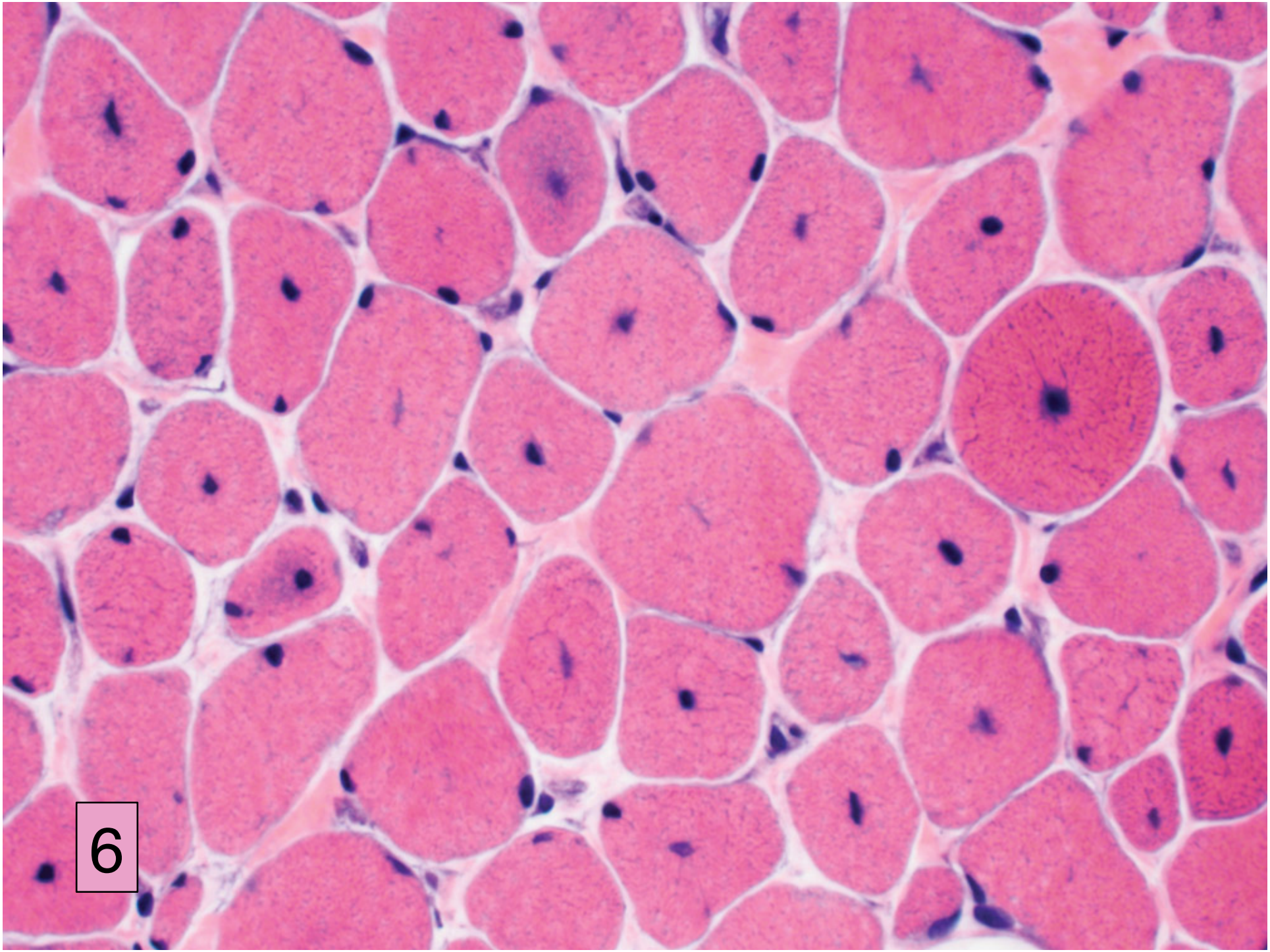
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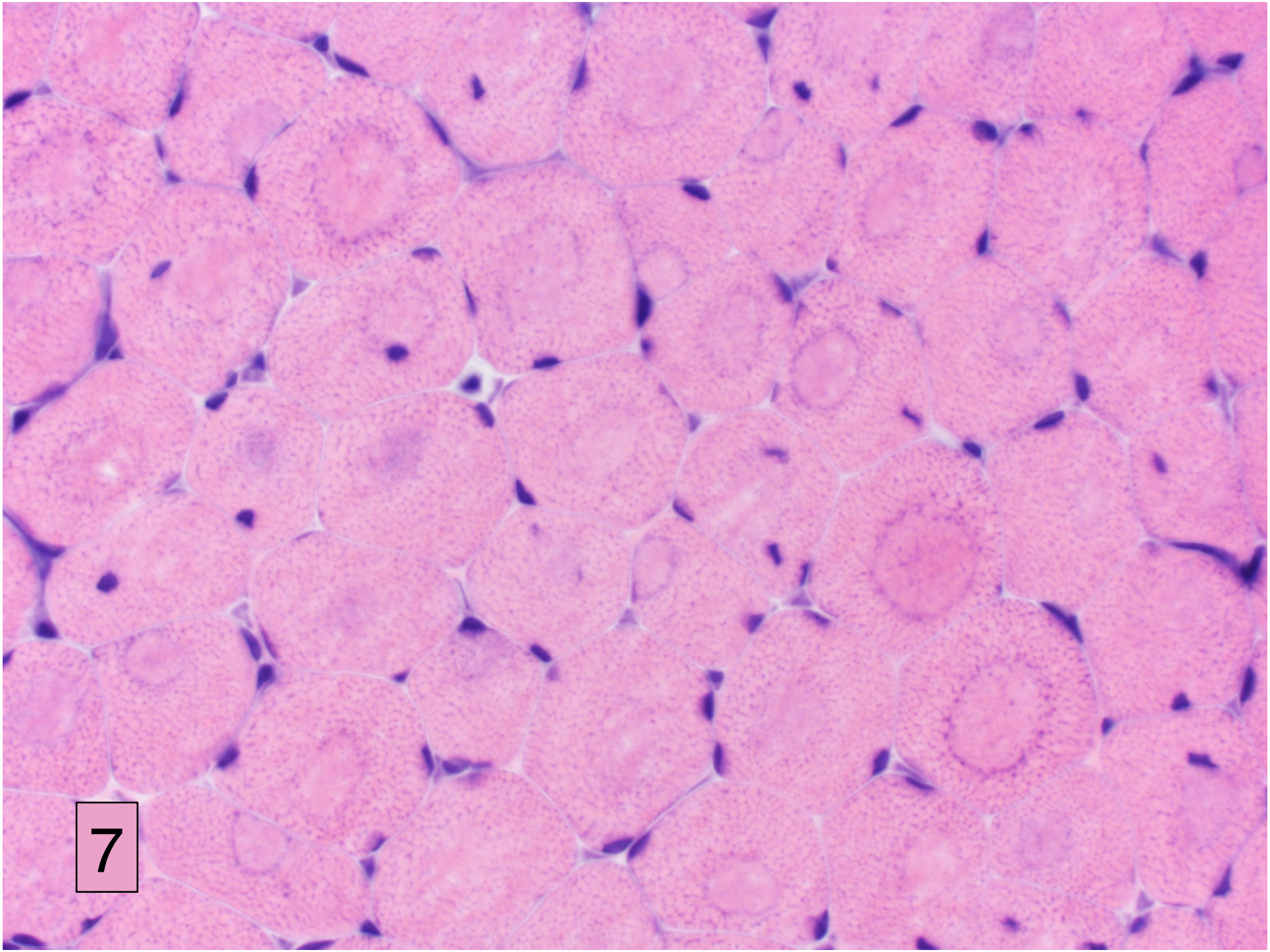
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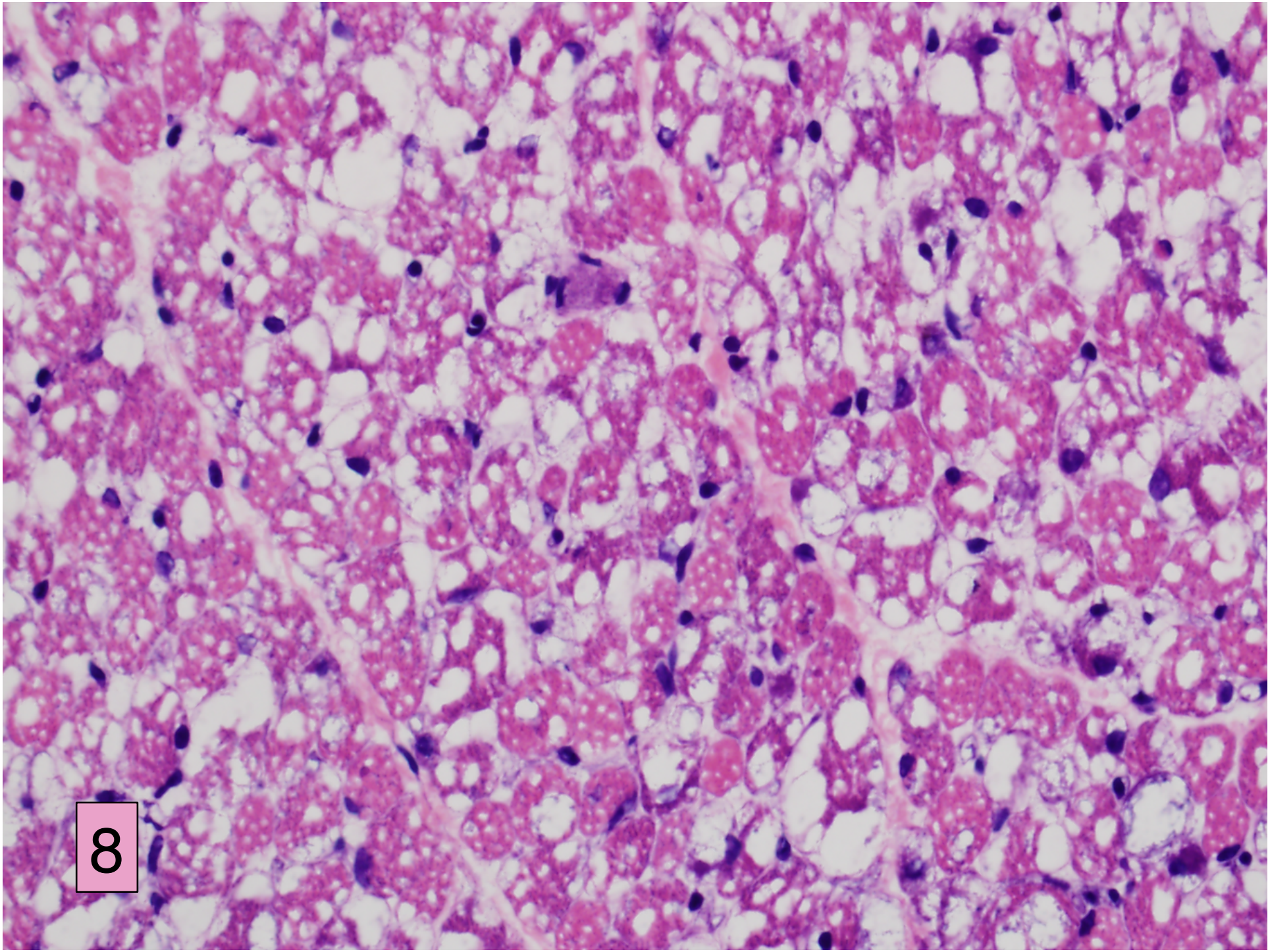
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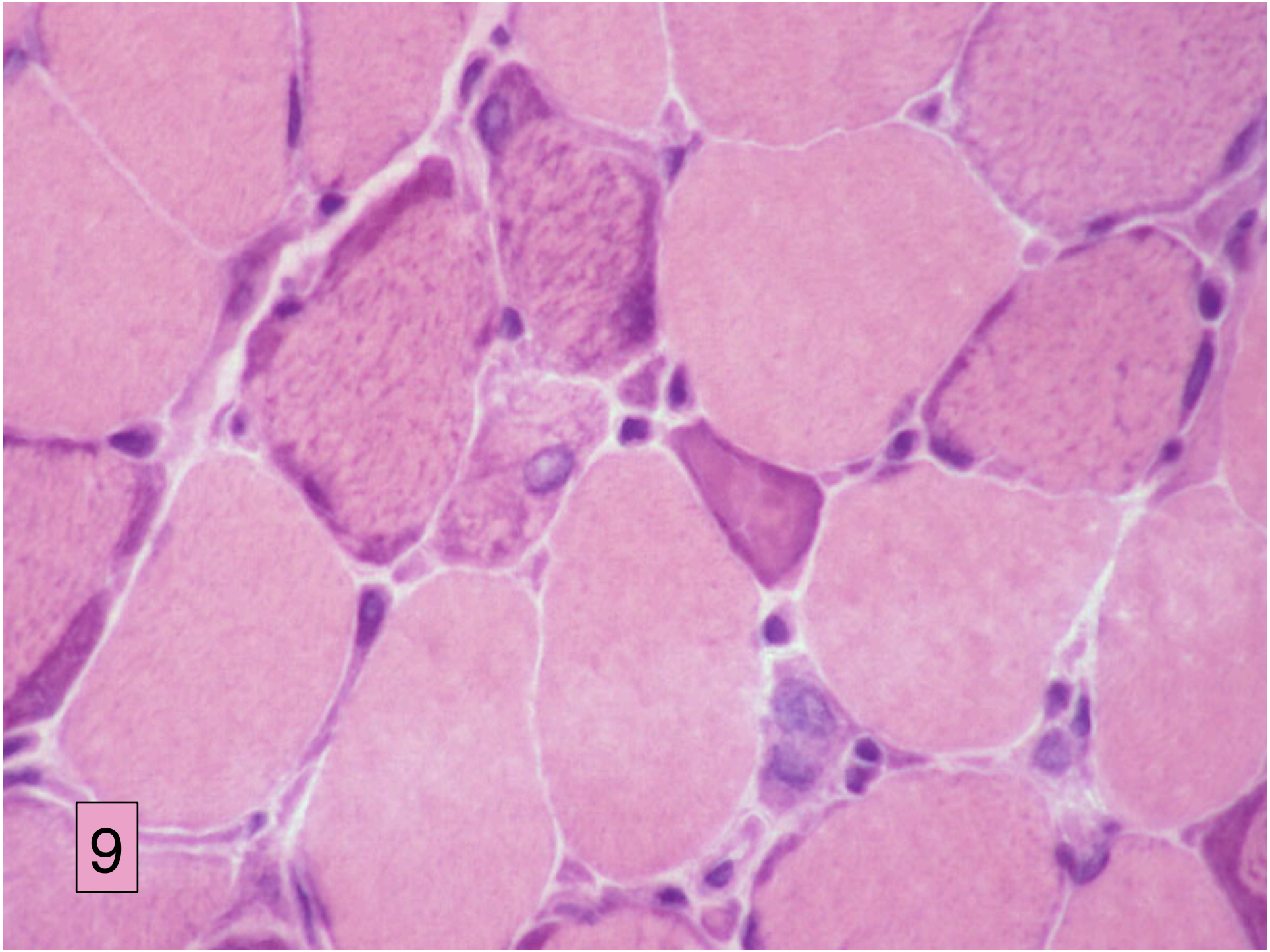
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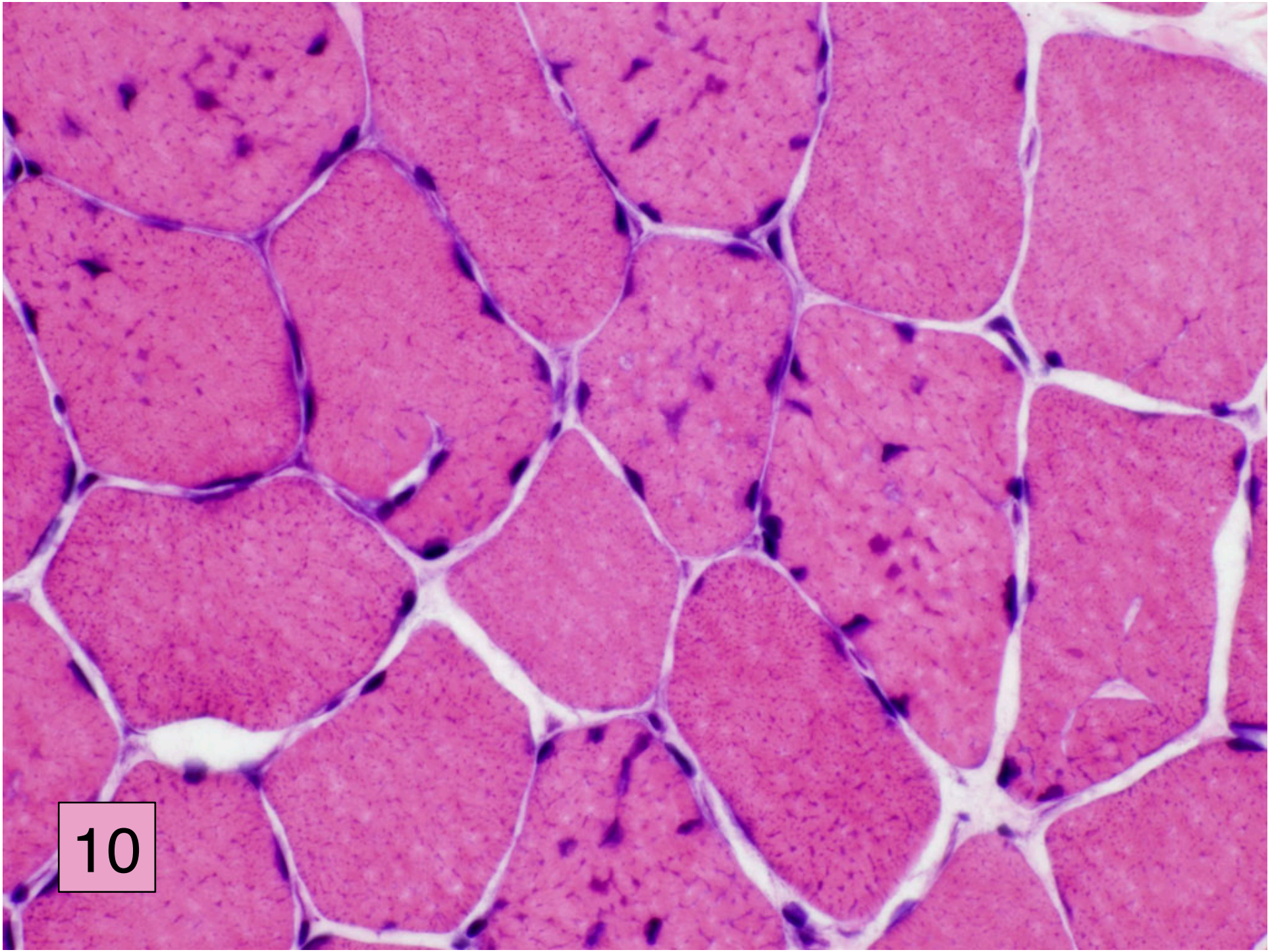
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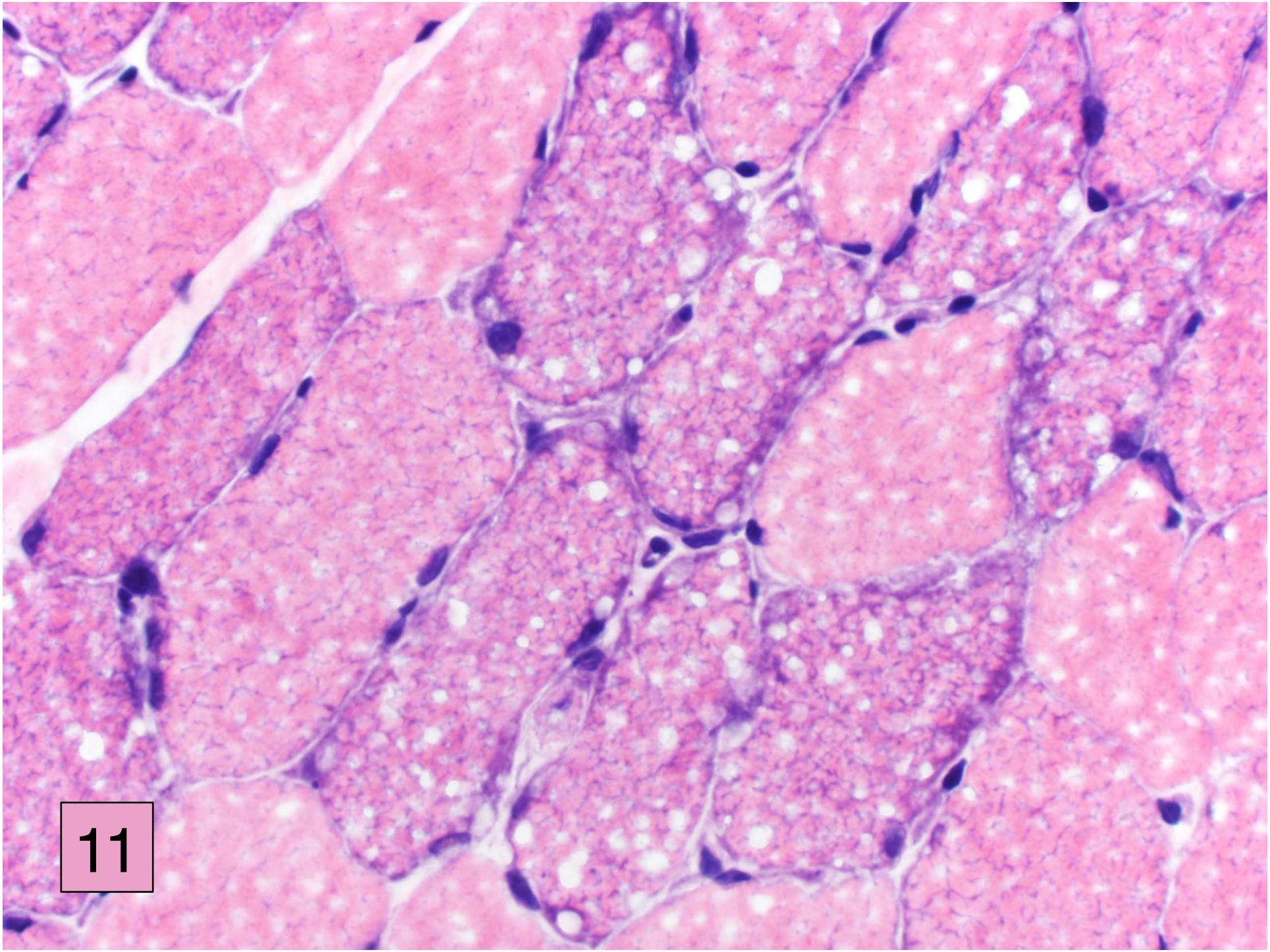
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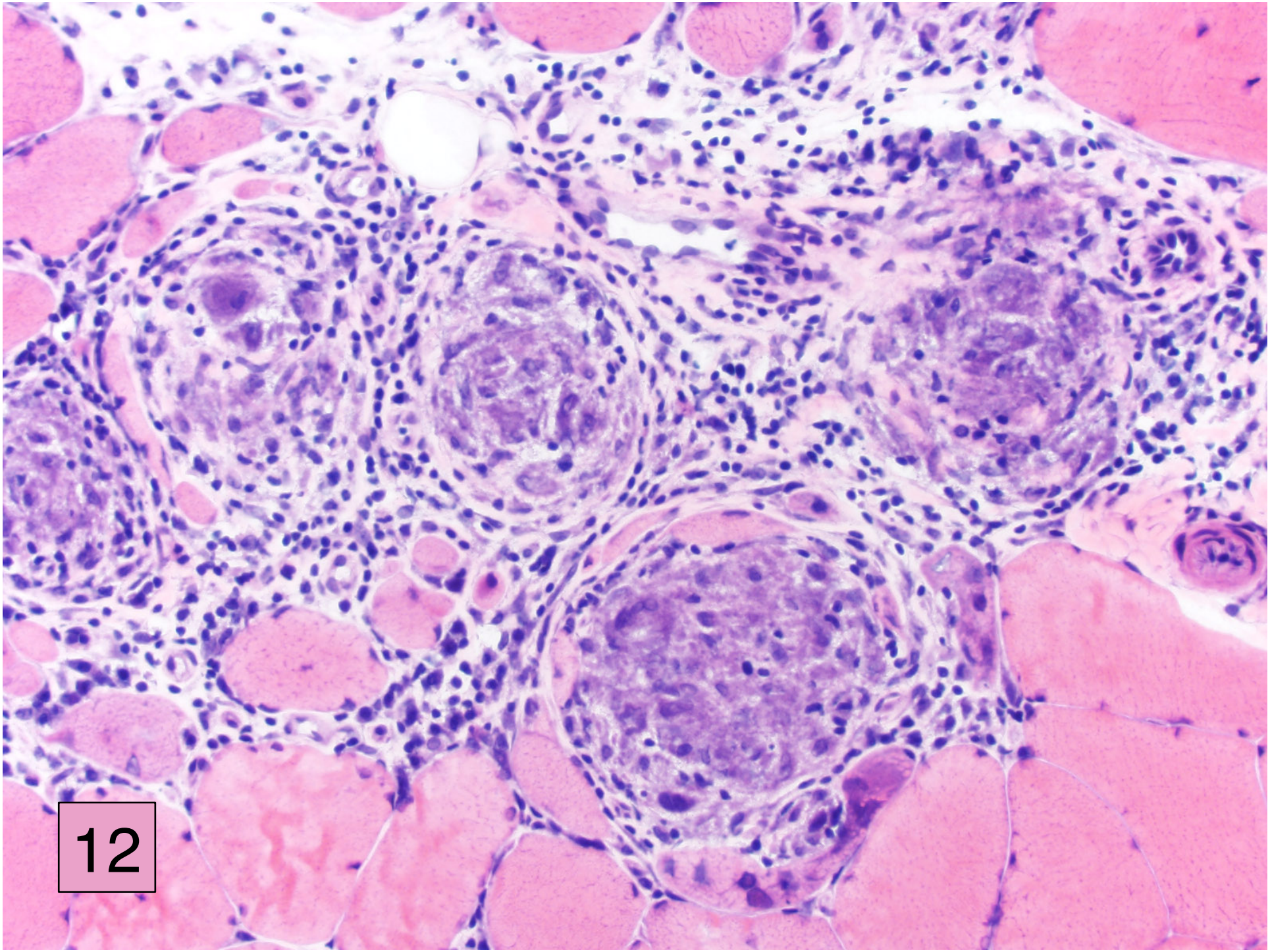
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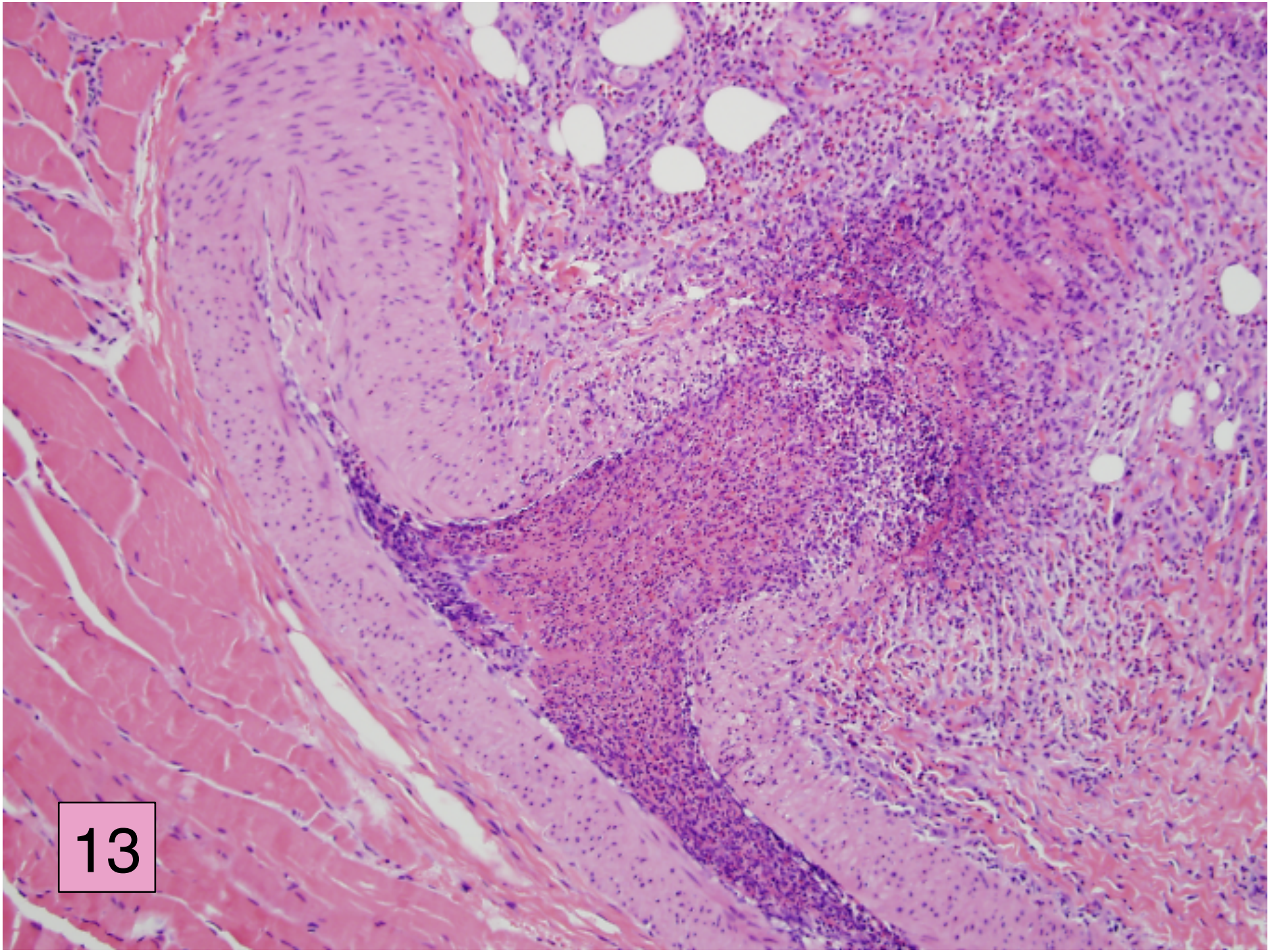
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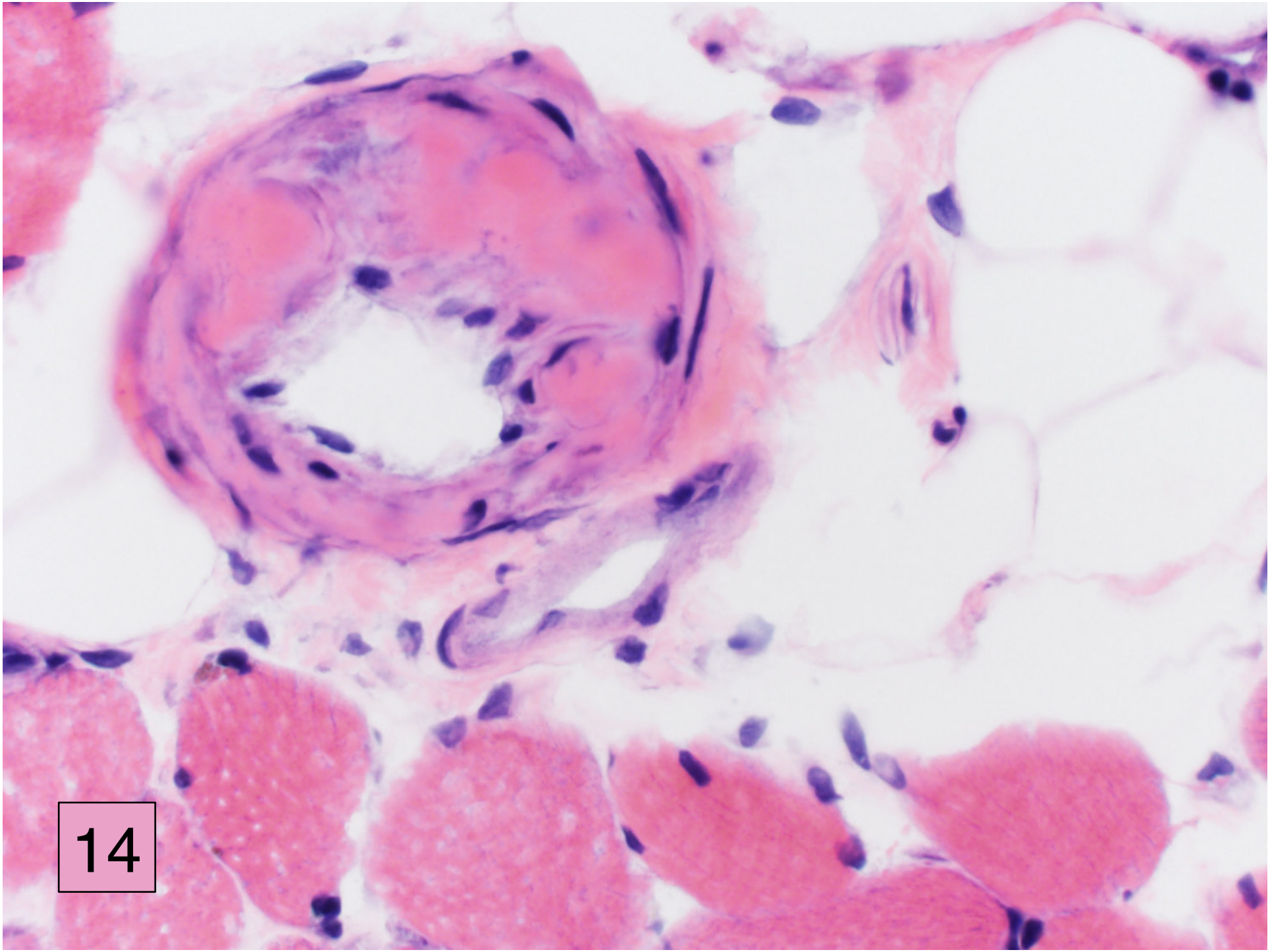
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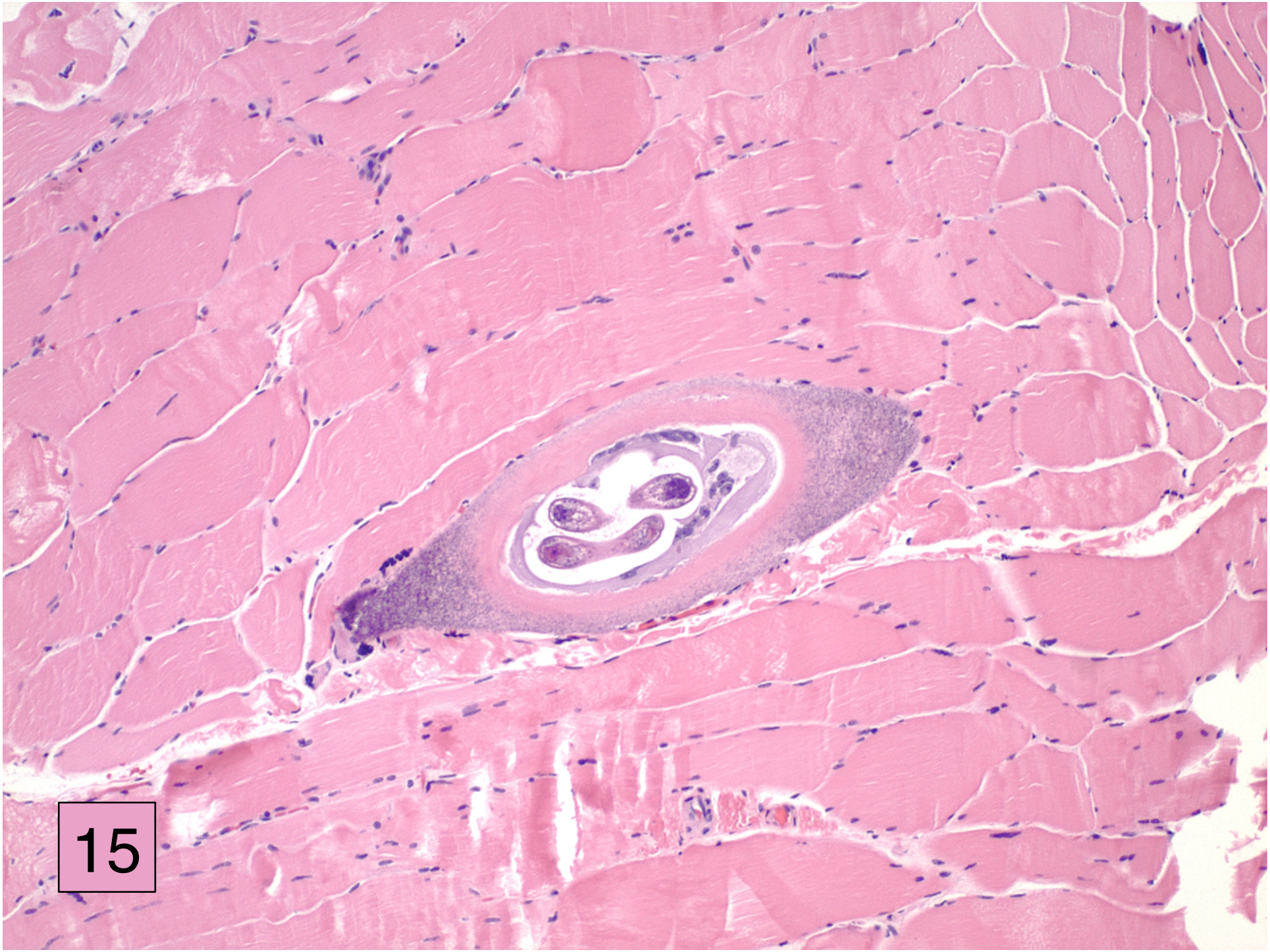
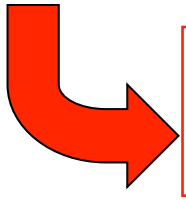

