R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

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ADVANCEMENTS IN GENETIC TESTING

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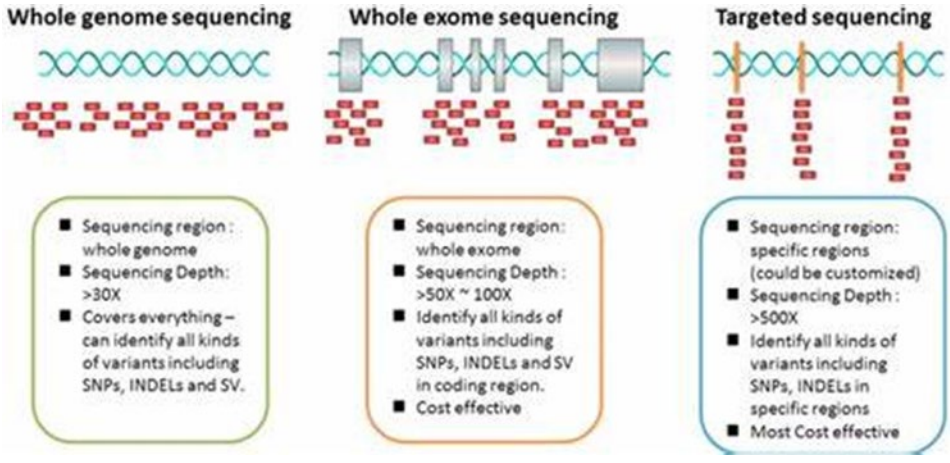
INTRODUCTION

In recent years, the landscape of healthcare and medicine has been rapidly evolving. Standardized solutions have given way to the new approach of personalized care. This new initiative, dubbed precision medicine, encourages creative thinking in healthcare settings and bold new ideas in research[1]. This push for individualized care has launched countless technological advancements, including many in the field of genetics and genomics. Clunky and costly gene sequencing techniques have undergone a dramatic transformation, as next-generation sequencing has risen to prominence. This laboratory methodology quickly produces accurate sequencing information, providing healthcare professionals with reliable results in an efficient manner[1]. Prior to next-generation sequencing, the diagnostic odyssey for an underlying genetic condition typically involved several clinical evaluations and investigational procedures, both of which were often expensive and invasive[2]. Despite lengthy and costly efforts, many patients were still left without a diagnosis[3]. Clinical next-generation sequencing offers a highly personalized approach to diagnostic processes, allowing for timely interventions, appropriate support to affected individuals, and expansion of the greater knowledge of genetics. This powerful diagnostic tool is most often employed in the form of multi-gene panels and whole exome sequencing, while whole genome sequencing remains most prevalent in a research setting.

Figure 1: Comparisons of Next-Gen genetic testing modalities.



Ref: https://www.omnia-health.com/product/human-genome-sequencing

MULTI-GENE PANELS

When a patient presents with a suspected, but specific diagnosis, gene panels are often one of the first steps of the diagnostic journey. In this type of genetic testing, next-generation sequencing is performed on a curated set of genes, each selected for their association with clinical phenotypes. The size of these panels can vary from a small handful of genes to a couple thousand genes, but each retains high coverage, sensitivity, and specificity[4]. Sequence variants are analyzed, filtered, and prioritized for clinical interpretation. Results can be positive, meaning a pathogenic variant was identified, negative if no potential disease-causing variant was found in the set of analyzed genes, or uncertain if an identified variant does not have a well-established gene-disease association[4]. Due to its precise nature, targeted panel testing typically has a high diagnostic rate, uncovering a genetic etiology for many patients. Results are then used to guide an appropriate treatment plan and determine if further testing is warranted.

CLINICAL WHOLE EXOME SEQUENCING

When panel testing fails to arrive at a diagnosis or a patient is presenting with complex clinical features not indicative of a specific genetic concern, whole exome sequencing (WES) is employed. WES utilizes next-generation sequencing to target only the protein-coding regions of the genome, known as the exome. The exome consists of about 22,000 known genes and accounts for approximately 1 to 2% of all human genetic material[4]. Despite covering a relatively small percentage of the genome, WES is a highly sophisticated diagnostic tool, as most genetic disorders are associated with mutations in protein coding genes. Studies into the clinical utility of WES have shown diagnostic rates ranging from 25 to 52%[2,3,4]. In patients with complex presentations, WES can also be cost effective as it can help arrive at a diagnosis before a lengthy and often wasteful diagnostic process of multiple evaluations and panel tests[4].

