

Navigating a new frontier for genomics

Introduction

“There’s lots of hype and excitement about these technologies, but I think we really need to ensure that we have the economic evidence that they’re actually a good value for the money for healthcare systems and payers.”

— Healthcare expert

“We believe that it is [the diagnostics] ecosystem and collaboration within the ecosystem that will make a genomics revolution feasible from a clinical perspective.”

— Industry participant

Genomics is poised to revolutionize the future of healthcare.¹ Genomic tests can enable the delivery of targeted treatments, inform individuals about personal health risks, proactively impact consumer behavior, and allow providers to intercept disease before it develops. Genomics offers many possibilities, but it has its skeptics. Some experts and stakeholders within the healthcare system question whether much of genomics’ purported potential is simply hype, emphasizing that the technology is too new and costly and our understanding of its clinical application is nascent.

Despite these hesitations, industry observers predict continued growth in the use of genomic sequencing. According to one estimate, individuals sequenced in clinical settings alone could reach 60 million by 2025.² Additionally, as the cost of sequencing continues to fall,³ more healthy individuals will be able to purchase tests through direct-to-consumer (DTC) channels. Lowered costs will not only increase the total number of individuals who have undergone some type of sequencing, but also expand the scale of the tests themselves and the data they capture. Today, sequencing a genome can cost as little as \$1,000.⁴ According to one industry player, new sequencing technologies may push this closer to \$100 in three to five years.

On December 14–15, 2017 in Washington, DC, Tapestry Networks convened the inaugural meeting of the Diagnostics Innovation Network (DxIN) to address the growth of genomics and genetic tests and their applications for patients and consumers. The DxIN’s focus includes screening tests that may be used by healthy populations, carrier screening or other predictive tests for at-risk individuals, diagnostic tests, and tests that inform targeted therapy selection.⁵

The DxIN, comprising health and life insurers, genomics experts, industry players, and clinicians, aims to identify specific improvements that would enable genomics to meaningfully advance patient and consumer outcomes in the United States, while drawing from comparisons and lessons from other countries. The network also aims to share approaches that can be adapted or scaled to further the identified improvements, particularly for healthcare payers, life insurers, and reinsurers. For these players, genomics is an area of mutual interest as well as mutual concern. It is poised to change how insurers of all kinds assess risk, use and maintain data, and deliver products and services to their plan sponsors, members, and policyholders.

The DxIN launch meeting built on pre-meeting discussions with participants and focused on the following topics, which are described in detail in this *ViewPoints*:

- Strengthening the evidence base for genomics, including improving our collective understanding of the genome and the costs, risks, and benefits of clinical application
- Determining where to direct future investment in genomics
- Improving how genomic data is captured, communicated, and used
- Responding to the shifting regulatory environment for genomics, including regulation of tests themselves and protections for patients and consumers

Participants considered current gaps and challenges on these topics, focusing primarily on the future of genomics and approaches that could help resolve the complexity involved in putting genomics into practice on a large scale. *“DxIN participants are a village of stakeholders, and it will take a village”* to responsibly apply genomics in the clinic and consumer populations, one participant said.



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Strengthening the evidence base for genomics

For predictive, prognostic, and diagnostic tests that are used for at-risk patients in a clinical setting, many DxIN participants agreed that the current evidence base for the analytical validity, clinical validity, and clinical utility of genomic testing is deficient.⁶ The dearth of evidence is especially stark when one considers the tens of thousands of genomic tests on the market, which, according to one participant, has now reached 75,000. Participants discussed several challenges facing the genomics evidence base today and current efforts to resolve them.

Improving what we know about the genome

Understanding how genomics can be integrated into clinical practice begins with evidence that shows how specific variants cause or influence disease. One participant explained, *“You first need to understand the genome. Then you need to understand if the genomic information is effective in healthcare. You can’t have the second part without the first.”*

Projects such as the National Institutes of Health’s (NIH) ClinGen and ClinVar have advanced standardized processes for classifying the relationship between variants and disease and offer platforms for sharing information to encourage consensus across labs and researchers.⁷ DxIN participants involved in these efforts provided an update on their progress and the state of play for variant interpretation more broadly.

An ongoing challenge, they underscored, was many labs’ lack of willingness to share data. Data sharing accelerates the community’s ability to understand how specific variants influence disease across populations. However, as one participant noted, *“some labs say they’re going to share, want the publicity, and never share, and then some labs come out adamantly and say, ‘We don’t believe in sharing.’ Some of the largest labs in the country have shared very little data. So we ask, are you really sharing? Or are you doing just enough so you don’t get shamed?”*

Participants noted that payers could substantially impact labs’ reluctance to share data. One payer, noting that insurers *“have a lot of power with the labs,”* suggested an approach to encourage data sharing: *“We instituted a policy that we only use labs that share data—so when you come knocking on the door and you want to sell your test, if you don’t share your data, we don’t buy.”*

Labs’ willingness aside, progress on variant interpretation is also hampered by such practical barriers as lack of funding and human resources. Interpretation requires expert curation, in-depth comparison with phenotypic data, and collaboration across researchers. One expert explained, *“Variant interpretation still is an art—it’s not just a science.”* The NIH efforts rely primarily on volunteers, participants noted, and would benefit significantly from more robust financial resources to pay contributors for their time and to automate processes through which labs can share and compare evidence and data.

