

## SUPPLEMENTARY INFORMATION

### **Automated Convolutional Neural Network (CNN) Segmentation Validation**

Previously published validation of the CNN algorithm for generating segmentations of healthy tibiofemoral cartilage (from non-osteoarthritic knees) demonstrated average surface differences  $\leq 0.13$  mm (i.e. smaller than the scan resolution) and Dice Similarity Coefficients  $> 0.92$ .<sup>1</sup>

Automatic segmentation of the menisci from an FFE sequence using this CNN had not been validated previously. Since the medial and lateral menisci are important secondary restraints against anterior force and internal rotation moment, respectively, we compared meniscal volume measurements ( $\text{mm}^3$ ) between auto-segmented and manually segmented menisci. Menisci were selected from the nine female knees in our cohort that corresponded to the three highest, lowest, and closest to average ACL force estimates. The manual segmentations were performed by a single trained examiner.

The differences in volume between automatically and manually segmented renderings of the medial and lateral menisci were calculated (Table S1). On average, auto-segmented medial menisci had 13% less volume than manually segmented, and auto-segmented lateral menisci had 21% less volume than manually segmented. There was no association between the volume difference (auto-segmented minus manually segmented) and estimated ACL force, indicating that under-estimation of meniscus volume does not systematically bias towards higher estimates of ACL force. Auto-segmentations of menisci for all 168 subjects were visually inspected to ensure that the anterior and posterior horns were fully captured.

**Table S1.** Mean and standard deviation of medial and lateral meniscus volume using both auto-segmentation and manual segmentation

| Side    | Automatically Segmented (mm <sup>3</sup> ) | Manually Segmented (mm <sup>3</sup> ) | Difference (mm <sup>3</sup> ) |
|---------|--------------------------------------------|---------------------------------------|-------------------------------|
| Medial  | 1696 ± 374                                 | 1949 ± 451                            | -253 ± 198                    |
| Lateral | 1427 ± 360                                 | 1816 ± 445                            | -389 ± 195                    |

mm<sup>3</sup> = cubic millimeters

## Mesh refinement

The 3D geometries of the bones, cartilage, and menisci outputted by the auto-segmentation algorithm were post-processed using an automated Python script in Geomagic Wrap 2021 (3D Systems Inc., Rock Hill, SC). The refinement process consisted of automated topological repair (addressing intersections, spikes, and small components with a 0.007 mm size threshold), followed by a remeshing operation to establish a uniform 1 mm edge length, and a final decimation to structure-specific resolutions ranging from 2,600 to 10,400 triangles. This reprocessing workflow standardized the mesh density across all subjects, facilitating high-efficiency simulations without compromising the anatomical detail of the geometries.

## Coordinate System Definition

A non-orthogonal knee coordinate system was constructed based on the conventions of Grood and Suntay.<sup>2</sup> The flexion-extension and internal-external rotation axes were defined using the trans-epicondylar axis of the femur and long axis of the tibia, respectively, and described in more detail below. Finally, the anterior-posterior axis was the common perpendicular of the femoral trans-epicondylar axis and tibial long axis.

The femoral trans-epicondylar and tibial long axes were defined from the 3D renderings of the distal femur and proximal tibia, respectively, using automated algorithms. The algorithm to identify the femoral trans-epicondylar axis consisted of the following four steps: 1) the femoral condyles were isolated via curvature estimation; 2) a cylinder was fit to the femoral condyles to define a medial-lateral axis; 3) all points on the femur were projected onto the axis of the cylinder; 4) the two points corresponding to the minimum and maximum value on this axis were selected as the epicondyles. The vector connecting these two points defined the trans-epicondylar axis.

The tibial long axis was calculated using an adaptation of the method described by Beynnon et al.<sup>3</sup> This method was automated, independent of the initial MRI orientation, and could account for the variable length of bone in the MRI field of view. This method consisted of the following six steps: 1) the rim of the tibial plateau was isolated via curvature estimation; 2) a plane was fit to the rim of the tibial plateau and a corresponding normal vector was calculated; 3) a reference ellipse was found corresponding to the largest combined major and minor axis that was perpendicular to the plateau normal vector; 4) the posterior cortex of the tibial diaphysis was identified by projecting all points of the tibia onto an initial sagittal plane defined by the plateau normal vector and the minor axis of this reference ellipse; 5) two more ellipses were fit distal to the reference ellipse, perpendicular to the posterior cortex, at fixed ratios of the reference ellipse's minor axis; 6) the tibial long axis was defined as the vector connecting the centroids of these two ellipses.

The algorithms were validated by comparing the automated measures of the femoral trans-epicondylar and tibial long axes to manually selected axes in 10 cadaveric

specimens. These cadaveric specimens had greater than 20 cm of tibia and femur available; thus, members of the study team were able to manually select the femoral trans-epicondylar and tibial mechanical axes from their 3D reconstructions using bony landmarks. On average, the automated femoral trans-epicondylar axis was internally rotated by  $2.4^{\circ}$  ( $\pm 0.6^{\circ}$ ) relative to the manually selected axis. On average, the automated tibial long axis was rotated by  $4.2^{\circ}$  ( $\pm 1.7^{\circ}$ ) proximal-posterior relative to the manually selected tibial mechanical axis. Thus, these average offsets were corrected for by rotating the femoral trans-epicondylar and tibial long axes by  $2.4^{\circ}$  externally and  $4.2^{\circ}$  proximal-anterior, respectively. This provided the best estimate of the anatomic coordinate system about which to apply loads and measure kinematics given the limitations of variable and limited field-of-view from clinical MRI images.

## **Ligament Insertion Identification**

The ACL consisted of six fibers with their tibial insertions divided into anteromedial (AM), anterolateral (AL), and posterolateral (PL) groups, based on the description by Butler et al.<sup>4</sup> The posterior cruciate ligament (PCL) was represented with seven fibers. The tibial insertions of the PCL fibers were divided into AL and posteromedial (PM) groups.<sup>5</sup> The superficial medial collateral ligament (sMCL) was divided into distal and proximal groups consisting of three fibers each. Wrapping of the sMCL was modeled by connecting its proximal and distal fiber groups with 1 mm diameter spheres located 10 mm distal to the joint line. Each sphere was constrained tangent to the proximal surface of the tibia via a planar joint and a linear spring on this plane. The posterior oblique ligament (POL), medial posterior capsule (MPC), and lateral posterior capsule (LPC) were each represented by three fibers spanning the area that they cover on the posterior aspects of the tibia and

femur.<sup>6</sup> The oblique popliteal ligament (OPL) was divided into posterior and distal fibers.<sup>6</sup> The lateral collateral ligament (LCL), the anterolateral ligament (ALL), and the fabellofibular ligament (FFL) were each represented with one fiber.<sup>6,7</sup> The horn attachments of the medial and lateral menisci were also modeled with one fiber each. Seven fibers represented the attachments of the coronary ligaments from the medial meniscus to the tibial plateau. The lateral coronary ligament attaching the lateral meniscus to the tibial plateau was represented with one fiber.

The automated algorithm to place ligament origins and insertions consisted of, first, manually placing origins and insertions of all forty-two spring elements on a single reference knee. The reference knee (Female Control 61) was selected due to it being the female knee with the closest to mean surface area of the cohort, as this would perform best during mesh correspondence. Manual placement of this knee's ligament insertions was done by the senior author (CI). Specific description of how the ACL fibers' femoral and tibial insertions were placed is as follows: The femoral insertions of the six ACL fibers were placed halfway between the lateral intercondylar ridge (i.e., resident's ridge) and the posterior femoral cartilage.<sup>8-11</sup> The three most proximal femoral insertions were connected to the AM and AL insertion groups on the tibia. The three most distal femoral insertions were connected to the PL group of tibial insertions. These connections were based on the fiber-level dissection of the ACL.<sup>12</sup> Specific description of how the PCL fibers' insertions were placed is as follows: The tibial insertions of the PCL fibers were divided into AL and posteromedial (PM) groups.<sup>5</sup> The femoral insertions were located along the medial intercondylar ridge.<sup>13</sup> The four insertions closest to the posterior cartilage on the lateral aspect of the medial femoral condyle were connected to the PM group of

tibial insertions. The three insertions closest to the top of the femoral notch were connected to the AL group of tibial insertions. The remainder of the ligament insertions were obtained from inspection of the MRI combined with the anatomical descriptions in the literature.<sup>6,14–19</sup>

Once the manual reference knee was complete, a mesh correspondence algorithm was used to automatically place the ligament insertions of the remaining 167 subjects. This consisted of using a nonrigid Coherent Point Drift algorithm to create corresponding mesh nodes between each of the bony geometries and the reference mesh. The origins and insertions of all 42 fibers for each subject were thus placed at the mesh node corresponding to that respective fiber in the reference mesh. This was implemented via CUDA on an NVIDIA RTX 4000 Ada Generation graphics card using the following parameters: weight of noise and outlier = 0.1; Gaussian smoothing filter size = 2; regularization weight = 3; maximum iterations = 150; tolerance criteria = 1e-5.

