

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549**

**POST-EFFECTIVE AMENDMENT NO. 2
TO
Form S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

Homology Medicines, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

47-3468154
(I.R.S. Employer
Identification Number)

One Patriots Park
Bedford, MA 01730
(781) 301-7277
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Arthur O. Tzianabos, Ph.D.
President and Chief Executive Officer
Homology Medicines, Inc.
One Patriots Park
Bedford, Massachusetts 01730
(781) 301-7277
(Address, including zip code, and telephone number, including area code, of agent for service)

Copies to:
Peter N. Handrinos, Esq.
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200 Clarendon Street
Boston, Massachusetts 02116
(617) 948-6000

APPROXIMATE DATE OF COMMENCEMENT OF PROPOSED SALE TO THE PUBLIC: From time to time after the effective date of this registration statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective on filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer
Non-accelerated filer

Accelerated filer
Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for comply with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of Securities Act.

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered/proposed maximum offering price per unit/proposed maximum aggregate offering price	Amount of registration fee
Primary Offering of Securities:		
Common Stock	(1)(2)	
Preferred Stock	(1)(2)	
Debt Securities	(1)	
Warrants	(1)	
Units	(1)	
Total	\$350,000,000(3)	\$38,185(4)(5)

- (1) An unspecified number of securities or aggregate principal amount, as applicable, is being registered as may from time to time be offered at unspecified prices and, in addition, an unspecified number of additional shares of Common Stock is being registered as may be issued from time to time upon conversion of any Debt Securities that are convertible into Common Stock or pursuant to any anti-dilution adjustments with respect to any such convertible Debt Securities.
- (2) Includes rights to acquire common stock or preferred stock of the Company under any shareholder rights plan then in effect, if applicable under the terms of any such plan.
- (3) Estimated solely for the purpose of calculating the registration fee. No separate consideration will be received for shares of common stock that are issued upon conversion of debt securities, depositary shares or preferred stock or upon exercise of common stock warrants registered hereunder. The aggregate maximum offering price of all securities issued pursuant to this registration statement will not exceed \$350,000,000.
- (4) The registration fee has been calculated in accordance with Rule 457(o) under the Securities Act of 1933, as amended.
- (5) Previously paid.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act or until the registration statement shall become effective on such date as the SEC, acting pursuant to said Section 8(a), may determine.

EXPLANATORY NOTE

Post-Effective Amendment No. 1 to the Registration Statement on Form S-3 (File No. 333-237131) (“Post-Effective Amendment No. 1”) of Homology Medicines, Inc. (the “Company”) was filed because the Company expected that it would no longer be a “well-known seasoned issuer” (as such term is defined in Rule 405 of the Securities Act of 1933, as amended) when it filed its Annual Report on Form 10-K for the fiscal year ended December 31, 2020. Accordingly, the Company filed Post-Effective Amendment No. 1 for the purpose of including disclosure required for a registrant other than a well-known seasoned issuer, identifying the securities being registered, registering a specific amount of securities and paying the associated filing fee. This Post-Effective Amendment No. 2 to the Registration Statement on Form S-3 (“Post-Effective Amendment No. 2”) is being filed using EDGAR submission type POS AM in order to convert the Registration Statement to the proper EDGAR submission type for a non-automatic shelf registration statement.

This Post-Effective Amendment No. 2 contains:

- a base prospectus which covers the offering, issuance and sale by us of up to \$350,000,000 in the aggregate of the securities identified above from time to time in one or more offerings; and
- a sales agreement prospectus supplement covering the offering, issuance and sale by us of up to a maximum aggregate offering price of \$148,391,990 of our common stock that may be issued and sold under a sales agreement with Cowen and Company, LLC.

The base prospectus immediately follows this explanatory note. The specific terms of any securities to be offered pursuant to the base prospectus will be specified in a prospectus supplement to the base prospectus. The sales agreement prospectus supplement immediately follows the base prospectus. The \$148,391,990 of common stock that may be offered, issued and sold under the sales agreement prospectus supplement is included in the \$350,000,000 of securities that may be offered, issued and sold by us under the base prospectus. Upon termination of the sales agreement with Cowen and Company, LLC, any portion of the \$148,391,990 included in the sales agreement prospectus supplement that is not sold pursuant to the sales agreement will be available for sale in other offerings pursuant to the base prospectus and a corresponding prospectus supplement, and if no shares are sold under the sales agreement, the full \$148,391,990 of securities may be sold in other offerings pursuant to the base prospectus and a corresponding prospectus supplement.

The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the U.S. Securities and Exchange Commission declares our registration statement effective. This preliminary prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any state or jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 11, 2021

PROSPECTUS SUPPLEMENT



\$350,000,000

**Common Stock
Preferred Stock
Debt Securities
Warrants
Units**

We may offer and sell up to \$350,000,000 in the aggregate of the securities identified above from time to time in one or more offerings. This prospectus provides you with a general description of the securities.

Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The prospectus supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in any of our securities.

We may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled "About this Prospectus" and "Plan of Distribution" for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE "[RISK FACTORS](#)" ON PAGE 4 OF THIS PROSPECTUS AND ANY SIMILAR SECTION CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT AND IN THE DOCUMENTS INCLUDED BY REFERENCE IN THIS PROSPECTUS OR ANY PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "FIXX." On March 9, 2021, the last reported sale price of our common stock on the Nasdaq Global Select Market was \$10.07 per share.

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

The date of this prospectus is _____, 2021.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the U.S. Securities and Exchange Commission, or the SEC using a “shelf” registration process. By using a shelf registration statement, we may sell securities from time to time and in one or more offerings up to a total dollar amount of \$350,000,000 as described in this prospectus. Each time that we offer and sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and sold and the specific terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement or free writing prospectus may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement or free writing prospectus, you should rely on the prospectus supplement or free writing prospectus, as applicable. Before purchasing any securities, you should carefully read both this prospectus and the applicable prospectus supplement (and any applicable free writing prospectuses), together with the additional information described under the heading “Where You Can Find More Information; Incorporation by Reference.”

We have not authorized anyone to provide you with any information or to make any representations other than those contained in this prospectus, any applicable prospectus supplement or any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate only as of the date on its respective cover, that the information appearing in any applicable free writing prospectus is accurate only as of the date of that free writing prospectus, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates. This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. In addition, the market and industry data and forecasts that may be included or incorporated by reference in this prospectus, any prospectus supplement or any applicable free writing prospectus may involve estimates, assumptions and other risks and uncertainties and are subject to change based on various factors, including those discussed under the heading “Risk Factors” contained in this prospectus, the applicable prospectus supplement and any applicable free writing prospectus, and under similar headings in other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

When we refer to “Homology,” “we,” “our company,” “our,” “us” and the “Company” in this prospectus, we mean Homology Medicines, Inc. and its consolidated subsidiaries, unless otherwise specified. When we refer to “you,” we mean the potential holders of the applicable series of securities.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is <http://www.sec.gov>.

Our website address is <http://www.homologymedicines.com>. The information on our website, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement or documents incorporated by reference in the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to "incorporate by reference" information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in this prospectus or a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or a subsequently filed document incorporated by reference modifies or replaces that statement.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC (other than those documents or the portions of those documents not deemed to be filed):

- Our Annual Report on [Form 10-K](#) for the year ended December 31, 2020, filed with the SEC on March 11, 2021.
- Our Current Reports on Form 8-K filed with the SEC on [February 8, 2021](#) and [March 1, 2021](#).
- The description of our Common Stock contained in our Registration Statement on [Form 8-A](#), filed with the SEC on March 19, 2018, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the "Exchange Act" in this prospectus, prior to the termination of this offering, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus by writing or telephoning us at the following address:

Homology Medicines, Inc.
One Patriots Park
Bedford, Massachusetts 01730
(781) 301-7277

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus or any accompanying prospectus supplement.

THE COMPANY

We are a clinical-stage genetic medicines company dedicated to transforming the lives of patients suffering from rare genetic diseases with significant unmet medical needs by curing the underlying cause of the disease. Our proprietary platform is designed to utilize our human hematopoietic stem cell derived adeno-associated virus vectors, or AAVHSCs, to precisely and efficiently deliver single administration genetic medicines *in vivo* either through gene therapy or nuclease-free gene editing across a broad range of genetic disorders. Our diverse set of AAVHSCs allows us to precisely target, via a single injection, a wide range of disease-relevant tissues, including the liver, central nervous system, peripheral nervous system, bone marrow, muscle and eye. Our genetic medicines platform is designed to provide us the flexibility to choose the method we believe is best suited from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit. Our product development strategy is to continue to develop in parallel both gene therapy and gene editing, while initially leveraging the experience from our gene therapy product candidates to further advance our gene editing. We believe our dual technology platform will allow us to provide transformative cures using either modality.

The unique properties of our proprietary family of 15 novel AAVHSCs enable us to focus on a method of gene editing called gene integration, through the replacement of an entire diseased gene in the genome with a whole functional copy by harnessing the naturally occurring deoxyribonucleic acid, or DNA, repair process of homologous recombination, or HR. We believe our HR-driven gene editing approach will allow us to efficiently perform gene editing at therapeutic levels without unwanted on- and off-target modifications, and to directly measure and confirm those modifications in an unbiased manner to ensure only the intended changes are made. By utilizing the body's natural mechanism of correcting gene defects, we also avoid the need for exogenous nucleases, or bacteria-derived enzymes used in other gene editing approaches to cut DNA, that are known to significantly increase the risk of unwanted modifications.

We were incorporated under the laws of the State of Delaware in 2015. Our principal executive offices are located at One Patriots Park, Bedford, Massachusetts 01730, and our telephone number is (781) 301-7277. Our website address is www.homologymedicines.com. The information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our securities. Our common stock is listed on the Nasdaq Global Select Market under the symbol "FIXX."

RISK FACTORS

Investment in any securities offered pursuant to this prospectus and the applicable prospectus supplement involves significant risks. You should carefully consider the risk factors incorporated by reference to our most recent Annual Report on Form 10-K and any subsequent Quarterly Reports on Form 10-Q or Current Reports on Form 8-K, and all other information contained or incorporated by reference into this prospectus, as updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in the applicable prospectus supplement and any applicable free writing prospectus before making a decision about investing in our securities. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of the securities as set forth in the applicable prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is not complete and may not contain all the information you should consider before investing in our capital stock. This description is summarized from, and qualified in its entirety by reference to, our certificate of incorporation, which has been publicly filed with the SEC. See “Where You Can Find More Information; Incorporation by Reference.”

Our authorized capital stock consists of:

- 200,000,000 shares of common stock, par value \$0.0001 per share; and
- 10,000,000 shares of preferred stock, par value \$0.0001 per share.

Common Stock

Our common stock is listed on the Nasdaq Global Select Market under the symbol “FIXX.”

Voting Rights. Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Subject to the supermajority votes for some matters, other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter. Our restated certificate of incorporation and amended and restated bylaws also provide that our directors may be removed only for cause and only by the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon. In addition, the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon is required to amend or repeal, or to adopt any provision inconsistent with, several of the provisions of our restated certificate of incorporation. See below under “—Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws—Amendment of Charter Provisions.”

Rights Upon Liquidation. In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately our net assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock.

Other Rights. Holders of common stock have no preemptive, subscription, redemption or conversion rights. Our outstanding shares of common stock are, and the shares offered by us under this prospectus will be, when issued and paid for, validly issued, fully paid and nonassessable. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Transfer Agent

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

Dividend

Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock. We have never declared or paid any cash dividends on our common stock. We do not intend to declare or pay cash dividends for the foreseeable future. We currently expect to retain all future earnings, if any, for use in the development, operation and expansion of our business. Any determination to pay cash dividends in the future will depend upon, among other things, our results of operations, plans for expansion, tax considerations, available net profits and reserves, limitations under law, financial condition, capital requirements and other factors that our board of directors considers to be relevant.

