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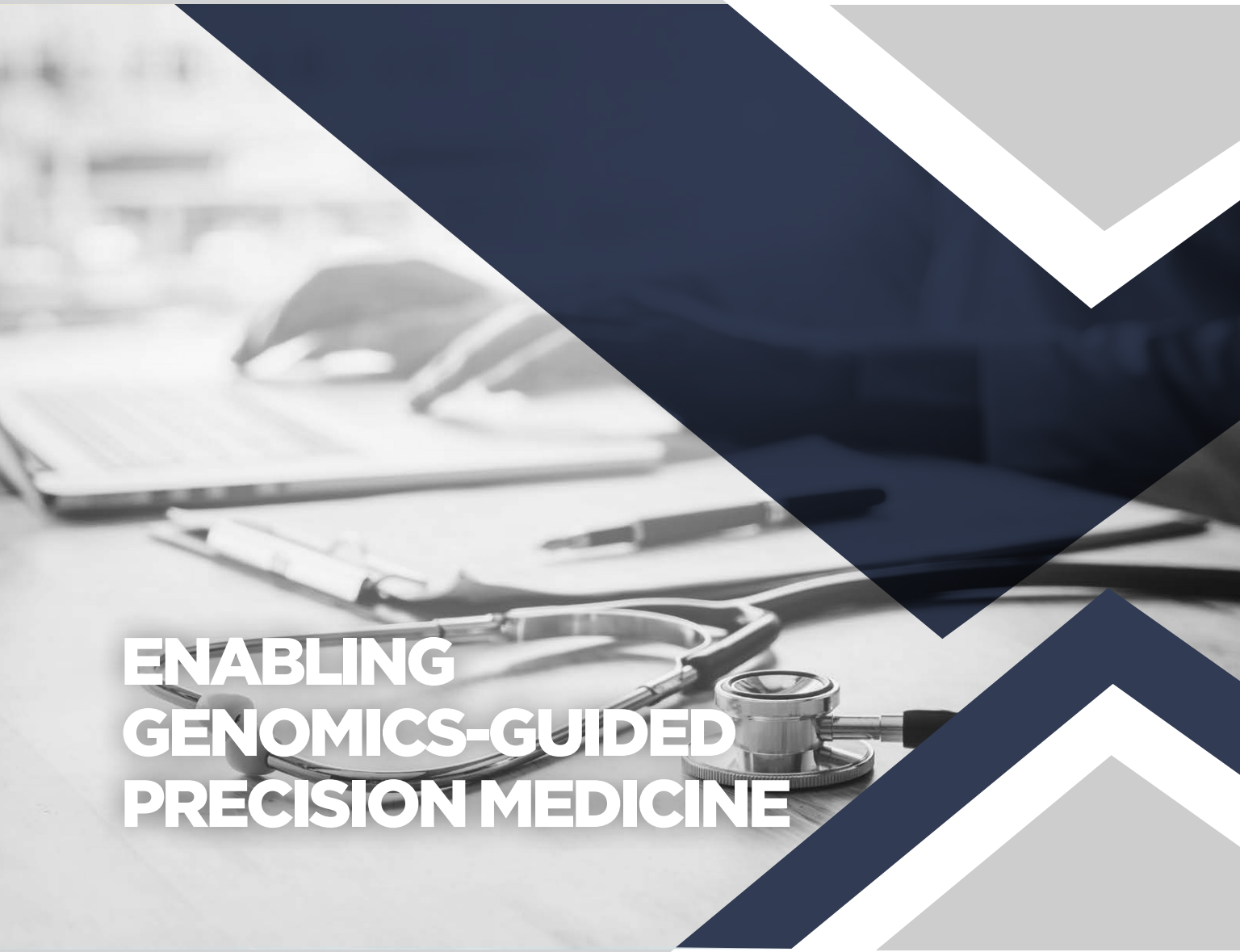

ENABLING GENOMICS-GUIDED PRECISION MEDICINE

QIAGEN

The power of precision medicine at your fingertips

We understand the importance of taking clinical genomic data and identifying current, relevant potential therapies and clinical trials for patients.

QIAGEN Clinical Insight (QCI™) Interpret software brings interpretation and reporting directly into your clinical workflow. Delivering the industry's largest, most up-to-date knowledge base at the touch of a button, QCI Interpret provides the clinical evidence you need to interpret and place the right information for each patient in the hands of their physician.

