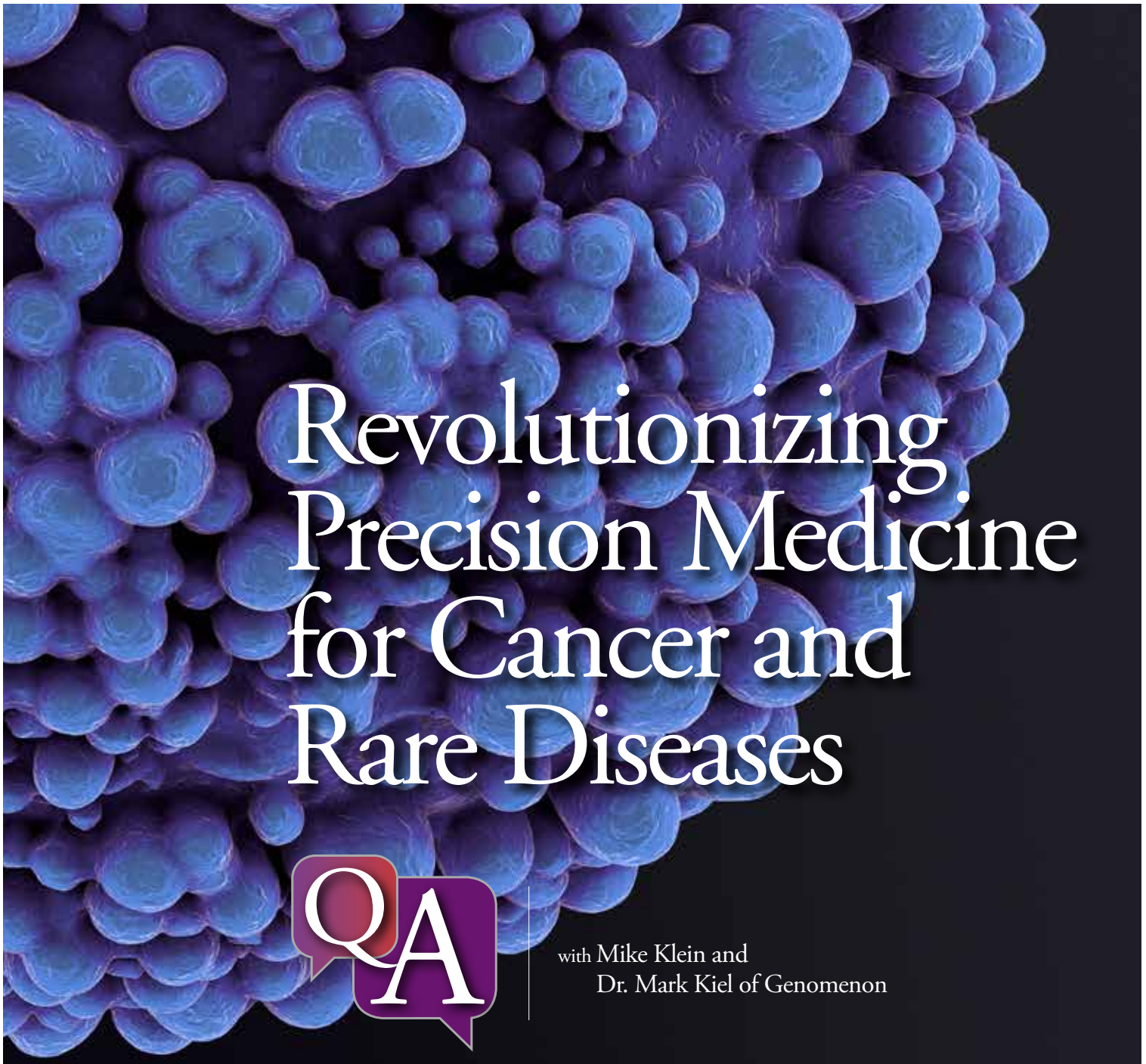