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Preferred Stock

Under the terms of our restated certificate of incorporation, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock.

Registration Rights

Certain holders of our common stock are entitled to rights with respect to the registration of such shares for public resale under the Securities Act, pursuant to an amended and restated investors' rights agreement by and among us and certain of our stockholders, as amended, until the rights otherwise terminate pursuant to the terms of the investors' rights agreement. The registration of shares of common stock as a result of the following rights being exercised would enable holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective.

Form S-1 Registration Rights

If the holders of registrable securities request in writing that we effect a registration with respect to all or part of such registrable securities then outstanding having an anticipated aggregate offering price that would exceed \$5,000,000, net of expenses, we may be required to register their shares. We are obligated to effect at most two registrations in response to these demand registration rights. If the holders requesting registration intend to distribute their shares by means of an underwriting, the managing underwriter of such offering will have the right to limit the numbers of shares to be underwritten for reasons related to the marketing of the shares.

Piggyback Registration Rights

If at any time we propose to register any shares of our common stock under the Securities Act, subject to certain exceptions, the holders of registrable securities will be entitled to notice of the registration and to include their shares of registrable securities in the registration. If our proposed registration involves an underwriting, the managing underwriter of such offering will have the right to limit the number of shares to be underwritten for reasons related to the marketing of the shares.

Form S-3 Registration Rights

If, at any time after we become entitled under the Securities Act to register our shares on a registration statement on Form S-3, the holders of the registrable securities request in writing that we effect a registration with respect to registrable securities at an aggregate price to the public in the offering of at least \$5,000,000, we will be required to effect such registration; provided, however, that we will not be required to effect such a registration if, within any 12-month period, we have already effected two registrations on Form S-3 for the holders of registrable securities.

Expenses and Indemnification

Ordinarily, other than underwriting discounts and commissions, we will be required to pay all expenses incurred by us related to any registration effected pursuant to the exercise of these registration rights. These expenses may

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include all registration and filing fees, printing expenses, fees and disbursements of our counsel, reasonable fees and disbursements of a counsel for the selling security holders and blue sky fees and expenses. Additionally, we have agreed to indemnify selling stockholders for damages, and any legal or other expenses reasonably incurred, arising from or based upon any untrue statement of a material fact contained in any registration statement, an omission or alleged omission to state a material fact in any registration statement or necessary to make the statements therein not misleading, or any violation or alleged violation by the indemnifying party of securities laws, subject to certain exceptions.

Termination of Registration Rights

The registration rights terminate as to any holder of registrable securities upon the earlier of (i) April 2, 2021, (ii) the closing of a deemed liquidation event, as defined in the investors' rights agreement, (iii) such time at which all shares held by such holder can be sold in any three month period without registration or volume limitations in compliance with Rule 144 or another similar exemption and (iv) such time at which such holder is not an affiliate (as defined under the Securities Act of 1933, as amended) of us.

Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws

Some provisions of Delaware law, our restated certificate of incorporation and our amended and restated bylaws could make the following transactions more difficult: an acquisition of us by means of a tender offer; an acquisition of us by means of a proxy contest or otherwise; or the removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions which provide for payment of a premium over the market price for our shares.

These provisions, summarized below, are intended to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of the increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Undesignated Preferred Stock

The ability of our board of directors, without action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with voting or other rights or preferences as designated by our board of directors could impede the success of any attempt to change control of us. These and other provisions may have the effect of deferring hostile takeovers or delaying changes in control or management of our company.

Stockholder Meetings

Our amended and restated bylaws provide that a special meeting of stockholders may be called only by our chairman of the board, chief executive officer or president (in the absence of a chief executive officer), or by a resolution adopted by a majority of our board of directors.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Our amended and restated bylaws establish advance notice procedures with respect to stockholder proposals to be brought before a stockholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors.

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Elimination of Stockholder Action by Written Consent

Our restated certificate of incorporation eliminates the right of stockholders to act by written consent without a meeting.

Staggered Board

Our board of directors is divided into three classes. The directors in each class will serve for a three-year term, one class being elected each year by our stockholders. This system of electing and removing directors may tend to discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors.

Removal of Directors

Our restated certificate of incorporation and amended and restated bylaws provide that, subject to the rights of holders of any series of preferred stock, no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote in the election of directors. Subject to the rights of holders of any series of preferred stock, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office, unless our board of directors determines by resolution that any such vacancy or newly created directorship shall be filled by our stockholders.

Stockholders Not Entitled to Cumulative Voting

Our restated certificate of incorporation does not permit stockholders to cumulate their votes in the election of directors. Accordingly, the holders of a majority of the outstanding shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they choose, other than any directors that holders of our preferred stock may be entitled to elect.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the General Corporation Law of the State of Delaware, which prohibits persons deemed to be “interested stockholders” from engaging in a “business combination” with a publicly held Delaware corporation for three years following the date these persons become interested stockholders unless the business combination is, or the transaction in which the person became an interested stockholder was, approved in a prescribed manner or another prescribed exception applies. Generally, an “interested stockholder” is a person who, together with affiliates and associates, owns, or within three years prior to the determination of interested stockholder status did own, 15% or more of a corporation’s voting stock. Generally, a “business combination” includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. The existence of this provision may have an anti-takeover effect with respect to transactions not approved in advance by the board of directors.

Choice of Forum

Our restated certificate of incorporation provides that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our restated certificate of incorporation or amended and restated bylaws; or (4) any action asserting a claim governed by the internal affairs doctrine. Our restated certificate of incorporation also provides that any

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person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision. It is possible that a court of law could rule that the choice of forum provision contained in our restated certificate of incorporation is inapplicable or unenforceable if it is challenged in a proceeding or otherwise.

In addition, our amended and restated bylaws provide that unless we consent in writing to the selection of an alternative forum, to the fullest extent permitted by law, the federal district courts of the United States of America shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act of 1933, as amended, and any person or entity purchasing or otherwise acquiring or holding any interest in our shares of capital stock shall be deemed to have notice of and consented to this choice of forum provision.

Amendment of Charter Provisions

The amendment of any of the above provisions, except for the provision making it possible for our board of directors to issue preferred stock and the provision prohibiting cumulative voting, would require approval by holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon.

The provisions of Delaware law, our restated certificate of incorporation and our amended and restated bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in the composition of our board and management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplement or free writing prospectus, summarizes certain general terms and provisions of the debt securities that we may offer under this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. We will also indicate in the supplement to what extent the general terms and provisions described in this prospectus apply to a particular series of debt securities.

We may issue debt securities either separately, or together with, or upon the conversion or exercise of or in exchange for, other securities described in this prospectus. Debt securities may be our senior, senior subordinated or subordinated obligations and, unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and may be issued in one or more series.

The debt securities will be issued under an indenture between us and a trustee to be named in the applicable indenture. We have summarized select portions of the indenture below. The summary is not complete. The form of the indenture has been filed as an exhibit to the registration statement and you should read the indenture for provisions that may be important to you. In the summary below, we have included references to the section numbers of the indenture so that you can easily locate these provisions. Capitalized terms used in the summary and not defined herein have the meanings specified in the indenture.

As used in this section only, “Homology,” “we,” “our” or “us” refer to Homology Medicines, Inc., excluding our subsidiaries, unless expressly stated or the context otherwise requires.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in a resolution of our board of directors, in an officer’s certificate or by a supplemental indenture. (Section 2.2) The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series (including any pricing supplement or term sheet).

We can issue an unlimited amount of debt securities under the indenture that may be in one or more series with the same or various maturities, at par, at a premium, or at a discount. (Section 2.1) We will set forth in a prospectus supplement (including any pricing supplement or term sheet) relating to any series of debt securities being offered, the aggregate principal amount and the following terms of the debt securities, if applicable:

- the title and ranking of the debt securities (including the terms of any subordination provisions);
- the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;
- any limit on the aggregate principal amount of the debt securities;
- the date or dates on which the principal of the securities of the series is payable;
- the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;
- the place or places where principal of, and interest, if any, on, the debt securities will be payable (and the method of such payment), where the securities of such series may be surrendered for registration of transfer or exchange, and where notices and demands to us in respect of the debt securities may be delivered;

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- the period or periods within which, the price or prices at which and the terms and conditions upon which we may redeem the debt securities;
- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities and the period or periods within which, the price or prices at which and in the terms and conditions upon which securities of the series shall be redeemed or purchased, in whole or in part, pursuant to such obligation;
- the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;
- the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;
- whether the debt securities will be issued in the form of certificated debt securities or global debt securities;
- the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;
- the currency of denomination of the debt securities, which may be U.S. Dollars or any foreign currency, and if such currency of denomination is a composite currency, the agency or organization, if any, responsible for overseeing such composite currency;
- the designation of the currency, currencies or currency units in which payment of principal of, premium and interest on the debt securities will be made;
- if payments of principal of, premium on or interest on the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;
- the manner in which the amounts of payment of principal of, premium, if any, or interest on the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index;
- any provisions relating to any security provided for the debt securities;
- any addition to, deletion of or change in the Events of Default described in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;
- any addition to, deletion of or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities;
- the provisions, if any, relating to conversion or exchange of any debt securities of such series, including, if applicable, the conversion or exchange price and period, provisions as to whether conversion or exchange will be mandatory, the events requiring an adjustment of the conversion or exchange price and provisions affecting conversion or exchange;
- any other terms of the debt securities, which may supplement, modify or delete any provision of the indenture as it applies to that series, including any terms that may be required under applicable law or regulations or advisable in connection with the marketing of the securities; and
- whether any of our direct or indirect subsidiaries will guarantee the debt securities of that series, including the terms of subordination, if any, of such guarantees. (Section 2.2)

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We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of and any premium and interest on any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Transfer and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, or the Depository, or a nominee of the Depository (we will refer to any debt security represented by a global debt security as a “book-entry debt security”), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a “certificated debt security”) as set forth in the applicable prospectus supplement. Except as set forth under the heading “Global Debt Securities and Book-Entry System” below, book-entry debt securities will not be issuable in certificated form.

Certificated Debt Securities. You may transfer or exchange certificated debt securities at any office we maintain for this purpose in accordance with the terms of the indenture. (Section 2.4) No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange. (Section 2.7)

You may effect the transfer of certificated debt securities and the right to receive the principal of, premium and interest on certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder.

Global Debt Securities and Book-Entry System. Each global debt security representing book-entry debt securities will be deposited with, or on behalf of, the Depository, and registered in the name of the Depository or a nominee of the Depository. Please see “Global Securities.”

Covenants

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities. (Article IV)

No Protection in the Event of a Change of Control

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

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Consolidation, Merger and Sale of Assets

We may not consolidate with or merge with or into, or convey, transfer or lease all or substantially all of our properties and assets to any person (a “successor person”) unless:

- we are the surviving corporation or the successor person (if other than Homology) is a corporation organized and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture; and
- immediately after giving effect to the transaction, no Default or Event of Default, shall have occurred and be continuing.

Notwithstanding the above, any of our subsidiaries may consolidate with, merge into or transfer all or part of its properties to us. (Section 5.1)

Events of Default

“Event of Default” means with respect to any series of debt securities, any of the following:

- default in the payment of any interest upon any debt security of that series when it becomes due and payable, and continuance of such default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);
- default in the payment of principal of any security of that series at its maturity;
- default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 60 days after we receive written notice from the trustee or we and the trustee receive written notice from the holders of not less than 25% in principal amount of the outstanding debt securities of that series as provided in the indenture;
- certain voluntary or involuntary events of bankruptcy, insolvency or reorganization of Homology; or
- any other Event of Default provided with respect to debt securities of that series that is described in the applicable prospectus supplement. (Section 6.1)

No Event of Default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an Event of Default with respect to any other series of debt securities. (Section 6.1) The occurrence of certain Events of Default or an acceleration under the indenture may constitute an event of default under certain indebtedness of ours or our subsidiaries outstanding from time to time.

