

The background of the slide is a close-up, shallow depth-of-field photograph of a microfluidic chip. The chip's channels and wells are visible, with a strong blue color cast. The focus is sharp on the right side, showing the fine details of the chip's structure, while the left side is blurred.

Bigger, Faster, Cheaper

Breaking the bottleneck in clinical genetic testing

Because every minute counts when children’s lives are at stake, Rady Children’s Hospital-San Diego set an ambitious goal in 2018: rapidly sequence an infant’s whole genome in a matter of hours—but do so at an affordable price.



The pilot program referred to as Project Baby Bear was the first of its kind. It demonstrated that a rapid precision medicine program for critically ill babies not only leads to better health outcomes and reduces suffering among the infants, it actually decreases the cost of care [1].

What the researchers in Project Baby Bear were able to accomplish for rare and undiagnosed diseases sets the bar for other applications of genetic testing. For example, Sun et al. (2019) found unselected genetic testing of all women with breast cancer to be highly cost-effective when compared with testing based on just clinical criteria or family history [2]. In simulations comparing multigene testing to single gene testing, Sun et al. reported only 2 percent of single gene testing to be cost effective, whereas 98 percent

of multigene testing to be cost-effective. This study joins a growing collection of publications demonstrating the cost-effectiveness of population-based testing for hereditary cancers [3-5].

Multigene testing for germline disorders is outperforming standard single gene testing not only in terms of cost-effectiveness, but in diagnostic accuracy, timeliness and patient outcomes. Sun et al. reports multigene testing for high penetrance breast cancer pathogenic variants actually leads to fewer breast cancer cases and fewer deaths related due breast cancer [2]. This study emphasizes the value of using large panels for hereditary cancer prevention and management.

Yet, if higher throughput is proving to be more accurate, efficient, and cost-effective, clinical labs will need to rethink their operating model moving forward. The demand of germline-specific NGS testing is rising, putting clinical labs in a position of having more decisions to make as they develop their test menus. For each test offered, clinical labs must select a technology strategy that balances clinical yield with implementation cost and complexity.

At the end of the day, the goal is to not only demonstrate the power of advanced genetic testing to improve treatment and outcomes, but to make NGS testing accessible and affordable. For most clinical labs, this means adopting efficiency-enhancing technologies and/or leveraging professional support services—especially when it comes to NGS variant interpretation.



The NGS Inflection Point

In the early days of genetic testing, the use of NGS in large healthcare systems was limited to niche applications for a small number of patients. Now, widespread adoption of NGS platforms to test a much broader range of patients has triggered an inflection point. NGS-based testing is now providing highly predictive and accurate information for many clinical applications — and at a larger cost savings. Today, there are three general NGS approaches being used by clinical labs:

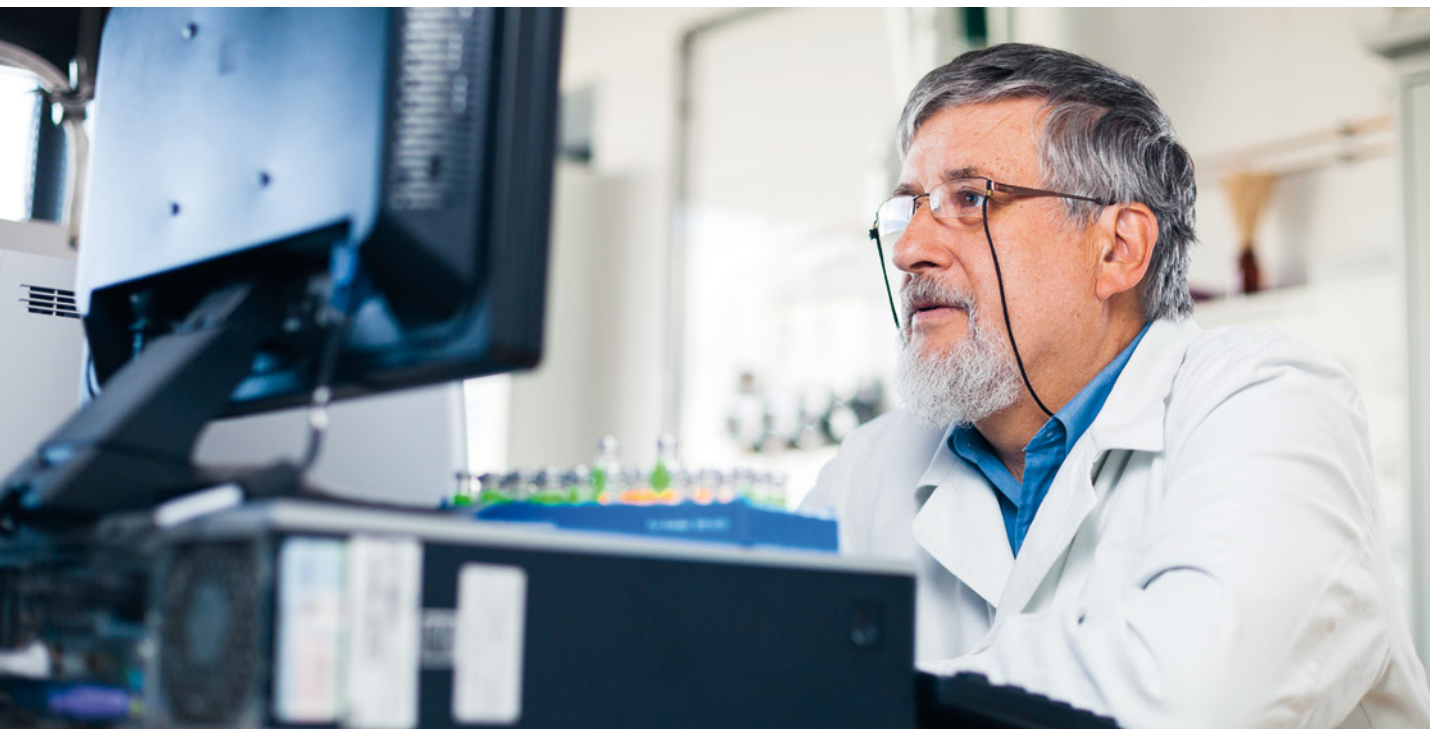
- **Targeted panels** contain a well-defined, narrow list of genes sequenced to very high coverage for a molecular diagnosis or confirmation. Use of a targeted panel is particularly appropriate for large-scale screening, especially when processing on a smaller platform or up to 100 patients a day, which is high for some laboratories.
- **Exome sequencing** focuses on all the protein-coding regions of the genome and is useful for discovery efforts. Exome sequencing can be more time-consuming and more complex than targeted panel testing.
- **Genome sequencing** characterizes both coding and non-coding regions to analyze the patient's full complement of DNA for the most comprehensive view of variation. In clinical labs it can be challenging to support the bioinformatics infrastructure required to analyze whole genome data.

These NGS tests all churn out long lists of variants, which are meaningless to a physician without differentiation and interpretation. Newly described or uncommonly mutated genes will inevitably reveal novel variants, and each variant that is reported must be assessed to determine whether it has a known pathogenic role or if it is a variant of unknown significance. For pathogenic variants, physicians want to know if there are any targeted therapies available, and if there is evidence that a variant can help to determine a prognosis or diagnosis.

To provide adequate support for their customers, laboratory teams must adopt and roll out tools to ease this burden. Variant curation solutions make actionable data more readily available and provide the exact type of information physicians need—all supported by evidence documented in scientific and medical literature.



“Variant curation solutions make actionable data more readily available and provide the exact type of information physicians need.”



Variant Curation Best Practices

It is important to identify and understand the attributes of a variant curation system. Any viable system provides basic details for curation of variance and making clinical decisions, including position, quality, coverage and zygosity. Based on the culmination of best practices, key attributes of a world-class variant curation system include:

- Allowing the analyst to work through guided American College of Medical Genetics and Genomics (ACMG) classification criteria for novel variants and assisting in the assignment of appropriate classifications
- Providing ClinVar references and clinical laboratory observations, as well as in vitro effects, population frequency, and protein effects
- Including reviewable links to published studies and relevant clinical cases
- Supplying a link to a genome browser that can help determine the quality of particular variants.

These key attributes should be at the core of a clinical lab's system for tertiary analysis. This will ensure that the quality of the data — and the analysis and interpretation that follow — is as good as possible.