#### **Ligament constitutive properties and fixed parameters**

With the ligament insertions defined, fibers were represented with straight line force elements connecting the bony insertions. The structural properties of each ligament fiber were described using a tension-only, nonlinear, viscoelastic force-elongation relationship. Force ( $F$ ) in each fiber is a function of  $l$ : the fiber's inter-insertional distance,  $\dot{l}$ : the first derivative of the fiber's inter-insertional distance with respect to time,  $l_0$ : the fiber's slack length, and  $\Delta t$ : the strain corresponding to the fiber's toe region (Eqs. 1-3).

For  $l < l_0$ :  $F = 0$  (Eq. 1)

133 For  $l_0 \leq l < l_0 + \Delta t$ , in the toe region:  $F = \{C * (l - l_0)^d + c_d * \dot{l}\} / n$  (Eq. 2)

134 For  $l \geq l_0 + \Delta t$ , in the linear region:  $F = \{C * (\Delta t)^d + K * (l - (l_0 + \Delta t)) + c_d * \dot{l}\} / n$  (Eq. 3)

135 where n is the number of fibers representing each ligament, C and d are the power  
136 function parameters for the toe-region, K is the linear stiffness in the linear region, and  
137  $c_d$  is a uniform parallel damping term of 1.5 Ns/mm used to represent the viscoelastic  
138 properties of ligaments.<sup>20</sup> The horn attachments of the menisci and the coronary  
139 attachments were modeled as linear elements with no slack length or toe region.

140 **Table S2.** Parameters C, d, K, and n for the non-linear spring elements representing the  
141 knee's soft tissues.

| Ligament | C (N/mm) | d    | K (N/mm) | n |
|----------|----------|------|----------|---|
| ACL - AL | 6.79     | 1.52 | 25.4     | 1 |
| ACL - AM | 10.15    | 1.57 | 19.09    | 2 |
| ACL - PL | 13.2     | 0.94 | 28.78    | 3 |
| PCL - AL | 16.96    | 1.76 | 120      | 3 |
| PCL - PM | 17.35    | 1.38 | 57       | 4 |
| sMCL     | 5.66     | 2.22 | 80       | 3 |
| POL      | 3.04     | 2.32 | 56       | 3 |
| LCL      | 8.39     | 2.06 | 59       | 1 |
| ALL      | 8.39     | 2.06 | 30       | 1 |
| MPC      | 5.66     | 2.22 | -        | 3 |
| LPC      | 5.66     | 2.22 | -        | 3 |
| OPL      | 3.04     | 2.32 | -        | 2 |
| FFL      | 3.04     | 2.32 | -        | 1 |

142 ACL = anterior cruciate ligament; PCL = posterior cruciate ligament; sMCL = superficial  
143 medial collateral ligament; POL = posterior oblique ligament; LCL = lateral collateral  
144 ligament; ALL = anterolateral ligament; MPC = medial posterior capsule; LPC = lateral  
145 posterior capsule; OPL = oblique popliteal ligament; FFL = fabellofibular ligament; N =  
146 Newton; mm = millimeter

The coefficients were  $K = 180$  N/mm for the four medial and lateral menisci horn attachments and  $K = 36$  N/mm for the eight meniscal coronary attachments.

The coefficients were  $A = 327$  N/mm,  $b = 2.07$  for cartilage–cartilage contact; and  $A = 19$  N/mm,  $b = 3.37$  for menisci–cartilage contact.<sup>21</sup>

### Ligament Slack Length Optimization

A generalized reduced-gradient optimization algorithm was utilized to determine the slack lengths,  $l_0$ , as a percentage of fiber length for 26 fibers comprising nine ligaments.<sup>22</sup> This optimization was performed only for the ligaments that carried force at full extension in a previous physical cadaveric experiment. These ligaments were the ACL, PCL PM bundle, sMCL, LCL, FFL, OPL, POL, MPC, and LPC. The experimentally measured forces were taken from a single 20 year old male cadaveric specimen, as this is the best representation of the young active population being simulated (Table S3). Details of the cadaveric testing protocol have been previously published.<sup>22</sup>

The objective function  $Z$  is the error (in Newtons to the 4<sup>th</sup> power) between the resultant forces predicted by the model,  $F^m$ , in the 26 fibers representing these nine ligaments and the experimentally measured forces,  $F^e$ , in these ligaments at full extension (Eq. 4).

$$Z = \sum_{i=1}^9 \left\{ \left| \sum_{j=1}^{n_i} F_{i,j}^m(l, \dot{l}, l_0) \right| - F_i^e \right\}^4 \quad \text{Eq. 4}$$

$n_i$  is the number of fibers representing each ligament  $i$ ;  $F_{i,j}^m$  is the model-estimated force in each fiber  $j$  of ligament  $i$  as a function of the inter-insertional distance ( $l$ ), its elongation rate ( $\dot{l}$ ), and slack length ( $l_0$ ) (Eqs 1-3); and  $F_i^e$  is the experimentally determined force in ligament  $i$  at full extension.

The model-estimated force for each ligament (i) was the resultant magnitude of the vector sum of forces in all of the fibers (j) representing each ligament. Altogether,  $l_0$  was optimized for 26 fibers across nine ligaments. The initial value of  $l_0$  was defined to be the point-to-point distance between insertions at full extension, and  $l_0$  was allowed to vary up to  $\pm 10\%$  from this initial value. The errors between estimated and measured forces were raised to the 4<sup>th</sup> power for all ligaments to penalize outliers and be more sensitive to large errors. The optimization was deemed acceptable when  $Z < 10 \text{ N}^4$ . The slack lengths of the 16 fibers not included in the slack length optimization were set as the insertion-to-insertion distance of the respective fiber in the knee's initial MRI reference pose.

**Table S3.** The experimentally-determined force  $F^e$  for 9 ligaments at full extension used for the standardized optimization. In the computational model, these ligaments consisted of  $n$  non-linear spring fibers whose slack lengths were determined via a standardized optimization algorithm to match the experimental measures.

| Ligament | $n$ | $F^e$ (N) |
|----------|-----|-----------|
| ACL      | 6   | 37        |
| PCL - PM | 4   | 10        |
| sMCL     | 3   | 4         |
| LCL      | 1   | 20        |
| FFL      | 1   | 1         |
| OPL      | 2   | 10        |
| POL      | 3   | 18        |
| MPC      | 3   | 1         |
| LPC      | 3   | 4         |

ACL = anterior cruciate ligament; PCL-PM = posterior cruciate ligament – posteromedial bundle; sMCL = superficial medial collateral ligament; POL = posterior oblique ligament; LCL = lateral collateral ligament; MPC = medial posterior capsule; LPC = lateral posterior capsule; OPL = oblique popliteal ligament; FFL = fabellofibular ligament; N = Newton

### **Simulation/solver parameters: ADAMS software and computer hardware parameters**

The equations of motion were generated and solved using ADAMS (MSC software; ADAMS 2021.4, Newport Beach, CA, USA). Acceleration due to gravity was set to 0 to eliminate gravitational forces. This was done to control for the variability in gravitational forces exerted on the joint due to differences in the mass of each tibia, which stems from variations in tibial geometry among subjects including different lengths of tibia captured in each MRI scan. In addition, the in vitro robotic testing system used for the

model credibility assessment compensates for the loads applied to the joint due to gravity acting on the tibia. Thus, setting gravity to zero also enabled more direct comparison of data obtained from the physical experiment to those estimated by the computational model. The solver parameters (GSTIFF integrator) (Gear, 1971) included an integrator error of 0.001, and simulation step size of 0.01 s. Each simulation took ~10 mins to complete using a desktop computer (3.2 GHz Intel Core i9 Processor 14900K) with 64 GB of RAM.

## **Model verification**

A sensitivity analysis was performed to assess the effect of simulation step size and loading parameters on the model estimates of ACL force, internal tibial rotation, valgus angulation, and anterior tibial translation. The two female subjects with the highest and lowest ACL force were selected for this purpose.