15

muscle fiber types

	Type I	Type II
action	sustained force weight-bearing	sudden movement purposeful motion
enzyme content	NADH dark ATPase light (pH 9.4) slow myosin heavy chain	NADH light ATPase dark (pH 9.4) fast myosin heavy chain
lipids	abundant	scant
glycogen	scant	abundant
physiology	slow-twitch	fast-twitch
color	red	white

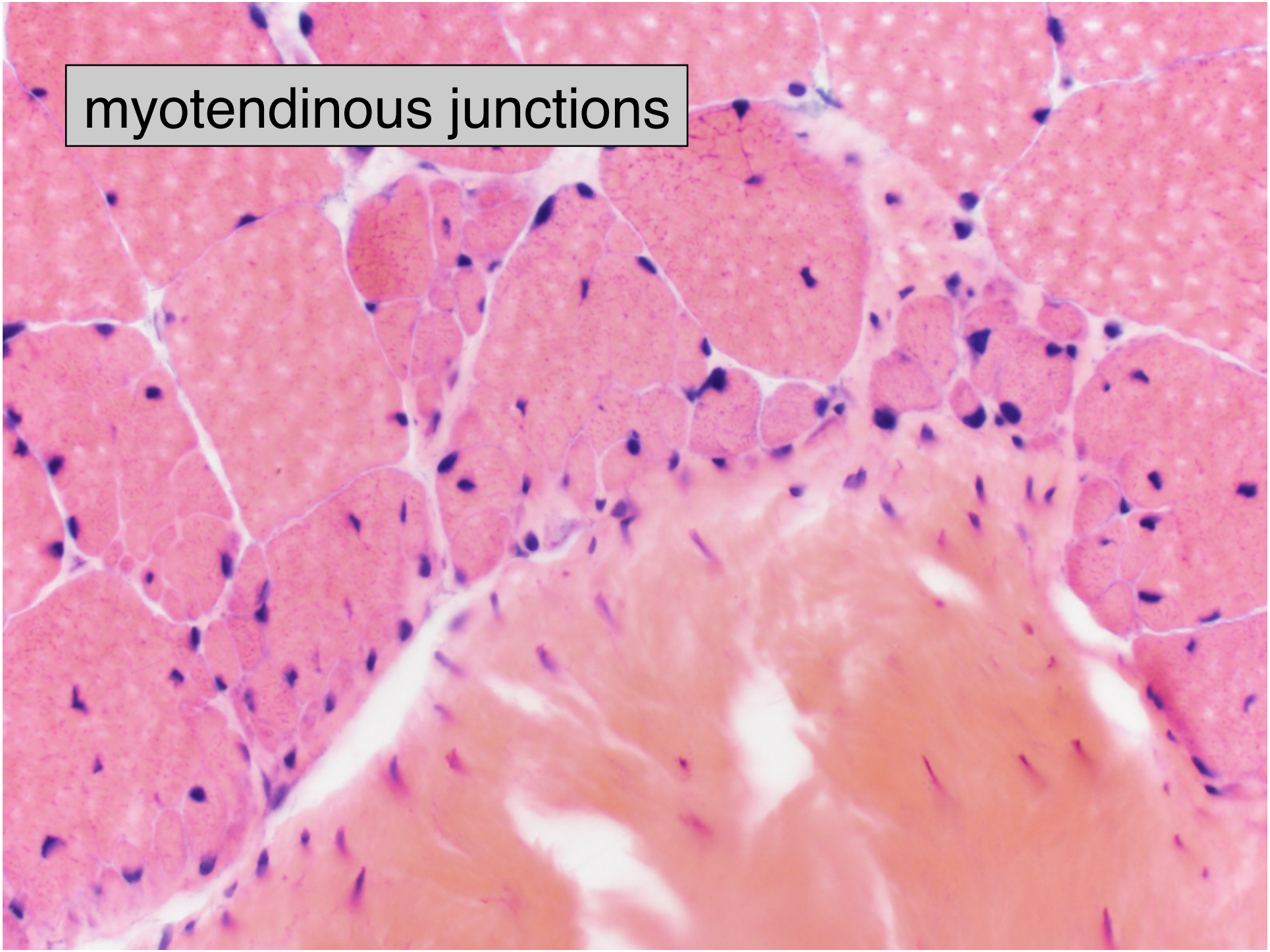
prefer epon sections over cryosection ORO and PAS stains

