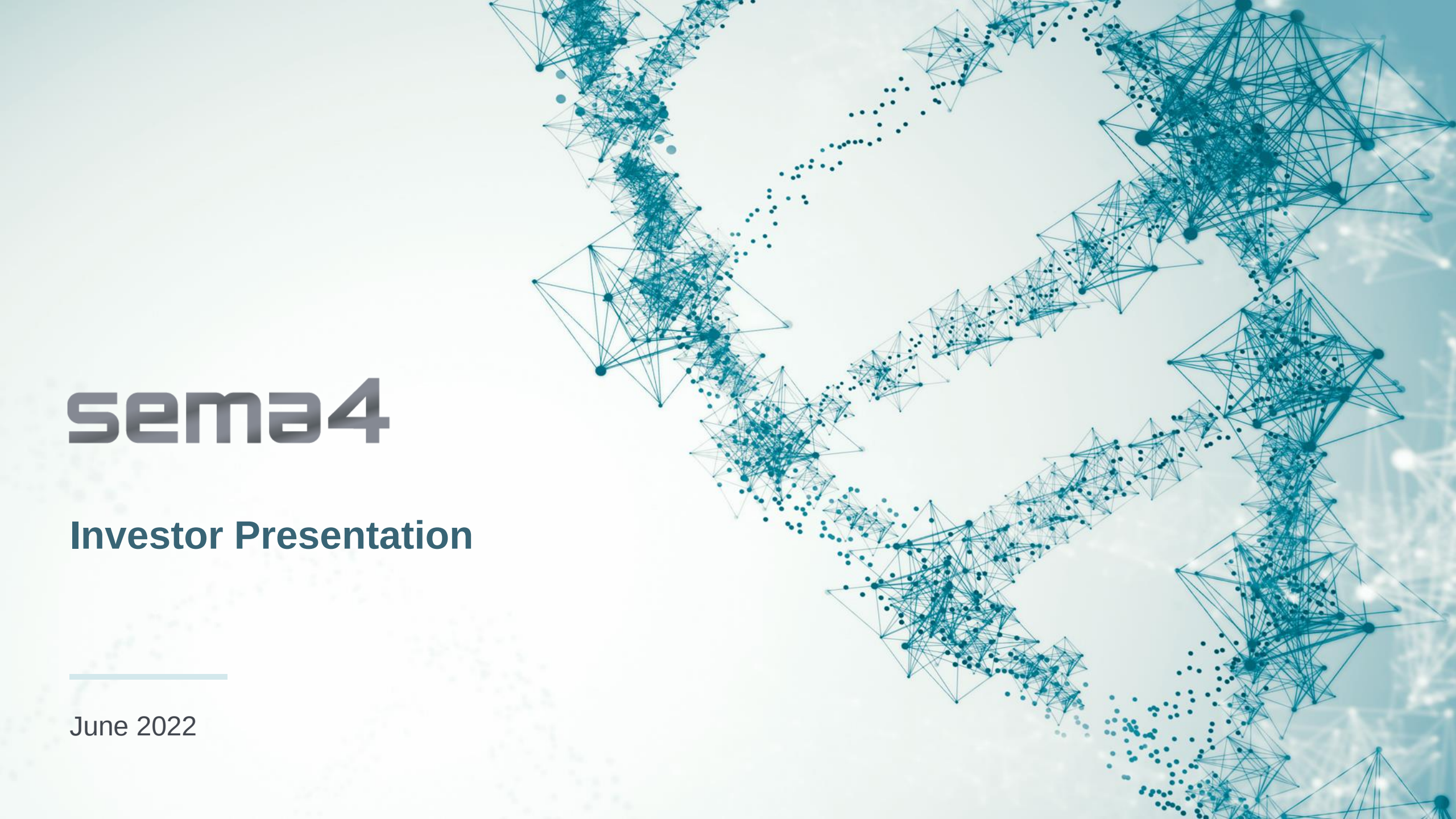

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Investor Presentation

June 2022

Disclaimer

This presentation contains forward-looking statements under the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements are statements that do not relate to historical facts and events and such statements and opinions pertaining to the future that, for example, contain wording such as “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “continue,” “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained in this presentation include, but are not limited to, statements about: our full year 2022 revenue, volume and gross margin guidance, our expectations of the anticipated benefits and synergies of the recently completed acquisition (the “Acquisition”) of GeneDx Inc. (“GeneDx), our estimates of our volumes and revenue for the first quarter, our addressable market, market growth, future revenue, key performance indicators, expenses, capital requirements and our needs for additional financing, our commercial launch plans, our strategic plans for our business and products, market acceptance of our products, and our competitive position and developments and projections relating to our competitors. We cannot assure that the forward-looking statements in this presentation will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements.