First, we tested the sensitivity of the model outputs to the simulation step size by running simulations with a step size 2-times and 0.5-times the baseline step size of 0.01 seconds. ACL force estimates differed by  $\leq 0.005$  N over these step sizes, and differences in kinematics were  $< 0.05^\circ$  and  $< 0.03$  mm (Table S4).

**Table S4:** Model outputs of ACL force and tibiofemoral kinematics (internal tibial rotation (ITR), valgus angulation, and anterior tibial translation (ATT)) using varying simulation step size for the female participants with the greatest and lowest ACL force.

| Subject                   | Simulation step size [s] | ACLF [N] | ITR [°]   | Valgus [°] | ATT [mm]  |
|---------------------------|--------------------------|----------|-----------|------------|-----------|
| <b>Lowest ACL force</b>   | (1x) 0.01                | 39.24783 | -1.767292 | 2.8473789  | 1.457555  |
|                           | (2x) 0.02                | 39.24663 | -1.792068 | 2.8530504  | 1.45348   |
|                           | (0.5x) 0.005             | 39.24716 | -1.752302 | 2.8434786  | 1.460214  |
| <b>Greatest ACL force</b> | (1x) 0.01                | 206.9924 | 19.930338 | 4.9750649  | 4.8674519 |
|                           | (2x) 0.02                | 206.9874 | 19.972323 | 4.9683263  | 4.8905675 |
|                           | (0.5x) 0.005             | 206.9874 | 19.972323 | 4.9683263  | 4.8905675 |

ACLF = anterior cruciate ligament force; ITR = internal tibial rotation; ATT = anterior tibial translation; N = Newtons; s = seconds; mm = millimeters

Second, we tested the sensitivity of the model outputs to the load magnitudes and loading rate by applying twice the load magnitude, twice the loading rate, and their combination. Twice the load magnitude corresponded to 200 N axial compression, 16 Nm valgus moment, and 60 N anterior force. Twice the loading rate meant that the loads were applied over 0.25, 1, and 0.25 seconds, respectively.

Doubling the load magnitudes further amplified the relative difference between the lowest and highest ACL loading female (168 N, original; 254 N, doubled) (Table S5).

Doubling the loading rate at either load magnitude resulted in ACL force estimates that differed by <1.5 N, and differences in kinematics were <0.5° and ≤0.2 mm (Table S5).

**Table S5:** Model outputs of ACL force and tibiofemoral kinematics using varying load magnitudes and loading rate for the female participants with the highest and lowest ACL force.

| Subject           | Load magnitude | Loading rate | ACLF [N] | ITR [°]   | Valgus [°] | ATT [mm]  |
|-------------------|----------------|--------------|----------|-----------|------------|-----------|
| Lowest ACL force  | 1x             | 1x           | 39.24783 | -1.767292 | 2.8473789  | 1.457555  |
|                   | 1x             | 2x           | 39.03333 | -2.003925 | 2.8561814  | 1.282687  |
|                   | 2x             | 1x           | 92.15314 | 0.364535  | 3.877387   | 2.234973  |
|                   | 2x             | 2x           | 91.32103 | -0.032433 | 3.925653   | 2.010407  |
| Highest ACL force | 1x             | 1x           | 206.9924 | 19.930338 | 4.9750649  | 4.8674519 |
|                   | 1x             | 2x           | 205.5865 | 19.549921 | 4.8688811  | 4.6958801 |
|                   | 2x             | 1x           | 346.3063 | 26.675823 | 9.28066    | 7.5912325 |
|                   | 2x             | 2x           | 347.747  | 26.72465  | 9.2648708  | 7.498466  |

ACLF = anterior cruciate ligament force; ITR = internal tibial rotation; ATT = anterior tibial translation; N = Newtons; mm = millimeters

### **Model credibility assessment comparing in silico ACL force to in vitro cadaveric measures**

Details of the experimental protocol for conducting the model credibility assessment in ten cadaveric specimens is described below.

#### **In Vitro Cadaveric Testing:**

Ten unpaired cadaveric knees consisting of five males (age 25-41, weight 140-200 lbs.) and five females (age 25-43, weight 145-182 lbs.) were procured. Knees were prepared for testing using previously described protocols.<sup>23</sup> Briefly, the testing process consisted of the following seven steps. 1) Six radiopaque glass spheres (6.35±0.015 mm diameter, Winsted Precision Ball Co., Winsted, CT) were each rigidly fixed to the tibia and femur diaphysis as fiducial markers. 2) Computed tomography (CT) scans

255 (Biograph mCT; Siemens, Erlangen, Germany) of each knee were conducted (0.625  
256 mm slice thickness; 0.5 x 0.5-mm in-plane resolution) and the tibia, femur, and fiducial  
257 markers were segmented. 3) Each knee was mounted to a six degree-of-freedom  
258 robotic manipulator (Kawasaki ZX165U) with a 3-force/3-torque universal force sensor  
259 (Theta; ATI, Apex, NC, USA) (resolution:  $F_x = F_y = 0.13$  N,  $F_z = 0.25$  N,  $T_x = T_y = T_z =$   
260  $0.008$  Nm; limits:  $F_x = F_y = 1500$  N,  $F_z = 3750$  N,  $T_x = T_y = T_z = 240$  Nm). 4) The  
261 fiducial markers were digitized using a coordinate measuring tool (Gage, FARO, Inc. FL;  
262 accuracy: 0.018 mm), and registration between specimen and robot was performed  
263 using previously published methods.<sup>24</sup> Tibiofemoral kinematics were described in both  
264 the model and experiment by adapting the coordinate system convention described by  
265 Grood and Suntay to the distal femur and proximal tibia bone segments.<sup>2,25</sup> 5) The  
266 flexion path for each knee was determined with 10 N compression applied to the  
267 tibiofemoral joint. 6) The soft tissues of the knee were preconditioned by, first, applying  
268 five cycles of an anterior force (100 N) at 30° of flexion and then five cycles of valgus  
269 moment (8 Nm) at 15° of flexion. 7) Finally, compression (100 N) and a valgus moment  
270 (8 Nm) were applied serially at 15° of flexion.

271 These compression and valgus loads applied at this flexion angle were selected  
272 because it is a key loading condition during both the pivot shift clinical exam and athletic  
273 cutting maneuvers associated with ACL injuries.<sup>26–29</sup> Compression was applied in  
274 increments of 25 N from 0 to 100 N, followed by the valgus moment in increments of 1  
275 Nm from 0 to 8 Nm. All other forces and moments were minimized. A force-feedback  
276 algorithm was used to determine a pose at each loading increment that satisfied all  
277 resultant forces and moments to within 5 N and 0.4 Nm, respectively, of their target

magnitudes.<sup>30</sup> All kinematic degrees of freedom except flexion were left unconstrained. Once the pose at the target load was determined, the ACL was sectioned, and the pose repeated. Forces carried by the ACL at peak applied compression and valgus moment were determined via the principle of superposition.<sup>31,32</sup> Tibiofemoral kinematics were the translations and rotations between the initial pose on the flexion path and the final pose of the knee.

#### In Silico Computational Simulation:

The computational models of each of the ten specimens were constructed as described above, with a few methodological differences to allow for direct one-to-one comparison. Notable differences in this validation experiment's methods are that the distal femur, proximal tibia, and tibiofemoral articular cartilages were manually segmented from a CT scan (0.625-mm slice thickness; 0.5 x 0.5-mm in-plane resolution) while the medial and lateral menisci were manually segmented from 3D Cube proton density weighted magnetic resonance imaging (MRI) using a 3 Tesla scanner (0.6-mm slice thickness; 0.3 x 0.3-mm in-plane resolution) (General Electric, Inc., Boston, MA, USA). The same bony-fixed coordinate systems were registered between computational and cadaveric experiments using the fiducial markers.

The models were assembled with same 42 non-linear spring elements described above, with the same standardized structural properties. Ligament slack lengths were calculated via the same standardized optimization algorithm. The loading sequence differed in that only 100 N compression and an 8 Nm valgus moment were applied serially over the spans of 0.5 and 2 seconds, respectively, at 15° of flexion. ACL force

was defined as the magnitude of the vector sum of the forces at the end of the loading sequence in each of the six spring elements that represented the ACL.

### **Evaluating sensitivity of results to standardized ligament properties**

Simulations were run for six additional physiological combinations of standardized ligament properties (SA1 through 6). The specific combinations of ligament properties (slack lengths,  $l_0$ , and stiffness,  $K$ ) that made up each laxity profile are in Table S6, and the results of case-control and female-male differences in ACL force are in Table S7. ACL slack was modulated at 95, 100, and 105% of the nominal condition, and MCL slack was modulated at 95 and 100%. A 5% decrease in ACL slack corresponds to an average of 2 mm less joint-level anterior laxity. A 5% decrease in MCL slack corresponds to an average of 1° less joint-level valgus laxity. Stiffness of the ligaments was also tested at 100 and 130% of the nominal condition.