For more information, visit
www.qiagenbioinformatics.com/QCI

Sample to Insight

Completing the Genomic Puzzle: The Promise of Precision Medicine

The era of precision medicine has arrived, and with it, a tidal wave of data from disparate sources, including electronic health records (EHRs), lab systems, pathology and genomics. By integrating data from all available sources and analyzing it in smart ways, clinicians can finally get a complete picture of an individual's medical profile and define a truly personalized approach to care. And while a clinician's skill lies in having the expertise and judgment to evaluate every factor involved and making the correct call, the true barrier he or she faces—where clinical decision support (CDS) tools become a critical ally—is the challenge of collecting, analyzing, and using this data to guide treatment decisions.

For the promise of precision medicine to become reality, a clinician's workflow needs to be augmented with relevant, timely access to the types of knowledge he or she needs to make decisions as quickly and reliably as possible.

Clinical Decision Support Tools: A Modern Necessity

Making the best clinical decisions for patients starts with accessing the right information at the right time. Yet, navigating clinical research to support evidence-based medicine can be both challenging and time-consuming. Clinicians need accurate, up-to-date information on which to base their decisions to ensure quality care. Clinicians need efficient and robust workflows that are cost-effective and scalable to test volume. Having the right tools to aid and enhance clinical decision support is more than a new-age convenience, it is a necessity.

Enter CDS tools. Designed to help sift through enormous amounts of clinical data to suggest next steps for treatments, alert clinicians to available information they may not have seen, or catch potential problems, such as dangerous medical interactions, CDS tools provide patient-specific information, intelligently filtered or presented, to improve health and health care. Especially in oncology, where there are a number of very precise genomic indicators to determine how a particular patient will respond, CDS tools help match cancer patients to the clinical trials and therapies best suited for their particular genetic mutation. For example, a particular gene mutation (BRAF V600) occurs in about 50% of melanoma patients, and those with that mutation are responsive to a particular therapy with BRAF and MEK inhibitors.[1]

In an age of overwhelming data access and rapid technological development, CDS tools are vital to optimizing health outcomes. The Global Clinical Decision Support System (CDSS), which was valued at USD 891.78 million in 2017, is expected to appreciate to reach an estimated USD 1.76 billion by the end of 2023. The CDSS market is set to witness a CAGR of 12%, which projects above-average growth for the global market.[2] The use of CDS tools in healthcare is becoming more prominent; hence the importance of CDS tool design, functionality, and accuracy.

Choosing the Right Clinical Decision Support Tool

CDS technology is a critical component of any health IT strategy aimed at elevating performance, and today's hospitals and health systems increasingly depend on these tools to drive outcomes improvement, streamline workflows and standardize evidence-based practices. CDS is not simply an alert, notification, or explicit care suggestion. CDS encompasses a variety of tools including, computerized alerts, clinical guidelines, condition-specific order sets, focused patient data reports and summaries, diagnostic support and contextually relevant reference information. These functionalities may be deployed on a variety of platforms (e.g. mobile, cloud-based, installed). CDS is not intended to replace clinician judgment, but rather to provide a tool to assist care team members in making timely, informed, and higher quality decisions.

In choosing a CDS technology vendor, clinicians are looking for solutions that are both consistent and individualized to fit their healthcare organization's particular needs. Effective CDS should:

- **Identify key factors in treatment decisions:** Knowledge should be presented contextually and consistently, with ratings that can assist in evaluating the strength of the evidence presented.
- **Reduce knowledge gaps:** Information should be curated, assuring that available content is up-to-date, consistently formatted, presented in context, and uniform across the patient care continuum.
- **Avoid treatment errors:** Clinicians need real-time access to all categories of knowledge so that their evaluations and decisions can be made faster and based on readily-available clinical evidence.
- **Protect clinician workflows:** Developers and vendors of CDS tools, especially those based on machine learning, must be transparent about their methodologies, capabilities, data sources, and limitations if providers are to rely on their products.