We will provide the trustee written notice of any Default or Event of Default within 30 days of becoming aware of the occurrence of such Default or Event of Default, which notice will describe in reasonable detail the status of such Default or Event of Default and what action we are taking or propose to take in respect thereof. (Section 6.1)

If an Event of Default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than 25% in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal of (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an Event of Default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid

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interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all Events of Default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. (Section 6.2) We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an Event of Default.

The indenture provides that the trustee may refuse to perform any duty or exercise any of its rights or powers under the indenture unless the trustee receives indemnity satisfactory to it against any cost, liability or expense which might be incurred by it in performing such duty or exercising such right or power. (Section 7.1(e)) Subject to certain rights of the trustee, the holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to the debt securities of that series. (Section 6.12)

No holder of any debt security of any series will have any right to institute any proceeding, judicial or otherwise, with respect to the indenture or for the appointment of a receiver or trustee, or for any remedy under the indenture, unless:

- that holder has previously given to the trustee written notice of a continuing Event of Default with respect to debt securities of that series; and
- the holders of not less than 25% in principal amount of the outstanding debt securities of that series have made written request, and offered indemnity or security satisfactory to the trustee, to the trustee to institute the proceeding as trustee, and the trustee has not received from the holders of not less than a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days. (Section 6.7)

Notwithstanding any other provision in the indenture, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, premium and any interest on that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment. (Section 6.8)

The indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. (Section 4.3) If a Default or Event of Default occurs and is continuing with respect to the securities of any series and if it is known to a responsible officer of the trustee, the trustee shall mail to each Securityholder of the securities of that series notice of a Default or Event of Default within 90 days after it occurs or, if later, after a responsible officer of the trustee has knowledge of such Default or Event of Default. The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any Default or Event of Default (except in payment on any debt securities of that series) with respect to debt securities of that series if the trustee determines in good faith that withholding notice is in the interest of the holders of those debt securities. (Section 7.5)

Modification and Waiver

We and the trustee may modify, amend or supplement the indenture or the debt securities of any series without the consent of any holder of any debt security:

- to cure any ambiguity, defect or inconsistency;

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- to comply with covenants in the indenture described above under the heading “Consolidation, Merger and Sale of Assets”;
- to provide for uncertificated securities in addition to or in place of certificated securities;
- to add guarantees with respect to debt securities of any series or secure debt securities of any series;
- to surrender any of our rights or powers under the indenture;
- to add covenants or events of default for the benefit of the holders of debt securities of any series;
- to comply with the applicable procedures of the applicable depository;
- to make any change that does not adversely affect the rights of any holder of debt securities;
- to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;
- to effect the appointment of a successor trustee with respect to the debt securities of any series and to add to or change any of the provisions of the indenture to provide for or facilitate administration by more than one trustee; or
- to comply with requirements of the SEC in order to effect or maintain the qualification of the indenture under the Trust Indenture Act. (Section 9.1)

We may also modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments. We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

- reduce the amount of debt securities whose holders must consent to an amendment, supplement or waiver;
- reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;
- reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;
- reduce the principal amount of discount securities payable upon acceleration of maturity;
- waive a default in the payment of the principal of, premium on or interest on any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);
- make the principal of, premium or interest on any debt security payable in currency other than that stated in the debt security;
- make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, premium and interest on those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or
- waive a redemption payment with respect to any debt security. (Section 9.3)

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. (Section 9.2) The holders of a majority in principal amount of the

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outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration. (Section 6.13)

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

Legal Defeasance. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (subject to certain exceptions). We will be so discharged upon the irrevocable deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money or U.S. government obligations in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

This discharge may occur only if, among other things, we have delivered to the trustee an opinion of counsel stating that we have received from, or there has been published by, the U.S. Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable U.S. federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for U.S. federal income tax purposes as a result of the deposit, defeasance and discharge and will be subject to U.S. federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit, defeasance and discharge had not occurred. (Section 8.3)

Defeasance of Certain Covenants. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, upon compliance with certain conditions:

- we may omit to comply with the covenant described under the heading “Consolidation, Merger and Sale of Assets” and certain other covenants set forth in the indenture, as well as any additional covenants that may be set forth in the applicable prospectus supplement; and
- any omission to comply with those covenants will not constitute a Default or an Event of Default with respect to the debt securities of that series (“covenant defeasance”).

The conditions include:

- depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal of, premium on and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and
- delivering to the trustee an opinion of counsel to the effect that the holders of the debt securities of that series will not recognize income, gain or loss for U.S. federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to U.S. federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred. (Section 8.4)

No Personal Liability of Directors, Officers, Employees or Securityholders

None of our past, present or future directors, officers, employees or securityholders, as such, will have any liability for any of our obligations under the debt securities or the indenture or for any claim based on, or in respect or by reason of, such obligations or their creation. By accepting a debt security, each holder waives and releases all such liability. This waiver and release is part of the consideration for the issue of the debt securities.

However, this waiver and release may not be effective to waive liabilities under U.S. federal securities laws, and it is the view of the SEC that such a waiver is against public policy.

Governing Law

The indenture and the debt securities, including any claim or controversy arising out of or relating to the indenture or the securities, will be governed by the laws of the State of New York.

The indenture will provide that we, the trustee and the holders of the debt securities (by their acceptance of the debt securities) irrevocably waive, to the fullest extent permitted by applicable law, any and all right to trial by jury in any legal proceeding arising out of or relating to the indenture, the debt securities or the transactions contemplated thereby.

The indenture will provide that any legal suit, action or proceeding arising out of or based upon the indenture or the transactions contemplated thereby may be instituted in the federal courts of the United States of America located in the City of New York or the courts of the State of New York in each case located in the City of New York, and we, the trustee and the holder of the debt securities (by their acceptance of the debt securities) irrevocably submit to the non-exclusive jurisdiction of such courts in any such suit, action or proceeding. The indenture will further provide that service of any process, summons, notice or document by mail (to the extent allowed under any applicable statute or rule of court) to such party's address set forth in the indenture will be effective service of process for any suit, action or other proceeding brought in any such court. The indenture will further provide that we, the trustee and the holders of the debt securities (by their acceptance of the debt securities) irrevocably and unconditionally waive any objection to the laying of venue of any suit, action or other proceeding in the courts specified above and irrevocably and unconditionally waive and agree not to plead or claim any such suit, action or other proceeding has been brought in an inconvenient forum. (Section 10.10)

DESCRIPTION OF WARRANTS

We may issue warrants for the purchase of shares of our common stock or preferred stock or of debt securities. We may issue warrants independently or together with other securities, and the warrants may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and the investors or a warrant agent. The following summary of material provisions of the warrants and warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and warrant certificate applicable to a particular series of warrants. The terms of any warrants offered under a prospectus supplement may differ from the terms described below. We urge you to read the applicable prospectus supplement and any related free writing prospectus, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants.

The particular terms of any issue of warrants will be described in the prospectus supplement relating to the issue. Those terms may include:

- the number of shares of common stock or preferred stock purchasable upon the exercise of warrants to purchase such shares and the price at which such number of shares may be purchased upon such exercise;
- the designation, stated value and terms (including, without limitation, liquidation, dividend, conversion and voting rights) of the series of preferred stock purchasable upon exercise of warrants to purchase preferred stock;
- the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
- the date, if any, on and after which the warrants and the related debt securities, preferred stock or common stock will be separately transferable;
- the terms of any rights to redeem or call the warrants;
- the date on which the right to exercise the warrants will commence and the date on which the right will expire;
- U.S. federal income tax consequences applicable to the warrants; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

- to vote, consent or receive dividends;
- receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or
- exercise any rights as stockholders of Homology.

Each warrant will entitle its holder to purchase the principal amount of debt securities or the number of shares of preferred stock or common stock at the exercise price set forth in, or calculable as set forth in, the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

A holder of warrant certificates may exchange them for new warrant certificates of different denominations, present them for registration of transfer and exercise them at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Until any warrants to purchase debt securities are

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exercised, the holder of the warrants will not have any rights of holders of the debt securities that can be purchased upon exercise, including any rights to receive payments of principal, premium or interest on the underlying debt securities or to enforce covenants in the applicable indenture. Until any warrants to purchase common stock or preferred stock are exercised, the holders of the warrants will not have any rights of holders of the underlying common stock or preferred stock, including any rights to receive dividends or payments upon any liquidation, dissolution or winding up on the common stock or preferred stock, if any.

DESCRIPTION OF UNITS

We may issue units consisting of any combination of the other types of securities offered under this prospectus in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units.

The following description, together with the additional information included in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions, and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

- the title of the series of units;
- identification and description of the separate constituent securities comprising the units;
- the price or prices at which the units will be issued;
- the date, if any, on and after which the constituent securities comprising the units will be separately transferable;
- a discussion of certain U.S. federal income tax considerations applicable to the units; and
- any other terms of the units and their constituent securities.

GLOBAL SECURITIES

Book-Entry, Delivery and Form

Unless we indicate differently in any applicable prospectus supplement or free writing prospectus, the securities initially will be issued in book-entry form and represented by one or more global notes or global securities, or, collectively, global securities. The global securities will be deposited with, or on behalf of, The Depository Trust Company, New York, New York, as depository, or DTC, and registered in the name of Cede & Co., the nominee of DTC. Unless and until it is exchanged for individual certificates evidencing securities under the limited circumstances described below, a global security may not be transferred except as a whole by the depository to its nominee or by the nominee to the depository, or by the depository or its nominee to a successor depository or to a nominee of the successor depository.

DTC has advised us that it is:

- a limited-purpose trust company organized under the New York Banking Law;
- a “banking organization” within the meaning of the New York Banking Law;
- a member of the Federal Reserve System;
- a “clearing corporation” within the meaning of the New York Uniform Commercial Code; and
- a “clearing agency” registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC holds securities that its participants deposit with DTC. DTC also facilitates the settlement among its participants of securities transactions, such as transfers and pledges, in deposited securities through electronic computerized book-entry changes in participants’ accounts, thereby eliminating the need for physical movement of securities certificates. “Direct participants” in DTC include securities brokers and dealers, including underwriters, banks, trust companies, clearing corporations and other organizations. DTC is a wholly-owned subsidiary of The Depository Trust & Clearing Corporation, or DTCC. DTCC is the holding company for DTC, National Securities Clearing Corporation and Fixed Income Clearing Corporation, all of which are registered clearing agencies. DTCC is owned by the users of its regulated subsidiaries. Access to the DTC system is also available to others, which we sometimes refer to as indirect participants, that clear through or maintain a custodial relationship with a direct participant, either directly or indirectly. The rules applicable to DTC and its participants are on file with the SEC.

Purchases of securities under the DTC system must be made by or through direct participants, which will receive a credit for the securities on DTC’s records. The ownership interest of the actual purchaser of a security, which we sometimes refer to as a beneficial owner, is in turn recorded on the direct and indirect participants’ records. Beneficial owners of securities will not receive written confirmation from DTC of their purchases. However, beneficial owners are expected to receive written confirmations providing details of their transactions, as well as periodic statements of their holdings, from the direct or indirect participants through which they purchased securities. Transfers of ownership interests in global securities are to be accomplished by entries made on the books of participants acting on behalf of beneficial owners. Beneficial owners will not receive certificates representing their ownership interests in the global securities, except under the limited circumstances described below.