**Table S6.** Combinations of ligament properties utilized in full sensitivity analysis. SA1 thru 5 represent laxity profiles tighter than the nominal, while SA6 represents a laxity profile looser than the nominal.

| <b>Combination</b> | <b>ACL Slack<br/>(% of nominal)</b> | <b>MCL Slack<br/>(% of nominal)</b> | <b>ACL Stiffness<br/>(% of nominal)</b> | <b>MCL Stiffness<br/>(% of nominal)</b> |
|--------------------|-------------------------------------|-------------------------------------|-----------------------------------------|-----------------------------------------|
| <b>SA1</b>         | 95                                  | 95                                  | 130                                     | 130                                     |
| <b>SA2</b>         | 95                                  | 95                                  | 100                                     | 100                                     |
| <b>SA3</b>         | 95                                  | 100                                 | 100                                     | 100                                     |
| <b>SA4</b>         | 100                                 | 95                                  | 100                                     | 100                                     |
| <b>SA5</b>         | 100                                 | 100                                 | 130                                     | 130                                     |
| <b>Nominal</b>     | 100                                 | 100                                 | 100                                     | 100                                     |
| <b>SA6</b>         | 105                                 | 100                                 | 100                                     | 100                                     |

SA = sensitivity analysis; ACL = anterior cruciate ligament; MCL = medial collateral ligament

**Table S7.** Differences between cohort averages of ACL force for each of the 6 combinations of ligament properties used in the sensitivity analysis

| Combination    | Male Cases v. Controls (%) | Female Cases v. Controls (%) | All Females v. All Males (%) |
|----------------|----------------------------|------------------------------|------------------------------|
| <b>Nominal</b> | 26                         | 20                           | 17                           |
| <b>SA1</b>     | 28                         | 27                           | 16                           |
| <b>SA2</b>     | 28                         | 24                           | 17                           |
| <b>SA3</b>     | 24                         | 25                           | 16                           |
| <b>SA4</b>     | 24                         | 15                           | 14                           |
| <b>SA5</b>     | 26                         | 21                           | 18                           |
| <b>SA6</b>     | 20                         | 8                            | 16                           |

SA = sensitivity analysis

Differences in ACL force between cases and controls as well as between all females and all males were preserved for all tested combinations of ligament properties. The differences between female cases and controls were reduced when ACL slack was increased to 105% of its standard nominal value (SA6). Further evaluation of kinematics during these simulations indicate that, in this increased laxity condition, almost all subjects experience increased coupled internal tibial rotation (Table S8).

**Table S8.** Coupled internal tibial rotation (°) during the multiplanar loading conditions for 7 different combinations of laxity properties

| Combination    | Male Controls (°) | Male Cases (°) | Female Controls (°) | Female Cases (°) |
|----------------|-------------------|----------------|---------------------|------------------|
| <b>Nominal</b> | 9.8 ± 5.3         | 13.1 ± 2.9     | 11.4 ± 5.5          | 13.8 ± 4.1       |
| <b>SA1</b>     | 6.9 ± 4.1         | 9.5 ± 3.3      | 8.0 ± 4.3           | 11.0 ± 4.2       |
| <b>SA2</b>     | 7.4 ± 4.3         | 10.2 ± 3.7     | 8.8 ± 4.3           | 11.5 ± 4.3       |
| <b>SA3</b>     | 5.7 ± 4.6         | 9.5 ± 4.3      | 7.6 ± 5.5           | 11.3 ± 4.9       |
| <b>SA4</b>     | 10.7 ± 4.5        | 12.1 ± 2.2     | 11.0 ± 4.3          | 12.6 ± 3.2       |
| <b>SA5</b>     | 9.1 ± 5.1         | 12.3 ± 3.1     | 10.6 ± 5.3          | 13.1 ± 4.1       |
| <b>SA6</b>     | 13.7 ± 4.9        | 15.7 ± 1.8     | 14.6 ± 4.7          | 15.2 ± 3.6       |

SA = sensitivity analysis

The ligament properties used to select SA1-6 were informed by in vitro cadaveric testing of 37 cadaveric specimens (Table S9).

**Table S9.** Average and standard deviation of laxity and ligament properties from 37 cadaveric knees (age:  $44 \pm 13$  years)

| Variable                                      | Females (n=17) | Males (n=20)  |
|-----------------------------------------------|----------------|---------------|
| <b>Coupled ITR – Compression + Valgus (°)</b> | $5.0 \pm 5.4$  | $5.0 \pm 5.8$ |
| <b>Valgus Laxity (°)</b>                      | $4.1 \pm 0.8$  | $3.5 \pm 1.3$ |
| <b>Anterior Laxity (mm)</b>                   | $8.8 \pm 1.7$  | $7.6 \pm 2.5$ |
| <b>ACL Slack (mm)</b>                         | $4.3 \pm 1.8$  | $3.4 \pm 1.9$ |
| <b>ACL Stiffness (N/mm)</b>                   | $24 \pm 5$     | $29 \pm 8$    |

ITR = internal tibial rotation; ACL = anterior cruciate ligament; N = Newtons; mm = millimeters

While these 37 cadaveric specimens are not fully representative of the young, high-risk athletes in the computational modeling cohort, the data can inform interpretation of the sensitivity analysis results, especially for the control (uninjured) subjects. Coupled ITR across the 37 cadavers in response to 100 N compression and 8 Nm valgus moment averaged  $5.0^\circ \pm 5.6^\circ$ . SA1-5 represent laxity profiles where the mean model estimates of coupled ITR for male and female controls are within 1 standard deviation of the cadaveric mean.

Many of these in vitro variables are directionally correlated: Anterior laxity is positively associated with valgus laxity ( $r=0.61$ ), ACL slack ( $r=0.80$ ), and negatively associated with ACL stiffness ( $r=-0.7$ ). Similarly, valgus laxity is positively associated with ACL slack ( $r=0.51$ ). This cadaveric data supports that laxity profiles with opposite directionality in ACL and MCL slack (like SA6) are unlikely to be representative of cohort averages.

Notably, ACL slack and stiffness are not associated, supporting that they should be modulated separately in a sensitivity analysis. The relative effect of 30% changes in ligament stiffness in the computational model were much smaller than the effects of 5% changes in ligament slack: SA1 vs SA2, SA5 vs Nominal, and SA7 vs SA8 differed by < 2% when comparing ACL force between groups, and ligament stiffness had < 1° changes in average coupled ITR.

Anterior laxity is positively correlated with age in these cadavers: + 0.06 mm / year (p=0.03). ACL slack increases (0.05 mm / year, p=0.02) and stiffness decreases with age (-0.15 N/mm / year, p=0.10). These data further support using ligament properties with decreased slack and increased stiffness to represent physiological combinations in a young cohort of athletes.

#### **Supplementary Video 1**

A supplementary video demonstrating the mechanism by which 3D knee shape governs ACL loading through coupled knee motion is available as a separate file. A representative female knee that exhibits high ACL force is shown.

