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Title: Frailty Assessment in an Aging Mouse Model

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Author Questionnaire

- 1. Microscopy:** Does your protocol require the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or something similar? **No**

- 2. Software:** Does the part of your protocol being filmed include step-by-step descriptions of software usage? **No**

- 3. Filming location:** Will the filming need to take place in multiple locations? **No**

- 4. Testimonials (optional):** Would you be open to filming two short testimonial statements **live during your JoVE shoot**? These will **not appear in your JoVE video** but may be used in JoVE's promotional materials. **No**

Current Protocol Length

Number of Steps: 18

Number of Shots: 40

Introduction

Videographer: Obtain headshots for all authors available at the filming location.

- 1.1. **Carlos Mantilla:** Aging involves progressive loss of normal functions and differs across individuals. Frailty reflects the inability to maintain function with stressors. Studying frailty can enhance understanding of aging variability and progression.
 - 1.1.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera. *Suggested B.roll:2.7.2*

What research gap are you addressing with your protocol?

- 1.2. **Carlos Mantilla:** Despite the frequent use of frailty assessments clinically, many pre-clinical aging projects don't include frailty as a variable of interest, potentially because of obstacles to implementing a frailty assessment tool.
 - 1.2.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

What advantage does your protocol offer compared to other techniques?

- 1.3. **Braydon Crum:** This frailty index requires no specialized equipment or stressful testing for mice. It is customizable, allowing investigators to tailor assessments to specific dimensions of frailty relevant to their research focus.
 - 1.3.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera. *Suggested B.roll:2.14.2*

How will your findings advance research in your field?

- 1.4. **Braydon Crum:** We hope that presenting the feasibility of simplifying and implementing a frailty index will encourage others to use frailty as a variable of interest, making for more clinically relevant projects.
 - 1.4.1. INTERVIEW: Named Talent says the statement above in an interview-style shot, looking slightly off-camera.

Videographer: Obtain headshots for all authors available at the filming location.

Ethics Title Card

This research has been approved by the Institutional Animal Care and Use Committee (IACUC) at the Mayo Clinic

Protocol

2. Standardized Frailty Assessment and Scoring in Aging Mice

Demonstrator: Braydon Crum

- 2.1. To begin, divide the assessment into open field examination, manual examination, and weighing [1-TXT].
 - 2.1.1. WIDE: Talent preparing the mouse assessment area with all required equipment. **TXT: Perform assessments at consistent location and at the same time**
- 2.2. For the open field examination, transfer the mouse of interest into an open environment [1]. Examine physical characteristics, including alopecia, loss of fur color, dermatitis, poor coat condition, kyphosis, tail stiffening, gait disorders, tremor, and abnormal breathing [2].
 - 2.2.1. Talent gently placing the mouse into an open arena for observation.
 - 2.2.2. Shot of the mouse moving in the arena while the talent observes physical characteristics.
- 2.3. For the manual examination, gently scruff the mouse [1]. Examine for alopecia, loss of fur color, dermatitis, tumors, distended abdomen, cataracts, eye discharge, rectal prolapse, vaginal or penile prolapse, and poor body condition score [2].
 - 2.3.1. Talent scruffing the mouse securely but gently.
 - 2.3.2. Talent examining the mouse's skin, eyes, abdomen, and body condition.
- 2.4. Assess weight following open field and manual examinations at a consistent time of day, within 2 to 4 hours of the beginning of the inactive period [1-TXT].
 - 2.4.1. Talent placing the mouse into the weighing container. **TXT: For consistency, measure the weight at the same time everyday**
- 2.5. During open field examination, assess for gait disorders [1]. Dragging limbs, circling, wobbling, or wide stance which are signs of gait disorders [2-TXT].
 - 2.5.1. Talent gently placing the mouse into an open arena for observation.
 - 2.5.2. Shot of the mouse displaying gait disorder. **TXT: Also monitor for paw shaking or any tremor**
- 2.6. To further evaluate gait disorders, place the mouse on a large cage lid and tilt it [1]. Lightly brush the mouse's rear to encourage climbing [2].

