Building the Digital Infrastructure to Enable Genetic Medicine:
Recommendations from a Multi-Stakeholder Summit

Running Title: Digital Infrastructure to Enable Genetic Medicine

Carlos D. Bustamante¹, Mara Aspinall², Gillian Hooker³, Suzanne Belinson⁴, Robert Nussbaum⁵, Dee Anna Smith⁶, Nick Tazik³, Kari Asuncion⁷, Sarah Bland⁸, Robert Burton⁹, George Cardoza¹⁰, Meg Doerr¹¹, Julie Eggington⁹, Gerald Feldman^{12, 13}, Mary Freivogel^{14, 15}, Erynn Gordon¹⁶, Sean Hofherr¹⁷, Katie Johansen Taber¹⁸, MaryAnn Jones¹⁹, Steven Keiles²⁰, Hannah Mamuszka²¹, Kurt Matthes²², Sean McEvoy²³, Bruce Quinn²⁴, Alex Ryder²⁵, Nikoletta Sidiropoulos²⁶, Kari Timothy¹⁸, Sue Tyler²⁷, Bas van der Baan²⁸, Mark Harris^{3*}

Affiliations:

¹Stanford University, ²Health Catalysts, ³Concert Genetics, ⁴Blue Cross Blue Shield Association, ⁵Invitae, ⁶Sarah Cannon, ⁷Mayo Medical Laboratories, ⁸Vanderbilt University, ⁹Center for Genomic Interpretation, ¹⁰NeoGenomics, ¹¹SAGE Bionetworks, ¹²Wayne State University, ¹³American College of Medical Genetics and Genomics ¹⁴Invision Sally Jobe ¹⁵National Society of Genetic Counselors, ¹⁶Genome Medical, ¹⁷GeneDx, ¹⁸Counsyl, ¹⁹CareFirst BlueCross BlueShield, ²⁰Quest Diagnostics, ²¹Alva10, ²²TELCOR, ²³Blueprint Genetics, ²⁴Bruce Quinn Associates LLC, ²⁵Le Bonheur Children's Hospital ²⁶The University of Vermont ²⁷Sue Tyler, LLC ²⁸Agendia

*Corresponding author: Mark Harris

Abstract

Practical barriers to implementation prevent the promises of genetic medicine from being realized across the U.S. healthcare system. Though new genetic technologies are introduced daily, the process of determining if, when, and how to use them can take decades. Last Fall, we convened a multi-stakeholder summit to address systemic barriers to delivering precision medicine at scale. In particular, we focused on digital infrastructure connecting genetic information in healthcare. Our group consists of stakeholders across the supply chain including health insurers, clinicians, hospital systems, researchers, policy makers, patient advocates, clinical laboratories, technology vendors, and drug developers. Through facilitated discussions, we identified barriers to ordering, performing, delivering, reimbursing, and regulating genetic tests and the information they provide, and generated proposals to overcome these barriers. In a series of in-depth panel discussions and solution-oriented breakout sessions, we explored five key focus areas: (1) Laboratory quality and patient safety; (2) clinical validity, utility, and value assessment at scale; (3) test identification for market tracking, evidence-gathering, billing, and payment; (4) provider education, communication, and support at the point-of-care; and (5) patient access and control of genetic data. Here, we present each focus area with potential solutions and suggested next steps. Consistent with the Summit, all five draw on multi-stakeholder solutions to pressing problems, ultimately enabling a more connected genetic health information network to serve patients more effectively. To maintain a near-to-mid-term time horizon, both the meeting and this paper focus on projects that can achieve meaningful advancement within a 3-year time frame.

Introduction

Genetics holds great promise for healthcare. However, two decades after the Human Genome Project began, the practical barriers to integrating genetics into the delivery of clinical care are undeniable. The infrastructure of the U.S. healthcare system wasn't designed for genetics. As a result, stakeholders across the system are challenged to deliver precision medicine in a reliable, efficient, and cost-effective way.

