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The Path(way) Less Traveled: A Pathway-Oriented Approach to Providing Information about Precision Cancer Medicine on My Cancer Genome[1,2]

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Abstract

This perspective describes the motivation, development, and implementation of pathway-based content for My Cancer Genome, an online precision medicine knowledge resource describing clinical implications of genetic alterations in cancer. As researchers uncover more about cancer pathogenesis, we are learning more not only about the specific genes and proteins involved but also about how those genes and proteins interact with others along cell signaling pathways. This knowledge has led researchers and clinicians to begin to think about cancer therapy using a pathway-based approach. To facilitate this approach, My Cancer Genome used a list of more than 800 cancer-related genes to identify 20 cancer-relevant pathways and then created content focused on demonstrating the therapeutic relevance of these pathways.

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Precision medicine has altered the standard of care for cancer treatment and has led to the rapid development of therapies that inhibit diverse cellular processes. As we learn more about cancer pathogenesis, the number of plausible therapeutic targets increases. Targeted therapies have evolved from the use of single agents that inhibit a single gene effector to the use of one or more agents that target multiple effectors in a single cell signaling pathway or multiple effectors in parallel signaling pathways. As such, successful therapeutic strategies are evolving from a single-gene/single-drug focus to a pathway-based focus. This evolution of thought in targeted cancer therapy is an opportunity to develop a pathway-oriented view of cancer genomic knowledge resources. In response to this shift, the team at *My Cancer Genome*, http://www.mycancergenome.org/ [1], a project spearheaded at the Vanderbilt-Ingram Cancer Center, has developed a pathway-based approach to education and knowledge curation for precision cancer medicine.

Targeted therapies revolutionized cancer medicine by enabling disease control in traditionally difficult to treat malignancies, such as *BRAF*-mutated melanoma, by targeting the mutated gene with a single inhibitor. As knowledge of cancer pathogenesis advanced, the number of targeted therapies rapidly increased—making it essential to understand the complex signaling networks through which altered genes function and interact to contribute to disease. Understanding these signaling pathways will facilitate the creation of rational combination therapies for cancer patients with the ultimate goal of increasing the depth and duration of response. Two approaches to pathway-based treatment strategies are vertical and parallel inhibition.

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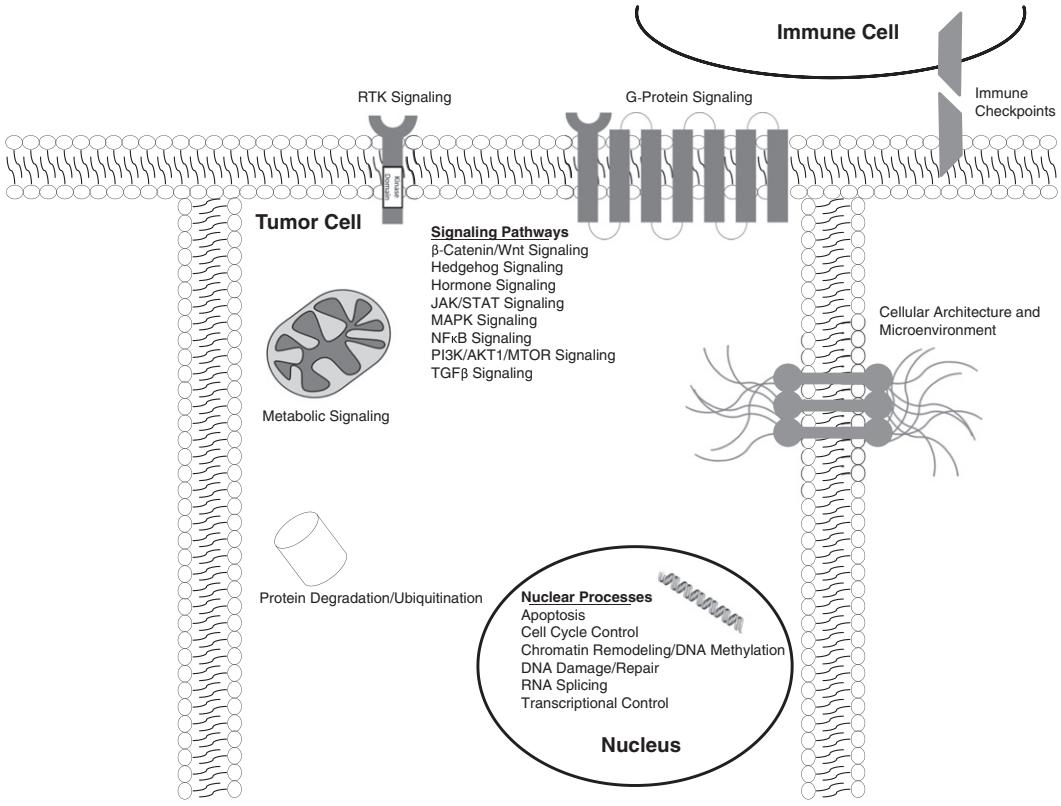

Figure 1. Cancer-relevant pathway map. This figure depicts the names of the most cancer-relevant pathways on *My Cancer Genome* and their sites of action within the tumor cell. For example, the G-protein signaling pathway commences at the cell membrane and then transduces downstream signals within the tumor cell. Individual pathway figures for each cell signaling pathway can be found on the My Cancer Genome website at http://www.MyCancerGenome.org/content/pathways [6]. Reprinted, with permission, from My Cancer Genome. Copyright 2016 Vanderbilt University.

