Tyche: a free novel web-based solution for efficient and unbiased analysis of scientific images

Philipp Schippers (philipp.schippers@gmail.com)
Orthopaedic University Hospital Friedrichsheim
Gundula Rösch
Orthopaedic University Hospital Friedrichsheim
Rebecca Sohn
Orthopaedic University Hospital Friedrichsheim
Matthias Holzapfel
Orthopaedic University Hospital Friedrichsheim
Marius Junker
Orthopaedic University Hospital Friedrichsheim
Anna E. Rapp
Orthopaedic University Hospital Friedrichsheim
Zsuzsa Jenei-Lanzl
Orthopaedic University Hospital Friedrichsheim
Frank Zaucke
Orthopaedic University Hospital Friedrichsheim
Andrea Meurer
Orthopaedic University Hospital Friedrichsheim

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Abstract

Background

Scientific image analysis is crucial in many research fields but it can be hampered by subjectivity and bias. Thus, image analysis should be performed anonymized by multiple observers and images displayed in a random order. Yet in radiology for example most PACS-viewers display patient metadata which could influence the analysis. Although desirable, including multiple observers can be logistically difficult as files have to be provided including spreadsheets to document the analyzed parameters.

Methods

To address these challenges we created a browser-based program displaying scientific images anonymized and in a random order. Observers are invited by the project master via a project-specific URL that is only temporarily valid. The project master can design an unlimited number of project-specific questions which will be displayed next to each image. As the analysis is performed online, results from all observers are summarized in real-time and the data are immediately visible to the project master. In this study, we present the process of analysis using histological and radiological images and compare Tyche with the traditional “offline” desktop bound way.

Results

Tyche allows users to upload anonymized images and create single choice and numeric questions specifically for these images. Via temporarily active URLs, access to the data can be provided to observers who can analyze images within any web browser using the integrated tools (zoom, length, etc.). Next to each image, the defined questions and answers are displayed and results are immediately visible. Aspects of traditional image analysis like laborious file sharing via clouds or e-mail with observers and data gathering via potentially error-prone spreadsheets become obsolete. Performing a histologic image analysis, no difference in results comparing Tyche with the offline analysis were found.

Conclusion

Tyche is a lightweight, web-based tool that facilitates anonymized image analysis by multiple observers and reduces subjectivity and bias.

Introduction

Reliable image analysis is an essential part of scientific work but comes along with several challenges. To minimize subjectivity and bias, any person included in study conduction and data analysis should be blinded (Karanicolas et al. 2010) and analyze the data in a randomized order.

Experts from outside the own work group/institution should ideally be included, but transferring the data, explaining the approach and gathering their results can be laborious and complicated. Finally, regardless of their location, hard- or software, all observers within one study should use the same standardized analysis tools (e.g. software version etc.).

In a daily practice, distribution of images for analysis is often done by sharing large file folders via clouds, sending by e-mail or USB-devices accompanied by an additional spreadsheet for evaluation and later statistical analysis. In a clinical setting, observers are often provided with a list of patients and analyze images using the hospital's local Picture Archiving and Communication System (PACS), in which patient data are visible, thereby possibly involuntarily influencing the analysis because e.g., gender or age is revealed. Also in basic research, where blinding during study conduction is often difficult, there is the risk of bias during image analysis due to known group allocations, that might be disclosed even by the specimen ID. Therefore, a system enabling blinding and randomization for image analysis easily, is highly favorable.

It should be kept in mind that all steps involving multiple observers can be laborious and time-consuming, this includes preparatory steps such as (pseudo)-anonymization, as well as gathering and merging of data after analysis via copy-and-paste or by hand, all of which are error-prone. To address the above-mentioned challenges in image analysis, we developed a free, browser-based tool named Tyche, referring to the ancient Greek goddess of fortune and destiny. After gathering imaging data, a user can upload images as single files or stacks (as in CTs or MRIs) as well as videos and create corresponding questions/tasks and answers which will be displayed next to each image to be analyzed. Via a project-specific URL, as many observers as needed/desired can be invited to analyze the data comfortably in their own browser making file sharing and spreadsheets obsolete. As a means of safety, the URL is only valid for 7 days, but can be renewed any time by the project master. Tyche displays image by image (or stack by stack) in a randomized order and anonymized, making it impossible to draw any conclusion from the filename or group the image belongs to. Observers can use standardized tools for display (pan, contrast, etc.) and measuring of different parameters (length, angle, count, freehand-area, etc.). As all analysis is done online, results can immediately be calculated and displayed either combined for all observers, individually per observer, or for definable observer groups e.g. reflecting different levels of expertise. By storing data and results centrally, they can easily be accessed in the future for further analysis in case new questions concerning the data arise.

Methods

In order to start a new image analysis with Tyche, the following steps create a project: (I) defining a project name, (II) creating questions/tasks and (III) uploading images. Questions or tasks can be individually created for each project and must be answered by each observer for every image with single choice or numeric responses (Figure 1). Image files can be uploaded easily via drag-and-drop, if needed assigned to different data-groups, e.g. placebo vs. verum or 2 weeks vs. 4 weeks etc. (Figure 2). Later, results can be displayed comparing such different data-groups.

If desired, observers can choose an observer-group at the beginning of their analysis (e.g. PhD-student or Postdoc, etc.) reflecting different levels of experience. These observer-groups can be defined by the project master at the creation of the project. Finally, the results can be displayed and evaluated separately according to the different observer-groups.

Once a project is created, it appears in the user's individual project list. From here, access to the data can be shared via a temporary URL or results can be displayed (Figure 3).

Tyche employs several open source libraries and software: *Joomla!*, a content management system mostly for user management, *dropzoneJS* to facilitate uploading data and *cornerstone* as well as *cornerstone Tools* to handle image display. Programming code is written in PHP, Javascript and MySQL. All connections are encrypted via SSL. Tyche can handle and display images (*.jpg, *.png), videos (*.mp4) and DICOM-files (*.dcm), as well as zip-compressed stacks of the latter.

Results

To demonstrate the different features and provide examples of how Tyche can be applied and facilitates the analysis of data collected by different observers, typical images that need to be analyzed in an orthopedic department/clinic/lab were selected. Of course, questions and parameters to be analyzed can be tailored to the user's requirements with almost unlimited possibilities.