A growing understanding of the importance of both rare variants and multi-gene effects in the disease process underscores the need for genome-scale sequencing, which we define as including multi-gene panels, exome, and clinical whole-genome testing. The vast amount of data created makes this a data-intensive digital process in a way many areas of medicine are not. As a result, many barriers stem from issues related to the data and infrastructure that span across health research, healthcare delivery, and healthcare payment. Addressing these issues is a fundamental prerequisite to the effective delivery of genomic medicine at scale, and doing so was the goal of the Genetic Health Information Network Summit.

Held in Nashville, Tennessee, from September 26-27, 2017, the Genetic Health Information Network Summit assembled leaders at the intersection of genetics, technology, and healthcare for a solution-oriented discussion about the data and digital infrastructure needed to deliver precision medicine at scale. This summit was a cross-stakeholder event by design, and event participants represented the broader healthcare system, including health insurers, clinicians, hospital system leaders, researchers, policy makers, patients & patient advocates, clinical laboratory leaders, technology vendors, and pharmaceutical companies. A list of participants, speakers, and Organizing Committee members appears in the Supplementary Information.

Although the nature of the event wasn't prescriptive (participants were free to raise the issues they felt most important), the following goals were outlined in advance of the meeting:

1. Improving the capture of clinical effectiveness and economic value data for genetics
2. Simplifying the test ordering and resulting workflow for clinicians, hospitals, and labs
3. Streamlining the genetic test billing, adjudication, and payment process
4. Reducing the frequency of misordered tests and surprise bills for patients
5. Improving patient access to evidence-based genetic tests and precision therapies
6. Enabling new data sharing and real-world evidence curation to accelerate the development and evaluation of new clinical interventions

Our panel topics included:

- ***The Value Equation in Genetics, Molecular Diagnostics:*** *If Value = Quality/Cost (or if, for that matter, value is defined some other way), how do we determine value for genetics, molecular diagnostics?*
- ***The Infrastructure to Enable Precision Medicine:*** *The integration of precision medicine into the healthcare system is, in many ways, a data problem. How can we establish an effective infrastructure to solve this and related problems?*
- ***A Shared Vision for a Connected Network:*** *What does a successful future look like, and what are our next steps?*

The 2-day event culminated in an extended working session for which participants gathered in small groups and developed proposed solutions to address the practical barriers identified in the earlier sessions. These proposals, which were reported to the group at large, serve as the foundation for the recommendations that appear in this paper. The views shared at the Summit, and those expressed in this paper, reflect the views of individuals and not necessarily their affiliate organizations.

Themes & Solutions

Participants identified two primary, interrelated gaps in implementation (Figure 1): first, the healthcare system lacks the data and infrastructure to support genetic testing across clinical and administrative systems; second, current systems do not adequately support practicing clinicians in the use of genetics, resulting in problems with quality, access, and value. Finally, at the center of these two overlapping areas are patients, who increasingly desire access to their genetic information and control over who else accesses it.

Five central themes of future action from the Summit are distilled below. Each identifies an addressable barrier to delivering precision medicine at scale and outlines the proposed solutions that emerged from the meeting. These are drawn from a workshop in which all meeting participants broke into small groups and outlined specific proposals to address a barrier of their choice.

In order to foster sustained progress, the solutions are focused on a 3-year time horizon, and the suggested next steps designed to enable action within a 6-month period.

#1: Stakeholder transparency regarding laboratory quality

Description: Labs vary in the tests they offer and effectiveness of their processes and the quality of their variant classifications, clinical interpretations, and reports. All of these are crucial factors in lab quality and patient safety, but current standards make it difficult for providers and health plans to compare metrics across the market. That is, current regulatory requirements and certifications are critical for maintaining a base standard, but do not provide detail necessary to facilitate comparison. As a result, clinicians, health plans, and patients have limited access to information they need to make differential decisions regarding laboratory selection, test ordering, insurance network contracting, and coverage.

Opportunity: Within a 3-year horizon, an opportunity to address these issues lies in the design and implementation of language and frameworks to compare genetic testing laboratories, consistent data presentation and measurement, and the availability of these measurements in an accessible way to the stakeholders who need them to make informed decisions.

Example Solution(s):

All proposed solutions acknowledged the need for clear communication of quality metrics to compare laboratory and test-specific performance, identifying laboratories that bundle value-additive services into their testing, as well as laboratories posing risks to patient safety.