The forward-looking statements and opinions contained in this presentation are based on our management’s beliefs and assumptions and are based upon information currently available to our management as of the date of this presentation and, while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. Many factors could cause actual future events to differ materially from the forward-looking statements in this press release, including but not limited to: (i) the ability to implement business plans, goals and forecasts, and identify and realize additional opportunities, (ii) the risk of downturns and a changing regulatory landscape in the highly competitive healthcare industry, (iii) the size and growth of the market in which we operate, and (iv) the risk that the anticipated benefits of the Acquisition of GeneDx may not be realized, if at all. The information, opinions and forward-looking statements contained in this announcement speak only as of its date, and are subject to change without notice.

Use of Non-GAAP Financial Measures

This presentation includes non-GAAP financial measures, including Adjusted EBITDA, Adjusted Gross Profit and Adjusted Gross Margin. Adjusted EBITDA is defined as net loss adjusted for interest expense, net, depreciation and amortization, stock-based compensation expenses, transaction costs, other (income) expense, net and COVID-19 testing costs. Management believes that these non-GAAP measures of financial results are useful in evaluating the Sema4's operating performance compared to that of other companies in its industry, as this metric generally eliminates the effects of certain items that may vary from company to company for reasons unrelated to overall operating performance. Please refer to the Appendix for Non-GAAP to GAAP Reconciliation.

This presentation contains estimates, projections and other information concerning our industry, our business, and the markets for our products and services. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties, and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from our own internal estimates and research as well as from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources. While we believe our internal company research as to such matters is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.
We discuss these and other risks and uncertainties in greater detail in the sections entitled “Risk Factors” and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in our periodic reports and other filings we make with the SEC from time to time. Given these uncertainties, you should not place undue reliance on the forward-looking statements. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations. We file reports, proxy statements, and other information with the SEC. Such reports, proxy statements, and other information concerning us is available at http://www.sec.gov. Requests for copies of such documents should be directed to our Investor Relations department at Sema4 Holdings Corp. 333 Ludlow Street, North Tower, 8th Floor, Stamford, CT 06902. Our telephone number is 800-298-6470.

A Patient-Centered Health Intelligence Company Leveraging Genomics and AI

The Problem

Rapid advances in Genomics & AI...

...but limited impact on patients

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Recent Business Highlights

1Q 2022[1] revenue growth of 4%[2]

1Q 2022[1] resulted volume growth of 27%[2]

Closed GeneDx acquisition and $200M PIPE[3] from leading investors, including Pfizer

Streamlined leadership team to enable focused execution and to drive growth

Reaffirming 2022 revenue guidance of $305-315M, now includes GeneDx for eight months which implies $350M of pro forma revenue at the midpoint[4]

[1] *3 months ended 3/31/22*
[2] *Excluding COVID-19 testing revenue*
[3] *PIPE (Private Investment in Public Equity) is contingent on the closing of the GeneDx acquisition*
[4] *$350M pro forma target previously excluded and continues to exclude any contribution from COVID-19 in 2022. Includes anticipated revenue growth and contribution from completed acquisition of GeneDX*

Path to Profitability

Growth at Scale[1]	• Market leading franchises in Women's Health & Rare Disease • On track to result 450K+ tests in 2022
Operating Efficiency	• Committed to $50M+ reduction in 2022 cash burn • Significant ASP/margin opportunities via revenue cycle and lab efficiency • Cash runway into 2024
Transformational Deals	• Significantly enhanced value proposition via GeneDx acquisition • Unique competitive moat with strategy to partner with health systems

[1] *includes anticipated contribution from completed acquisition of GeneDX*

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Strong Start to 2022

1Q Resulted Volume

Resulted ~85,000 tests excluding COVID-19

+27% yoy and +2% qoq

1Q Total Revenue

$54M in total revenue

+4% yoy (excluding COVID-19 testing)[1]

1Q Balance Sheet

$315M in cash & equivalents as of 3/31/22

+$125M undrawn revolver = $440M total liquidity

[1] *1Q22 Revenue excluding COVID-19 was $50.1 million*

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2022 Guidance (now includes GeneDx for eight months)

Resulted Volume[1]

55%+ growth YoY

Implies 450k+ patient tests resulted

Revenue

$305–315M total revenue[2]

Includes 8 months from GeneDx which implies $350M of pro forma revenue at the midpoint[3]

Adj. Gross Margin[4]

20%+ gross margin for 2022

Exit GM of 30% in 4Q

Year End Cash

$200M+

Sequential reduction in cash burn throughout 2022

Cash runway into 2024

[1] Excluding COVID-19 testing
[2] The midpoint of the updated guidance implies $350 million of pro-forma revenue excluding COVID-19 testing, assuming a full year 2022 contribution of GeneDx.
[3] $350M pro forma target previously excluded and continues to exclude any contribution from COVID-19 in 2022
[4] Adjusted Gross Margin is a non-GAAP measure. Refer to Appendix for non-GAAP Reconciliation