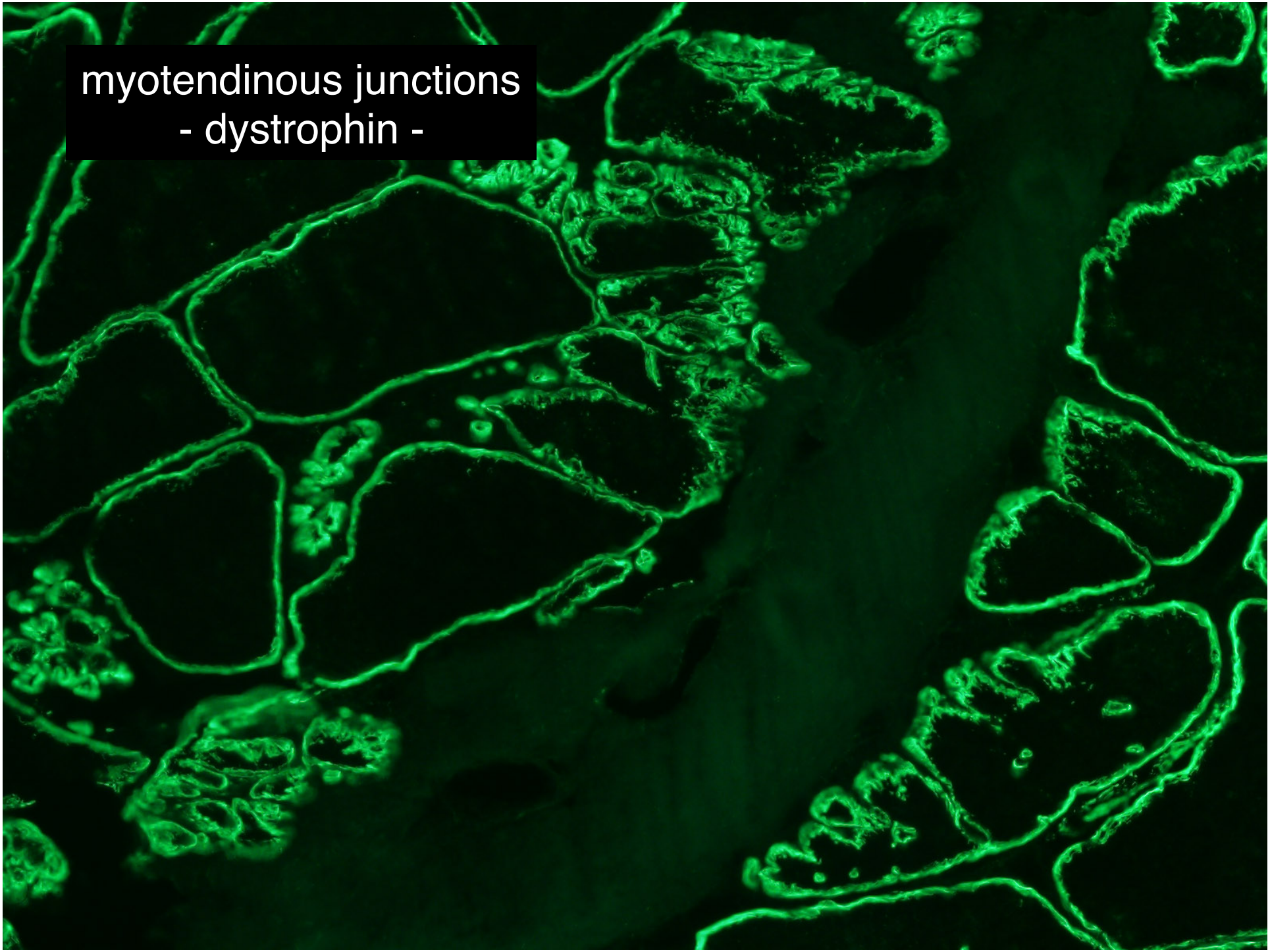


"One mighty slow fat red ox."
- Bob Schelper, circa 1984

normal structures or features that may be confused with pathology

- myotendinous junctions (tendons and fascia)
  - complex splitting and numerous internal nuclei
  - sometimes, cytoplasmic inclusion bodies
- terminal branches of intramuscular nerve twigs
- neuromuscular junctions
- muscle spindles
- muscle to muscle variations (not all muscles are created equal)
  - fiber type distribution
  - mitochondrial content (ragged-red fibers)
  - endomysial fibrous tissue


myotendinous junctions


myotendinous junctions
- dystrophin -

classic biomarkers of disease

neuropathic/neurogenic

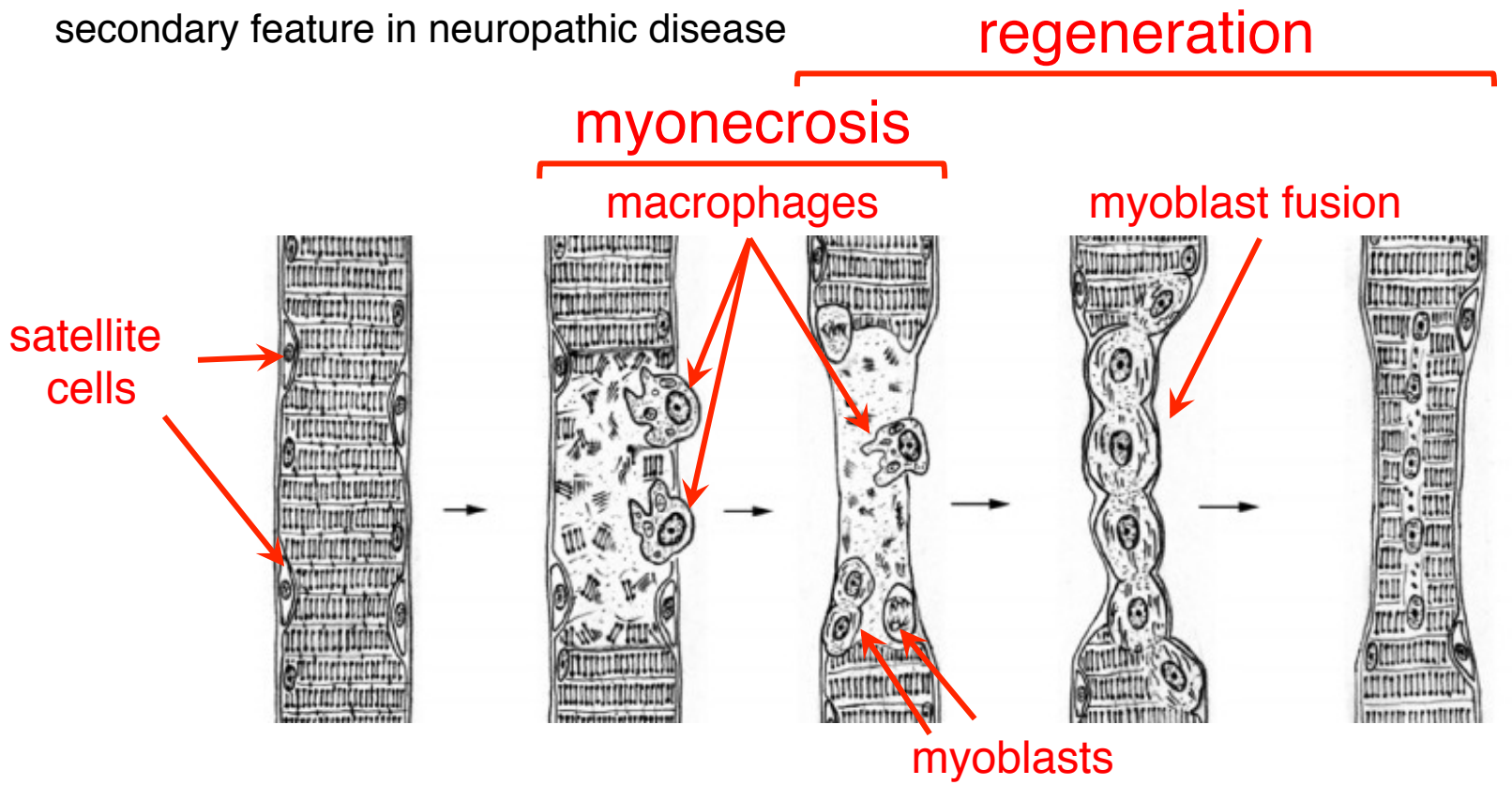
- atrophy and hypertrophy
  - motor unit distribution of angulated atrophic fibers
  - pyknotic nuclear clusters
  - SMA appearance
- fiber type grouping
- target fibers

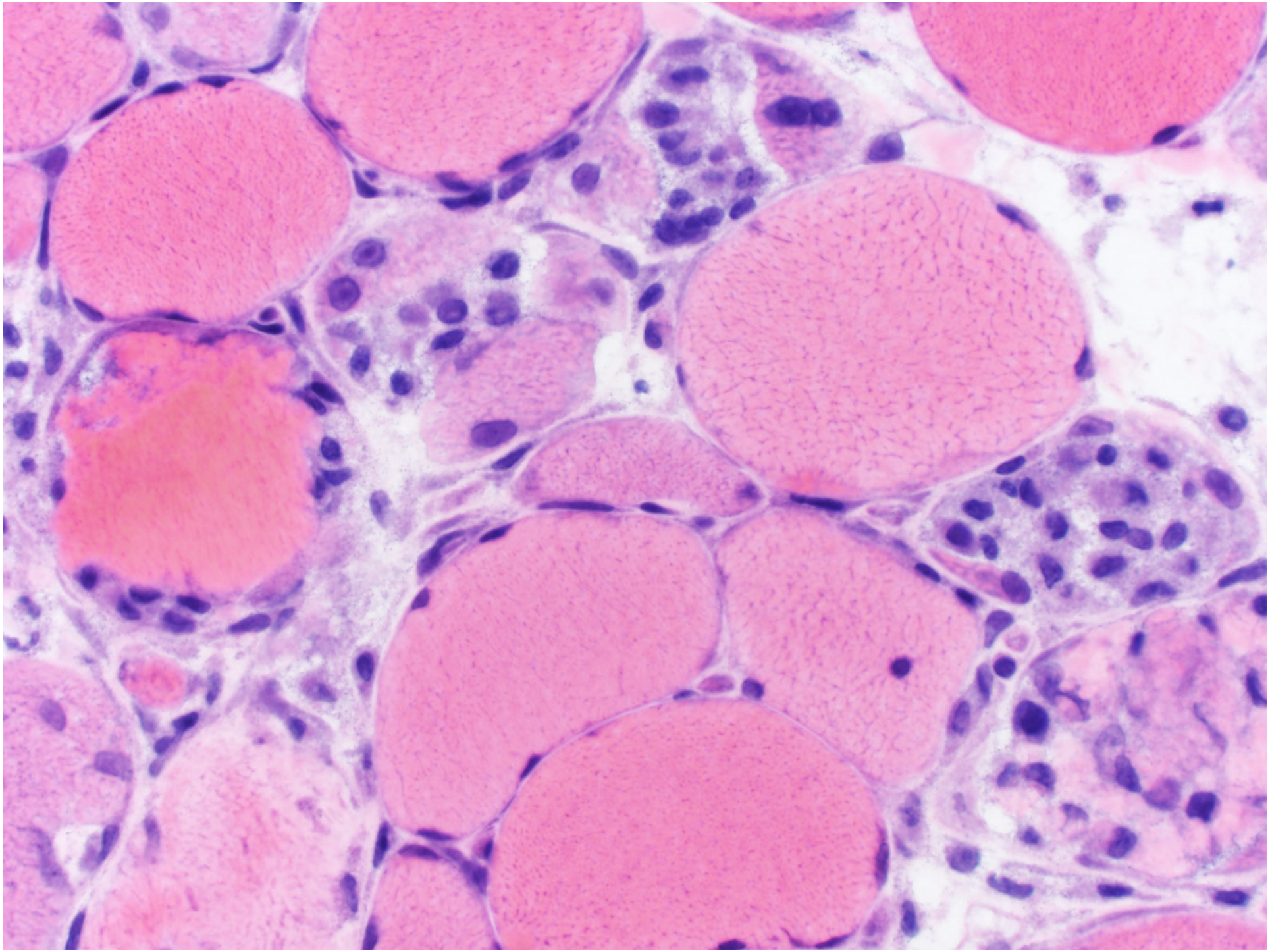
myopathic (partial list)

- atrophy and hypertrophy
  - usually scattered distribution
- fiber type predominance
- cores
- rods
- central nuclei
- internal nuclei with splits
- internalized capillaries
- ragged-red fibers, COX-negative fibers
- myonecrosis, regeneration
- autophagic vacuoles
- inflammatory cell infiltrates
- MHC class I expression
- complement C5b-9 deposition

myonecrosis and regeneration

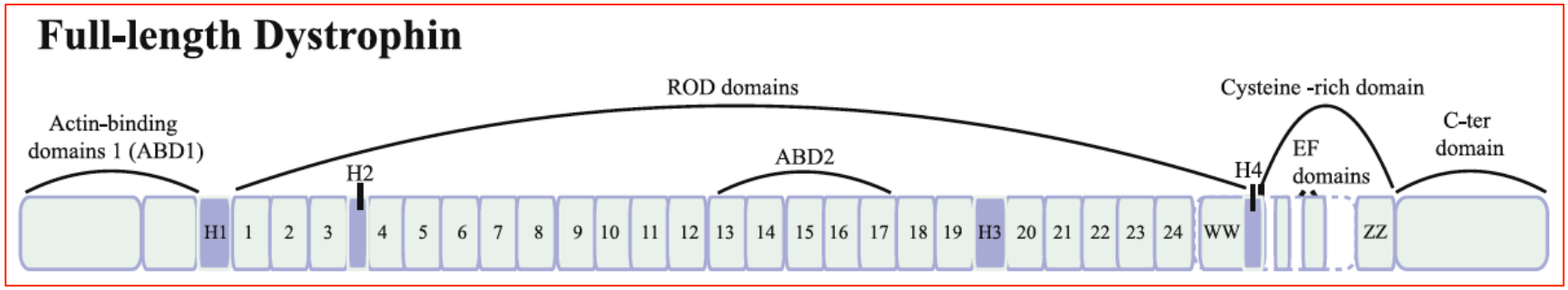
- muscular dystrophies – genetic (inherited)
- inflammatory myopathies – acquired
- toxic/metabolic – both
- secondary feature in neuropathic disease





Duchenne muscular dystrophy (DMD)

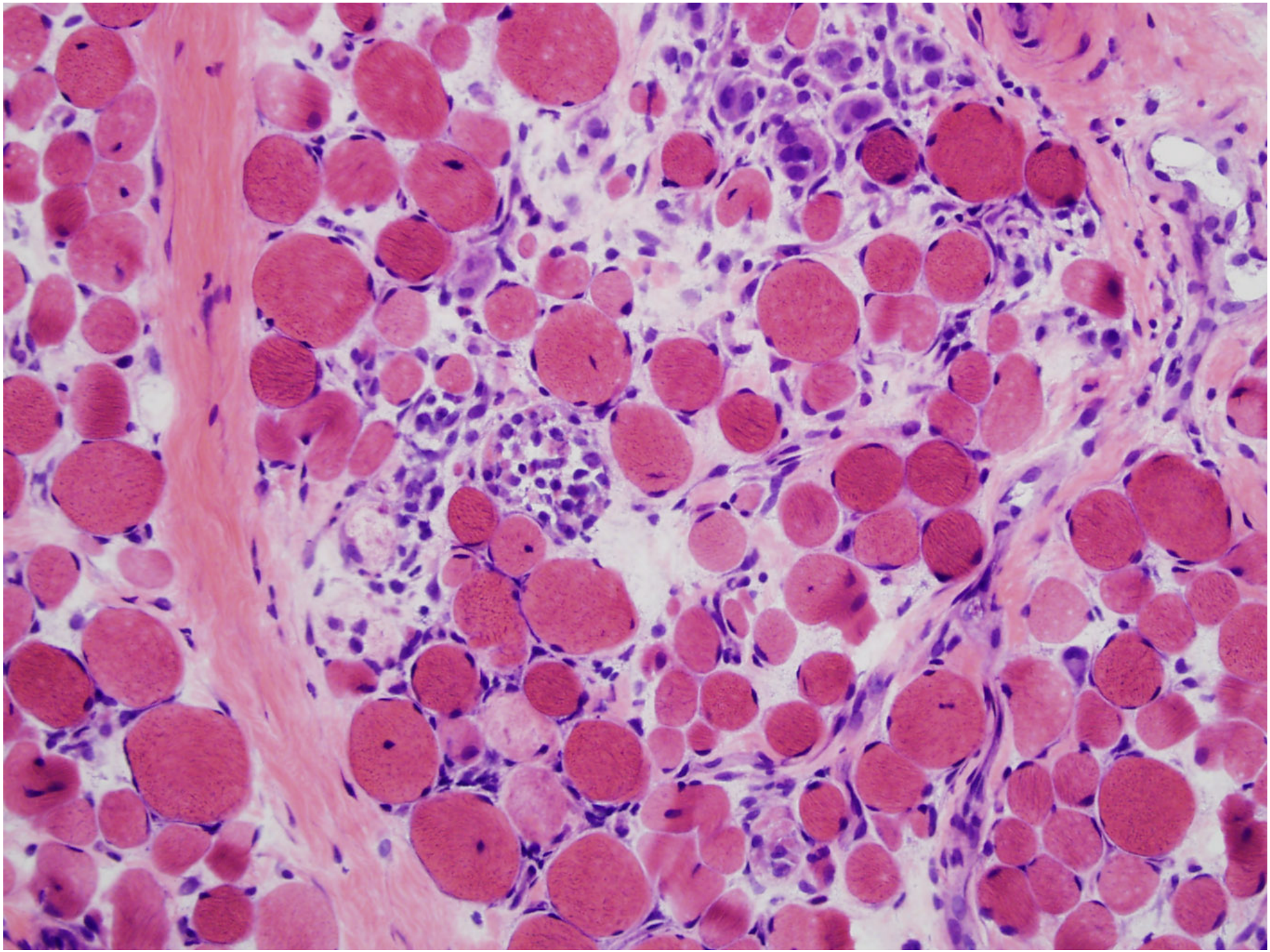
- X-linked recessive disorder
- incidence of ~1/5000 male births
- dystrophin gene (*DMD*) – 2.6 million bp
  - 79 coding exons; 14kb transcript
  - 427 kd dystrophin protein; subsarcolemmal location

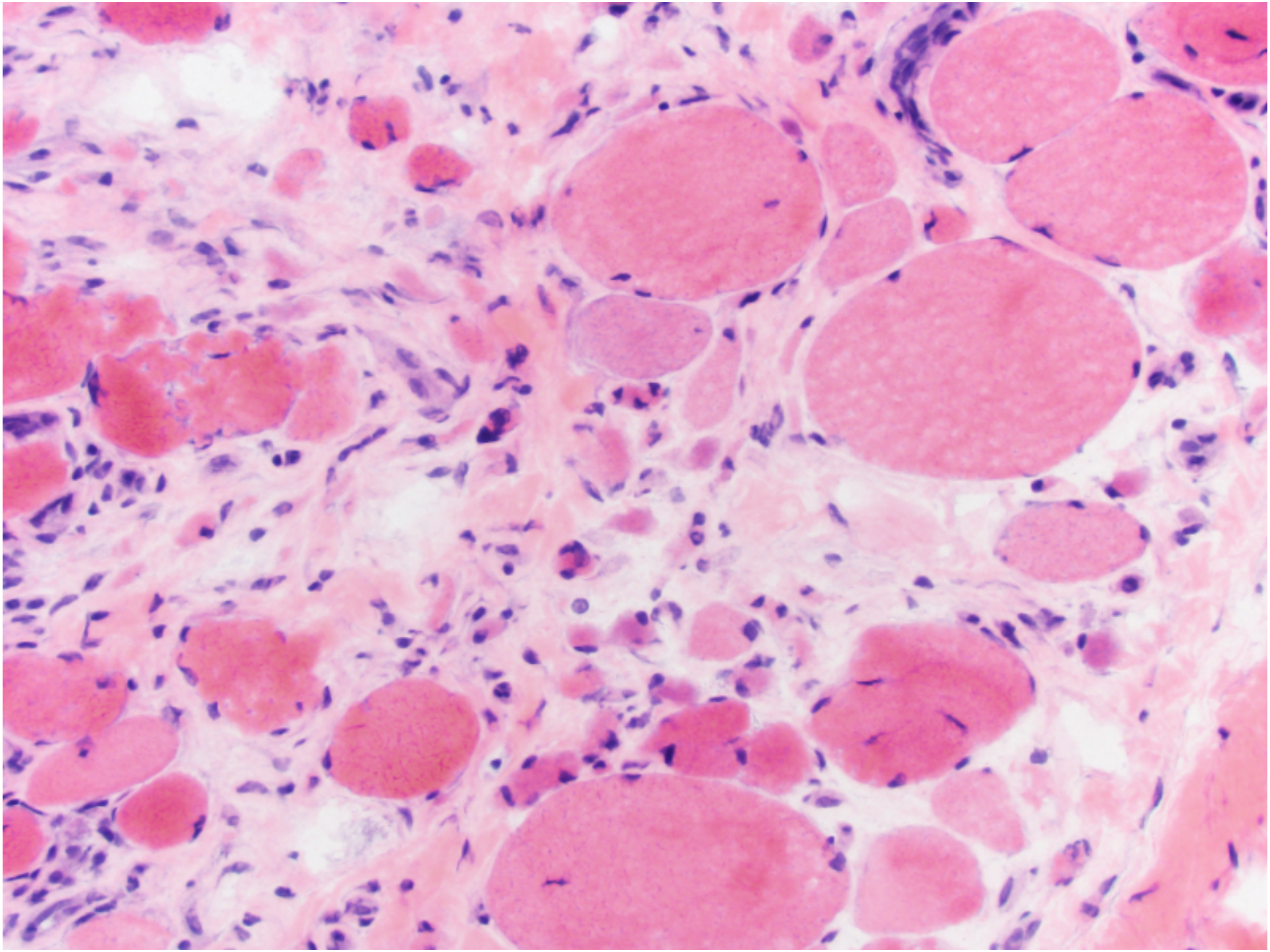


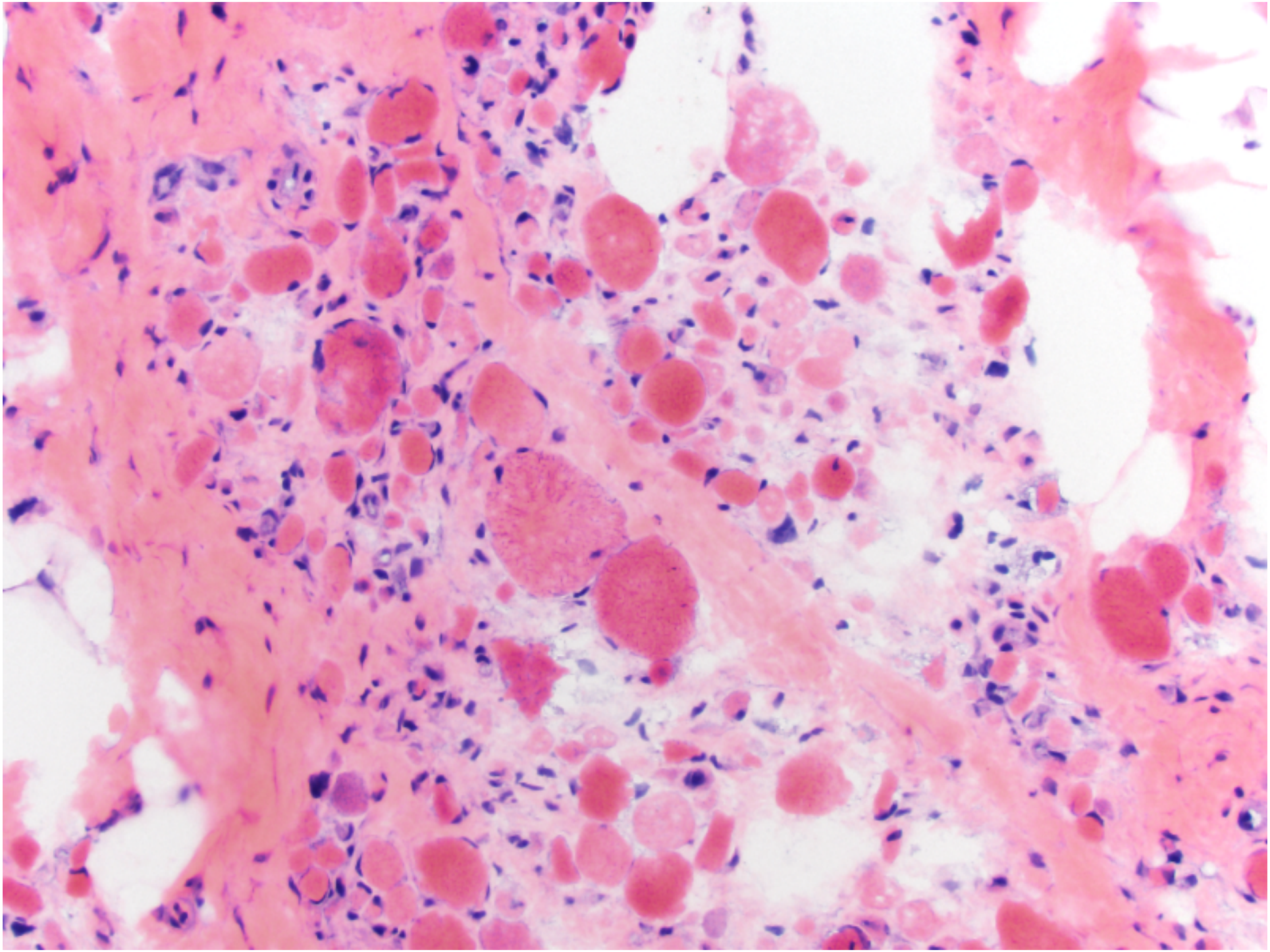
- Becker muscular dystrophy (BMD) – milder allelic variant of DMD
- female carriers, manifesting and non-manifesting
- collectively - dystrophinopathies

diagnostic approach for dystrophinopathies

- molecular genetics (>95% of patients)
  - deletion/duplication detection by targeted CGH array (~70% of mutations)
  - *DMD* gene sequencing (~25% more)
- muscle biopsy – dystrophic features
  - immunostaining
  - dystrophin western blots (select cases)



