

PROSPECTUS



Sema4 Holdings Corp.

356,524,688 Shares of Class A Common Stock

7,236,667 Warrants to Purchase Shares of Class A Common Stock

21,994,972 Shares of Class A Common Stock Underlying Warrants

This prospectus relates to the offer and sale from time to time by the selling securityholders named in this prospectus (the "Selling Securityholders") of (A) up to 356,524,688 shares of our Class A common stock, par value \$0.0001 per share (the "Class A common stock"), consisting of (i) up to 18,550,000 shares of our Class A common stock (the "Business Combination PIPE Shares") issued in a private placement pursuant to subscription agreements each entered into on February 9, 2021 (the "Business Combination PIPE Investment"); (ii) up to 11,068,750 shares of our Class A common stock (the "Founder Shares") issued in connection with the consummation of the Business Combination (as defined herein) in exchange for shares of our Class B common stock originally issued in a private placement to CMLS Holdings LLC (the "Former Sponsor"); (iii) up to 158,805,073 shares of our Class A common stock issued or issuable to certain former stockholders in connection with or as a result of the consummation of the Business Combination, consisting of (a) up to 139,783,497 shares of our Class A common stock and (b) up to 19,021,576 shares of Class A common stock (the "Earn-Out Shares") that certain Legacy Sema4 Equity Holders have the contingent right to receive upon the achievement of certain vesting conditions; (iv) up to 7,236,667 shares of our Class A common stock issuable upon the exercise of the private placement warrants (as defined herein); (v) up to 80,000,000 shares of our Class A common stock (the "Stock Consideration Shares") issued to OPKO Health, Inc. ("OPKO") as a portion of the consideration for the Acquisition (as defined herein); (vi) up to 30,864,198 shares of our Class A common stock (the "Milestone Shares") that may be issuable to OPKO in connection with the achievement of certain revenue-based milestones for each of the fiscal years ending December 31, 2022 and December 31, 2023; and (vii) up to 50,000,000 shares of our Class A common stock (the "Acquisition PIPE Shares") issued in a private placement pursuant to subscription agreements each entered into on January 14, 2022 (the "Acquisition PIPE Investment"); and (B) up to 7,236,667 warrants (the "private placement warrants") originally issued in a private placement to the Former Sponsor and certain of the other Initial Stockholders (as defined herein).

In addition, this prospectus relates to the offer and sale of: (i) up to 14,758,305 shares of our Class A common stock that are issuable by us upon the exercise of 14,758,305 warrants (the "public warrants") originally issued in our initial public offering (the "IPO"); and (ii) up to 7,236,667 shares of our Class A common stock that are issuable by us upon the exercise of the private placement warrants following the public resale of the private placement warrants by the Selling Securityholders pursuant to this prospectus.

The Selling Securityholders may offer, sell or distribute all or a portion of the securities hereby registered publicly or through private transactions at prevailing market prices or at negotiated prices. We will not receive any of the proceeds from such sales of the shares of our Class A common stock or warrants, except with respect to amounts received by us upon the exercise of the warrants for cash. We will bear all costs, expenses and fees in connection with the registration of these securities, including with regard to compliance with state securities or "blue

sky” laws. The Selling Securityholders will bear all commissions and discounts, if any, attributable to their sale of shares of our Class A common stock or warrants. See “[Plan of Distribution](#)” beginning on page [26](#) of this prospectus.

Our Class A common stock and public warrants are traded on the Nasdaq Global Select Market (the “Nasdaq”) under the symbols “SMFR” and “SMFRW,” respectively. On September 6, 2022, the last reported sales price of our Class A common stock was \$0.99 per share and the last reported sales price of our public warrants was \$0.24 per warrant.

We are an “emerging growth company” as defined in Section 2(a) of the Securities Act of 1933, as amended, and, as such, have elected to comply with certain reduced disclosure and regulatory requirements.

Investing in our securities involves risks. See the section entitled “[Risk Factors](#)” beginning on page [9](#) of this prospectus, as well as the sections entitled “Risk Factors” beginning on page 30 of our Annual Report on Form 10-K for the year ended December 31, 2021, beginning on page 46 of our Quarterly Report on Form 10-Q for the quarter ended March 31, 2022 and beginning on page 60 of our Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, which reports are incorporated by reference in this prospectus, to read about factors you should consider before buying our securities.

The registration statement to which this prospectus relates registers the resale of a substantial number of shares of our Class A common stock by the Selling Securityholders. Sales in the public market of a large number of shares, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our Class A common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is September 7, 2022

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission (the “SEC”) using the “shelf” registration process. Under this shelf registration process, the Selling Securityholders may, from time to time, sell or otherwise distribute the securities offered by them as described in the section titled “*Plan of Distribution*” in this prospectus. We will not receive any proceeds from the sale by such Selling Securityholders of the securities offered by them described in this prospectus. This prospectus also relates to the issuance by us of the shares of Class A common stock issuable upon the exercise of warrants. We will receive proceeds from any exercise of the warrants for cash.

Neither we nor the Selling Securityholders have authorized anyone to provide you with any information or to make any representations other than those contained or incorporated by reference in this prospectus or any applicable prospectus supplement or, if permitted, any free writing prospectuses prepared by or on behalf of us or to which we have referred you. Neither we nor the Selling Securityholders take responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. Neither we nor the Selling Securityholders will make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted.

We may also provide a prospectus supplement or, if required, a post-effective amendment, to the registration statement to add information to, or update or change information contained or incorporated by reference in, this prospectus. You should read both this prospectus and any applicable prospectus supplement or post-effective amendment to the registration statement together with the additional information to which we refer you in the section of this prospectus entitled “*Where You Can Find More Information; Incorporation by Reference.*” Information incorporated by reference after the date of this prospectus may add, update or change information contained in this prospectus. Any information in such subsequent filings that is inconsistent with this prospectus will supersede the information in this prospectus or any earlier prospectus supplement.

Unless the context otherwise requires, references in this prospectus to the “Company,” “Sema4” and “we,” “us” and “our” refer to (i) Mount Sinai Genomics, Inc. d/b/a as Sema4 (“Legacy Sema4”) prior to the consummation of our business combination with CM Life Sciences, Inc. (“CMLS”) on July 22, 2021 (the “Business Combination”) and (ii) Sema4 Holdings Corp. (“Sema4 Holdings”) and its consolidated subsidiaries following the consummation of the Business Combination. References in this prospectus to “GeneDx” refer to GeneDx, LLC, a Delaware limited liability company (formerly, GeneDx, Inc., a New Jersey corporation), which we acquired on April 29, 2022.

SELECTED DEFINITIONS

Unless otherwise stated in this prospectus or the context otherwise requires, references to:

“*Acquisition*” means the transactions contemplated by the Acquisition Merger Agreement, including the Mergers, pursuant to which the Company acquired GeneDx on April 29, 2022.

“*Acquisition Merger Agreement*” means that certain Agreement and Plan of Merger and Reorganization, dated as of January 14, 2022, by and among the Company, Merger Sub I, Merger Sub II, GeneDx, OPKO, and Holdco, as amended by the Amendment to Agreement and Plan of Merger and Reorganization, dated as of April 29, 2022.

“*Acquisition PIPE Investment*” means the private placement pursuant to which the Acquisition PIPE Investors collectively subscribed for the Acquisition PIPE Shares at \$4.00 per share, for an aggregate purchase price of \$200 million, on the closing of the Acquisition.

“*Acquisition PIPE Investors*” means certain institutional investors that invested in the Acquisition PIPE Investment pursuant to, and on the terms and subject to the conditions of, the Acquisition Subscription Agreements.

“*Acquisition PIPE Shares*” means the 50,000,000 shares of Class A common stock issued in the Acquisition PIPE Investment.

“*Acquisition Subscription Agreements*” means, collectively, those certain subscription agreements entered into on January 14, 2022, between the Company and the Acquisition PIPE Investors, pursuant to which such investors agreed to purchase the Acquisition PIPE Shares in the Acquisition PIPE Investment on the terms and subject to the conditions of the Acquisition Subscription Agreements.

“*Amended and Restated Certificate of Incorporation*” means our Third Amended and Restated Certificate of Incorporation, dated as of July 22, 2021, as amended by the Amendment to the Amended and Restated Certificate of Incorporation, dated as of April 29, 2022.

“*Amended and Restated Registration Rights Agreement*” means that certain Amended and Restated Registration Rights Agreement, dated as of July 22, 2021, by and among the Company, the Former Sponsor and certain other parties thereto.

“*Board*” or “*Board of Directors*” means the board of directors of the Company.

“*Business Combination*” means the transactions contemplated by the Business Combination Merger Agreement pursuant to which Legacy Sema4 consummated its business combination with CMLS on July 22, 2021.

“*Business Combination Merger Agreement*” means that certain Agreement and Plan of Merger, dated as of February 9, 2021, as amended, by and among CMLS, S-IV Sub, Inc. and Legacy Sema4.

“*Business Combination PIPE Investment*” means the private placement pursuant to which the Business Combination PIPE Investors collectively subscribed for the Business Combination PIPE Shares at \$10.00 per share, for an aggregate purchase price of \$350 million, on the closing of the Business Combination.

“*Business Combination PIPE Investors*” means certain institutional investors that invested in the Business Combination PIPE Investment pursuant to, and on the terms and subject to the conditions of, the Business Combination Subscription Agreements.

“*Business Combination PIPE Shares*” means the 35,000,000 shares of our Class A common stock issued in the Business Combination PIPE Investment.

“*Business Combination Subscription Agreements*” means, collectively, those certain subscription agreements, entered into on February 9, 2021, between the Company and the Business Combination PIPE Investors.

“*Bylaws*” means the Restated Bylaws of the Company.

“*Class A common stock*” means the shares of Class A common stock, par value \$0.0001 per share, of the Company.

“*Class B common stock*” means the shares of Class B common stock, par value \$0.0001 per share, of the Company, which automatically converted into shares of Class A common stock in connection with the closing of the Business Combination.

“*CMLS*” means CM Life Sciences, Inc. prior to the closing of the Business Combination.

“*DGCL*” means the General Corporation Law of the State of Delaware.

“*Earn-Out Shares*” means the shares of Class A common stock issuable pursuant to the Business Combination Merger Agreement upon the achievement of certain vesting conditions.

“*Earn-Out RSU Shares*” means up to 2,689,764 shares of our Class A common stock issuable pursuant to the Earn-Out RSUs upon achievement of certain vesting conditions.

“*Earn-Out RSUs*” certain restricted stock unit (“RSU”) awards granted to certain Legacy Sema4 Equity Holders pursuant to the Business Combination Merger Agreement.

“*Exchange Act*” means the Securities Exchange Act of 1934, as amended.

“*First Merger*” means the merger of Merger Sub I with and into HoldCo, with HoldCo as the surviving corporation in the First Merger.