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Our Financial Profile Exiting 2022

Annualized revenue of $350 million on a trailing pro forma basis[1]

Q4 exiting adjusted **gross margin[2] of 30%** with a path to 50% by 2025

Total liquidity of **$325M at year-end** ($200M+ in cash + $125M revolver)

Cash **runway into 2024[3]**

Revised operating model enables **positive free cash flow** in 2025

[1] $350 million pro forma revenue includes revenue generated by GeneDx in 2022 prior to Deal Close on April 29th
[2] Adjusted Gross Margin is a non-GAAP measure. Refer to Appendix for non-GAAP Reconciliation
[3] Includes Cash & Equivalents, does not include drawing on Sema4's $125M Revolver

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sema4 + GeneDx

Deal Rationale

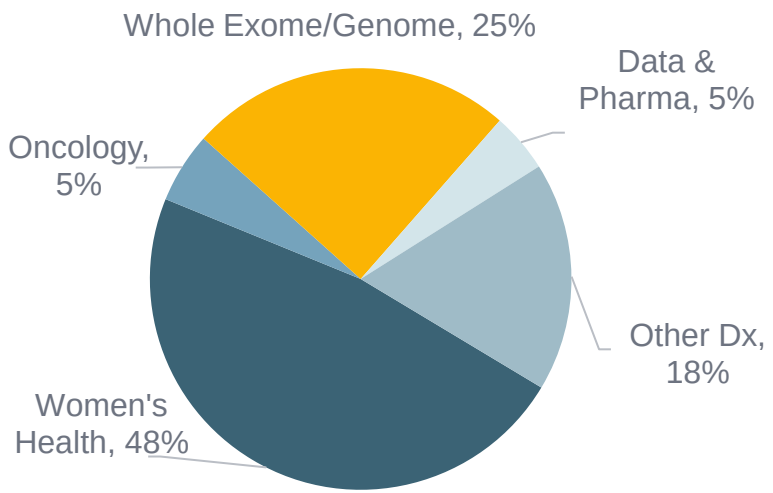
1. **Health Systems:** Accelerating uptake of the clinical exome into our core channels
2. **Data:** Leveraging GeneDx's market-leading exome database with Sema4's Centrellis® platform
3. **Scale:** Market leader in Women's Health and market leader in Rare Disease
4. **Synergy:** Accelerating our path to profitability

Clinical NGS
80%+ of 2022E pro forma revenue

Clinical Exomes
30% of revenue growing to 80% next few years[2]

Managing 49+ petabytes of data growing at an accelerated pace

2022E Pro Forma Revenue[1]



Our Health System Partners serve 20M+ patients

NorthShore University HealthSystem
Avera
AdventHealth
Mount Sinai

[1] Estimated and pro forma results are subject to certain assumptions, risks and uncertainties. See Disclaimer on slide 2.
[2] Clinical exomes includes "Whole Exome/Genome" and "Oncology" 2022E pro forma revenue.

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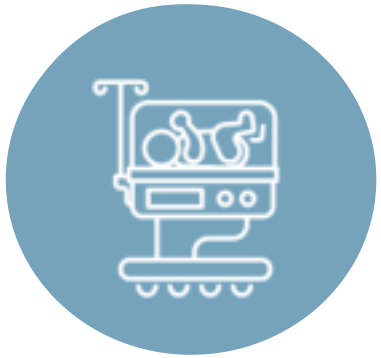
Broad Portfolio Increases Longitudinal Engagement and Enhances Centrellis®

Expanding From Patient Engagement into Family Health ($50B+ TAM)[1]

Women's Health: $4B

Reimbursement expanding via ACOG guidelines



NICU & Outpatient: $3B

Substantial cost savings via early screening

Current Gap for Sema4

Newborn Screening: $10B

Increasing inclusion of genetics in screening programs

Underdeveloped Solution for Sema4

Genomic Health Screening: $16B

Rapidly expanding into oncology, cardio and neuro

Accelerating our move to Exome/WGS

Oncology: $18B

Rapid uptake of genomic profiling for therapy selection and MRD

Newborn Screening and Reproductive Medicine

Hereditary risk and disease

[1] Addressable Markets Source: Company Estimates

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A Market-Leading AI-Driven Genomic & Clinical Data Platform

Generating Data/ Growing Patient Base

- **Sema4:** ~300K tests/year, 500K+ genomic profiles
- **GeneDx:** ~150K tests/year, 350K+ clinical exomes

Increasing Scale

More holistic patient engagement → bigger data

- **Sema4:** 12M patients with de-identified records
- **GeneDx:** Adding 2.7M expert-curated phenotypes

Delivering Insights

- Platform for delivering differentiated, actionable insights
- Adding >100 new disease-gene relationships published annually