Understanding genomics' utility in clinical practice

Most healthcare payers seek robust, high-quality evidence of a test's clinical utility as a prerequisite for reimbursement. A payer said, *"One of the things I hear frequently from molecular diagnostic companies is that we do not have reimbursement. And one of the common replies to that is: Where is the clinical utility and economic utility?"* The quality and amount of evidence required remains a topic of significant debate, as do the standards by which different stakeholders evaluate the evidence.

DxIN participants engaged in a robust discussion on approaches payers are using to develop coverage criteria for some genomic tests, focusing on diagnostic tests used in cancer. They hailed the Center for Medicare and Medicaid Services' (CMS) November 2017 preliminary coverage determination for next-generation-sequencing assays for advanced cancers as a bold step forward. The evidence CMS considered included over 300 peer-reviewed articles and an internal technology assessment of the evidence.⁸

Although the determination will enable coverage for markers in Foundation Medicine's FoundationOne assay that are used as companion diagnostics, it will be manufacturer-agnostic in principle, provided that other test developers meet similar criteria. The CMS framework offers full coverage for tests that have proven their analytical and clinical validity through a Food and Drug Administration (FDA) approval process and that are being used to inform a clinical management decision in advanced cancer. The clinical utility of the test, according to the proposed framework, is inherent in the test's status as a companion diagnostic. For tests that fall outside this category but are cleared by the FDA and are being used as part of a clinical trial, study, or prospective registry, CMS has proposed a coverage-with-evidence-development (CED) pathway designed to encourage the development of evidence for clinical utility and enable more rapid access to diagnostics for patients with advanced cancers. As one participant described it, the CED pathway aims to *"try to look into the future"* of testing.

Participants were generally supportive of the overarching approach. However, they raised several questions about the path forward for tests that were subject to CED. Many recognized the benefits of rapid market access but underscored that CMS will need to be able to cease reimbursement if needed. Reversing a coverage decision, they emphasized, can be very hard to do.

More broadly, participants called for greater transparency and alignment across payers on evaluations of clinical utility. Some payers agreed that they could better elucidate the criteria they use to assess the evidence that developers provide and that *"allowing for a predictable path"* was important. One payer said, *"We want to be clear about where the goal line is."*

Assuring quality and implications for reimbursement

Building from the discussion on clinical utility, participants addressed gaps in quality assurance in genomics, both with respect to the quality of the tests themselves and the data that labs

generate. Experts underscored that the variability in quality across labs and individual tests can be considerable. However, they also said strong quality-assurance processes and a robust regulatory framework could help overcome many of the associated challenges.

In the United Kingdom, the 100,000 Genomes Project has made concerted efforts to ensure quality across laboratory workflow and its broader data-collection protocol. Even in a single-payer system like the United Kingdom's, data standardization and interoperability is a challenge. The 100,000 Genomes Project has worked with 13 selected genomic medicine centers—hubs that lead lab networks in specific geographic areas of the country to implement the project—to ensure that their data is entered in a harmonized fashion. *For further information, see text box below.*

In working across the diverse laboratories involved in the project's quality-control process, the 100,000 Genomes Project found that *"people measure quality in very different ways,"* according to a participant. This prompted the UK government to deliver frequent and rigorous quality-assessment schemes and benchmarking exercises at various levels throughout the system. Additionally, to harmonize variant classification, the UK health authorities have conducted trainings of lab leadership and developed a system through which all specialty genomic medicine centers can see and compare one another's data.

Genomics England and the 100,000 Genomes Project

The UK government is using genomics to help transform the country's medical system through its groundbreaking 100,000 Genomes Project.⁹ The project focuses not only on advancing research but also on understanding how genomics can be applied in clinical settings to enhance diagnoses, treatment, and patient outcomes.

The project is implemented by Genomics England, a private company wholly owned by the UK Department of Health. The project is sequencing 100,000 genomes from individuals in the United Kingdom with a focus on cancer, rare disorders, and infectious disease. One participant noted that the therapeutic areas were chosen in part because of their potential to demonstrate clear health gains not only for patients but also for the public healthcare system. Rare diseases, for example, are especially expensive and difficult to diagnose, manage, and treat.

Genomic data collected through Genomics England will be accessible to and reviewed by healthcare providers. Academics and scientists can also apply to access anonymized data for research purposes. In addition to sequencing data, the project collects information about an individual's general state of health and well-being, combining clinical data with whole-genome-sequencing (WGS).¹⁰

Genomics England and the 100,000 Genomes Project *contd.*

The project also aims to help build “an evidence base for the clinical utility and relevance of the WGS findings,”¹¹ including determining the patients for which WGS is most cost-effective to implement in the broader healthcare system. Project leadership has indicated that specific rare diseases and cancers are likely to be the target.¹² One stakeholder noted, *“While the cost of WGS is coming down, it’s not yet at the price point where it can be rolled out throughout the UK’s National Health Service. So we are asking, For which diseases should it be used first?”*

In terms of results to date, the project has sequenced 34,000 genomes of the 100,000 target, according to a participant. The most recent data from cancer patients enrolled in the program indicate that as many as 60% have “actionable genes,” meaning they could benefit from existing targeted therapies or clinical trials.¹³ The project has also absorbed several lessons from its implementation to date and recently announced that it would reduce and centralize laboratory operations.¹⁴ According to one project stakeholder, this would result in a *“hub and spoke”* model designed to drive high-throughput, high-quality sequencing, and an equitable level of service across the population.