“*Former Sponsor*” means CMLS Holdings LLC, a Delaware limited liability company.

“*Founder Shares*” means the 11,068,750 shares of our Class A common stock issued in connection with the consummation of the Business Combination in exchange for shares of our Class B common stock originally issued in a private placement to the Former Sponsor.

“*GeneDx*” means (i) GeneDx, Inc., a New Jersey corporation prior to the closing of the Acquisition and (ii) GeneDx, LLC, a Delaware limited liability company, following the closing of the Acquisition.

“*HoldCo*” means GeneDx Holding 2, Inc., which held 100% of GeneDx immediately following the time the First Merger became effective.

“*Initial Stockholders*” means the Former Sponsor together with Munib Islam, Emily Leproust and Nat Turner.

“*IPO*” means the Company’s initial public offering, consummated on September 4, 2020, of 44,275,000 units (including 5,775,000 units that were subsequently issued to the underwriters in connection with the partial exercise of their over-allotment option) at \$10.00 per unit.

“*Legacy Sema4*” means Mount Sinai Genomics, Inc., a Delaware corporation, doing business as Sema4 prior to the consummation of the Business Combination.

“*Legacy Sema4 Equity Holders*” means certain former stockholders and equity award holders of Legacy Sema4.

“*Lock-Up Holder*” means certain stockholders of OPKO who entered into the Shareholder Agreements with the Company.

“*Merger Sub I*” means Orion Merger Sub I, Inc.

“*Merger Sub II*” means Orion Merger Sub II, LLC.

“*Mergers*” means the First Merger and the Second Merger.

“*Milestone Payments*” means the up to \$150 million payable by the Company to OPKO Health, Inc. pursuant to the Acquisition Merger Agreement following the closing of the Acquisition, if certain revenue-based milestones are

achieved for each of the fiscal years ending December 31, 2022 and December 31, 2023. Each Milestone Payment, if and to the extent earned under the terms of the Acquisition Merger Agreement, will be satisfied through the payment and/or issuance of a combination of cash and shares of Class A common stock (valued at \$4.86 per share based on the average of the daily volume average weighted price of our Class A common stock over the period of 30 trading days ended January 12, 2022), with such mix to be determined in our sole discretion.

“*Milestone Shares*” means the up to 30,864,198 shares of our Class A common stock that may be issuable to OPKO in connection with the Milestone Payments.

“*Nasdaq*” means the Nasdaq Global Select Market.

“*OPKO*” means OPKO Health, Inc.

“*private placement warrants*” means the 7,236,667 warrants originally issued to the Former Sponsor and certain of the other initial stockholders of CMLS in a private placement in connection with our IPO.

“*public shares*” means shares of Class A common stock included in the units issued in our IPO.

“*public warrants*” means the warrants included in the units issued in our IPO.

“*SEC*” means the United States Securities and Exchange Commission.

“*Second Merger*” means the merger of HoldCo, as the surviving corporation in the First Merger, with and into Merger Sub II, with Merger Sub II as the surviving company.

“*Securities Act*” means the Securities Act of 1933, as amended.

“*Sema4*” means (i) Mount Sinai Genomics, Inc. d/b/a Sema4, a Delaware corporation, prior to the closing of the Business Combination or (ii) Sema4 Holdings Corp., a Delaware corporation, following the closing of the Business Combination.

“*Sema4 Holdings*” means Sema4 Holdings Corp., a Delaware corporation, following the closing of the Business Combination.

“*Shareholder Agreements*” means, collectively, those certain shareholder agreements entered into on January 14, 2022, between the Company and OPKO and the Lock-Up Holders, pursuant to which OPKO and the Lock-Up Holders have agreed, among other things, to certain transfer restrictions in respect of the shares of Class A common stock issued and to be issued pursuant to the Acquisition Merger Agreement.

“*Selling Securityholders*” means the selling securityholders named in this prospectus.

“*Stock Consideration Shares*” means the 80,000,000 shares of Class A common stock issued by the Company to OPKO at the closing of the Acquisition pursuant to the Acquisition Merger Agreement.

“*stockholders*” means holders of shares of our Class A common stock.

“*Transfer Agent*” means Continental Stock Transfer & Trust Company.

“*warrant agreement*” means the warrant agreement between us and Continental Stock Transfer & Trust Company, as warrant agent, governing the terms of the warrants.

“*warrants*” means the public warrants and the private placement warrants.

PROSPECTUS SUMMARY

This summary may not contain all the information that you should consider before investing in our Class A common stock and warrants. You should read the entire prospectus and the information incorporated by reference in this prospectus carefully, including “Risk Factors” and the financial statements and related notes incorporated by reference herein, before making an investment decision.

Company Overview

We are a health insights company dedicated to accelerating the use of genomics and leveraging large-scale clinical data to enhance the standard of care through the more extensive use of precision medicine. Our mission is to unlock insights from data, leading to healthier lives and a healthier society. We are one of the largest and most advanced providers of genomic testing in the U.S. and have an industry-leading health information database to transform patient care and improve therapeutic development.

We are focused on effectively delivering our portfolio of genomic and data solutions to guide patients through their family health journey. That includes family planning, delivery, pediatrics, hereditary cancer screening, and rare disorders for children and adults. We are committed to helping families make better health decisions with our panels, exome, and genome – fueled by our interpretation platform designed for a genome’s worth of information and a data engine built to combine genomic and clinical data to deliver better insights.

Our integrated information platform leverages longitudinal patient data, artificial intelligence (“AI”)-driven predictive modeling, and genomics in combination with other molecular and high-dimensional data in our efforts both to deliver better outcomes for patients and to transform the practice of medicine, including how disease is diagnosed, treated, and prevented. We now maintain a database that includes patient data available for research on approximately 12 million patients from a number of public and proprietary sources, including more than five million patients available with clinical data through our partner health systems and genomic testing solutions. Our data asset also includes one of the world’s largest datasets of approximately 400,000 clinical exomes, the vast majority of which are associated with rare disease, providing us an unparalleled platform for pharmaceutical and biotech (“Biopharma”) companies to leverage.

Today, by providing differentiated insights through diagnostic testing solutions to physicians and patients across the United States (the “U.S.”) in areas such as reproductive and women’s health, pediatric and rare disease health, and population health, we are reimbursed by payors, providers, and patients for providing these services. In collaboration with Biopharma companies, we receive payments for a broad range of services relating to the aggregated data on our information platform, such as consenting and recontacting patients, the development and implementation of a wide range of predictive models, including drug discovery programs, conducting real-world evidence studies, and aiding in the identification and recruitment of patients into clinical trials. Over the next several years, we expect to focus on expanding the revenue from our health system and Biopharma partners, while also working to continue to grow the volumes and revenues from our diagnostics test solutions.

While there are many companies seeking to harness the potential of “big data” to address the challenges within the healthcare ecosystem, we believe that few have the scale of our company combined with our revenue-generating diagnostics testing business and origins as a company conceived and nurtured within a world-class health system. These characteristics have enabled us to build a significant and highly differentiated technological and informational asset positioned to drive precision medicine solutions into the standard of care in an unparalleled way.

Corporate Information

We were incorporated on July 10, 2020 as a special purpose acquisition company and a Delaware corporation under the name CM Life Sciences, Inc. (“CMLS”). On September 4, 2020, CMLS completed its initial public offering. On July 22, 2021, CMLS consummated the Business Combination with Legacy Sema4 pursuant to the Business Combination Merger Agreement. In connection with the Business Combination, CMLS changed its name to Sema4 Holdings Corp. (“Sema4 Holdings”).

Our address is 333 Ludlow Street, North Tower, 8th Floor, Stamford, Connecticut 06902. Our telephone number is 1(800) 298-6470. Our website address is <https://sema4.com>. Information contained on our website or connected thereto does not constitute part of, and is not incorporated by reference into, this prospectus or the registration statement of which it forms a part.

The Offering

Issuer	Sema4 Holdings Corp.
Issuance of Class A common stock	
Shares of Class A common stock offered by us	Up to 21,994,972 shares of Class A common stock issuable upon exercise of warrants, consisting of: <ul style="list-style-type: none">a. up to 14,758,333 shares of Class A common stock that are issuable upon the exercise of the public warrants; andb. up to 7,236,667 shares of Class A common stock that are issuable upon the exercise of the private placement warrants following the public resale of the private placement warrants by the Selling Securityholders
Shares of Class A common stock outstanding as of August 9, 2022	380,641,510 shares of Class A common stock
Exercise price of public warrants and private placement warrants	\$11.50 per share, subject to adjustments as described herein
Use of proceeds	We will receive up to an aggregate of approximately \$252.9 million from the exercise of the warrants, assuming the exercise in full of all of the warrants for cash. We expect to use the net proceeds from the exercise of the warrants for investment in growth and general corporate purposes. See “Use of Proceeds”
Resale of Class A common stock and warrants	
Shares of Class A common stock offered by the Selling Securityholders	Up to 356,524,688 shares of Class A common stock, consisting of: <ul style="list-style-type: none">a. up to 18,550,000 Business Combination PIPE Shares;b. up to 11,068,750 Founder Shares;c. up to 158,805,073 shares of Class A common stock issued or issuable to the Legacy Sema4 Equity Holders in connection with or as a result of the consummation of the Business Combination consisting of:<ul style="list-style-type: none">(i) up to 139,783,497 shares of Class A common stock; and(ii) up to 19,021,576 Earn-Out Shares;d. to 7,236,667 shares of Class A common stock issuable upon the exercise of the private placement warrants;e. up to 80,000,000 Stock Consideration Shares;f. up to 30,864,198 Milestone Shares; andg. up to 50,000,000 Acquisition PIPE Shares.
Warrants offered by the Selling Securityholders	Up to 7,236,667 private placement warrants
Terms of the offering	The Selling Securityholders will determine when and how they will dispose of the shares of Class A common stock and warrants registered under this prospectus for resale.
Use of proceeds	We will not receive any proceeds from the sale of shares of Class A common stock or warrants by the Selling Securityholders.
Lock-up restrictions	110,864,198 shares registered on behalf of OPKO are subject to transfer restrictions pursuant to the Shareholder Agreements. See “ <i>Risk Factors.</i> ”

Nasdaq symbols

Risk factors

Our Class A common stock and public warrants are listed on the Nasdaq under the symbols SMFR and SMFRW, respectively.

Investing in our securities involves a high degree of risk. Before buying any of our securities, you should carefully read the discussion of material risks of investing in our securities. Please see the section entitled “Risk Factors” beginning on page 9 of this prospectus, as well as the sections entitled “Risk Factors” beginning on page 30 of our Annual Report on Form 10-K for the year ended December 31, 2021, beginning on page 46 of our Quarterly Report on Form 10-Q for the quarter ended March 31, 2022 and beginning on page 60 of our Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, which reports are incorporated by reference in this prospectus.