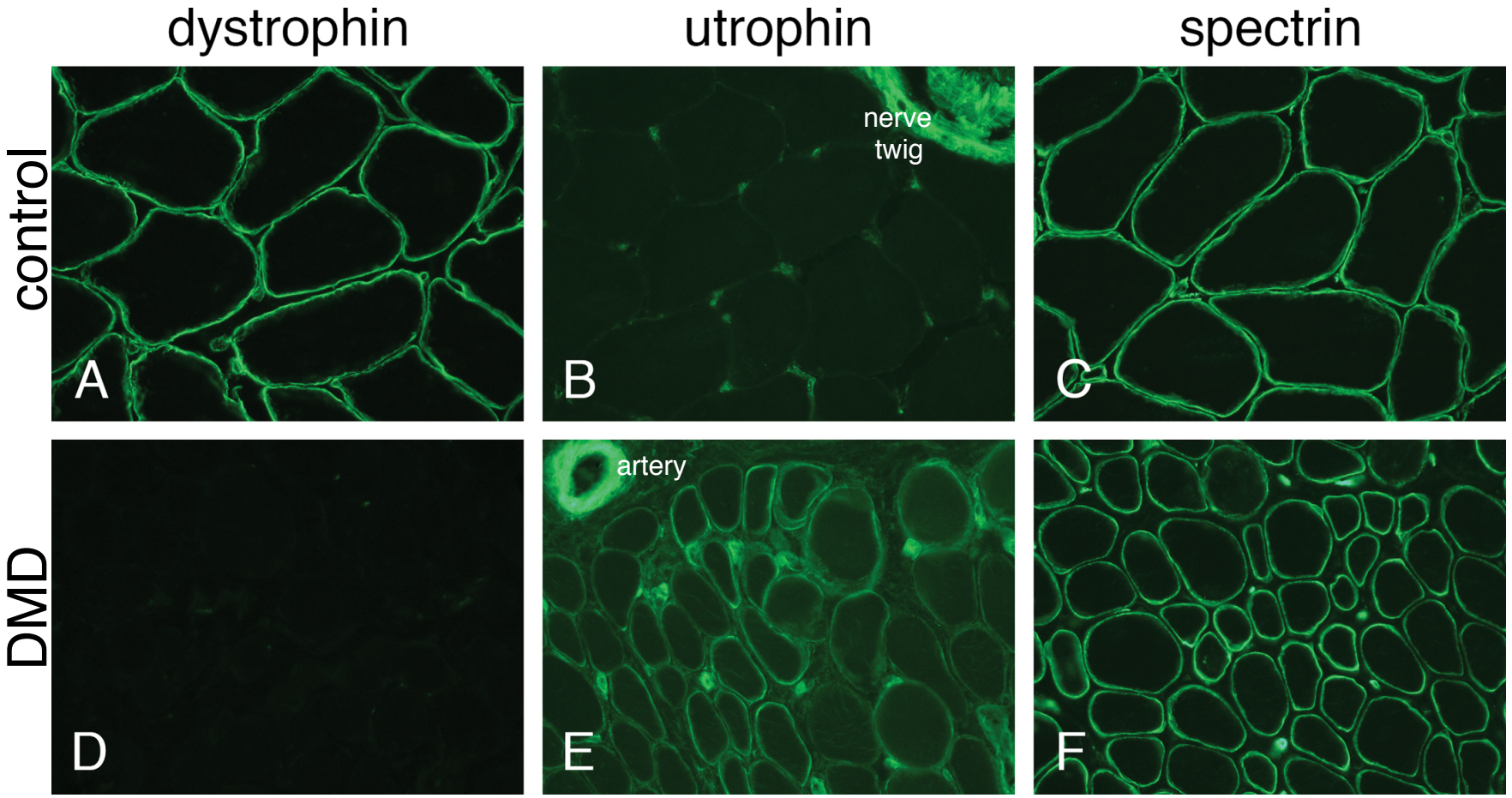




immunostaining approach to dystrophinopathies

- dystrophin (multiple antibodies)
  - carboxy terminus
  - rod domain (preferably, in frame deletion hot spots)
  - near amino terminus
- utrophin and spectrin
- dystrophin-glycoprotein complex (DGC)
  - nNOS (secondary absence or partial deficiency)
  - dystroglycans (secondary partial deficiency)
  - sarcoglycans (secondary partial deficiency)

immunostaining for diagnosis of DMD



loss of dystrophin

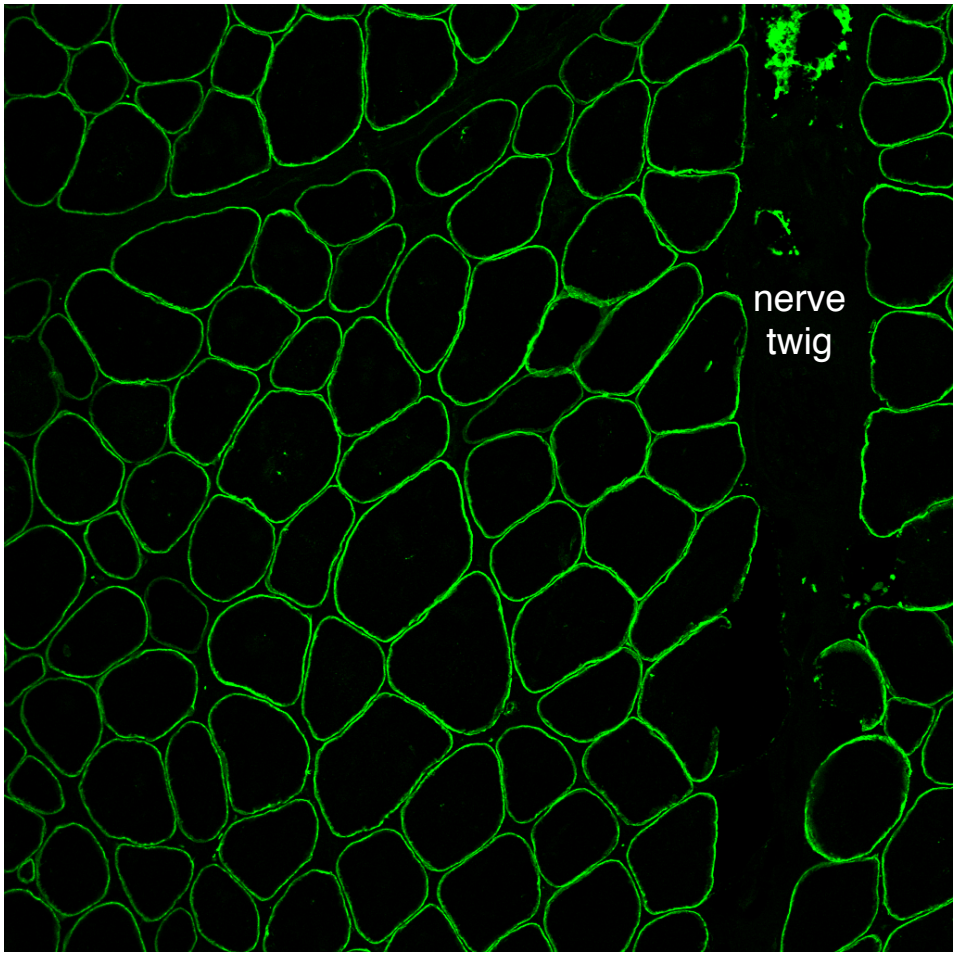
gain of utrophin

non-necrotic muscle fibers
in a non-degraded biopsy

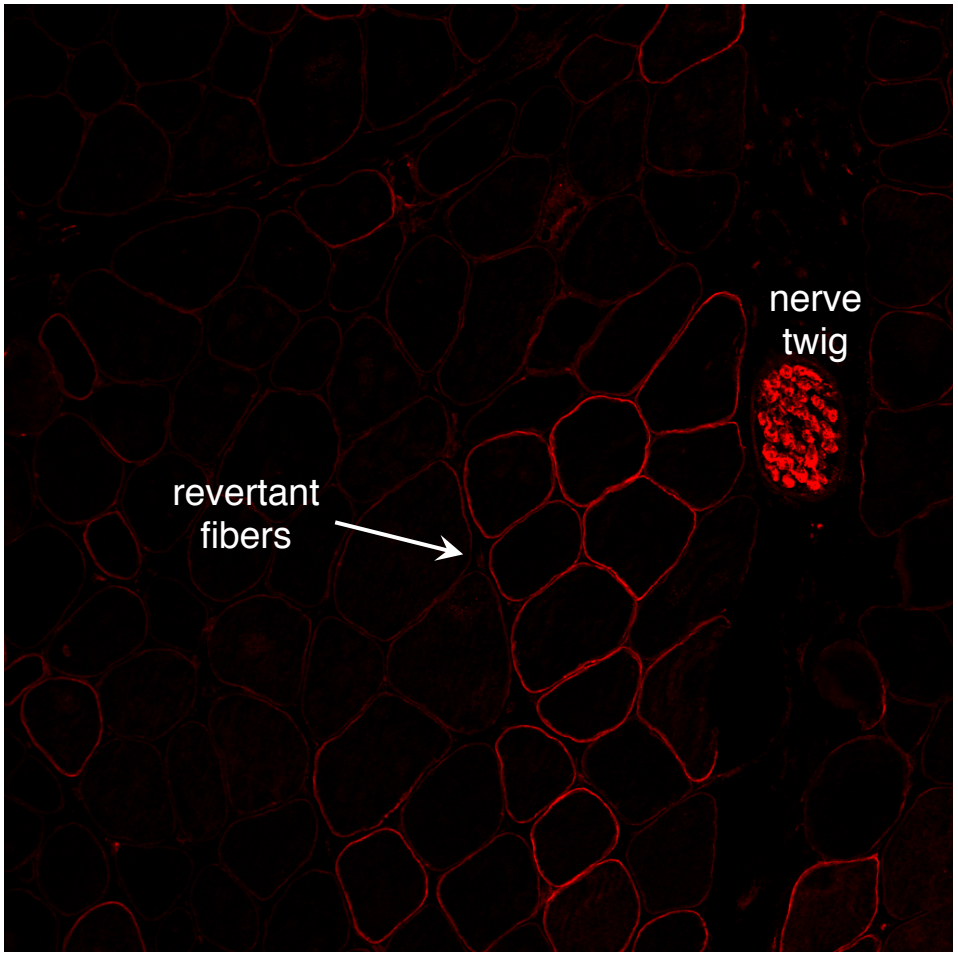
DMD muscle biopsy

dual label immunofluorescence
laser confocal microscopy

spectrin - monoclonal



dystrophin - polyclonal

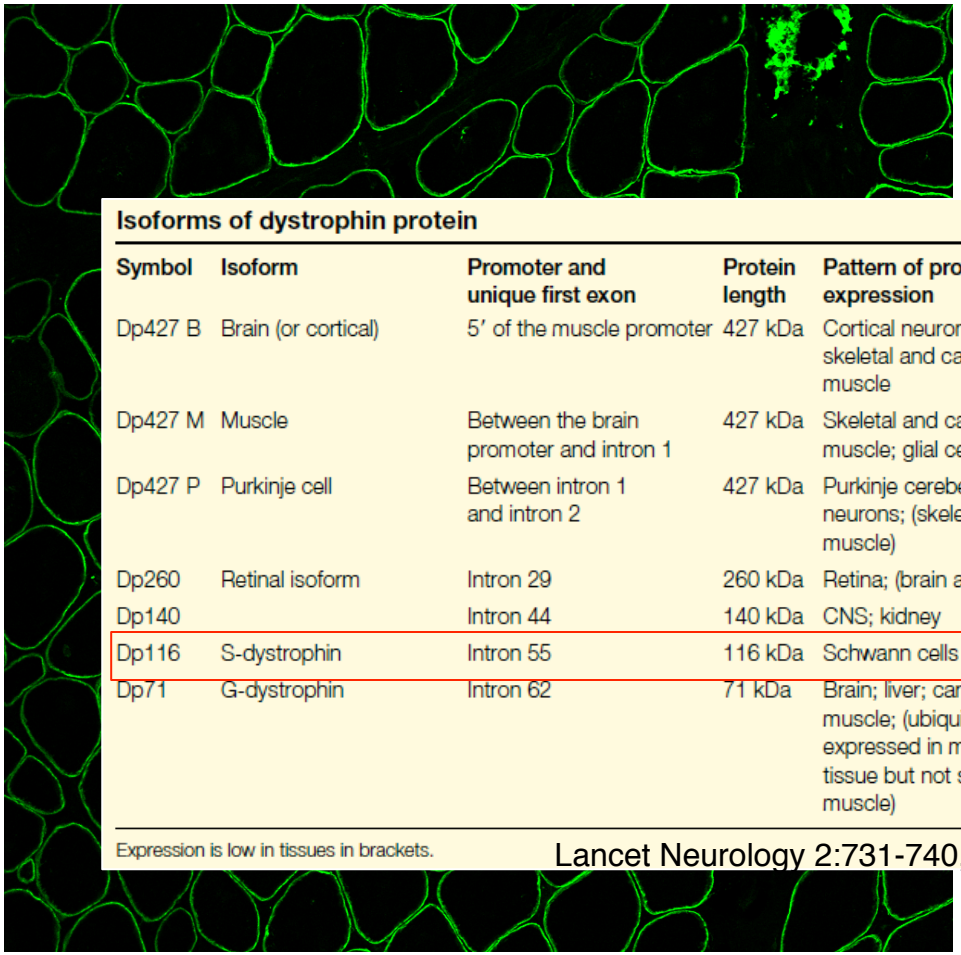


DMD muscle biopsy

dual label immunofluorescence
laser confocal microscopy

spectrin - monoclonal

dystrophin - polyclonal

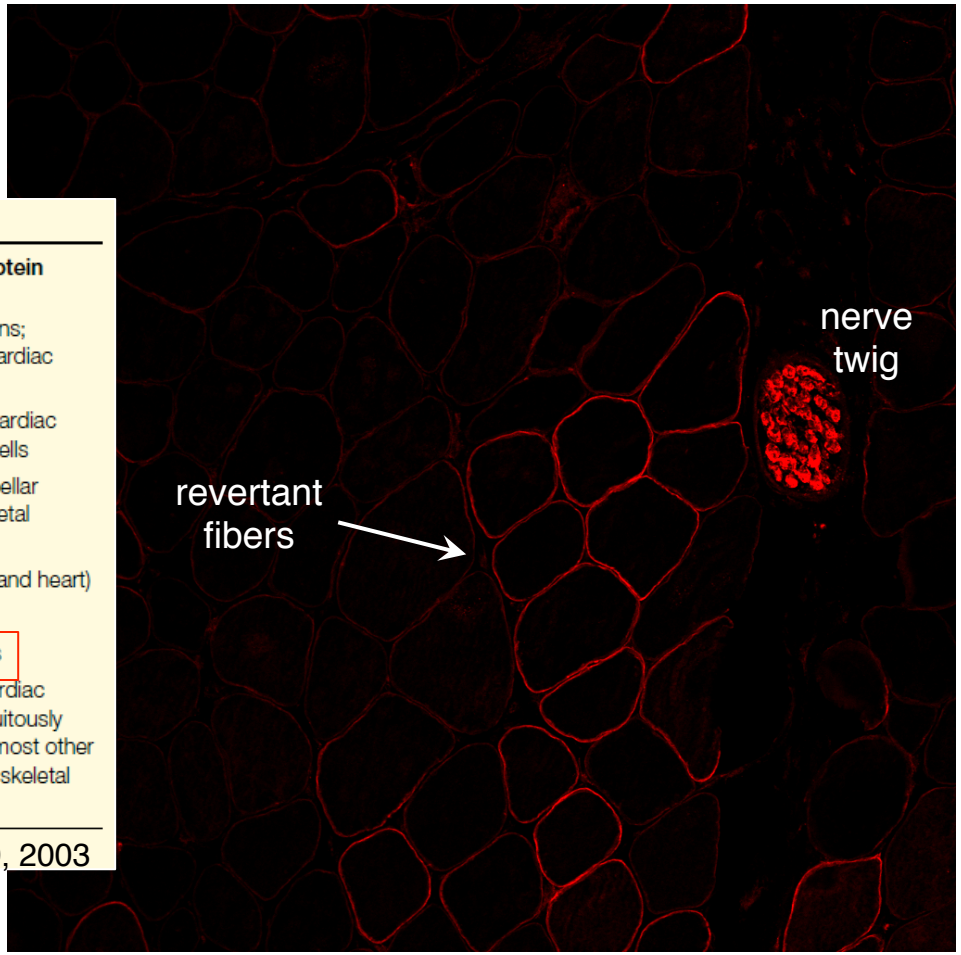


Isoforms of dystrophin protein

Symbol	Isoform	Promoter and unique first exon	Protein length	Pattern of protein expression
Dp427 B	Brain (or cortical)	5′ of the muscle promoter	427 kDa	Cortical neurons; skeletal and cardiac muscle
Dp427 M	Muscle	Between the brain promoter and intron 1	427 kDa	Skeletal and cardiac muscle; glial cells
Dp427 P	Purkinje cell	Between intron 1 and intron 2	427 kDa	Purkinje cerebellar neurons; (skeletal muscle)
Dp260	Retinal isoform	Intron 29	260 kDa	Retina; (brain and heart)
Dp140		Intron 44	140 kDa	CNS; kidney
Dp116	S-dystrophin	Intron 55	116 kDa	Schwann cells
Dp71	G-dystrophin	Intron 62	71 kDa	Brain; liver; cardiac muscle; (ubiquitously expressed in most other tissue but not skeletal muscle)

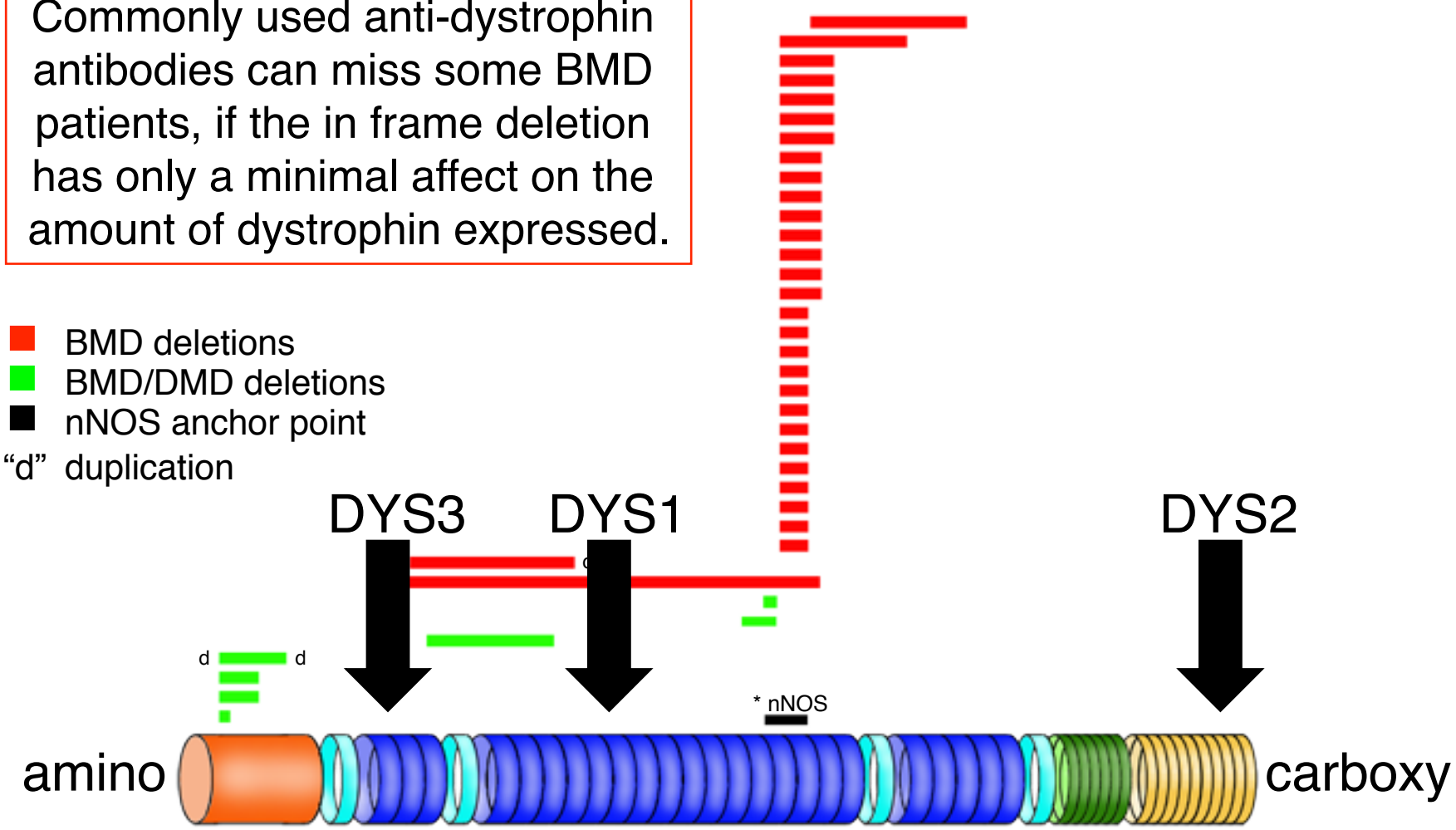
Expression is low in tissues in brackets.

Lancet Neurology 2:731-740, 2003



immunostaining for diagnosis of BMD

Commonly used anti-dystrophin antibodies can miss some BMD patients, if the in frame deletion has only a minimal affect on the amount of dystrophin expressed.



