

Carlsbad, California 92008

(760) 537-4100

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Samuel D. Riccitelli
President and Chief Executive Officer
Signal Genetics, Inc.
5740 Fleet Street Carlsbad, California
(760) 537-4100**

(Address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

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

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

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

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

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

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

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

Large accelerated filer Accelerated filer
 Non-accelerated filer (Do not check if a smaller reporting company) Smaller reporting company

CALCULATION OF REGISTRATION FEE

| Title of each class of securities to be registered | Amount to be registered/proposed maximum offering price per unit/proposed maximum aggregate offering price | Amount of registration fee |
|---|--|----------------------------|
| Common Stock, par value \$0.01 per share ⁽¹⁾⁽²⁾ | | |
| Preferred Stock, par value \$0.01 per share ⁽¹⁾⁽²⁾ | | |
| Debt Securities ⁽¹⁾ | | |
| Warrants ⁽¹⁾ | | |
| Rights ⁽¹⁾ | | |
| Units ⁽¹⁾ | | |
| Total ⁽³⁾ | \$ 50,000,000 | \$ 5,810 (4) |

- (1) An unspecified number of securities or aggregate principal amount, as applicable, is being registered as may from time to time be offered at unspecified prices.
- (2) Includes rights to acquire common stock or preferred stock of the Company under any shareholder rights plan then in effect, if applicable under the terms of any such plan.
Estimated solely for the purpose of calculating the registration fee. No separate consideration will be received for shares of common stock that are issued upon conversion of debt securities, rights, units or preferred stock or upon exercise of common stock warrants registered hereunder. The aggregate maximum offering price of all securities issued by the registrant pursuant to this registration statement will not exceed \$50,000,000.
- (3)
- (4) The registration fee has been calculated in accordance with Rule 457(o) under the Securities Act of 1933, as amended.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

EXPLANATORY NOTE

This registration statement contains two prospectuses:

- a base prospectus which covers the offering, issuance and sale by us of up to \$50,000,000 in the aggregate of the securities identified above from time to time in one or more offerings; and

- a sales agreement prospectus covering the offering, issuance and sale by us of up to a maximum aggregate offering price of \$4.45 million of our common stock that may be issued and sold under a sales agreement with Cantor Fitzgerald & Co.

The base prospectus immediately follows this explanatory note. The specific terms of any securities to be offered pursuant to the base prospectus will be specified in a prospectus supplement to the base prospectus. The sales agreement prospectus immediately follows the base prospectus. The \$4.45 million of common stock that may be offered, issued and sold under the sales agreement prospectus is included in the \$50,000,000 of securities that may be offered, issued and sold by us under the base prospectus. Upon termination of the sales agreement with Cantor Fitzgerald & Co., any portion of the \$4.45 million included in the sales agreement prospectus that is not sold pursuant to the sales agreement will be available for sale in other offerings pursuant to the base prospectus, and if no shares are sold under the sales agreement, the full \$50,000,000 of securities may be sold in other offerings pursuant to the base prospectus and a corresponding prospectus supplement.

The information in this prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell nor does it seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion, dated JULY 10, 2015

PROSPECTUS

SIGNAL GENETICS, INC.

\$50,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

Rights

Units

We may offer and sell up to \$50,000,000 in the aggregate of the securities identified above from time to time in one or more offerings. This prospectus provides you with a general description of the securities.

Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The supplement may also add,

update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement before you invest in any of our securities.

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

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE "RISK FACTORS" ON PAGE 6 OF THIS PROSPECTUS AND ANY SIMILAR SECTION CONTAINED IN THE APPLICABLE PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

Our common stock is listed on the NASDAQ Capital Market under the symbol "SGNL." On July 7, 2015, the last reported sale price of our common stock on the NASDAQ Capital Market was \$2.38 per share. As of July 10, 2015, the aggregate market value of our outstanding shares of common stock held by non-affiliates was approximately \$13,430,853, based on 7,849,493 shares of common stock outstanding, of which 5,246,427 shares of common stock were held by non-affiliates, and a per share price of \$2.56 based on the closing sale price of our shares of common stock on July 6, 2015. Other than the securities offered by this prospectus supplement, we have not offered any securities pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus supplement.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and will be eligible for reduced public company disclosure requirements.

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

The date of this prospectus is , 2015.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the U.S. Securities and Exchange Commission, or the SEC, using a “shelf” registration process. By using a shelf registration statement, we may sell securities from time to time and in one or more offerings up to a total dollar amount of \$50 million of common stock from time to time in one or more offerings as described in this prospectus. Each time that we offer and sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and sold and the specific terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you should rely on the prospectus supplement. Before purchasing any securities, you should carefully read both this prospectus and the applicable prospectus supplement, together with the additional information described under the heading “Where You Can Find More Information; Incorporation by Reference.”

We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate as of the date on its respective cover, and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates.

When we refer to “Signal Genetics,” “we,” “our,” “us” and the “Company” in this prospectus, we mean Signal Genetics, Inc., unless otherwise specified. When we refer to “you,” we mean the holders of the applicable series of securities.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Room of the SEC at prescribed rates. Further information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site 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 web site address is <https://www.signalgenetics.com>. The information on our web site, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. 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 at the SEC's Public Reference Room in Washington, D.C. or 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 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 modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the “Exchange Act” in this prospectus, between the date of this prospectus and the termination of the offering of the securities described in this prospectus. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed “filed” with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

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, 2014, filed with the SEC on March 27, 2015, including the information specifically incorporated by reference into our Annual Report on Form 10-K from our Definitive Proxy Statement on Schedule 14A filed with the SEC on May 26, 2015;
- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, filed with the SEC on May 15, 2015;
- Our Current Report on Form 8-K, filed with the SEC on June 23, 2015; and
- The description of our Common Stock contained in our registration statement on Form 8-A, filed with the SEC on June 6, 2014, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act 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.

You may request a free copy of any of the documents incorporated by reference in this prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Signal Genetics, Inc.

Attn: Corporate Secretary

5740 Fleet Street

Carlsbad, California 92008

(760) 537-4100

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

THE COMPANY

Overview

We are a commercial stage, molecular genetic diagnostic company focused on providing innovative diagnostic services that help physicians make better-informed decisions concerning the care of their patients suffering from cancer. Our mission is to develop, validate and deliver innovative diagnostic services that enable better patient-care decisions. The patient-care decisions we impact include the field of personalized medicine, wherein diagnostic tests guide treatment decisions with genetically-targeted therapies as well as traditional chemotherapy regimens. We hold an exclusive license in our licensed field to the intellectual property stemming from the renowned research on multiple myeloma (“MM”), performed at the University of Arkansas for Medical Sciences (“UAMS”).

MM is a hematologic, or blood, cancer that develops in the bone marrow and specifically affects the plasma cells of the bone marrow. Normal plasma cells produce immunoglobulins, otherwise known as antibodies, which help the body fight infection and disease. In MM, the normal plasma cells become malignant and inhibit the production of normal blood cells and antibodies, including red blood cells, white blood cells and blood platelets, and crowd the bone marrow with malignant plasma cells, which produce an abnormal antibody called a monoclonal protein (“M protein”). The hallmark characteristic of MM is a high level of M protein in the blood. MM can also cause soft spots in the bone known as osteolytic lesions. MM is the second most common blood cancer after non-Hodgkin’s lymphoma (NHL) and represents approximately 15% of all hematological malignancies. According to the American Cancer Society and the National Cancer Institute, approximately 26,850 new cases of MM are expected to be diagnosed in the United States in 2015 and approximately 11,240 deaths from MM are expected to occur in the United States in 2015. More Americans will die from MM in 2015 than from any other blood cancer. Although a relatively rare disease, MM is responsible for 2% of all cancer deaths in the United States each year and will kill more Americans than melanoma, the deadliest form of skin cancer. There are an estimated 89,658 people currently living with MM in the United States. The five-year survival rate for people with MM is about 47%. The American Cancer Society estimates that the lifetime risk in the United States of getting MM is 1 in 143.