As illustrated in Figure 4, Tyche can display DICOM-images as in x-rays. Standard tools like zoom, pan, and contrast can be used as well as tools for analysis, including count, length, angle, freehand-area, and probe. Tyche recognizes length-per-pixel ratios stored as meta-data in DICOM-images and translates measurements from pixel (px) to length (mm) and area (mm^2) accordingly. Alternatively, Tyche provides a calibration tool that allows to enter a scaling factor directly or calculate the scale by measuring the current size (in px or mm) of an object with known size, e.g. ball marker (usually 25 or 30 mm) in orthopedic imaging (Figure 5).

Micrographs stored as JPG or PNG can be analyzed as well (Figure 6) using the tools mentioned above. In Figure 7, the count-tool is used on a tissue section of tibial cartilage to count specific cells and calculate a density by respecting a predefined area.

In this study, we asked 4 observers to analyze a series of tissue sections from murine knee joints in which osteoarthritis was surgically induced by destabilization of the medial meniscus (Glasson et al. 2007). The medial tibial cartilage was evaluated according to the recommendations of the OARSI (Osteoarthritis Research Society International) histopathology initiative (Glasson et al. 2010) using a score between 0 and 6.

First, a new project was created as described in Figure 1 and 2. We uploaded images of sections generated from samples 2, 4, 8 and 12 weeks after surgery and assigned them to different groups. The results obtained from the different observers and groups, respectively, are shown in Figure 8. Immediately after each observer has finished the analysis, results will be available and ready to be exported if necessary. They are displayed either for all 4 observers together or for each observer individually. In order to validate the results gathered by Tyche we analyzed the same tissue sections in parallel using the traditional offline approach on a desktop. Figure 9 shows the comparison of the two approaches as total score per group (Figure 9A) as well as Spearman's correlation (Figure 9B). No significant difference between Tyche and the offline method was observed.

Conclusion

Image analysis is done on a daily basis in basic research as well as in a clinical setting. A variety of tools with differing advantages and limitations are available to analyze images. Amongst these, there are tools like *ImageJ/Fiji* (open source) (Schindelin et al. 2012; Schneider et al. 2012) that are often used in basic research and comprise powerful tools to create complex image analysis pipelines. Medical images including x-rays, CTs, or MRIs are usually visualized on PACS-viewers with basic tools for measurements, while more complex measurements (e.g. joint replacement planning) are performed by exporting the images to tools like *mediCAD®* (mediCAD Hectec GmbH, Altdorf, Germany). The above-mentioned tools are mostly desktop-bound and results are stored separately.

Survey-tools like *SurveyMonkey®* (SurveyMonkey Inc., San Mateo, California/USA) or *Qualtrics®* (Qualtrics International Inc., Provo, Utah/USA) can be used to reach out to multiple observers but are more qualified to gather opinions rather than analyze data. Besides, they offer limited possibilities to display medical images or tools for measurements. Each question and answer is created individually which can be challenging in projects comprising many images to analyze where a project master would have to create the same question n-times, one after another.

Another way to analyze images is by employing artificial intelligence (Pedoia and Majumdar 2018; Pedoia et al. 2018; Lee et al. 2020). This highly efficient method relies largely on algorithms that can process vast amounts of data without the risk of human error. Yet the accuracy of these algorithms is not only based on their code but also on the quality of the images, they were trained with. Additionally, setting up an algorithm for specific analyses can be laborious and require some technical skills.

The goal of TYCHE was to create a lightweight browser-based tool to simplify image analysis by multiple observers, even across labs and countries. It certainly has – as of today – rather basic measurement tools in contrast to advanced desktop-bound tools. However, results are stored online and can immediately be seen by the project master. In contrast to existing survey tools, it is well prepared for scenarios in which the same score or measurement has to be applied on multiple images. Questions/tasks and answers are only created once and are then applied to all the uploaded images within one project. In case a different question/task is asked for each image, a classic survey tool is the better option.

Blinding and randomization during data analysis is gaining more and more importance in science to increase objectivity. Nowadays, journals such as Nature request information about blinding and randomization in studies, including if and how randomization was achieved, if data analysis was done blinded and, if not, why randomization/blinding were not done. (https://www.nature.com/documents/nr-reporting-summary-flat.pdf, accessed on Nov 4th, 2021). Sometimes, group allocation is disclosed due to sample labelling, and especially when more than one staining is applied to tissue sections, bias can be introduced in a way that features are over- or underrated, dependent on group allocations. Furthermore, if randomization was not possible during sample preparation, specimens of one treatment group might come after each other and are analyzed in that same order. Here, Tyche provides an easily applicable solution, as pictures are displayed without annotations/file names visible to the observer and in a randomized order. The same holds true for clinical data that is analyzed for a specific scientific context, also here, blinding for conditions and randomization is highly advised. It has to be noted, that Tyche does not anonymize the image files itself but displays them anonymized. It is impossible for the observer to view the filename or any metadata stored in the header of the image. Neither the image nor the image storage path can be accessed directly as opposed to images normally displayed on websites where all this information can be visualized with a right-click. Meta-data or any information that had been written or painted on the image using a graphic program like Microsoft Paint® or Photoshop® can not be removed by Tyche.

An increasing number of scores and grading systems is being established in basic research and medicine. The OARSI-score, which was used in this study, can be considered a broadly accepted means of analyzing histological images in the scientific community working on osteoarthritis. In the clinical environment, scores and grades applied to medical images are a substantial part in finding the right treatment options and thus the demand for reliable analysis is high. With TYCHE we aim to facilitate and standardize the approach of analyzing images while trying to minimize subjectivity and bias. In the present study, we used the OARSI-score to validate TYCHE for the use of a score to analyze images. As opposed to the traditional offline analysis on a desktop, images were analyzed in a random order by multiple blinded observers online. Results were immediately visible for the project master.

In summary, we present a novel, free, browser-based tool to facilitate image and video analysis by multiple observers. By displaying anonymized data in a random order, TYCHE helps to reduce subjectivity and bias. Furthermore, as the analysis is done online, file sharing of the imaging material with observers as well as gathering results via spreadsheets become obsolete, and therefore Tyche facilitates collaborations of different labs.