Accelerating Our “One Test” Platform with GeneDx's Universal Genomics Chassis

Sequence Once, Analyze for a Lifetime

CAPTURE MAJORITY OF PATIENTS

During initial order across expansive offering of genomic testing solutions

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Provider-initiated order across all Sema4 germline genomic tests

SEQUENCE ONCE

GeneDx Whole Exome/ Genome Products

Automated software query of generated data

Carrier Screening
Newborn Screening
NICU/PICU Dx
PGx
Polygenic Risk Scores
Hereditary Cancer
Somatic Tumor Profiling

GENERATE MANY CLINICAL REPORTS

Repeated insights from existing data → increasing tech-like gross margins for genomic tests

Ability to order subsequent tests for insights across a broad array of diseases and conditions/wellness

RICH REFERENCE DATA SETS

easily accessed and queried for collaborations

Resulting whole exome/genome data linked to longitudinal clinical annotation

Patient’s Lifetime

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Enhancing Our Reach into Health Systems & Biopharma

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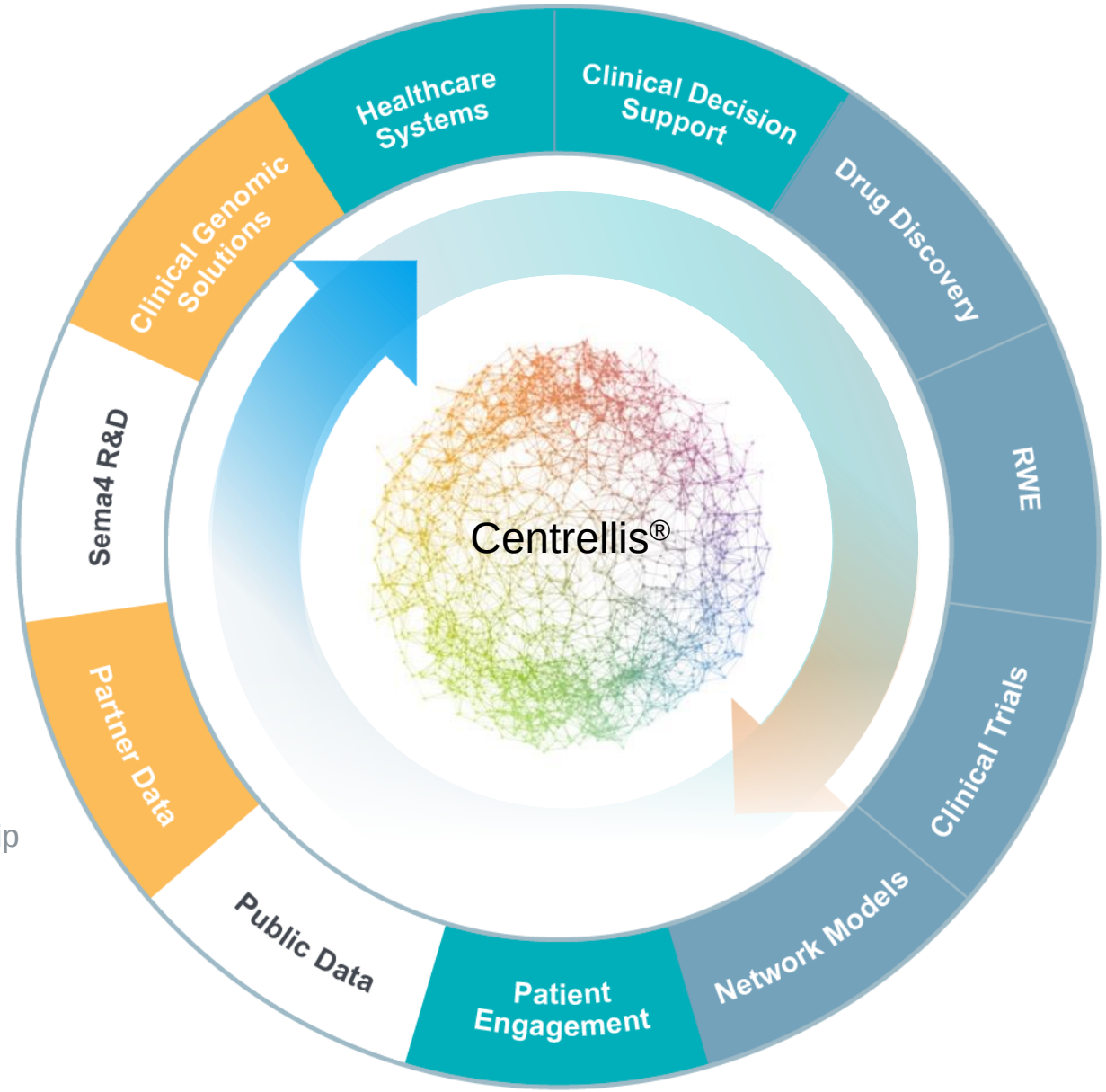