To date, there are no known causes of MM. The most significant risk factor for developing MM is age. According to Nature: International Weekly Journal of Science’s supplement on MM published on December 15, 2011 in volume 480, page S-33 through S-80, or Nature’s MM supplement, 96% of MM cases are diagnosed in people older than 45 years of age, and more than 63% are diagnosed in people older than 65 years of age. There are usually no early stage symptoms of MM and a suspicion of a MM diagnosis is often made incidentally through routine blood tests which reveal low numbers of red blood cells and high levels of protein. Once diagnosed, MM is classified into one of three categories in a process known as staging. Staging is the process of determining how widespread or advanced the cancer is. Under the International Staging System (“ISS”), MM is classified into three stages based upon the presence of serum beta-2 microglobulin and serum albumin, which are blood proteins that are measured through a blood test. Staging is the key factor in a physician’s choice of treatment for a patient and that patient’s outlook or prognosis, often framed as progression free survival (PFS) or overall survival (OS). Prognosis is typically based on the existence of different signs, symptoms and circumstances. Certain laboratory and clinical findings, or prognostic indicators,

provide important information for MM, including when treatment should begin and what treatments to use, based upon a patient's individual prognosis and risk for relapse. However, the experts caring for MM patients have been burdened by a staging system that predates and thus fails to capture the rich body of new genomic information that has been shown to assist in the staging process. Similar genetic information has proven transformational in a number of solid tumor types, including breast, colon and lung cancer. In each case, specific genetic determinants enable doctors to identify patients who are likely to respond to genetically targeted therapies, resulting in better outcomes for these patients, including a higher rate of survival. According to the National Cancer Institute, these benefits have not yet been recognized in MM treatment. The traditional approach in MM treatment which utilizes cytogenetic techniques, such as karyotyping and fluorescent in-situ hybridization ("FISH"), for staging may not accurately stage MM patients or accurately assess the risk of relapse. Perhaps the greatest shortcoming of the current staging system for MM is its inability to classify MM patients into high and low risk prognosis groups. A tool that can further define risk-stratification by classifying MM patients in this manner would better inform physicians when to treat and what drugs to treat patients with, potentially improving health outcomes in MM patients. We believe a more comprehensive, systematic approach utilizing current genetic technologies is necessary to meet this unmet medical need.

Our flagship diagnostic service is the Myeloma Prognostic Risk Signature, or MyPRS® test. The MyPRS® test is a microarray-based gene expression profile (“GEP”), assay that measures the expression level of specific genes and groups of genes that are designed to predict an individual’s long-term clinical outcome/prognosis, giving a basis for personalized treatment options and helping physicians classify MM patients into either high or low risk groups. The MyPRS® test provides a whole-genomic expression profile of a patient’s MM. The GEP is a genetic fingerprint of a cancer, with each cancer being unique, just as each fingerprint is unique. Many recent studies show that the GEP of cancerous tumors makes personalized treatment possible, and our MyPRS® test is the first genetic test to be developed specifically for MM according to the 2007 John Shaughnessy paper in the journal Blood (A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Mar 15;109(6):2276-84. Epub 2006 Nov 14). MyPRS® is designed to be used at the time of initial MM diagnosis and also when the patient has experienced a relapse as an aid to physicians in selecting the optimal treatment regimen for each patient’s unique condition. Specifically, the test helps allow:

- risk stratification to help distinguish patients with indolent MM that may not need treatment from those patients with aggressive MM that requires more aggressive treatment; and
- identification of important genomic alterations that allow for MM sub-classification that may affect the therapy selection, and potentially enable a personalized medicine approach.

Recent Developments

In June we announced that we executed a Master Service Agreement (“MSA”) with a leading pharmaceutical company. Under the MSA, our proprietary MyPRS® genetic test will be run across multiple clinical trials in connection with the development of novel treatments for patients with multiple myeloma. We have triggered the first of four studies as part of the MSA. Under the agreement, MyPRS® will help inform patterns of response to novel therapy regimens with the aim of enabling physicians to better manage multiple myeloma patients based on their specific genetic profile. Developing a pipeline of pharmaceutical company relationships is a key objective for us, and we plan to pursue additional clinical trial service agreements with multiple companies as part of our overarching commercial strategy going forward.

Corporate Information

We were founded in New York as a Delaware limited liability company in January 2010 under the name Myeloma Health LLC. Signal Genetics LLC was formed as a Delaware limited liability company in December 2010. Effective January 1, 2011, substantially all of the member interests in Myeloma Health LLC were exchanged for member interests in Signal Genetics LLC and Myeloma Health LLC became a subsidiary of the Company. Immediately prior

to the pricing of our initial public offering, on June 17, 2014, Signal Genetics LLC converted from a Delaware limited liability company to a Delaware corporation (the “Corporate Conversion”). In connection with the Corporate Conversion, each unit of Signal Genetics LLC was converted into a share of common stock of Signal Genetics, Inc., the members of Signal Genetics LLC became stockholders of Signal Genetics, Inc. and Signal Genetics, Inc. succeeded to the business of Signal Genetics LLC and its consolidated subsidiaries. Our principal executive offices are located at 5740 Fleet Street, Carlsbad, California 92008, and our telephone number is (760) 537-4100.

RISK FACTORS

Investment in any securities offered pursuant to this prospectus and the applicable prospectus supplement involves risks. You should carefully consider the risk factors incorporated by reference to our most recent Annual Report on Form 10-K, our most recent Quarterly Report on 10-Q and any subsequent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q or Current Reports on Form 8-K we file after the date of this prospectus, and all other information contained or incorporated by reference into this prospectus, as updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in the applicable prospectus supplement before acquiring any of such securities. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

USE OF PROCEEDS

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

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RATIO OF EARNINGS TO FIXED CHARGES

If we offer preference equity securities or debt securities under this prospectus, then we will, at that time, provide a ratio of earnings to fixed charges and/or ratio of combined fixed charges and preference dividends to earnings, respectively, in the applicable prospectus supplement for such offering.

DESCRIPTION OF CAPITAL STOCK

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

General

Our authorized capital stock consists of 50,000,000 shares of common stock, par value \$0.01 per share, and 5,000,000 shares of preferred stock, par value \$0.01 per share.

As of the date of this prospectus, we have 7,849,493 shares of common stock issued and outstanding, which are held by 6 holders of record.

Common Stock

Voting rights. The holders of common stock are entitled to one vote per share on all matters to be voted upon by the stockholders, except on matters relating solely to terms of preferred stock.

Dividend rights. Subject to preferences that may be applicable to any outstanding preferred stock, the holders of common stock are entitled to receive ratably such dividends, if any, as may be declared from time to time by the board of directors out of funds legally available therefor.

Rights upon liquidation. In the event of our liquidation, dissolution or winding up, the holders of common stock are entitled to share ratably in all assets remaining after payment of liabilities, subject to prior distribution rights of preferred stock, if any, then outstanding.

Other rights. The holders of our common stock have no preemptive or conversion rights or other subscription rights. There are no redemption or sinking fund provisions applicable to our common stock.