A free TYCHE-account can be requested at philipp.schippers@gmail.com.

Declarations

Authors' contributions

PS created Tyche and owns all rights. PS analyzed and interpreted the data and was a major contributor in writing the manuscript.

GR, RS, MH and MJ analyzed and interpreted the data. GR, AER, ZJL and FZ were major contributors in writing the manuscript.

All authors read and approved the final manuscript

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Login credentials for www.tyche.expert

The results were acquired using the personal Tyche account from the first author and creator of Tyche. In this account other projects are visible, hence login credentials cannot be provided. If desired, test-accounts on Tyche can be provided to reviewers upon request: philipp.schippers@gmail.com.

Ethics approval and consent to participate

For knee x-ray:

Patients were informed about the purpose of the study and gave their written consent. The Ethics Committee of the Johann Wolfgang Goethe-Universität Frankfurt am Main approved the project (vote number 19-347). All investigations were performed in accordance with relevant guidelines and regulations.

For histologic images:

All experiments were approved by and conducted according to institutional and governmental regulations for experimental animal usage (Ethical Review Committee, Government of Unterfranken, GZ 55.2-2532-2-368).

Competing interests

PS created and owns all rights about Tyche. PS has no competing financial interests.

The other authors declare that they have no competing interests.

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Figures

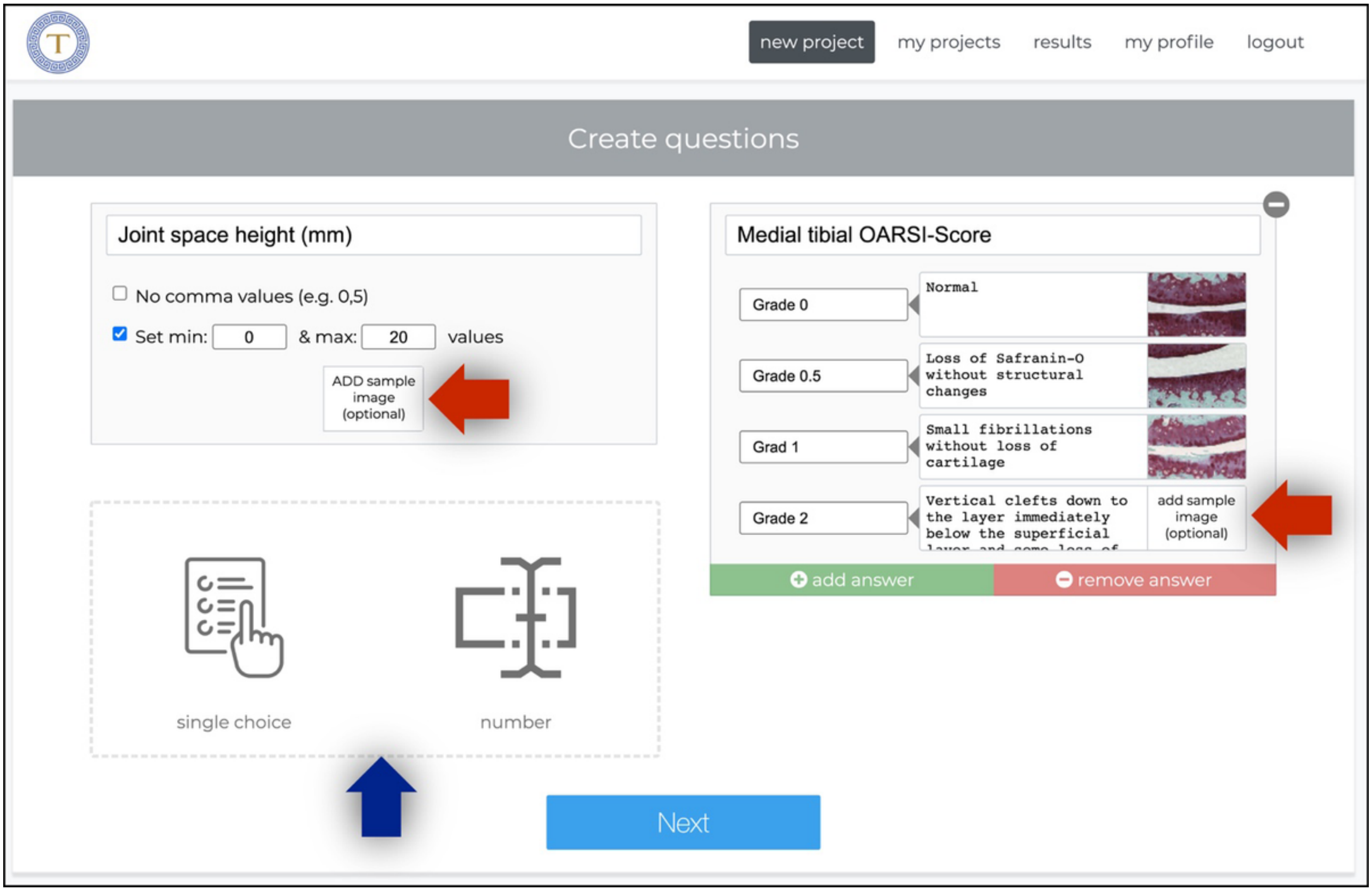

Figure 1

Create single-choice and numerical questions for a new project

The first grey box shows a numerical question (“Joint space height (mm)”). Min and max values are predefined here (0 – 20). The second grey box shows the creation of a single choice question (“Medial tibial OARSI-Score”). The red arrows point at boxes to upload example images. Clicking at the box with the blue arrow adds a single-choice or numerical question. Unlimited questions and answers can be created. Questions and answers will be applied to every image.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche. Histologic images with permission from Rösch et al. 2021)