One solution, in particular, proposed that leaders start by focusing on very detailed standards for comparing processes of genetic testing interpretation, aimed at reducing false positives and negatives in variant calls, and increasing transparency regarding limitations of interpretation. Once these standards are set, blinded (*in silico*, potentially) samples would be sent to participating laboratories on a recurring (e.g., monthly) basis to assess variant calling pipelines, and that data would be aggregated in a central repository and made available to labs, health plans, and others. Subsequently, standards to support comparison of documentation and reporting could be developed and used across stakeholders. The funding for this proposed effort would be established in agreement with the underlying economic incentives, drawing funds from a diverse set of stakeholders to balance incentives, for example from (1) health plans (or consortiums thereof) who benefit from clear data in making coverage determinations and/or laboratory network selection, (2) laboratories who want to be certified by this process to improve or maintain market access, (3) users of the database, regardless of who they are.

Next Steps:

We propose that a third-party organization convene a meeting or series of meetings, similar in approach to the Summit, to gather input from key leaders from diverse stakeholders, including laboratories, health insurers, researchers, and policymakers to define a clear and relevant framework against which to measure genetic testing laboratories and their tests. Standards should specifically focus on the data that clinicians and health plans need in order to select between laboratories for genetic test ordering and network contracting decisions.

#2: Clinical validity, utility, and value assessment at scale

Description: Inefficiencies in the collection and analysis of clinical validity, utility, and value data in genetic testing slow the clinical introduction of new tests. The variety of tests and the array of clinical scenarios to which they might apply are broad, making traditional research methods, such as prospective clinical research trials, impractical. However, without the needed evidence, clinical and economic value are nearly impossible to calculate. Without this information, health insurers struggle to determine which tests to cover (and under what circumstances), laboratories lack key information to guide the development of new tests, and clinicians are faced with selecting focused tests with proven utility though a strong likelihood of being incomplete vs. broader tests with suspected utility but limited data. The net impact includes market confusion, the potential for missed diagnoses in patients, and the subsequent missed diagnosis and opportunity to treat or prevent disease in relatives.

Opportunity: Within a 3-year horizon, the opportunities to address these issues include (1) integrating relevant data that already exists, such as data from clinical and payment systems, and (2) generating new data through innovative mechanisms to enable analyses that are currently impossible or impractical to undertake.

Example Solution(s):

One proposal outlined the creation of a shared data resource, a so-called “Swiss data pool,” that would aggregate data from disparate sources, such as clinical data from clinical information systems, economic data from health insurer payment systems, and/or test result data from laboratories. Once assembled, this platform could be made accessible to a community of problem solvers who would complete analyses in exchange for a bounty of compensation. The specific proposal suggested a non-profit owner for the data resource and a shared funding pool from both private and public sources.

Another related proposal suggested the establishment of a fund and a granting mechanism that would allocate resources exclusively to studies designed to evaluate clinical utility of genetic diagnostics. In order to accelerate the real-world significance of the research funded by this source, health insurers and policymakers would establish the granting criteria such that the output of the studies would include all necessary information to prompt coverage and/or regulatory decisions. Further still, it would be possible to confirm up-front buy-in from these stakeholders on an individual project basis to automatically trigger key decisions pending the results of the study.

Another even larger-scale proposal focused on a model to accelerate the accumulation of whole exome/genome sequences and leverage the value of that data for both research and market value. In this proposal, a health insurer or consortium of insurers would establish agreements with a select group of laboratories to perform an exome/genome sequence as a complement to every approved single-gene or panel test performed for a member of that health plan. The data from these exome/genome sequences would be stored in a central database, ultimately controlled by the patient, and accessible to various stakeholders (laboratory, health plan, etc.), under very specific circumstances. In the case of laboratories, these data could be queried for

the purposes of future testing rather than de novo sequencing. In the case of insurance, plan members could approve, or opt out of, health plan access to these data for the purpose of health- and marketing-related communications to members.

Next Steps:

A common denominator of all proposals in this category was the intent to generate data that inform and accelerate health plan coverage decisions. Therefore, we propose that a group with expertise in evidence-review and medical policy development, affiliated with a health plan or consortium of health plans, chair a meeting series involving a cross-section of stakeholders from the genetic health information network to evaluate proposed solutions, most specifically, according to the criteria that will generate the largest and most valuable data to inform coverage decisions.