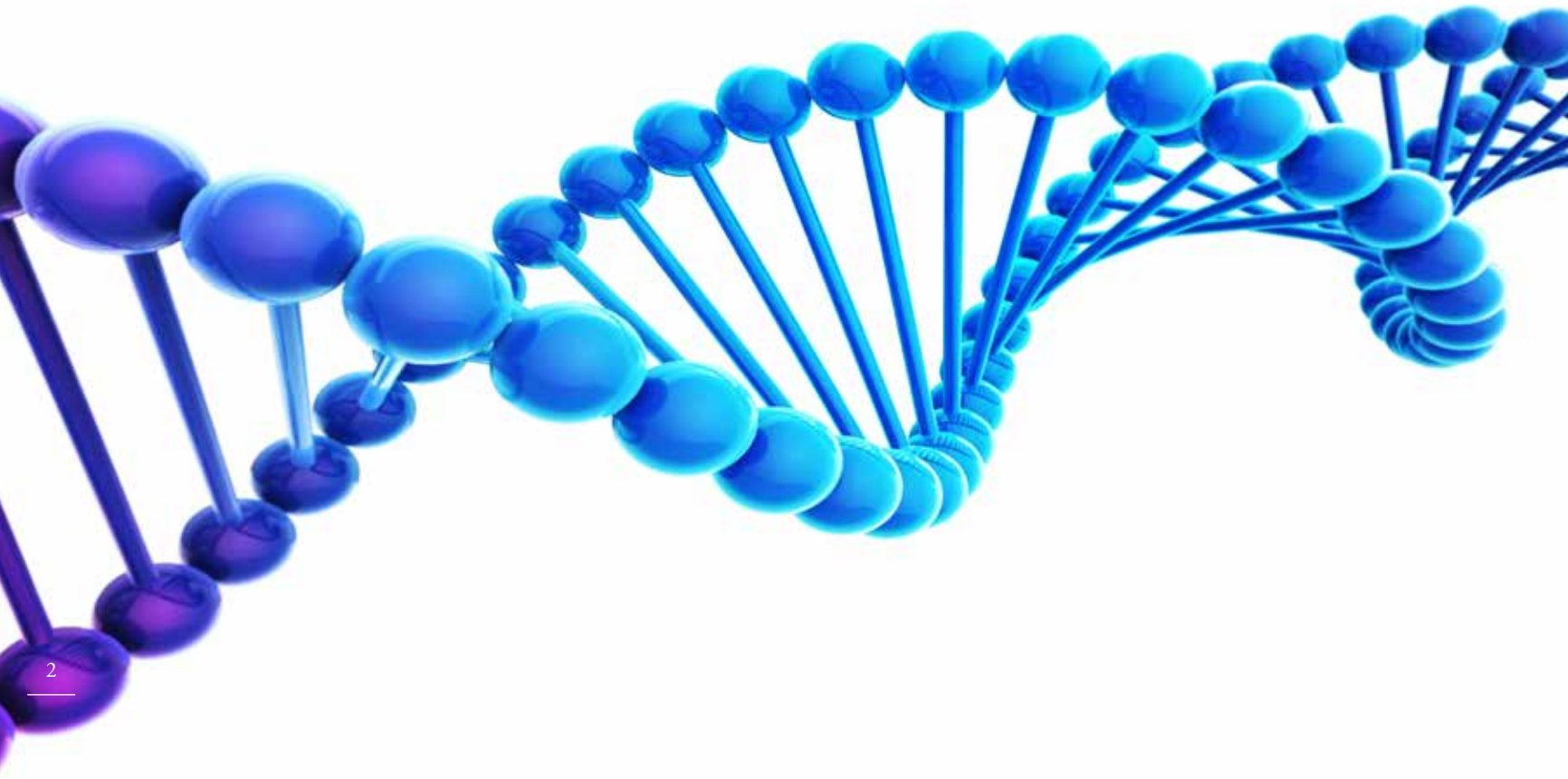