# Additional Supplementary Tables

**Table S10| Summary Statistics for ACL Force, ACL Cross-Sectional Area (C SA), ACL Force/C SA**

| Parameter                                | [n]<br>Mean (SD)     | 95% CI         | [n]<br>Mean (SD)      | 95% CI         | Difference<br>Mean | 95% CI        | Test-statistic (t)<br>Degrees of<br>freedom | P value |
|------------------------------------------|----------------------|----------------|-----------------------|----------------|--------------------|---------------|---------------------------------------------|---------|
|                                          | Male Controls        |                | Male Cases            |                |                    |               |                                             |         |
| ACL Force (N)                            | [24]<br>94.3 (32.6)  | [80.5, 108.1]  | [24]<br>118.6 (28.0)  | [106.8, 130.4] | 24.3               | [6.6, 42.0]   | (2.8)<br>46                                 | 0.008   |
| Scaled ACL<br>Force (N/mm <sup>2</sup> ) | [24]<br>2.1 (1.1)    | [1.7, 2.6]     | [24]<br>3.4 (1.3)     | [2.8, 3.9]     | 1.2                | [0.5, 1.9]    | (3.6)<br>46                                 | < 0.001 |
| ACL CSA (mm <sup>2</sup> )               | [24]<br>47.7 (11.6)  | [42.8, 52.6]   | [24]<br>38.2 (10.7)   | [33.6, 42.7]   | -9.5               | [-16.0, -3.0] | (-2.9)<br>46                                | 0.005   |
|                                          | Female Controls      |                | Female Cases          |                |                    |               |                                             |         |
| ACL Force (N)                            | [59]<br>113.2 (34.7) | [104.2, 122.3] | [61]<br>135.3 (27.9)  | [128.2, 142.5] | 22.1               | [10.7, 33.5]  | (3.9)<br>118                                | < 0.001 |
| Scaled ACL<br>Force (N/mm <sup>2</sup> ) | [59]<br>3.0 (1.2)    | [2.7, 3.4]     | [60]<br>4.0 (1.3)     | [3.6, 4.3]     | 0.9                | [0.5, 1.4]    | (3.9)<br>117                                | < 0.001 |
| ACL CSA (mm <sup>2</sup> )               | [59]<br>39.5 (10.7)  | [36.7, 42.3]   | [60]<br>36.9 (10.7)   | [34.1, 39.7]   | -2.6               | [-6.5, 1.3]   | (-1.3)<br>117                               | 0.188   |
|                                          | All Males            |                | All Females           |                |                    |               |                                             |         |
| ACL Force (N)                            | [48]<br>106.5 (32.5) | [97.0, 115.9]  | [120]<br>124.5 (33.2) | [118.5, 130.5] | 18.0               | [6.9, 29.1]   | (3.2)<br>166                                | 0.002   |
| Scaled ACL<br>Force (N/mm <sup>2</sup> ) | [48]<br>2.8 (1.3)    | [2.4, 3.1]     | [119]<br>3.5 (1.3)    | [3.3, 3.7]     | 0.7                | [0.3, 1.2]    | (3.3)<br>165                                | 0.001   |
| ACL CSA (mm <sup>2</sup> )               | [48]<br>42.9 (12.1)  | [39.4, 46.4]   | [119]<br>38.2 (10.7)  | [36.2, 40.1]   | -4.7               | [-8.5, -1.0]  | (-2.5)<br>165                               | 0.014   |

Mean, standard deviation (SD), sample size [n], 95 % confidence interval [CI], test-statistic (t), degrees of freedom, and P-values for ACL force, ACL cross-sectional area (CSA), ACL force/CSA, for male controls, male cases, female controls, and female cases, as well for all males and all females. mm = millimeters; N = Newtons.

Table S11| Summary Statistics for Internal Tibial Rotation, Anterior Tibial Translation, and Valgus Angulation

| Parameter             | [n]<br>Mean (SD)   | 95% CI       | [n]<br>Mean (SD)    | 95% CI       | Difference<br>Mean | 95% CI      | Test-statistic (t)<br>Degrees of<br>freedom | P value |
|-----------------------|--------------------|--------------|---------------------|--------------|--------------------|-------------|---------------------------------------------|---------|
|                       | Male<br>Controls   |              | Male Cases          |              |                    |             |                                             |         |
| ITR (°)               | [24]<br>9.8 (5.4)  | [7.5, 12.1]  | [24]<br>13.1 (3.0)  | [11.8, 14.4] | 3.3                | [0.8, 5.9]  | (2.6)<br>35.9*                              | 0.013   |
| ATT (mm)              | [24]<br>1.7 (0.7)  | [1.4, 2.0]   | [24]<br>2.1 (0.9)   | [1.7, 2.5]   | 0.4                | [-0.0, 0.9] | (1.8)<br>46                                 | 0.07    |
| Valgus Angulation (°) | [24]<br>3.2 (0.8)  | [2.9, 3.5]   | [24]<br>3.5 (1.0)   | [3.1, 3.9]   | 0.3                | [-0.2, 0.8] | (1.3)<br>46                                 | 0.2     |
|                       | Female<br>Controls |              | Female Cases        |              |                    |             |                                             |         |
| ITR (°)               | [59]<br>11.4 (5.5) | [10.0, 12.9] | [61]<br>13.9 (4.1)  | [12.8, 14.9] | 2.5                | [0.7, 4.2]  | (2.8)<br>107.3*                             | 0.007   |
| ATT (mm)              | [59]<br>1.8 (0.9)  | [1.6, 2.0]   | [61]<br>2.5 (1.0)   | [2.2, 2.8]   | 0.7                | [0.3, 1.0]  | (3.8)<br>118                                | < 0.001 |
| Valgus Angulation (°) | [59]<br>4.1 (1.2)  | [3.7, 4.4]   | [61]<br>4.7 (1.3)   | [4.4, 5.0]   | 0.7                | [0.2, 1.1]  | (2.9)<br>118                                | 0.005   |
|                       | All Males          |              | All Females         |              |                    |             |                                             |         |
| ITR (°)               | [48]<br>11.4 (4.6) | [10.1, 12.8] | [120]<br>12.7 (5.0) | [11.8, 13.6] | 1.2                | [-0.4, 2.9] | (1.5)<br>166                                | 0.141   |
| ATT (mm)              | [48]<br>1.9 (0.9)  | [1.7, 2.2]   | [120]<br>2.2 (1.0)  | [2.0, 2.3]   | 0.2                | [-0.1, 0.6] | (1.4)<br>166                                | 0.166   |
| Valgus Angulation (°) | [48]<br>3.4 (0.9)  | [3.1, 3.6]   | [120]<br>4.4 (1.3)  | [4.2, 4.6]   | 1.0                | [0.7, 1.4]  | (6.0)<br>125.7*                             | < 0.001 |

Mean, standard deviation (SD), sample size [n], 95% confidence interval [CI], test-statistic (t), degrees of freedom, and P-values for internal tibial rotation (ITR), anterior tibial translation (ATT), and valgus angulation for male controls, male cases, female controls, and female cases, as well for all males and all females. (\*) indicates that Welch's unequal variance t-test was performed with Satterthwaite's degrees of freedom reported. mm = millimeters.

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**Table S12| Sex Interactions in Associations Between ACL Force and Coupled Knee Motions**

| Dependent Variable: ACL Force (N)<br>n = 168 |                    |         |
|----------------------------------------------|--------------------|---------|
| Independent Variable                         | $\beta$ [95% CI]   | P-value |
| Sex                                          | -13.7 [-33.6, 6.1] | 0.175   |
| ITR (°)                                      | 3.7 [3.1, 4.3]     | < 0.001 |
| ATT (mm)                                     | 15.8 [13.0, 18.7]  | < 0.001 |
| Valgus Angulation (°)                        | 0.5 [-1.7, 2.6]    | 0.676   |
| ITR Sex Interaction                          | 1.8 [0.6, 3.0]     | 0.003   |
| ATT Sex Interaction                          | -9.6 [-16.2, -2.9] | 0.005   |
| Valgus Angulation Sex Interaction            | 0.6 [-4.9, 6.1]    | 0.825   |

Multiple linear regression to test for sex interactions in associations between ACL force and coupled knee motions. Sex interaction terms are the variables of interest. ITR = internal tibial rotation. ATT = anterior tibial translation. Sex is coded as female = 0 and male = 1. mm = millimeter.  $\beta$  = regression coefficient. CI = confidence interval. N = Newtons. n = sample size.

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**Table S13| Associations Between ACL Force and Coupled Knee Motions in Females and Males Separately**

| <b>Females</b><br>Dependent Variable: ACL Force (N)<br>n = 120 |                   |         |
|----------------------------------------------------------------|-------------------|---------|
| Independent Variable                                           | $\beta$ [95% CI]  | P-value |
| ITR (°)                                                        | 3.7 [3.1, 4.3]    | < 0.001 |
| ATT (mm)                                                       | 15.8 [13.0, 18.6] | < 0.001 |
| Valgus Angulation (°)                                          | 0.5 [-1.6, 2.5]   | 0.670   |
| <b>Males</b><br>Dependent Variable: ACL Force (N)<br>n = 48    |                   |         |
| Independent Variable                                           | $\beta$ [95% CI]  | P-value |
| ITR (°)                                                        | 5.5 [4.4, 6.6]    | < 0.001 |
| ATT (mm)                                                       | 6.3 [-0.2, 12.7]  | 0.055   |
| Valgus Angulation (°)                                          | 1.1 [-4.4, 6.5]   | 0.694   |

Multiple linear regression to test for associations between ACL force and coupled knee motions in females and males separately. ITR = internal tibial rotation. ATT = anterior tibial translation. ITR and ATT are the variables of interest. mm = millimeter.  $\beta$  = regression coefficient. CI = confidence interval. N = Newtons. n = sample size.