To facilitate subsequent transfers, all global securities deposited by direct participants with DTC will be registered in the name of DTC’s partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other nominee will not change the beneficial ownership of the securities. DTC has no knowledge of the actual beneficial owners of the securities. DTC’s records reflect only the identity of the direct participants to whose accounts the securities are credited, which may or may not be the beneficial owners. The participants are responsible for keeping account of their holdings on behalf of their customers.

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So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depository and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities and the indenture may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

Conveyance of notices and other communications by DTC to direct participants, by direct participants to indirect participants and by direct participants and indirect participants to beneficial owners will be governed by arrangements among them, subject to any legal requirements in effect from time to time.

Redemption notices will be sent to DTC. If less than all of the securities of a particular series are being redeemed, DTC's practice is to determine by lot the amount of the interest of each direct participant in the securities of such series to be redeemed.

Neither DTC nor Cede & Co. (or such other DTC nominee) will consent or vote with respect to the securities. Under its usual procedures, DTC will mail an omnibus proxy to us as soon as possible after the record date. The omnibus proxy assigns the consenting or voting rights of Cede & Co. to those direct participants to whose accounts the securities of such series are credited on the record date, identified in a listing attached to the omnibus proxy.

So long as securities are in book-entry form, we will make payments on those securities to the depository or its nominee, as the registered owner of such securities, by wire transfer of immediately available funds. If securities are issued in definitive certificated form under the limited circumstances described below and unless if otherwise provided in the description of the applicable securities herein or in the applicable prospectus supplement, we will have the option of making payments by check mailed to the addresses of the persons entitled to payment or by wire transfer to bank accounts in the United States designated in writing to the applicable trustee or other designated party at least 15 days before the applicable payment date by the persons entitled to payment, unless a shorter period is satisfactory to the applicable trustee or other designated party.

Redemption proceeds, distributions and dividend payments on the securities will be made to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC. DTC's practice is to credit direct participants' accounts upon DTC's receipt of funds and corresponding detail information from us on the payment date in accordance with their respective holdings shown on DTC records. Payments by participants to beneficial owners will be governed by standing instructions and customary practices, as is the case with securities held for the account of customers in bearer form or registered in "street name." Those payments will be the responsibility of participants and not of DTC or us, subject to any statutory or regulatory requirements in effect from time to time. Payment of redemption proceeds, distributions and dividend payments to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC, is our responsibility; disbursement of payments to direct participants is the responsibility of DTC, and disbursement of payments to the beneficial owners is the responsibility of direct and indirect participants.

Except under the limited circumstances described below, purchasers of securities will not be entitled to have securities registered in their names and will not receive physical delivery of securities. Accordingly, each beneficial owner must rely on the procedures of DTC and its participants to exercise any rights under the securities and the indenture.

The laws of some jurisdictions may require that some purchasers of securities take physical delivery of securities in definitive form. Those laws may impair the ability to transfer or pledge beneficial interests in securities.

DTC may discontinue providing its services as securities depository with respect to the securities at any time by giving reasonable notice to us. Under such circumstances, in the event that a successor depository is not obtained, securities certificates are required to be printed and delivered.

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As noted above, beneficial owners of a particular series of securities generally will not receive certificates representing their ownership interests in those securities. However, if:

- DTC notifies us that it is unwilling or unable to continue as a depository for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depository is not appointed within 90 days of the notification to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be;
- we determine, in our sole discretion, not to have such securities represented by one or more global securities; or
- an Event of Default has occurred and is continuing with respect to such series of securities,

we will prepare and deliver certificates for such securities in exchange for beneficial interests in the global securities. Any beneficial interest in a global security that is exchangeable under the circumstances described in the preceding sentence will be exchangeable for securities in definitive certificated form registered in the names that the depository directs. It is expected that these directions will be based upon directions received by the depository from its participants with respect to ownership of beneficial interests in the global securities.

Euroclear and Clearstream

If so provided in the applicable prospectus supplement, you may hold interests in a global security through Clearstream Banking S.A., which we refer to as "Clearstream," or Euroclear Bank S.A./N.V., as operator of the Euroclear System, which we refer to as "Euroclear," either directly if you are a participant in Clearstream or Euroclear or indirectly through organizations that are participants in Clearstream or Euroclear. Clearstream and Euroclear will hold interests on behalf of their respective participants through customers' securities accounts in the names of Clearstream and Euroclear, respectively, on the books of their respective U.S. depositories, which in turn will hold such interests in customers' securities accounts in such depositories' names on DTC's books.

Clearstream and Euroclear are securities clearance systems in Europe. Clearstream and Euroclear hold securities for their respective participating organizations and facilitate the clearance and settlement of securities transactions between those participants through electronic book-entry changes in their accounts, thereby eliminating the need for physical movement of certificates.

Payments, deliveries, transfers, exchanges, notices and other matters relating to beneficial interests in global securities owned through Euroclear or Clearstream must comply with the rules and procedures of those systems. Transactions between participants in Euroclear or Clearstream, on one hand, and other participants in DTC, on the other hand, are also subject to DTC's rules and procedures.

Investors will be able to make and receive through Euroclear and Clearstream payments, deliveries, transfers and other transactions involving any beneficial interests in global securities held through those systems only on days when those systems are open for business. Those systems may not be open for business on days when banks, brokers and other institutions are open for business in the United States.

Cross-market transfers between participants in DTC, on the one hand, and participants in Euroclear or Clearstream, on the other hand, will be effected through DTC in accordance with the DTC's rules on behalf of Euroclear or Clearstream, as the case may be, by their respective U.S. depositories; however, such cross-market transactions will require delivery of instructions to Euroclear or Clearstream, as the case may be, by the counterparty in such system in accordance with the rules and procedures and within the established deadlines (European time) of such system. Euroclear or Clearstream, as the case may be, will, if the transaction meets its settlement requirements, deliver instructions to its U.S. depository to take action to effect final settlement on its behalf by delivering or receiving interests in the global securities through DTC, and making or receiving

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payment in accordance with normal procedures for same-day fund settlement. Participants in Euroclear or Clearstream may not deliver instructions directly to their respective U.S. depositaries.

Due to time zone differences, the securities accounts of a participant in Euroclear or Clearstream purchasing an interest in a global security from a direct participant in DTC will be credited, and any such crediting will be reported to the relevant participant in Euroclear or Clearstream, during the securities settlement processing day (which must be a business day for Euroclear or Clearstream) immediately following the settlement date of DTC. Cash received in Euroclear or Clearstream as a result of sales of interests in a global security by or through a participant in Euroclear or Clearstream to a direct participant in DTC will be received with value on the settlement date of DTC but will be available in the relevant Euroclear or Clearstream cash account only as of the business day for Euroclear or Clearstream following DTC's settlement date.

Other

The information in this section of this prospectus concerning DTC, Clearstream, Euroclear and their respective book-entry systems has been obtained from sources that we believe to be reliable, but we do not take responsibility for this information. This information has been provided solely as a matter of convenience. The rules and procedures of DTC, Clearstream and Euroclear are solely within the control of those organizations and could change at any time. Neither we nor the trustee nor any agent of ours or of the trustee has any control over those entities and none of us takes any responsibility for their activities. You are urged to contact DTC, Clearstream and Euroclear or their respective participants directly to discuss those matters. In addition, although we expect that DTC, Clearstream and Euroclear will perform the foregoing procedures, none of them is under any obligation to perform or continue to perform such procedures and such procedures may be discontinued at any time. Neither we nor any agent of ours will have any responsibility for the performance or nonperformance by DTC, Clearstream and Euroclear or their respective participants of these or any other rules or procedures governing their respective operations.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods or through underwriters or dealers, through agents and/or directly to one or more purchasers. The securities may be distributed from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each time that we sell securities covered by this prospectus, we will provide a prospectus supplement or supplements that will describe the method of distribution and set forth the terms and conditions of the offering of such securities, including the offering price of the securities and the proceeds to us, if applicable.

Offers to purchase the securities being offered by this prospectus may be solicited directly. Agents may also be designated to solicit offers to purchase the securities from time to time. Any agent involved in the offer or sale of our securities will be identified in a prospectus supplement.

If a dealer is utilized in the sale of the securities being offered by this prospectus, the securities will be sold to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If an underwriter is utilized in the sale of the securities being offered by this prospectus, an underwriting agreement will be executed with the underwriter at the time of sale and the name of any underwriter will be provided in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we or the purchasers of securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for which they may act as agent. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis and a dealer will purchase securities as a principal, and may then resell the securities at varying prices to be determined by the dealer.

Any compensation paid to underwriters, dealers or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers will be provided in the applicable prospectus supplement. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act of 1933, as amended, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof and to reimburse those persons for certain expenses.

Any common stock will be listed on the Nasdaq Global Select Market, but any other securities may or may not be listed on a national securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than were sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option, if any. In addition, these persons may stabilize or maintain the price of the securities by bidding for or

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purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement so indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in such sale transactions will be an underwriter and, if not identified in this prospectus, will be named in the applicable prospectus supplement (or a post-effective amendment). In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus and an applicable prospectus supplement. Such financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

The specific terms of any lock-up provisions in respect of any given offering will be described in the applicable prospectus supplement.

The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business for which they receive compensation.

LEGAL MATTERS

Latham & Watkins LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Homology Medicines, Inc. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The financial statements incorporated in this prospectus by reference from our Annual Report on Form 10-K have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.



Up to \$350,000,000

**Common Stock
Preferred Stock
Debt Securities
Warrants
Units**

PROSPECTUS

, 2021

The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the U.S. Securities and Exchange Commission declares our registration statement effective. This preliminary prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any state or jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 11, 2021

PROSPECTUS

\$148,391,990



Common Stock

We have entered into a sales agreement with Cowen and Company, LLC, or Cowen, dated March 12, 2020, relating to the sale of shares of our common stock offered by this prospectus supplement. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock, \$0.0001 par value per share, from time to time through Cowen, acting as our agent. The sales agreement originally provided that we may offer and sell shares of our common stock having an aggregate offering price of up to \$150,000,000. Prior to the date of this prospectus supplement, we have offered and sold shares of our common stock having an aggregate offering price of \$1,608,010. As a result, under this prospectus supplement, in accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$148,391,990 from time to time through Cowen, acting as our agent.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "FIXX." On March 9, 2021, the last reported sale price of our common stock on the Nasdaq Global Select Market was \$10.07 per share.

Sales of our common stock, if any, under this prospectus supplement will be made by any method permitted that is deemed an "at the market offering" as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended, or the Securities Act, including sales made directly on or through the Nasdaq Global Select Market or any other existing trading market for our common stock. Cowen is not required to sell any specific amount, but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices on mutually agreed terms between the sales agent and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The aggregate compensation payable to Cowen as sales agent equals 3.0% of the gross sales price of the shares of our common stock sold through it pursuant to the sales agreement. See "Plan of Distribution" beginning on page S-17 for additional information regarding the compensation to be paid to Cowen. In connection with the sale of the common stock on our behalf, Cowen will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Cowen will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cowen with respect to certain liabilities, including liabilities under the Securities Act.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE "[RISK FACTORS](#)" ON PAGE S-7 OF THIS PROSPECTUS SUPPLEMENT AND IN THE DOCUMENTS INCORPORATED BY REFERENCE IN THIS PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR COMMON STOCK.

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

Cowen

, 2021

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ABOUT THIS PROSPECTUS SUPPLEMENT

This sales agreement prospectus supplement is part of a registration statement that we have filed with the U.S. Securities and Exchange Commission, or the SEC, utilizing a “shelf” registration process. By using a shelf registration statement, we may offer shares of our common stock having an aggregate offering price of up to \$148,391,990 from time to time under this prospectus supplement at prices and on terms to be determined by market conditions at the time of offering.