RISK FACTORS

An investment in our securities involves a high degree of risk. You should consider the risk factors described in the “Risk Factors” sections of our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, our Quarterly Report on Form 10-Q for the quarter ended March 31, 2022 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2022, which reports are incorporated herein by reference, in addition to the factors set forth below and other information contained in or incorporated by reference in this prospectus or in any prospectus supplement or post-effective amendment, if required, before purchasing any of our Class A common stock or warrants. We may face additional risks and uncertainties that are not presently known to us, or that we currently deem immaterial, which may also impair our business or financial condition. See “*Where You Can Find More Information; Incorporation by Reference*” and “*Cautionary Note Regarding Forward-Looking Statements.*”

Future resales of our Class A common stock could cause the market price of our Class A common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our Class A common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our Class A common stock.

We had outstanding 380,641,510 shares of Class A common stock as of August 9, 2022. The registration statement to which this prospectus relates registers the offer and sale from time to time by the Selling Securityholders of up to 356,524,688 shares of our Class A common stock, although the 110,864,198 shares registered on behalf of OPKO will be subject to transfer restrictions pursuant to the Shareholder Agreements. To the extent shares are sold into the market pursuant to this prospectus, under Rule 144 under the Securities Act or otherwise, particularly in substantial quantities and including following the end of the transfer restrictions provided for in the Shareholder Agreements in the case of OPKO and the other Lock-Up Holders, the market price of our Class A common stock could decline.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Certain matters discussed in this prospectus and the documents incorporated by reference in this prospectus may constitute forward-looking statements for purposes of the Securities Act of 1933, as amended (the “Securities Act”), and the Securities Exchange Act of 1934, as amended (the “Exchange Act”), and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from the future results, performance or achievements expressed or implied by such forward-looking statements. The words “anticipate,” “believe,” “estimate,” “may,” “expect” and similar expressions are generally intended to identify forward-looking statements. Our actual results may differ materially from the results anticipated in these forward-looking statements due to a variety of factors, including, without limitation, those discussed in the section entitled “*Risk Factors*,” and elsewhere in this prospectus and the documents incorporated by reference herein, where such forward-looking statements appear. All written or oral forward-looking statements attributable to us are expressly qualified in their entirety by these cautionary statements. Such forward-looking statements include, but are not limited to, statements about:

- our ability to realize the benefits expected from the Acquisition and the other transactions contemplated by the Acquisition Merger Agreement and the related Acquisition PIPE Investment;
- our estimates of the sufficiency of our existing capital resources combined with future anticipated cash flows to finance our operating requirements;
- our expected losses;
- our expectations for incurring capital expenditures;
- unforeseen circumstances or other disruptions to normal business operations, including supply chain interruptions and manufacturing constraints, arising from or related to the ongoing COVID-19 pandemic;
- our expectations regarding our plans to exit out somatic tumor testing business and the associated cost savings and impact on our gross margins;
- our expectations for generating revenue or becoming profitable on a sustained basis;
- our expectations or ability to enter into service, collaboration and other partnership agreements;
- our expectations or ability to build our own commercial infrastructure to scale market and sell our products;
- actions or authorizations by the U.S. Food and Drug Administration (the “FDA”) or other regulatory authorities;
- risks related to governmental regulation and other legal obligations, including privacy, data protection, information security, consumer protection, and anti-corruption and anti-bribery;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- our ability to compete against existing and emerging technologies;
- our stock price and its volatility;
- our ability to attract and retain key personnel;
- third-party payor reimbursement and coverage decisions, negotiations and settlements;
- our reliance on third-party laboratories and service providers for our test volume in connection with our diagnostic solutions and data programs;
- our ability to satisfy Nasdaq listing rules;
- our expectations for future capital requirements;

- our accounting estimates, including the adequacy of our reserves for third party payor claims and our estimates of the fair value of milestone payments related to the Acquisition;
- our ability to successfully implement our business strategy; and
- other factors detailed under the section entitled “*Risk Factors*.”

The forward-looking statements contained in this prospectus and the documents incorporated by reference herein reflect our views and assumptions only as of the date of this prospectus or such document, as applicable. Except as required by law, we assume no responsibility for updating any forward-looking statements.

We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

USE OF PROCEEDS

All of the securities offered by the Selling Securityholders pursuant to this prospectus will be sold by the Selling Securityholders for their respective accounts. We will not receive any of the proceeds from these sales.

Assuming the exercise of all outstanding warrants for cash, we will receive an aggregate of approximately \$252.9 million, but will not receive any proceeds from the sale of the shares of Class A common stock issuable upon such exercise. We expect to use the net proceeds from the exercise of the warrants, if any, for investment in growth, and general corporate purposes. We will have broad discretion over the use of any proceeds from the exercise of the warrants. There is no assurance that the holders of the warrants will elect to exercise for cash any or all of such warrants. To the extent that any warrants are exercised on a "cashless basis," the amount of cash we would receive from the exercise of the warrants will decrease.

The Selling Securityholders will pay any underwriting discounts and commissions and expenses incurred by the Selling Securityholders for brokerage, accounting, tax or legal services or any other expenses incurred by the Selling Securityholders in disposing of the securities. We will bear the costs, fees and expenses incurred in effecting the registration of the securities covered by this prospectus, including all registration and filing fees, Nasdaq listing fees and fees and expenses of our counsel and our independent registered public accounting firm.

DESCRIPTION OF SECURITIES

The following summary sets forth certain material terms and provisions of our securities. This description also summarizes relevant provisions of the General Corporation Law of Delaware (the “DGCL”). The following description is a summary and does not purport to be a complete description of the rights and preferences of our securities. It is subject to, and qualified in its entirety by reference to, the applicable provisions of the DGCL and our third amended and restated certificate of incorporation, as amended (our “Amended and Restated Certificate of Incorporation”), our restated bylaws (our “Bylaws”), and the warrant agreement governing our warrants (the “warrant agreement”), each of which is incorporated by reference as an exhibit to the registration statement of which this prospectus forms a part. We encourage you to read our Amended and Certificate of Incorporation, our Bylaws, the warrant agreement and the applicable provisions of the DGCL for additional information.

Authorized and Outstanding Stock

Our Amended and Restated Certificate of Incorporation authorizes the issuance of 1,000,000,000 shares of Class A common stock, \$0.0001 par value per share, and 1,000,000 shares of preferred stock, \$0.0001 par value per share. As of June 30, 2022, there were 379,896,799 shares of our Class A common stock outstanding, no shares of preferred stock outstanding and 21,994,972 warrants outstanding. The outstanding shares of our Class A common stock are duly authorized, validly issued, fully paid and non-assessable.

Common Stock

Our Amended and Restated Certificate of Incorporation provides that each share of our Class A common stock has the same relative rights and is identical in all respects to each other share of our Class A common stock. The rights, preferences and privileges of holders of our Class A common stock are subject to the rights, preferences and privileges of the holders of shares of any series of preferred stock that we have issued or may issue in the future.

Voting Power

Except as otherwise required by law or as otherwise provided in any certificate of designation for any series of preferred stock, or under our Amended and Restated Certificate of Incorporation, the holders of Class A common stock possess all voting power for the election of our directors and all other matters requiring stockholder action and are entitled to one vote per share on matters to be voted on by stockholders. The holders of Class A common stock shall at all times vote together as one class on all matters submitted to a vote of the holders of Class A common stock under our Amended and Restated Certificate of Incorporation.

Dividends

Subject to the rights, if any of the holders of any outstanding shares of preferred stock, under our Amended and Restated Certificate of Incorporation, holders of Class A common stock are entitled to receive such dividends and other distributions, if any, as may be declared from time to time by our board of directors (the “Board”) in its discretion out of funds legally available therefor and shall share equally on a per share basis in such dividends and distributions.

Liquidation, Dissolution and Winding Up

In the event of the voluntary or involuntary liquidation, dissolution or winding-up of the Company, under our Amended and Restated Certificate of Incorporation, holders of Class A common stock will be entitled to receive all the remaining assets of the Company available for distribution to stockholders, ratably in proportion to the number of shares of Class A common stock held by them, after the rights of the holders of the preferred stock have been satisfied.

Preemptive or Other Rights

Under our Amended and Restated Certificate of Incorporation, our stockholders have no preemptive or other subscription rights and there are no sinking fund or redemption provisions applicable to our Class A common stock.

Election of Directors

Our Amended and Restated Certificate of Incorporation provides for a classified board of directors with staggered three-year terms, consisting of the three classes: Class I, Class II and Class III. The term of the Class I Directors will expire at our 2025 annual meeting of the stockholders, the term of the Class II Directors will expire at our 2023 annual meeting of the stockholders and the term of the Class III Directors will expire at our 2024 annual meeting of the stockholders.

Preferred Stock

Our Amended and Restated Certificate of Incorporation provides that shares of preferred stock may be issued from time to time in one or more series. Our Board is authorized to fix the voting rights, if any, designations, powers, preferences and relative, participating, optional, special and other rights, if any, and any qualifications, limitations and restrictions thereof, applicable to the shares of each series. Our Board is able, without stockholder approval, to issue preferred stock with voting and other rights that could adversely affect the voting power and other rights of the holders of the Class A common stock and could have anti-takeover effects. The ability of our Board to issue preferred stock without stockholder approval could have the effect of delaying, deferring or preventing a change of control of us or the removal of existing management. We have no preferred stock outstanding at the date hereof. Although we do not currently intend to issue any shares of preferred stock, we cannot assure you that we will not do so in the future.

Warrants

Public Warrants

Each whole public warrant entitles the registered holder to purchase one share of our Class A common stock at a price of \$11.50 per whole share, subject to adjustment as discussed below, at any time commencing on September 4, 2021. Pursuant to the warrant agreement, a warrant holder may exercise its public warrants only for a whole number of shares of Class A common stock. This means that only a whole public warrant may be exercised at any given time by a warrant holder. No fractional public warrants will be issued upon separation of the units and only whole public warrants will trade. The public warrants will expire September 4, 2026, at 5:00 p.m., New York City time, or earlier upon redemption or liquidation.

We are not obligated to deliver any shares of Class A common stock pursuant to the exercise of a public warrant and will have no obligation to settle such public warrant exercise unless a registration statement under the Securities Act of 1933, as amended (the "Securities Act"), with respect to the shares of Class A common stock underlying the public warrants is then effective and a prospectus relating thereto is current, subject to our satisfying our obligations described below with respect to registration. No public warrant will be exercisable for cash or on a cashless basis, and we will not be obligated to issue any shares to holders seeking to exercise their public warrants, unless the issuance of the shares upon such exercise is registered or qualified under the securities laws of the state of the exercising holder, or an exemption is available. In the event that the conditions in the two immediately preceding sentences are not satisfied with respect to a public warrant, the holder of such public warrant will not be entitled to exercise such public warrant and such public warrant may have no value and expire worthless.