In the United States, the foremost quality-assurance challenges participants described involved the quality of the tests themselves, particularly tests used in diagnostics. In vitro diagnostics (IVDs) require FDA approval, and labs developing their own molecular tests (laboratory-developed tests, or LDTs) have their processes certified under the CMS’ Clinical Laboratory Improvement Amendments (CLIA). Through CLIA, CMS oversees laboratory practices and operations and approves organizations’ “deeming authority,” whereby organizations such as the College of American Pathologists can offer accreditation and voluntary proficiency testing services to labs.¹⁵ This dual path to the market creates, in the eyes of some, significant variability in test quality, which is spurred by the fact that some payers do not differentiate in vitro diagnostics from LDTs in their coding and reimbursement practices.

A new regulatory framework that better differentiates LDTs from IVDs, including their intended uses and risks, would, according to some participants, promote a *“virtuous cycle”* across the diagnostics ecosystem. Referencing recent regulatory changes in Europe, which mandate that tests undergo an IVD approval process requiring clinical evidence and postmarket performance data,¹⁶ one participant said: *“I hope we get to the day [in the United States] where LDTs and IVDs actually complement and not duplicate each other. This is the direction in which the EU is headed with their new IVD regulations that will shortly take effect. They*

created a regulatory framework where tests that are the equivalent of LDTs cannot duplicate tests that go through an IVD process.”

A more stringent regulatory framework could also enable better reimbursement for IVDs, recognizing their costly and more rigorous development process. However, such changes would be contingent upon payers’ willingness to change current practice, as one participant explained: *“Payers have to be willing and able to recognize and reward high-quality evidence. The problem is that you can have someone that’s gone through the rigor of the FDA process, with the time and money that’s involved in doing that, but somebody else can say they have a CLIA-certified lab and say, ‘I have the same thing at a tenth the price.’ And when payers do not actually recognize the difference between those two, you’re setting yourself up for failure.”*

Determining where to direct future investment

The group debated which of genomics’ many applications, both clinical and consumer facing, were most ripe for future investment and the criteria they might use to make such a determination. They also considered how national-level initiatives, including the 100,000 Genomes Project and the United States’ All of Us Research Program, were making decisions about where to invest their resources and define their program priorities.

Criteria for prioritizing genomics investments

Participants proposed criteria for prioritizing where to direct future investment in genomics. Several suggested that unmet clinical need should be the topmost criterion, followed by the probability of the appearance of disease, influence on therapeutic decision-making, current demand and utilization, and, for some, return on investment for the private sector. They also discussed which of genomics’ many clinical applications should be priorities for further investment and research. Some recommended starting with non-invasive prenatal testing, since it is the most frequently ordered type of genomic testing in the United States, and others prioritized cancer and rare diseases.

Life insurers prioritized genomic applications differently from their health insurance counterparts. For them, an area like pharmacogenomics, about which several healthcare payers are skeptical because of a lack of data on patient outcomes, represents a potentially attractive area of investment from a business innovation perspective. Because life insurers are interested in applications that enable them to offer new services to and multiple touch points with their policyholders, they are considering providing pharmacogenomic testing as a benefit. As a predictive test offered to healthy policyholders, pharmacogenomics, as envisioned through this model, exemplifies a potential consumer-facing application of genomics, albeit one that could have clinical utility for policyholders in the future. Pharmacogenomics, in one life insurer’s view, is particularly attractive because *“the scope is clear, and the value is understandable for patients.”*

Investment priorities for national initiatives

Participants also considered how national initiatives are prioritizing specific genomic applications, data collection, and related issues. The 100,000 Genomes Project has prioritized using WGS to support patients with cancer and rare diseases. It is also devoting resources to understanding the economic impact of integrating WGS in clinical practice. As some players involved in the project emphasized, the cost of WGS varies and is a significant challenge. One participant explained, *“The \$1,000 genome has been hailed as a miracle, but that doesn’t include interpretation or reporting back results.”* Those additional services can double the cost of the test. Indeed, several participants underscored that current research on genomics fails to capture the full cost of sequencing, which is why further investment in understanding the economic impact of WGS within the total cost of care is sorely needed.

The All of Us Research Program, which will amass health information on 1 million people residing in the United States, will sequence individuals and collect their phenotypic information, medical records, and other details. It will not focus on specific disease areas, but rather aims to understand the health of individuals over decades and on a significant scale. The program formally launches in the spring of 2018 and is seen to be an adaptable study that could accommodate evolving research questions. In this spirit, DxIN participants were asked to consider what types of data they might use from such an effort and would want to see captured in the protocols.¹⁷ Their recommendations were wide ranging but included the following points:

- To promote enrollee retention over time, the program could take an enrollee-centered approach to data collection by asking program participants what they would like to learn over time, and prioritize those data points.
- Sound mortality data on study participants would be of strong interest to life insurers; currently, death certificates, electronic medical records, and other sources of information on cause of death can be inaccurate.
- In choosing its sequencing strategy, some said the program could consider a *“go big”* approach and opt to use WGS, but others believe whole-exome sequencing could suffice, given the high costs of WGS.¹⁸
- Epigenetics and other *“-omics”* data are as important to capture as genomic data.
- Behavioral data, mental health information, and quality of life data (e.g., through standardized measurement instruments such as EQ-5D) are all important for the program to capture.
- To manage the scope of the program, the NIH might initially focus on specific disease areas or, at minimum, specific framing questions to guide the project’s implementation over time; otherwise, given its current scale, the program may be *“looking for needles in the haystack.”*

Improving how genomic data is captured, communicated, and used

The operations of genomics—from test ordering to bioinformatics to sharing results and storing data—are complex and fraught with gaps, but, in the eyes of several participants, potentially solvable with investment in an appropriate workforce and technology infrastructure. Participants also addressed how emerging technologies can aid in analyzing and storing genomic information and integrating genomic data with other medical information to provide more meaningful diagnoses.