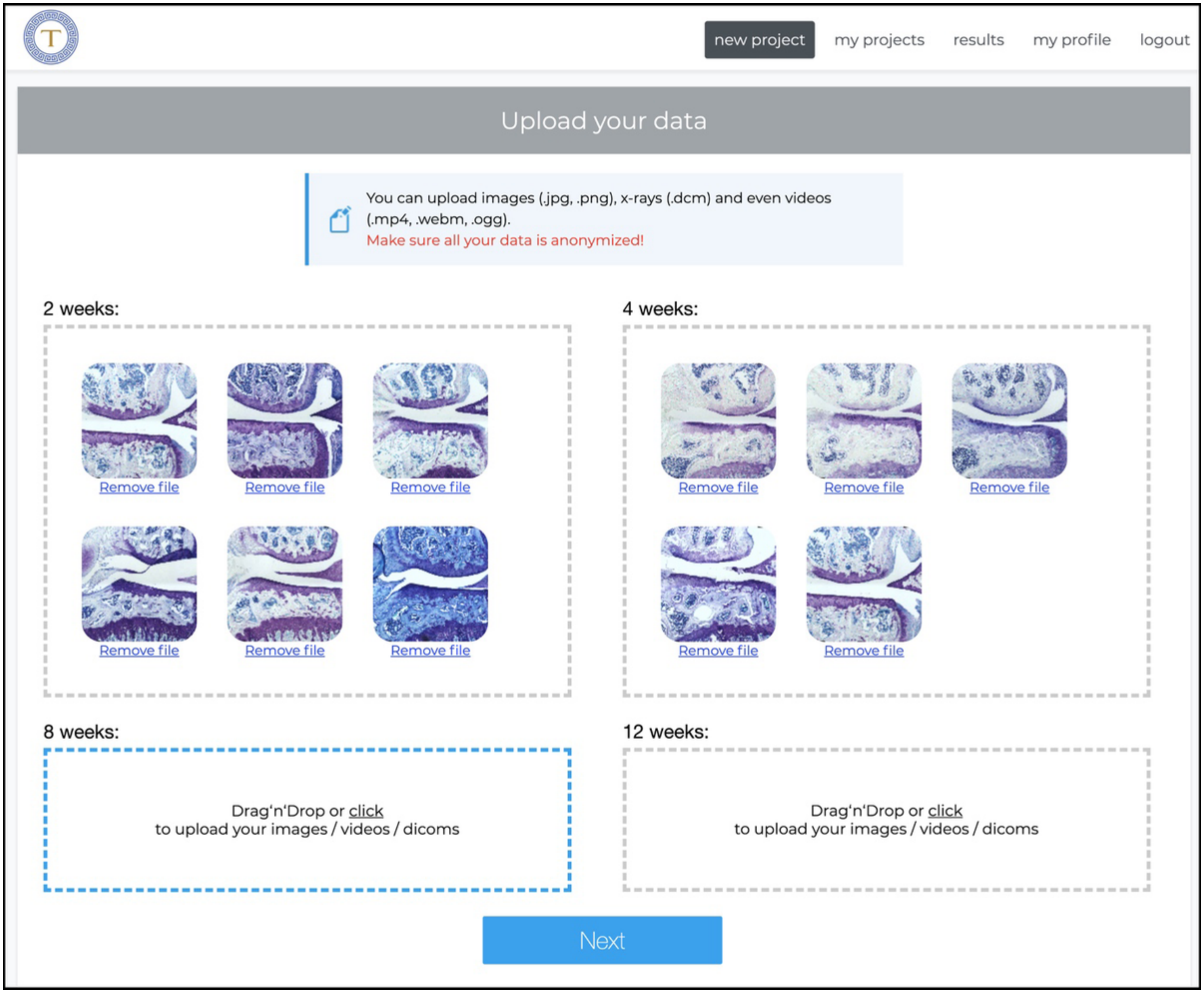

Figure 2

Upload data

Images can be uploaded via drag-and-drop, optionally into different groups as shown here ("2 weeks", "4 weeks", "8 weeks", "12 weeks").

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche. Histologic images with permission from Rösch et al. 2021)

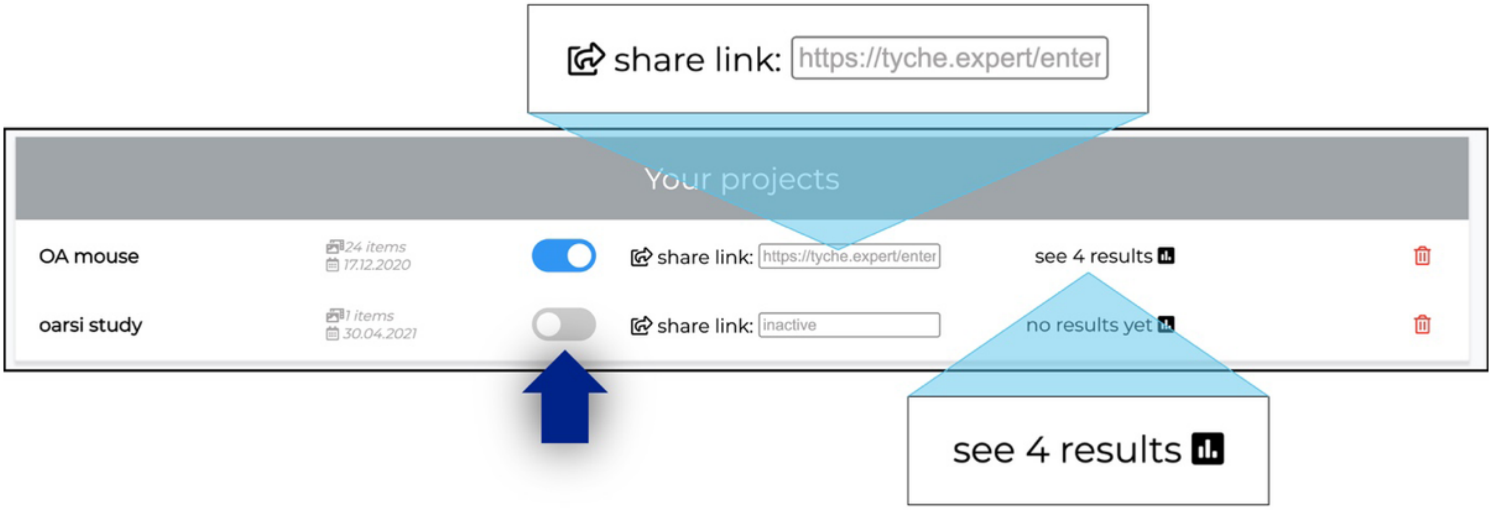

Figure 3

Homepage of a TYCHE-user

A TYCHE-user's list of projects is shown. Each project has a specific URL ("share link") to share the images with peers for analysis. To see the results, one clicks on ("see x results"). The vertical blue arrow points at the switch button. In active state (blue, first row) the share link is visible and accessible. 7 days after creation of the project or activation of the switch button, the button turns grey (second row) and the share link is invisible as well as inaccessible.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche)