Redemption of Warrants When the Price per Share of Class A Common Stock Equals or Exceeds \$18.00 - We may redeem the outstanding public warrants:

- in whole and not in part;
- at a price of \$0.01 per public warrant;
- upon not less than 30 days' prior written notice of redemption to each warrant holder; and
- if, and only if, the closing price of the Class A common stock equals or exceeds \$18.00 per share (as adjusted) for any 20 trading days within a 30-trading day period ending three trading days before sending the notice of redemption to warrant holders (the "Reference Value").

If and when the warrants become redeemable by us, we may exercise its redemption right even if we are unable to register or qualify the underlying securities for sale under all applicable state securities laws.

Redemption of Warrants When the Price per Share of Class A Common Stock Equals or Exceeds \$10.00 - We may redeem the outstanding warrants:

- in whole and not in part;
- at \$0.10 per warrant upon a minimum of 30 days' prior written notice of redemption provided that holders will be able to exercise their warrants on a cashless basis prior to redemption and receive that number of shares based on the redemption date and the fair market value of the Class A common stock;
- if, and only if, the closing price of the Class A common stock equals or exceeds \$10.00 per share (as adjusted) for any 20 trading days within the 30-trading day period ending three trading days before we send the notice of redemption to the warrant holders; and
- if the closing price of the Class A common stock for any 20 trading days within a 30-trading day period ending three trading days before we send notice of redemption to the warrant holders is less than \$18.00 per share (as adjusted), the private placement warrants must also be concurrently called for redemption on the same terms as the outstanding public warrants, as described above.

We have established the last of the redemption criterion discussed above to prevent a redemption call unless there is at the time of the call a significant premium to the warrant exercise price. If the foregoing conditions are satisfied and we issue a notice of redemption of the public warrants, each warrant holder will be entitled to exercise his, her or its public warrant prior to the scheduled redemption date. However, the price of the Class A common stock may fall below the \$18.00 redemption trigger price as well as the \$11.50 warrant exercise price after the redemption notice is issued.

Redemption procedures and cashless exercise.

If we call the public warrants for redemption as described above, our management will have the option to require any holder that wishes to exercise his, her or its public warrant to do so on a "cashless basis." In determining whether to require all holders to exercise their public warrants on a "cashless basis," our management will consider, among other factors, our cash position, the number of public warrants that are outstanding and the dilutive effect on our stockholders of issuing the maximum number of shares of Class A common stock issuable upon the exercise of our public warrants. If our management takes advantage of this option, all holders of public warrants would pay the exercise price by surrendering their public warrants for that number of shares of Class A common stock equal to the quotient obtained by dividing (i) the product of the number of shares of Class A common stock underlying the public warrants, multiplied by the difference between the exercise price of the public warrants and the "fair market value" (defined below) by (ii) the fair market value. The "fair market value" shall mean the average reported last sale price of the Class A common stock for the 10 trading days ending on the third trading day prior to the date on which the notice of redemption is sent to the holders of public warrants. If our management takes advantage of this option, the notice of redemption will contain the information necessary to calculate the number of shares of Class A common stock to be received upon exercise of the public warrants, including the "fair market value" in such case. Requiring a cashless exercise in this manner will reduce the number of shares to be issued and thereby lessen the dilutive effect of a warrant redemption. We believe this feature is an attractive option to us if we do not need the cash from the exercise of the public warrants. If we call our public warrants for redemption and our management does not take advantage of this option, the Former Sponsor and its permitted transferees would still be entitled to exercise their private placement warrants for cash or on a cashless basis using the same formula described above that other warrant holders would have been required to use had all warrant holders been required to exercise their public warrants on a cashless basis, as described in more detail below.

A holder of a public warrant may notify us in writing in the event it elects to be subject to a requirement that such holder will not have the right to exercise such public warrant, to the extent that after giving effect to such exercise, such person (together with such person's affiliates), to the warrant agent's actual knowledge, would

beneficially own in excess of 9.8% (or such other amount as a holder may specify) of the shares of Class A common stock outstanding immediately after giving effect to such exercise.

Anti-dilution Adjustments. If the number of outstanding shares of Class A common stock is increased by a stock dividend payable in shares of Class A common stock, or by a split-up of shares of Class A common stock or other similar event, then, on the effective date of such stock dividend, split-up or similar event, the number of shares of Class A common stock issuable on exercise of each public warrant will be increased in proportion to such increase in the outstanding shares of Class A common stock. A rights offering to holders of Class A common stock entitling holders to purchase shares of Class A common stock at a price less than the fair market value will be deemed a stock dividend of a number of shares of Class A common stock equal to the product of (i) the number of shares of Class A common stock actually sold in such rights offering (or issuable under any other equity securities sold in such rights offering that are convertible into or exercisable for Class A common stock) multiplied by (ii) one minus the quotient of (a) the price per share of Class A common stock paid in such rights offering divided by (b) the fair market value. For these purposes (1) if the rights offering is for securities convertible into or exercisable for Class A common stock, in determining the price payable for Class A common stock, there will be taken into account any consideration received for such rights, as well as any additional amount payable upon exercise or conversion and (2) fair market value means the volume weighted average price of Class A common stock as reported during the 10 trading day period ending on the trading day prior to the first date on which the shares of Class A common stock trade on the applicable exchange or in the applicable market, regular way, without the right to receive such rights.

In addition, if we, at any time while the public warrants are outstanding and unexpired, pay a dividend or make a distribution in cash, securities or other assets to the holders of Class A common stock on account of such shares of Class A common stock (or other shares of our capital stock into which the public warrants are convertible), other than (i) as described above; or (ii) certain ordinary cash dividends, then the warrant exercise price will be decreased, effective immediately after the effective date of such event, by the amount of cash and/or the fair market value of any securities or other assets paid on each share of Class A common stock in respect of such event.

If the number of outstanding shares of our Class A common stock is decreased by a consolidation, combination, reverse stock split or reclassification of shares of Class A common stock or other similar event, then, on the effective date of such consolidation, combination, reverse stock split, reclassification or similar event, the number of shares of Class A common stock issuable on exercise of each public warrant will be decreased in proportion to such decrease in outstanding shares of Class A common stock.

Whenever the number of shares of Class A common stock purchasable upon the exercise of the public warrants is adjusted, as described above, the warrant exercise price will be adjusted by multiplying the warrant exercise price immediately prior to such adjustment by a fraction (x) the numerator of which will be the number of shares of Class A common stock purchasable upon the exercise of the public warrants immediately prior to such adjustment, and (y) the denominator of which will be the number of shares of Class A common stock so purchasable immediately thereafter.

In case of any reclassification or reorganization of the outstanding shares of Class A common stock (other than those described above or that solely affects the par value of such shares of Class A common stock), or in the case of any merger or consolidation of us with or into another corporation (other than a consolidation or merger in which we are the continuing corporation and that does not result in any reclassification or reorganization of our outstanding shares of Class A common stock), or in the case of any sale or conveyance to another corporation or entity of the assets or other property of us as an entirety or substantially as an entirety in connection with which we are dissolved, the holders of the public warrants will thereafter have the right to purchase and receive, upon the basis and upon the terms and conditions specified in the public warrants and in lieu of the shares of our Class A common stock immediately theretofore purchasable and receivable upon the exercise of the rights represented thereby, the kind and amount of shares of stock or other securities or property (including cash) receivable upon such reclassification, reorganization, merger or consolidation, or upon a dissolution following any such sale or transfer, that the holder of the public warrants would have received if such holder had exercised their public warrants immediately prior to such event. Additionally, if less than 70% of the consideration receivable by the holders of Class A common stock in such a transaction is payable in the form of common stock in the successor entity that is listed for trading on a national securities exchange or is quoted in an established over-the-counter market, or is to be so listed for trading or quoted

immediately following such event, and if the registered holder of the public warrant properly exercises the public warrant within 30 days following public disclosure of such transaction, the warrant exercise price will be reduced as specified in the warrant agreement based on the per share consideration minus Black-Scholes Warrant Value (as defined in the warrant agreement) of the public warrant.

The public warrants have been issued in registered form under a warrant agreement between Continental Stock Transfer & Trust Company, as warrant agent, and us. You should review a copy of the warrant agreement, which is filed as an exhibit to the registration statement of which this prospectus forms a part, for a complete description of the terms and conditions applicable to the public warrants. The warrant agreement provides that the terms of the public warrants may be amended without the consent of any holder to cure any ambiguity or correct any defective provision, but requires the approval by the holders of at least 50% of the then outstanding public warrants to make any change that adversely affects the interests of the registered holders of public warrants.

The public warrants may be exercised upon surrender of the warrant certificate on or prior to the expiration date at the offices of the warrant agent, with the exercise form on the reverse side of the warrant certificate completed and executed as indicated, accompanied by full payment of the exercise price (or on a cashless basis, if applicable), by certified or official bank check payable to us, for the number of public warrants being exercised. The warrant holders do not have the rights or privileges of holders of Class A common stock and any voting rights until they exercise their public warrants and receive shares of Class A common stock. After the issuance of shares of Class A common stock upon exercise of the public warrants, each holder will be entitled to one vote for each share held of record on all matters to be voted on by stockholders.

Warrants may be exercised only for a whole number of shares of Class A common stock. No fractional shares will be issued upon exercise of the public warrants. If, upon exercise of the public warrants, a holder would be entitled to receive a fractional interest in a share, we will, upon exercise, round down to the nearest whole number the number of shares of Class A common stock to be issued to the warrant holder. As a result, warrant holders not purchasing public warrants in multiples of three warrants will not obtain value from the fractional interest that will not be issued.

Private Placement Warrants

The private placement warrants are identical to the public warrants, except that (1) the private placement warrants are exercisable on a cashless basis, (2) the private placement warrants are non-redeemable (except as described above in “Redemption of Warrants When the Price per Share of Class A Common Stock Equals or Exceeds \$10.00”) so long as they are held by the initial purchasers or their permitted transferees, and (3) the holders of the private placement warrants and the Class A common stock issuable upon the exercise of the private placement warrants have certain registration rights. If the private placement warrants are held by someone other than the initial purchasers or their permitted transferees, the private placement warrants are redeemable by us and exercisable by such holders on the same basis as the public warrants.

Dividends

We have not paid any cash dividends on our Class A common stock to date and do not intend to pay cash dividends. The payment of cash dividends in the future will be dependent upon our revenues and earnings, if any, capital requirements and general financial condition. The payment of any cash dividends will be within the discretion of our Board at such time. In addition, our Board is not currently contemplating and does not anticipate declaring any stock dividends in the foreseeable future. Further, if we incur any indebtedness, our ability to declare dividends may be limited by restrictive covenants we may agree to in connection therewith.

