

PROSPECTUS SUPPLEMENT NO. 3
(to Prospectus dated May 11, 2022)



Sema4 Holdings Corp.
160,864,198 Shares of Common Stock

This prospectus supplement supplements the prospectus dated May 11, 2022 (the “Prospectus”), which forms a part of our registration statement on Form S-1 (No. 333-264626). This prospectus supplement is being filed to update and supplement the information in the Prospectus with the information contained in Item 5.02 from our Current Report on Form 8-K, filed with the Securities and Exchange Commission (the “SEC”) on July 1, 2022. Accordingly, we have attached the Current Report on Form 8-K to this prospectus supplement.

The Prospectus and this prospectus supplement relate to the offer and sale from time to time by the selling stockholders named in this prospectus (the “Selling Stockholders”) of up to 160,864,198 shares of our Class A common stock, par value \$0.0001 per share (“Class A common stock”), consisting of (i) 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 below), (ii) 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 (iii) up to 50,000,000 shares of our Class A common stock (the “PIPE Shares”) issued in a private placement pursuant to subscription agreements each entered into on January 14, 2022 (the “PIPE Investment”).

On April 29, 2022, we consummated the transactions contemplated by that certain Agreement and Plan of Merger, dated as of January 14, 2022 (as amended, the “Merger Agreement”), by and among us and our wholly-owned subsidiaries, Orion Merger Sub I, Inc. (“Merger Sub I”) and Orion Merger Sub II, LLC (“Merger Sub II” and, together with Merger Sub I, “Merger Subs”), and GeneDx, Inc., a New Jersey corporation and wholly-owned subsidiary of OPKO (“GeneDx”), GeneDx Holding 2, Inc., which held 100% of GeneDx at the Effective Time (as defined below) (“Holdco2”), and OPKO. Pursuant to the terms of the Merger Agreement, we acquired GeneDx through the merger of Merger Sub I with and into Holdco2 (the “First Merger”), with Holdco2 as the surviving corporation in the First Merger. Immediately after the consummation of the First Merger, as part of the same overall transaction, Holdco2, as the surviving corporation in the First Merger, merged with and into Merger Sub II (the “Second Merger” and, together with the First Merger, the “Mergers”), with Merger Sub II as the surviving company. After giving effect to the Mergers and the other transactions contemplated by the Merger Agreement, GeneDx was converted into a Delaware limited liability company and became our wholly-owned indirect subsidiary. At the closing of the Acquisition, we paid OPKO \$150 million of Cash Consideration (as defined herein) and issued to OPKO the Stock Consideration Shares. Concurrently with the closing, we also consummated the PIPE Investment, issuing the PIPE Shares for aggregate gross proceeds of \$200 million. We have filed the registration statement to which this prospectus relates to satisfy certain registration rights obligations we have to the Selling Stockholders in respect of the Stock Consideration Shares, the Milestone Shares and the PIPE Shares.

Our common stock and public warrants are listed on the Nasdaq Global Select Market (the “Nasdaq”) under the symbol “SMFR” and “SMFRW”, respectively. On June 30, 2022, the last reported sales price of our common stock was \$1.26 per share and the last reported sales price of our public warrants was \$0.33 per warrant.

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

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 8 of the Prospectus to read about factors you should consider before buying our securities.

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 supplement is July 1, 2022

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 8-K

CURRENT REPORT

Pursuant to Section 13 OR 15(d) of The Securities Exchange Act of 1934

Date of Report (date of earliest event reported): **July 1, 2022 (June 27, 2022)**

Sema4 Holdings Corp.

(Exact name of registrant as specified in its charter)

Delaware <hr/> (State or other jurisdiction of incorporation or organization)	001-39482 <hr/> (Commission File Number)	85-1966622 <hr/> (I.R.S. Employer Identification No.)
333 Ludlow Street, North Tower, 8th Floor Stamford, Connecticut <hr/> (Address of Principal Executive Offices)		06902 <hr/> (Zip Code)

(800) 298-6470

Registrant's telephone number, including area code
(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Class A common stock, par value \$0.0001 per share	SMFR	The Nasdaq Global Select Market
Warrants to purchase one share of Class A common stock, each at an exercise price of \$11.50 per share	SMFRW	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 5.02 Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers.

(b) Departure of Directors or Certain Officers.

On June 27, 2022, Shawn Assad notified Sema4 Holdings Corp. (the “Company”) that he will resign from his role as Chief Accounting Officer of the Company, effective August 30, 2022. Mr. Assad’s resignation is not related to any disagreement with the Company’s accounting principles or practices or financial statement disclosures. Effective upon Mr. Assad’s departure, Richard Miao will serve as the Company’s Principal Accounting Officer. Mr. Miao will continue to serve as the Company’s Interim Chief Financial Officer, Deputy Chief Financial Officer and Principal Financial Officer.

Mr. Miao has served as Senior Vice President of Financial Planning & Analysis and Treasurer of the Company since May 2021. Prior to joining the Company, Mr. Miao served as Senior Vice President of Corporate Finance and Treasurer at Endeavor Group Holdings, a global talent and media agency, from October 2017 to May 2021. Prior to that role, Mr. Miao served as Senior Vice President of Corporate Finance at William Morris Endeavor, a global talent and media agency, from December 2014 to October 2017. Mr. Miao received a B.A. in Economics from Northwestern University and an M.B.A from the NYU Stern School of Business.

Mr. Miao has no family relationships that require disclosure pursuant to Item 401(d) of Regulation S-K and has not been involved in any transactions that require disclosure pursuant to Item 404(a) of Regulation S-K. There is no arrangement or understanding between Mr. Miao and any other person pursuant to which Mr. Miao was named Principal Accounting Officer of the Company.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Sema4 Holdings Corp.

Date: July 1, 2022

By: /s/ Katherine Stueland

Name: Katherine Stueland

Title: Chief Executive Officer