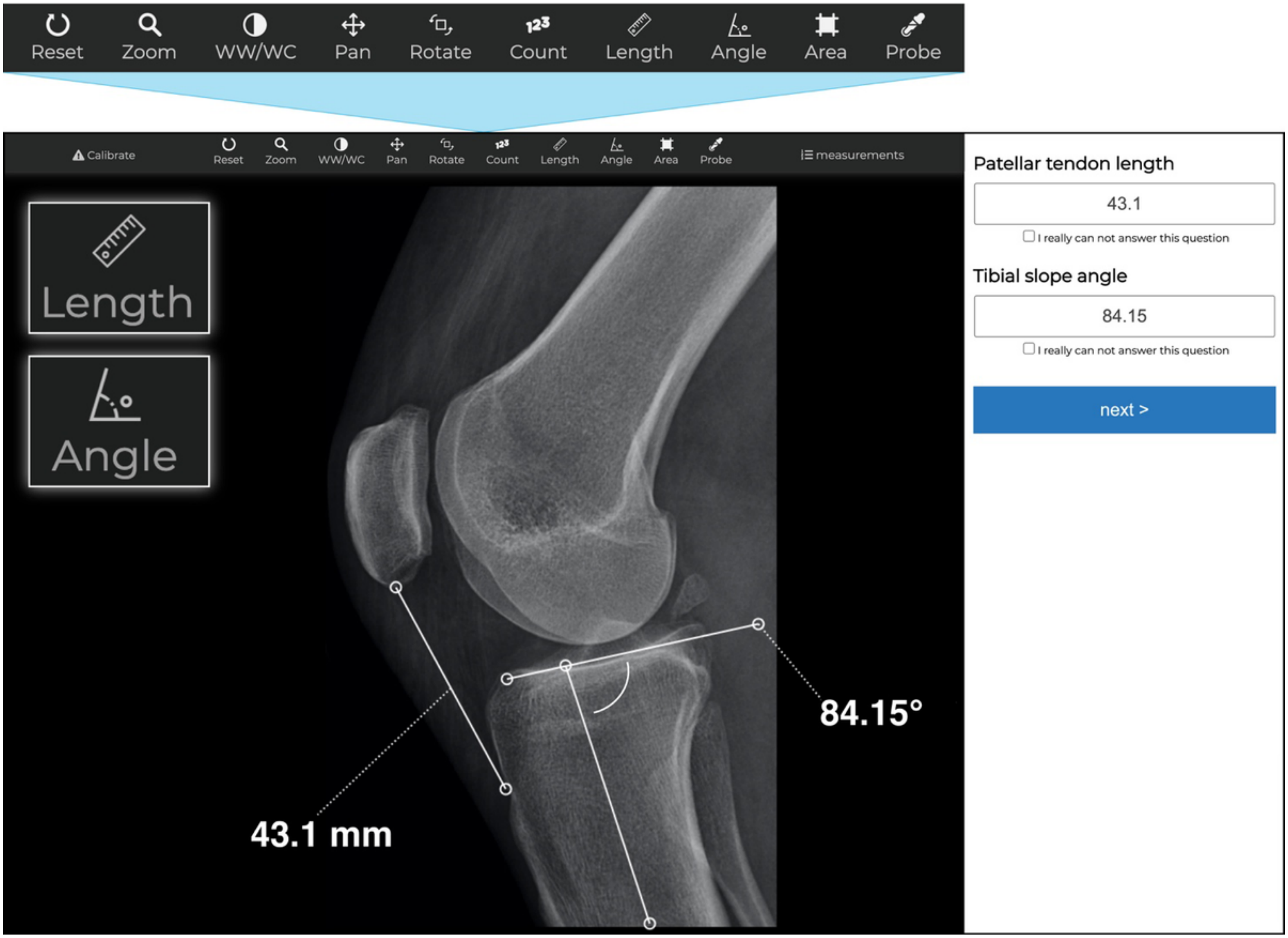

Figure 4

Length- and Angle-tool in lateral knee x-ray

This screen is seen by observers when they analyze the data. On the left side, a random image from the database is displayed. The right side shows the questions and answers defined by the project master. In this example, a lateral radiograph of a human knee joint is shown. The observer picks the Length- and Angle-tool from the toolbox (top) to determine “patellar tendon length” and “tibial slope” and enters the results in the text field on the right side.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche. Knee x-ray from our database with informed consent from patient)