#3: Test identification for market tracking, evidence-gathering, billing, and payment

Description: The rapid evolution of genetic testing products coming to market makes it impossible for most healthcare organizations to track, much less dispassionately evaluate. This confounds many important processes, from the ordering of tests, to the gathering of clinical utility evidence about these tests, to their billing and reimbursement. As a result, clinicians and health plans spend more time communicating with one another than implementing new tests.

Opportunity: Within a 3-year horizon, we recommend establishing a market-wide process to identify, catalog, and track genetic testing units – similar to product bar codes or manufacturing part numbers. Doing so would enable stakeholders to link evidence, clinical data, regulatory factors, and insurance coverage decisions directly to the relevant genetic test(s).

Example Solution(s):

Summit participants proposed the creation of an identification system for genetic tests that is comparable to part numbers in manufacturing or product codes in inventory management systems. This identification system would identify a genetic testing unit (i.e., specific gene or genes assayed via analytic methodology offered by a laboratory at a given point in time) as the fundamental unit of measurement and assign a unit number to that test. From there, the system could be directly implemented where applicable, such as into clinical information systems, and crosswalk tables could be established to link this system to other established coding systems such as billing and diagnosis codes. Initial setup would require combining a market-wide database of available genetic tests with the publishers (and primary users) of key coding systems in healthcare, particularly billing codes. Operationalizing such a system would require coordination with potential users of the new identification system, including laboratories, technology companies, and researchers. Even when most sequencing moves to whole-genome for economies of scale reasons, there will still be a great need to evaluate and catalog interpretation strategies, so we believe this is a long-term structural need of the U.S. (and global) health supply chain.

Next Steps:

Given the requirements, we propose an initial meeting or meeting series including groups focused on data standards and coding in healthcare and information technology partners to bring the test database and market tracking capabilities to bear. Other participants should include health plans and organizations who administer on behalf of health plans, laboratories, and others, such as researchers working on related topics in the field of genetics and genetic testing.

#4: Provider education, communication, and support at the point-of-care

Description: Appropriate test ordering is difficult for clinical and administrative reasons.

Clinicians trained before the human genome was sequenced may lack professional education in the use of genetic testing in clinical practice. Meanwhile, administration and economics of genetic testing vary greatly from health plan to health plan, and for that matter, from lab to lab. Clinicians ordering genetic tests need a host of practical information – coverage status, coverage criteria, prior authorization requirements, price, etc. – in order to make high-value ordering choices. Finally, once the order is placed and the test is complete, support is often needed during the reporting, results interpretation, clinical decision-making, and patient communication phases. Underutilization of well-established recommended tests is an increasingly recognized problem and patients' reports of inadequate support abound.

Opportunity: This is a complex, layered problem that spans across many dimensions, including the phases of the diagnostic process, the varying levels of clinician comfort with genetics, and the vast array of clinical scenarios in which genetic tests may be clinically indicated. Within a 3-year horizon, an opportunity exists to support and educate clinicians within the existing clinical workflow with the processes of determining when genetic testing is appropriate and selecting the best test and laboratory based on clinical appropriateness, quality comparisons, coverage status, and other factors.

Example Solution(s):

One proposal suggested an information system to deliver case-specific education and support to clinicians as they are (or should be) considering whether/how genetic information could aid in the diagnostic or treatment process. The mechanism for delivery would be integration with clinical information systems, thereby offering relevant information to clinicians specific to the patient they are treating, the clinical scenario at hand, and perhaps even cost and insurance

coverage factors. Doing this would enable case-based learning on a just-in-time basis. This approach may serve as an alternative (or complement) to long-form continuing medical education courses and contrast with data-dumping that often occurs for clinicians in attempts to support decision-making. Although this implementation focuses on the test ordering process, future development could expand into report interpretation, treatment decision-making, and patient communication. In all of these cases, the intent would be to build a system that hooks into updatable information that can adapt as science, test availability, and insurance coverage evolve.