To understand vertical inhibition, consider *BRAF*-mutated melanoma. Single-agent BRAF inhibition induced response rates in 53% of patients with *BRAF*-mutated melanoma [2]; however, acquired resistance invariably developed in these tumors. This therapeutic escape created a problem: how could clinicians extend the drug response and delay or overcome acquired resistance? The solution depends on understanding the complex interactions BRAF maintains with other proteins in a cancer cell. By combining BRAF with MEK inhibitors, two targets in the same pathway, clinicians can extend the drug response [3]. This method of targeted cancer therapy is known as vertical inhibition—simultaneously targeting multiple proteins with multiple inhibitors within the same signaling pathway. With vertical inhibition, clinicians may create stronger, on-target inhibition of nodes in the same pathway.

To understand parallel inhibition, consider the example of ER+ breast cancer. In 2012, the aromatase inhibitor exemestane was FDA approved for use in combination with mTOR inhibitor everolimus for patients with ER+ metastatic breast cancer [4]. Exemestane targets the hormone signaling pathway, whereas everolimus targets the PI3K/AKT1/mTOR pathway. In 2015, the aromatase inhibitor letrozole was FDA approved for use in combination with CDK4/6 inhibitor palbociclib for postmenopausal patients with ER+, HER2-negative advanced breast cancer [5]. Letrozole targets the hormone signaling pathway, whereas palbociclib targets the cell cycle. This method of targeted cancer therapy is known as parallel inhibition—simultaneously targeting multiple nodes in different cell signaling pathways.

Currently available resources can provide a seemingly overwhelming amount of information regarding the complex entanglement of upstream, downstream, and parallel signaling pathways involved in the cellular circuitry. The complexity may make it difficult and time consuming for a busy clinician to search for a given protein target of interest. Furthermore, currently available resources may not be able to easily connect the pathway information to information directly pertaining to the therapeutic strategies. The team at *My Cancer Genome* recognizes that keeping up with the rapid development of targeted therapies amidst a busy clinical schedule is challenging; therefore, the team has restructured typical complex signaling pathways to be more digestible to clinicians in practice. The goal was to create a resource from which a clinician would be able to quickly glean the information necessary to understand the significance of an individual pathway that drives cancer pathogenesis or a therapeutic strategy within the context of precision cancer medicine.

The creation of a pathway-based resource for genomic information reflects the emergence of combination therapies used in current cancer treatment. The methodology behind the creation of the pathway content focused on ease of understanding while maintaining clinical relevance; the team aimed to create pathway diagrams that were clinically applicable, gearing the level of information toward

clinicians in practice. This involved working with the *My Cancer Genome* editorial team to outline a map of the most cancer-relevant pathways (Figure 1) [6]. We then categorized a master list of approximately 820 cancer-related genes [7] compiled from several commonly used next-generation sequencing cancer platforms. From there, we created diagrams that were isolated from surrounding pathway interactions. Each diagram included the most relevant proteins in each pathway with a focus on therapeutic targets. Descriptive text that defined each pathway's function, activators, inhibitors, and cellular outputs was created to accompany the pathway diagram. Each figure includes a pathway summary describing the components of the pathway, diseases in which the pathway is aberrantly activated, and a drug list—all of which link to more detailed information where available on the My Cancer Genome website.

A single-gene to single-drug approach was once the most effective strategy in cancer medicine. However, diagnostic tools and cancer therapies continue to advance, as do complex cancer mechanisms. With the capability to identify multiple mutations within a tumor, clinicians will benefit from understanding why and how to effectively inhibit multiple, co-occurring genomic alterations within the tumor. A pathway-based approach to cancer medicine may help clinicians find answers to hard questions: Are the alterations related? Which genes do the altered genes interact with? Are the alterations targetable? If so, do drugs exist that can effectively inhibit each alteration? A pathway-based approach also creates an opportunity to explore rational combination strategies that will target not only the tumor but also the tumor microenvironment and surrounding immune system. With the new pathway-based approach to education and knowledge curation, *My Cancer Genome* hopes that the path(way) less traveled will positively impact patient care using precision cancer medicine.

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