- Health System Dominant Partnership
- Pharma Dominant Partnership
- HS-Pharm Synergistic Partnership

gsk
Molecular Profiling and Real-World Evidence

Merus
Patient ID and Recruitment

SANOFI
Drug Discovery Collaboration

janssen
Clinical Trial Match and Recruitment into Trials w/Health System Partners

Lilly
Precision Medicine Drug Screening Collaboration

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…Combined with Centrellis, our Flywheel for Patient Data and Insights

Enhanced Data Feed

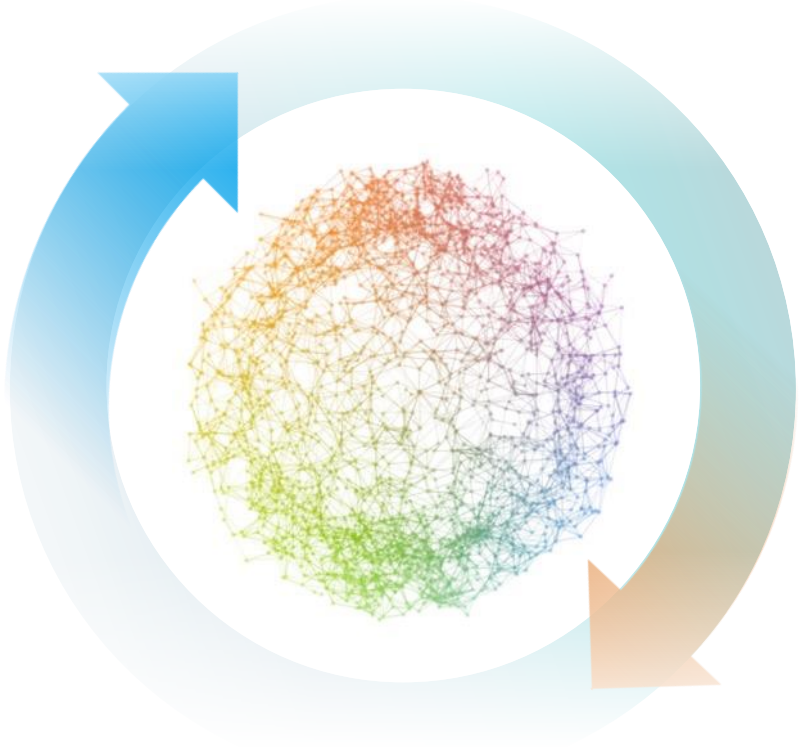
Channels

Health Systems
EMR, Imaging, Molecular, Claims

Third Parties
EMR, Imaging, Molecular, Claims

Outside Data Source
Literature, Knowledge Graph, Omics Repositories

+



Insights & Engagement

