

I-Study: Genomic Interpretation™ Report

Who Will Pay, What is Needed and How to Mobilize?

A Landmark Study in Genomic Interpretation to Identify How to **Break Through** to a Future of Across-the-Board Personalized Medicine

The I-Study is a healthcare industry calibration study on genomic interpretation with the goal of helping to accelerate the advancement of personalized medicine and related scientific discovery into day-to-day clinical healthcare practice. The study findings include:

Consistent and clinically useful interpretation of genomic data will require a major collaborative effort across healthcare-related sectors – consider that a “network effect” will be required to succeed.

Three major themes emerged in the roadmap for advancing genomics into healthcare: Settling the Question: “Who Will Pay?,” Maturing the Required Technologies, and Mobilizing the Ecosystem to Deliver Personalized Medicine.

A new disease framework, the Genomic Interpretation Continuum™, is proposed to help understand, plan, and fund the advance of genomics into healthcare.

I. Background

Work on mapping the human genome started more than 20 years ago and the first full sequence of the human genome was published more than 10 years ago in 2001 as a result of the Human Genome Project. There have been significant advances made during the past 10 years and we have quickly arrived at a point where the genomics industry is now moving from research into clinical practice, with the ability to witness major breakthroughs in disease diagnosis and treatment at an unparalleled pace. At the 2011 Personalized Medicine Conference at Harvard, 80 percent of attendees voted **genomic interpretation as the top challenge** in medical genomic sequencing. Realizing that interpretation will be a collaborative effort across healthcare, the I-Study set out to determine how well the healthcare ecosystem is aligned in its genomic plans and offer recommendations to improve the collaboration that will be necessary to move forward.

Specifically, the I-Study was undertaken to:

- Determine how well the healthcare ecosystem is calibrated in related plans and efforts
- Identify areas of alignment or misalignment
- Offer recommendations to improve collaboration and accelerate the advance of genomics into healthcare

The study included interviews with more than 55 industry leaders across 12 healthcare segments. The transcripts were reviewed by an expert panel representing all disciplines key to incorporating genomic interpretation into patient care. The panel produced a comprehensive set of findings (collaboration challenges) and recommendations (proposed solutions).

In the interviews, participants were asked five questions:

1. How and where is genomic interpretation important to your organization in the next three years?
2. What are your organization's top 3-5 initiatives to improve interpretation?
3. What 3-5 enabling advances are you anticipating from outside organizations in order to achieve your own interpretation-related goals?
4. What incentives models will encourage the collective sharing of interpretation findings?
5. How can the diagnostic industry best prove the value of interpretation to payers?

Participants were scientific, medical and business leaders across the following sectors: pharmaceuticals, contract research organizations (CROs), academic laboratories, commercial laboratories, diagnostic companies, decision support (software) suppliers, healthcare providers, sequencing providers, healthcare equipment makers, care management, healthcare IT, and payers.

Panel members and their discipline or area of expertise were:

Scientific:

Kevin Davies, Ph.D., editor Bio-IT World; author *The \$1000 Genome*

Medical:

Raju Kucherlapati, Ph.D., Harvard Medical School

IT and Content:

Richard Resnick, CEO, GenomeQuest

Business Model:

Dawn Van Dam, General Manager, Cambridge Healthtech Associates

Financial:

Brian Atwood, Managing Director, Co-Founder, Versant Ventures

Payer:

John Edwards, Director, Health Economic Studies, PricewaterhouseCoopers

II. Roadmap Themes

A. Settling the Question: Who Will Pay?

Without an answer to the questions of “who” and “how” we will pay for genomic interpretation, we will be stalled in our efforts to translate the major scientific advances to help patients. Here, a new disease framework emerged to help understand, plan, and fund the advance of genomics into healthcare.