Transfer Agent and Warrant Agent

The transfer agent for our Class A common stock and warrant agent for our warrants is Continental Stock Transfer & Trust Company. We have agreed to indemnify Continental Stock Transfer & Trust Company in its roles as transfer agent and warrant agent, its agents and each of its stockholders, directors, officers and employees against all liabilities, including judgments, costs and reasonable counsel fees that may arise out of acts performed or omitted

for its activities in that capacity, except for any liability due to any gross negligence, willful misconduct or bad faith of the indemnified person or entity.

Certain Anti-Takeover Provisions of Delaware Law and Our Amended and Restated Certificate of Incorporation and Bylaws

Provisions of the DGCL and our Amended and Restated Certificate of Incorporation could make it more difficult to acquire us by means of a tender offer, a proxy contest or otherwise, or to remove incumbent officers and directors. These provisions, summarized below, are intended to discourage coercive takeover practices and inadequate takeover bids and to encourage persons seeking to acquire control of us to first negotiate with the board of directors. We believe that the benefits of these provisions outweigh the disadvantages of discouraging certain takeover or acquisition proposals because, among other things, negotiation of these proposals could result in an improvement of their terms and enhance the ability of our Board to maximize stockholder value. However, these provisions may delay, deter or prevent a merger or acquisition of us that a stockholder might consider is in its best interest, including those attempts that might result in a premium over the prevailing market price of the Class A common stock.

In addition, our Amended and Restated Certificate of Incorporation provide for certain other provisions that may have an anti-takeover effect:

- There is no cumulative voting with respect to the election of directors.
- Our Board is empowered to elect a director to fill a vacancy created by the expansion of the Board or the resignation, death, or removal of a director in certain circumstances.
- Directors may only be removed from the Board for cause.
- Our Board will be classified into three classes of directors. As a result, in most circumstances, a person can gain control of our Board by successfully engaging in a proxy contest at two or more annual meetings.
- A prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders.
- A prohibition on stockholders calling a special meeting and the requirement that a meeting of stockholders may only be called by members of our Board, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors.
- Our authorized but unissued Class A common stock and preferred stock are available for future issuances without stockholder approval and could be utilized for a variety of corporate purposes, including future offerings to raise additional capital, acquisitions and employee benefit plans. Our Board is entitled, without further stockholder approval, to designate one or more series of preferred stock and the associated voting rights, preferences and privileges of such series of preferred stock. The existence of authorized but unissued and unreserved Class A common stock and preferred stock could render more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

Forum Selection Clause

Our Amended and Restated Certificate of Incorporation includes a forum selection clause. Our Amended and Restated Certificate of Incorporation provides that, subject to limited exceptions, the Court of Chancery of the State of Delaware and federal court within the State of Delaware will be exclusive forums for any:

- derivative action or proceeding brought on our behalf;
- action asserting a claim of breach of a fiduciary duty owed by, or other wrongdoing by, any of our directors, officers, stockholders, employees or agents to us or our stockholders;

- action asserting a claim against us or any of our directors, officers, stockholders, employees or agents arising pursuant to any provision of the DGCL, our Amended and Restated Certificate of Incorporation or Bylaws or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware;
- action to interpret, apply, enforce or determine the validity of our Amended and Restated Certificate of Incorporation or the Bylaws; or
- other action asserting a claim against us or any of our directors, officers, stockholders, employees or agents that is governed by the internal affairs doctrine.

This choice of forum provision does not apply to actions brought to enforce a duty or liability created by the Exchange Act or any other claim for which federal courts have exclusive jurisdiction. Furthermore, in accordance with our Bylaws, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States will be, to the fullest extent permitted by law, the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. We intend for this provision to apply to any complaints asserting a cause of action under the Securities Act despite the fact that Section 22 of the Securities Act creates concurrent jurisdiction for the federal and state courts over all actions brought to enforce any duty or liability created by the Securities Act or the rules and regulations promulgated thereunder.

Listing of Securities

Our Class A common stock and warrants are listed on Nasdaq under the symbols “SMFR” and “SMFRW,” respectively.

SELLING SECURITYHOLDERS

The Selling Securityholders may offer and sell, from time to time, any or all of the shares of Class A common stock or warrants being offered for resale by this prospectus, which consists of:

- up to 18,550,000 Business Combination PIPE Shares;
- up to 11,068,750 Founder Shares;
- up to 158,805,073 shares of Class A common stock issued or issuable to the Legacy Sema4 Equity Holders in connection with or as a result of the consummation of the Business Combination, consisting of:
 - up to 139,783,497 shares of our Class A common stock (“Legacy Sema4 Holder Shares”); and
 - up to 19,021,576 Earn-Out Shares.
- up to 7,236,667 shares of Class A common stock issuable upon the exercise of private placement warrants;
- up to 80,000,000 Stock Consideration Shares;
- up to 30,864,198 Milestone Shares;
- up to 50,000,000 Acquisition PIPE Shares; and
- up to 7,236,667 private placement warrants.

The term “Selling Securityholders” includes the securityholders listed in the tables below and their permitted transferees.

The following tables provide, as of the date of this prospectus, information regarding the beneficial ownership of our Class A common stock and warrants of each Selling Securityholder, the number of shares of Class A common stock and number of warrants that may be sold by each Selling Securityholder under this prospectus and that each Selling Securityholder will beneficially own after this offering.

Pursuant to the earn-out provisions of the Business Combination Merger Agreement, we may issue an aggregate of up to 19,021,576 shares of Class A common stock upon the occurrence of certain triggering events provided for in the Business Combination Merger Agreement, which shares are comprised of Earn-Out Shares issuable to pre-closing Legacy Sema4 Equity Holders and shares of Class A common stock (“Earn-Out RSU Shares”) issuable upon the vesting of certain RSU awards (“Earn-Out RSUs”) granted to certain Legacy Sema4 Equity Holders. As of the closing date of the Business Combination, the initial allocation of such shares comprised up to 16,331,812 Earn-Out Shares and up to 2,689,764 Earn-Out RSU Shares. Upon any forfeiture of Earn-Out RSUs following the closing date of the Business Combination (for example, as a result of a Legacy Sema4 Equity Holder no longer being an employee of our company), the Business Combination Merger Agreement provides for a forfeiture pool in respect of the Earn-Out RSU Shares that were originally allocated to such forfeited Earn-Out RSUs, with such Earn-Out RSU Shares becoming available for issuance to the other recipients of Earn-Out Shares and Earn-Out RSUs. In the case of a Selling Securityholder that is entitled to receive Earn-Out Shares pursuant to the Business Combination Merger Agreement, the table below includes such Selling Securityholder’s pro rata portion of the initial allocation of Earn-Out Shares as of the closing date of the Business Combination (such Selling Securityholder’s “Initially Allocated Earn-Out Shares”), as well as such Selling Securityholder’s pro rata portion of the reallocated Earn-Out RSU Shares (such Selling Securityholder’s “Reallocated Earn-Out Shares”), assuming that 100% of the Earn-Out RSUs are forfeited after the closing date of the Business Combination.

In addition, pursuant to the terms of the Acquisition Merger Agreement, we may issue an aggregate of up to 30,864,198 Milestone Shares to OPKO as consideration for the \$150 million in Milestone Payments. Each Milestone Payment, if and to the extent earned under the terms of the Merger Agreement, will be satisfied through the payment and/or issuance of a combination of cash and shares of Class A common stock (valued at \$4.86 per share based on the average of the daily volume average weighted price of our Class A common stock over the period of 30 trading days ended January 12, 2022), with such mix to be determined in our sole discretion.

Because each Selling Securityholder may dispose of all, none or some portion of their securities, no estimate can be given as to the number of securities that will be beneficially owned by a Selling Securityholder upon termination of this offering. For purposes of the table below, however, we have assumed that after termination of this offering none of the securities covered by this prospectus will be beneficially owned by the Selling Securityholder and further assumed that the Selling Securityholders will not acquire beneficial ownership of any additional securities during the offering. In addition, the Selling Securityholders may have sold, transferred or otherwise disposed of, or may sell, transfer or otherwise dispose of, at any time and from time to time, our securities in transactions exempt from the registration requirements of the Securities Act after the date on which the information in the tables is presented.

We may amend or supplement this prospectus from time to time in the future to update or change this Selling Securityholders list and the securities that may be resold.

Please see the section titled "[*Plan of Distribution*](#)" for further information regarding the Selling Securityholders' method of distributing these shares of Class A common stock and warrants.

Shares of Class A Common Stock				
Name	Number Beneficially Owned Prior to Offering ⁽¹⁾	Number Registered for Sale Hereby	Number Beneficially Owned After Offering	Percent Owned After Offering ⁽²⁾
Entities affiliated with Avidity ⁽³⁾	950,000	950,000	—	—
Entities affiliated with BlackRock, Inc. ⁽⁴⁾	665,899	665,899	—	—
Entities affiliated with Blackstone ⁽⁵⁾	30,945,879	30,845,879	100,000	*
Entities affiliated with Casdin ⁽⁶⁾	16,437,500	16,437,500	—	—
CMLS Holdings LLC ⁽⁷⁾	17,730,419	17,730,419	—	—
Connecticut Innovations, Incorporated ⁽⁸⁾	578,722	578,722	—	—
Entities advised by Corvex Management ⁽⁹⁾	15,437,500	15,437,500	—	—
Decheng Capital China Life Sciences USD Fund III, L.P. ⁽¹⁰⁾	3,795,012	3,795,012	—	—
Entities affiliated with Deerfield Management Company, L.P. ⁽¹¹⁾	18,382,120	18,382,120	—	—
Emily Leproust ⁽¹²⁾	204,502	191,666	12,836	*
Icahn School of Medicine at Mount Sinai ⁽¹³⁾	106,202,671	106,202,671	—	—
JS Capital LLC ⁽¹⁴⁾	1,000,000	1,000,000	—	—
M. Munib Z. Islam ⁽¹⁵⁾	291,666	291,666	—	—
Entities affiliated with Moore ⁽¹⁶⁾	110,977	110,977	—	—
Nat Turner ⁽¹⁷⁾	204,502	191,666	12,836	*
Oak HC/FT Partners II, L.P. ⁽¹⁸⁾	6,302,462	6,302,462	—	—
OPKO Health, Inc. ⁽¹⁹⁾	110,864,198	110,864,198	—	—
Perceptive Life Sciences Master Fund, Ltd. ⁽²⁰⁾	5,000,000	5,000,000	—	—
Pfizer Inc. ⁽²¹⁾	6,250,000	6,250,000	—	—
Section 32 Fund 2, L.P. ⁽²²⁾	9,518,643	9,518,643	—	—
Entities affiliated with Third Point Loan LLC ⁽²³⁾	2,750,000	2,750,000	—	—
Entities affiliated with T. Rowe Price Associates, Inc. ⁽²⁴⁾	750,000	750,000	—	—
Entities affiliated with Vaal Investment Partners Q9 LP ⁽²⁵⁾	2,125,000	2,125,000	—	—
TOTALS	356,497,672	356,524,688	125,672	*