Preferred Stock

Our board of directors has the authority to issue preferred stock in one or more classes or series and to fix the designations, powers, preferences and rights, and the qualifications, limitations or restrictions thereof, including dividend rights, conversion right, voting rights, terms of redemption, liquidation preferences and the number of shares constituting any class or series, without further vote or action by the stockholders. We have no present plans to issue any shares of preferred stock. The issuance of shares of preferred stock, or the issuance of rights to purchase such shares, could decrease the amount of earnings and assets available for distribution to the holders of common stock, could adversely affect the rights and powers, including voting rights, of the common stock, and could have the effect of delaying, deterring or preventing a change of control of us or an unsolicited acquisition proposal.

Warrants

As of March 31, 2015, we had an aggregate of 203,214 outstanding warrants to acquire an aggregate of shares of our common stock at a weighted average exercise price of \$5.38 per share, and which expire in dates ranging from June 17, 2019 to February 17, 2020.

Anti-Takeover Effects of Delaware Law

The provisions of Delaware law, our certificate of incorporation and our bylaws described below may have the effect of delaying, deferring or discouraging another party from acquiring control of us.

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the Delaware General Corporation Law, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (1) by persons who are directors and also officers and (2) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines business combination to include the following:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loss, advances, guarantees, pledges or other financial benefits by or through the corporation.

Certificate of Incorporation and Bylaws

Our certificate of incorporation and bylaws provide that:

the authorized number of directors can be changed only by resolution of our board of directors;

our bylaws may be amended or repealed by our board of directors or our stockholders;

stockholders may not call special meetings of the stockholders or fill vacancies on the board of directors;

our board of directors will be authorized to issue, without stockholder approval, preferred stock, the rights of which will be determined at the discretion of the board of directors and that, if issued, could operate as a “poison pill” to dilute the stock ownership of a potential hostile acquirer to prevent an acquisition that our board of directors does not approve;

our stockholders do not have cumulative voting rights, and therefore our stockholders holding a majority of the shares of common stock outstanding will be able to elect all of our directors; and

our stockholders must comply with advance notice provisions to bring business before or nominate directors for election at a stockholder meeting.

Potential Effects of Authorized but Unissued Stock

We have shares of common stock and preferred stock available for future issuance without stockholder approval. We may utilize these additional shares for a variety of corporate purposes, including future public offerings to raise additional capital, to facilitate corporate acquisitions or payment as a dividend on the capital stock.

The existence of unissued and unreserved common stock and preferred stock may enable our board of directors to issue shares to persons friendly to current management or to issue preferred stock with terms that could render more difficult or discourage a third-party attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise, thereby protecting the continuity of our management. In addition, the board of directors has the discretion to determine designations, rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences of each series of preferred stock, all to the fullest extent permissible under the Delaware General Corporation Law and subject to any limitations set forth in our certificate of incorporation. The purpose of authorizing the board of directors to issue preferred stock and to determine the rights and preferences applicable to such preferred stock is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing desirable flexibility in connection with possible financings, acquisitions and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from acquiring, a majority of our outstanding voting stock.

Limitations of Director Liability and Indemnification of Directors, Officers and Employees

Our certificate of incorporation limits the liability of directors to the maximum extent permitted by Delaware law. Delaware law provides that directors of a corporation will not be personally liable for monetary damages for breach of their fiduciary duties as directors, except for liability for any:

• breach of their duty of loyalty to us or our stockholders;

• act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;

• unlawful payments of dividends or unlawful stock repurchases or redemptions as provided in Section 174 of the Delaware General Corporation Law; or

• transaction from which the directors derived an improper personal benefit.

These limitations of liability do not apply to liabilities arising under the federal or state securities laws and do not affect the availability of equitable remedies such as injunctive relief or rescission.

Our bylaws provide that we will indemnify our directors and officers to the fullest extent permitted by law, and may indemnify employees and other agents. Our bylaws also provide that we are obligated to advance expenses incurred by a director or officer in advance of the final disposition of any action or proceeding.

We have obtained a policy of directors' and officers' liability insurance.

We have entered into separate indemnification agreements with our directors and officers. These agreements, among other things, require us to indemnify our directors and officers for any and all expenses (including reasonable attorneys' fees, retainers, court costs, transcript costs, fees of experts, witness fees, travel expenses, duplicating costs, printing and binding costs, telephone charges, postage, delivery service fees) judgments, fines and amounts paid in settlement actually and reasonably incurred by such directors or officers or on his or her behalf in connection with any action or proceeding arising out of their services as one of our directors or officers, or any of our subsidiaries or any other company or enterprise to which the person provides services at our request provided that such person follows the procedures for determining entitlement to indemnification and advancement of expenses set forth in the indemnification agreement. We believe that these bylaw provisions and indemnification agreements are necessary to attract and retain qualified persons as directors and officers.

The limitation of liability and indemnification provisions in our certificate of incorporation and bylaws may discourage stockholders from bringing a lawsuit against directors for breach of their fiduciary duties. They may also reduce the likelihood of derivative litigation against directors and officers, even though an action, if successful, might provide a benefit to us and our stockholders. Our results of operations and financial condition may be harmed to the extent we pay the costs of settlement and damage awards against directors and officers pursuant to these indemnification provisions.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers or persons controlling us, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

At present, there is no pending litigation or proceeding involving any of our directors or officers as to which indemnification is required or permitted, and we are not aware of any threatened litigation or proceeding that may result in a claim for indemnification.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Our Bylaws establish advance notice procedures with respect to stockholder proposals and nomination of candidates for election as directors.

Limits on Special Meetings

Special meetings of the stockholders may be called at any time only by the board of directors, the Chairman of the board of directors or our Chief Executive Officer or, in the absence of a Chief Executive Officer, our President, subject to the rights of the holders of any series of preferred stock.

Election and Removal of Directors

Our stockholders may only remove directors for cause. Our board of directors may elect a director to fill a vacancy, including vacancies created by the expansion of the board of directors. This system of electing and removing directors may discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of our directors. Our certificate of incorporation and bylaws will not provide for cumulative voting in the election of directors.

Amendments to Our Governing Documents

Generally, the amendment of our certificate of incorporation requires approval by our board of directors and a majority vote of stockholders. Any amendment to our bylaws requires the approval of either a majority of our board of directors or approval of at least a majority of the votes entitled to be cast by the holders of our outstanding capital stock in elections of our board of directors.

Listing

Our common stock is listed on the NASDAQ Capital Market under the symbol “SGNL.”

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is VStock Transfer, LLC. Its address is 18 Lafayette Place Woodmere, NY 11598.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplement, summarizes certain general terms and provisions of the debt securities that we may offer under this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. We will also indicate in the supplement to what extent the general terms and provisions described in this prospectus apply to a particular series of debt securities. To the extent the information contained in the prospectus supplement differs from this summary description, you should rely on the information in the prospectus supplement.