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**Table S14 | Associations Between ACL Force and Coupled Knee Motions in All Subjects**

| Dependent Variable: ACL Force (N)<br>n = 168 |                    |         |
|----------------------------------------------|--------------------|---------|
| Independent Variable                         | $\beta$ [95% CI]   | P-value |
| Sex                                          | -12.1 [-25.9, 1.6] | 0.083   |
| ITR (°)                                      | 3.7 [3.1, 4.3]     | < 0.001 |
| ATT (mm)                                     | 15.8 [13.0, 18.6]  | < 0.001 |
| Valgus Angulation (°)                        | 0.5 [-1.4, 2.5]    | 0.585   |
| ITR Sex Interaction                          | 1.8 [0.6, 3.0]     | 0.003   |
| ATT Sex Interaction                          | -9.3 [-15.5, -3.1] | 0.003   |

Multiple linear regression to test for associations between ACL force and coupled knee motions in all subjects. Valgus angulation is the variable of interest. ITR = internal tibial rotation. ATT = anterior tibial translation. Sex is coded as female = 0 and male = 1. mm = millimeter.  $\beta$  = regression coefficient. CI = confidence interval. N = Newtons. n = sample size.

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Table S15 | Relative Impacts of Sex-Specific Coupled Knee Motions on ACL force

| Females (n = 120)     |                      |                                                                        |                                                        |             |             |
|-----------------------|----------------------|------------------------------------------------------------------------|--------------------------------------------------------|-------------|-------------|
| Knee Motion           | 1 IQR in Knee Motion | Relation to ACL Force (N) $\beta$ , p-value<br>[95% CI of $\beta$ ]    | $\Delta$ 1 IQR in Knee Motion = $\Delta$ ACL Force (N) |             |             |
|                       |                      |                                                                        | mean                                                   | Lower 95 CI | Upper 95 CI |
| ITR (°)               | 5.0                  | $\beta = + 3.7\text{N}$ per 1° increase, $p < 0.001$<br>[3.1, 4.3]     | + 18.8 N                                               | + 15.8 N    | + 21.7 N    |
| ATT (mm)              | 1.5                  | $\beta = + 15.8\text{N}$ per 1mm increase, $p < 0.001$<br>[13.0, 18.6] | + 23.1 N                                               | + 19.0 N    | + 27.2 N    |
| Valgus Angulation (°) | 1.7                  | $\beta = + 0.5\text{ N}$ per 1° increase, $p = 0.585$<br>[-1.4, 2.5]   | + 0.9 N                                                | - 2.4 N     | + 4.3 N     |
| Males (n = 48)        |                      |                                                                        |                                                        |             |             |
| ITR (°)               | 6.1                  | $\beta = + 5.5\text{N}$ per 1° increase, $p < 0.001$<br>[4.4, 6.6]     | + 33.6 N                                               | + 27.0 N    | + 40.2 N    |
| ATT (mm)              | 1.3                  | $\beta = + 6.3\text{N}$ per 1mm increase, $p = 0.055$<br>[-0.2, 12.7]  | + 8.1 N                                                | - 0.2 N     | + 16.4 N    |
| Valgus Angulation (°) | 1.7                  | $\beta = + 0.5\text{ N}$ per 1° increase, $p = 0.585$<br>[-1.4, 2.5]   | + 0.9 N                                                | - 2.4 N     | + 4.3 N     |

Results of multiple linear regressions that relate internal tibial rotation (ITR), anterior tibial translation (ATT), and valgus angulation to ACL force in males and females. IQR = interquartile range. N = newtons. mm = millimeter.  $\beta$  = regression coefficient. CI = confidence interval. n = sample size.

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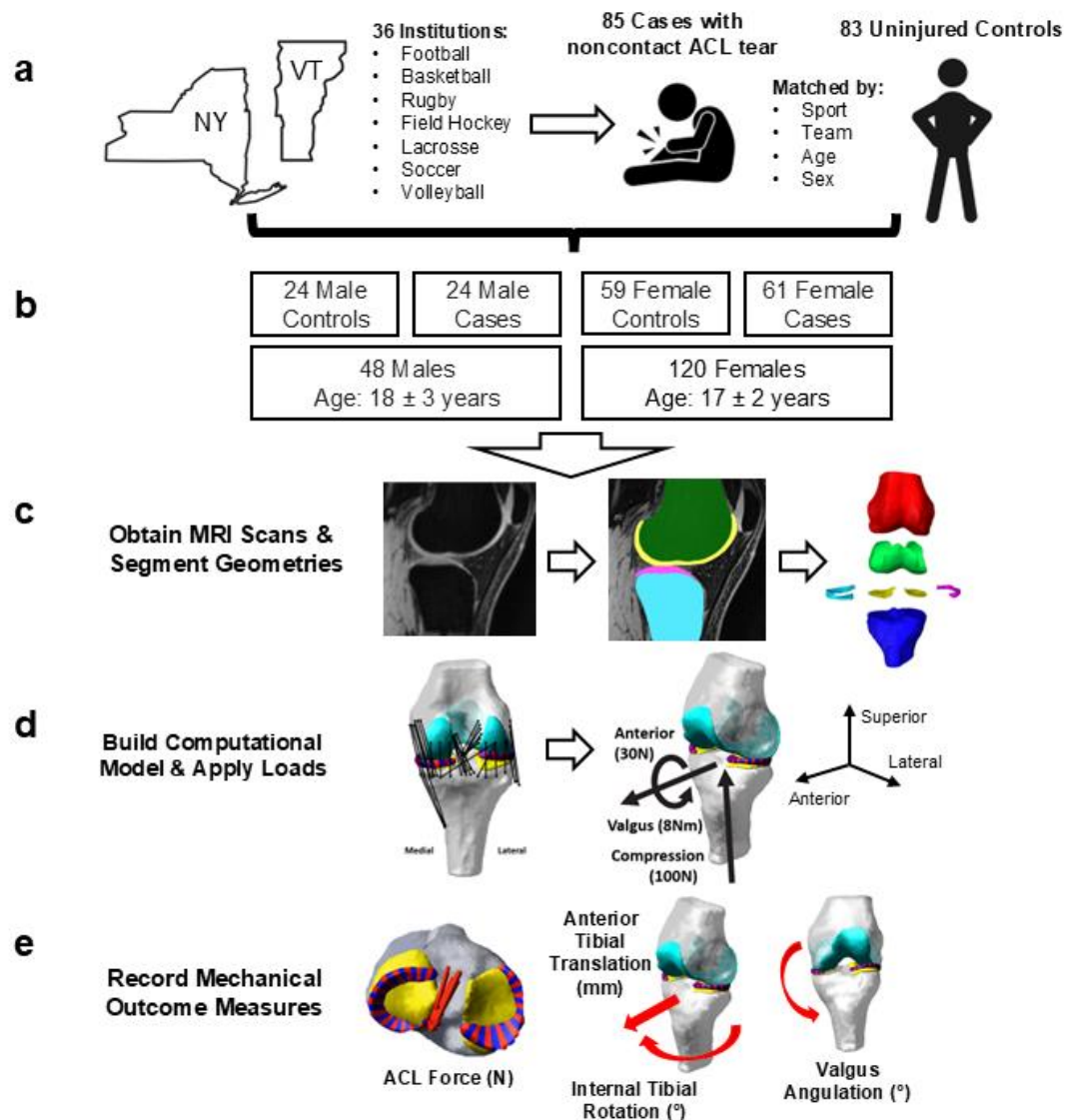
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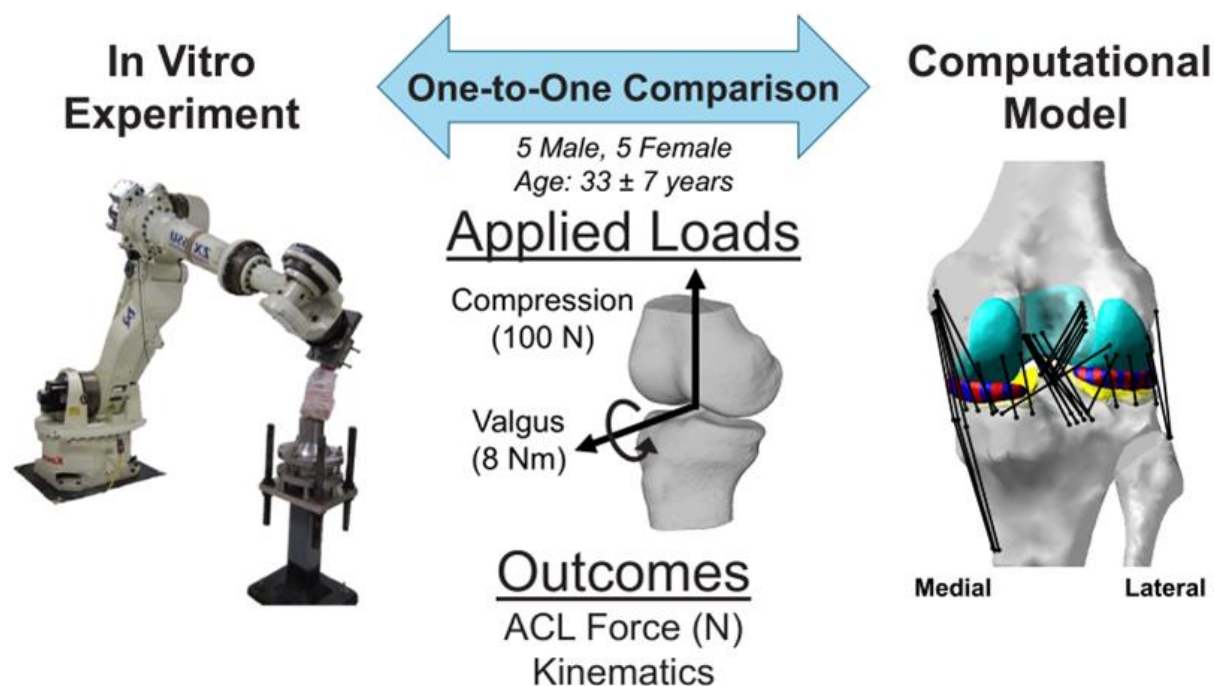
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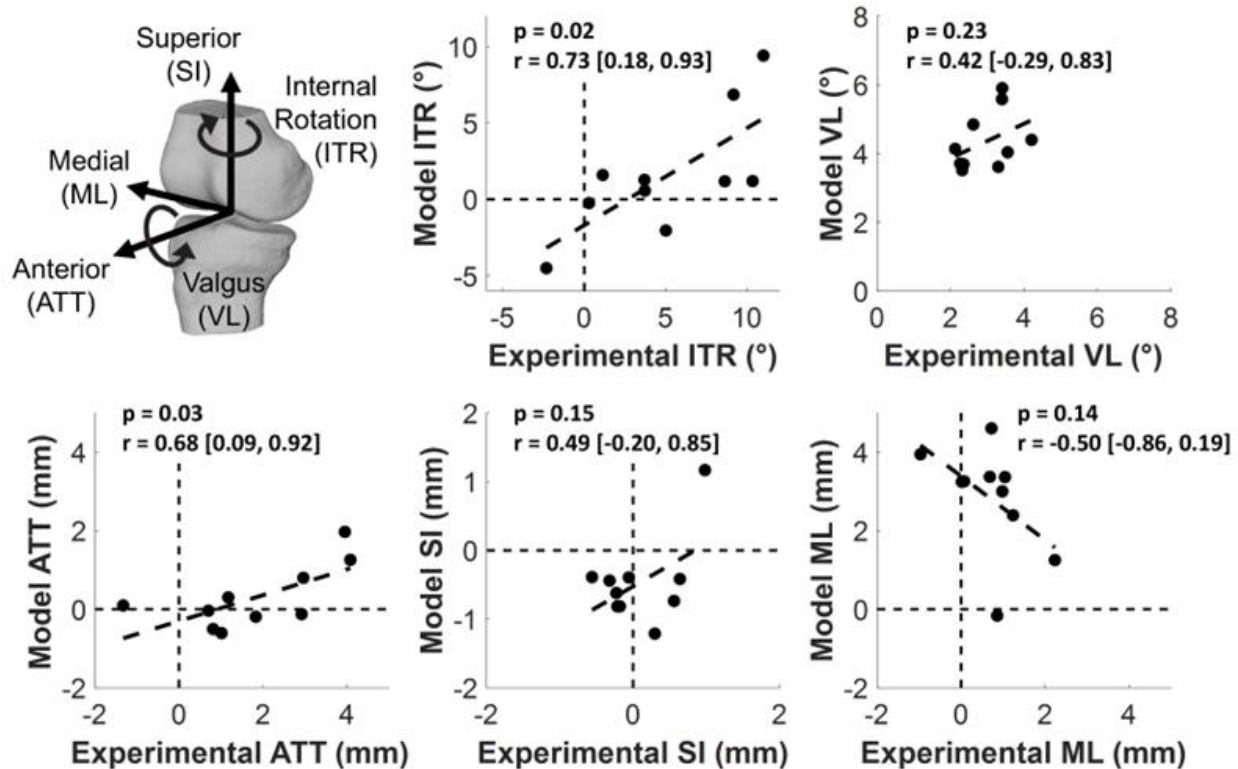
Supplementary Figures