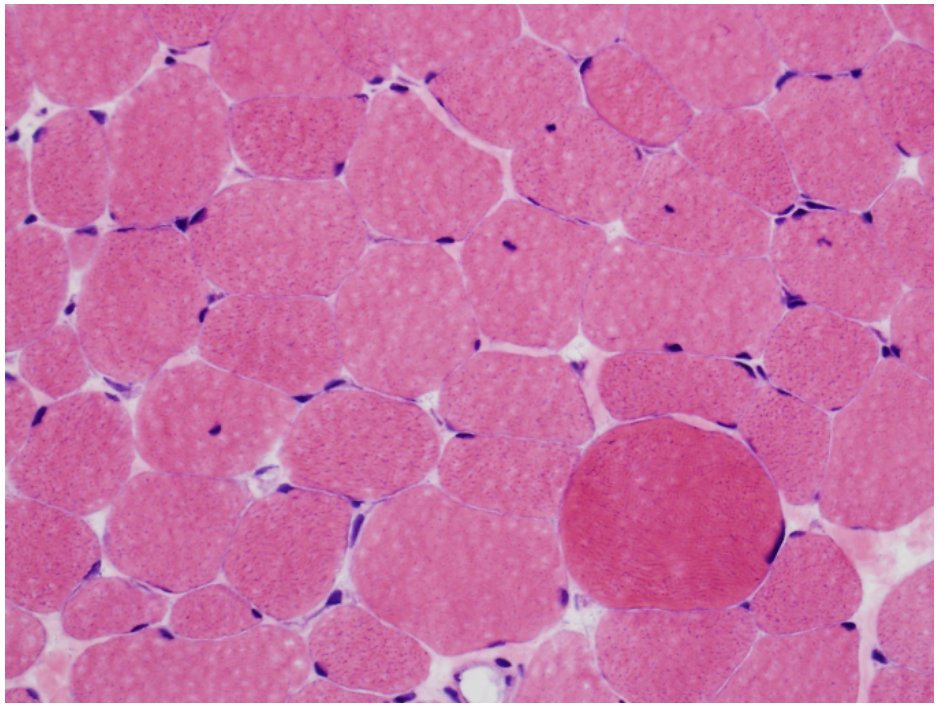
* nNOS anchor point Lai Y et al (2009) J Clin Invest 119:624

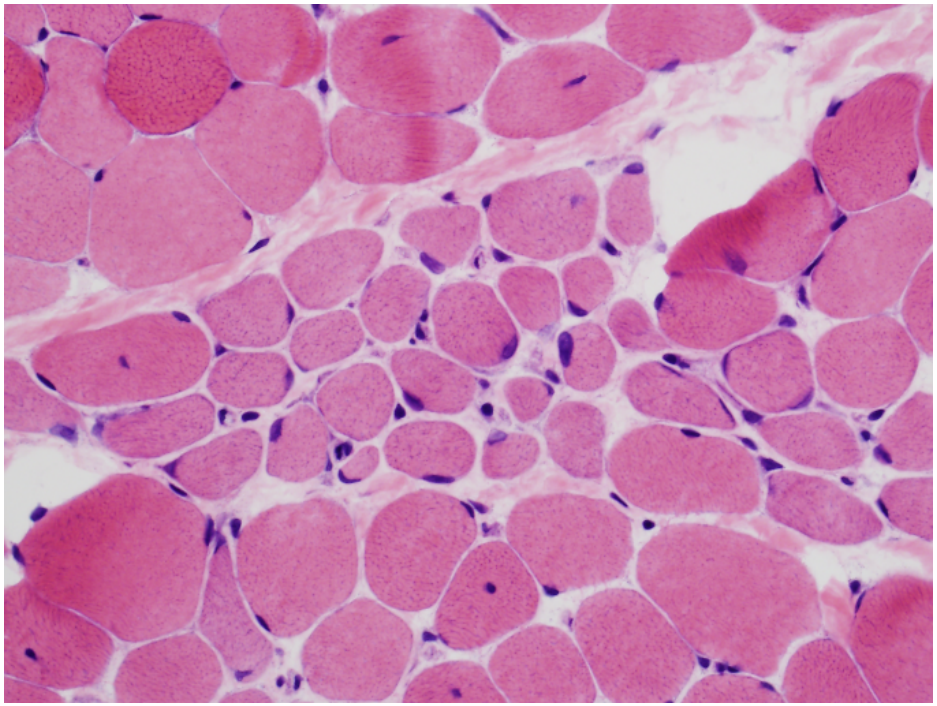
adapted from Anderson "Dystrophinopathies" (2002)

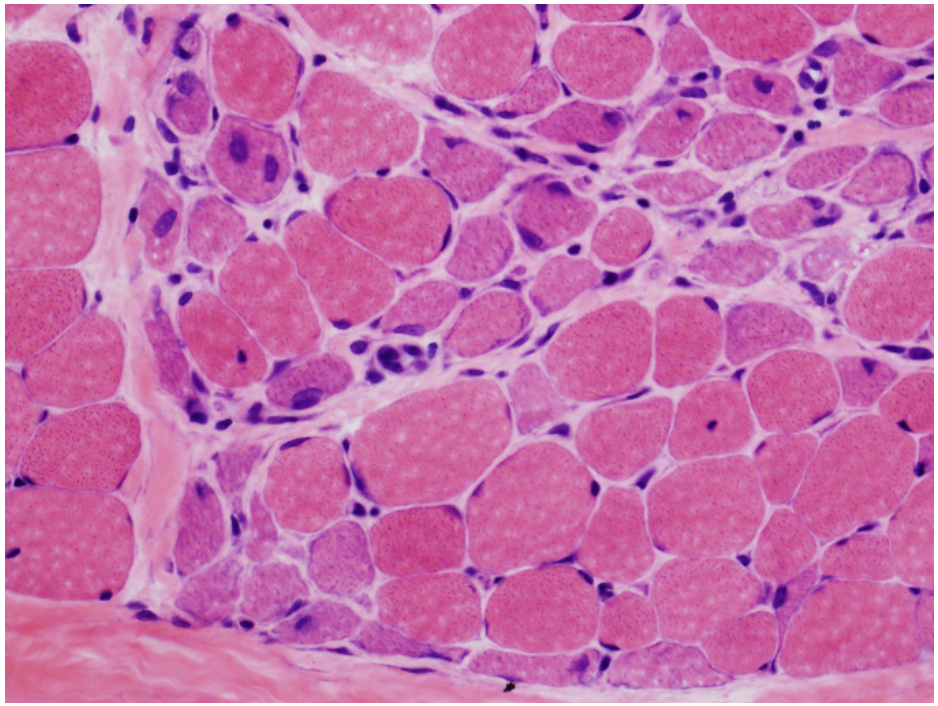
4 yo boy

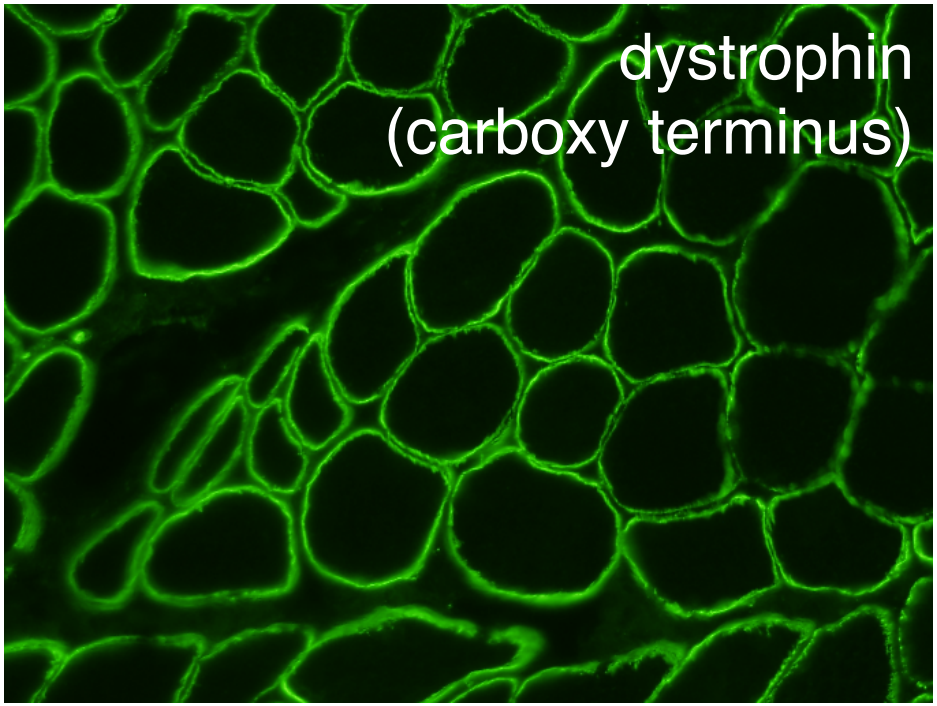
- Muscle pain and rhabdomyolysis
- CK persistently 3000, but with episodes as high as 60,000
- Seizures that are not controlled medically
- Muscle biopsy for diagnosis

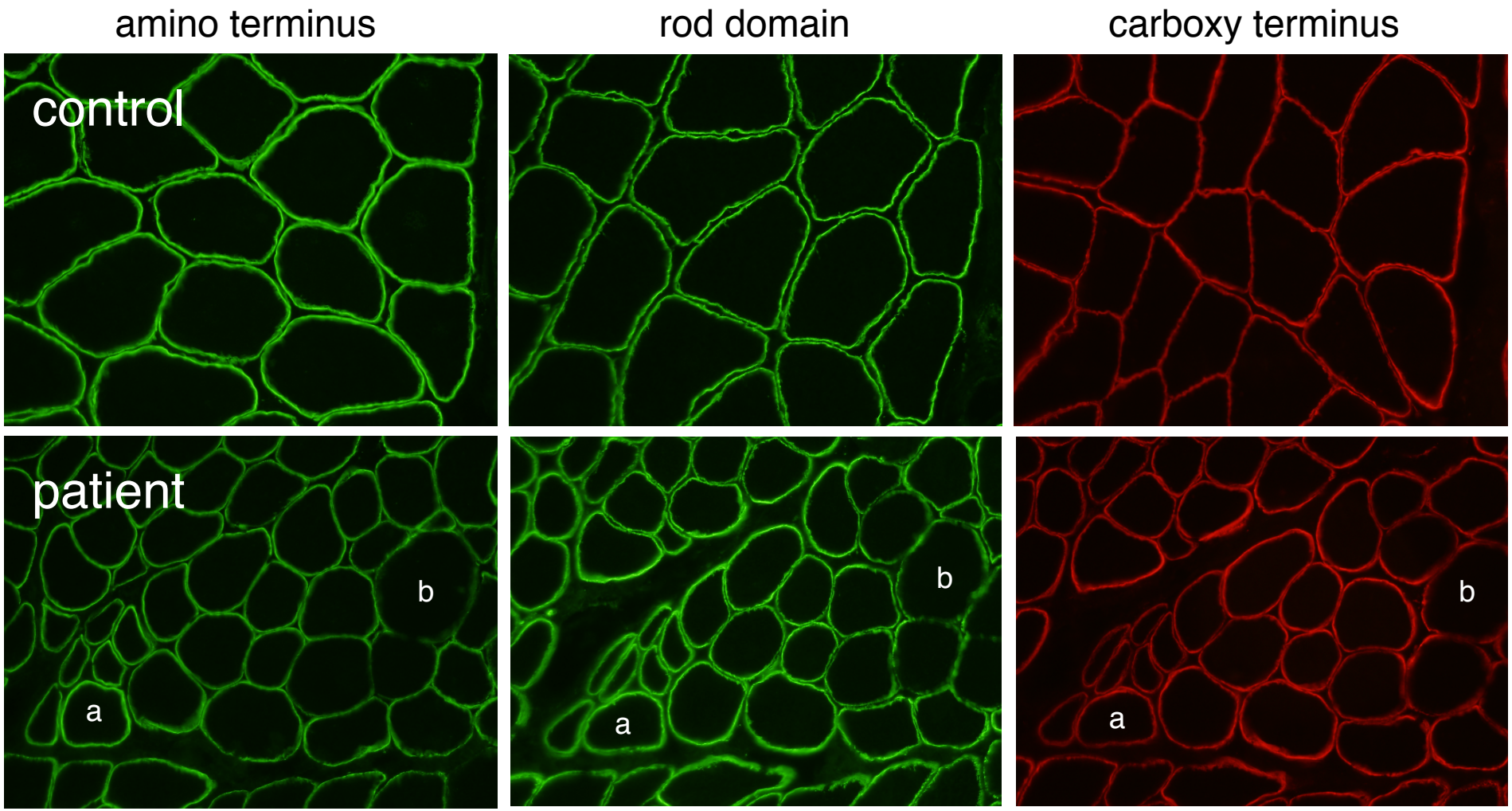
Duh moment!

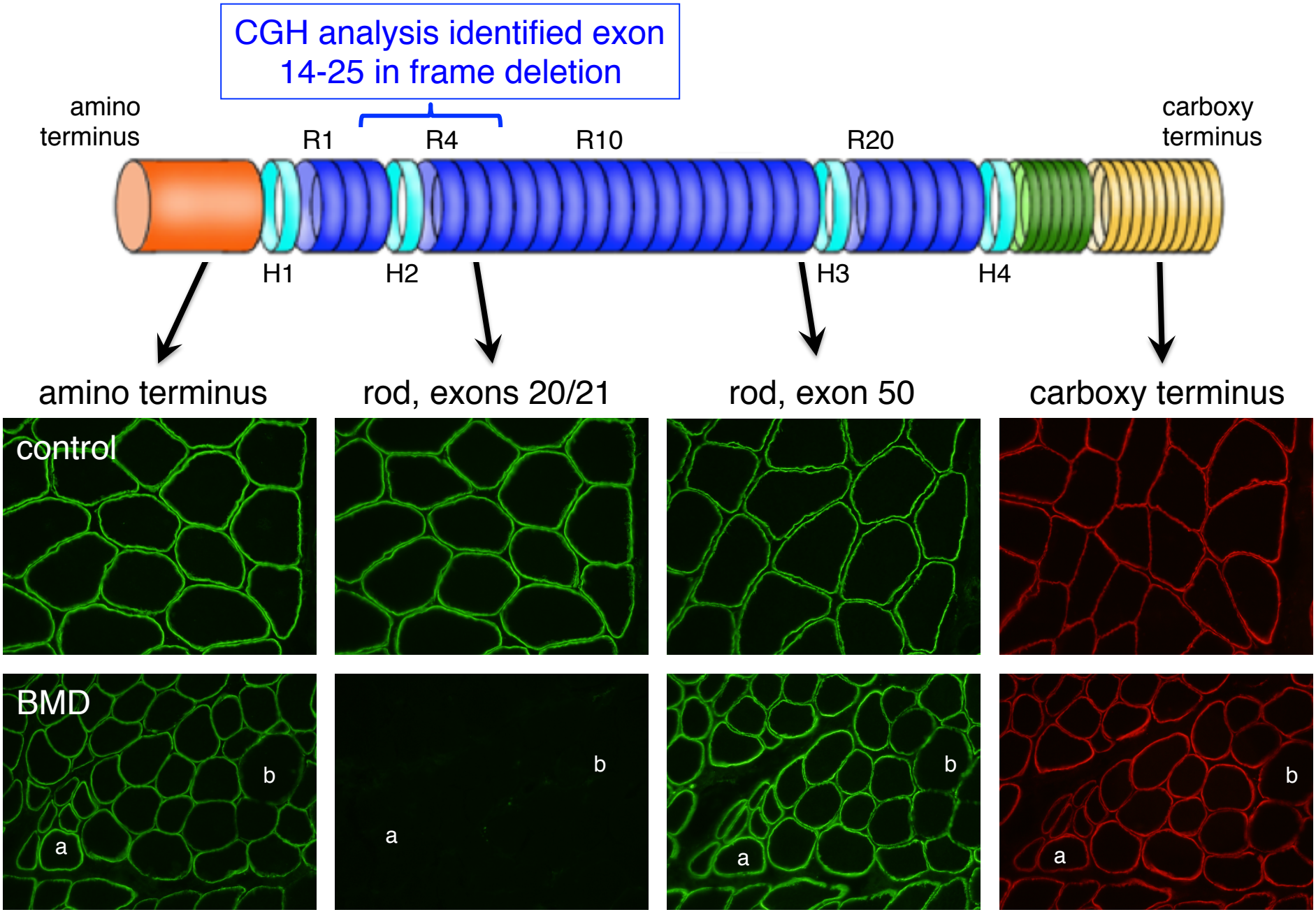







dystrophin
(carboxy terminus)


amino terminus
rod domain
carboxy terminus
control
patient
a
b
a
b
a
b


CGH analysis identified exon
14-25 in frame deletion
amino
terminus
carboxy
terminus
R1
R4
R10
R20
H1
H2
H3
H4
amino terminus
rod, exons 20/21
rod, exon 50
carboxy terminus
control
BMD
a
b

French study of 2400 dystrophinopathy patients - BMD deletions

BMD patients	
5′ hot spot	3′ hot spot
del 3–7 (× 19)	del 45–47 (× 131)
del 3–4 (× 16)	del 45–48 (× 97)
	del 45–55 (× 35)
	del 45–53 (× 31)
	del 45–49 (× 27)
	del 48–49 (× 23)
	del 48 (× 16)
	del 45–51 (× 10)

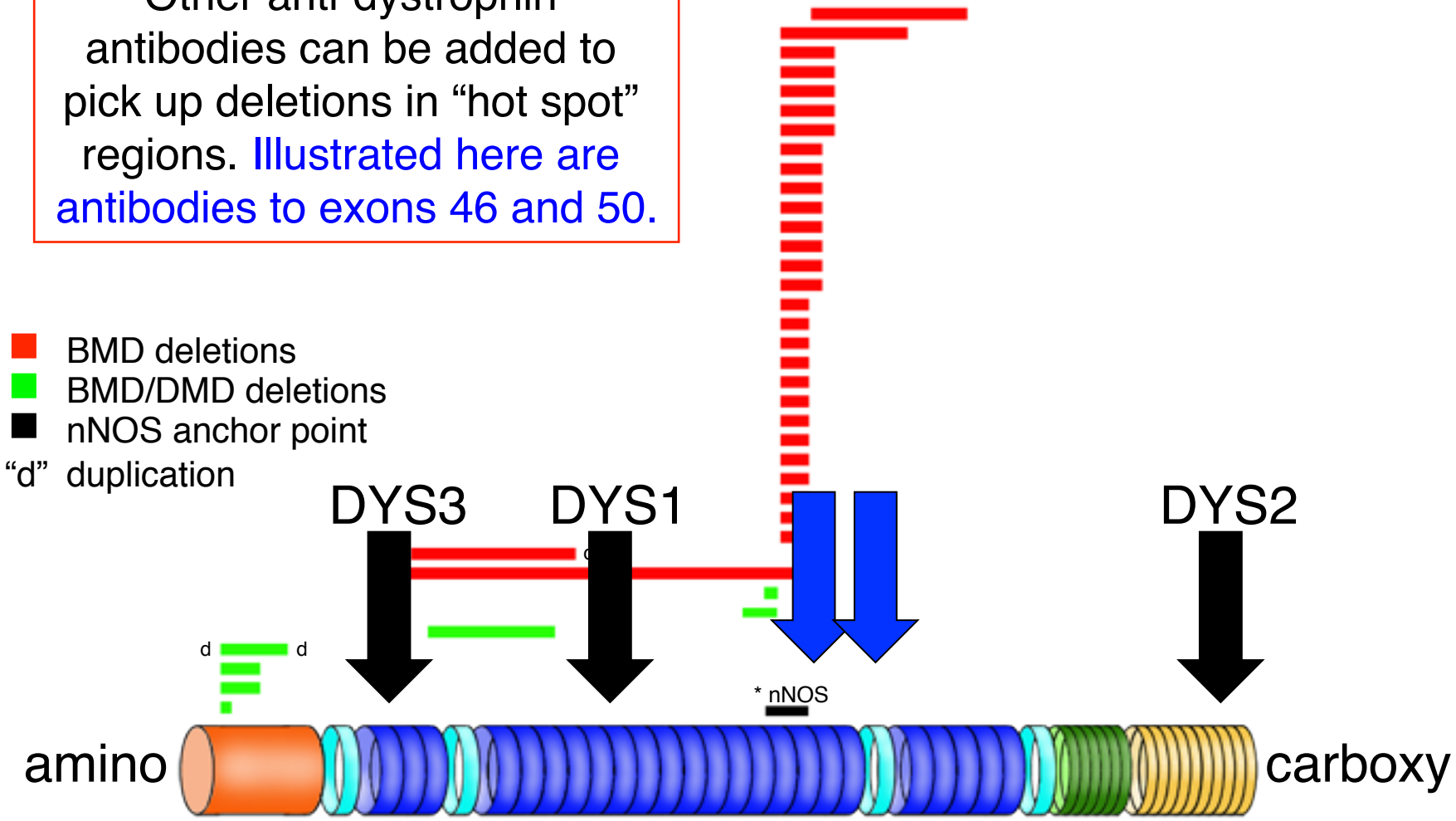
Unless dystrophin is significantly reduced, DYS1, DYS2, and DYS3 miss all of these in frame deletions.

exon 46 or exon 50 antibodies detect 87% of hot spot deletions

data from Table 1
Hum Mut 30:394-945, 2009

immunostaining for diagnosis of BMD

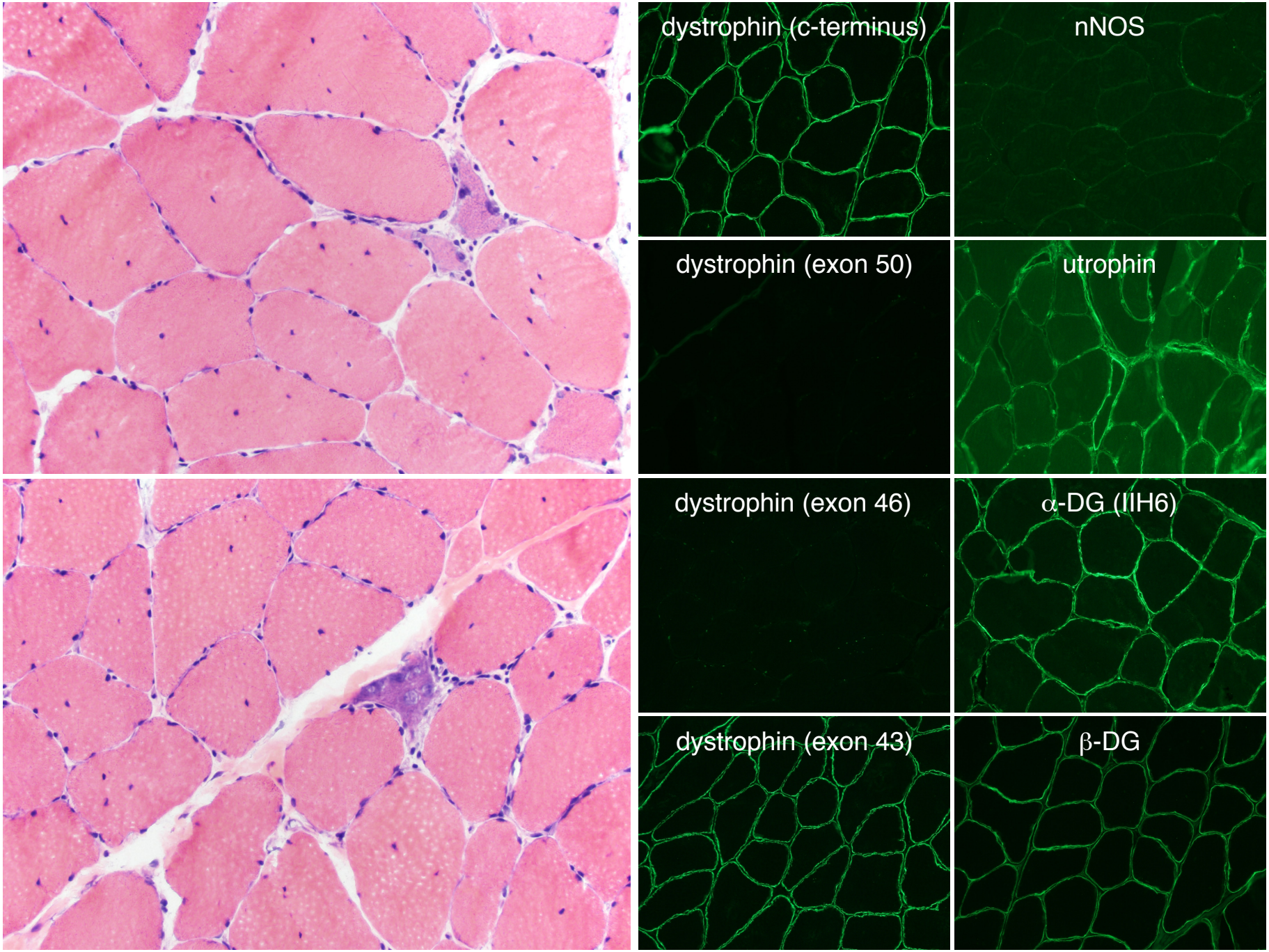
Other anti-dystrophin antibodies can be added to pick up deletions in “hot spot” regions. Illustrated here are antibodies to exons 46 and 50.