- 2.6.1. Talent placing the mouse on a cage lid then tilting it to assess climbing.
- 2.6.2. Talent brushing the mouse's rear.
- 2.7. Next, allow the mouse to acclimatize and observe the mouse at rest for changes to breathing rate and depth [1-TXT]. ~~The presence of a resting tremor can be observed [2-1]. Gently stroke the tail with a finger to assess tail stiffness [3]. and observe the tail responsiveness for free curling around the finger or for stiffness [4].~~
Videographer's Note: 2.7.2 and 2.7.4 could not be completed since they did not have any mice with a tremor or stiff tail
- 2.7.1. Shot of the mouse at rest. **TXT: Observe for resting tremor**
- ~~2.7.2. Shot of the resting tremor in the mouse.~~
- 2.7.3. Talent stroking the mouse's tail with a finger, showing the curling response.
- 2.7.4. ~~Shot of stiff tail.~~
- 2.8. During the open field examination, assess integumentary criteria, including alopecia, loss of fur color, dermatitis, and poor coat condition [1]. Alopecia is commonly present on the back of the neck and will be visible as the mouse moves freely [2].
- 2.8.1. Shot of the mouse moving in the arena.
- 2.8.2. Shot of the back of the mouse's neck from above, demonstrating thinning of the fur.
- 2.9. Kyphosis is best assessed by observing the mouse's spinal curvature during the open field examination both at rest and while moving [1]. Kyphosis is scored based on the extent of abnormal curvature of the spine visible during movement and hunched posture at rest [2].
- 2.9.1. Shot of mouse at rest, then moving.
- 2.9.2. Shot of a mouse with visible, abnormal spinal curvature.
- 2.10. Manually examine by scruffing the mouse [1]. Use fingers to assess the extent of fat and muscle loss around the pubic bone and lower spine, which are used to evaluate body condition score [2-TXT].
- 2.10.1. Talent gently scruffing mouse.
- 2.10.2. Shot of the fat and muscle loss around pubic bone and lower spine being assessed. **TXT: This can be used to confirm any abnormal spinal curvature and monitor for tumors/abdominal distension**
- 2.11. While holding the mouse, examine the eyes for signs of eye discharge, crusting, or discoloration, and for cataracts [1]. Observe the thoracic and abdominal areas for additional signs of alopecia, which occur commonly around joints, change in fur color, and dermatitis [2]. Gently rub a finger along the abdomen to assess for the presence of tumors or distended abdomen [3].

- 2.11.1. Shot of the mouse's eye area.
- 2.11.2. Shot of the front of the mouse, showing signs of fur thinning and color change.
- 2.11.3. Talent gently rubbing finger along the abdomen, showing signs of abdominal distension.
- 2.12. Carefully tilt the mouse head down to assess for the presence of rectal and vaginal or penile prolapse [1]. If there is suspected prolapse, gently lower mouse to the open field area [2]. Once it has returned to rest, gently lift the tail to confirm prolapse in the absence of any strain caused by handling [3].
 - 2.12.1. Talent tilting the mouse head down and assessing for prolapse.
 - 2.12.2. Shot of the mouse being gently lowered to the open field area.
 - 2.12.3. Talent gently lifting tail to confirm prolapse.
- 2.13. Following the open field and manual examinations, weigh the mouse [1]. Zero the scale between each animal and record the weight to the nearest 0.1 gram [2].
 - 2.13.1. Talent resetting the scale to zero.
 - 2.13.2. Talent placing the mouse into a weighing container on a digital scale.
- 2.14. During evaluation of each mouse, assign a score of 0, 0.5, or 1.0 to each frailty measure [1]. Record the weight and calculate the average of all sixteen measures to generate a final frailty score [2]. Take notes on any health or behavioral changes requiring follow-up, as well as any abnormal post-handling behaviors [3-TXT].
 - 2.14.1. Talent writing the scores for the mouse on a data sheet during an evaluation.
 - 2.14.2. Talent writing the weight and final frailty score for a mouse.
 - 2.14.3. Talent writing notes regarding the mouse's abnormal behaviors or health concerns. **TXT: Ensure data is cross-referenced to the correct mouse throughout the study**