A genomics-capable workforce

Many stakeholders are concerned that there are not enough healthcare professionals with expertise or training in genomics. They wonder whether non-expert providers are currently handling genomic test ordering and returning results in an appropriate way. Looking to the future, they question whether efforts should focus on the expansion of expert cadres, such as genetic counselors, or whether ongoing training and education can help primary care clinicians make sound decisions about genomic testing and its impact on clinical management.

DxIN participants noted several ongoing potential solutions to expanding the number of experts and making them more accessible to patients. Genomics England, the parent company of the 100,000 Genomes Project, is developing a master of science degree in genomic medicine, as part of its goal of integrating genomics into the UK National Health Service. In the United States, a participant noted, some venture capitalists are investing in Genome Medical, a new Uber-like model for genetics expertise that allows genetic counselors to provide on-demand advisory services through video-conferencing platforms.¹⁹ Chatbots and artificial intelligence may also help provide on-demand counseling to patients or consumers.

Other participants shared examples of initiatives that trained primary care physicians to deliver genomic results to patients, such as Geisinger's MyCode community health initiative and the recent MedSeq study.²⁰ The success of such efforts suggested to some participants that fears about the lack of an appropriate workforce might be overblown. *"As with many things in genomics, potentially bad outcomes don't happen that much when genomics is put into practice. If you have the right support for physicians, they can do it,"* one participant said. Others, especially payers, challenged this assertion. One said, *"I'm a little concerned about doling this out to the primary care physicians. I think there is enough newness and uniqueness to a lot of this information that we want to be careful with who's guiding the decisions made. It can be very confusing, even in surprisingly common situations."*

Emerging technologies to enhance data collection, integration, and analysis

The state and cost of the sequencing technology itself will have considerable influence on the future direction of genomics. Soon, WGS will be significantly cheaper and offer greater depth than it does today. Participants noted that the cost of sequencing has been dropping at a rate that exceeds Moore's Law, and, as noted above, may be *"on a path to a \$100 genome."*²¹

While the cost of sequencing is only one factor among many in shaping a genomics-ready ecosystem, some believe that increasing affordability is likely to promote standardization in interpretation, analysis, and quality.

Affordable WGS will undoubtedly increase utilization and uptake, and, as a result, genomics will generate massive amounts of data that healthcare systems, providers, patients, and consumers will need to analyze and manage. Some observers hope that technologies such as machine learning will make this practical. Participants acknowledged that although there is considerable hype around the benefits of machine learning, for genomics in particular, it could be helpful in the very near term. Clinical application of genomic data, one participant explained, *“needs computational abilities”* for sorting, reinforcement learning, and analyzing genomic information alongside other medical data—all of which, if used effectively, could enable better diagnoses and adherence to clinical pathways. An industry participant said, *“This is really the key chance to move the technology that’s coming along.”*

Nonetheless, using machine learning to help integrate genomics into clinical practice will be immensely challenging. First and foremost, it currently lacks a business model. *“There are no payment structures to make it work, and as a result, we may lose good innovation,”* a participant said. Furthermore, the cost of machine learning, added to the expense of sequencing itself, may not reduce costs to healthcare systems—a much-desired outcome of genomics-guided clinical management.

One participant summarized the potential economic impact of machine-guided genomics: *“We see things getting cheaper and more expensive at the same time. Machine learning and genomics can make interpretation cheaper and optimize clinical pathways, which will help get the cost down, but the more you know about an individual and the more you can predict about an individual, the more you can treat—and the more you will treat.”*

Responding to the shifting regulatory environment for genomics

As with any emerging technology, the direction of regulation—and the extent to which it may empower or hinder the acceleration of genomics—is at the forefront of many stakeholders’ concerns. DxIN participants addressed two aspects of the regulatory environment for genomics: oversight of the tests themselves, especially those used in clinical settings, and how insurers use genomic information.

The balance between making tests accessible and mitigating risk

As an extension of the discussion on test quality, participants discussed shifting regulations around proof of analytical and clinical validity for genomic tests. A payer said, *“I think it is a balancing act of the potential value but also the potential risks. I think sometimes we focus more on the potential value and ignore some of the risks—so I think it’s important that we think about both sides.”*

For genomic tests used in clinical diagnostics, participants questioned whether randomized controlled trials, the gold standard of clinical evidence, make sense in this rapidly changing field. Many emphasized the value of real-world evidence and the potential utility of more flexible approval pathways, which would allow regulators to initially approve a test—enabling prompt market access to patients—but later reverse the decision if, over time, evidence indicates lack of efficacy, accuracy, or safety. Some payers support this approach. *“I see value in fast access, if tests can be peeled back,”* one said. Some participants proposed incentives that could help make such a system a reality, such as insurance policies that could reduce the risk to manufacturers if FDA clearance or approval is reversed.