* nNOS anchor point Lai Y et al (2009) J Clin Invest 119:624

adapted from Anderson “Dystrophinopathies” (2002)

42 year old BMD patient with hot spot in frame *DMD* deletion



muscle biopsies evaluated at Iowa:
20-year period from May 1998 through May 2018

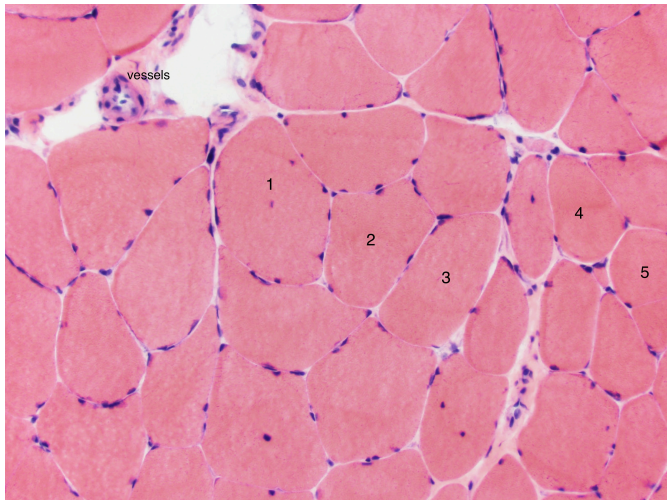
years	total muscle biopsies	male dystrophinopathy cases	**female dystrophinopathy cases**	total dystrophinopathy cases	% of total that are dystrophinopathy cases	% of dystrophinopathy cases that are female carriers
1998-2002	957	64	**6**	70	7.3%	9.4%
2003-2007	1465	59	**4**	63	4.3%	6.8%
2008-2012	2057	57	**5**	62	3.0%	8.8%
2013-2018	1780	63	**8**	71	4.0%	12.7%
1998-2018	**6259**	**243**	**23***	**266**	**4.2%**	**9.5%**

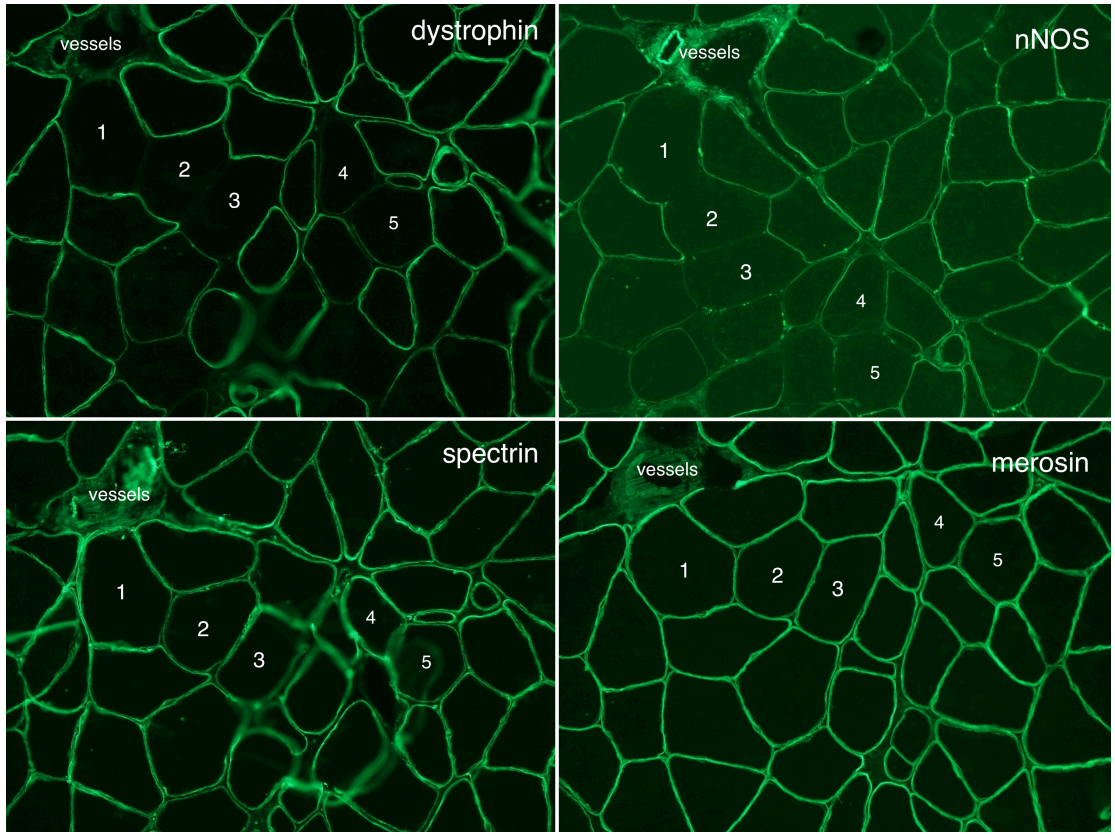
* Female dystrophinopathy cases evaluated between May 1998 and May 2018.

Dystrophinopathy cases are 4.2% of all biopsies.
DMD carriers are 9.5% of all dystrophinopathies.

immunostaining for diagnosis of carriers

loss of dystrophin and nNOS



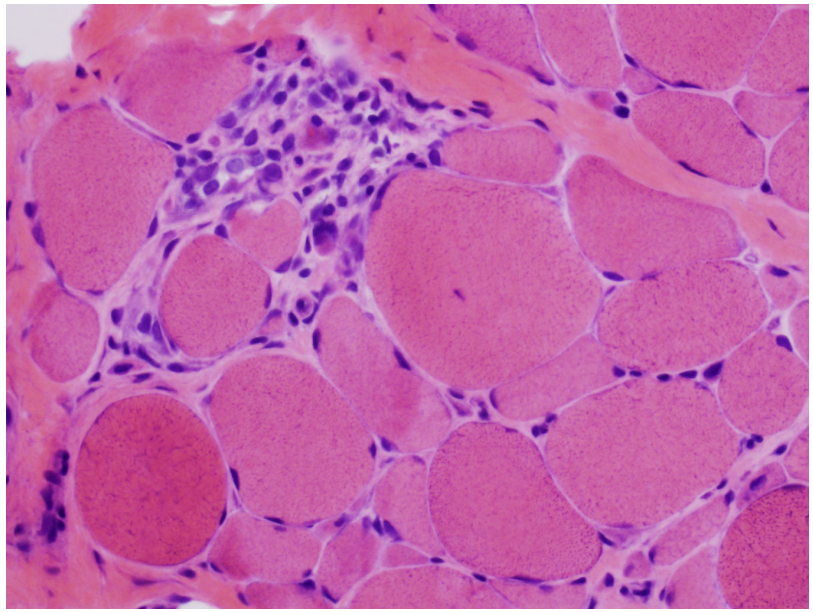


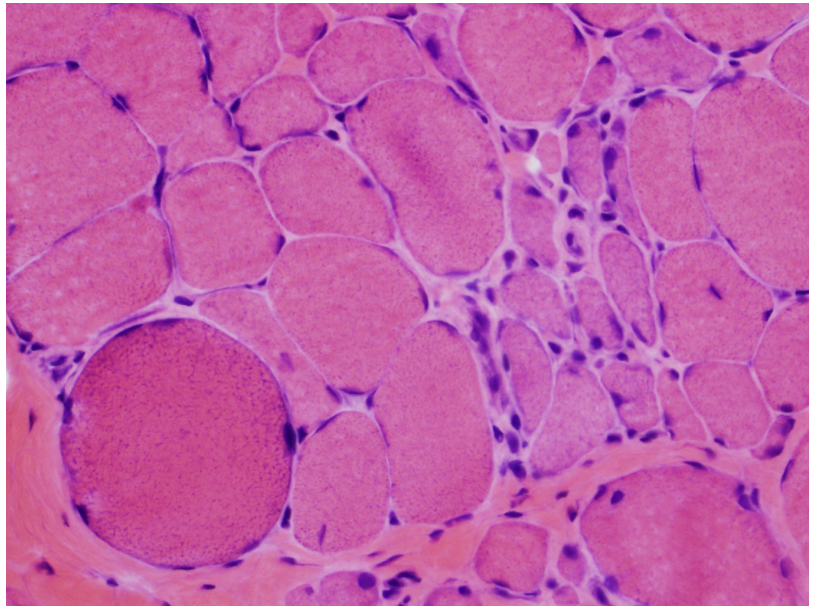
dystrophin-negative, non-necrotic muscle fibers

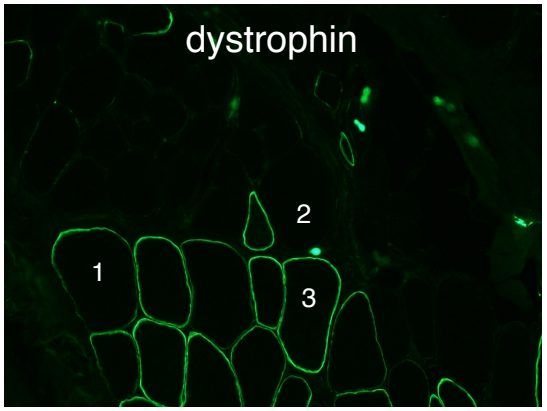
9 yo female

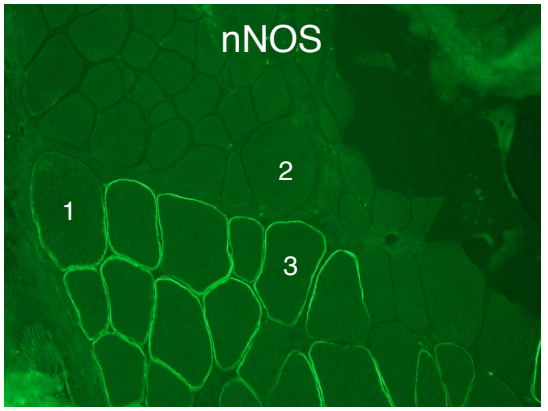
- proximal weakness and positive Gowers
- CK 19,000 to 24,000
- mother and brother with large calves

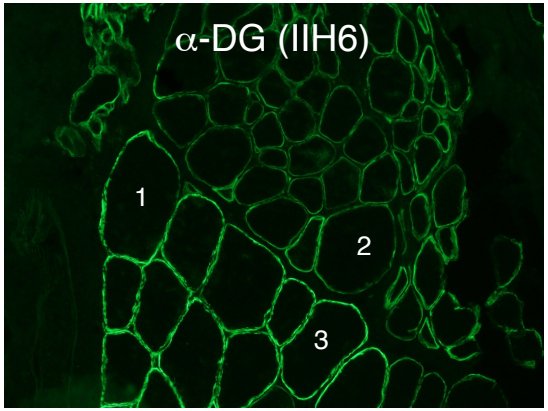
9 year old, probable manifesting *DMD* female carrier