Warrants to Purchase Class A Common Stock				
Name	Number Beneficially Owned Prior to Offering	Number Registered for Sale Hereby	Number Beneficially Owned After Offering	Percent Owned After Offering ⁽²⁾
CMLS Holdings LLC ⁽⁷⁾	6,736,669	6,736,669	—	—
Nat Turner ⁽³¹⁾	166,666	166,666	—	—
Emily Leproust ⁽¹⁴⁾	166,666	166,666	—	—
M. Munib Z. Islam ⁽¹⁸⁾	166,666	166,666	—	—
TOTALS	7,236,667	7,236,667	—	—

* Less than 1%

(1) The first table includes Business Combination PIPE Shares, Founder Shares, Legacy Sema4 Holder Shares, Earn-Out Shares (includes both shares beneficially owned as determined in accordance with Rule 13d-3 of the Exchange Act and shares which the holder has a contingent right to receive), shares of Class A common stock issuable upon exercise of the private placement warrants, Stock Consideration Shares (including both shares beneficially owned as determined in accordance with Rule 13d-3 of the Exchange Act and additional shares the

- holder has the contingent right receive), Milestone Shares (including both shares beneficially owned as determined in accordance with Rule 13d-3 of the Exchange Act and additional shares the holder has the contingent right receive) and Acquisition PIPE Shares, and the second table includes the private placement warrants included in this table (collectively, the “Resale Securities”). We do not know when or in what amounts the Selling Securityholders will offer the Resale Securities for sale, if at all.
- (2) The percentage of shares to be beneficially owned after completion of the offering is calculated on the basis of 380,641,510 shares of Class A common stock outstanding, assuming the issuance of 30,864,198 Milestone Shares, the issuance of all Earn-Out Shares and the exercise of all currently outstanding warrants, and the sale of all Resale Securities by the Selling Securityholders.
 - (3) Shares hereby offered consist of 107,000 Business Combination PIPE Shares held by Avidity Capital Fund II LP (“Avidity Capital”) and 843,000 Business Combination PIPE Shares held by Avidity Master Fund LP (“Avidity Master”).
 - (4) Shares hereby offered consist of 24,410 Earn-out Shares (consisting of 20,957 Initially Allocated Earn-Out Shares and 3,453 Reallocated Earn-Out Shares) held by BlackRock Global Allocation Collective Fund, 4,005 Earn-out Shares (consisting of 3,438 Initially Allocated Earn-Out Shares and 567 Reallocated Earn-Out Shares) held by BlackRock Global Allocation Fund (Aust), 233,680 Earn-out Shares (consisting of 200,637 Initially Allocated Earn-Out Shares and 33,043 Reallocated Earn-Out Shares) held by BlackRock Global Allocation Fund, Inc., 1,840 Earn-out Shares (consisting of 1,579 Initially Allocated Earn-Out Shares and 261 Reallocated Earn-Out Shares) held by BlackRock Global Allocation Portfolio of BlackRock Series Fund, Inc., 81,840 Earn-out Shares (consisting of 70,268 Initially Allocated Earn-Out Shares and 11,572 Reallocated Earn-Out Shares) held by BlackRock Global Allocation V.I. Fund of BlackRock Variable Series Funds, Inc., 141,325 Earn-out Shares (consisting of 121,342 Initially Allocated Earn-Out Shares and 19,983 Reallocated Earn-Out Shares) held by BlackRock Global Funds - Global Allocation Fund, 12,328 Earn-out Shares (consisting of 10,584 Initially Allocated Earn-Out Shares and 1,744 Reallocated Earn-Out Shares) held by BlackRock Global Funds - Global Dynamic Equity Fund, 166,471 Earn-out Shares (consisting of 142,931 Initially Allocated Earn-Out Shares and 23,540 Reallocated Earn-Out Shares) held by BlackRock Strategic Income Opportunities Portfolio of BlackRock Funds V. The registered holders of the referenced shares to be registered are the following funds and accounts under management by subsidiaries of BlackRock, Inc.: BlackRock Strategic Income Opportunities Portfolio of BlackRock Funds V; BlackRock Global Allocation Collective Fund; BlackRock Global Funds – Global Dynamic Equity Fund; BlackRock Global Allocation Portfolio of BlackRock Series Fund, Inc.; BlackRock Global Allocation Fund, Inc.; BlackRock Global Funds – Global Allocation Fund; BlackRock Global Allocation V.I. Fund of BlackRock Variable Series Funds, Inc.; and BlackRock Global Allocation Fund (Aust). BlackRock, Inc. is the ultimate parent holding company of such subsidiaries. On behalf of such subsidiaries, the applicable portfolio managers, as managing directors (or in other capacities) of such entities, and/or the applicable investment committee members of such funds and accounts, have voting and investment power over the shares held by the funds and accounts which are the registered holders of the referenced shares. Such portfolio managers and/or investment committee members expressly disclaim beneficial ownership of all shares held by such funds and accounts. The address of such funds and accounts, such subsidiaries and such portfolio managers and/or investment committee members is 55 East 52nd Street, New York, NY 10055. Shares shown include only the securities being registered for resale and may not incorporate all shares deemed to be beneficially held by the registered holders or BlackRock, Inc.
 - (5) Shares hereby offered consist of (i) 2,434,863 Acquisition PIPE Shares, 24,404,324 Legacy Sema4 Holder Shares and 3,203,218 Earn-out Shares (consisting of 2,750,264 Initially Allocated Earn-Out Shares and 452,954 Reallocated Earn-Out Shares) held by BTO Sema4 Holdings L.P. (“BTO Sema4 Holdings”), (ii) 50,402 Acquisition PIPE Shares, 505,095 Legacy Sema4 Holder Shares and 66,297 Earn-out Shares (consisting of 56,922 Initially Allocated Earn-Out Shares and 9,375 Reallocated Earn-Out Shares) held by Blackstone Tactical Opportunities Fund - FD L.P. (“Blackstone Opportunities Fund”), and (iii) 14,735 Acquisition PIPE Shares, 147,574 Legacy Sema4 Holder Shares and 19,371 Earn-out Shares (consisting of 16,632 Initially Allocated Earn-Out Shares and 2,739 Reallocated Earn-Out Shares) held by Blackstone Family Tactical Opportunities Investment Partnership III ESC L.P. (“Blackstone Opportunities Partnership”) held by Blackstone Family Tactical Opportunities Investment Partnership III ESC L.P.
 - (6) Shares hereby offered consist of 11,437,500 Acquisition PIPE Shares and 5,000,000 Business Combination PIPE Shares held by Casdin Partners Master Fund, L.P. Casdin Capital, LLC is the investment adviser to Casdin Partners Master Fund, LP and Casdin Partners GP, LLC is the general partner of Casdin Partners Master Fund LP. Eli Casdin is the managing member of Casdin Capital, LLC and Casdin Partners GP, LLC. As such, each of the foregoing may be deemed to have or share beneficial ownership of the Class A common stock held directly by Casdin Partners Master Fund, LP. Mr. Casdin is member of Sema4 Holdings’ board of directors. The business address of Casdin Partners Master Fund L.P. and Mr. Casdin is c/o Casdin Capital, LLC, 1350 Avenue of the Americas, Suite 2600, New York, NY 10019.
 - (7) For the purposes of the first table, shares hereby offered consists of 10,993,750 Founder Shares and 6,736,669 shares of Class A common stock underlying warrants that are exercisable within 60 days of the date of this prospectus held by the Former Sponsor. For the purposes of the second table, consists of 6,736,669 warrants held by the Former Sponsor. The first table assumes the exercise in full of the warrants held by the Former Sponsor, and the second table assumes no exercise of the warrants held by the Former Sponsor. The Board of Managers of the Former Sponsor, or CMLS Holdings LLC, is comprised of Mr. Eli Casdin and Mr. Keith Meister who share voting and investment discretion with respect to the Class A common stock held of record by CMLS Holdings LLC. Mr. Casdin is a member of Sema4 Holdings’ board of directors. C-LSH LLC and M-LSH LLC are the members of CMLS Holdings LLC, and Mr. Casdin and Mr. Meister are the 5 managing members of C-LSH LLC and M-LSH LLC, respectively. As such, each of the foregoing may be deemed to have or share beneficial ownership of the Class A common stock held directly by CMLS Holdings LLC. The business address of the Former Sponsor is c/o Corvex Management LP, 667 Madison Avenue, New York, NY 10065. Since January 2022, Keith Meister, Managing Partner and Chief Investment Officer of Corvex Management LP, has served as a director on the Board and as Chairman of the Audit Committee.
 - (8) Shares hereby offered consist of 520,380 Legacy Sema4 Holder Shares and 58,342 Earn-out Shares (consisting of 50,093 Initially Allocated Earn- Out Shares and 8,249 Reallocated Earn-Out Shares).
 - (9) Shares hereby offered consist of f (i) 7,320,000 Acquisition PIPE Shares and 3,696,000 Business Combination PIPE Shares held by Corvex Select Equity Master Fund LP (“Corvex Select Fund”), (ii) 3,557,000 Acquisition PIPE Shares and 240,000 Business Combination PIPE Shares held by Corvex Master Fund LP (“Corvex Master Fund”), and (iii) 560,500 Acquisition PIPE Shares and 64,000 Business Combination PIPE Shares held by Corvex Dynamic Equity Select Master Fund LP (“Corvex Dynamic Fund”). Since January 2022, Keith Meister, Managing Partner and Chief Investment Officer of Corvex Management LP, has served as a director on the Board and as Chairman of the Audit Committee.
 - (10) Shares hereby offered consist of 3,418,929 Legacy Sema4 Holder Shares and 376,083 Earn-out Shares (consisting of 322,902 Initially Allocated Earn-Out Shares and 53,181 Reallocated Earn-Out Shares).