We provide information to you about this offering of our common stock in two separate documents that are bound together: (1) this sales agreement prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying base prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this “prospectus supplement,” we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying base prospectus, you should rely on this prospectus supplement. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in any document incorporated by reference in this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus supplement—the statement in the document having the later date modifies or supersedes the earlier statement.

We have not, and Cowen has not, authorized anyone to provide you with information other than that contained in this prospectus supplement, the accompanying base prospectus and any free writing prospectus. We are not, and Cowen is not, making an offer to sell or soliciting any offer to buy these securities in any jurisdiction where the offer or sale is not permitted or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering in their entirety before making an investment decision.

Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus supplement, the accompanying base prospectus and all of the information incorporated by reference herein and therein, as well as the additional information described under the heading “Where You Can Find More Information; Incorporation by Reference.” These documents contain important information that you should consider when making your investment decision.

We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement outside the United States. This prospectus supplement does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

When we refer to “Homology,” “we,” “our” and “us” in this prospectus supplement, we mean Homology Medicines, Inc. or its consolidated subsidiaries, unless otherwise specified. When we refer to “you,” we mean the holders of the applicable series of securities.

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We use our registered trademark, Homology Medicines, Inc., in this prospectus supplement. This prospectus supplement also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this prospectus supplement appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is www.sec.gov.

Our website address is www.homologymedicines.com. The information on our website, however, is not, and should not be deemed to be, a part of this prospectus supplement.

This prospectus supplement and the accompanying base prospectus are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus supplement or the accompanying base prospectus about these documents are summaries, and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

Incorporation by Reference

The SEC's rules allow us to "incorporate by reference" information in this prospectus supplement, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement modifies or replaces that statement.

This prospectus supplement incorporates by reference the documents set forth below that have previously been filed with the SEC:

- Our Annual Report on [Form 10-K](#) for the year ended December 31, 2020, filed with the SEC on March 11, 2021.
- Our Current Reports on Form 8-K filed with the SEC on [February 8, 2021](#) and [March 1, 2021](#).
- The description of our Common Stock contained in our Registration Statement on [Form 8-A](#), filed with the SEC on March 19, 2018, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the "Exchange Act" in this prospectus supplement, prior to the termination of this offering will also be incorporated by reference in this prospectus supplement and deemed to be part of this prospectus supplement from the date of the filing of such reports and documents. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed above or filed in the future, that are not deemed "filed" with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

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You may request a free copy of any of the documents incorporated by reference in this prospectus supplement by writing or telephoning us at the following address:

Homology Medicines, Inc.
One Patriots Park Bedford, Massachusetts 01730
(781) 301-7277

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus supplement.

SALES AGREEMENT PROSPECTUS SUPPLEMENT SUMMARY

This summary provides a general overview of selected information and does not contain all of the information you should consider before buying our common stock. Therefore, you should read this entire prospectus supplement, the accompanying base prospectus and any free writing prospectus that we have authorized for use in connection with this offering carefully, including the information incorporated by reference, before deciding to invest in our common stock. Investors should carefully consider the information set forth under “Risk Factors” beginning on page S-7 of this prospectus supplement and incorporated by reference to our annual report on Form 10-K and our quarterly reports on Form 10-Q.

We are a clinical-stage genetic medicines company dedicated to transforming the lives of patients suffering from rare genetic diseases with significant unmet medical needs by curing the underlying cause of the disease. Our proprietary platform is designed to utilize our human hematopoietic stem cell derived adeno-associated virus vectors, or AAVHSCs, to precisely and efficiently deliver single administration genetic medicines *in vivo* either through gene therapy or nuclease-free gene editing across a broad range of genetic disorders. Our diverse set of AAVHSCs allows us to precisely target, via a single injection, a wide range of disease-relevant tissues, including the liver, central nervous system, peripheral nervous system, bone marrow, muscle and eye. Our genetic medicines platform is designed to provide us the flexibility to choose the method we believe is best suited from either gene therapy or gene editing for each disease we pursue, based on such factors as the targeted disease biology, the biodistribution of our AAVHSCs to key tissues, and the rate of cell division the tissues exhibit. Our product development strategy is to continue to develop in parallel both gene therapy and gene editing, while initially leveraging the experience from our gene therapy product candidates to further advance our gene editing. We believe our dual technology platform will allow us to provide transformative cures using either modality.

The unique properties of our proprietary family of 15 novel AAVHSCs enable us to focus on a method of gene editing called gene integration, through the replacement of an entire diseased gene in the genome with a whole functional copy by harnessing the naturally occurring deoxyribonucleic acid, or DNA, repair process of homologous recombination, or HR. We believe our HR-driven gene editing approach will allow us to efficiently perform gene editing at therapeutic levels without unwanted on- and off-target modifications, and to directly measure and confirm those modifications in an unbiased manner to ensure only the intended changes are made. By utilizing the body’s natural mechanism of correcting gene defects, we also avoid the need for exogenous nucleases, or bacteria-derived enzymes used in other gene editing approaches to cut DNA, that are known to significantly increase the risk of unwanted modifications.

We were incorporated under the laws of the State of Delaware in 2015. Our principal executive offices are located at One Patriots Park, Bedford, Massachusetts 01730, and our telephone number is (781) 301-7277. Our website address is www.homologymedicines.com. The information contained on our website is not incorporated by reference into this prospectus supplement, and you should not consider any information contained on, or that can be accessed through, our website as part of this prospectus supplement or in deciding whether to purchase our securities. Our common stock is listed on the Nasdaq Global Select Market under the symbol “FIXX.”

THE OFFERING

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to \$148,391,990.
Manner of offering	“At the market offering” that may be made from time to time on the Nasdaq Global Select Market or other existing trading market for our common stock through our agent, Cowen. See the section entitled “Plan of Distribution” on page S-17 of this prospectus supplement.
Use of proceeds	We intend to use the net proceeds of this offering for general corporate purposes, which may include clinical trials, research and development expenditures, acquisitions or in-licenses of complementary companies, medicines or technologies, expenditures to build our initial development and commercial capabilities, further expansion of our manufacturing capacity, repayment and refinancing of debt, working capital and capital expenditures. See the section entitled “Use of Proceeds” on page S-10 of this prospectus supplement.
Risk factors	See “Risk Factors” beginning on page S-7 of this prospectus supplement and the other information included in, or incorporated by reference into, this prospectus supplement for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock.
Nasdaq Global Select Market symbol	FIXX

RISK FACTORS

Investment in any securities offered pursuant to this prospectus supplement and the accompanying base prospectus involves risks. You should carefully consider the risk factors described below and in our Annual Report on Form 10-K for the year ended December 31, 2020 incorporated by reference in this prospectus supplement, any amendment or update thereto reflected in subsequent filings with the SEC, including in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q, and all other information contained or incorporated by reference in this prospectus supplement, as updated by our subsequent filings under the Exchange Act. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

Risks Relating to this Offering

If you purchase shares of our common stock sold in this offering, you will experience immediate and substantial dilution in the net tangible book value of your shares. In addition, we may issue additional equity or convertible debt securities in the future, which may result in additional dilution to you.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. Assuming that an aggregate of 14,736,046 shares of our common stock are sold at a price of \$10.07 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on March 9, 2021, for aggregate gross proceeds of approximately \$148.4 million, and after deducting commissions and estimated offering expenses payable by us, new investors in this offering will incur immediate dilution of \$4.84 per share. For a more detailed discussion of the foregoing, see the section entitled “Dilution” below. To the extent outstanding stock options or warrants are exercised, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled “Use of Proceeds,” and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We expect to use the net proceeds from this offering for general corporate purposes, which may include clinical trials, research and development expenditures, acquisitions or in-licenses of complementary companies, medicines or technologies, expenditures to build our initial development and commercial capabilities, repayment and refinancing of debt, working capital and capital expenditures. The failure by our management to apply these funds effectively could harm our business. Pending their use, we plan to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government. These investments may not yield a favorable return to our stockholders. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

Future sales or issuances of our common stock in the public markets, or the perception of such sales, could depress the trading price of our common stock.

The sale of a substantial number of shares of our common stock or other equity-related securities in the public markets, or the perception that such sales could occur, could depress the market price of our common stock and

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impair our ability to raise capital through the sale of additional equity securities. We may sell large quantities of our common stock at any time pursuant to this prospectus supplement or in one or more separate offerings. We cannot predict the effect that future sales of common stock or other equity-related securities would have on the market price of our common stock.

The actual number of shares we will issue under the sales agreement, at any one time or in total, is uncertain.

Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to Cowen at any time throughout the term of the sales agreement. The number of shares that are sold by Cowen after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with Cowen. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued.

The common stock offered hereby will be sold in “at the market offerings,” and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different outcomes in their investment results. We will have discretion, subject to market demand, to vary the timing, prices, and numbers of shares sold, and there is no minimum or maximum sales price. Investors may experience a decline in the value of their shares as a result of share sales made at prices lower than the prices they paid.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering may contain forward-looking statements. All statements other than statements of historical facts contained in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, including statements regarding our future results of operations and financial position, anticipated use of cash, business strategy, prospective products, product approvals, research and development costs, anticipated timing and likelihood of success of clinical trials, expected timing of the release of clinical trial data, the plans and objectives of management for future operations, future results of anticipated products and our intended use of proceeds from this offering, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus may also contain estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other similar expressions. The forward-looking statements in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus are only predictions. We have based these forward- looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the respective dates of this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, as applicable, and are subject to a number of risks, uncertainties and assumptions, including those described under “Risk Factors” and elsewhere in this prospectus supplement. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward- looking statements contained in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein and any free writing prospectus, whether as a result of any new information, future events, changed circumstances or otherwise.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sales proceeds of up to \$148,391,990 from time to time. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time.

We intend to use the net proceeds of this offering for general corporate purposes, which may include clinical trials, research and development expenditures, acquisitions or in-licenses of complementary companies, medicines or technologies, expenditures to build our initial development and commercial capabilities, further expansion of our manufacturing capacity, repayment and refinancing of debt, working capital and capital expenditures.

The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our clinical trials and other development efforts and other factors described under “Risk Factors” in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein, as well as the amount of cash used in our operations. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of the net proceeds. Pending the use of the net proceeds described above, we plan to invest the net proceeds from this offering in a variety of capital preservation investments, including short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value of our common stock as of December 31, 2020 was approximately \$196.0 million, or approximately \$3.90 per share of common stock based upon 50,268,666 shares outstanding. Net tangible book value per share is equal to our total tangible assets, less our total liabilities, divided by the total number of shares outstanding as of December 31, 2020.

After giving effect to the sale of our common stock in the aggregate amount of \$148.4 million at an assumed offering price of \$10.07 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on March 9, 2021, and after deducting commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of December 31, 2020 would have been \$339.6 million, or \$5.23 per share of common stock. This represents an immediate increase in net tangible book value of \$1.33 per share to our existing stockholders and an immediate dilution in net tangible book value of \$4.84 per share to new investors in this offering.

The following table illustrates this calculation on a per share basis. The as adjusted information is illustrative only and will adjust based on the actual price to the public, the actual number of shares sold and other terms of the offering determined at the time shares of our common stock are sold pursuant to this prospectus supplement. The as adjusted information assumes that all of our common stock in the aggregate amount of \$148.4 million is sold at the assumed offering price of \$10.07 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on March 9, 2021. The shares sold in this offering, if any, will be sold from time to time at various prices.