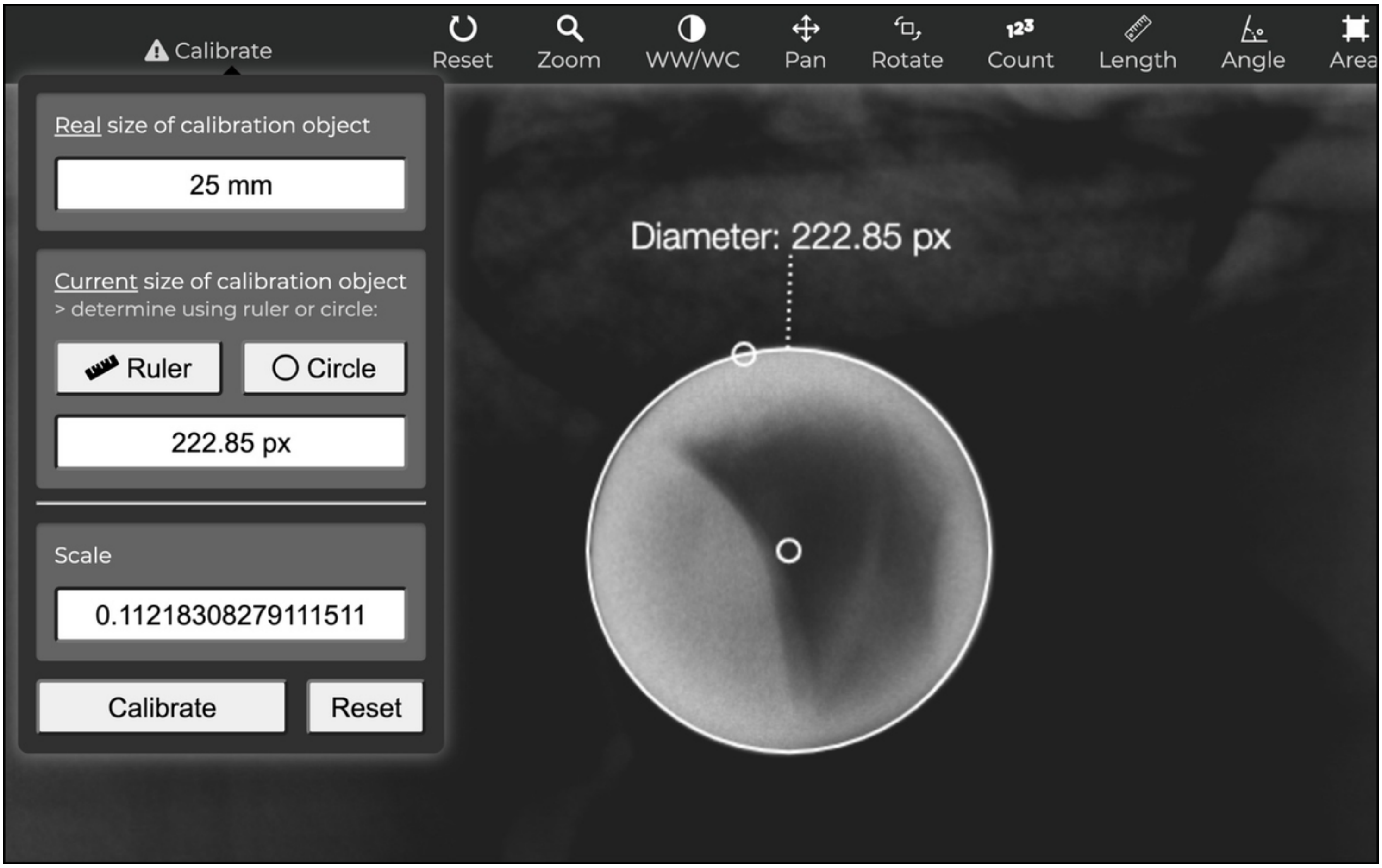

Figure 5

Calibration-tool: determine the size of the ball marker diameter to calibrate measurements

Hoovering “Calibrate” in the top left corner of the toolbar opens the calibration tool. Here, the size of a 25 mm ball marker is measured as 222.85 px using the circle tool. The calibration scale is automatically calculated and displayed in “Scale”. Alternatively a calibration scale could be entered directly. Clicking on the “Calibrate”-button in the bottom left corner of the calibration tool applies the scale and all measurements are now shown in mm.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche)

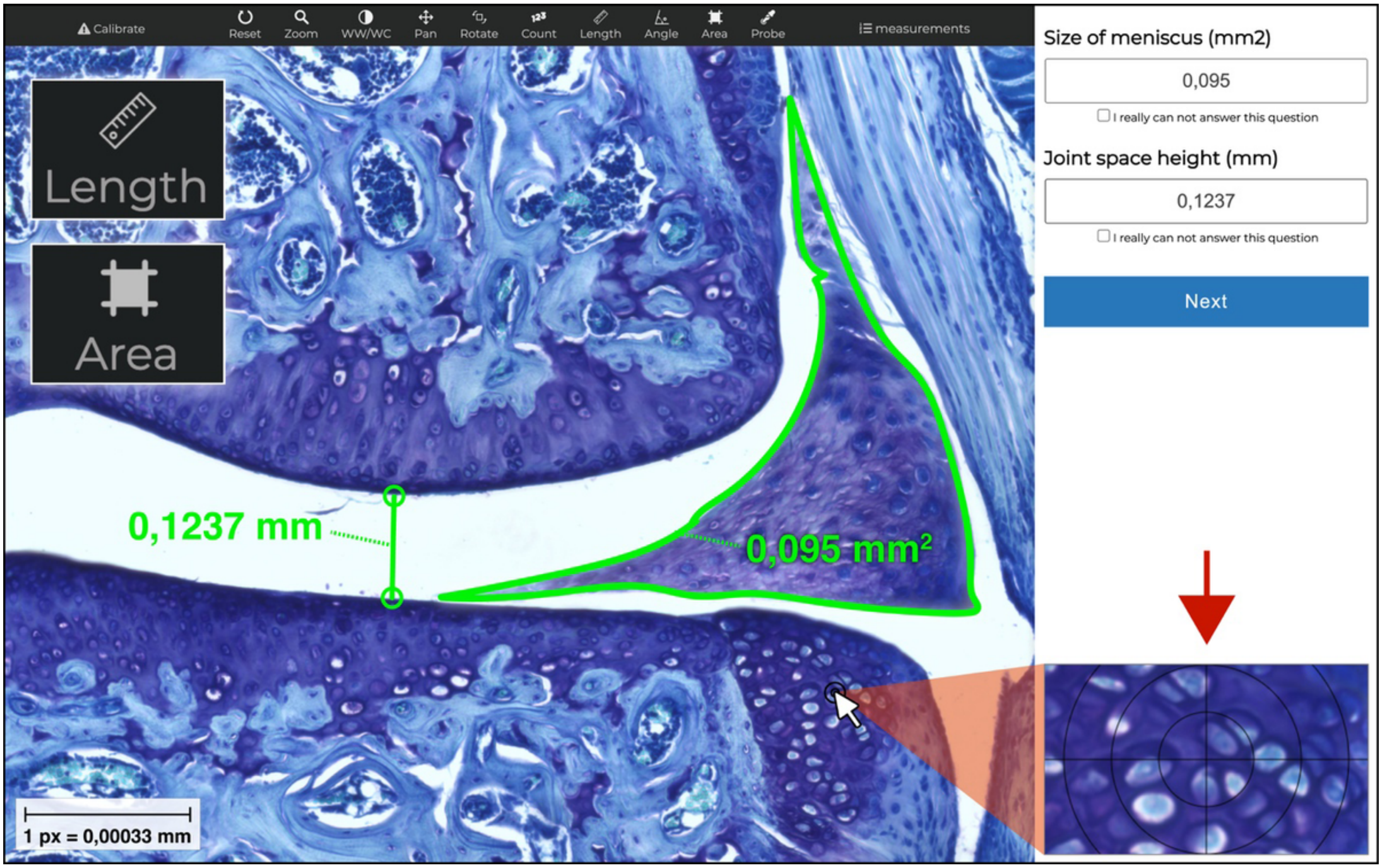

Figure 6

Length- and Area-tool in histological image of murine knee joint

Observer uses Length- and Area-tool to determine "size of meniscus" and "joint space height". Since 1 px equals 0,00033 mm, a scale-factor (Figure 5) of "0,00033" was applied and thus measurements shown in mm.