Many noted that recent FDA decisions that embrace a more flexible, standards-based approach are already a step in the right direction. For example, the FDA recently piloted a new authorization pathway for a tumor profiling test, MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets), which relied on data that Memorial Sloan Kettering provided to a third-party-reviewer, New York State, as the basis for FDA clearance.²² Such pathways would allow developers and labs to demonstrate test quality and receive clearance without randomized controlled trials and the costs and time needed for FDA approval. *For more information, see box below.*

A new phase in regulation from the clinic to consumers

The FDA recently took several steps toward streamlining and clarifying regulation of clinical diagnostic tests, including those that use genomic sequencing. Among these, tests used to diagnose and treat cancer are top priority. First, the agency announced that it will streamline regulatory paths for NGS-based technologies for tumor profiling tests, acknowledging that “multiplexed tumor profiling tests assess many biomarkers that may have a range of clinical evidence associated with them that is constantly changing as new science emerges.”²³ It published a three-tier, flexible approach that defines how it will regulate companion diagnostics, which are used to identify patients that should or should not receive specific targeted therapies, and other tests for biomarkers with evidence or potential evidence of clinical significance.²⁴ Tier assignment depends on the specific claims a test developer makes.

For companion diagnostics specifically, the approach clarifies that developers will need to demonstrate analytical validity for each specific biomarker through a clinical study or by clinical concordance to a previously approved companion diagnostic.²⁵ FDA approved biomarkers included within the FoundationOne test noted above using the latter criterion.

A new phase in regulation from the clinic to consumers contd.

For other tests for biomarkers with evidence of clinical significance, the FDA has offered a new authorization pathway. For example, for MSK-IMPACT, a next-generation-sequencing (NGS) tumor profiling test, FDA evaluated data submitted by MSK to the New York State Department of Health.²⁶ Moving forward, similar LDTs could seek FDA clearance through the same approach or by using another accredited third-party-reviewer.²⁷ This pathway only authorizes tests to provide information on specific biomarkers and demonstrate clinical validity. It does not authorize them to recommend corresponding treatments, which is the purview of companion diagnostics, as noted above. For other mutations “with potential clinical significance,” tests should provide evidence of analytical validation and a clinical rationale for why the biomarker should be included in a panel.²⁸

Outside of clinical diagnostics, the FDA is also turning its attention to predictive screening tests offered through DTC channels, such as those marketed by 23andMe. The FDA recently enabled these types of tests to be marketed directly to consumers without prior review if test manufacturers undergo a pre-certification process.²⁹ However, it simultaneously acknowledged that these tests “are not without their own risks, especially if they provide consumers with incorrect or misleading information that may be used to make health choices without considering the advice of a medical professional.”³⁰

In addition to tests used in clinical contexts, some DxIN participants, including both life and health insurers, noted concerns about the growing proliferation of DTC tests. Currently, DTC tests offer only predictive information on an individual’s health risks, and, as per recent FDA guidance, can only do so for certain diseases.³¹ *For more information, see box above.* Some DxIN participants question the quality and regulation of the DTC space, the potential impact on medical decision-making for individuals and their providers, and appropriate utilization of results. Other experts, however, have a rosier view: *“I was surprised to hear that the health and life insurers present were very concerned about direct-to-consumer offerings. I think that they are democratizing genomics, educating people, and forcing the field forward in ways that our collective cultures would resist.”*

Appropriate use of genomic information

Many stakeholders are asking how insurers, who are universally in the business of managing risk, will deal with the incoming glut of genomic information—some of which they may not be able to access—about their insureds. Many insurers are looking to recent events in Canada, where legislators passed a sweeping new law to protect consumers and patients against

discrimination that, in effect, will limit insurers' ability to price premiums according to patients' genomic information.³² *For more information, see box below.*

The challenge of adverse selection: Canada case study

Canada's Genetic Non-Discrimination Act will prohibit companies, including insurance companies and excepting health providers and researchers, from requiring that individuals undergo or disclose the results of genomic testing.³³ Parliament's vote to pass the bill was considered a victory for privacy advocates. "Taking a test that could help save your life shouldn't have to be a calculated risk. Every Canadian deserves these important protections so that we can all live without fear of our genetic information one day being used against us," said Marie-Claude Landry, chief commissioner of the Canadian Human Rights Commission.³⁴

Critics claim that the law will undermine the ability of insurers to accurately predict risk, which is the "basis of insurance."³⁵ They say that insurers may be compelled to increase prices for all policyholders as a consequence.³⁶ The Canadian Life and Health Insurance Association (CLHIA) had a voluntary code that prohibited insurers from demanding genetic tests of policyholders but did permit insurers to require that, if testing was done, they could access results for policies above \$250,000 (a threshold that does not apply to 85% of Canadians); however, that voluntary code did not appease privacy advocates.³⁷ The CLHIA believes parts of the law are unconstitutional and may challenge it in court.³⁸ In the meantime, some practitioners believe that the new law is encouraging more patients to get tested.³⁹ The law's long-term impact on pricing and other aspects remains to be seen.

DxIN participants discussed how the regulatory environment in the United States and elsewhere could evolve to protect and balance the interests of both patients and the insurance industry. In the United States, the Genetic Information Nondiscrimination Act of 2008 protects people from genetic discrimination by health insurers and employers.⁴⁰ Life insurers, however, are not covered under the law. Some participants noted that when patients who were considering genomic sequencing were informed about these facts, their hesitations about sequencing became more acute. They feared that genomic information captured now could negatively impact life insurance policies they might obtain later.

Many DxIN participants appreciated, however, that understanding individual risks is the very essence of the insurance business model. One said, *"We think of discrimination as a negative, but discrimination divides people into the appropriate risk pool and has them pay for what pool they're in."* An industry representative emphasized that all too often *"people forget about*

the other pool—those policyholders that may face higher prices if insurers are not able to adequately understand and manage risk across their insureds.