Yet, one of the most important features of a variant interpretation tool or service is the quality of its underlying knowledge base. The knowledge base is the primary source of information used to determine if a variant has been previously reported, how the variant should be classified, and what clinical implications are associated with the variant. To ensure clinical labs are using the latest content to interpret the NGS tests, the knowl-

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“One of the most important features of a variant interpretation tool or service is the quality of its underlying knowledge base.”

edge base should be supported by professional curators who manually source and analyze the content to ensure accuracy and consistency.

Variant curation continues to be a bottleneck for many clinical labs performing NGS-based testing. As the volume of literature on genomic variants grows exponentially, it is becoming increasingly difficult for a clinical lab's

curation team, which often consists of one or two variant scientists, to keep up with, read, and extract relevant information from all the published papers.

Therefore, if a clinical lab can leverage a variant interpretation tool or service that employs professional curators to handle the manual curation for them, the variant interpretation process will be accelerated.



Buy or Build?

Clinical labs need to decide how much they will do themselves and how much they will use commercially available variant curation tools. For example, for a clinical lab to build its own knowledge base, tremendous expertise, staffing resources, and budgets are required to implement, maintain, and grow the database.

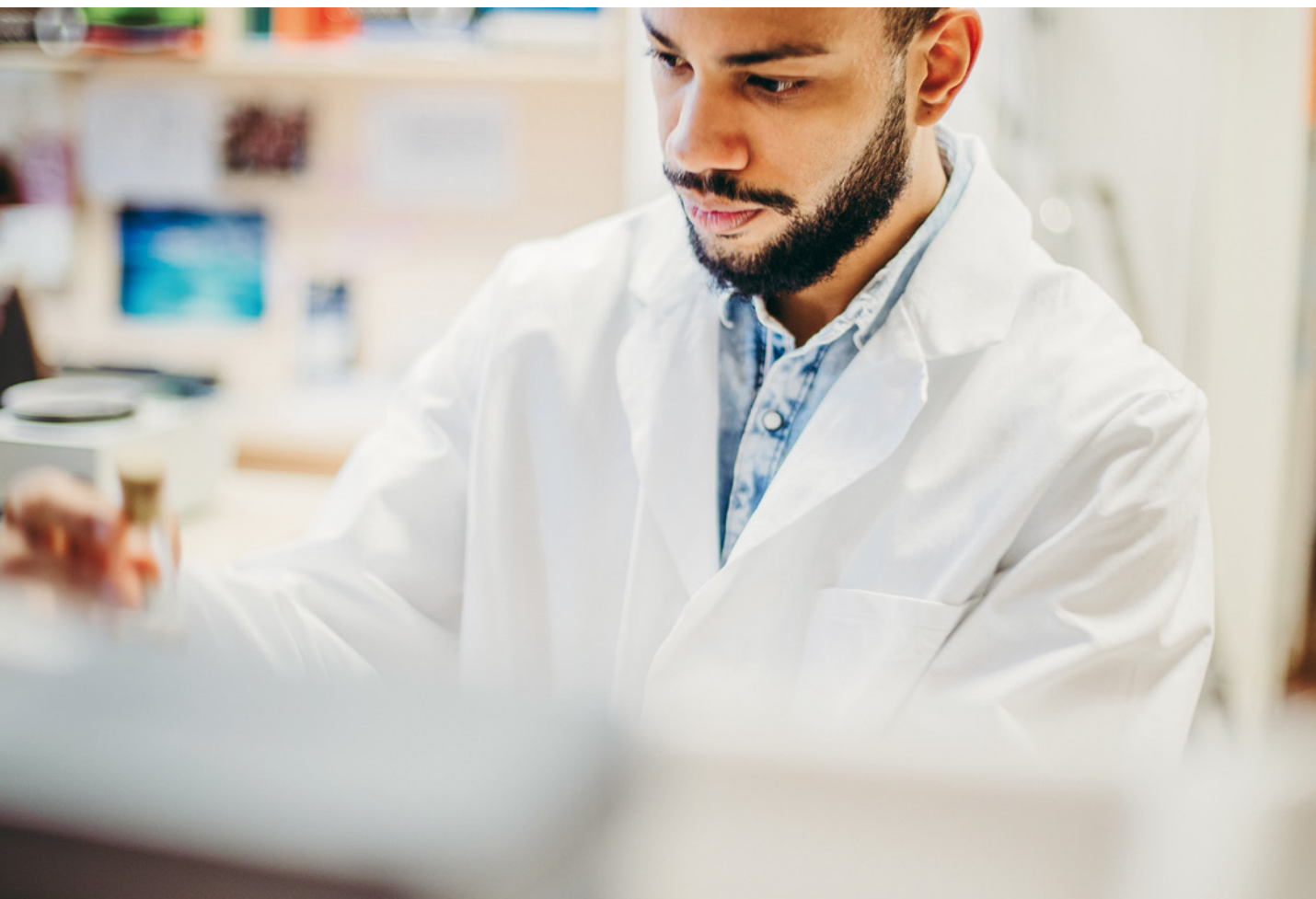
Variant curation solutions, such as the QIAGEN Knowledge Base, are perpetually updated to ensure that users always have access to the latest findings. Buying a tool to curate variant interpretation saves the laboratory time, money, and personnel expenses.