- (11) Shares hereby offered consist of (i) an aggregate of 10,049,244 Acquisition PIPE Shares, Business Combination PIPE Shares and Legacy Sema4 Holder Shares and 610,416 Earn-out Shares (consisting of 524,100 Initially Allocated Earn-Out Shares and 86,316 Reallocated Earn-Out Shares) held by Deerfield Private Design Fund V, L.P. (“Deerfield Private Design”), and (ii) an aggregate of 7,112,044 Acquisition PIPE Shares, Business Combination PIPE Shares and Legacy Sema4 Holder Shares and 610,416 Earn-out Shares (consisting of 524,100 Initially Allocated Earn-Out Shares and 86,316 Reallocated Earn-Out Shares) held by Deerfield Partners, L.P. (“Deerfield Partners”). Deerfield Private Design and Deerfield Partners have informed us that they do not delineate among the Acquisition PIPE Shares, Business Combination PIPE Shares and Legacy Sema4 Holder Shares they respectively hold and, accordingly, we have assumed their shares comprise 3,125,000 Acquisition PIPE Shares, 1,375,000 Business Combination PIPE Shares and 5,549,244 Legacy Sema4 Holder Shares held by Deerfield Private Design, and 1,875,000 Acquisition PIPE Shares, 1,375,000 Business Combination PIPE Shares and 3,862,044 Legacy Sema4 Holder Shares held by Deerfield Partners. Deerfield Mgmt V, L.P. is the general partner of Deerfield Private Design Fund V, L.P. Deerfield Mgmt, L.P. is the general partner of Deerfield Partners, L.P. Deerfield Management Company, L.P. is the investment manager of each of Deerfield Private Design Fund V, L.P. and Deerfield Partners, L.P. Mr. James E. Flynn is the sole member of the general partner of each of Deerfield Private Design Fund V, L.P., Deerfield Partners, L.P. and Deerfield Management Company, L.P. Deerfield Mgmt V, L.P. may be deemed to beneficially own the securities held by Deerfield Partners, L.P. Each of Deerfield Management Company, L.P. and Mr. Flynn may be deemed to beneficially own the securities held by each of Deerfield Private Design Fund V, L.P. and Deerfield Partners, L.P. The address for the foregoing entities and individual is 345 Park Avenue South, 12th Floor, New York, NY 10010.
- (12) For purposes of the first table, shares hereby offered consist of 166,666 shares of Class A common stock underlying warrants that are exercisable within 60 days of the date of this prospectus held by Emily Leproust and 25,000 Founder Shares. For the purposes of the second table, consists of 166,666 warrants. The first table assumes the exercise in full of the warrants held by Ms. Leproust, and the second table assumes no exercise of the warrants held by Ms. Leproust. Ms. Leproust is member of Sema4 Holdings’ board of directors.
- (13) Shares hereby offered consist of 6,250,000 Acquisition PIPE Shares, 88,355,473 Legacy Sema4 Holder Shares and 11,597,198 Earn-out Shares (consisting of 9,957,284 Initially Allocated Earn-Out Shares and 1,639,914 Reallocated Earn-Out Shares). The shares are held by ISMMS, a New York Education Corporation. The responsibility and authority for the voting and investment decisions with respect to the shares held by ISMMS is vested in those persons who from time to time are the executive officers of ISMMS under the oversight and direction of its board of directors and its sole member, Mount Sinai Health System, Inc., a New York Not-for-Profit Corporation. The address for Icahn School of Medicine at Mount Sinai is One Gustave L. Levy Place, New York, New York 10029.
- (14) Shares hereby offered consist of 1,000,000 Business Combination PIPE Shares held by JS Capital LLC.
- (15) For purposes of the first table, shares hereby offered consist of 100,000 Business Combination PIPE Shares and 166,666 shares of Class A common stock underlying warrants that are exercisable within 60 days of the date of this prospectus held by M. Munib Z. For the purposes of the second table, consists of 166,666 warrants. The first table assumes the exercise in full of the warrants held by M. Munib Z., and the second table assumes no exercise of the warrants held by M. Munib Z.
- (16) Shares hereby offered consist of 110,977 Earn-out Shares (consisting of 95,283 Initially Allocated Earn-Out Shares and 15,694 Reallocated Earn-Out Shares) held by Moore Strategic Ventures, LLC (“MSV LLC”). Louis Bacon is the indirect majority owner of MSV LLC, has voting and investment control over shares held by MSV LLC, and may be deemed the beneficial owner of shares held by MSV LLC. The address of MSV LLC and Mr. Bacon is 11 Times Square, 38th Floor, New York, New York 10036.
- (17) For purposes of the first table, shares hereby offered consist of 166,666 shares of Class A common stock underlying warrants that are exercisable within 60 days of the date of this prospectus held by Nat Turner and 25,000 Founder Shares. For the purposes of the second table, consists of 166,666 warrants. The first table assumes the exercise in full of the warrants held by Mr. Turner, and the second table assumes no exercise of the warrants held by Mr. Turner.
- (18) Shares hereby offered consist of 5,571,207 Legacy Sema4 Holder Shares and 731,255 Earn-Out Shares (consisting of 627,851 Initially Allocated Earn-Out Shares and 103,404 Reallocated Earn-Out Shares).
- (19) Shares hereby offered consist of (i) 80,000,000 Stock Consideration Shares and (ii) 30,864,198 Milestone Shares held by OPKO.
- (20) Shares hereby offered consist of 2,500,000 Acquisition PIPE Shares and 2,500,000 Business Combination PIPE Shares held by Perceptive Life Sciences Master Fund, Ltd.
- (21) Shares hereby offered consist of 6,250,000 Acquisition PIPE Shares held by Pfizer Inc.
- (22) Shares hereby offered consist of 1,250,000 Acquisition PIPE Shares, 7,449,227 Legacy Sema4 Holder Shares and 819,416 Earn-Out Shares (consisting of 703,545 Initially Allocated Earn-Out Shares and 115,871 Reallocated Earn-Out Shares), held by Section 32 Fund 2, L.P. The general partner of Section 32 Fund 2, LP is Section 32 GP 2, LLC. The general partner of Section 32 Fund 2, LP, may be deemed to have voting and dispositive power over the shares held by Section 32 Fund 2, LP. Investment decisions with respect to the shares held by Section 32 Fund 2, LP are made by the managing member of Section 32 GP 2, LLC, William J. Maris, and, therefore, Mr. Maris may be deemed to be the beneficial ownership of all shares held by Section 32 Fund 2, LP. Michael Pellini serves on the Board of Directors of Sema4 and is a Member of Section 32 GP 2, LLC. The address for all entities and individuals affiliated with Section 32 Fund 2, LP is 171 Main St. #671, Los Altos, CA 94022.
- (23) Shares hereby offered consist of 1,250,000 Acquisition PIPE Shares and 1,500,000 Business Combination PIPE Shares held by Third Point Loan LLC. (“TP Loan”). TP Loan holds the securities listed herein as nominee for funds managed and/or advised by Third Point LLC (Third Point”) and not in its individual capacity. Daniel S. Loeb is the Chief Executive Officer of Third Point. By reason of the provisions of Rule 13d-3 under the Securities Exchange Act of 1934, as amended, Third Point and Mr. Loeb may be deemed to be the beneficial owners of the securities beneficially owned by TP Loan. Third Point and Mr. Loeb hereby disclaim beneficial ownership of all such securities, except to the extent of any indirect pecuniary interest therein. The business address for Mr. Loeb and the entities identified in this footnote is c/o Third Point LLC, 55 Hudson Yards, 51st Floor, New York, NY 10001.
- (24) Shares hereby offered consist of 666,431 Business Combination PIPE Shares held by T. Rowe Price Health Sciences Fund (“T. Rowe Health Sciences Fund”), 53,808 Business Combination PIPE Shares held by TD Mutual Funds - TD Health Sciences Fund (“TD Health Sciences Fund”) and 29,761 Business Combination PIPE Shares held by T. Rowe Price Health Sciences Portfolio (“T. Rowe Health Sciences Portfolio”).

(25) Shares hereby offered consist of (i) 1,632,963 Acquisition PIPE Shares held by Vaal Investment Partners Q9 LP, (ii) 329,665 Acquisition PIPE Shares held by RUGU2 LLC and (iii) 162,372 Acquisition PIPE Shares held by Kariba LLC. These entities are affiliated with Joshua Ruch, a member of our Board.

We have entered into the Amended and Restated Registration Rights Agreement, the Business Combination Subscription Agreements, the Shareholder Agreements and/or the Acquisition Subscription Agreements with the Selling Securityholders party thereto pursuant to which, among other things, we have provided them with certain registration rights and agreed to pay certain expenses and indemnify them from certain liabilities in connection with this offering. For more information, see “Plan of Distribution”.

For additional information regarding certain related party transactions involving our officers, directors and other related parties, see the section “Certain Relationships and Related Party Transactions and Director Independence” beginning on page 171 of our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, which is incorporated herein by reference.

PLAN OF DISTRIBUTION

The Selling Securityholders, which as used herein includes donees, pledgees, transferees, distributees or other successors-in-interest selling shares of our Class A common stock or warrants or interests in our Class A common stock or warrants received after the date of this prospectus from the Selling Securityholders as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer, distribute or otherwise dispose of certain of their shares of Class A common stock or warrants or interests in our Class A common stock or warrants on any stock exchange, market or trading facility on which shares of our Class A common stock or warrants are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The Selling Securityholders may use any one or more of the following methods when disposing of their shares of Class A common stock or warrants or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- one or more underwritten offerings; block trades (which may involve crosses) in which the broker-dealer will attempt to sell the shares of Class A common stock or warrants as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its accounts;
- an exchange distribution and/or secondary distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- distributions to their employees, partners, members or stockholders;
- short sales (including short sales “against the box”) effected after the date of the registration statement of which this prospectus is a part is declared effective by the SEC;
- through the writing or settlement of standardized or over-the-counter options or other hedging transactions, whether through an options exchange or otherwise;
- in market transactions, including transactions on a national securities exchange or quotations service or over-the-counter market;
- by pledge to secure debts and other obligation;
- directly to purchasers, including our affiliates and stockholders, in a rights offering or otherwise;
- through agents;
- broker-dealers may agree with the Selling Securityholders to sell a specified number of such shares of Class A common stock or warrants at a stipulated price per share; and
- through a combination of any of these methods or any other method permitted by applicable law.

The Selling Securityholders may effect the distribution of our Class A common stock and warrants from time to time in one or more transactions either:

- at a fixed price or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices relating to the prevailing market prices; or

- at negotiated prices.

The Selling Securityholders may, from time to time, pledge or grant a security interest in some shares of our Class A common stock or warrants owned by them and, if a Selling Securityholder defaults in the performance of its secured obligations, the pledgees or secured parties may offer and sell such shares of Class A common stock or warrants from time to time, under this prospectus, or under an amendment or supplement to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of the Selling Securityholders to include the pledgee, transferee or other successors in interest as the Selling Securityholders under this prospectus. The Selling Securityholders also may transfer shares of our Class A common stock or warrants in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

We and the Selling Securityholders may agree to indemnify an underwriter, broker-dealer or agent against certain liabilities related to the sale of our Class A common stock and warrants, including liabilities under the Securities Act. The Selling Securityholders have advised us that they have not entered into any agreements, understandings or arrangements with any underwriters or broker-dealers regarding the sale of their Class A common stock and warrants. Upon our notification by a Selling Securityholder that any material arrangement has been entered into with an underwriter or broker-dealer for the sale of Class A common stock and warrants through a block trade, special offering, exchange distribution, secondary distribution or a purchase by an underwriter or broker-dealer, we will file a supplement to this prospectus, if required, pursuant to Rule 424(b) under the Securities Act, disclosing certain material information, including:

- the name of the Selling Securityholder;
- the number of shares of Class A common stock and warrants being offered;
- the terms of the offering;
- the names of the participating underwriters, broker-dealers or agents;
- any discounts, commissions or other compensation paid to underwriters or broker-dealers and any discounts, commissions or concessions allowed or reallocated or paid by any underwriters to dealers;
- the public offering price;
- the estimated net proceeds to us from the sale of the Class A common stock and warrants;
- any delayed delivery arrangements; and
- other material terms of the offering.