A second, related proposal outlined a solution to simplify communication and coordination between clinicians and health plans at the point of order. Specifically, a technology platform could integrate the tests on the market with insurance coverage and laboratory network information such that the workflow to order a genetic test would also serve to satisfy requirements such as prior authorization and medical necessity certification. Such a platform would ideally issue coverage determinations in real time to reduce time demands on the clinician and administrative re-work on the back end. It could stand alone at first, later integrating with clinical information systems once the data exchanges and workflow were operational and well-understood.

Next Steps:

This is a multi-dimensional problem, and thus, more likely to be solved in phases than all at once. We propose a model that uses the test order itself as the anchor point and begins by leveraging health plan medical policies as a proxy for both order appropriateness and likelihood of coverage. Given this focus, we propose a meeting or series of meetings involving senior health plan executive(s), technology developers, and clinical/research leaders or associations, to discuss possible technical and operational approaches designing and implementing such a

solution. Participants would include clinicians who order genetic tests, healthcare provider leaders who support the genetic test prior authorization and billing processes, and laboratories in the space.

#5: Patient access and control of genetic data

Description: Genetic information is increasingly valuable to patients. It can already provide a life-changing diagnosis in the case of many diseases, and the number of health conditions it can inform and help address will almost certainly continue to expand as the science of genetics and health advances. Genetic information is also becoming more in-demand as direct-to-consumer testing, news coverage, and high-profile cases raise consumer awareness. As the end-user of the healthcare system, patients will increasingly want and need access to their genetic information to inform health decision-making, making the issue of access a hot topic. However, growing access also introduces risks. Chief among these is the risk of data breach. Genetic data is personal and highly sensitive, meaning patients both deserve and will likely demand control of their data and who can access it.

Opportunity: The opportunity at hand today is to expand access to genetic data in responsible ways while maintaining security of that data and ceding control to patient-owners. This aspiration carries a host of considerations, including cost, education, technological literacy, security, and mechanisms to grant control.

Example Solution(s):

As discussed previously, one large-scale proposal suggested a model to accelerate the accumulation of whole exome/genome sequences via health plan funding. In this proposal, an exome/genome sequence would be performed as a complement to every approved single gene or panel test performed for a member of that health plan. This proposal supposed that the

patient would remain the ultimate owner of that data, and that other healthcare entities could access it under predetermined circumstances.

The data from these exome/genome sequences would be stored in a central database, ultimately controlled by the patient, and accessible to various stakeholders (laboratory, health plan, etc.), under very specific circumstances. In the case of laboratories, these data could be queried for the purposes of future testing rather than de novo sequencing. In the case of health plans, these data could be accessed for the purposes of health- and marketing-related communications to members as approved by the member him/herself via an opt-out method. Although the financial and technical challenges of this proposal are considerable, the benefit to science, the healthcare system, and ultimately to human health, are potentially vast.

Next Steps:

Clearly, critical issues include access and security, or stated differently, models to fund the generation of the data, secure it, and manage access. Therefore, we recommend next steps focus on (1) a survey of relevant projects enabling these capabilities in the market today, and (2) the outline of a data security model to manage these requirements should such a project be initiated. Satisfying these precursors could, indeed, clear the path for market players to move forward with larger-scale access and funding initiatives. As a starting point, we propose a meeting or series of meetings be organized by laboratories and health plans and include information security experts, clinicians, provider organizations, patient advocates, and technology developers.

Conclusion

Meaningful, multi-stakeholder engagement and discussion is critical to building a more efficient and effective Genetic Health Information Network. The ideas outlined in this piece map a short-term path toward a more connected network, which would allow information to flow more effectively between stakeholders, thereby achieving the overarching goal of delivering genetic medicine to patients in a way that truly benefits their health. At the center of the decision making process on who controls access to a person's genetic data has to be the individual. Healthcare providers, insurers, and drug/device innovators need to make the value proposition clear to patients, their families, and their care teams as to why sharing genetic information is critical to enabling precision medicine and health at scale in this country.

Acknowledgements

We would like to thank Katie Kanagawa for her review and feedback of the manuscript in preparation for submission.

Competing Interests

All authors' employer affiliations are listed. The meeting was organized by Concert Genetics, a health IT company that sells software and analytic services to laboratories, hospitals and health plans.

Figure 1: Drawing from discussions and proposals at the meeting, this map illustrates issues and opportunities identified by summit stakeholders.