WHOLE GENOME SEQUENCING

In complex situations where both panel testing and WES have been nondiagnostic, whole genome sequencing (WGS) remains an option, though it is typically only available in a research setting. However, once preformed, WGS can provide diagnostic answers in the clinical sphere. Genome sequencing is a broad, untargeted form of testing that analyzes not just the protein-coding regions as in WES, but regulatory, intronic, and intergenic regions as well[4]. Because of its expansive nature, WGS is currently more expensive and time-consuming. As technologies improve, WGS may be employed more in a clinical setting, as studies have demonstrated its clinical utility in certain situations. A 2018 study reported a reduction in length of stay and facility cost for NICU infants receiving rapid WGS and subsequent precision medicine interventions[5].

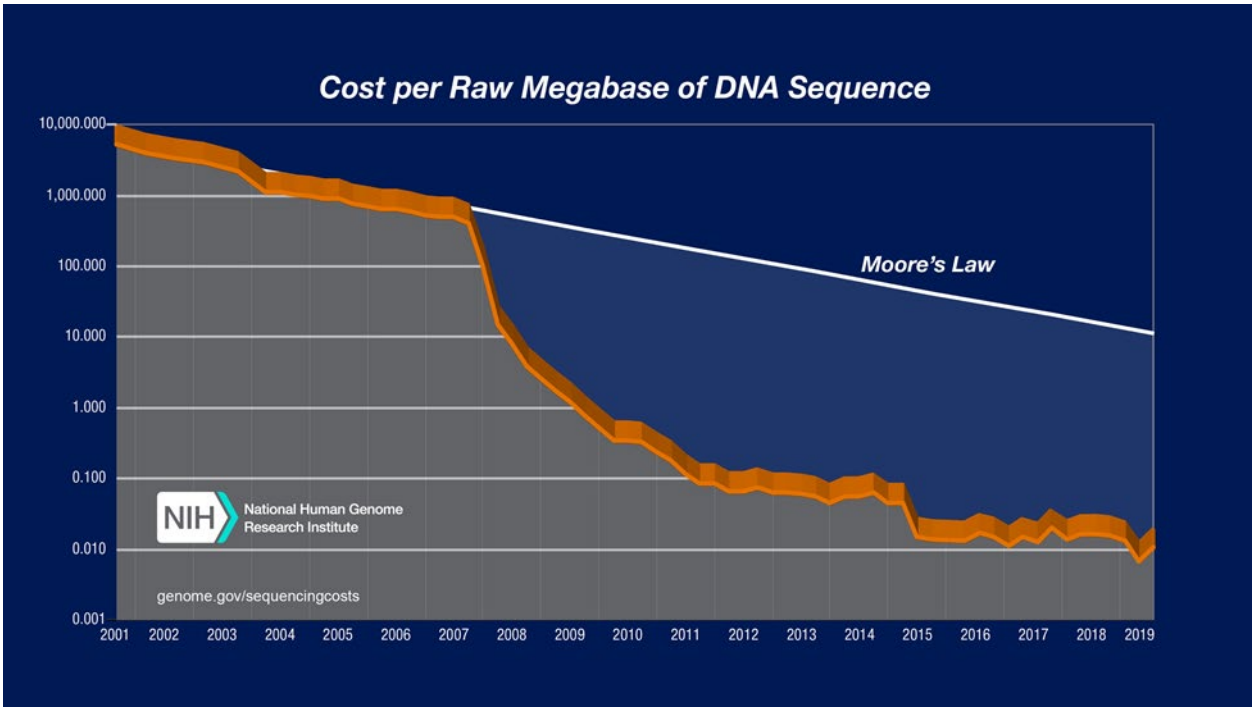
LIMITATIONS AND BARRIERS

Advancements in genetic testing are currently outpacing the advancements and growth of associated resources. Genetic testing is becoming more accessible, but there is still a need for robust, collective databases to store genomic data and aid in interpretation. There currently exists several variant databases and storage platforms, though they mostly operate independently of each other. Without the tools to add to collective knowledge in a streamlined way, results of genetic testing may not be interpreted in the most efficient manner[4]. Although our knowledge of the human genome has improved significantly in recent decades, there is much left to still be discovered. Therefore, the etiology and severity of a disease may not be met with a comprehensive treatment plan, especially if the genetic variant identified is unique.

Other limitations unrelated to scientific knowledge include cost of testing and ethical issues. Although the overall cost of sequencing has decreased in recent years, it can still be pricey. Issues with insurance coverage and denial of payment are common, placing patients in potentially precarious financial situations. The potential financial burdens and hassle of negotiating with insurance payers can be a deterrent for many. Ethical issues of proper consenting practices, involvement of family members, and reporting of secondary findings must also be addressed in the genetic testing process. As genetic testing becomes more routine, there is a growing need for genetic counselors to communicate such implications to patients.

FUTURE OUTLOOK

With the push for individualized care through precision medicine and the rapid growth in the field of genetics, clinical next generation sequencing is becoming more prevalent in routine medical practice. With these improvements, more relationships between genetic variants and clinical presentations are being uncovered and understood, and this knowledge is growing every day.



Source: NHGRI

https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

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