Clinical Trials

Clinical Decision Support

Population Health Models

Patients & Provider Portals

Real-World Evidence

Drug Discovery Models

+

Laboratory
Molecular, Clinical, Patient Gen. Data

Standard Dx Pathway

Clinical Reports

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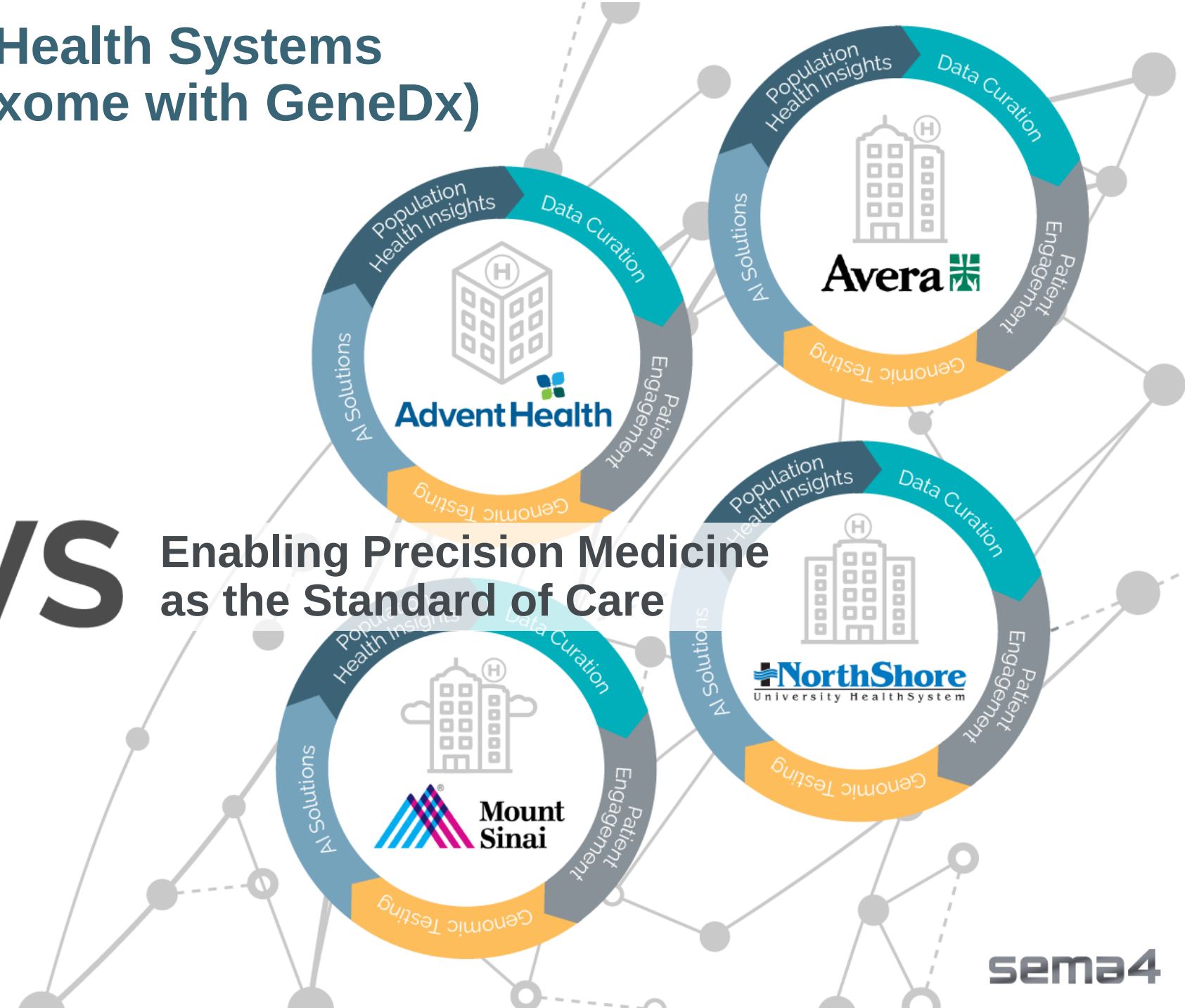
Deep Partnership with Health Systems (Accelerating clinical exome with GeneDx)

Conventional Genomics Model
narrow menu
sold direct to physicians
no (or limited) data integration
no or limited patient engagement

VS

Enabling Precision Medicine as the Standard of Care



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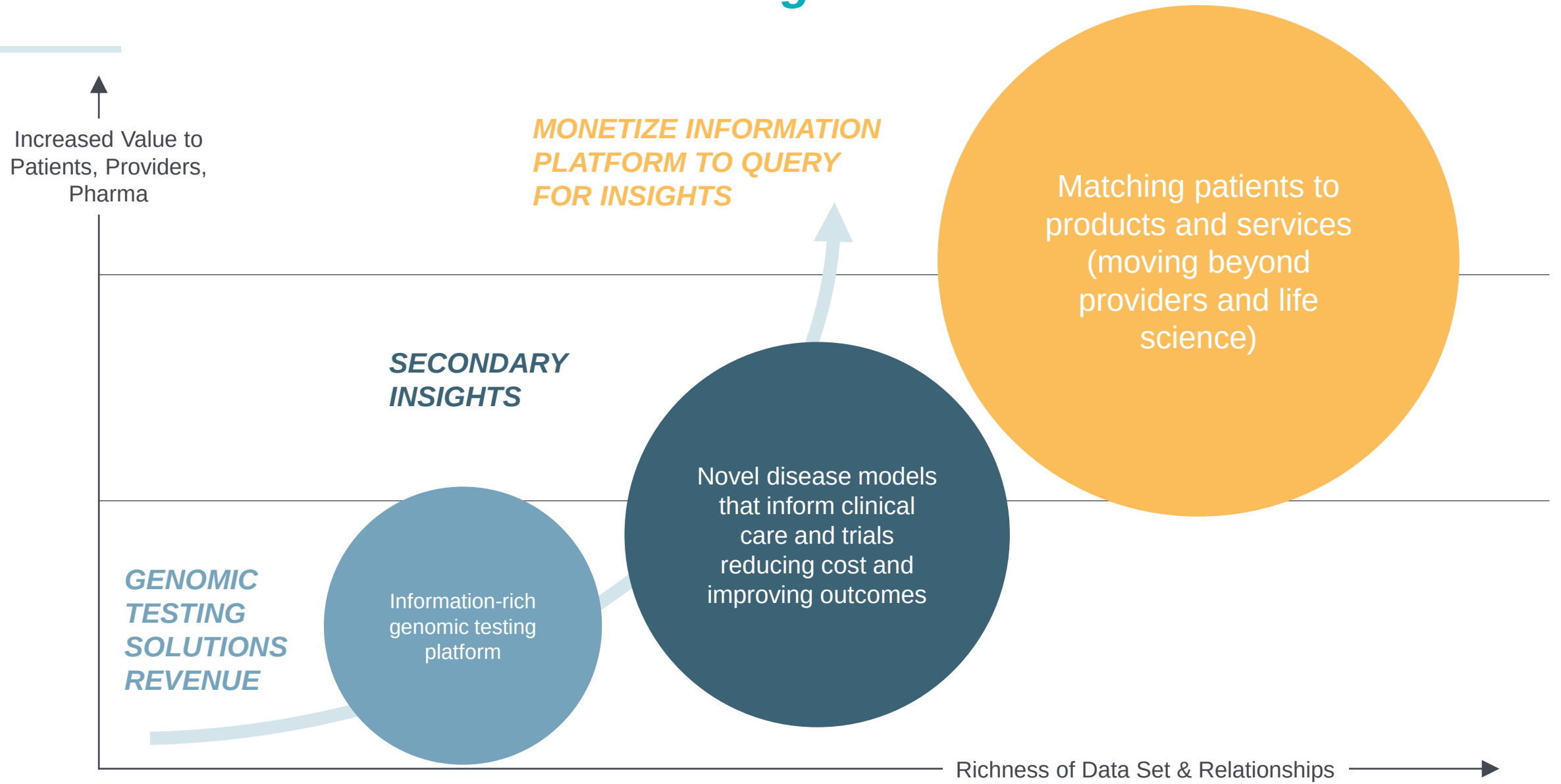
Evolution Towards a *Platform of Algorithms*



