

Prospectus Supplement No. 2
(To Prospectus dated March 30, 2023)

Comera Life Sciences Holdings, Inc. 5,000,000 Shares of Common Stock

This prospectus supplement no. 2 (this "Prospectus Supplement") updates, amends and supplements the prospectus dated March 30, 2023 (as amended or supplemented from time to time, the "Prospectus") which forms a part of the Registration Statement on Form S-1 (Registration Statement No. 333-267283) filed by Comera Life Sciences Holdings, Inc. ("Holdco"). Capitalized terms used in this Prospectus Supplement and not otherwise defined herein have the meanings specified in the Prospectus.

This Prospectus Supplement is being filed to update, amend and supplement the information included or incorporated by reference in the Prospectus with the information contained in our Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission (the "SEC") on May 12, 2023 (the "Quarterly Report"). Accordingly, we have attached the Quarterly Report to this Prospectus Supplement.

This Prospectus Supplement is not complete without, and may not be delivered or utilized except in combination with, the Prospectus, including any amendments or supplements thereto. This Prospectus Supplement should be read in conjunction with the Prospectus and any amendments or supplements thereto. If there is any inconsistency between the information in the Prospectus and this Prospectus Supplement, you should rely on the information in this Prospectus Supplement.

The Holdco Common Stock is listed on The Nasdaq Capital Market ("Nasdaq") under the symbol "CMRA", and the Holdco Warrants are listed on Nasdaq under the symbol "CMRAW". On May 11, 2023, the closing sale price of the Holdco Common Stock as reported on Nasdaq was \$0.7299 per share, and the closing sale price of the Holdco Warrants as reported on Nasdaq was \$0.0312 per warrant.

Investing in our securities is highly speculative and involves a high degree of risk. Before buying any securities, you should review carefully the risks and uncertainties of investing in our securities described in the section titled "Risk Factors" beginning on page 17 of the Prospectus, and under similar headings in any amendments or supplements thereto.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of the securities to be issued under the Prospectus or passed upon the accuracy or adequacy of the Prospectus. Any representation to the contrary is a criminal offense.

The date of this Prospectus Supplement is May 12, 2023