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

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

General

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

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

- the title and ranking of the debt securities (including the terms of any subordination provisions);
- the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;
- any limit on the aggregate principal amount of the debt securities;
- the date or dates on which the principal on a particular series of debt securities is payable;

- the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;

- the place or places where principal of, and interest, if any, on the debt securities will be payable (and the method of such payment), where the debt securities of such series may be surrendered for registration of transfer or exchange, and where notices and demands to us in respect of the debt securities may be delivered;

- the period or periods within which, the price or prices at which and the terms and conditions upon which we may redeem the debt securities;

- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities and the period or periods within which, the price or prices at which and the terms and conditions upon which the debt securities of a particular series shall be redeemed or purchased, in whole or in part, pursuant to such obligation;

- the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;

- the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;

- whether the debt securities will be issued in the form of certificated debt securities or global debt securities;

- the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;

- the currency of denomination of the debt securities, which may be United States Dollars or any foreign currency,
- and if such currency of denomination is a composite currency, the agency or organization, if any, responsible for overseeing such composite currency;

- the designation of the currency, currencies or currency units in which payment of principal of, and premium and interest on, the debt securities will be made;

- if payments of principal of, or premium or interest on, the debt securities will be made in one or more currencies or
- currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;

- the manner in which the amounts of payment of principal of, and premium, if any, and interest on, the debt securities
- will be determined, if these amounts may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index;

- any provisions relating to any security provided for the debt securities;

- any addition to, deletion of or change in the Events of Default described in this prospectus or in the indenture with
- respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;

- any addition to, deletion of or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;

- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities;

- the provisions, if any, relating to conversion or exchange of any debt securities of such series, including if
- applicable, the conversion or exchange price and period, provisions as to whether conversion or exchange will be mandatory, the events requiring an adjustment of the conversion or exchange price and provisions affecting conversion or exchange;

any other terms of the debt securities, which may supplement, modify or delete any provision of the indenture as it applies to that series, including any terms that may be required under applicable law or regulations or advisable in connection with the marketing of the securities; and

- whether any of our direct or indirect subsidiaries will guarantee the debt securities of that series, including the terms of subordination, if any, of such guarantees. (Section 2.2)

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

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

Transfer and Exchange

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

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

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

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

Covenants

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities. (Article 4)

No Protection in the Event of a Change of Control

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

Consolidation, Merger and Sale of Assets

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

we are the surviving corporation or the successor person (if other than Signal Genetics) is a corporation organized

- and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture;

- immediately after giving effect to the transaction, no Default or Event of Default, shall have occurred and be continuing; and

- certain other conditions are met.

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

Events of Default

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

- default in the payment of any interest upon any debt security of that series when it becomes due and payable, and
- continuance of such default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);

- default in the payment of principal of any debt security of that series at its maturity;

- default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 60 days after we receive written notice from the trustee or Signal Genetics and the trustee receive written notice from the holders of not less than 25% in principal amount of the outstanding debt securities of that series as provided in the indenture;

- certain voluntary or involuntary events of bankruptcy, insolvency or reorganization of Signal Genetics;

- any other Event of Default provided with respect to debt securities of that series that is described in the applicable prospectus supplement. (Section 6.1)

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

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

If an Event of Default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than 25% in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal of (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an Event of Default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all Events of Default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. (Section 6.2) We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an Event of Default.

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

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

- that holder has previously given to the trustee written notice of a continuing Event of Default with respect to debt securities of that series; and

the holders of not less than 25% in principal amount of the outstanding debt securities of that series have made written request, and offered indemnity or security satisfactory to the trustee, to the trustee to institute the proceeding

- as trustee, and the trustee has not received from the holders of not less than a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days. (Section 6.7)

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

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

Modification and Waiver

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

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

We may also modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments. We may not

make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

- reduce the amount of debt securities whose holders must consent to an amendment, supplement or waiver;

- reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;

- reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;

- reduce the principal amount of discount securities payable upon acceleration of maturity;

- waive a Default or Event of Default in the payment of the principal of, or premium or interest on, any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);

- make the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security;

- make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, and premium and interest on, those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or

- waive a redemption payment with respect to any debt security. (Section 9.3)

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. (Section 9.2) The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration. (Section 6.13)

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

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

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

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

- we may omit to comply with the covenant described under the heading “Consolidation, Merger and Sale of Assets”
- and certain other covenants set forth in the indenture, as well as any additional covenants which may be set forth in the applicable prospectus supplement; and

- any omission to comply with those covenants will not constitute a Default or an Event of Default with respect to the debt securities of that series (“covenant defeasance”).

The conditions include:

- depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and

- delivering to the trustee an opinion of counsel to the effect that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred. (Section 8.4)

No Personal Liability of Directors, Officers, Employees or Stockholders

None of our past, present or future directors, officers, employees or stockholders, as such, will have any liability for any of our obligations under the debt securities or the indenture or for any claim based on, or in respect or by reason of, such obligations or their creation. By accepting a debt security, each holder waives and releases all such liability. This waiver and release is part of the consideration for the issue of the debt securities. However, this waiver and release may not be effective to waive liabilities under U.S. federal securities laws, and it is the view of the SEC that such a waiver is against public policy.

Governing Law

The indenture and the debt securities, including any claim or controversy arising out of or relating to the indenture or the debt securities, will be governed by the laws of the State of New York. (Section 10.10).

DESCRIPTION OF WARRANTS

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

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

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

Holders of equity warrants will not be entitled:

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

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

A holder of warrant certificates may exchange them for new warrant certificates of different denominations, present them for registration of transfer and exercise them at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement. Until any warrants to purchase debt securities are exercised, the holder of the warrants will not have any rights of holders of the debt securities that can be purchased upon exercise, including any rights to receive payments of principal, premium or interest on the underlying debt securities or to enforce covenants in the applicable indenture. Until any warrants to purchase common stock or preferred stock are exercised, the holders of the warrants will not have any rights of holders of the underlying common stock or preferred stock, including any rights to receive dividends or payments upon any liquidation, dissolution or winding up on the common stock or preferred stock, if any.

DESCRIPTION OF RIGHTS

We may issue rights to purchase our securities. The rights may or may not be transferable by the persons purchasing or receiving the rights. In connection with any rights offering, we may enter into a standby underwriting or other arrangement with one or more underwriters or other persons pursuant to which such underwriters or other persons would purchase any offered securities remaining unsubscribed for after such rights offering. Each series of rights will be issued under a separate rights agent agreement to be entered into between us and one or more banks, trust companies or other financial institutions, as rights agent that we will name in the applicable prospectus supplement. The rights agent will act solely as our agent in connection with the rights and will not assume any obligation or relationship of agency or trust for or with any holders of rights certificates or beneficial owners of rights.

The prospectus supplement relating to any rights that we offer will include specific terms relating to the offering, including, among other matters:

- the date of determining the security holders entitled to the rights distribution;
- the aggregate number of rights issued and the aggregate amount of securities purchasable upon exercise of the rights;
- the exercise price;
- the conditions to completion of the rights offering;
- the date on which the right to exercise the rights will commence and the date on which the rights will expire; and
- any applicable federal income tax considerations.

Each right would entitle the holder of the rights to purchase for cash the principal amount of securities at the exercise price set forth in the applicable prospectus supplement. Rights may be exercised at any time up to the close of business on the expiration date for the rights provided in the applicable prospectus supplement. After the close of business on the expiration date, all unexercised rights will become void.

If less than all of the rights issued in any rights offering are exercised, we may offer any unsubscribed securities directly to persons other than our security holders, to or through agents, underwriters or dealers or through a combination of such methods, including pursuant to standby arrangements, as described in the applicable prospectus supplement.

DESCRIPTION OF UNITS

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

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

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

- the title of the series of units;

- identification and description of the separate constituent securities comprising the units;

- the price or prices at which the units will be issued;

- the date, if any, on and after which the constituent securities comprising the units will be separately transferable;

- a discussion of certain United States federal income tax considerations applicable to the units; and

- any other terms of the units and their constituent securities.