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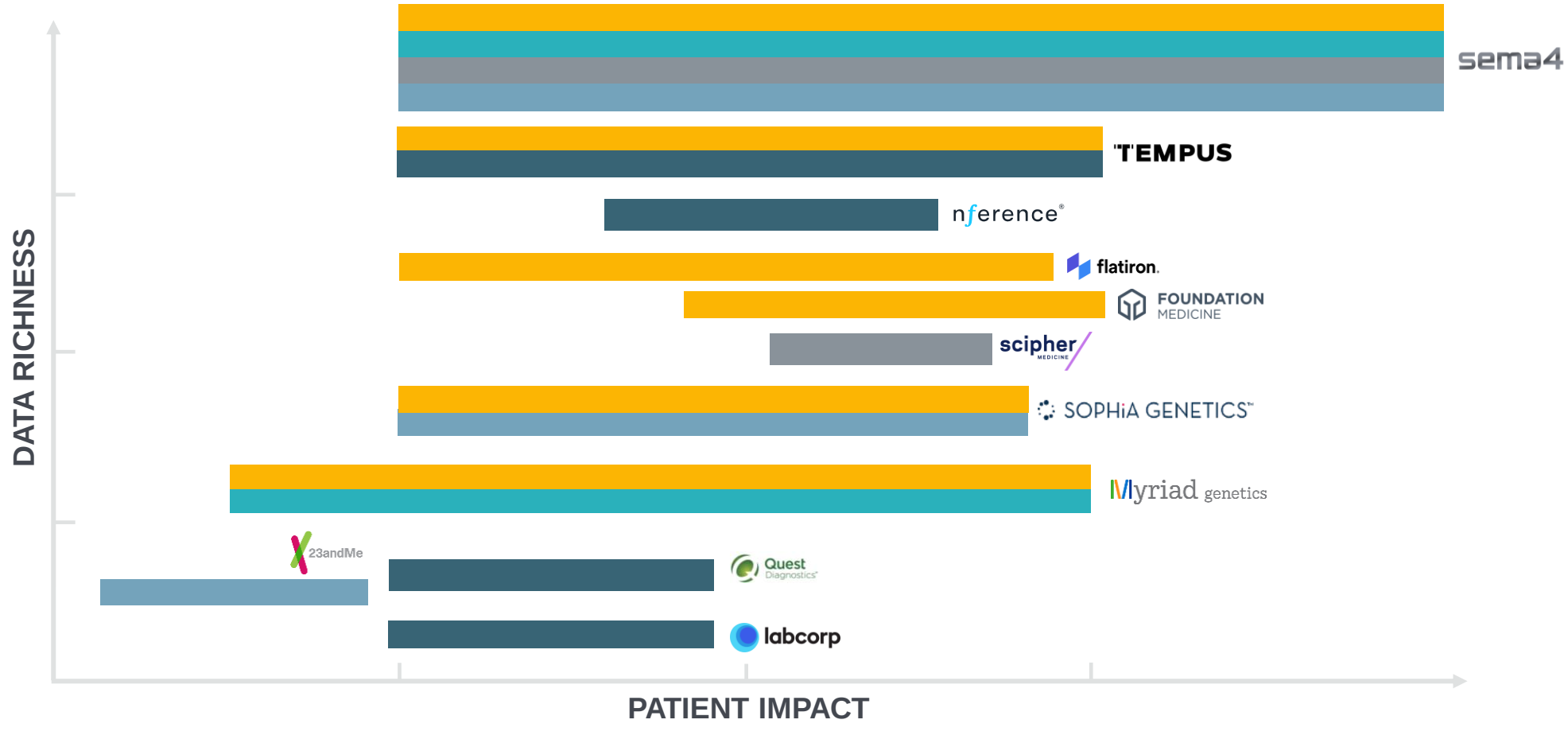
The Value of Data: Must be Longitudinal and Prescriptive