The red arrow points at the magnifier tool which constantly displays a magnification of the current cursor position.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche. Histologic images with permission from Rösch et al. 2021)

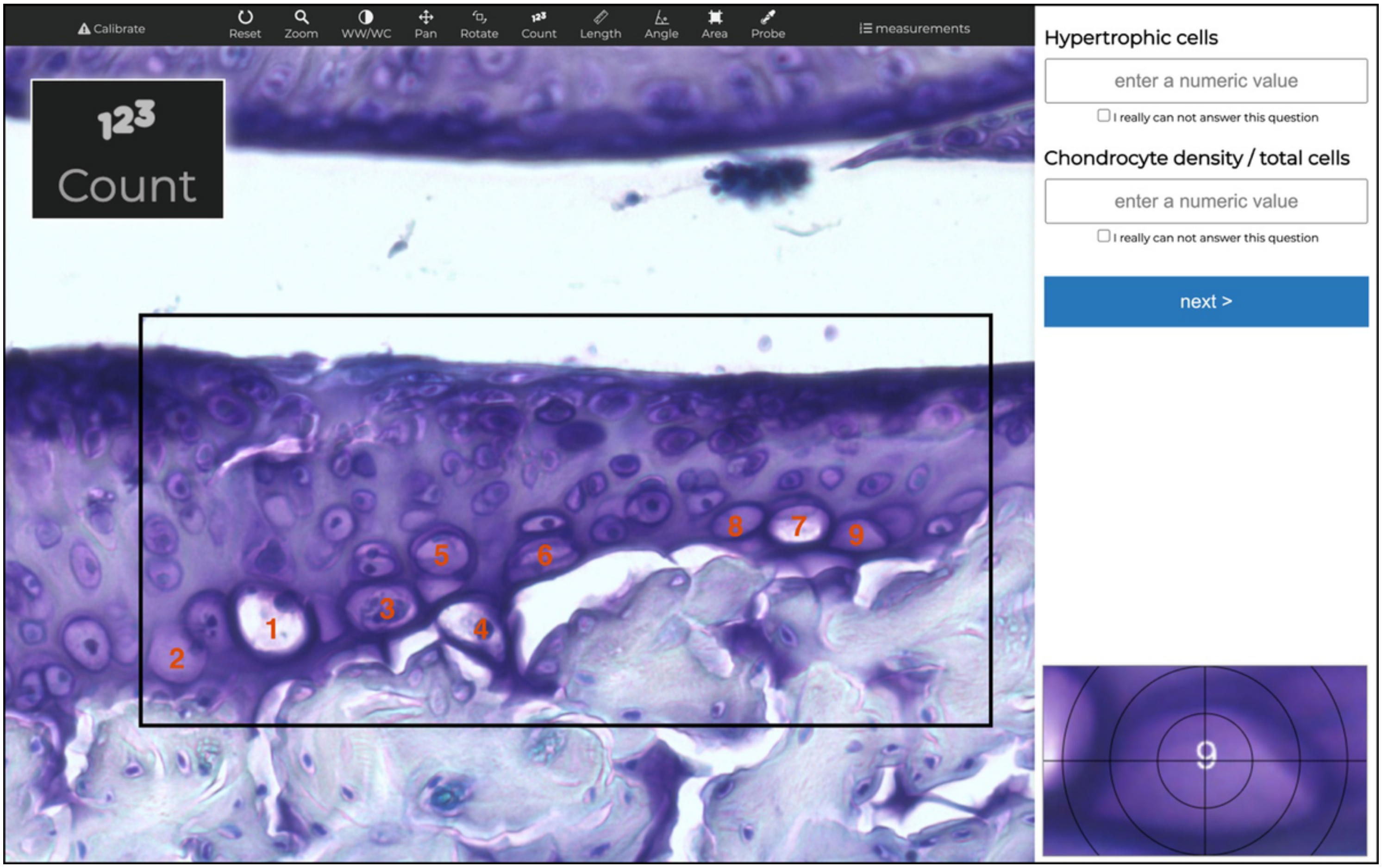

Figure 7

Count-tool in histological image of murine tibial cartilage

The Count-tool pins an incrementing number with every click and is used here to count hypertrophic chondrocytes. By counting all cells inside a predefined square, a density can be calculated as demanded on the right in the second question.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche. Histologic images with permission from Rösch et al. 2021)

2 weeks	Medial ti[…]							
Filename ↓	Grade 0	Grade 0.5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
205-90.jpg	3	0	1	0	0	0	0	0
206-86.jpg	0	2	1	1	0	0	0	0
207-50.jpg	2	1	1	0	0	0	0	0
208-70.jpg	2	2	0	0	[illegible]	[illegible]	[illegible]	[illegible]
229-60.jpg	3	1	0	0	0	0	0	0
231-30.jpg	3	0	1	0	0	0	0	0
Sum:	13 / 54%	6 / 25%	4 / 17%	1 / 4%	0 / 0%	0 / 0%	0 / 0%	0 / 0%

8 weeks	Medial tibial OARSI-Score							
Filename ↓	Grade 0	Grade 0.5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
80-60.jpg	0	0	0	2	1	1	0	0
82-70.jpg	0	1	2	1	0	0	0	0
86-42.jpg	2	1	1	0	0	0	0	0
87-86.jpg	0	2	2	0	0	0	0	0
88-50.jpg	0	0	1	2	0	0	0	1
90-40.jpg	0	0	0	2	0	2	0	0
Sum:	2 / 8%	4 / 17%	6 / 25%	7 / 29%	1 / 4%	3 / 13%	0 / 0%	1 / 4%