GLOBAL SECURITIES

Book-Entry, Delivery and Form

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

DTC has advised us that it is:

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

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

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

To facilitate subsequent transfers, all global securities deposited by direct participants with DTC will be registered in the name of DTC's partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other nominee will not change the beneficial ownership of the securities. DTC has no knowledge of the actual beneficial owners of the securities. DTC's records reflect only the identity of the direct participants to whose accounts the securities are credited, which may or may not be the beneficial owners. The participants are responsible for keeping account of their holdings on behalf of their customers. So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depository and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities and the indenture may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

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

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

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

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

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

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

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

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

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

DTC notifies us that it is unwilling or unable to continue as a depository for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depository is not appointed within 90 days of the notification to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be;

- we determine, in our sole discretion, not to have such securities represented by one or more global securities; or
- an Event of Default has occurred and is continuing with respect to such series of securities,

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

We have obtained the information in this section and elsewhere in this prospectus concerning DTC and DTC's book-entry system from sources that are believed to be reliable, but we take no responsibility for the accuracy of this information.

PLAN OF DISTRIBUTION

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

- at a fixed price or prices, which may be changed;

- at market prices prevailing at the time of sale;
 - at prices related to such prevailing market prices; or

- at negotiated prices.

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

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

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

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

otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis and a dealer will purchase securities as a principal, and may then resell the securities at varying prices to be determined by the dealer.

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

Any common stock will be listed on the NASDAQ Capital Market, but any other securities may or may not be listed on a national securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than were sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option, if any. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

If indicated in the applicable prospectus supplement, underwriters or other persons acting as agents may be authorized to solicit offers by institutions or other suitable purchasers to purchase the securities at the public offering price set forth in the prospectus supplement, pursuant to delayed delivery contracts providing for payment and delivery on the date or dates stated in the prospectus supplement. These purchasers may include, among others, commercial and savings banks, insurance companies, pension funds, investment companies and educational and charitable institutions. Delayed delivery contracts will be subject to the condition that the purchase of the securities covered by the delayed delivery contracts will not at the time of delivery be prohibited under the laws of any jurisdiction in the United States to which the purchaser is subject. The underwriters and agents will not have any responsibility with respect to the validity or performance of these contracts.

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

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

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

LEGAL MATTERS

Reed Smith LLP, New York, New York, will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Signal Genetics, Inc. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The financial statements as of December 31, 2014 and 2013 and for each of the two years in the period ended December 31, 2014 incorporated by reference in this Prospectus have been so incorporated in reliance on the report of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting.

The information in this prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell nor does it seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion, dated JULY 10, 2015

PROSPECTUS

Up to \$4,450,000 of Shares

Common Stock

We have entered into a Controlled Equity OfferingSM sales agreement with Cantor Fitzgerald & Co., or Cantor, dated July 10, 2015, relating to the sale of shares of our common stock offered by this prospectus. In accordance with the terms of the sales agreement, under this prospectus, we may offer and sell shares of our common stock, \$0.01 par value per share, having an aggregate offering price of up to \$4.45 million from time to time through Cantor, acting as agent.

Our common stock is listed on the NASDAQ Capital Market under the symbol "SGNL." On July 7, 2015, the last reported sale price of our common stock on the NASDAQ Capital Market was \$2.38 per share. As of July 10, 2015, the aggregate market value of our shares of common stock held by non-affiliates was approximately \$13,430,853, based on 7,849,493 shares of common stock outstanding, of which 5,246,427 shares of common stock were held by non-affiliates, and a per share price of \$2.56 based on the closing sale price of our shares of common stock on July 6, 2015. Other than the securities offered by this prospectus supplement, we have not offered any securities pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar months prior to and including the date of this prospectus supplement.

Sales of our common stock, if any, under this prospectus will be made by any method permitted that is deemed an "at-the-market offering" as defined in Rule 415 under the Securities Act of 1933, as amended, or the Securities Act, including sales made directly on or through the NASDAQ Capital Market, the existing trading market for our common stock, sales made to or through a market maker other than on an exchange or otherwise, in negotiated transactions at market prices, and/or any other method permitted by law. Cantor is not required to sell any specific

amount, but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Cantor will be entitled to compensation at a commission rate of up to 4.0% of the gross sales price per share sold. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of Cantor will be deemed to be underwriting commissions or discounts.

We are an “emerging growth company” under applicable Securities and Exchange Commission rules and will be eligible for reduced public company disclosure requirements.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE “RISK FACTORS” ON PAGE S-7 OF THIS PROSPECTUS CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

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

The date of this prospectus is _____, 2015.

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ABOUT THIS PROSPECTUS

This prospectus relates to the offering of our common stock. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus, together with the information incorporated by reference as described under the heading “Where You Can Find More Information; Incorporation by Reference.” These documents contain important information that you should consider when making your investment decision.

This prospectus describes the specific terms of the common stock we are offering and also adds to and updates information contained in the documents incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus, on the one hand, and the information contained in any document incorporated by reference in this prospectus, on the other hand, you should rely on the information in this prospectus. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference into this prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

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

When we refer to “Signal Genetics,” “we,” “our,” “us” and the “Company” in this prospectus, we mean Signal Genetics, Inc., unless otherwise specified. When we refer to “you,” we mean the holders of the applicable series of securities.

WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Room of the SEC at prescribed rates. Further information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site 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 web site address is <https://www.signalgenetics.com>. The information on our web site, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. 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 at the SEC's Public Reference Room in Washington, D.C. or 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 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 modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the “Exchange Act” in this prospectus, between the date of this prospectus and the termination of the offering of the securities described in this prospectus. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed “filed” with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

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, 2014, filed with the SEC on March 27, 2015, including the information specifically incorporated by reference into our Annual Report on Form 10-K from our Definitive Proxy Statement on Schedule 14A filed with the SEC on May 26, 2015;
- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, filed with the SEC on May 15, 2015;
- Our Current Reports on Form 8-K, filed with the SEC on June 23, 2015; and
- The description of our Common Stock contained in our registration statement on Form 8-A, filed with the SEC on June 6, 2014, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act 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.

You may request a free copy of any of the documents incorporated by reference in this prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Signal Genetics, Inc.

Attn: Corporate Secretary

5740 Fleet Street

Carlsbad, California 92008

(760) 537-4100

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

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THE COMPANY

Overview

We are a commercial stage, molecular genetic diagnostic company focused on providing innovative diagnostic services that help physicians make better-informed decisions concerning the care of their patients suffering from cancer. Our mission is to develop, validate and deliver innovative diagnostic services that enable better patient-care decisions. The patient-care decisions we impact include the field of personalized medicine, wherein diagnostic tests guide treatment decisions with genetically-targeted therapies as well as traditional chemotherapy regimens. We hold an exclusive license in our licensed field to the intellectual property stemming from the renowned research on multiple myeloma (“MM”), performed at the University of Arkansas for Medical Sciences (“UAMS”).

MM is a hematologic, or blood, cancer that develops in the bone marrow and specifically affects the plasma cells of the bone marrow. Normal plasma cells produce immunoglobulins, otherwise known as antibodies, which help the body fight infection and disease. In MM, the normal plasma cells become malignant and inhibit the production of normal blood cells and antibodies, including red blood cells, white blood cells and blood platelets, and crowd the bone marrow with malignant plasma cells, which produce an abnormal antibody called a monoclonal protein (“M protein”). The hallmark characteristic of MM is a high level of M protein in the blood. MM can also cause soft spots in the bone known as osteolytic lesions. MM is the second most common blood cancer after non-Hodgkin’s lymphoma (NHL) and represents approximately 15% of all hematological malignancies. According to the American Cancer Society and the National Cancer Institute, approximately 26,850 new cases of MM are expected to be diagnosed in the United States in 2015 and approximately 11,240 deaths from MM are expected to occur in the United States in 2015. More Americans will die from MM in 2015 than from any other blood cancer. Although a relatively rare disease, MM is responsible for 2% of all cancer deaths in the United States each year and will kill more Americans than melanoma, the deadliest form of skin cancer. There are an estimated 89,658 people currently living with MM in the United States. The five-year survival rate for people with MM is about 47%. The American Cancer Society estimates that the lifetime risk in the United States of getting MM is 1 in 143.

