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WHITE PAPER

Translating Cancer Genomics Into a Personalized Approach for Cancer Patients

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EXECUTIVE SUMMARY

This white paper provides a brief history of oncology genomics, including development, uses in improving patient care, current achievements and challenges, and the future direction of cancer genomics.

A HISTORY OF CANCER GENOMICS

Over the past few decades, the approach to prevention, diagnosis, and treatment of cancer has radically shifted from organ-based to morphology-based and most recently, to genetics-based. Personalized or precision medicine (tailoring a treatment for a patient's particular disease at a precise time point) is being performed every day at different levels in the clinical setting.

The study of cancer genomics has dramatically evolved over the last 30 years. The era of genomic medicine in oncology started in the 1980s when the relationship between karyotype abnormalities and diseases were identified, thereby allowing better patient stratification. Soon this approach became common in leukemia as well as in solid tumors treatment. The next step was to define the role of oncogenes and proto-oncogenes in tumor formation and progression.

Early research centered on increasing test sensitivity and shortening the time required to perform testing. For example, in the early 1980's the research community focused on the genome-wide loss of heterozygous looking at familial (ie, hereditary) cancers and homozygous deletions, such as the BRCA1 breast cancer gene.

From a clinical point of view, diagnostic turn-around times that are extremely important for adequate patient management could be reduced from several months to only 14 days. Furthermore, clinical significance has increased immensely with failure rates or "variants of uncertain significance (VUS)" reduced from approximately 30% to about 1%.

Later in the 1990's, science focused more on genome-wide copy analysis, which led to discoveries of gene amplification, such as HER2. Gene amplification studies enabled the medical community to use targets like HER2 in treating cancer, especially breast cancer.

The greatest discoveries in the field have been driven by advancements in technology. In the 1990s, the human genome project and the use of polymerase chain reaction (PCR)-based target sequencing led to some of the most important genomic discoveries and corresponding pathways to date, such as BRAF (a prominent proto-oncogene), the EGFR (epidermal growth factor receptor) family, and the JAK-STAT (Janus-associated kinase-signal transducer and activator of transcription) pathway.

The next major milestone in oncology genomics transpired in 2008 with next-generation sequencing (NGS), which enabled the research community to perform whole genome transcriptome and exome sequencing. This latest breakthrough has led to several discoveries of targets in cancer treatment and accelerated the overall discovery and development process.

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LEVERAGING CANCER GENOMICS TO IMPROVE PATIENT CARE

The field of cancer genomics has been instrumental not only in the diagnosis of cancer, but also in the equally important classification of cancer. This has enabled the research community to implement a more modern classification system, shifting away from the previously used classic rating and microscopic classification systems.

Cancer genomics has also played a critical role in predicting which oncology drugs will work in specific targeted treatments. It has also proven to be a strong marker of prognosis and in determining the ideal tools for monitoring clinical outcomes and treatment responses.

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Genetically based tests also serve as so-called "companion diagnostics." Companion diagnostics are medical devices that help physicians tailor treatment plans and medication dosages for individual patients. Companion diagnostics are essential to the safe and effective use of drugs.

The development of companion diagnostics began in 1998 with the FDA approval of Herceptin, a cancer drug that shuts off a protein that occurs in abnormally high amounts in about one-quarter to one-third of breast cancers. These breast tumors are typically very aggressive. The companion diagnostic test looks for excessive levels of a particular protein, called HER2, or extra copies of the HER2 gene in a patient's tumor, indicating that Herceptin could be an effective treatment for that patient's breast cancer.

At present, there are 19 FDA-approved companion diagnostic tests to assist in drug selection to treat various diseases and conditions.

Since the companion diagnostic test is developed to be combined with a specific drug, the development of both products requires close collaboration between experts in both the FDA's device center, which evaluates the test to determine approval, and the FDA's drug center, which evaluates the drug to determine approval.