Assumed public offering price per share		\$10.07
Net tangible book value per share as of December 31, 2020	\$3.90	
Increase in net tangible book value per share attributable to the offering	<u>1.33</u>	
As adjusted net tangible book value per share after giving effect to the offering		<u>5.23</u>
Dilution per share to new investors participating in the offering		<u>\$ 4.84</u>

The above discussion and table are based on 50,268,666 shares of our common stock legally outstanding as of December 31, 2020, which included 3,091 shares of unvested restricted stock subject to repurchase and excludes:

- 1,661,468 shares of common stock issuable upon exercise of stock options outstanding under our 2015 Stock Incentive Plan at a weighted-average exercise price of \$3.95 per share, as of December 31, 2020;
- 4,179,356 shares of common stock issuable upon the exercise of stock options outstanding under our 2018 Incentive Award Plan, or the 2018 Plan, at a weighted-average exercise price of \$19.65 per share, as of December 31, 2020;
- 2,397,547 shares of our common stock available for future issuance under our 2018 Plan, as of December 31, 2020, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under our 2018 Plan; and
- 1,039,650 shares of common stock available for future issuance under our 2018 Employee Stock Purchase Plan, or 2018 ESPP, as of December 31, 2020, as well as any automatic increases in the number of shares of our common stock reserved for future issuance under our 2018 ESPP.

The foregoing table does not give effect to the exercise of any outstanding options. To the extent options are exercised, there may be further dilution to new investors.

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax consequences to Non-U.S. Holders (as defined below) of the purchase, ownership and disposition of the shares of common stock to be issued pursuant to this offering, but does not purport to be a complete analysis of all potential tax effects. The effects of other U.S. federal tax laws, such as estate and gift tax laws, and any applicable state, local or foreign tax laws are not discussed. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service, or IRS, in each case as in effect as of the date of this offering. These authorities may change or be subject to differing interpretations. Any such change or differing interpretation may be applied retroactively in a manner that could adversely affect a Non-U.S. Holder. We have not sought and do not currently intend to seek any rulings from the IRS regarding the matters discussed below. There can be no assurance the IRS or a court will not take a contrary position regarding the tax consequences of the purchase, ownership and disposition of our common stock.

This discussion is limited to Non-U.S. Holders that hold our common stock as a “capital asset” within the meaning of Section 1221 of the Code (generally, property held for investment). This discussion does not address all U.S. federal income tax consequences relevant to a Non-U.S. Holder’s particular circumstances, including the impact of the alternative minimum tax or the unearned income Medicare contribution tax. In addition, it does not address consequences relevant to Non-U.S. Holders subject to particular rules, including, without limitation:

- U.S. expatriates and certain former citizens or long-term residents of the United States;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies, and other financial institutions;
- brokers, dealers or traders in securities or currencies;
- “controlled foreign corporations,” “passive foreign investment companies,” and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- “qualified foreign pension funds” as defined in Section 897(1)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds;
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and
- tax-qualified retirement plans.

If a partnership (or other entity treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner in the partnership will depend on the status of the partner, the activities of the partnership and certain determinations made at the partner level. Accordingly, partnerships holding our common stock and the partners in such partnerships should consult their tax advisors regarding the U.S. federal income tax consequences to them.

THIS DISCUSSION IS NOT LEGAL OR TAX ADVICE. INVESTORS SHOULD CONSULT THEIR TAX ADVISORS WITH RESPECT TO THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AS WELL AS ANY TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK ARISING UNDER THE U.S. FEDERAL ESTATE OR GIFT TAX LAWS OR UNDER THE LAWS OF ANY STATE, LOCAL OR NON-U.S. TAXING JURISDICTION OR UNDER ANY APPLICABLE INCOME TAX TREATY.

Definition of Non-U.S. Holder

For purposes of this discussion, a “Non-U.S. Holder” is a beneficial owner of our common stock that is neither a “U.S. person” nor an entity treated as a partnership for U.S. federal income tax purposes. A U.S. person is any person that, for U.S. federal income tax purposes, is or is treated as any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or
- a trust that (1) is subject to the primary supervision of a U.S. court and all substantial decisions of which are subject to the control of one or more “United States persons” (within the meaning of Section 7701(a)(30) of the Code), or (2) has made a valid election under applicable Treasury Regulations to continue to be treated as a United States person.

Distributions

As described in the section entitled “Dividend Policy,” we do not anticipate paying any cash dividends in the foreseeable future. However, if we do make distributions on our common stock, such distributions of cash or property on our common stock will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Amounts not treated as dividends for U.S. federal income tax purposes will constitute a return of capital and first be applied against and reduce a Non-U.S. Holder’s adjusted tax basis in our common stock, but not below zero. Any excess will be treated as capital gain and will be treated as described below in the section relating to the sale or disposition of our common stock. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of the withholding rules discussed below, we, or the applicable withholding agent, may treat the entire distribution as a dividend.

Dividends paid to a Non-U.S. Holder that are not effectively connected with the Non-U.S. Holder’s conduct of a trade or business within the United States will be subject to U.S. federal withholding tax at a rate of 30% of the gross amount of the dividends (or such lower rate specified by an applicable income tax treaty).

Non-U.S. Holders will be entitled to a reduction in or an exemption from such withholding on dividends as a result of either (a) an applicable income tax treaty or (b) the Non-U.S. Holder holding our common stock in connection with the conduct of a trade or business within the United States and dividends being effectively connected with that trade or business. To claim such a reduction in or exemption from withholding, the Non-U.S. Holder must provide the applicable withholding agent with a properly executed (a) IRS Form W-8BEN or W-8BEN-E (or other applicable documentation) claiming an exemption from or reduction of the withholding tax under the benefit of an income tax treaty between the United States and the country in which the Non-U.S. Holder resides or is established, or (b) IRS Form W-8ECI stating that the dividends are not subject to withholding tax because they are effectively connected with the conduct by the Non-U.S. Holder of a trade or business within the United States, as may be applicable. These certifications must be provided to the applicable withholding agent prior to the payment of dividends and must be updated periodically. Non-U.S. Holders that do not timely provide the applicable withholding agent with the required certification, but that qualify for a reduced rate under an applicable income tax treaty, may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

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If dividends paid to a Non-U.S. Holder are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such dividends are attributable), then, although exempt from U.S. federal withholding tax (provided the Non-U.S. Holder provides appropriate certification, as described above), the Non-U.S. Holder will be subject to U.S. federal income tax on such dividends on a net income basis at the regular U.S. federal income tax rates. In addition, a Non-U.S. Holder that is a corporation may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on its effectively connected earnings and profits for the taxable year that are attributable to such dividends, as adjusted for certain items. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

Sale or Other Taxable Disposition of Common Stock

Subject to the discussion below on backup withholding, a Non-U.S. Holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

- the gain is effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, the Non-U.S. Holder maintains a permanent establishment in the United States to which such gain is attributable);
- the Non-U.S. Holder is a nonresident alien individual present in the United States for 183 days or more during the taxable year of the disposition and certain other requirements are met; or
- our common stock constitutes a U.S. real property interest, or USRPI, by reason of our status as a U.S. real property holding corporation, or USRPHC, for U.S. federal income tax purposes.

Gain described in the first bullet point above will generally be subject to U.S. federal income tax on a net income basis at the regular U.S. federal income tax rates. A Non-U.S. Holder that is a corporation also may be subject to a branch profits tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on such effectively connected gain, as adjusted for certain items.

A Non-U.S. Holder described in the second bullet point above will be subject to U.S. federal income tax at a rate of 30% (or such lower rate specified by an applicable income tax treaty) on any gain derived from the disposition, which may be offset by certain U.S. source capital losses of the Non-U.S. Holder (even though the individual is not considered a resident of the United States) provided the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

With respect to the third bullet point above, we believe we are not currently and do not anticipate becoming a USRPHC. Because the determination of whether we are a USRPHC depends on the fair market value of our USRPIs relative to the fair market value of our other business assets and our non-U.S. real property interests, however, there can be no assurance we are not a USRPHC or will not become one in the future. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition of our common stock by a Non-U.S. Holder will not be subject to U.S. federal income tax if our common stock is "regularly traded," as defined by applicable Treasury Regulations, on an established securities market, and such Non-U.S. Holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the Non-U.S. Holder's holding period. Non-U.S. Holders should consult their tax advisors regarding potentially applicable income tax treaties that may provide for different rules.

Information Reporting and Backup Withholding

Subject to the discussion below on foreign accounts, a Non-U.S. Holder will not be subject to backup withholding with respect to distributions on our common stock we make to the Non-U.S. Holder, provided the

applicable withholding agent does not have actual knowledge or reason to know such holder is a United States person and the holder certifies its non-U.S. status, such as by providing a valid IRS Form W-8BEN, W-8BEN-E or W-8ECI, or otherwise establishes an exemption. However, information returns generally will be filed with the IRS in connection with any distributions (including deemed distributions) made on our common stock to the Non-U.S. Holder, regardless of whether any tax was actually withheld. Copies of these information returns may also be made available under the provisions of a specific treaty or agreement to the tax authorities of the country in which the Non-U.S. Holder resides or is established.

Information reporting and backup withholding may apply to the proceeds of a sale or other taxable disposition of our common stock within the United States, and information reporting may (although backup withholding generally will not) apply to the proceeds of a sale or other taxable disposition of our common stock outside the United States conducted through certain U.S.-related financial intermediaries, in each case, unless the beneficial owner certifies under penalty of perjury that it is a Non-U.S. Holder on IRS Form W-8BEN or W-8BEN-E, or other applicable form (and the payor does not have actual knowledge or reason to know that the beneficial owner is a United States person) or such owner otherwise establishes an exemption. Proceeds of a disposition of our common stock conducted through a non-U.S. office of a non-U.S. broker generally will not be subject to backup withholding or information reporting.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a Non-U.S. Holder's U.S. federal income tax liability, provided the required information is timely furnished to the IRS.

Additional Withholding Tax on Payments Made to Foreign Accounts

Withholding taxes may be imposed under the Foreign Account Tax Compliance Act, or FATCA, on certain types of payments made to non-U.S. financial institutions and certain other non-U.S. entities. Specifically, a 30% withholding tax may be imposed on dividends (including deemed dividends) paid on our common stock, or (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of our common stock, paid to a "foreign financial institution" or a "non-financial foreign entity" (each as defined in the Code), unless (1) the foreign financial institution undertakes certain diligence and reporting obligations, (2) the non-financial foreign entity either certifies it does not have any "substantial United States owners" (as defined in the Code) or furnishes identifying information regarding each substantial United States owner, or (3) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the diligence and reporting requirements in (1) above, it must enter into an agreement with the U.S. Department of the Treasury requiring, among other things, that it undertake to identify accounts held by certain "specified United States persons" or "United States owned foreign entities" (each as defined in the Code), annually report certain information about such accounts, and withhold 30% on certain payments to non-compliant foreign financial institutions and certain other account holders. Foreign financial institutions located in jurisdictions that have an intergovernmental agreement with the United States governing FATCA may be subject to different rules.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends (including deemed dividends) paid on our common stock. Because we may not know the extent to which a distribution is a dividend for U.S. federal income tax purposes at the time it is made, for purposes of these withholding rules, we, or the applicable withholding agent, may treat the entire distribution as a dividend. While, beginning on January 1, 2019, withholding under FATCA would have applied also to payments of gross proceeds from the sale or other disposition of our common stock, proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued. Prospective investors should consult their tax advisors regarding the potential application of these withholding provisions.