To date, there are no known causes of MM. The most significant risk factor for developing MM is age. According to Nature: International Weekly Journal of Science’s supplement on MM published on December 15, 2011 in volume 480, page S-33 through S-80, or Nature’s MM supplement, 96% of MM cases are diagnosed in people older than 45 years of age, and more than 63% are diagnosed in people older than 65 years of age. There are usually no early stage symptoms of MM and a suspicion of a MM diagnosis is often made incidentally through routine blood tests which reveal low numbers of red blood cells and high levels of protein. Once diagnosed, MM is classified into one of three categories in a process known as staging. Staging is the process of determining how widespread or advanced the cancer is. Under the International Staging System (“ISS”), MM is classified into three stages based upon the presence of serum beta-2 microglobulin and serum albumin, which are blood proteins that are measured through a blood test. Staging is the key factor in a physician’s choice of treatment for a patient and that patient’s outlook or prognosis, often framed as progression free survival (PFS) or overall survival (OS). Prognosis is typically based on the existence of different signs, symptoms and circumstances. Certain laboratory and clinical findings, or prognostic indicators,

provide important information for MM, including when treatment should begin and what treatments to use, based upon a patient's individual prognosis and risk for relapse. However, the experts caring for MM patients have been burdened by a staging system that predates and thus fails to capture the rich body of new genomic information that has been shown to assist in the staging process. Similar genetic information has proven transformational in a number of solid tumor types, including breast, colon and lung cancer. In each case, specific genetic determinants enable doctors to identify patients who are likely to respond to genetically targeted therapies, resulting in better outcomes for these patients, including a higher rate of survival. According to the National Cancer Institute, these benefits have not yet been recognized in MM treatment. The traditional approach in MM treatment which utilizes cytogenetic techniques, such as karyotyping and fluorescent in-situ hybridization ("FISH"), for staging may not accurately stage MM patients or accurately assess the risk of relapse. Perhaps the greatest shortcoming of the current staging system for MM is its inability to classify MM patients into high and low risk prognosis groups. A tool that can further define risk-stratification by classifying MM patients in this manner would better inform physicians when to treat and what drugs to treat patients with, potentially improving health outcomes in MM patients. We believe a more comprehensive, systematic approach utilizing current genetic technologies is necessary to meet this unmet medical need.

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Our flagship diagnostic service is the Myeloma Prognostic Risk Signature, or MyPRS® test. The MyPRS® test is a microarray-based gene expression profile (“GEP”), assay that measures the expression level of specific genes and groups of genes that are designed to predict an individual’s long-term clinical outcome/prognosis, giving a basis for personalized treatment options and helping physicians classify MM patients into either high or low risk groups. The MyPRS® test provides a whole-genomic expression profile of a patient’s MM. The GEP is a genetic fingerprint of a cancer, with each cancer being unique, just as each fingerprint is unique. Many recent studies show that the GEP of cancerous tumors makes personalized treatment possible, and our MyPRS® test is the first genetic test to be developed specifically for MM according to the 2007 John Shaughnessy paper in the journal Blood (A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Mar 15;109(6):2276-84. Epub 2006 Nov 14). MyPRS® is designed to be used at the time of initial MM diagnosis and also when the patient has experienced a relapse as an aid to physicians in selecting the optimal treatment regimen for each patient’s unique condition. Specifically, the test helps allow:

risk stratification to help distinguish patients with indolent MM that may not need treatment from those patients with aggressive MM that requires more aggressive treatment; and

identification of important genomic alterations that allow for MM sub-classification that may affect the therapy selection, and potentially enable a personalized medicine approach.

Recent Developments

In June we announced that we executed a Master Service Agreement (“MSA”) with a leading pharmaceutical company. Under the MSA, our proprietary MyPRS® genetic test will be run across multiple clinical trials in connection with the development of novel treatments for patients with multiple myeloma. We have triggered the first of four studies as part of the MSA. Under the agreement, MyPRS® will help inform patterns of response to novel therapy regimens with the aim of enabling physicians to better manage multiple myeloma patients based on their specific genetic profile. Developing a pipeline of pharmaceutical company relationships is a key objective for us, and we plan to pursue additional clinical trial service agreements with multiple companies as part of our overarching commercial strategy going forward.

Corporate Information

We were founded in New York as a Delaware limited liability company in January 2010 under the name Myeloma Health LLC. Signal Genetics LLC was formed as a Delaware limited liability company in December 2010. Effective January 1, 2011, substantially all of the member interests in Myeloma Health LLC were exchanged for member interests in Signal Genetics LLC and Myeloma Health LLC became a subsidiary of the Company. Immediately prior to the pricing of our initial public offering, on June 17, 2014, Signal Genetics LLC converted from a Delaware limited liability company to a Delaware corporation (the “Corporate Conversion”). In connection with the Corporate

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Conversion, each unit of Signal Genetics LLC was converted into a share of common stock of Signal Genetics, Inc., the members of Signal Genetics LLC became stockholders of Signal Genetics, Inc. and Signal Genetics, Inc. succeeded to the business of Signal Genetics LLC and its consolidated subsidiaries. Our principal executive offices are located at 5740 Fleet Street, Carlsbad, California 92008, and our telephone number is (760) 537-4100.

S-5

THE OFFERING

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| Common stock offered by us pursuant to this prospectus | Shares of our common stock having an aggregate offering price of up to \$4.45 million. |
| Manner of offering | “At-the-market offering” that may be made from time to time on the NASDAQ Capital Market or other market for our common stock in the United States through our agent, Cantor Fitzgerald & Co. See the section entitled “Plan of Distribution” on page S-11 of this prospectus. |
| Common stock to be outstanding after this offering | Up to 9,374,737 shares (as more fully described in the notes following this table), assuming sales of 1,869,747 shares of our common stock in this offering at an offering price of \$2.38 per share, which was the last reported sale price of our common stock on the NASDAQ Capital Market on July 7, 2015. The actual number of shares issued will vary depending on the sales price under this offering. |
| Use of Proceeds | We intend to use the net proceeds of this for working capital and general corporate purposes. |
| Risk Factors | See “Risk Factors” beginning on page S-7 of this prospectus and the other information included in, or incorporated by reference into, this prospectus for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock. |
| NASDAQ Capital Market symbol | “SGNL” |

The number of shares of our common stock to be outstanding immediately after this offering is based on 7,504,990 shares of our common stock outstanding as of March 31, 2015. The number of shares outstanding as of March 31, 2015 excludes:

- 903,704 shares of common stock issuable upon vesting of restricted stock unit awards outstanding as of March 31, 2015;
- 180,000 shares of common stock issuable upon exercise of stock options outstanding as of March 31, 2015, at a weighted exercise price of \$4.19 per share;
- 135,761 shares of our common stock reserved for future issuance under our 2014 Stock Incentive Plan as of March 31, 2015;
- 854,601 additional shares of our common stock reserved for future issuance under our first amendment to our 2014 Stock Incentive Plan as approved by our stockholders on June 18, 2015; and
- 203,214 shares of common stock issuable upon exercise of warrants outstanding as of March 31, 2015, at a weighted average exercise price of \$5.38 per share.