Some noted that there are already solutions in play. In the United Kingdom, the insurance industry has voluntarily agreed not to consider predictive genetic information when offering policies, with the exception of Huntington’s disease, which is highly genetically predictable and typically leads to premature death, for policies above £500,000.⁴¹ Such an approach could work elsewhere, given that, as one expert noted, *“the number of genetic tests that make a big difference—such as Huntington’s—is small.”*

Many called for shared agreements and thoughtful discussions between the industry in the United States and other stakeholders. Better dialogue and collaboration could pave the way for considering a voluntary model like the United Kingdom’s and help avoid the scenario that played out in Canada, where, as one participant noted, *“lack of shared agreement led to bad legislation.”* That legislation, in the view of some participants, could undermine insurers’ ability to adequately predict risk and, as a result, push them to raise premiums for all policyholders.

Furthermore, DxIN participants described how some in the industry are seeking to use genomics proactively as part of a *“virtuous cycle”* of services offered to their policyholders under a *“life assurance”* approach. In this model, life insurers would work with policyholders to use genomic information to enable behavior change and individualize risk management strategies.

Conclusions and recommended areas of focus

As utilization of genomics expands, greater multistakeholder collaboration will help ensure meaningful, appropriate, and sustainable use of genomic information. DxIN participants identified several areas in which improvements could be made to support an enabling environment for genomics and which may benefit from a multistakeholder approach. These are as follows:

Understanding effective and appropriate use of genomics in the clinic

Harmonizing and clarifying payer standards for clinical utility

Participants want to better understand how payers view, assess, and use the existing evidence base for making reimbursement decisions and how these differ across payers. Currently, many labs are doing *“lots of promoting, not investing.”* Clarified views from payers would help labs build better evidence earlier in their product development processes. One participant said, *“We want to think more about clinical and economic utility premarket.”* Opportunities to obtain feedback from payers before tests are approved, cleared, or marketed would help developers with planning and budgeting for evidence generation.

Designing and implementing flexible reimbursement pathways

Participants are eager to better understand how US payers could meaningfully implement CED and/or other flexible pathways for reimbursement. Understanding practical, clear criteria and mechanisms for reversing a test's coverage—cited by many as a significant challenge to overcome—could be a place to start and may benefit from inputs from a variety of stakeholders.

Advancing new frameworks for clinical utility studies

Some participants proposed that one way to help prove clinical utility would be for stakeholders to identify diseases or health conditions with high unmet need that genomics might help solve. One participant noted that the current *“test-first approach to clinical utility is backwards.”* Stakeholders would have to further consider appropriate structures and resources for refining and implementing a needs-based framework.

Better assessment of the economic impact of sequencing

Some participants called for more studies and projects that better track patient outcomes and help researchers, payers, and others understand the costs and benefits of genomic sequencing, especially when compared with current standards of care. Participants also called for more partnerships between academia, payers, and industry on studies that look beyond individual sites to obtain a macro-level assessment of the economics of genomics. Sharing research and lessons from across the United States, the United Kingdom, and other countries can help accelerate collective learning on the above topics. One participant noted, *“People are really, really keen to get more evidence on the economics. But we need to collaborate more, not just grouped across the US, but collaborate across the pond.”*

Breaking down data siloes

While all participants agreed that better sharing, integration, and interoperability of data from labs, medical records, and other sources was sorely needed, several recognized the myriad challenges in solving this complex problem. One stakeholder said, *“I’m daunted by the number of large data streams that are out there. It seems relatively unlikely that there’s going to be a lot of communication across these data streams in the intermediate term.”* Others suggested stopgap approaches that could encourage data sharing in specific contexts to help advance genomics research. These include the following:

- **Academia–industry partnerships.** Many labs and industry players are reluctant to share proprietary data given its importance to their commercial business models. To overcome this challenge, one participant suggested that industry could lend its data to academics for the exclusive purposes of research and publication: *“Industry needs to work with other stakeholders, particularly academics, in terms of publishing. That could take care of the data-sharing issue because industry’s holding the data. They don’t have to give the data to*

other people, but if they'll work with other people and together they analyze and publish the results, it's the best of both worlds."

- **New incentives and investment to accelerate the progress of ClinGen and ClinVar.** Some participants believe that providing incentives to labs to share data with public databases like ClinGen and ClinVar could accelerate progress in understanding the genome. In doing so, labs could add significant value to the field of genomics more broadly. Health insurers could play a role by not reimbursing labs that do not share data. Furthermore, more investment could allow these programs to more rapidly curate information and automate data comparisons and analysis across labs.

Exploring genomics' application beyond the clinic

Laying the groundwork for a balanced approach to risk classification

Some believe that a focused effort addressing individuals' fears about discrimination by insurers, especially the life insurance industry, may be beneficial. Such an effort could deal directly with individuals who are considering genomic sequencing, especially through DTC channels. It could also explore voluntary industry models such as the one being implemented in the United Kingdom. One participant explained, *"My biggest concern is that I think there are a lot of people that could potentially benefit from the information that are scared of it because of insurance. Could we do some pilot projects with life insurance companies to see if we can figure out how to help the public understand that we have to work on this together?"*

Fostering learning between life and health insurers

Several participants valued having life and health insurers come together to jointly assess how the democratization of genomics will affect their industry. One life reinsurer said, *"I wanted to have a better understanding as an introduction to who the key players are and what the key issues are from the health perspective. I came away seeing a shift toward evidence- and outcome-based approaches. And that's the first step in terms of how we [as life and reinsurers] can contribute to and complement what others are doing."* Life and health insurers may benefit by considering the emergence of the DTC testing space together, given that it is a common concern for some of them.