Cancer genomics play a critical role in pharmacogenomics, or the study of how genes impact a patient's response to drugs. Pharmacogenomics combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to help develop effective, safe medications, and doses that can be tailored to a person's genetic profile. Moreover, cancer genomics is also used to monitor recurrence and the risk of recurrence. A perfect example is the Oncotype DX test used to assess recurrence in breast cancer. Lastly, we are using cancer genomics to help develop treatment targets in cancer and to ultimately help prevent cancer.

DEVELOPMENT OF GENOMIC BIOMARKERS AND TARGETS

Genomic biomarkers and target development begins with locating the appropriate cancer patients, obtaining material (ie, tissue or circulating cells) from those patients via tumor biopsies/sampling and performing genomic analysis on the samples to establish the clinical validity of the test and the target, and ultimately, determine the clinical utility in the indication of interest.

Several trial designs have been used to develop genomic biomarkers and targets thus far. Historically, the main trial design has focused on testing the genomic biomarker, establishing a target, and eventually developing an inhibitor. The early development phase assesses the resistance mechanism and compares the genomics of responders and non-responders to identify a biomarker that can be used to select patients who could benefit from a targeted treatment.

Once a biomarker has been identified, the study is expanded to include additional patients, some who receive the matching therapy, and others who are randomized into a control arm. At the end of the trial, data between the new therapy and the control therapy are evaluated and compared to validate the biomarker target and the ensuing targeted therapy.

A multi-agent sequential design starts with a tumor genomic analysis to establish a target, and then all patients are treated with the investigational drug. This design evaluates the patients' resistance mechanisms and response/non-response. Depending on the results, patients either continue on the investigational drug, or we combine additional drugs with the investigational drug. This is the future of oncology drug development. We are going to see more collaboration between companies as they come together to use this multi-agent sequential design in the development of different products.

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CHALLENGES FACING CANCER GENOMICS

Cancer genomics clinical research faces several challenges, such as regulatory concerns and trial guidelines. For instance, the collection and storage of tissue from patients in large, potentially worldwide biobanks pose several grave ethical and legal challenges that must be addressed and resolved.

From a molecular diagnostic perspective, though, determining the assay and the trial design are typically the two greatest challenges confronting clinical researchers. This process is limited by several factors, such as tissue quality, the tumor content in the tissue, as well as the analytical validity and cost of performing the tests.

From a scientific perspective, the process remains a very lengthy endeavor with many result interpretation challenges due to the need for further exploration to appropriately determine the overall impact of cancer genomics (eg, the role of micro-RNA and non-coding RNA).

From a clinical implementation perspective, the tissue acquisition and tissue hetero-geneity remain the most challenging aspects in genomics. Determining trial designs and endpoints are also challenges facing the development of cancer genomic targets.

ACHIEVEMENTS IN CANCER GENOMICS

We have seen several successes thus far in cancer genomics, including some genomic changes and discoveries that have been linked to the pathways in different cancers. Not surprisingly, more advancement has been made in some cancers more than others. A recent success in melanoma research is the discovery that the RAS, BRAF (BRAF is a serine/threonine kinase that signals downstream of RAS protein), and MEK genes are linked to the Ras/Raf/MEK/ERK pathways. Inhibitors of Ras, Raf, MEK, and some downstream targets have been developed and many are currently in clinical trials. Alteration of the Ras/Raf/MEK/ERK pathway influences proliferation, invasion, and survival of melanoma cells in vitro. This discovery suggests that B-Raf mutation has a pivotal role in determining melanoma biology, even if its exact function in melanoma progression remains controversial.

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Researchers have also made strides in solid tumor genomic studies. Lung cancers are characterized by abundant genetic diversity with relatively few recurrent mutations occurring at high frequency. Lung cancer mutations have been identified in the GTPase KRAS (also known as V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue), the EGFR, the BRAF, and the phosphatidylinositol 3-kinase (PI3K) pathway oncogenes and more recently in MEK and HER2. Research has also shown structural rearrangements in ALK and ROS1, which provide new therapeutic targets. Somatic KRAS mutations are also found at high rates in different types of leukemia, colon, and pancreatic cancers.