RISK FACTORS

Investment in any securities offered pursuant to this prospectus involves risks. You should carefully consider the risk factors described below and the risk factors incorporated by reference to our most recent Annual Report on Form 10-K, our most recent Quarterly Report on Form 10-Q and any subsequent Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q or Current Reports on Form 8-K we file after the date of this prospectus, and all other information contained or incorporated by reference into this prospectus, as updated by our subsequent filings under the Exchange Act, before acquiring any of such securities. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

Risks Relating to this Offering

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

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. Assuming that an aggregate of 1,869,747 shares of our common stock are sold at a price of \$2.38 per share, the last reported sale price of our common stock on the NASDAQ Capital Market on July 7, 2015, for aggregate gross proceeds of approximately \$4.45 million, and after deducting commissions and estimated offering expenses payable by us, new investors in this offering will incur immediate dilution of \$0.55 per share. For a more detailed discussion of the foregoing, see the section entitled “Dilution” below. To the extent outstanding stock options or warrants are exercised, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

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

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled “Use of Proceeds,” and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We expect to use the net proceeds from this offering to continue clinical development of new products and services, expand of our commercialization efforts, and for working capital

and general corporate purposes. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share in this offering. As of March 31, 2015, 1,422,679 shares of common stock that are either subject to outstanding options, issuable upon vesting of outstanding restricted stock units, reserved for future issuance under our equity incentive plan or subject to outstanding warrants are eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements. Such forward-looking statements include those that express plans, anticipation, intent, contingency, goals, targets or future development and/or otherwise are not statements of historical fact. These forward-looking statements are based on our current expectations and projections about future events and they are subject to risks and uncertainties known and unknown that could cause actual results and developments to differ materially from those expressed or implied in such statements.

In some cases, you can identify forward-looking statements by terminology, such as “expects,” “anticipates,” “intends,” “estimates,” “plans,” “believes,” “seeks,” “may,” “should,” “could,” “would,” “will” or the negative of such terms or other similar expressions. Accordingly, these statements involve estimates, assumptions and uncertainties that could cause actual results to differ materially from those expressed in them. Any forward-looking statements are qualified in their entirety by reference to the factors discussed throughout this prospectus.

You should read this prospectus and the documents that we reference herein and therein and have filed as exhibits to the registration statement, of which this prospectus is part, completely and with the understanding that our actual future results may be materially different from what we expect. You should assume that the information appearing in this prospectus is accurate as of the date on the front cover of this prospectus only. Because the risk factors referred to above could cause actual results or outcomes to differ materially from those expressed in any forward-looking statements made by us or on our behalf, you should not place undue reliance on any forward-looking statements. These risks and uncertainties, along with others, are described above under the heading “Risk Factors.” Further, any forward-looking statement speaks only as of the date on which it is made, and we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. We qualify all of the information presented in this prospectus, and particularly our forward-looking statements, by these cautionary statements.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sales proceeds of up to \$4.45 million from time to time. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time.

We intend to use the net proceeds of this offering for working capital and general corporate purposes.

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

DIVIDEND POLICY

We do not anticipate paying dividends on our common stock. We currently intend to retain all of our future earnings, as applicable, to finance the growth and development of our business. We are not subject to any legal restrictions respecting the payment of dividends, except that we may not pay dividends if the payment would render us insolvent. Any future determination as to the payment of cash dividends on our common stock will be at our board of directors’ discretion and will depend on our financial condition, operating results, capital requirements and other factors that our board of directors considers to be relevant.

DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value of our common stock as of March 31, 2015 was \$13.1 million, or \$1.75 per share of common stock based upon 7,504,990 shares outstanding. Net tangible book value per share is equal to our total tangible assets, less our total liabilities, divided by the total number of shares outstanding as of March 31, 2015.

After giving effect to the sale of our common stock in the aggregate amount of \$4.45 million at an assumed offering price of \$2.38 per share, the last reported sale price of our common stock on the NASDAQ Capital Market on July 7, 2015, and after deducting estimated offering commissions payable by us, our net tangible book value as of March 31, 2015 would have been \$17.2 million, or \$1.83 per share of common stock. This represents an immediate increase in net tangible book value of \$0.08 per share to our existing stockholders and an immediate dilution in net tangible book value of \$0.55 per share to new investors in this offering.

The following table illustrates this calculation on a per share basis:

| | |
|---|--------|
| Assumed public offering price per share | \$2.38 |
| Net tangible book value per share | \$1.75 |
| Increase in net tangible book value per share attributable to the offering | \$0.08 |
| As adjusted net tangible book value per share after giving effect to the offering | 1.83 |
| Dilution in net tangible book value per share to new investors in this offering | \$0.55 |

The number of shares of our common stock to be outstanding immediately after this offering is based on 7,504,990 shares of our common stock outstanding as of March 31, 2015. The number of shares outstanding as of March 31, 2015 excludes:

- 903,704 shares of common stock issuable upon vesting of restricted stock unit awards outstanding as of March 31, 2015;
- 180,000 shares of common stock issuable upon exercise of stock options outstanding as of March 31, 2015, at a weighted exercise price of \$4.19 per share;
- 135,761 shares of our common stock reserved for future issuance under our 2014 Stock Incentive Plan as of March 31, 2015;
- 854,601 additional shares of our common stock reserved for future issuance under our first amendment to our 2014 Stock Incentive Plan as approved by our stockholders on June 18, 2015; and
- 203,214 shares of common stock issuable upon exercise of warrants outstanding as of March 31, 2015, at a weighted average exercise price of \$5.38 per share.

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PLAN OF DISTRIBUTION

We have entered into a Controlled Equity OfferingSM sales agreement with Cantor Fitzgerald & Co., or Cantor, under which we may issue and sell shares of our common stock having an aggregate gross sales price of up to \$4.45 million from time to time through Cantor acting as agent. The sales agreement has been filed as an exhibit to the registration statement of which this prospectus forms a part.

Upon delivery of a placement notice and subject to the terms and conditions of the sales agreement, Cantor may sell our common stock by any method permitted by law deemed to be an “at-the-market offering” as defined in Rule 415 promulgated under the Securities Act, including sales made directly on the NASDAQ Capital Market, on any other existing trading market for our common stock or to or through a market maker. Cantor may also sell our common stock by any other method permitted by law, including in negotiated transactions. We may instruct Cantor not to sell common stock if the sales cannot be effected at or above the price designated by us from time to time. We or Cantor may suspend the offering of common stock upon notice and subject to other conditions.

We will pay Cantor commissions, in cash, for its services in acting as agent in the sale of our common stock. Cantor will be entitled to compensation at a commission rate of up to 4% of the gross sales price per share sold. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. We have also agreed to reimburse Cantor for certain specified expenses, including the fees and disbursements of its legal counsel in an amount not to exceed \$65,000. We estimate that the total expenses for the offering, excluding compensation and reimbursements payable to Cantor under the terms of the sales agreement, will be approximately \$125,000. In addition, we have agreed to pay 1.0% of the gross proceeds of this offering, or a maximum of \$50,000, to Aegis Capital Corp. in consideration for its waiver of certain provisions contained in the underwriting agreement we entered into in February 2015.

Settlement for sales of common stock will occur on the third business day following the date on which any sales are made, or on some other date that is agreed upon by us and Cantor in connection with a particular transaction, in return for payment of the net proceeds to us. Sales of our common stock as contemplated in this prospectus will be settled through the facilities of The Depository Trust Company or by such other means as we and Cantor may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

Cantor will use its commercially reasonable efforts, consistent with its normal sales and trading practices, to solicit offers to purchase the common stock shares under the terms and subject to the conditions set forth in the sales agreement. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of Cantor will be deemed to be underwriting commissions or discounts. We have agreed to provide indemnification and contribution to Cantor against certain civil liabilities, including liabilities under the Securities Act.