Putting the Pieces Together

Precision medicine is built on a foundation of new sequencing technologies that generate massive amounts of patient-specific data—both a blessing and a curse for hospitals and clinical labs. On one hand, it is the sheer volume of genomic information and our ever-improving understanding of disease genetics that make it possible to provide an accurate, customized prognosis or select just the right treatment for a patient. On the other hand, without an army of PhD geneticists and bioinformaticians helping to make sense of it all, healthcare facilities that want to adopt precision medicine are often intimidated by the daunting task of keeping pace in such a rapidly advancing field.

Similar to how the top of a puzzle box reveals the "complete picture," CDS tools collect and display all the relevant clinical information across lab data sources, EHR data, and the clinical literature that best captures our understanding of disease. CDS tools help clinicians identify missing pieces, predict how "pieces" fit together, and ultimately solve the puzzle faster with fewer mismatches or "false positives."

If precision medicine is a billion-piece jigsaw puzzle with 90 percent blue sky and 10 percent clouds, CDS tools are the extra sets of hands and eyes working to create the "bigger" picture.

References

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QCI™ Interpret: Enabling Clear Clinical Decisions

Across the healthcare sector, every role is being affected by precision medicine, from researchers involved in drug development who can now study more specific subgroups of patients, to payers determining how to cover medications, to providers on the front lines of care, to the patients themselves. The ability to collect and access vast data sets, such as a patient's entire genome, is transforming how we look at disease. QIAGEN Clinical Insight (QCI™) Interpret is bringing this view into a clearer focus.

QCI Interpret is a cloud-based CDS platform that enables clinical labs to easily and efficiently extract actionable information from clinical NGS tests. A clinician relies on his or her expertise and judgment to evaluate every factor involved in a case in order to make the correct call, but information overload presents a considerable barrier. This—the challenge of collecting, analyzing, and using the data available to guide treatment decisions—is where QCI Interpret becomes a critical ally.

QCI Interpret brings together all the resources necessary to enable clinicians to make informed medical decisions. When it comes to clinical decision making, it is critical for providers and patients to have as much transparency as possible—especially if a computer is helping to make recommendations about diagnoses or treatment protocols. Most CDS tools use machine learning and advanced algorithms to deduce associations. These sophisticated tools are able to rapidly query patient-specific data and identify associations that the software has seen in previous cases. To build a high degree of confidence in the reliability of the system, CDS tools should include an explanation of the guidelines or methodologies underpinning the recommendation.

Offering the highest level of interpretation transparency currently available in the market, QCI Interpret displays every piece of supporting evidence included in the interpretation process. The software is connected to the QIAGEN Knowledge Base, the industry's largest, most-up-to-date clinical database with over 16 million biological findings.

Pulling data from clinical trials, case studies, peer-reviewed literature, drug labels, external databases, professional guidelines, and the direct experience of interpreting over 750,000 human samples, the QIAGEN Knowledge Base is unrivalled in clinical breadth and depth. The content of the knowledgebase ensures clinicians using QCI Interpret are considering the latest research to inform their treatment decisions. Clinicians can easily assess and review this information through direct links, changing any classifications based on personal patient experiences. This step not only replaces the complex and manual clinical NGS variant research with automated interpretation, it lends a higher degree of confidence in interpretation accuracy by showing the classification "homework."

Consider how this kind of tool could work in a pipeline for reporting the results of a tumor genetic analysis. The tumor would be sequenced, yielding a list of millions of variants spanning many types of genetic variation: single nucleotide variants, insertions and deletions, copy number variations, fusions, and more. When appropriate, a matched normal sample would also be sequenced so that germline variants could be quickly and automatically filtered out of the list. Variants deemed unique to the tumor would then be fed as a first data input into QCI Interpret, which integrates the second data input: the QIAGEN Knowledge Base representing all known information about each variant—even if that variant's name, function, or clinical impact has changed over time. QCI Interpret then applies intelligent algorithms to determine what kind of downstream biological effect each variant might have, its possible corresponding impact on disease physiology, a differential clinical diagnosis, and potential responsiveness or resistance to an array of available therapeutic options. All of these steps are automated, running rapidly in the background, and the eventual output provides a detailed explanation for the algorithmic reasoning that led to the given conclusion. QCI Interpret generates a short list of the variants most likely to be medically relevant—those that might be driving the cancer, as well as those that could be used to guide treatment selection or clinical trial enrollment.