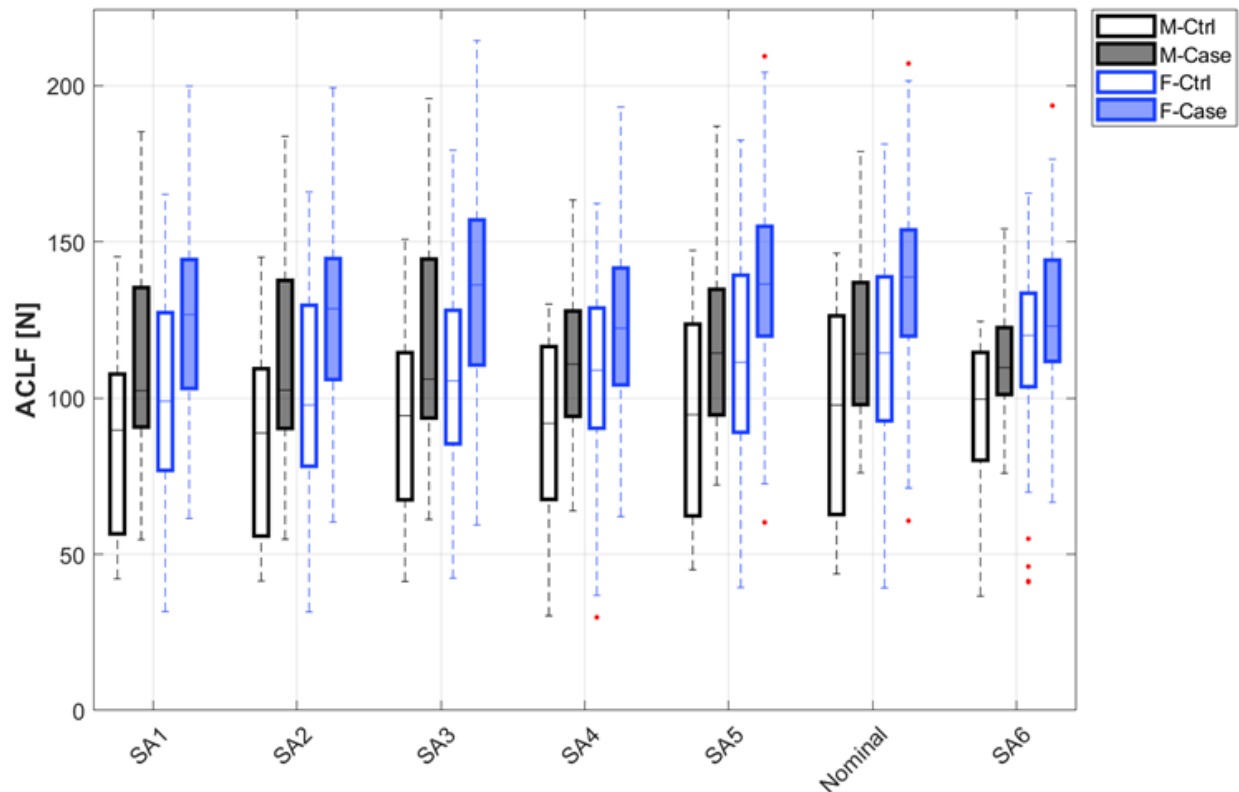
**Figure S1 | Cohort enrollment and computational modeling overview.** **a**, 168 young, active individuals participating in common sports across 36 institutions were enrolled. NY, New York; VT, Vermont. **b**, The cohort consisted of 48 males and 120 females, half of whom had sustained first-time noncontact ACL tear. **c**, Subject-specific knee geometries were segmented from MRI. **d**, Computational models were built with non-linear spring representations of the cruciate, collateral, and capsular ligaments and standardized slack length optimization. A standardized multiplanar loading condition was applied to each knee. **e**, The mechanical outcome measures were ACL force and anterior tibial translation, internal tibial rotation, and valgus angulation. N = Newtons. Nm = Newton-meters.