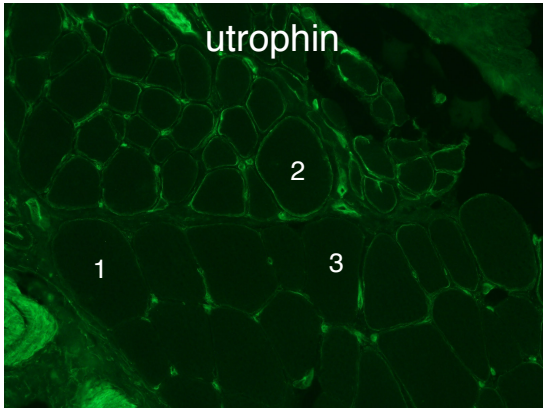


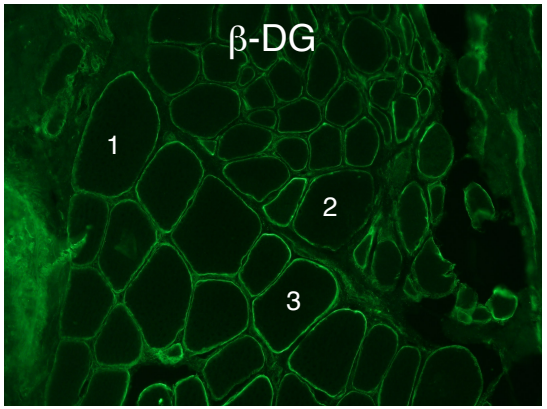


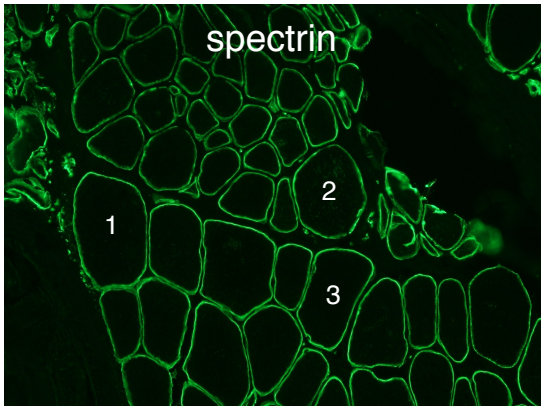


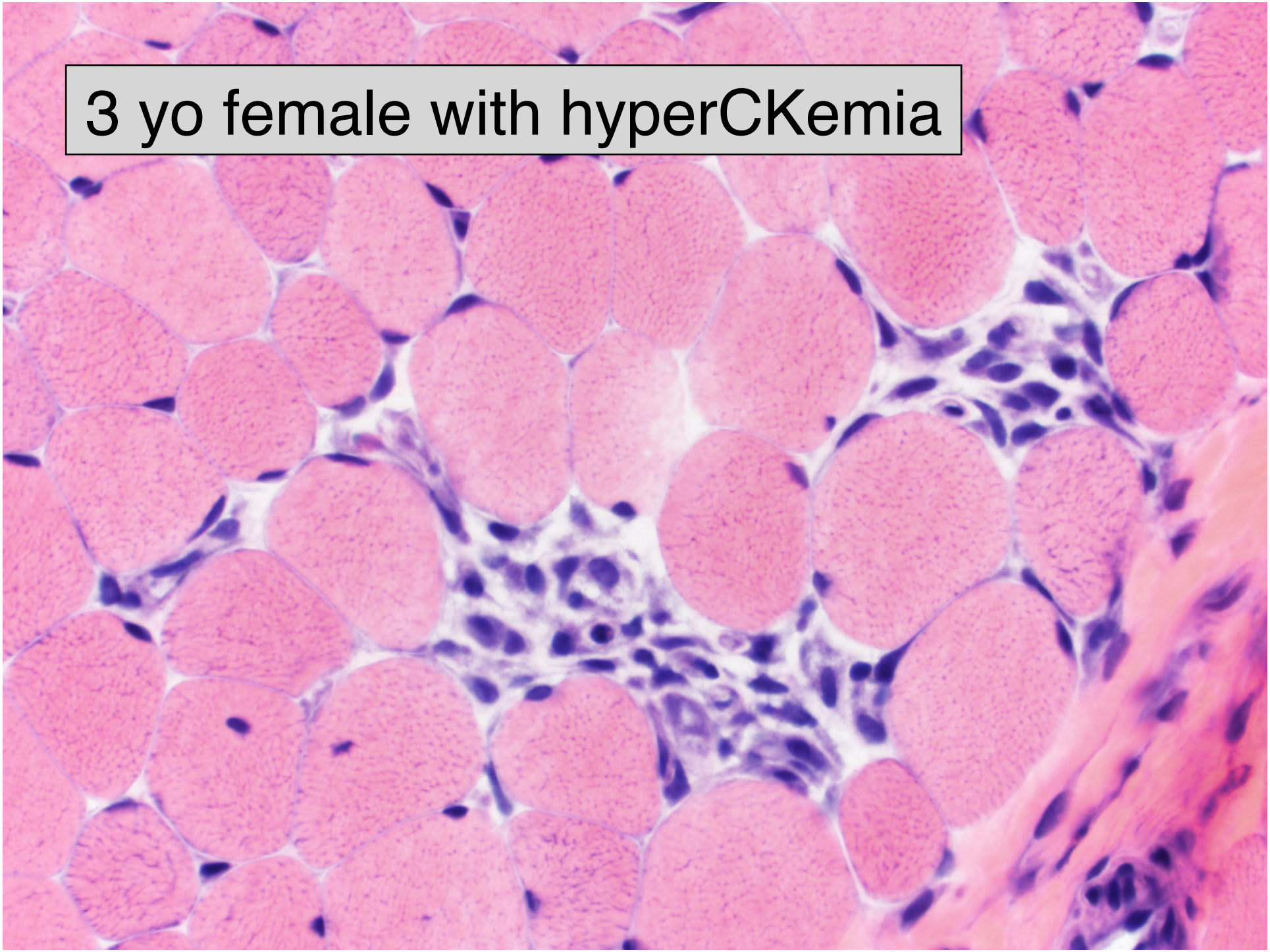




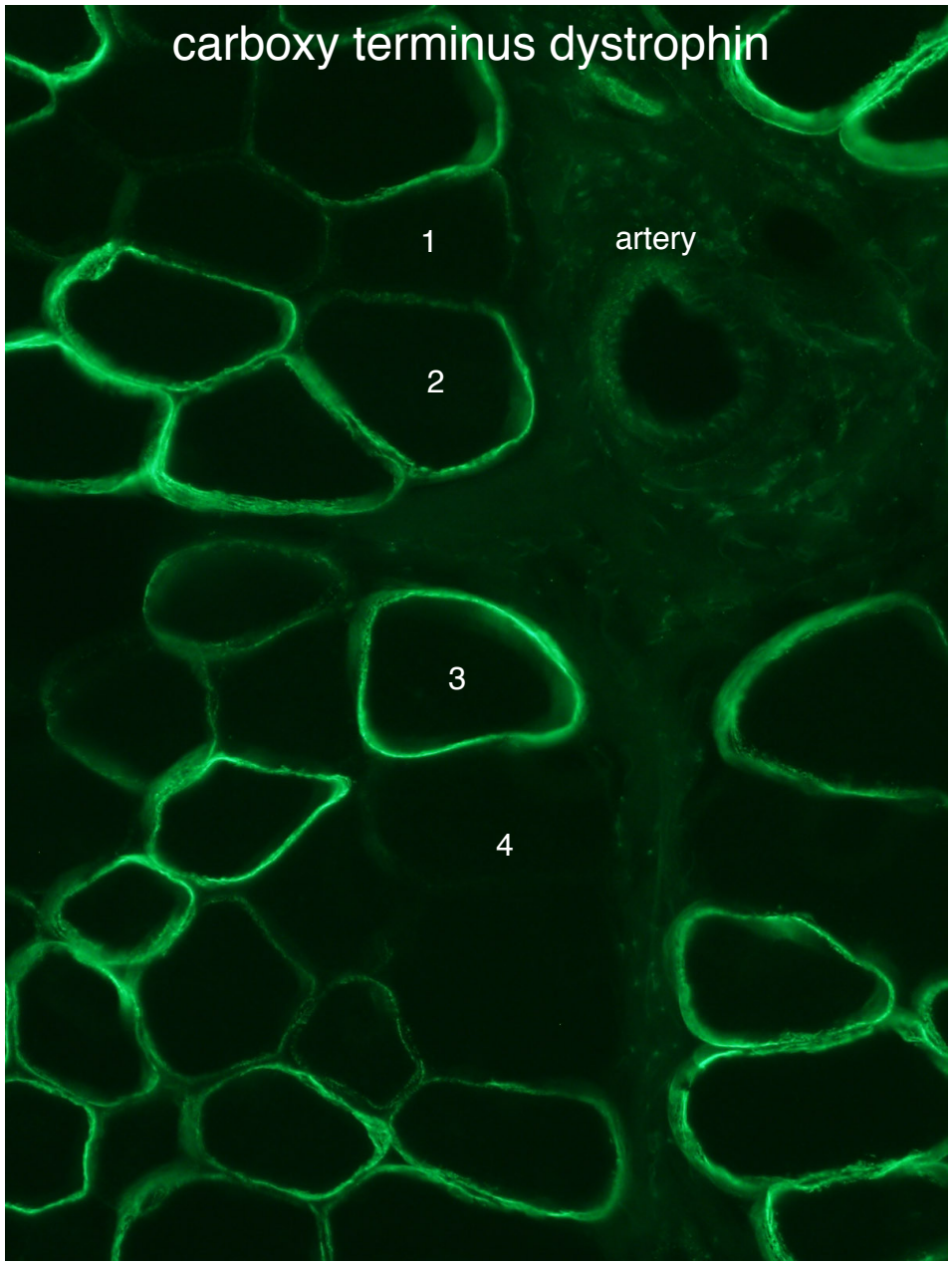


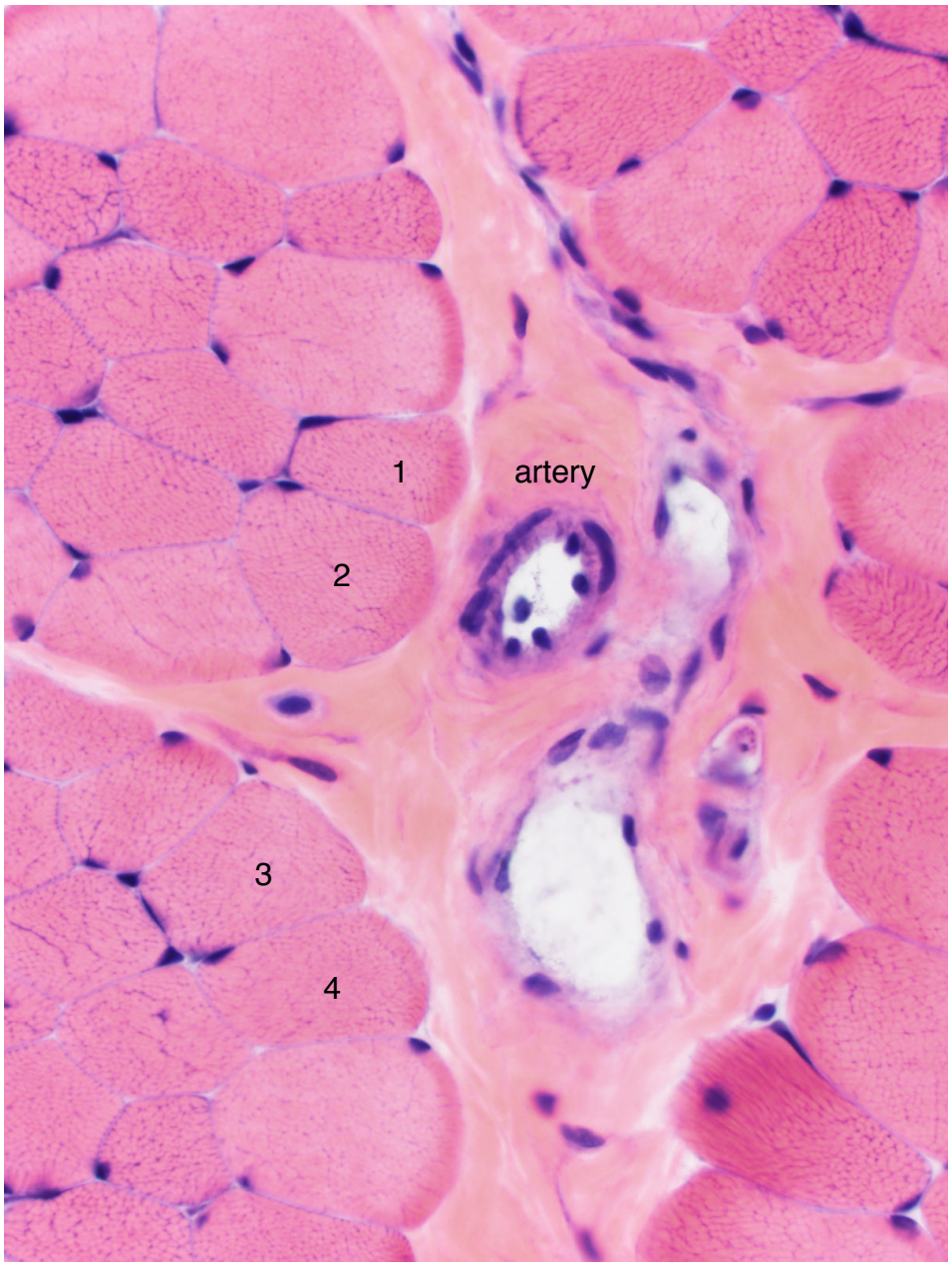




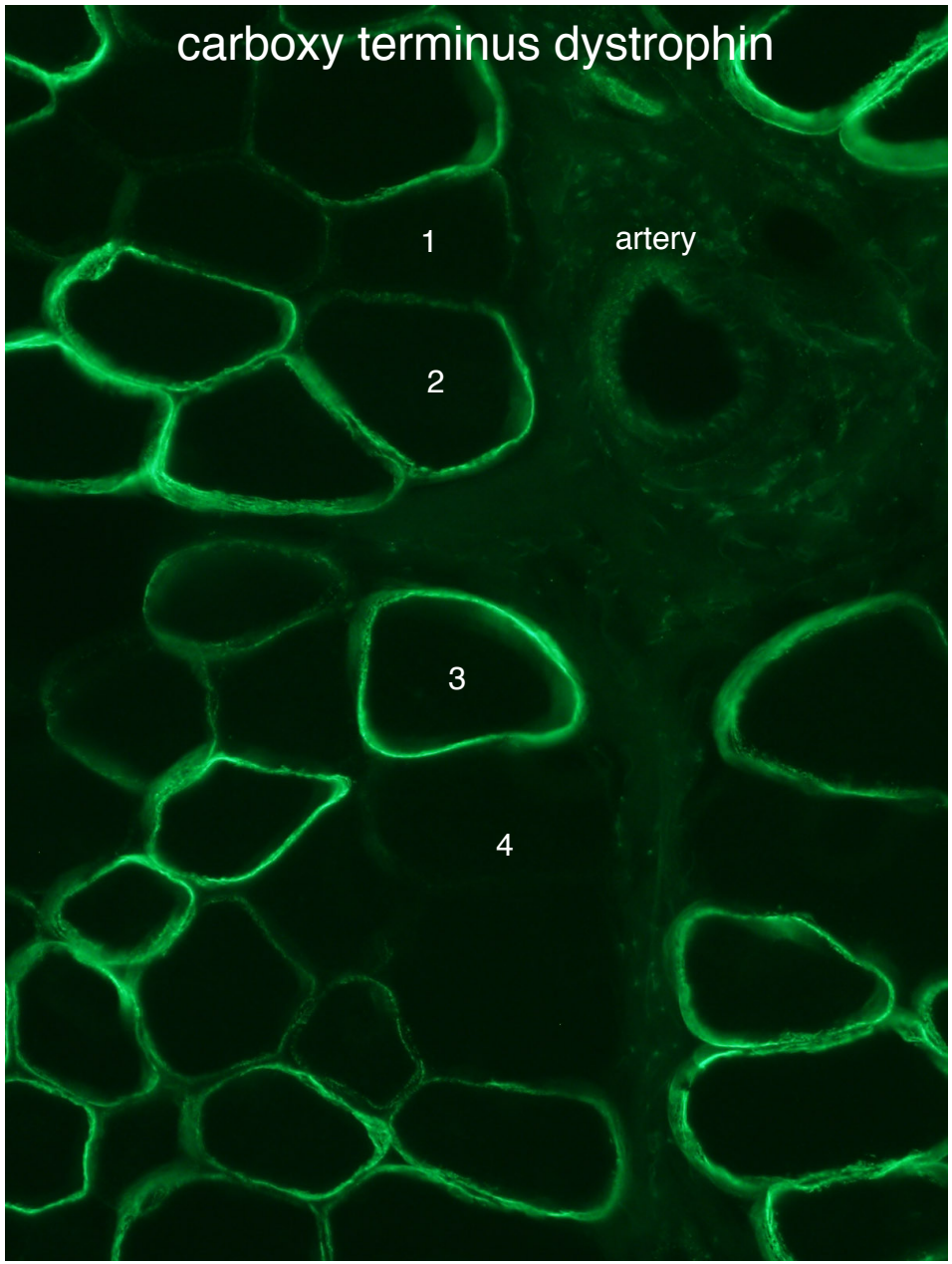

3 yo female with hyperCKemia

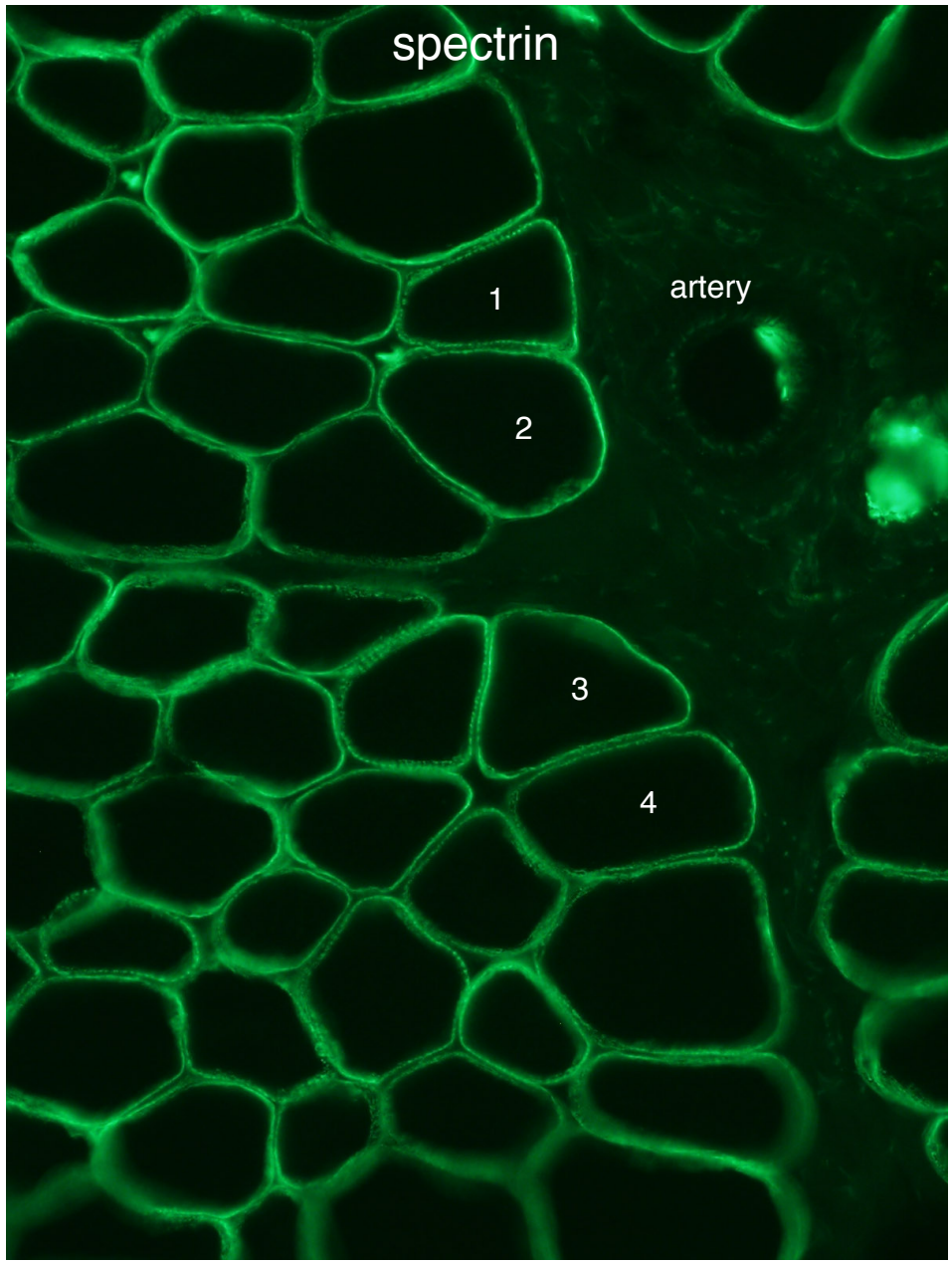
3 yo female with hyperCKemia





3 yo female with hyperCKemia





dystrophinopathy summary

- More than 95% of dystrophinopathy patients can be diagnosed by readily available molecular genetic testing.
- However, dystrophinopathy patients of all ages (male and female) are likely to continue to undergo muscle biopsies for a wide variety of reasons.
- Be vigilant and diligent!

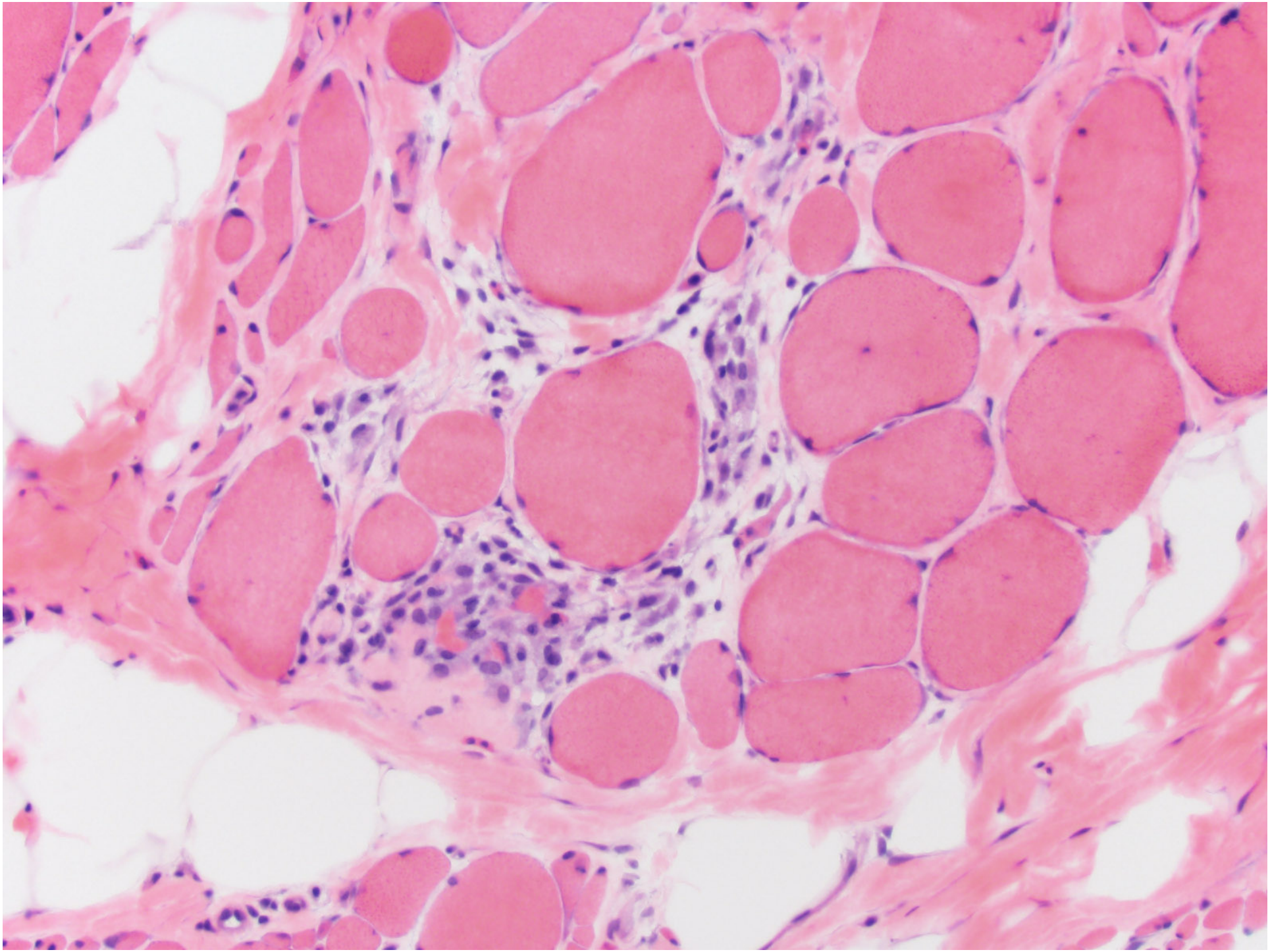
variants of unknown significance – VUS or VOUS –

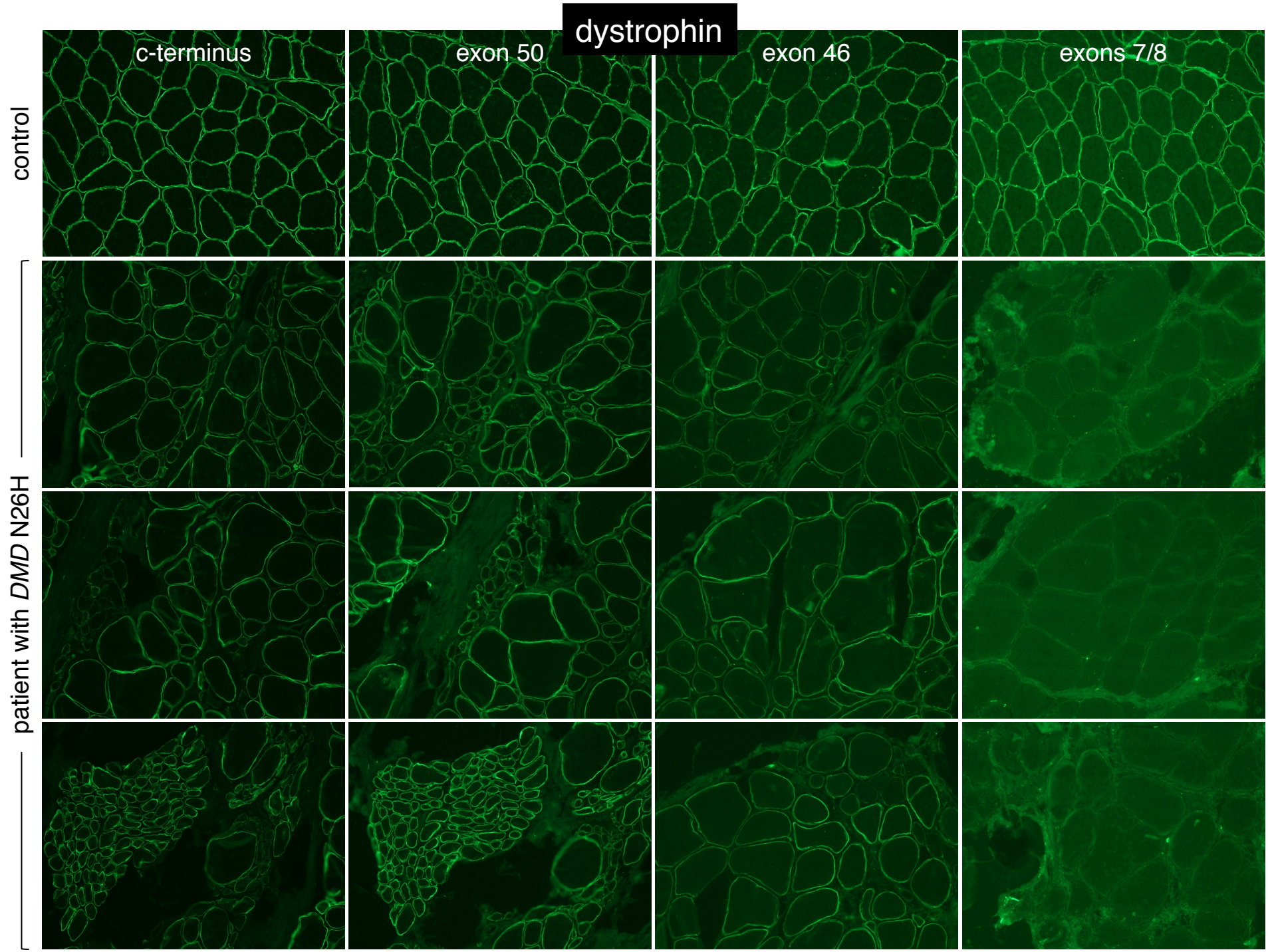
- increasing utilization of next generation sequencing panels for diagnosis prior to muscle biopsy
- increasingly stringent criteria for sequence variants to be classified as pathologic
- muscle biopsies increasingly utilized to verify pathogenicity of VUS
  - apply classic biomarkers of disease and/or specific immunostaining panels

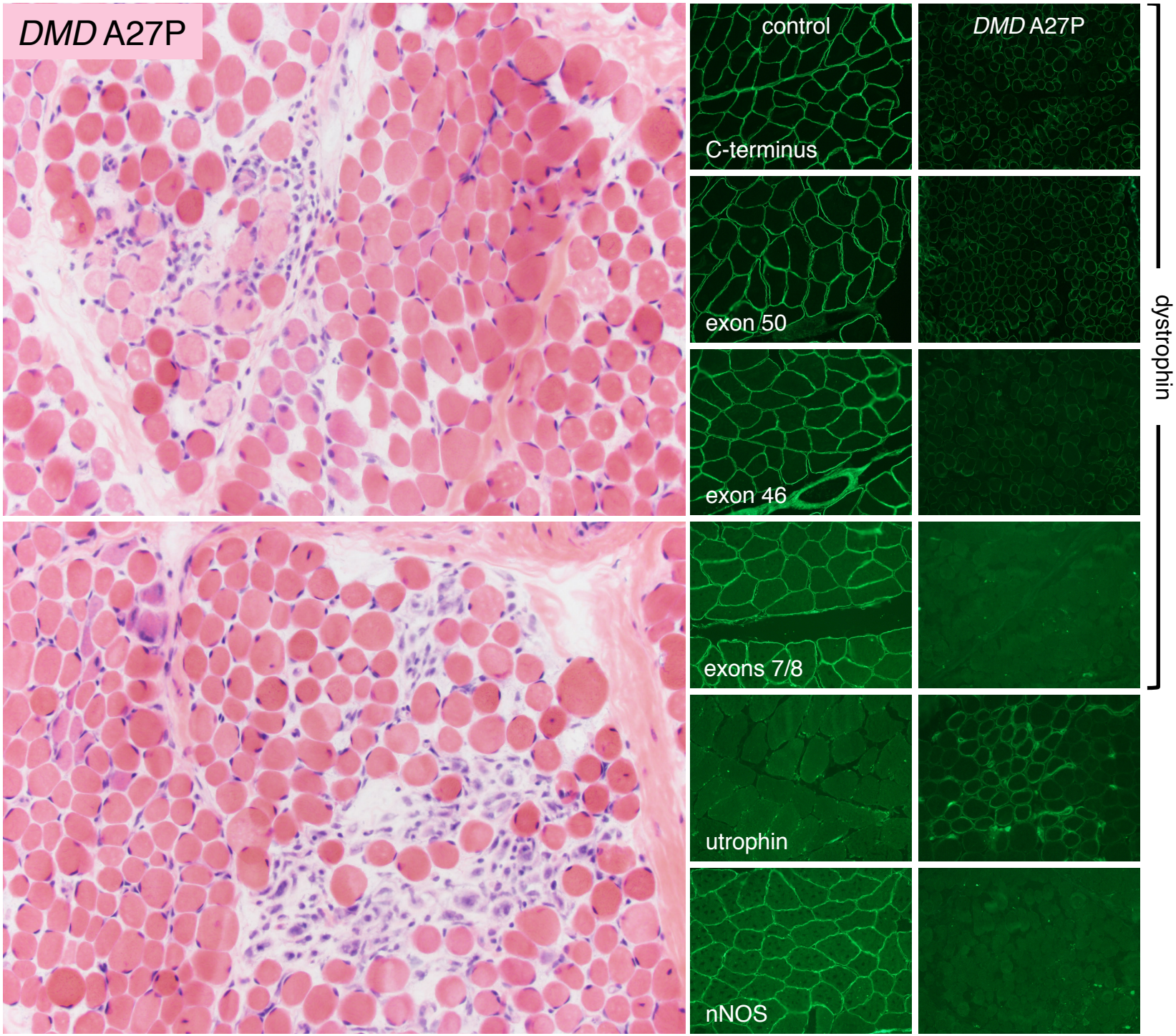
11 yo male

- proximal weakness
- CK >3000
- *DMD* variant of unknown significance (VUS): c.76A>C, p.N26H
- muscle biopsy done to evaluate dystrophin