Finally, participants considered how the DxIN, as a unique cross-section of stakeholders with a vested interest in genomics, could be a platform to help meet the above challenges and bring momentum to the proposed ideas. Some participants recommended that the DxIN consider a more international scope—bringing in perspectives from Asia, for example—and include more provider and patient perspectives. They acknowledged that forums such as the DxIN reflect strong good will across parties that do not engage with one another or, in some cases, may have competitive or directly opposing views. One participant noted, *"I'm most encouraged by the positive comments about the partnerships because I think partnerships, public-private, between different groups, will truly be the way forward and probably the only way forward."*



Moving forward, the DxIN aims to advance the shared interests across stakeholders represented at the December launch meeting and beyond. One participant said, *“We need to think about a prioritized list of next steps and areas to work on. I don’t just mean alone—I mean groups of us, where there’s shared interest. My mindset is: where do we take this?”* In this spirit, the DxIN looks forward to making progress and helping to realize the promise of genomics to deliver the right treatment to the right patient at the right time.

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About this document

About *ViewPoints*

This *ViewPoints* reflects the network's use of a modified version of the Chatham House Rule whereby participants' names and affiliations are a matter of public record, but comments are not attributed to individuals or corporations. Italicized quotations reflect comments made during or prior to the meeting by participants.

About Tapestry Networks

Tapestry Networks is a privately held professional services firm. Its mission is to advance society's ability to govern and lead across the borders of sector, geography, and constituency. To do this, Tapestry forms multi-stakeholder collaborations that embrace the public and private sector, as well as civil society. The participants in these initiatives are leaders drawn from key stakeholder organizations who realize the status quo is neither desirable nor sustainable, and are seeking a goal that transcends their own interests and benefits everyone. Tapestry has used this approach to address critical and complex challenges in corporate governance, financial services, and healthcare.

The views expressed in this document represent those of the Diagnostics Innovation Network, a group of leading stakeholders from the public and private sectors committed to addressing the growth of genomics and genetic tests and their applications for patients and consumers. This document is not intended to represent the particular policies or positions of the network's individual participants or their affiliated organizations. This material is prepared and copyrighted by Tapestry Networks with all rights reserved. It may be reproduced and redistributed, but only in its entirety, including all copyright and trademark legends. Tapestry Networks and the associated logo are trademarks of Tapestry Networks, Inc.

Endnotes

- ¹ Throughout this document, we use the term genomics as defined by Dana-Farber Cancer Institute. See [“Genetics vs. Genomics: What’s the difference?”](#) Dana-Farber Cancer Institute, accessed January 29, 2018.
- ² Ewan Birney, Jessica Vamathevan, and Peter Goodhand, [“Genomics in Healthcare: GA4GH Looks to 2022.”](#) abstract, *BioRxiv*, October 15, 2017.
- ³ [“The Cost of Sequencing a Human Genome.”](#) National Institutes of Health, updated July 6, 2016.
- ⁴ The real cost of WGS is debatable. A \$1,000-\$1,500 price tag is typically for raw sequencing data alone, not interpretation. Recently, genomics company Veritas announced it will offer WGS with interpretation for \$999; however, other sources note that for complex clinical questions, WGS and interpretation can cost \$15,000. See Antonio Regalado, [“For \\$999, Veritas Genetics Will Put Your Genome on a Smartphone App.”](#) *MIT Technology Review*, March 4, 2016 and Sharon Begley, [“Sequencing a genome for less than the cost of an X-ray? Not quite yet.”](#) *STAT*, January 11, 2017.
- ⁵ For details on types of genomic and genetic tests, see [“Frequently Asked Questions About Genetic Testing.”](#) National Human Genome Research Institute, accessed January 29, 2018.
- ⁶ For definitions of analytical validity, clinical validity, and clinical utility, see National Academies of Sciences, Engineering, and Medicine, [An Evidence Framework for Genetic Testing](#) (Washington, DC: The National Academies Press, 2017), 35–36. For an assessment of the current evidence base for the impact of genomic testing on health outcomes, see Phillips et al., [“Making Genomic Medicine Evidence-Based and Patient-Centered: A Structured Review and Landscape Analysis of Comparative Effectiveness Research.”](#) *Genetics in Medicine* 19 (2017), 1081–91.
- ⁷ Heidi Rehm, [“A New Era in the Interpretation of Human Genomic Variation,”](#) *Genetics in Medicine* 19 (2017), 1092–95. ClinGen is an effort that aims to standardize variant classification and serve as an authoritative resource on the clinical relevance of genes and variants.
- ⁸ [“Proposed Decision Memo for Next Generation Sequencing \(NGS\) for Medicare Beneficiaries with Advanced Cancer \(CAG-00450N\).”](#) Center for Medicare and Medicaid Services, accessed December 1, 2017.
- ⁹ See Mark Caulfield et al., [The 100,000 Genomes Project Protocol](#) (London: Genomics England, 2017).
- ¹⁰ [“Frequently Asked Questions about Data Access and Use.”](#) Genomics England, accessed October 30, 2017.
- ¹¹ Caulfield et al., 45.
- ¹² Julia Karow, [“As 100K Genomes Project Returns Patient Reports, NHS Prepares to Commission WGS for Diagnostics.”](#) *GenomeWeb*, November 6, 2017.
- ¹³ Sarah Neville, [“UK Medical Chief Vows to Spread ‘Genetics Dream.’”](#) *Financial Times*, July 3, 2017.
- ¹⁴ Neville, [“UK Medical Chief Vows to Spread ‘Genetics Dream.’”](#)
- ¹⁵ [“Accreditation Organizations/Exempt States.”](#) Centers for Medicare and Medicaid Services, accessed January 11, 2018.
- ¹⁶ Justin Petrone, [“Dx Companies, Facing New CE-IVD Regulations, Reassess Strategies, Pipelines, Portfolios.”](#) *GenomeWeb*, October 5, 2017.
- ¹⁷ The current protocol is available at National Institutes of Health, [All of Us Research Program—Protocol V1](#) (National Institutes of Health, 2017).
- ¹⁸ After the DxIN meeting, the All of Us Research Program’s Genomics Working Group considered various approaches to collecting genomic data on participants, including the comparative value of WGS versus whole-exome sequencing. They recommended that the program develop pilots to explore the feasibility of using WGS