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Cowen, under which we may issue and sell shares of our common stock from time to time up to an aggregate sales price of \$148,391,990 through Cowen. The sales agreement is filed as Exhibit 1.2 to our registration statement on Form S-3 of which this prospectus supplement forms a part, and is incorporated by reference in this prospectus supplement. Sales of our common stock, if any, under this prospectus supplement will be made at market prices by any method that is deemed to be an “at the market offering” as defined in Rule 415(a)(4) under the Securities Act, including sales made directly on or through the Nasdaq Global Select Market or any other existing trading market for our common stock. If authorized by us in writing, Cowen may purchase shares of our common stock as principal.

When requested by us, Cowen will offer the shares of common stock subject to the terms and conditions of the sales agreement, which may be on a daily basis for periods of time, or as otherwise agreed upon by us and Cowen. We will designate the maximum amount of shares of common stock to be sold through Cowen when we request Cowen to do so. Cowen has agreed, subject to the terms and conditions of the sales agreement, to use commercially reasonable efforts to execute our orders to sell, as our sales agent and on our behalf, shares of our common stock submitted to Cowen from time to time by us, consistent with its normal sales and trading practices on mutually agreed terms between the sales agent and us. We may instruct Cowen not to sell common stock if the sales cannot be effected at or above a price designated by us in any such instruction. We or Cowen may suspend the offering of shares of common stock under the sales agreement upon proper notice to the other party. Cowen and we each have the right, by giving written notice as specified in the sales agreement, to terminate the sales agreement in each party’s sole discretion at any time.

The aggregate compensation payable to Cowen as sales agent equals 3.0% of the gross sales price of the shares of our common stock sold through it pursuant to the sales agreement. We agreed to reimburse Cowen for reasonable out-of-pocket expenses, including the reasonable fees and disbursements of counsel incurred by Cowen, up to a maximum aggregate amount of \$60,000 (inclusive of any amounts reimbursed for associated legal expenses of Cowen’s outside counsel for filings with FINRA). The estimated offering expenses payable by us, in addition to such commission and expenses, are approximately \$250,000, which includes legal, accounting and printing costs and various other fees associated with registering the shares of common stock. The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by a governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds from the sale of such shares.

Cowen will provide written confirmation to us following the close of trading on the Nasdaq Global Select Market each day on which shares of common stock are sold under the sales agreement. Each confirmation will include the number of shares sold through Cowen as sales agent on that day, the volume weighted average price of the shares sold, the percentage of the daily trading volume and the net proceeds to us. Settlement for sales of common stock will occur, unless the parties agree otherwise, on the second business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

We will report at least quarterly the number of shares of common stock sold through Cowen under the sales agreement, the net proceeds to us and the compensation paid by us to Cowen in connection with the sales of common stock.

In connection with the sale of our common stock on our behalf, Cowen will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation paid to Cowen will be deemed to be underwriting commissions or discounts.

We have agreed in the sales agreement to provide indemnification and contribution to Cowen against certain liabilities, including liabilities under the Securities Act. As a sales agent, Cowen will not engage in any

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transactions that stabilizes our common stock. We have also agreed to contribute to payments Cowen may be required to make in respect of such liabilities.

Our common stock is listed on the Nasdaq Global Select Market and trades under the symbol "FIXX." The transfer agent of our common stock is American Stock Transfer Trust Company, LLC.

The offering of shares of common stock pursuant to the sales agreement will terminate upon the earliest of (i) the sale of all shares of common stock subject to the sales agreement and this prospectus supplement, and (ii) the termination of the sales agreement according to its terms by either Cowen or us.

Cowen has provided, and may in the future provide, various investment banking, commercial banking, financial advisory and other financial services to us and our affiliates for which services they have received, and may in the future receive, customary fees. In the course of their respective businesses, Cowen may actively trade our securities for their own respective accounts or for the accounts of customers, and, accordingly, Cowen may at any time hold long or short positions in such securities.

LEGAL MATTERS

Latham & Watkins LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Homology Medicines, Inc. Shearman & Sterling LLP, New York, New York, is counsel for Cowen in connection with this offering.

EXPERTS

The financial statements incorporated in this prospectus supplement by reference from our Annual Report on Form 10-K have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

\$148,391,990



Common Stock

PROSPECTUS SUPPLEMENT

Cowen

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following is an estimate of the expenses (all of which are to be paid by the registrant) that we may incur in connection with the securities being registered hereby.

SEC registration fee	\$ 38,185(1)
FINRA filing fee	\$ 225,500
Printing expenses	\$ (2)
Legal fees and expenses	\$ (2)
Accounting fees and expenses	\$ (2)
Blue Sky, qualification fees and expenses	\$ (2)
Transfer agent fees and expenses	\$ (2)
Trustee fees and expenses	\$ (2)
Warrant agent fees and expenses	\$ (2)
Miscellaneous	\$ (2)
Total	\$ (2)

- (1) This amount includes \$17,986.10 of fees related to the offering, issuance and sale of up to \$148,391,990 of the registrant's common stock pursuant to this registration statement and a sales agreement, dated as of March 12, 2020, by and between the registrant and Cowen and Company LLC. The \$350,000,000 of shares of common stock registered pursuant to this registration statement includes \$148,391,990 of shares of common stock (the "Unsold Shares") registered pursuant to Registration Statement No. 333-230664 which became effective on April 9, 2019. Pursuant to Rule 415(a)(6) under the Securities Act of 1933, as amended, the filing fees previously paid in connection with the Unsold Shares will continue to be applied to the Unsold Shares.
- (2) These fees are calculated based on the securities offered and the number of issuances and accordingly cannot be estimated at this time.

Item 15. Indemnification of Directors and Officers

Subsection (a) of Section 145 of the General Corporation Law of the State of Delaware, or the DGCL, empowers a corporation to indemnify any person who was or is a party or who is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of the corporation) by reason of the fact that the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with such action, suit or proceeding if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe the person's conduct was unlawful.

Subsection (b) of Section 145 empowers a corporation to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor by reason of the fact that the person acted in any of the capacities set forth above, against expenses (including attorneys' fees) actually and reasonably incurred by the person in connection with the defense or settlement of such action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been

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adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

Section 145 further provides that to the extent a director or officer of a corporation has been successful on the merits or otherwise in the defense of any action, suit or proceeding referred to in subsections (a) and (b) of Section 145, or in defense of any claim, issue or matter therein, such person shall be indemnified against expenses (including attorneys' fees) actually and reasonably incurred by such person in connection therewith; that indemnification provided for by Section 145 shall not be deemed exclusive of any other rights to which the indemnified party may be entitled; and the indemnification provided for by Section 145 shall, unless otherwise provided when authorized or ratified, continue as to a person who has ceased to be a director, officer, employee or agent and shall inure to the benefit of such person's heirs, executors and administrators. Section 145 also empowers the corporation to purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise against any liability asserted against such person and incurred by such person in any such capacity, or arising out of his status as such, whether or not the corporation would have the power to indemnify such person against such liabilities under Section 145.

Section 102(b)(7) of the DGCL provides that a corporation's certificate of incorporation may contain a provision eliminating or limiting the personal liability of a director to the corporation or its stockholders for monetary damages for breach of fiduciary duty as a director; provided that such provision shall not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the DGCL, or (iv) for any transaction from which the director derived an improper personal benefit.

Any underwriting agreement or distribution agreement that the registrant enters into with any underwriters or agents involved in the offering or sale of any securities registered hereby may require such underwriters or dealers to indemnify the registrant, some or all of its directors and officers and its controlling persons, if any, for specified liabilities, which may include liabilities under the Securities Act of 1933, as amended.

Our restated certificate of incorporation provides that we will indemnify each person who was or is a party or threatened to be made a party to any threatened, pending or completed action, suit or proceeding (other than an action by or in the right of us) by reason of the fact that he or she is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an "Indemnitee"), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful. Our restated certificate of incorporation provides that we will indemnify any Indemnitee who was or is a party to an action or suit by or in the right of us to procure a judgment in our favor by reason of the fact that the Indemnitee is or was, or has agreed to become, a director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees) and, to the extent permitted by law, amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding, and any appeal therefrom, if the Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, except that no

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indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to us, unless a court determines that, despite such adjudication but in view of all of the circumstances, he or she is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that any Indemnitee has been successful, on the merits or otherwise, he or she will be indemnified by us against all expenses (including attorneys' fees) actually and reasonably incurred in connection therewith. Expenses must be advanced to an Indemnitee under certain circumstances.

We have entered into indemnification agreements with each of our directors and officers. These indemnification agreements may require us, among other things, to indemnify our directors and officers for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by a director or officer in any action or proceeding arising out of his or her service as one of our directors or officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request.

We maintain a general liability insurance policy that covers certain liabilities of directors and officers of our corporation arising out of claims based on acts or omissions in their capacities as directors or officers.

Item 16. Exhibits

(a) Exhibits

Exhibit Number	Description
1.1*	Form of Underwriting Agreement.
1.2	Sales Agreement, dated as of March 12, 2020, by and between Homology Medicines, Inc. and Cowen and Company, LLC (incorporated by reference to Exhibit 1.2 of the Company's Registration Statement on Form S-3ASR (Reg. No. 333-237131) filed with the SEC on March 12, 2020).
3.1	Restated Certificate of Incorporation of Homology Medicines, Inc., dated April 2, 2018 (incorporated by reference to Exhibit 3.1 of the Company's Current Report on Form 8-K (File No. 001-38433), filed with the SEC on April 3, 2018).
3.2	Amended and Restated Bylaws of Homology Medicines, Inc. (incorporated by reference to Exhibit 3.1 of the Company's Current Report on Form 8-K (File No. 001-38433), filed with the SEC on December 18, 2020).
4.1	Form of Specimen Certificate Representing Common Stock (incorporated by reference to Exhibit 4.2 of the Company's Registration Statement on Form S-1/A (File No. 333- 223409), filed with the SEC on March 19, 2018).
4.2*	Form of Specimen Certificate Representing Preferred Stock.
4.3	Form of Indenture (incorporated by reference to Exhibit 4.3 of the Company's Registration Statement on Form S-3ASR (Reg. No. 333-237131) filed with the SEC on March 12, 2020).
4.4*	Form of Note.
4.5*	Form of Warrant.
4.6*	Form of Warrant Agreement. 4.7* Form of Unit Agreement.
5.1	Opinion of Latham & Watkins LLP.
23.1	Consent of Latham & Watkins LLP (included in Exhibit 5.1).
23.2	Consent of Independent Registered Public Accounting Firm.
24.1	Powers of Attorney (incorporated by reference to the signature page hereto).
25.1**	Statement of Eligibility on Form T-1 under the Trust Indenture Act of 1939 of Debt Trustee (to be filed prior to any issuance of Debt Securities).

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- * To be filed by amendment or incorporated by reference in connection with the offering of the securities.
- ** To be filed in accordance with the requirements of Section 305(b)(2) of the Trust Indenture Act of 1939.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that paragraphs (a)(1)(i), (a)(1)(ii), and (a)(1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to section 13 or section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is a part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(5) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof; provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

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(6) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities:

The undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

- (i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;
- (iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and
- (iv) Any other communications that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(h) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

(j) The undersigned registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act (the "Act") in accordance with the rules and regulations prescribed by the SEC under section 305(b)(2) of the Act.