Revolutionizing Precision Medicine for Cancer and Rare Diseases

QA

with Mike Klein and
Dr. Mark Kiel of Genomenon

Investments in the Human Genome Project and the Precision Medicine Initiative have positioned genomics to revolutionize precision medicine for cancer and rare diseases. In parallel, the cost of sequencing DNA has fallen dramatically over the last 15 years, and the consequent ability to generate an overwhelming amount of data from DNA sequencing has grown exponentially. Making sense of the vast amount of patient DNA data has become the bottleneck for precision medicine.



Genomenon's mission is to alleviate the DNA interpretation bottleneck by connecting patient DNA with insights from genomic research to diagnose and cure cancer patients and infants with rare diseases. With this approach to evidence-based genomics, the company is able to help its users deliver faster and more comprehensive diagnosis and treatment decisions.

Tools and Applications

Genomenon's flagship product, the Mastermind Genomic Search Engine, is used by hundreds of diagnostic and clinical laboratories around the world to accelerate genomic interpretation, a practice carried out to date by time-consuming and laborious manual literature curation. Mastermind uses Genomic Language Processing (GLP) to index the entire corpus of published genomic research for every disease, gene or variant, in every way that an author can describe them. The search engine allows users to find every piece of research containing a gene or variant in seconds, and provides deep insight into each research article. This eliminates hours of time that clinicians spend searching for literature containing the information needed to diagnose and treat their patients.

"GENOMENON ALSO DELIVERS THE MASTERMIND DATABASE AS A COMPREHENSIVE GENOMIC LANDSCAPE FOR EVERY DISEASE"

Genomenon also delivers the Mastermind database as a comprehensive genomic landscape for every disease. Pharmaceutical and bio-pharma researchers use the Mastermind database to better understand the genomics driving drug discovery and for selecting clinical trial targets.

Genomenon's stated goal is to develop automated platforms to search and curate the rapidly growing body of medical literature for disease-related genes and variants.

Q a. To that end, what is the search methodology that identifies and pulls out the prioritized, clinically relevant genomics from the scientific literature?

A Mastermind starts with the titles and abstracts of every scientific medical paper published (over 30 million articles to date) to find any paper with genomic content. The full text of those genomic papers are then indexed to find every disease, gene, variant and phenotype contained within the article. The data found in these publications is processed through our GLP software, which normalizes the widely disparate variant nomenclature and creates a search index into each paper. More sophisticated than Natural Language Processing, GLP is a heuristic approach that identifies every way that an author can describe a gene or

Figure 1: Mastermind Genomic Search Engine Dashboard

variant, and filters out information that can be falsely mistaken for genomic data. To date, Mastermind has indexed the full text of over 6.4 million genetic publications and indexed over 4.1 million variants from those articles.

This Mastermind data is accessed through two solutions: 1) the Mastermind Genomic Search Engine is a web-based application for geneticists and pathogists seeking clinically relevant publications to support patient diagnosis and treatment decisions (see **Figure 1**); 2) the Mastermind Database provides a genomic landscape for disease that gives researchers the data they need to understand any disease at the molecular level.

Q b. How is Genomenon's search methodology different from other search strategies?

A We took a decidedly different approach than the manual curation process that databases such as QIAGEN's Human Gene Mutation Database (HGMD) use. With over 500,000 new genomic articles published just last year, manual curation is an intractable problem to an exponentially growing challenge. There simply are not enough qualified scientists available to read and curate every genomic article being published. As sequencing costs decrease, the amount of published genomic research is expected to continue to grow each year, exacerbating the problem even further.

We saw the opportunity to develop an approach that will scale with the expected flood of genomic data. Where manual curation efforts such as HGMD have been able to review less than 60,000 articles and 30,000 supplemental reports over the last 18 years, Mastermind has been able to index over 6.4 million articles and 300,000 supplemental data sets in just 4 years, adding an average 10,000 new articles per week.

Q How are Genomenon's results qualitatively different from other search strategies?

A One of the challenges with manually curated databases is how quickly the data gets out of date. Most manually curated databases are released on a quarterly basis, and curators cannot keep up with the nearly 40,000 new genomic articles that are published each month. As a result, manually curated databases lack many of the most up-to-date publications

A Mastermind User

The Genomenon leadership team

and citations. The benefit of an automated approach is the ability to keep the search engine current. Mastermind is updated weekly, so our users are always seeing the latest publications in their search results.

Comprehensiveness is another factor. When diagnosing a patient, it's critical that information isn't missed or overlooked. We've seen cases where a single paper made the difference in a patient's diagnosis and treatment decision. Recently, a leading genetics laboratory was unable to diagnose a patient using manually curated databases for a variant interpretation. When the patient's DNA was reexamined by Rare Genomics Institute using Mastermind, they found a single research report that matched the patient's DNA variant, leading to a correct diagnosis, and ending the patient's 7-year diagnostic odyssey.

Q How are Genomenon's results quantitatively different from competitors?