As clinical knowledge advances, it is also critical to have formalized processes for reassessing genomic content. Clinicians need to be able to make meaningful comparisons

from one laboratory to the next laboratory, but interoperability of data between laboratories is an ongoing challenge. Another challenge is reimbursement: there is no universal guideline on when or how often it is appropriate to carry out reanalysis. Having a clinical decision support system in place can help a laboratory team navigate the NGS results from different labs as well as build confidence in the variant interpretation.



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Dealing with Complexity

Ideally, a variant curation solution should provide a clinical geneticist with a sample-level view of coverage depth and allelic balance. However, documenting idiosyncratic behaviors in the library prep is often missing from validation studies.

The quality of results can be limited because of some common pitfalls in such areas as validation quality, coverage depth, inversions, copy number variants, allelic balance, and false positives/false negatives. Therefore, a laboratory's post-analytic quality processes should include clear definitions of which variants (such as low-quality variants) require confirmation.

An effective variant curation tool should provide the analyst with key NGS metrics in a clear, easy-to-interpret format. Ultimately, the value of a variant curation system is its ability to help avoid potentially inaccurate reporting of clinical results that may facilitate incorrect or unnecessary treatment of a patient.



“We value QIAGEN’s commitment to deliver the highest quality of manually curated knowledge for analysis and interpretation of content through its extensive and comprehensive portfolio of solutions that enable accurate and standardized clinical reporting.”

Augusto Rendon, PhD, Director of Bioinformatics at Genomics England

Preparing for the Future

In June 2020, when Rady Children’s Hospital-San Diego published the results of the Baby Bear Project, a trending approach to NGS testing was confirmed: sequence more DNA faster for better health and cost outcomes. But for the small to mid-sized clinical labs looking to this landmark study as a paradigm for what’s to come, the question becomes how? How do we expand our testing panels, speed up our turnaround time, and save money?

The answer is through technology and partnership. To prepare for the future of NGS testing, clinical labs will need to adopt automation as a broad strategy and partner with commercial companies that can support and streamline their informatics workflow.

QIAGEN Digital Insights offers a comprehensive portfolio of clinical informatics solutions for NGS testing. Whether a clinical lab is looking to bring NGS testing in-house or partner with a professional variant interpretation service to supplement their existing informatics workflow, QIAGEN Digital Insights has a variety of variant interpretation and reporting solutions to meet the unique needs of each lab.

With more than two decades of experience in variant curation, QIAGEN Digital Insights understands the challenges facing clinical labs and employs a world-class team of curators to stay current on the daily advancements and

discoveries being made in the field of NGS, as well as the latest recommendations from professional organizations (ACMG, AMP/ASCO/CAP, etc.), and list of approved therapies and clinical trials as they become available. The QIAGEN Knowledge Base is the world’s most comprehensive, manually curated knowledge base for NGS variant interpretation and reporting and is at the core of the industry leading QIAGEN Clinical Insights (QCI®) portfolio—a portfolio containing clinical decision support software and professional variant interpretation services for inherited diseases and oncology.

In the next decade, NGS testing will revolutionize diagnostics and clinical care. For those at the forefront of the industry, how are you preparing today for the promise of tomorrow?

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