LATHAM & WATKINS LLP

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March 11, 2021

Homology Medicines, Inc.
 One Patriots Park
 Bedford, Massachusetts 01730

Re: Post-Effective Amendment No. 2 to the Registration Statement on Form S-3

Ladies and Gentlemen:

We have acted as special counsel to Homology Medicines, Inc., a Delaware corporation (the “**Company**”), in connection with its filing on the date hereof with the Securities and Exchange Commission (the “**Commission**”) of a Post-Effective Amendment No. 2 to the Registration Statement on Form S-3 (Registration No. 333-237131) (as amended, the “**Registration Statement**”), including a base prospectus (the “**Base Prospectus**”), which provides that it will be supplemented by one or more prospectus supplements (each such prospectus supplement, together with the Base Prospectus, a “**Prospectus**”), under the Securities Act of 1933, as amended (the “**Act**”), relating to the registration for issue and sale by the Company of up to \$350,000,000 aggregate offering amount of (i) shares of the Company’s common stock, par value \$0.0001 per share (the “**Common Stock**”), (ii) shares of one or more series of the Company’s preferred stock, par value \$0.0001 per share (the “**Preferred Stock**”), (iii) one or more series of the Company’s debt securities (collectively, “**Debt Securities**”) to be issued under an indenture to be entered into between the Company, as issuer, and a trustee (a form of which is included as Exhibit 4.3 to the Registration Statement) and one or more board resolutions, supplements thereto or officer’s certificates thereunder (such indenture, together with the applicable board resolution, supplement or officer’s certificate pertaining to the applicable series of Debt Securities, the “**Applicable Indenture**”), (iv) warrants (“**Warrants**”), and (v) units (“**Units**”). The Debt Securities, Common Stock, Preferred Stock, Warrants and Units, plus any additional Debt Securities, Common Stock, Preferred Stock, Warrants and Units that may be registered pursuant to any subsequent registration statement that the Company may hereafter file with the Commission pursuant to Rule 462(b) under the Act in connection with the offering by the Company contemplated by the Registration Statement, are referred to herein collectively as the “**Securities**.”

We also have acted as special counsel to the Company in connection with the sale through Cowen and Company, LLC as the sales agent (the “**Sales Agent**”) from time to time by the Company of shares of Common Stock (the “**Sales Agreement Shares**”) having an aggregate offering price of up to \$148,391,990 pursuant to the Registration Statement, the Base Prospectus and the related prospectus supplement for the sale of the Sales Agreement Shares included in the Registration Statement (the Base Prospectus and such prospectus supplement, collectively, the “**Sales Agreement Prospectus**”), and that certain Sales Agreement dated as of March 12, 2020 between the Sales Agent and the Company, as amended (the “**Sales Agreement**”).

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This opinion is being furnished in connection with the requirements of Item 601(b)(5) of Regulation S-K under the Act, and no opinion is expressed herein as to any matter pertaining to the contents of the Registration Statement or related applicable Prospectus or the Sales Agreement Prospectus, other than as expressly stated herein with respect to the issuance of the Securities, including the issuance of the Sales Agreement Shares.

As such counsel, we have examined such matters of fact and questions of law as we have considered appropriate for purposes of this letter. With your consent, we have relied upon certificates and other assurances of officers of the Company and others as to factual matters without having independently verified such factual matters. We are opining herein as to the General Corporation Law of the State of Delaware, and with respect to the opinions set forth in paragraphs 3 through 5 below, the internal laws of the State of New York, and we express no opinion with respect to the applicability thereto, or the effect thereon, of the laws of any other jurisdiction or, in the case of Delaware, any other laws, or as to any matters of municipal law or the laws of any local agencies within any state.

Subject to the foregoing and the other matters set forth herein, it is our opinion that, as of the date hereof:

1. When an issuance of Common Stock has been duly authorized by all necessary corporate action of the Company, upon issuance, delivery and payment therefor in an amount not less than the par value thereof in the manner contemplated by the applicable Prospectus and by such corporate action, and in total amounts and numbers of shares that do not exceed the respective total amounts and numbers of shares (a) available under the certificate of incorporation, and (b) authorized by the board of directors in connection with the offering contemplated by the applicable Prospectus, such shares of Common Stock will be validly issued, fully paid and nonassessable. In rendering the foregoing opinion, we have assumed that the Company will comply with all applicable notice requirements regarding uncertificated shares provided in the General Corporation Law of the State of Delaware.

2. When a series of Preferred Stock has been duly established in accordance with the terms of the Company's certificate of incorporation and authorized by all necessary corporate action of the Company, upon issuance, delivery and payment therefor in an amount not less than the par value thereof in the manner contemplated by the applicable Prospectus and by such corporate action, and in total amounts and numbers of shares that do not exceed the respective total amounts and numbers of shares (a) available under the certificate of incorporation, and (b) authorized by the board of directors in connection with the offering contemplated by the applicable Prospectus, such shares of such series of Preferred Stock will be validly issued, fully paid and nonassessable. In rendering the foregoing opinion, we have assumed that the Company will comply with all applicable notice requirements regarding uncertificated shares provided in the General Corporation Law of the State of Delaware.

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3. When the Applicable Indenture has been duly authorized, executed and delivered by all necessary corporate action of the Company, and when the specific terms of a particular series of Debt Securities have been duly established in accordance with the terms of the Applicable Indenture and authorized by all necessary corporate action of the Company and such Debt Securities have been duly executed, authenticated, issued and delivered against payment therefor in accordance with the terms of the Applicable Indenture and in the manner contemplated by the applicable Prospectus and by such corporate action, such Debt Securities will be legally valid and binding obligations of the Company, enforceable against the Company in accordance with their terms.

4. When the applicable warrant agreement has been duly authorized, executed and delivered by all necessary corporate action of the Company, and when the specific terms of a particular issuance of Warrants have been duly established in accordance with the terms of the applicable warrant agreement and authorized by all necessary corporate action of the Company, and such Warrants have been duly executed, authenticated, issued and delivered against payment therefor in accordance with the terms of the applicable warrant agreement and in the manner contemplated by the applicable Prospectus and by such corporate action (assuming the securities issuable upon exercise of such Warrants have been duly authorized and reserved for issuance by all necessary corporate action), such Warrants will be the legally valid and binding obligations of the Company, enforceable against the Company in accordance with their terms.

5. When the applicable unit agreement has been duly authorized, executed and delivered by all necessary corporate action of the Company, and when the specific terms of a particular issuance of Units have been duly authorized in accordance with the terms of the applicable unit agreement and authorized by all necessary corporate action of the Company, and such Units have been duly executed, authenticated, issued and delivered against payment therefor in accordance with the terms of the applicable unit agreement and in the manner contemplated by the applicable Prospectus and by such corporate action (assuming the securities issuable upon exercise of such Units have been duly authorized and reserved for issuance by all necessary corporate action), such Units will be the legally valid and binding obligations of the Company, enforceable against the Company in accordance with their terms.

6. Upon the completion of all Corporate Proceedings (as defined below) relating to the Sales Agreement Shares, when the Sales Agreement Shares shall have been duly registered on the books of the transfer agent and registrar therefor in the name or on behalf of the purchasers, and have been issued by the Company against payment therefor (not less than par value) in accordance with the Corporate Proceedings and the terms of the Sales Agreement, the issuance and sale of the Sales Agreement Shares will have been duly authorized by all necessary corporate action of the Company, and the Sales Agreement Shares will be validly issued, fully paid and nonassessable. In rendering the foregoing opinion, we have assumed that (i) the Company will comply with all applicable notice requirements regarding uncertificated shares provided in the General Corporation Law of the State of Delaware (the "DGCL"), (ii) upon the issuance of any of the Sales Agreement Shares, the total number of shares of Common Stock issued and outstanding will not exceed the total number of shares of Common Stock that the Company is then authorized to issue under the Company's certificate of incorporation and (iii) certain terms of the Sales Agreement Shares to be issued by the Company from time to time will be authorized and approved by the board of directors of the Company or one or more committees thereof established by the board of directors of the Company with the authority to issue and sell Sales Agreement Shares pursuant to the Sales Agreement in accordance with the DGCL, the Company's certificate of incorporation, the by-laws of the Company and certain resolutions of the board of directors of the Company and one or more committees thereof (with such approvals referred to herein as the "**Corporate Proceedings**") prior to issuance thereof.

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Our opinions set forth in paragraphs 1 through 5 are subject to: (i) the effect of bankruptcy, insolvency, reorganization, preference, fraudulent transfer, moratorium or other similar laws relating to or affecting the rights and remedies of creditors; (ii) the effect of general principles of equity, whether considered in a proceeding in equity or at law (including the possible unavailability of specific performance or injunctive relief), concepts of materiality, reasonableness, good faith and fair dealing and the discretion of the court before which a proceeding is brought; (iii) the invalidity under certain circumstances under law or court decisions of provisions providing for the indemnification of or contribution to a party with respect to a liability where such indemnification or contribution is contrary to public policy; and (iv) we express no opinion as to (a) any provision for liquidated damages, default interest, late charges, monetary penalties, make-whole premiums or other economic remedies to the extent such provisions are deemed to constitute a penalty, (b) consents to, or restrictions upon, governing law, jurisdiction, venue, arbitration, remedies or judicial relief, (c) waivers of rights or defenses, (d) any provision requiring the payment of attorneys' fees, where such payment is contrary to law or public policy, (e) any provision permitting, upon acceleration of any Debt Securities, collection of that portion of the stated principal amount thereof which might be determined to constitute unearned interest thereon, (f) the creation, validity, attachment, perfection, or priority of any lien or security interest, (g) advance waivers of claims, defenses, rights granted by law, or notice, opportunity for hearing, evidentiary requirements, statutes of limitation, trial by jury or at law, or other procedural rights, (h) waivers of broadly or vaguely stated rights, (i) provisions for exclusivity, election or cumulation of rights or remedies, (j) provisions authorizing or validating conclusive or discretionary determinations, (k) grants of setoff rights, (l) proxies, powers and trusts, (m) provisions prohibiting, restricting, or requiring consent to assignment or transfer of any right or property, (n) any provision to the extent it requires that a claim with respect to a security denominated in other than U.S. dollars (or a judgment in respect of such a claim) be converted into U.S. dollars at a rate of exchange at a particular date, to the extent applicable law otherwise provides, and (o) the severability, if invalid, of provisions to the foregoing effect.

With your consent, we have assumed (a) that each of the Debt Securities, Warrants, Units, Applicable Indenture, warrant agreements and unit agreements (collectively, the "**Documents**") will be governed by the internal laws of the State of New York, (b) that each of the Documents has been or will be duly authorized, executed and delivered by the parties thereto, (c) that each of the Documents constitutes or will constitute legally valid and binding obligations of the parties thereto other than the Company, enforceable against each of them in accordance with their respective terms, and (d) that the status of each of the Documents as legally valid and binding obligations of the parties will not be affected by any (i) breaches of, or defaults under, agreements or instruments, (ii) violations of statutes, rules, regulations or court or governmental orders, or (iii) failures to obtain required consents, approvals or authorizations from, or to make required registrations, declarations or filings with, governmental authorities.

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This opinion is for your benefit in connection with the Registration Statement and may be relied upon by you and by persons entitled to rely upon it pursuant to the applicable provisions of the Act. We consent to your filing this opinion as an exhibit to the Registration Statement and to the reference to our firm contained in each of the Prospectus and the Sales Agreement Prospectus under the heading "Legal Matters." We further consent to the incorporation by reference of this letter and consent into any registration statement or post-effective amendment to the Registration Statement filed pursuant to Rule 462(b) under the Act with respect to the Securities. In giving such consent, we do not thereby admit that we are in the category of persons whose consent is required under Section 7 of the Act or the rules and regulations of the Commission thereunder.

Very truly yours,

/s/ LATHAM & WATKINS LLP

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in this Registration Statement No. 333-237131 on Form S-3 of our report dated March 11, 2021, relating to the financial statements of Homology Medicines, Inc. appearing in the Annual Report on Form 10-K of Homology Medicines, Inc. for the year ended December 31, 2020. We also consent to the reference to us under the heading “Experts” in such Registration Statement.

/s/ Deloitte & Touche LLP

Boston, Massachusetts
March 11, 2021