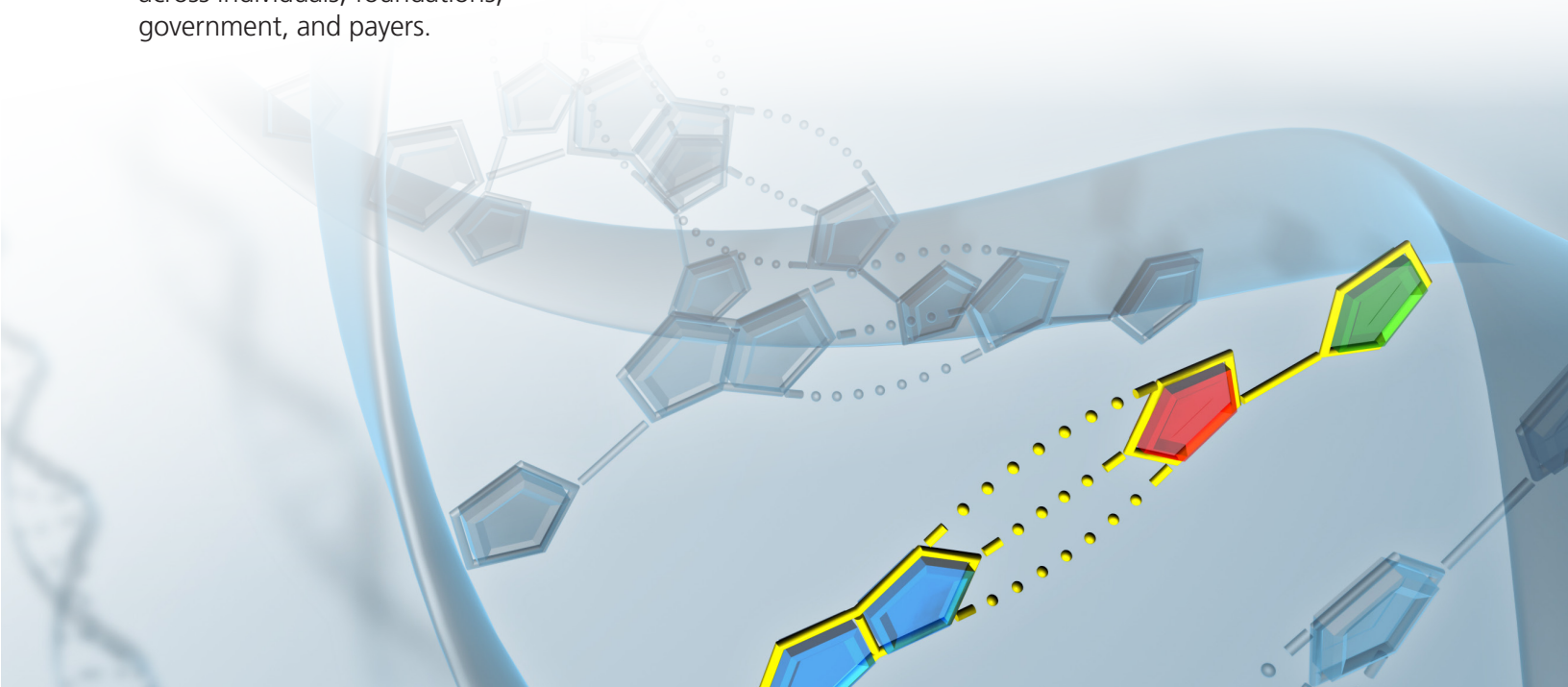
Interpretation is not “one thing,” because the process of interpretation fundamentally differs by disease. The *Genomic Interpretation Continuum* broadly classifies disorders into four categories: Rare Disorders, Mixed Patient Profiles (e.g., diabetes), Diseases that Mutate (resulting from somatic genetic changes) (i.e., cancer), and Screening for Diseases. It then analyzes these segments across key funding characteristics including: patient population, cost to quantify proof, and clarity of the solution. Ultimately, it reveals payment motivations, challenges, and opportunities across individuals, foundations, government, and payers.

B. Maturing the Required Technologies

The field of genetic testing and genomic interpretation is evolving from research into the clinical application of these findings to improve patient care. To facilitate this process of clinical application, and better support findings that will have the evidence to motivate payers to fund these tests, the market must continue to mature the technologies of genomics -- both testing and interpretation. Various areas of focus have been identified in the recommendations which will be required to move the industry to a more robust and stable level of technology.

C. Mobilizing the Ecosystem to Deliver Personalized Medicine

The industry is in a very predictable stage of development. It is following a classic model as it is evolving and growing, and moving from the “storming” to “forming” stage. To accelerate the adoption of genomics into healthcare, and therefore the more widespread adoption of personalized medicine, the main players in this industry have been categorized. The goal must be to collectively educate all groups, as they are all interrelated: clinicians, the genomic industry (pharma/biotech and diagnostic companies), genomic interpretation teams, and patients. Since clinicians are the key drivers and gatekeepers in healthcare, the most urgent need is to provide them with the appropriate information and tools to incorporate genomics into clinical practice.



III. Findings and Recommendations

A. Settling the Question: Who will Pay?

Finding: Payers and Diagnostic Organizations Both want a Clearer Definition of “Proof”

Before approving the reimbursement of a genetic test for inclusion in their plan, payers are becoming more rigorous about demanding “proof” that the test will improve outcomes and lower costs. Diagnostic organizations welcome this rigor as it makes their business more predictable. There is a long list of words to describe proof: utility, validity, actionable, evidence, cost-effective, trial results, outcomes, assessment, and so on. However, the definitions seem to be rather amorphous. Given the time and spend in this area by all parties, it seems to be a point of major inefficiency in the market..