Results

3. Results

- 3.1. Frailty index values increased progressively with age across all measured groups at 12, 18, 24, and 30 months[2].
 - 3.1.1. LAB MEDIA: Figure 1. *Video editor: Highlight the increasing height of the gray box plots from left to right*
- 3.2. At 18 months, alopecia, kyphosis, and loss of fur color were the most frequently observed deficits, particularly in male mice [1]. At 24 months, body condition score and poor coat condition deficits became common [2].
 - 3.2.1. LAB MEDIA: Figure 2. *Video editor: Highlight the red (18 months) bars for alopecia, kyphosis, and fur color.*
 - 3.2.2. LAB MEDIA: Figure 2. *Video editor: Highlight the blue (24 months) bars for body condition score and coat condition*
- 3.3. Longitudinal data showed that frailty rose with age for both sexes [1], with male mice having higher frailty values at similar ages [2]. Very few males were observed beyond 120 weeks of age, indicating reduced survival in males [3].
 - 3.3.1. LAB MEDIA: Figure 4.
 - 3.3.2. LAB MEDIA: Figure 4. *Video editor: Emphasize the + points on the graph.*
 - 3.3.3. LAB MEDIA: Figure 4. *Video editor: Highlight the near absence of male (+) symbols beyond 120 weeks on the x-axis.*
- 3.4. Mice that experienced more than 10% body weight loss were of advanced age had frailty index values exceeding 0.15 [1].
 - 3.4.1. LAB MEDIA: Figure 5A. *Video editor: Highlight the largest circles located in the upper-right of the plot above 0.15 on the y-axis and over 100 weeks on the x-axis.*
- 3.5. Most mice had minimal changes in frailty index changes of less than 0.05 over two-week intervals [1]. Larger frailty increases were more frequent at older ages and accompanied by notable weight loss [2].
 - 3.5.1. LAB MEDIA: Figure 5B. *Video editor: Highlight the tight cluster of points around the center horizontal dashed line*
 - 3.5.2. LAB MEDIA: Figure 5B. *Video editor: Emphasize the large circles after 100 w*
- 3.6. Four phenotypes of frailty-weight change were observed [1], with the most common being frailty increase without weight change, present in 46% of tracked animals [2]. 30%

exhibited no change in either frailty or weight [3]. 12% of mice showed either frailty increase with weight gain or frailty increase with weight loss [4].

3.6.1. LAB MEDIA: Figure 6.

3.6.2. LAB MEDIA: Figure 6. *Video editor: Highlight the bottom-right panel*

3.6.3. LAB MEDIA: Figure 6. *Video editor: Highlight the top-right panel*

3.6.4. LAB MEDIA: Figure 6. *Video editor: Highlight the left panels*

Pronunciation Guide:

❓ **frailty**

Pronunciation link: <https://www.merriam-webster.com/dictionary/frailty> Merriam-Webster

IPA: /'freɪlti/

Phonetic spelling: *FRAYL-tee*

❓ **alopecia**

Pronunciation link: <https://www.merriam-webster.com/dictionary/alopecia>

IPA: /ˌæl.əʊˈpiː.ʃə/

Phonetic spelling: *al-oh-PEE-shuh*

❓ **dermatitis**

Pronunciation link: <https://www.merriam-webster.com/dictionary/dermatitis>

IPA: /ˌdɜrmeɪˈtɑɪtɪs/

Phonetic spelling: *dur-may-TY-tis*

❓ **kyphosis**

Pronunciation link: <https://dictionary.cambridge.org/us/pronunciation/english/kyphosis>
[Cambridge Dictionary](https://dictionary.cambridge.org/us/pronunciation/english/kyphosis)

IPA: /kaɪˈfoʊsɪs/

Phonetic spelling: *ky-FOH-sis*

❓ **rectal**

Pronunciation link: <https://www.merriam-webster.com/dictionary/rectal>

IPA: /ˈrektəl/

Phonetic spelling: *REK-tuhl*

❓ **prolapse**

Pronunciation link: <https://www.merriam-webster.com/dictionary/prolapse>

IPA: /ˈprɒlæps/

Phonetic spelling: *PROH-laps*

❓ **abdomen**

Pronunciation link: <https://www.merriam-webster.com/dictionary/abdomen>

IPA: /ˈæb.də.mən/

Phonetic spelling: *AB-duh-muhn*

❓ **vaginal**

Pronunciation link: <https://www.merriam-webster.com/dictionary/vaginal>

IPA: /ˈvædʒ.ə.nəl/

Phonetic spelling: *VAJ-uh-nul*