The offering of our common stock pursuant to the sales agreement will terminate as permitted therein. We and Cantor may each terminate the sales agreement at any time upon ten days' prior notice.

Cantor and its affiliates may in the future provide various investment banking, commercial banking and other financial services for us and our affiliates, for which services they may in the future receive customary fees. To the extent required by Regulation M, Cantor will not engage in any market making activities involving our common stock while the offering is ongoing under this prospectus supplement.

This prospectus in electronic format may be made available on a website maintained by Cantor and Cantor may distribute this prospectus and the accompanying base prospectus electronically.

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LEGAL MATTERS

Reed Smith LLP, New York, New York, will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Signal Genetics, Inc. LeClairRyan, A Professional Corporation, Newark, New Jersey, is counsel for Cantor in connection with this offering.

EXPERTS

The financial statements as of December 31, 2014 and 2013 and for each of the two years in the period ended December 31, 2014 incorporated by reference in this Prospectus have been so incorporated in reliance on the report of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting.

Up to \$4,450,000 of Shares

Common Stock

PROSPECTUS

, 2015

PART II**INFORMATION NOT REQUIRED IN PROSPECTUS****Item 14. *Other Expenses of Issuance and Distribution***

The following is an estimate of the expenses that we may incur in connection with the securities being registered hereby. All amounts are estimates except the SEC registration fee and the FINRA filing fee.

| | |
|----------------------------------|---------|
| SEC registration fee | \$5,810 |
| FINRA filing fee | \$8,000 |
| NASDAQ Capital Market fee | \$* |
| Fees and expenses of the trustee | \$* |
| Printing expenses | \$* |
| Legal fees and expenses | \$* |
| Accounting fees and expenses | \$* |
| Miscellaneous | \$* |
| Total | \$* |

*These fees are calculated based on the securities offered and the number of issuances and accordingly cannot be estimated at this time.

Item 15. *Indemnification of Directors and Officers*

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

Subsection (b) of Section 145 empowers a corporation to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to

procure a judgment in its favor by reason of the fact that the person acted in any of the capacities set forth above, against expenses (including attorneys' fees) actually and reasonably incurred by the person in connection with the defense or settlement of such action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

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

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

Our certificate of incorporation and our bylaws provide that we will indemnify our directors and officers to the fullest extent permitted by the Delaware General Corporation Law, which prohibits our certificate of incorporation from limiting the liability of our directors for the following:

- any breach of the director's duty of loyalty to us or our stockholders;

- acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
 - unlawful payment of dividends or unlawful stock repurchases or redemptions; or

- any transaction from which the director derived an improper benefit.

Our certificate of incorporation provides for indemnification of our directors and executive officers to the maximum extent permitted by the Delaware General Corporation Law, and our bylaws provide for indemnification of our directors and executive officers to the maximum extent permitted by the Delaware General Corporation Law.

We have entered into indemnification agreements with each of our current directors and executive officers. These agreements will require us to indemnify these individuals to the fullest extent permitted under Delaware law against liabilities that may arise by reason of their service to us and to advance expenses incurred as a result of any proceeding against them as to which they could be indemnified. We also intend to enter into indemnification agreements with our future directors and executive officers.

In any underwriting agreement we enter into in connection with the sale of common stock being registered hereby, the underwriters will agree to indemnify, under certain conditions, us, our directors, our officers and persons who control us, within the meaning of the Securities Act, against certain liabilities.

Item 16. Exhibits

(a) Exhibits

A list of exhibits filed with this registration statement on Form S-3 is set forth on the Exhibit Index and is incorporated herein by reference.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

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

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

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

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

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

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

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

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

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

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

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

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

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

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

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

(j) To file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Securities and Exchange Commission under Section 305(b)(2) of the Trust Indenture Act.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Carlsbad, State of California, on the 10th day of July, 2015.

SIGNAL GENETICS, INC.

By: /s/ Samuel D. Riccitelli
Samuel D. Riccitelli
President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Samuel D. Riccitelli and or Tamara A. Seymour, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to file and sign any and all amendments, including post-effective amendments and any registration statement for the same offering that is to be effective under Rule 462(b) of the Securities Act, to this registration statement, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their substitute or substitutes may lawfully do or cause to be done by virtue hereof. This power of attorney shall be governed by and construed with the laws of the State of Delaware and applicable federal securities laws.

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement has been signed below by the following persons on behalf of the registrant in the capacities and on the dates indicated.

| SIGNATURE | TITLE | DATE |
|---|--|---------------|
| /s/ Samuel D. Riccitelli Samuel D. Riccitelli | President, Chief Executive Officer and Director <i>(Principal Executive Officer)</i> | July 10, 2015 |
| /s/ Tamara A. Seymour Tamara A. Seymour | Chief Financial Officer <i>(Principal Financial and Principal Accounting Officer)</i> | July 10, 2015 |

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| | | |
|--|------------------------------------|---------------|
| <i>/s/ Bennett S. LeBow</i> Bennett S. LeBow | Chairman of the Board of Directors | July 10, 2015 |
| <i>/s/ David A. Gonyer, R. Ph.</i> David A. Gonyer, R. Ph. | Director | July 10, 2015 |
| <i>/s/ Douglas A. Schuling</i> Douglas A. Schuling | Director | July 10, 2015 |
| <i>/s/ Robin L. Smith, M.D.</i> Robin L. Smith, M.D. | Director | July 10, 2015 |

EXHIBIT INDEX

| Exhibit Number | Description |
|---------------------------|---|
| 1.1* | Form of Underwriting Agreement. |
| 1.2 | Controlled Equity Offering SM Sales Agreement, dated July 10, 2015, by and between Signal Genetics, Inc. and Cantor Fitzgerald & Co. |
| 3.1 | Certificate of Incorporation of Signal Genetics, Inc. (incorporated by reference to Exhibit 3.1 to the Quarterly Report on Form 10-Q (No. 001-36483) filed with the Securities and Exchange Commission on August 14, 2014). |
| 3.2 | Bylaws of Signal Genetics, Inc. (incorporated by reference to Exhibit 3.2 to the Quarterly Report on Form 10-Q (No. 001-36483) filed with the Securities and Exchange Commission on August 14, 2014). |
| 4.1 | Reference is made to Exhibits 3.1 through 3.2 |
| 4.2 | Specimen Common Stock Certificate (incorporated by reference to Exhibit 4.1 to the Registration Statement on Form S-1 (No. 333-194668) filed with the Securities and Exchange Commission on March 19, 2014). |
| 4.3* | Form of Preferred Stock Certificate. |
| 4.4 | Form of Indenture. |
| 4.5* | Form of Note. |
| 4.6* | Form of Warrant. |
| 4.7* | Form of Warrant Agreement. |
| 4.8* | Form of Rights Agreement. |
| 4.9* | Form of Unit Agreement. |
| 5.1 | Opinion of Reed Smith LLP. |
| 12.1* | Computation of Ratio of Earnings to Fixed Charges. |
| 23.1 | Consent of BDO USA, LLP, independent registered public accounting firm. |
| 23.2 | Consent of Reed Smith LLP (included in Exhibit 5.1). |
| 24.1 | Powers of Attorney (incorporated by reference to the signature page hereto). |

25.1* Statement of Eligibility of Trustee on Form T-1 under the Trust Indenture Act of 1939, as amended.

To be filed by amendment or incorporated by reference in connection with the offering of the securities.

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