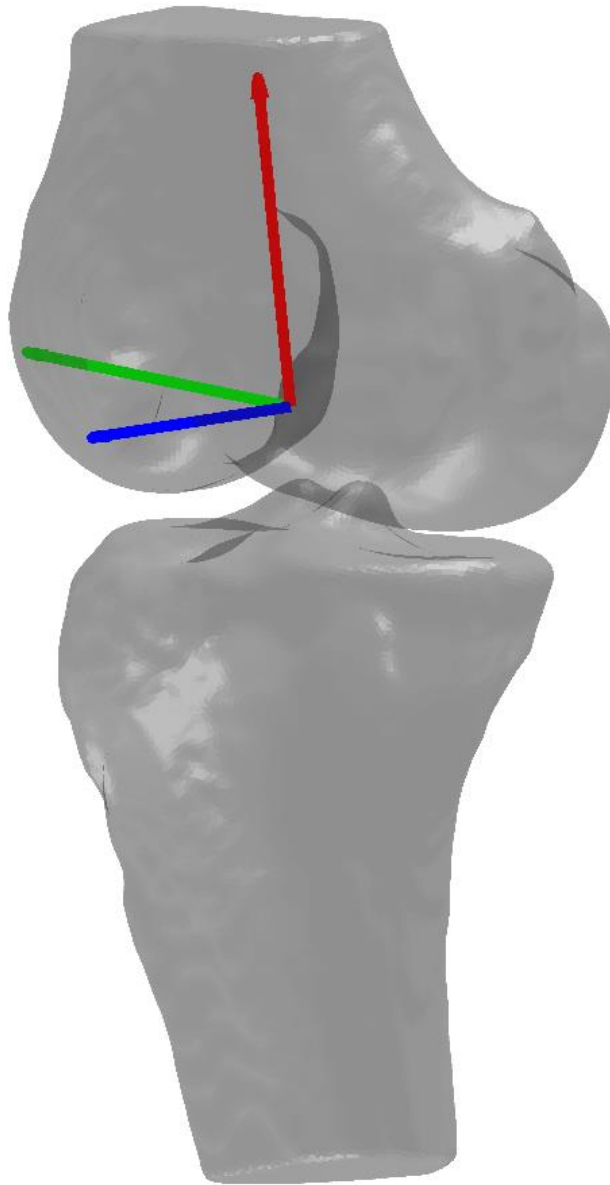
**Figure S2 | Correspondence experiment between computational model estimates and in vitro measures.** ACL force and tibiofemoral kinematics from an in vitro cadaveric experiment (left) in 10 cadaveric specimens were compared on a one-to-one basis to estimates from corresponding computational models (right) of the tibiofemoral joint (posterior view). Applied loads were compression (100 N) and valgus moment (8 Nm) applied serially at 15° of flexion. N = Newtons. Nm = Newton-meters.



**Figure S3 | Credibility assessment of kinematics from shape-specific computational model.** Model estimates of tibiofemoral kinematics were compared to measures from cadaveric experiment in 10 specimens using Pearson correlation coefficients. Positive kinematics represent anterior, superior, medial translations; internal, valgus rotations. P-values, estimate of the correlation coefficient ( $r$ ) and its [95% confidence interval] are reported for each kinematic variable. ITR = internal tibial rotation; VL = valgus rotation; ATT = anterior tibial translation; SI = superior-inferior translation; ML = medial-lateral translation.



**Figure S4| Shape-driven differences in anterior cruciate ligament (ACL) force between subgroups were robust to ligament properties.** ACL force (ACLF) estimates in male controls (M-Ctrl), male cases (M-Case), female controls (F-Ctrl), and female cases (F-Case) across seven different combinations of physiological ligament properties of the ACL and medial collateral ligament (MCL) including their slack lengths and stiffnesses (sensitivity analyses (SA) 1 thru 6, in addition to the nominal value). These combinations of ligament slack lengths and stiffness values range from representing the lowest (SA1) through highest (SA6) laxities. The boxes represent the interquartile range (IQR) of data, the horizontal line represents the median, and red points represent outlier data greater than 1.5-IQR from the median. ACLF was compared between male controls and male cases, and female controls and female cases for each combination of ligament properties using two-sample, two-tailed t-tests. No adjustment for multiple comparisons was performed. N=Newton



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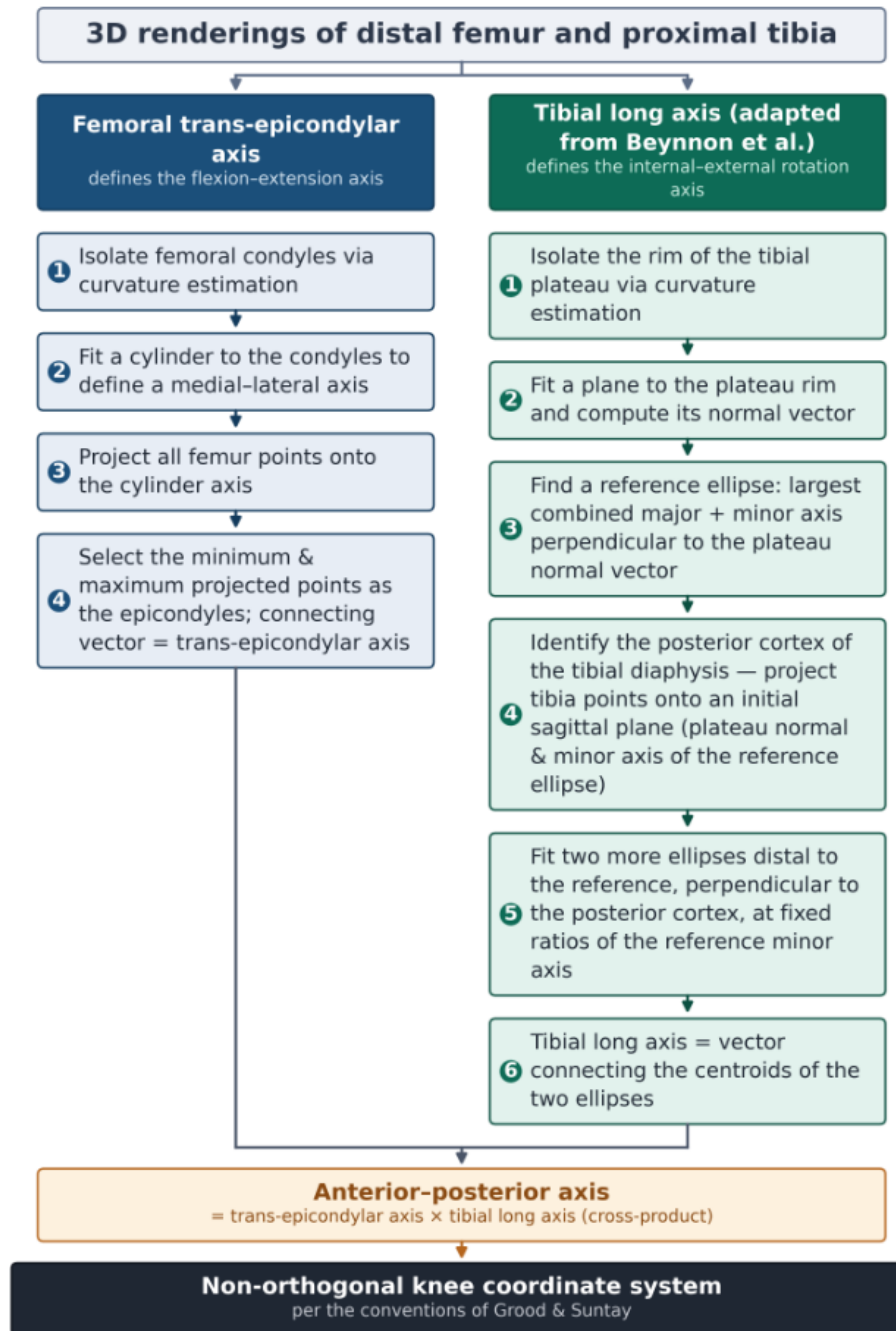
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**Figure S5| Knee coordinate system established from the 3D renderings of the tibia and femur bones.** The flexion-extension axis (green) was the transepicondylar axis of the femur. The internal-external rotation axis (red) was the long axis of the tibia. The anterior-posterior axis (blue) was the common perpendicular of the flexion axis and the internal-external rotation axis.



**Figure S6| Procedure for constructing a non-orthogonal knee coordinate system from 3D renderings of the distal femur and proximal tibia, based on the conventions of Grood and Suntay.**

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