In addition, upon being notified by a Selling Securityholder that a donee, pledgee, transferee or other successor-in-interest intends to sell Class A common stock and warrants, we will, to the extent required, promptly file a supplement to this prospectus to name specifically such person as a Selling Securityholder.

Agents, broker-dealers and underwriters or their affiliates may engage in transactions with, or perform services for, the Selling Securityholders (or their affiliates) in the ordinary course of business. The Selling Securityholders may also use underwriters or other third parties with whom such Selling Securityholders have a material relationship. The Selling Securityholders (or their affiliates) will describe the nature of any such relationship in the applicable prospectus supplement.

There can be no assurances that the Selling Securityholders will sell, nor are the Selling Securityholders required to sell, any or all of the Class A common stock and warrants offered under this prospectus.

In connection with the sale of shares of our Class A common stock or warrants or interests therein, the Selling Securityholder may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of our Class A common stock or warrants in the course of hedging the positions they

assume. The Selling Securityholders may also sell shares of our Class A common stock or warrants short and deliver these securities to close out their short positions, or loan or pledge shares of our Class A common stock or warrants to broker-dealers that in turn may sell these securities. The Selling Securityholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities that require the delivery to such broker-dealer or other financial institution of shares of our Class A common stock offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the Selling Securityholders from the sale of shares of our Class A common stock or warrants offered by them will be the purchase price of such shares of our Class A common stock or warrants less discounts or commissions, if any. The Selling Securityholders reserve the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of shares of our Class A common stock or warrants to be made directly or through agents. We will not receive any of the proceeds from any offering by the Selling Securityholders.

The Selling Securityholders also may in the future resell a portion of our Class A common stock or warrants in open market transactions in reliance upon Rule 144 under the Securities Act, provided that they meet the criteria and conform to the requirements of that rule, or pursuant to other available exemptions from the registration requirements of the Securities Act.

The Selling Securityholders and any underwriters, broker-dealers or agents that participate in the sale of shares of our Class A common stock or warrants or interests therein may be “underwriters” within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of shares of our Class A common stock or warrants may be underwriting discounts and commissions under the Securities Act. If any Selling Securityholder is an “underwriter” within the meaning of Section 2(11) of the Securities Act, then the Selling Securityholder will be subject to the prospectus delivery requirements of the Securities Act. Underwriters and their controlling persons, dealers and agents may be entitled, under agreements entered into with us and the Selling Securityholders, to indemnification against and contribution toward specific civil liabilities, including liabilities under the Securities Act.

To the extent required, our Class A common stock or warrants to be sold, the respective purchase price and public offering price, the names of any agent, dealer or underwriter, and any applicable discounts, commissions, concessions or other compensation with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

To facilitate the offering of shares of our Class A common stock and warrants offered by the Selling Securityholders, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of our Class A common stock or warrants. This may include over-allotments or short sales, which involve the sale by persons participating in the offering of more shares of Class A common stock or warrants 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 our Class A common stock or warrants by bidding for or purchasing shares of Class A common stock or warrants in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if shares of Class A common stock or warrants 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 our Class A common stock or warrants at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time. These transactions may be effected on any exchange on which the securities are traded, in the over-the-counter market or otherwise.

Pursuant to the Amended and Restated Registration Rights Agreement, the Business Combination Subscription Agreements, the Shareholder Agreements and the Acquisition Subscription Agreements, we have agreed to indemnify the applicable Selling Securityholders party thereto against certain liabilities that they may incur in connection with the sale of the securities registered hereunder, including liabilities under the Securities Act, and to contribute to payments that the Selling Securityholders may be required to make with respect thereto. In addition,

we and the Selling Securityholders may agree to indemnify any underwriter, broker-dealer or agent against certain liabilities related to the selling of the securities, including liabilities arising under the Securities Act.

Pursuant to the Amended and Restated Registration Rights Agreement and the Shareholder Agreements, we have agreed to use our commercially reasonable efforts to cause the registration statement of which this prospectus forms a part to remain effective with respect to any securities registered hereunder pursuant to such agreement, as applicable, until: (i) such securities have been sold, transferred, disposed of or exchanged in accordance with such registration statement; (ii) such securities have ceased to be outstanding; (iii) such securities have been otherwise transferred, new certificates for such securities not bearing a legend restricting further transfer will have been delivered by us and subsequent public distribution of such securities will not require registration under the Securities Act; (iv) with respect to a Selling Securityholder party to such agreement, as applicable, all such securities held by such Selling Securityholder could be sold pursuant to Rule 144 without restriction on volume or manner of sale in any three-month period and without the requirement for us to be in compliance with the public information required under Rule 144; or (v) such securities have been sold to, or through, a broker, dealer or underwriter in a public distribution or other public securities transaction. Under each Business Combination Subscription Agreement and Acquisition Subscription Agreement, we have agreed to our commercially reasonable efforts to maintain the continuous effectiveness of the registration statement of which this prospectus forms a part with respect to any securities registered hereunder pursuant to such agreement, as applicable, until: (A) with respect to a Selling Securityholder party to such agreement, as applicable, such Selling Securityholder ceases to hold any such securities; (B) the date all such securities held by such Selling Securityholder may be sold without restriction under Rule 144, including without limitation, any volume and manner of sale restrictions which may be applicable to affiliates under Rule 144, and without the requirement for us to be in compliance with the current public information required under Rule 144; or (C) when such securities shall have ceased to be outstanding or three years from the date of effectiveness of our registration statement on Form S-1 (File No. 333-258467), originally filed with the SEC on August 4, 2021, or our registration statement on Form S-1 (File No. 333-264626), originally filed with the SEC on May 3, 2022, as applicable; or (B) such shorter period upon which such Selling Securityholder has notified us that such securities have actually been sold. Under the warrant agreement, we have agreed to maintain the effectiveness of this registration statement in respect of the shares of Class A common stock issuable upon the exercise of the public warrants and the private placement warrants until the expiration or redemption of such warrants. We have agreed to pay all expenses in connection with this offering, other than underwriting fees, discounts, selling commissions, stock transfer taxes and certain legal expenses. The Selling Securityholders will pay, on a pro rata basis, any underwriting fees, discounts, selling commissions, stock transfer taxes and certain legal expenses relating to the offering.

Selling Securityholders may use this prospectus in connection with resales of shares of our Class A common stock and warrants. This prospectus and any accompanying prospectus supplement will identify the Selling Securityholders, the terms of our Class A common stock or warrants and any material relationships between us and the Selling Securityholders. Selling Securityholders may be deemed to be underwriters under the Securities Act in connection with shares of our Class A common stock or warrants they resell and any profits on the sales may be deemed to be underwriting discounts and commissions under the Securities Act. Unless otherwise set forth in a prospectus supplement, the Selling Securityholders will receive all the net proceeds from the resale of shares of our Class A common stock or warrants.

A Selling Securityholders that is an entity may elect to make an in-kind distribution of Class A common stock or warrants to its members, partners or stockholders pursuant to the registration statement of which this prospectus is a part by delivering a prospectus, as amended or supplemented. To the extent that such transferees are not affiliates of ours, such transferees will receive freely tradable shares of Class A common stock or warrants pursuant to the distribution effected through this registration statement.

LEGAL MATTERS

The validity of the securities offered hereby has been passed upon for us by Fenwick & West LLP. Any underwriters or agents will be advised about other issues relating to the offering by counsel to be named in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Sema4 Holdings Corp. appearing in Sema4 Holdings Corp.'s Annual Report (Form 10-K) for the year ended December 31, 2021, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein, and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

The combined carve out financial statements of GeneDx, Inc. and subsidiary at December 31, 2021 and 2020, and for each of the two years in the period ended December 31, 2021, included in the Proxy Statement of Sema4 Holdings Corp. dated March 31, 2022, incorporated by reference in this Prospectus and Registration Statement have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon, and are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

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 www.sema4.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 applicable 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. 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:

- our Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on [March 14, 2022](#);

- our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2022, filed with the SEC on [May 12, 2022](#), and our Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2022, filed with the SEC on [August 15, 2022](#);
- our Current Reports on Form 8-K filed with the SEC on [January 18, 2022](#) (but only with respect to Items 1.01, 3.02, 5.02 and Exhibits 2.1, 10.1, 10.2, 10.3 and 10.4 thereto), [January 31, 2022](#), [March 14, 2022](#) (but only with respect to Item 4.02 and 9.01 thereto), [April 27, 2022](#), [May 2, 2022](#) (but only with respect to Items 1.01, 2.01, 3.02, 5.02, 5.03, 8.01, 9.01(a) and 9.01(b), and Exhibits 2.1, 3.1, 10.1, 10.2, 23.1, 99.2 and 99.3 thereto), [June 14, 2022](#) (but only with respect to Items 5.02 and 9.01), [July 1, 2022](#), and [August 26, 2022](#) (but only with respect to Items 5.02, 8.01, 9.01(a) and 9.01(b), and Exhibits 10.1, 99.2 and 99.3);
- the audited combined carve-out balance sheets of GeneDx and subsidiary as of December 31, 2021 and 2020, the related audited combined carve out statements of comprehensive loss, equity and cash flows for each of the two years in the period ended December 31, 2021, and the related notes are included in our definitive proxy statement filed with the SEC on [March 31, 2022](#) beginning on page F-41; and
- the description of our Class A common stock contained in our Registration Statement on [Form 8-A](#) filed with the SEC on August 31, 2020, as updated by the description of our Class A common stock contained in Exhibit 4.4 to our Annual Report on [Form 10-K](#) for the year ended December 31, 2021, including any subsequent amendments or reports filed for the purpose of updating such description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act in this prospectus, prior to the termination of this offering, including all such documents we may file with the SEC after the date of the initial registration statement and prior to the effectiveness of the registration statement, 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.

We will provide, without charge, to each person, including any beneficial owner, to whom a copy of this prospectus is delivered, upon written or oral request of such person, a copy of any or all of the documents incorporated by reference in this prospectus, other than exhibits to such documents unless such exhibits are specifically incorporated by reference into such documents. Requests may be made by telephone at 1(800) 298-6470, or by sending a written request to Sema4 Holdings Corp., 333 Ludlow Street, North Tower, 8th Floor, Stamford, Connecticut 06902, Attention: Investor Relations.