Finding: The Current Universal Reimbursement Schema Needs to Be Upgraded

Current procedural terminology (CPT) codes applied to genetic testing remain a serious concern to the practical, day-to-day application of genomic testing and interpretation. Top concerns from participants were difficulty in tracking billing information (to tests performed) and time-consuming administration.

Recommendation: **Stratify the Applications for Testing**

Genetic tests and genomic interpretation have three basic purposes: detection of disease, treatment selection, and risk assessment – each having distinct justifications, payback periods, caregivers and challenges. Treating all three roles as a single group clouds understanding and planning. For example, we noticed that that negative comments around screening tests (e.g., long payback period or the ethics of searching for a future disease) were often unfairly attributed to all genetic tests. Maturing our language by stratifying genetic testing would add clarity and aid acceptance of all three genetic testing types.

Recommendation: **Commence Payer-Industry Forums**

Most communication between payers and genetic testing organizations happens at the test evaluation stage – the tail end of a long product

development process. Nearly all participants agreed that broader, more strategic and more regular communication between payers and the industry would better inform the planning of all players. Forum topics could include: identifying high impact areas, clarifying the definition of proof, connecting outcomes, establishing common boards, sharing risks/rewards, and preparing for scientific progress.

B. Maturing the Required Technologies

Finding: Assumption of Continued Progress in Research and Sequencing

The first answer to “what enabling technologies” are you expecting was nearly unanimously: “Keep improving sequencing price/performance.” This assumption is built into the business, medical and/or science plans of nearly every participant. A close second was the continued investment and returns of deep research into understanding the molecular mechanisms of disease. Together, these two form a virtuous cycle that powers this industry.

Finding: The Anticipated Sequencing Technology Mix in the Coming Three Years

Genetic testing (also known as molecular diagnostics) is a major contributor to healthcare across inherited disorders and cancer – today, tests for nearly 3000 disorders are listed in genetests.org. While whole-genome sequencing holds major advantages of data resolution and economies-of-scale, the most common sequencing methodologies in the coming two to three years will be gene panels and whole exome sequencing, followed by the increasingly more compelling whole-genome sequencing.

Finding: Variant Databases are Unresolved

Participants called for vast improvement in reference databases that contain the variants that have been discovered and their association with particular disorders. Specifically, experienced interpreters consistently reported that databases were too error-prone and that discovery organizations did not share new data. All told, this creates major problems of delays, extended effort, and worries about results.

Finding: The Community is Eager for Incentives and Methods to Share New Findings

Our knowledge of the genomic structure is vast; but we are much earlier in our knowledge of genomic variations and how they are associated with a particular disease or disorder. Sharing related findings clearly benefits the community – as we increase our collective knowledge, we accelerate future discoveries. While the intellectual property (IP) drive of commercial groups, and the need to publish for academic groups, can be a disincentive for sharing, most organizations (academic and commercial) want to share. However, there is no clear way to do so broadly and reliably.

Finding: Interpretation Software Priorities are Unresolved

While many respondents asked for better interpretation software, most were not able to clarify what exactly they needed beyond concepts such as better “management” or “analysis” or “more scale.” The promising area of “big data”, or inference software, was often mentioned but real application of it seemed beyond the experience of most participants.

Finding: It's a Multi-Disciplinary Science

Most participants argued that genomics should not be a standalone, unique data set in healthcare but must be combined with other biological results– such as proteomics, metabolomics, and imaging – along with other laboratory results and the clinical findings, to offer practitioners an integrated analysis and a system-level picture of the patient and the disorder.

Recommendation: Urge Continued Academic & Government Funding

The continued investment in deep research into genetic mechanisms of disease is critical to the progress and success of across-the-board personalized medicine. Participants unanimously stated that this foundational work powers this industry and the collective goals of optimal treatments and better health outcomes.

Recommendation: Collectively Upgrade Interpretation Software

The bioinformatics software market is quite fragmented (more than 90 commercial suppliers), has no market leader, and much of the software is provided free of charge from academic

institutions and foundations. To make up for this lack of natural market forces, we call for a forum of bioinformatics players to convene and collectively evaluate gaps between today's capabilities versus emerging requirements and set shared priorities. Ideally, the forum would span academic developers, commercial developers, and funding sources; and address these requested capabilities in their evaluation: integrated analysis, multi-source enrichment, structural variation and disease-specific algorithms.

Recommendation: Commence Big Data Workshops

Clearly “big data” software (inference engines) will play a major and enabling role in genomic interpretation. Today, however, the conceptual gap between the technology players and this application area is wide and the pick-up is slow. We call for a series of workshops and public reports between the technology leaders in big data, and each of the study's 12 sectors, to help close this gap. Overall, this could speed the adoption and value-add of these transformational technologies.