In terms of hematologic cancers, the JAK-STAT pathway is one of the most important pathways. The erythropoietin receptor (EPOR) gene, interleukin 7 receptor, and the MPL (MPL proto-oncogene, thrombopoietin receptor) gene are linked to the different JAK-STAT genes. All of those have been successfully targeted with several inhibitors thus far.

FUTURE DIRECTION FOR CANCER GENOMICS

Despite numerous achievements in cancer genomics, we must continue with the co-evolution of sequencing technologies and the innovative genomic trial designs we have used so far. We must also increase the incorporation of epigenetic changes into our strategies and look further into clinical grade evaluation of single cells, which will help us study cancer stem cells, tumor subclones, and components of the tumor microenvironment. Whole genome sequencing has also proven to be very successful.

Particularly from a clinical point of view, research has entered a new era in cancer treatment. The growth of knowledge through cancer genomics within the last few years has already permanently altered our view of cancer therapies. For instance, once treated as an amorphous entity, breast cancers such as triple-receptor-negative breast cancer (TRNBC) can now be treated with some level of specificity. We have shifted from treating melanoma as a single entity, to specifically identifying and treating BRAF-mutated melanoma.

While one can only be enthusiastic when looking at the tremendous quantity of data now being collected, there is still a long path to clinically apply our broad knowledge of tumor biology. The gap between our basic knowledge and clinical application is still wide and is only slowly being filled in through the implementation of well designed, personalized medicine trials.

In the future, we anticipate there will be more collaboration amongst life science organizations to develop a combination of targeted treatments and pathways. Only then can we really move into true patient genetic profiling and drug combination therapies to treat cancers and overcome resistance.

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CONTACT INFORMATION

For further information, or to discuss any aspect of PRA's services offered in cancer genomics, please contact your Business Development Manager or the employee listed below:

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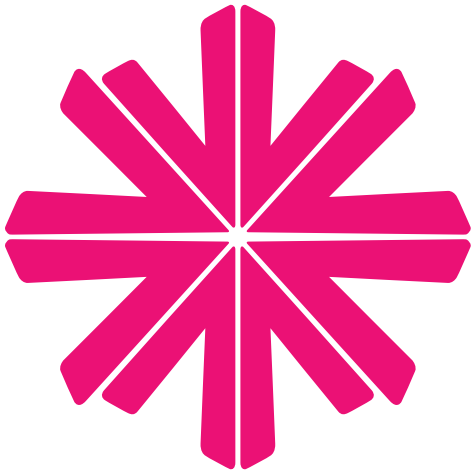

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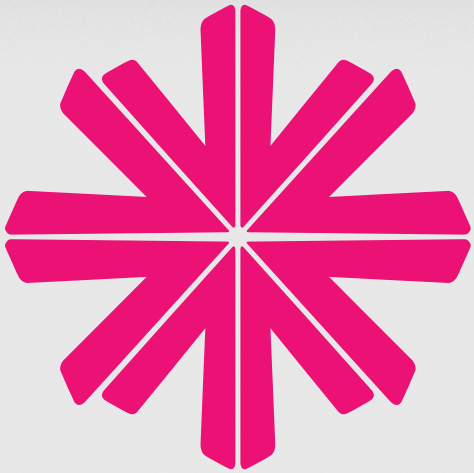
ABOUT PRAHEALTHSCIENCES

PRA Health Sciences delivers innovative drug development solutions that improve patients' lives. Our people are passionate about clinical research, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas, and a broad spectrum of solutions, ranging from full-service clinical development to our pioneering Embedded model.

With 11,000+ employees covering 80+ countries, we bolster an impressive global presence with keen local insights. Our project teams harness their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each study's unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of numerous drugs now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today's complex studies.

To learn more about PRA, please visit www.prahs.com or email us at prahealthsciences@prahs.com.



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