Clarity through Consistency

The growth of clinical NGS testing has revealed just how challenging the act of identifying, classifying and reporting variants can be, especially when it comes to cancer. The sheer volume of what current NGS panels interrogate is daunting. They look at multiple genes and multiple mutations. When you add in different levels—including copy number variations, insertions and deletions, and point mutations—the interpretation and reporting process becomes increasingly complex.

In fact, NGS remains in the high complexity testing category as defined by the Clinical Laboratory Improvement Amendments (CLIA). As the number of labs offering NGS continues to increase, variability of how results are reported and variability in test results between labs have become a greater concern. In a 2015 survey conducted by the Association for Molecular Pathology (AMP), astonishing variation in reporting was found between labs interpreting sequence variants from somatic cancer. Labs differed in the number of categories for classifying variants, in reporting variants that failed quality control, and in reporting therapeutic implications of variants to oncologists.[1]

The AMP survey underscored the need to provide interpretation guidelines for NGS testing. AMP teamed up with the American College of Medical Genetics and Genomics (ACMG), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) to publish frameworks for interpreting and reporting sequence variants for actionability. For somatic cancer, their recommendations include a four-tiered system which considers the clinical evidence from drug labels, peer-reviewed publications, and other sources to establish the significance of this evidence for the identified variants, with the goal of helping physicians identify potential treatments for their patients.

QCI Interpret integrates the ACMG/AMP and AMP/ASCO/CAP tiering system into the QIAGEN Knowledge Base. Through the

cloud-based application, clinical labs can immediately access carefully curated genetic information, along with automated pathogenicity and actionability classifications for sequence variants, according to the recommended guidelines. QCI Interpret then links each patient's molecular profile with potential treatment strategies, including multiple clinically-relevant features such as clinical trials, multivariant analyses, curation of predictive immunotherapy biomarkers, and prognostic relevance of hematological biomarkers. With this approach, compliance with guidelines becomes straightforward and automatic.

Yet, QCI Interpret differs from other CDS tools in that it respects the role of human judgment and experience. Any tool that incorporates genomic guidelines should also emphasize transparency. QCI Interpret allows users to click through to relevant source material and report information based on their own expertise in cases where they may disagree with a variant assessment or the supporting clinical evidence. This "final review" element is what makes QCI Interpret a true CDS tool—it does not replace traditional variant interpretation and reporting with "black box" automation, but rather gives clinicians the resources needed to make consistent and informed decisions.

For genomics-guided precision medicine to enter routine clinical care, service providers must develop informatics workflows that are reproducible and transparent. QCI Interpret is a standardized, automated pipeline built on high-quality, curated data that can improve the reliability of variant interpretation and accelerate the process to help patients. QCI Interpret supports open communication and sharing of information among labs, so they can compare results and more readily determine the best treatment for a patient.

Optimizing and standardizing the analysis and interpretation of genomic data for patient care means reducing the opportunity for human error, scaling for higher sample volumes, and ensuring that interpretation is robust and reproducible by basing it on a foundation of trustworthy scientific content. QCI Interpret is clearing the way.

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STREAMLINE AND SCALE-UP WITH QCI™ INTERPRET

A FLEXIBLE AND COST-EFFECTIVE CLINICAL NGS REPORTING SOLUTION

	PROCESS	TIMELINE
COLLECTING PATIENT SAMPLES AND HEALTH RECORDS	Patient Consultation → Collecting Patient Samples (Biopsy • FFPE) → Algorithms for Integrating EHRs → Extracting, Fragmenting, and Amplifying DNA	1-2 days
DNA/RNA/ PROTEOME SEQUENCING AND GENOTYPING	Whole Exome Sequencing • Whole Genome Sequencing • Pyrosequencing • Sequencing by Ligation • Sequencing by Synthesis • Methylation Sequencing • ChIP Sequencing • Ribosome Profiling • SNP Genotyping	1-4 days
QCI INTERPRET	Upload VCF File & Metadata → Variant Identification → Variant Classification → Selection of Variants & Evidence for Report → Medical Interpretation → Customized Actionable Report	15 minutes total per test*

*Value obtained from a study by Kambiz Karimi, PhD, et al. (2017) of Counysl comparing QCI software for interpretation of NGS results from 19,000 variants in hereditary cancer and other diseases to manual interpretation by PhD scientists and genetic counselors.