given its expected price reductions, “research value, and potential for return of information.” [“All of Us Genomics Working Group Recommends Genotyping, WGS for Pilot Study,”](#) *GenomeWeb*, December 22, 2017.

¹⁹ [Genome Medical](#) (website), accessed January 9, 2018.

²⁰ For information on the MedSeq experience, see Vassy et al., [“The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial,”](#) *Annals of Internal Medicine* 167, no. 3 (June 2017).

²¹ For example, Illumina’s recently unveiled iSeq 100, which costs only \$19,900, may lower costs across the genomics industry by reducing investment required by labs for sequencing equipment. Monica Heger, [“Illumina Launches Semiconductor Sequencer, Partners with Thermo Fisher, Releases Prelim Earnings,”](#) *GenomeWeb*, January 9, 2018.

²² Turna Ray, [“Labs Mull New Regulatory Path for NGS Tumor Panels in Wake of FDA Decision on MSK-IMPACT,”](#) *GenomeWeb*, November 20, 2017.

²³ Food and Drug Administration, [“CDRH’S APPROACH TO TUMOR PROFILING NEXT GENERATION SEQUENCING TESTS,”](#) accessed January 17, 2018.

²⁴ [Ibid.](#)

²⁵ [Ibid.](#)

²⁶ Ray, [“Labs Mull New Regulatory Path for NGS Tumor Panels in Wake of FDA Decision on MSK-IMPACT.”](#)

²⁷ Food and Drug Administration, [“FDA unveils a streamlined path for the authorization of tumor profiling tests alongside its latest product action,”](#) news release, November 15, 2017.

²⁸ Food and Drug Administration, [“CDRH’S APPROACH TO TUMOR PROFILING NEXT GENERATION SEQUENCING TESTS.”](#)

²⁹ Food and Drug Administration, [“Statement from FDA Commissioner Scott Gottlieb, M.D., on implementation of agency’s streamlined development and review pathway for consumer tests that evaluate genetic health risks,”](#) news release, November 6, 2017.

³⁰ [Ibid.](#)

³¹ Jessica Boddy, [“FDA Approves Marketing Of Consumer Genetic Tests For Some Conditions,”](#) NPR, April 7, 2017.

³² See Office of the Privacy Commissioner of Canada, [“New Genetic Non-discrimination Law Will Promote Privacy and Human Rights in Canada,”](#) news release, May 5, 2017, and André Picard, [“Anti-Genetic-Discrimination Bill Is Little More Than Virtue Signaling,”](#) *Globe and Mail*, March 9, 2017.

³³ For the text of the act, see [Genetic Non-Discrimination Act](#), S.C. 2017, c. 3 (Can.).

³⁴ Office of the Privacy Commissioner of Canada, [“New Genetic Non-discrimination Law Will Promote Privacy and Human Rights in Canada.”](#)

³⁵ André Picard, [“Anti-Genetic-Discrimination Bill Is Little More Than Virtue Signaling,”](#) and Canadian Life and Health Insurance Association, [“Genetic Discrimination Law Urgently Needed, Medical Experts Say,”](#) news release, January 30, 2016.

³⁶ Mike Hoy, [“Why Insurers Are Wrong About Canada’s Genetic Non-discrimination Law,”](#) *Conversation*, September 12, 2017.

³⁷ Canadian Life and Health Insurance Association, [“Canada’s Life and Health Insurers Announce Commitment on Use of Genetic Testing Information,”](#) news release, January 11, 2017.

³⁸ Jordan Pearson, [“Canada’s New Genetic Discrimination Law Will Prevent a ‘Gattaca’ Future,”](#) *Motherboard*, March 9, 2017.

³⁹ Victoria Gibson, [“Genetic Testing Back on Radar for Parents,”](#) *Toronto Star*, August 9, 2017.

⁴⁰ A potential challenge to this act, the Preserving Employee Wellness Programs Act, introduced in the US House of Representatives in 2017, would make it more difficult for employees to prevent employers from accessing their medical data, including genetic testing results, and increase financial penalties for employees who opt out of workplace wellness programs. See Reed Abelson, [“How Healthy Are You? G.O.P. Bill Would Help Employers Find Out.”](#) *New York Times*, March 10, 2017.

⁴¹ [“Insurance and Genetic Conditions.”](#) Genetic Alliance UK, May 12, 2016.