

PROSPECTUS SUPPLEMENT NO. 5  
(to Prospectus dated May 11, 2022)



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

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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 Items 5.02, 8.01 and 9.01(a) and (b), and the related exhibits to such items from our current report on Form 8-K, filed with the Securities and Exchange Commission (the “SEC”) on August 26, 2022. Accordingly, we have attached the information contained in Items 5.02, 8.01 and 9.01(a) and (b), and the related exhibits to such items in 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 August 25, 2022, the last reported sales price of our common stock was \$1.22 per share and the last reported sales price of our public warrants was \$0.31 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 August 26, 2022**

**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 August 26, 2022, Sema4 Holdings Corp. (“Sema4 Holdings” or the “Company”) announced that its Interim Chief Financial Officer and Deputy Chief Financial Officer, Richard Miao, will leave the Company. Mr. Miao’s last day of employment will be September 2, 2022. Pursuant to his employment agreement with the Company, Mr. Miao will be entitled to receive accrued and unpaid compensation owed to him through the last day of his employment.

*(c) Appointment of Certain Officers.*

On August 25, 2022, Kevin Feeley, the Company’s current Senior Vice President of Operations and Head of GeneDx, was appointed to also serve as the Chief Financial Officer, effective August 25, 2022. In this role, Mr. Feeley has assumed the responsibilities of Principal Financial Officer and Principal Accounting Officer.

Mr. Feeley has served as Senior Vice President of Operations of the Company and Head of GeneDx since April 2022. Prior to joining the Company, Mr. Feeley held the position of Chief Financial Officer of BioReference Laboratories, Inc. and GeneDx, Inc. from January 2018 to April 2022. Mr. Feeley also spent more than a decade in the audit practice of KPMG LLP, working closely with large multinational pharmaceutical companies. He is a certified Public Accountant and holds a B.B.A. in Accounting from James Madison University.

In connection with the appointment, the Company and Mr. Feeley entered into an amendment to Mr. Feeley’s employment agreement providing for (i) a salary increase for a total annual base salary of \$450,000, (ii) target annual bonus of 50% of annual base salary, and (iii) a grant of stock options and restricted stock units with an aggregate grant-date value of \$750,000. The foregoing description of the amendment to Mr. Feeley’s employment agreement does not purport to be complete and is qualified in its entirety by reference to the full text of such amendment, a copy of which is attached as Exhibit 10.1 and is incorporated herein by reference.

Mr. Feeley 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. Feeley and any other person pursuant to which Mr. Feeley was named Chief Financial Officer of the Company.

**Item 8.01 Other Events.**

On May 2, 2022, the Company filed a Current Report on Form 8-K (the “GeneDx Acquisition Form 8-K”) to report, among other items, the completion of the acquisition (the “Acquisition”) of GeneDx, Inc. (“GeneDx”) pursuant to that certain Agreement and Plan of Merger, dated January 14, 2022 (as amended, the “Merger Agreement”), among the Company, GeneDx, OPKO Health, Inc. and the other parties thereto. The GeneDx Acquisition Form 8-K incorporated by reference 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 (the “GeneDx Annual Financial Statements”), and included the unaudited pro forma combined financial information of the Company giving effect to the Acquisition of GeneDx as of and for the year ended December 31, 2021, and the related notes (the “Company Annual Pro Forma Financial Information”).

In connection with the filing of Registration Statements on Form S-3 by the Company on the date hereof, this Current Report on Form 8-K is also being filed to provide updated combined carve out financial statements of GeneDx and subsidiary for the three months ended March 31, 2022 and 2021 (the “GeneDx Interim Financial Statements”) and updated unaudited pro forma combined financial information of the Company giving effect to the Acquisition for the six months ended June 30, 2022 (the “Company Interim Pro Forma Financial Information”), as required by Form S-3. These GeneDx Interim Financial Statements and the Company Interim Pro Forma Financial Information updates and supplements the GeneDx Annual Financial Statements and the Company Annual Pro Forma Financial Information. To the extent that information in Item 8.01 and Item 9.01(a) and (b) of this Current Report on Form 8-K and the related Exhibits 99.2 and 99.3 hereto differs from or updates information contained in the GeneDx Acquisition Form 8-K, the information

in such items of and exhibits to this Current Report on Form 8-K shall supersede or supplement the information in the GeneDx Acquisition Form 8-K.

**Item 9.01 Financial Statement and Exhibits.**

(a) Financial Statements of Business Acquired.

- (1) The combined carve-out financial statements of GeneDx and Subsidiary for the three months ended March 31, 2022 and March 2021, are being filed as Exhibit 99.2 to this Current Report on Form 8-K and are included herein.

(b) Pro Forma Financial Information.

- (1) The unaudited pro forma combined financial information of the Company giving effect to the Acquisition for the six months ended June 30, 2022, is being filed as Exhibit 99.3 to this Current Report on Form 8-K and is included herein.

(d) Exhibits.

**Exhibit**

**Number**

**Description**

10.1	<a href="#">Amendment No.1 to the Employment of Agreement of Kevin Feeley, dated August 25, 2022</a>
99.2	<a href="#">Combined Carve-out Financial Statements of GeneDx and Subsidiary for the Three Months Ended March 31, 2022</a>
99.3	<a href="#">Unaudited Pro Forma Combined Financial Information of the Company for the Six Months ended June 30, 2022</a>
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

**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: August 26, 2022

By: /s/ Katherine Stueland  
Name: Katherine Stueland  
Title: Chief Executive Officer