- also, a 20 month old male with weakness and hypotonia, CK 10,000, and VUS in *DMD* found by sequencing: c.79G>C, p.A27P




dystrophin
c-terminus
exon 50
exon 46
exons 7/8
control
patient with *DMD* N26H


DMD A27P
control
DMD A27P
C-terminus
exon 50
exon 46
exons 7/8
utrophin
nNOS
dystrophin

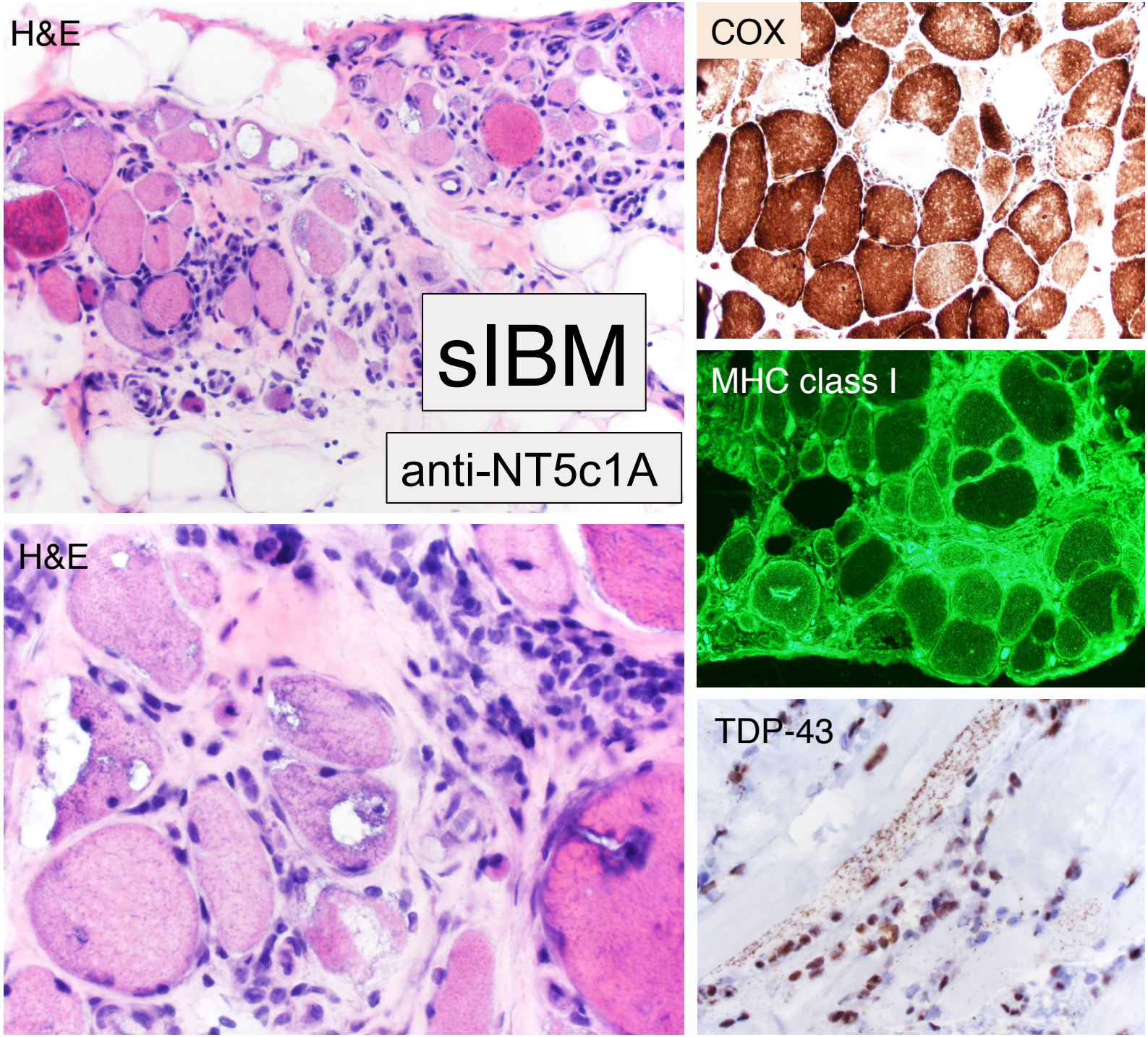
newborn male

- at birth – hypotonia, very little spontaneous movement, no tongue fasciculations, required intubation
- a prior pregnancy – *in utero* fetal demise (male)
- metabolic disease, SMA, Prader Willi, and congenital myotonic dystrophy testing normal
- CMA detected small X-chromosome deletion at the *MTM1* locus
- commercial testing confirmed an in-frame exon 7 deletion in *MTM1*; reported as a VUS
- muscle biopsy to evaluate pathogenicity of VUS


Was the biopsy useful?

inflammatory myopathies

- The terms dermatomyositis, inclusion body myositis, and polymyositis largely replaced by…
  - dermatomyositis spectrum disorders
  - anti-synthetase syndrome myositis
  - sporadic inclusion body myositis (sIBM)
  - immune-mediated necrotizing myopathy


H&E
sIBM
anti-NT5c1A
COX
MHC class I
H&E
TDP-43

Neuropathology and Applied Neurobiology (2017), **43**, 62–81 doi: 10.1111/nan.12380

Integrated classification of inflammatory myopathies

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Y. Allenbach, O. Benveniste, H-H. Goebel and W. Stenzel (2017) *Neuropathology and Applied Neurobiology* **43**, 62–81

Integrated classification of inflammatory myopathies

Inflammatory myopathies comprise a multitude of diverse diseases, most often occurring in complex clinical settings. To ensure accurate diagnosis, multidisciplinary expertise is required. Here, we propose a comprehensive myositis classification that incorporates clinical, morphological and molecular data as well as autoantibody profile. This review focuses on recent advances in myositis research, in particular, the correlation between autoantibodies and morphological or clinical phenotypes that can be used as the basis for an 'integrated' classification system.

Keywords: autoantibodies, classification of IIMs, Morphology, Myositis

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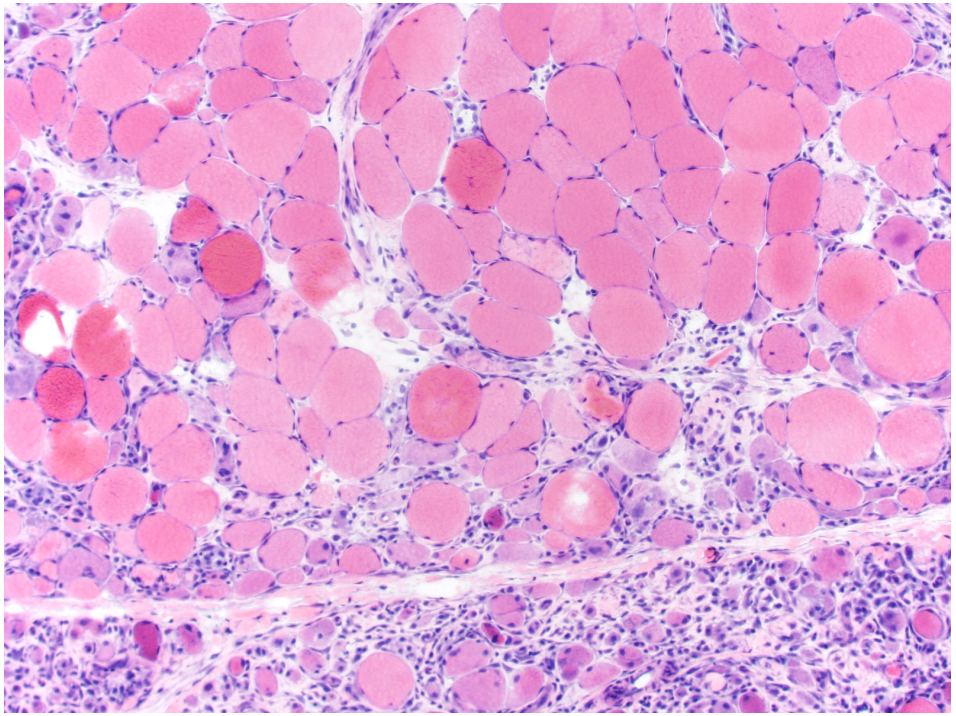
Table 1. Phenotypes of IIM

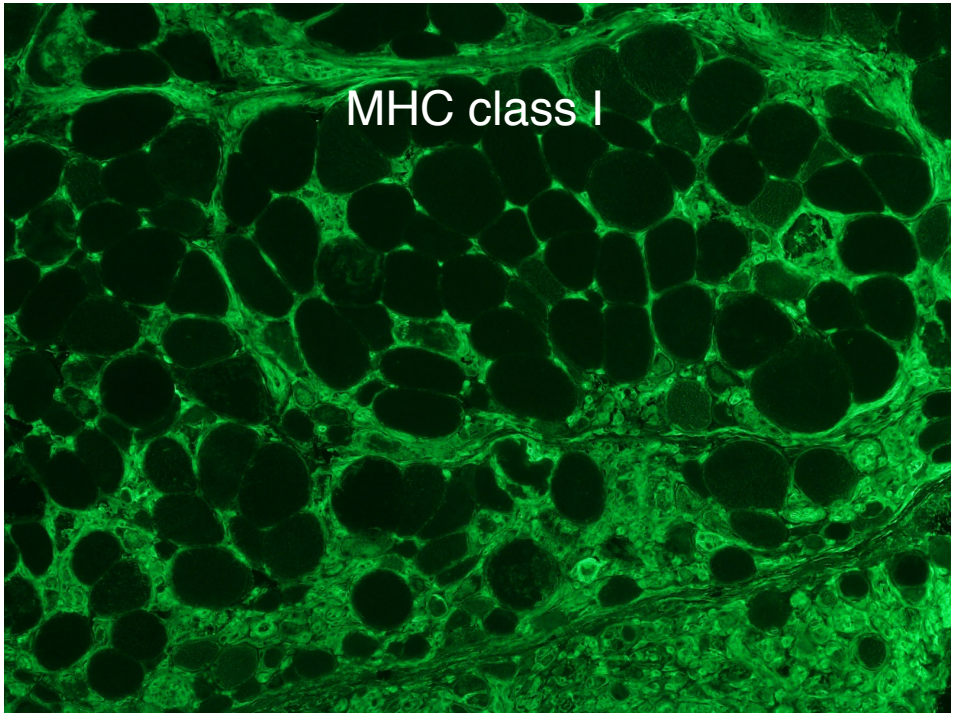
	DM spectrum					IMNM spectrum					ASS-myositis spectrum	PM	NM
Associated auto-Abs	Anti-Mi-2	Anti-MDA5	Anti-TIF1γ	Anti-NXP-2	Anti-SAE	Anti-SRP	Anti-HMGCR	CA-IMNM	Pipestem capillaries	with systemic disease	Anti-Jo1, -PL-7, -PL-12, -OJ, -EJ, etc.		
Clinical Phenotype	Proximal muscle weakness Typical DM skin rash * Ulcers at fingertips	No or mild proximal muscle weakness ILD	Proximal muscle weakness Typical DM skin rash * Dysphagia	Proximal muscle weakness Variable typical DM skin rash*	Mild proximal muscle weakness Varariable typical DM skin rash*	Proximal muscle weakness Acute-subacute Chronic evolution possible Pulmonary and cardiac involvement possible	Proximal muscle weakness Acute-subacute Chronic evolution possible	Proximal muscle weakness Acute-subacute Chronic evolution possible	Proximal muscle weakness Severe disease Acute-subacute	Proximal muscle weakness Depending on systemic disease Subacute evolution	Proximal muscle weakness ILD Mechanics hands Raynaud's phenomenon Arthritis Fever Weight loss	Proximal muscle weakness Subacute evolution Variable additional signs No unique features	Proximal muscle weakness Variable additional signs No skin changes typical for DM
Morphological Phenotype	Severe involvement Pf atrophy Single or grouped myofibre necrosis Dense lymphocytic infiltrates in peri- & endomysium Pf MHC class I Complement on sarcolemma UT on EM	Mild involvement No pf atrophy No myofibre necrosis Only focal lymphocytic infiltrates in perimysium Pf MHC class I Mild or no complement on sarcolemma UT in ±50% of myofibres	Severe involvement Pf atrophy Punched out vacuoles Lymphocytic infiltrates in peri- and endomysium Pf MHC class I Complement on capillaries and on sarcolemma UT on EM	Severe involvement Pf atrophy Lymphocytic infiltrates in peri- and endomysium Pf MHC class I Complement on sarcolemma UT on EM	Mild involvement Mild pf atrophy No myofibre necrosis Only focal lymphocytic infiltrates in perimysium Pf MHC class I Mild or no complement deposition UT on EM	Diffuse myofibre necrosis in different stages of necrosis & regeneration Mild lymphocytic infiltrate Mild MHC I no MHC II Compl. on sarcolemma Fibre size variation Enlarged capillaries	Diffuse myofibre necrosis in different stages of necrosis & regeneration Mild lymphocytic infiltrate Mild MHC I no MHC II Compl. on sarcolemma Fibre size variation Enlarged capillaries	Diffuse myofibre necrosis in different stages of necrosis & regeneration Mild MHC I no MHC II Compl. on sarcolemma Fibre size variation Enlarged capillaries	Diffuse myofibre necrosis in different stages of necrosis & regeneration Mild lymphocytic infiltrate Mild MHC I no MHC II Compl. on capillaries Thickened vessel walls of capillaries	Diffuse myofibre necrosis in different stages of necrosis & regeneration MHC I, possible mild MHC II Compl. on sarcolemma Fibre size variation Enlarged capillaries	Perifascicular necrosis Permimysial fragmentation of fibrous tissue Prominent lymphocytic infiltrate in endo- and peri-mysium Complement on sarcolemma of pf fibres MHC I and II in pf region Myonuclear actin inclusions on EM	Nonspecific: Endomysial inflammatory infiltrates surrounding or invading 'non-necrotic' myofibres No perifascicular atrophy	Perimysial/ perivascular inflammatory infiltrate No/mild endomysial lymphocytic infiltrate No clear perifascicular atrophy UT on EM possible

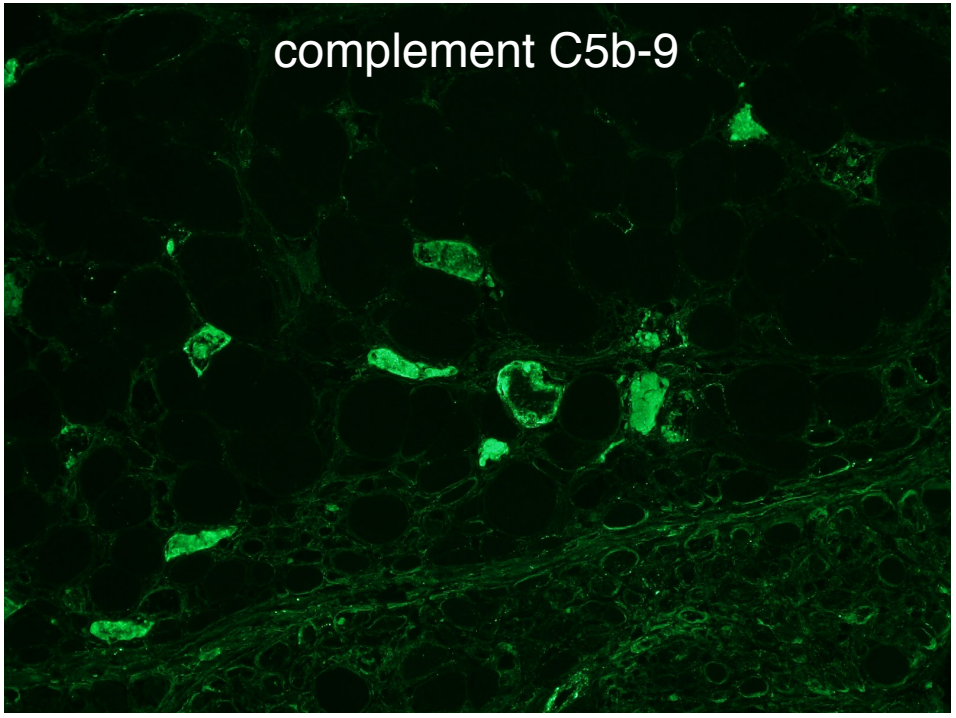
Allenbach et al., Neuropathol Appl Neurobiol 43:62-81, 2017

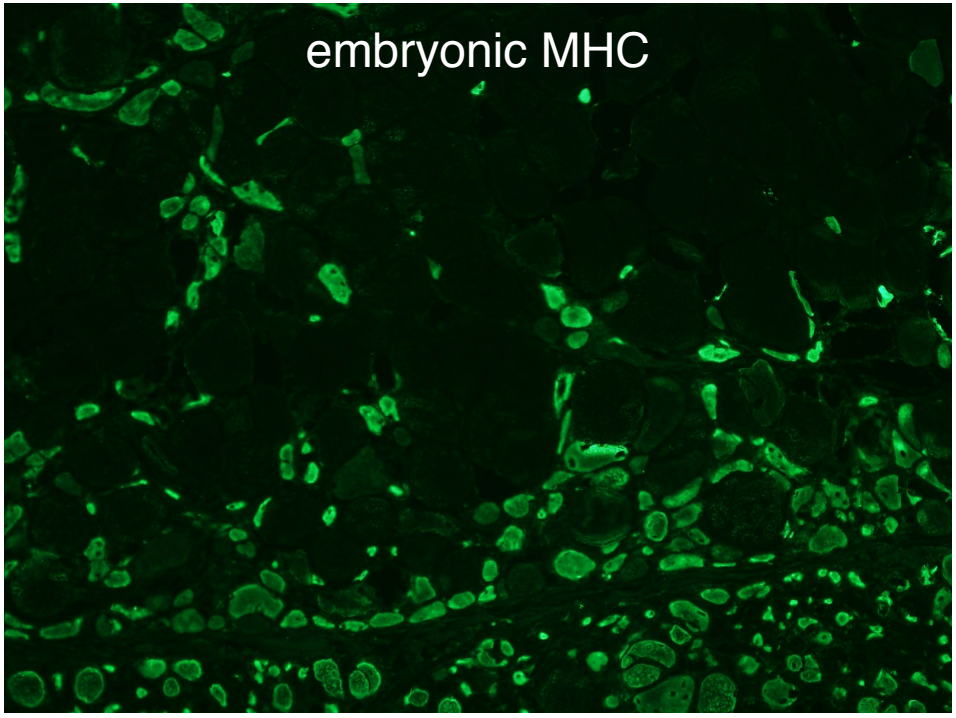
inflammatory myopathies

- dermatomyositis spectrum disorders
  - autoantibodies to Mi-2, MDA-5, TIF1γ, etc.
  - perifascicular pattern of pathology
- anti-synthetase syndrome myositis
  - autoantibodies to Jo-1, PL-7, etc.
  - perifascicular pattern of pathology
- immune-mediated necrotizing myopathy
  - anti-SRP and anti-HMGCR
  - myonecrosis and regeneration with minimal lymphocytic infiltrates; patchy MHC class I
  - clinical and histopathologic overlap with LGMD




MHC class I


complement C5b-9


embryonic MHC

inflammatory myopathies

- The terms dermatomyositis, inclusion body myositis, and polymyositis largely replaced by…
  - dermatomyositis spectrum disorders
  - anti-synthetase syndrome myositis
  - sporadic inclusion body myositis (sIBM)
  - immune-mediated necrotizing myopathy
- "Pestronk" classification
  - Current Opinion Rheumatol 23:595-604, 2011
- ENMC workshops
  - De Bleeker et al., Neuromusc Dis 23:945-951, 2013
  - De Bleeker et al., Neuromusc Dis 25:268-272, 2015

myths

- Ring fibers are diagnostic of myotonic dystrophy.
- Numerous internal nuclei are diagnostic of myotonic dystrophy.
- Muscle tissue obtained at autopsy is not useful for methodologies typically applied to muscle biopsies.

autopsy evaluation of neuromuscular diseases

- with standard complete autopsy permission
  - muscle from diaphragm or from thoracic and abdominal/pelvic walls; deltoid is plausible using the standard incision
  - phrenic nerves, lumbar/sacral plexus, spinal nerve rootlets

- or with specific permission to evaluate skeletal muscle and nerves in the limbs
  - sample some or all the standard sites (quad, deltoid, biceps, gastroc, sural nerve, etc.)
  - or target specific muscles or nerves of interest

- use all the special techniques used for biopsy tissue preparation and evaluation

Every neuropathologist needs to …

- know how to prepare a pristine, frozen muscle biopsy.
- be familiar with and comfortable evaluating a core panel of histologic stains and/or immunostains.
- recognize and interpret core biomarkers of disease.
- understand the tools for diagnosing dystrophinopathy.
- recognize and interpret patterns of inflammatory myopathy.
- partner with the clinical care team to sort through clinical-pathologic correlations.


Resources
2ND EDITION
Neuromuscular Disorders
AMATO
RUSSELL
Mc Graw Hill Education
DUBOWITZ
SEWRY
OLDFORS
Muscle Biopsy
A Practical Approach
FOURTH EDITION
SAUNDERS
MUSCLE DISEASE
SECOND EDITION
Goebel, Sewry, Weller
WILEY Blackwell
Engel
Franzini-Armstrong
Myology
Volume I
1-958
third edition
Mc Graw Hill
Engel
Franzini-Armstrong
Myology
Volume II
959-1960
third edition
Mc Graw Hill
WHO Classification Tumours of the Central Nervous System
IARC 2016
Burger
Scheithauer
Vogel
SURGICAL PATHOLOGY OF THE NERVOUS SYSTEM AND ITS COVERINGS
Fourth Edition
CHURCHILL LIVINGSTONE
BIOPSY DIAGNOSIS of PERIPHERAL NEUROPATHY
MIDRONI
BILBAO
Bilbao · Schmidt
Biopsy Diagnosis of Peripheral Neuropathy
2nd Ed.
Dyck
Thomas
PERIPHERAL NEUROPATHY
VOLUME
1
Pages 1-1190
FOURTH EDITION
ELSEVIER SAUNDERS
Dyck
Thomas
PERIPHERAL NEUROPATHY
VOLUME
2
Pages 1191-2754
FOURTH EDITION
ELSEVIER SAUNDERS