MULTI-DISEASE
Collected over time + Curated disease specific clinical notes

ENRICHED LONGITUDINAL
Collected over time + Curated clinical notes

LONGITUDINAL
Collected over time

EPISODIC
Point-in-time



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Enabling Biopharma Partners and Customers

SEMA4 OFFERING

Clinical trial matching

SaaS-based licensing

Deep Partnerships leveraging data science

LEAD IDENTIFICATION

Drive increased probability of success and terminate bad molecules sooner

EARLY CLINICAL

Reduce trial duration, minimize dose finding / escalation, better patient selectivity

PROTOCOL OPTIMIZATION

Maximize trial opportunity, reduce time to market, and optimize market access

REAL WORLD DATA

Characterize patient journeys and diagnostic odysseys

Research	Preclinical	Phase I	Phase II	Phase III	Phase IV / RWE

DISCOVERY — DEVELOPMENT — COMMERCIALIZATION →

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Creating the Leading Genomic Data Platform, from Generation to Insights

1. Serving Patients Throughout Life, Deeply Integrated Within Health Systems
2. Driving Growth and Scale in Genomic Diagnostics
3. Complementary Revenue Streams and Margin Optimization Opportunity
4. Strengthening Market-Leading Data & Analytics Capabilities
5. Joining Forces as a Team With Unparalleled Expertise in Shaping the Market

Thank you

Appendix

Historical COVID Revenue Mix

% of Total Revenue[1]

	1Q20	2Q20	3Q20	FY20	1Q21	2Q21	3Q21	4Q21	1Q22
Diagnostic Test	99%	93%	84%	79%	73%	87%	86%	79%	91%
COVID	0%	6%	14%	18%	25%	8%	10%	18%	6%
Other	1%	1%	2%	2%	2%	4%	4%	3%	3%

[1] Certain periods do not add to 100% due to rounding

Non-GAAP Gross Margin Reconciliation

USD in thousands

	Three months ended March 31,	
	2022	2021
	(in thousands)	
Revenue	$ 53,941	$ 64,201
Cost of services	48,316	68,524
Gross Profit (Loss)	**5,625**	**(4,323)**
Gross Margin	**10 %**	**(7)%**
Add:		
Stock-based compensation expense	1,381	18,475
Restructuring costs [(1)]	106	—
Adjusted Gross Profit	**$ 7,112**	**$ 14,152**
Adjusted Gross Margin	**13 %**	**22 %**

(1) Represents costs incurred for restructuring activities, which include severance packages offered to impacted employees and third party consulting costs incurred in the first quarter of 2022.

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Non-GAAP EBITDA Reconciliation

USD in thousands

	Three months ended March 31,	
	2022	2021
	(in thousands)	
Net loss	$ (76,896)	$ (191,775)
Interest expense, net [1]	781	702
Depreciation and amortization	5,803	4,902
Stock-based compensation expense	17,559	164,962
Transaction and acquisition costs [2]	4,337	1,954
Restructuring costs [3]	2,729	—
Change in fair market value of warrant and earn-out contingent liabilities [4]	(13,190)	—
Other income [5]	—	(5,584)
Adjusted EBITDA	$ (58,877)	$ (24,839)

(1) Represents the total of interest expense related to our finance leases and interest-bearing loans and interest income on money market funds. This also includes the unused line fee and amortization of deferred transaction costs related to the loan and security agreement entered into with Silicon Valley Bank.

(2) Represents professional service costs incurred in connection with pursuing the business combination transaction that did not meet the requirement for capitalization in 2021. In the first quarter of 2022, this represents professional service costs incurred in connection with the Acquisition transaction, which include due diligence and legal costs.

(3) Represents costs incurred for restructuring activities, which include severance packages offered to impacted employees and third party consulting costs incurred in the first quarter of 2022.

(4) Represents the change in fair market value of the liabilities associated with our public warrants and private placement warrants and the earn-out shares issuable under the terms of the merger agreement related to our business combination with CMLS.

(5) For the three months ended March 31, 2021, primarily consists of funding received under the CARES Act Provider Relief Fund.

SMFR

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