Recommendation: Normalize and Share New Findings

Some entities need to build a system to share and normalize interpretation discovery data. It's that simple – the stakes are too high, and enough parties are motivated to participate and help. It clearly benefits the community to share discovery data and increase our collective knowledge. And most organizations are eager to share – today, they just don't have a means to do so.

Recommendation: Establish Testing Standards

In any emerging technology area, there is a delicate balance between innovation and standards. On the one hand, setting standards prematurely may slow innovation. On the other, standards can trigger larger innovations (e.g., HTML and the Internet revolution). We feel that by bringing standards to the “upstream analysis” of sequencing reads, we can collectively spur larger innovation. We call for a consortium of suppliers to establish standards in related formats and algorithms. Stabilizing the environment surrounding sequencing technologies would enable and encourage bigger systems (with bigger rewards) to be conceived and built.

C. Mobilizing the Ecosystem to Deliver Personalized Medicine

Finding: Pharma is Coming On Board

According to the participants, the pharmaceutical industry is increasingly committed to and investing in personalized medicine and patient stratification. A number of new drug development/discovery programs now require a translational medicine or companion diagnostic component at program start.

Finding: It Takes a Village

Today, interpretation is rarely just a matter of a simple, automated report – in fact, it takes a multi-disciplinary team to formulate and interpret each patient's report. Team members can include bioinformaticists, geneticists, oncologists, pathologists and physicians. While collaboration is a good thing, the typical size and cost of the interpretation team is not sustainable for wide application in healthcare. Also, there was little certainty or agreement on the make-up of the team going forward, assignments to members, and preparing professions for these new roles.

Finding: Patients are Highly Motivated to Learn

Patients with life-changing disorders, and their friends/family networks, are highly motivated to learn. Information on personalized medicine services and providers, for their disease, is just about the most important information in the world to them. And, given that patient knowledge is a top demand-side driver in healthcare, such a connection would add market efficiencies, improve outcomes, and accelerate adoption of effective genetic testing.

Recommendation: Prepare a System Plan for Molecular-based Treatment of Cancer

Many interviewees feel that cancer is best treated as a molecular disorder and not an organ disorder. There is growing frustration with the present mismatch between this inevitable approach, and the organ-based structure of the present healthcare system. We urge cancer associations to prepare a system plan for this transformation of cancer care, to recognize that cancer mutates and is more similar across organs than previously understood.

Recommendation: Embrace Integrated Care

There is great synergy between the market dynamic of integrated care and genetic testing. For example, integrated care organizations take the long view, inherently consider diagnostics and therapy as an integrated cost, and are in a position to incorporate outcomes into their care analysis – all values shared with genetic testing. We encourage genetic testing organizations and associations to build relationships with integrated care and accountable care organizations (ACOs) – there is much to learn and gain from each other.

Recommendation: Educate and Prepare the Village

While many education efforts have started, it would be valuable to first agree on the general make-up of teams going forward and assignments to members. Therefore, preparation and education could be far more targeted. For example, do physicians need to be experts at interpretation of tests or experts on which tests to order? What is the interplay and synergy between genetic counselors and pathologists? More clarity would lower anxiety, better prepare caregivers, and speed the advance of personalized medicine into healthcare.

Recommendation: Academic Medical Center Collaboration

Many academic medical centers are implementing personalized medicine and instituting standard processes – indeed, we are seeing increasing and well-planned collaboration within these organizations. However, we would ask for more collaboration and knowledge sharing between these institutions, with a goal to collectively create the larger sustainable village and ensuring that the knowledge that is gained is disseminated into the larger community.



IV. Credits / Acknowledgements

The I-Study was performed by Cambridge Healthtech Associates™ (CHA) and GenomeQuest, Inc. with support from the Personalized Medicine Coalition. For more information, contact:

Dawn Van Dam

General Manager, CHA at +1-781-707-8289;
email: dvandam@chacorporate.com

Anthony Flynn

Director of Healthcare Strategy &
Commercialization, GenomeQuest;
email: anthony.flynn@genomequest.com.

About Cambridge Healthtech Associates

CHA leverages its extensive network and unique collaborative model in consulting, technology evaluations and community-based communication services to help clients in the life sciences industry commercialize and penetrate the marketplace to increase revenue. More at www.chacorporate.com.

About GenomeQuest

GenomeQuest is a global provider and consistent pioneer in large-scale genomic software applications. The company serves major pharmaceutical companies, global agriculture firms, biotech firms, IP legal teams, genome centers, academic research centers, diagnostic labs, and universities around the world. More at www.genomequest.com.

About the Personalized Medicine Coalition

The Personalized Medicine Coalition representing innovators, scientists, patients, providers and payers, promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system. More at www.personalizedmedicinecoalition.org.