4 weeks	Medial tibial OARSI-Score							
Filename ↓	Grade 0	Grade 0.5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
9-80.jpg	0	1	0	3	0	0	0	0
10-41.jpg	0	0	3	1	0	0	0	0
15-130.jpg	0	0	1	2	0	1	0	0
16-70.jpg	0	1	2	1	0	0	0	0
19-80.jpg	0	1	2	1	0	0	0	0
25-50.jpg	0	0	0	0	0	3	1	0
Sum:	0 / 0%	3 / 13%	8 / 33%	8 / 33%	0 / 0%	4 / 17%	1 / 4%	0 / 0%

12 weeks	Medial tibial OARSI-Score							
Filename ↓	Grade 0	Grade 0.5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
136-28.jpg	1	2	1	0	0	0	0	0
140-100.jpg	0	0	0	1	1	2	0	0
142-60.jpg	0	0	0	0	1	1	2	0
149-40.jpg	0	0	0	0	1	2	1	0
159-49.jpg	0	0	0	1	0	3	0	0
137-50.jpg	0	0	0	0	1	3	0	0
Sum:	1 / 4%	2 / 8%	1 / 4%	2 / 8%	4 / 17%	11 / 46%	3 / 13%	0 / 0%

Figure 8

Results

This screen opens when a TYCHE-user clicks “results” on the menu at the top right corner. First, a project is selected (green arrow). All the observers that finished the analysis are listed (blue arrow) and can be in- or excluded in the results using the checkbox next to the name. Usually the name each observer chooses is shown but here they are listed numerically to protect their privacy. Results are then shown for each group (red arrow), here “8 weeks”. As an example, the orange arrow points at results for image “87-

86.jpg”, showing that 2 observers scored “Grade 0.5” and 2 observers “Grade 1” (orange boxes respectively) for the “Medial tibial OARSI-Score”.

(Source: Screenshot from Tyche interface, taken by first author and creator of Tyche)

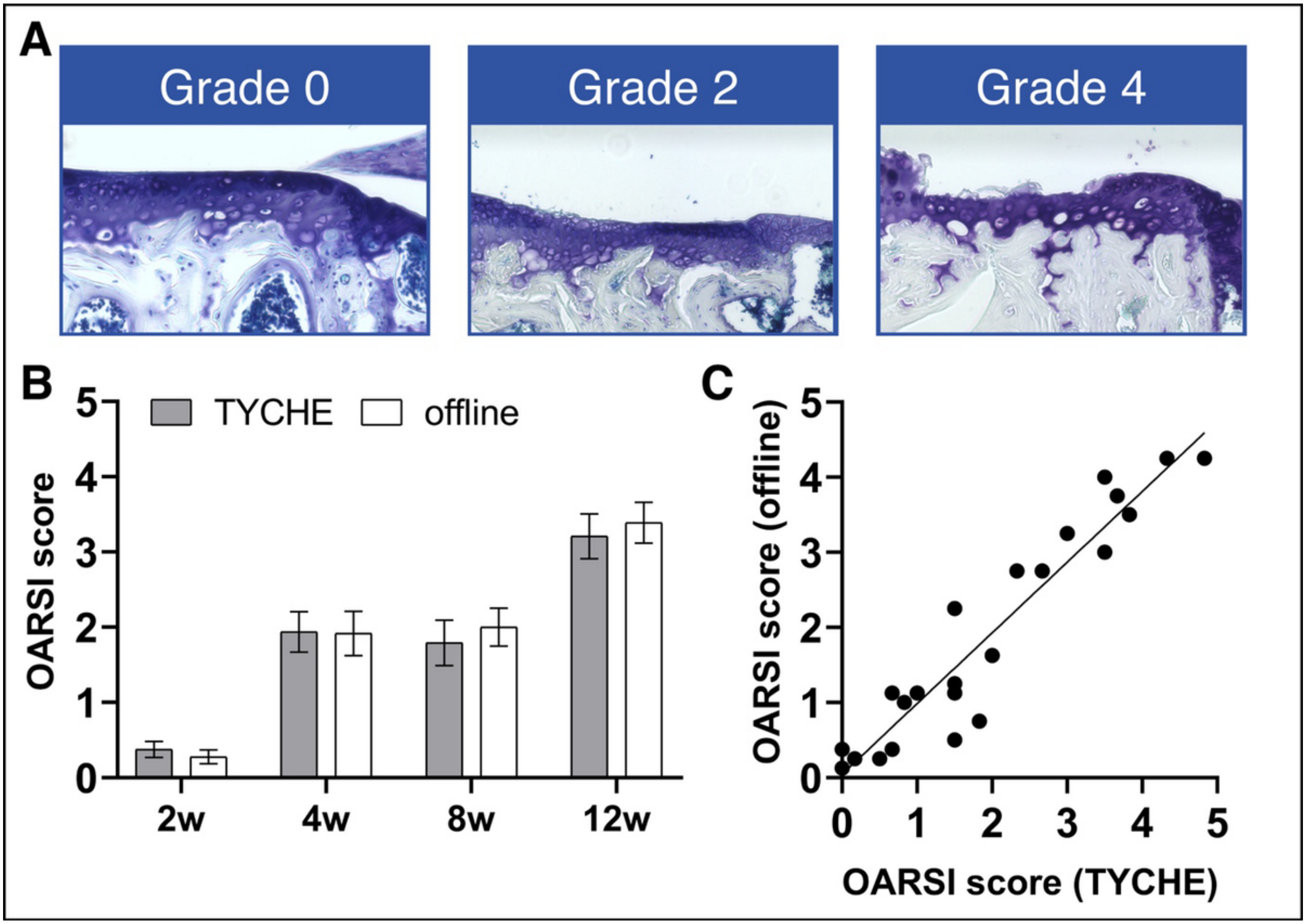

Figure 9

Analyzing the OARSI score using TYCHE and offline method

Representative pictures of the medial tibial articular cartilage contact area using histological staining (A) and the quantitative analysis of the OARSI score (n=6) using TYCHE and the common method (offline) (B), as well as the Spearman´s correlation (r = 0.951) between these methods (C).

(Source: Histologic images with permission from Rösch et al. 2021)