A Mastermind has indexed over 4.1 million somatic and germline variants across over 6.4 million published research articles and supplemental materials, compared to about 250,000 variants in HGMD from 60,000 articles

Table 1: Side-by-side comparison of Mastermind's search results versus other search engines

	MASTERMIND® GENOMIC SEARCH ENGINE	HGMD	COSMIC
Genes	31,825	10,736	200
Variants	4,100,000	248,700	408,000
Journals	32,085	3,000	N/A
Full-Text Articles Indexed	6,450,000	57,000	26,494

http://www.hgmd.cf.ac.uk/ac/stats.php
https://cancer.sanger.ac.uk/cosmic/release_notes/

"WITH THE ADVENT OF PRECISION MEDICINE, PHARMA COMPANIES HAVE A GROWING NEED TO UNDERSTAND THE GENOMICS ASSOCIATED WITH CANCER AND RARE DISEASES"

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and 408,000 somatic variants in COSMIC (Catalog Of Somatic Mutations in Cancer) found in 25,000 articles (see **Table 1**).

Could you please comment about how you recommend Mastermind be used by:

Q a. Pharmaceutical and Bio-pharma Companies

A With the advent of precision medicine, pharma companies have a growing need to understand the genomics associated with cancer and rare diseases. Mastermind's database connects the genomic landscape from the published literature with specific diseases. This provides pharma and biopharma companies insight for both drug discovery and clinical trial selection based on patients' DNA. Researchers need to connect the real-world evidence from population data with computational prediction models and the published research to get a 360 degree view of the genomics in their disease pathway. Mastermind can uniquely contribute the genomic data from published research.

Mastermind includes a visualization tool for researchers to interact with these large databases to see the variant landscape associated with a rare disease, a functional variants landscape for a specific cancer, or a gene-fusion database culled from the published literature.

Q b. Clinical Laboratories

A Clinical diagnostic labs are facing a critical bottleneck in curating the overwhelming amount of data produced by whole exome or whole genome sequencing of their patients. Researching a single variant amounts to a significant cost in terms of time, effort, and money. A highly skilled clinician can spend 90 minutes to research one variant through search engines like Google or Google Scholar – to find and read publications citing the patient's variant. The cost compounds when dozens or hundreds of variants need to be examined to interpret a patient's whole genome or exome.

Mastermind significantly reduces the time required to research variants by comprehensively identifying all the literature containing the variant, prioritizing the search results by clinical relevance, and providing immediate insight into the genomic context of each article. By reducing manual search work, cutting genomic interpretation time, and increasing case throughput, clinical labs are using Mastermind to cut curation costs and free up their skilled scientists to focus on higher value work.

"I CAN SAY WITH CERTAINTY THAT WITHOUT THE FINDINGS OBTAINED FROM MASTERMIND, I WOULD NOT HAVE BEEN ABLE TO PROVIDE A DIAGNOSIS FOR MY PATIENT"

Q What user feedback has Genomenon received on evidence-based genomics enabling precision medicine (that is, identifying therapies specific to a patient population or profile)?

A Pharma users see the comprehensive genomic landscape culled from the published genomic literature as a complement to the Genome-Wide Association Studies (GWAS) and population datasets they have been exploring. Users like Rhythm Pharmaceuticals that have been using Mastermind for the past year cite the benefit of deeper insight into disease and drug pathways of interest. "The Mastermind database hit a level of comprehensiveness unlike any other approach we've ever seen." according to Alistair Garfield, Vice President of Translational Research & Development at Rhythm Pharmaceuticals. "It literally saved us man-years of manual effort that would have yielded far less-comprehensive results."

Clinical users see significantly shorter literature curation times, finding they can curate a patient's variant up to five times faster than prior methods. Lipika Ray, a computational geneticist on the Patient Research Services team at Rare Genomics Institute used Mastermind to find a single paper leading to a diagnosis for her patient: "I can say with certainty that without the findings obtained from Mastermind, I would not have been able to provide a diagnosis for my patient." ■

Mike Klein, CEO, Genomenon. Mike has spent the last 25 years starting and building successful software and IT businesses. He joined Genomenon in 2016 to help the founders implement their vision of building a leading genomic search engine to improve patient diagnosis and precision medicine development.

Mark Kiel, MD, PhD, Founder and CSO, Genomenon. Dr. Kiel oversees the company's scientific direction and product development. Prior to starting Genomenon, Mark completed his residency in Clinical Pathology and fellowship in Molecular Diagnostics at the University of Michigan. While at Michigan, he built the informatics framework for clinical next-generation sequencing in the Molecular Diagnostics Laboratory.