Deliver Better Care with Better Knowledge

The ultimate goal of precision medicine is to utilize the precise knowledge of a person's genes, surroundings, and way-of-life to find the best possible route to prevent or treat disease.[1,2] To make this a reality, the National Institutes of Health (NIH) have established short and long-term goals. First, the tools of precision medicine, such as NGS technology, need to be widely adopted and implemented to better understand genetic perturbations in cancer biology. This in turn will increase the effectiveness, efficiency, and safety of treatment protocols of various forms of the disease. Then, the long-term goal is to apply precision medicine to all areas of healthcare. The NIH has recently launched the *All of Us* research program—a cumulative effort to gather genetic and biological data over many years from at least one million individuals residing in the United States. The data will then be made publicly available in an open-access database that can be used by the research, medical and patient community.[3]

Long before the NIH laid the groundwork for the *All of Us* Research Program, QIAGEN started building what today is recognized as the largest biomedical knowledgebase currently available to researchers and clinicians alike. The QIAGEN Knowledge Base is renowned for its breadth and depth. A culmination of more than 20 years of expert knowledge curation, the QIAGEN Knowledge Base contains more than 16 million biological findings, spans more than 4,000 peer-reviewed journals, and includes over 35,000 scientific publications. The QIAGEN Knowledge Base has the direct experience of analyzing over 750,000 human samples from over 100 countries of origin through QIAGEN bioinformatics platforms. Bottomline, the QIAGEN Knowledge Base is a leviathan of clinical evidence.

Yet, massive amounts of clinical information are useless if the information is not reproducible or distributed in a timely manner. Similar to how clinical decision support (CDS) tools need to be transparent in how recommendations are achieved, clinical knowledgebases must be held to the same standard of quality assurance. The QIAGEN Knowledge Base enables clinicians to find disease-causing variants faster, and with fewer false leads, by tapping into the knowledge of millions of scientific findings that have been manually curated by hundreds of MDs and PhDs. It is precisely this differentiator—QIAGEN's team of expert curation—that makes the QIAGEN Knowledge Base a trusted resource in modern genetic testing.

The QIAGEN Knowledge Base includes multiple layers of manual and automated quality control to maintain accuracy and consistency of phenotype and genotype representations. Researchers and clinicians who rely solely upon public databases, such as the widely-used ClinVar, run the risk of misinterpreting results with absent, inadequate, or outdated information. As of 2018, ClinVar reported just over 110,000 clinically-relevant variants. In comparison, the QIAGEN Knowledge Base reported 6.2 million.

For genomics-guided precision medicine to become a reality, genomic tests require granular accuracy. This requires an evidence-based and systematic approach, and constant updating of curated data as new studies emerge. Many public databases, like ClinVar, are crowd-sourced and have the potential for incorrectly classified variants and inconsistencies in terminologies and methods. Public databases have little or no reviewing or screening of submitted evidence, and occasionally, contradictory reports can be curated. Further, data in public datasets tend to be outdated.

The expert curation team at QIAGEN updates QIAGEN Knowledge Base content on a weekly basis. On average, 4,000 new publications are added per month and the curation team ensures the information is peer-reviewed and consistent with previous reports. In today's fast paced clinical setting, the QIAGEN Knowledge Base mitigates the occurrence of clinical knowledge "blind spots" and can improve clinical outcomes.

The Future of Precision Medicine: Better Care through Better Knowledge

To make precision medicine the global standard of care – including the development of high-volume genome-analysis as a feasible diagnostic solution, a variety of logistic decisions will need to be considered. Health policy makers, medical institutions, manufacturers, clinicians, biomedical researchers, as well as patients and the general public will need to be involved in this process through global initiatives. Exponentially growing amounts of biological knowledge will need to be assimilated, annotated, curated, and integrated into sharable databases in real time. Standardizing ontologies, meta-data, guidelines for manual data-curation, and establishing best-practices for data extraction from primary literature will make such databases comprehensive and inter-operable. Intricate, user-friendly, and widely accessible bioinformatics tools will need to be developed to analyze these databases to generate reliable and reproducible data for patients, clinicians, and researchers. Developing specialized and multifaceted reporting systems customized for disseminating this knowledge in a comprehensive manner will need to be part of the solution.

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