Open

Citation: J Med Discov (2016); 1(1):jmd16005; doi:10.24262/jmd.1.1.16005

Commentary

Personalized oncology: the potential for tissue and cell-free DNA biopsies to capture tumor heterogeneity

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Journal of Medical Discovery (2016); 1(1):JMD16005; Received October 18th , Revised November 5th , Accepted November 7th, Published November 14th.

A goal of personalized oncology is to adapt treatment in real-time in response to an individual patient's dynamic genetic profile. Circulating tumor cell-free DNA (cfDNA) has emerged as an alternative technology to non-invasively monitor genomic mutations, copy number variants, and translocations in the peripheral blood. While multiple studies have reported high concordance when examining individual genes comparing tissue-based next generation sequencing with circulating tumor cfDNA, few prior studies had examined concordance of genomic alterations across multiple different genes.(1-4)

Our recently published work entitled "Concordance between genomic alterations assessed by next-generation sequencing (NGS) in tumor tissue or circulating cell-free DNA" compared mutational profiles of paired samples of tissue and tumor cfDNA in advanced solid tumors treated at our institution.(5) The goal of the work was to comprehensively examine concordance across a large number of genes, including all types of genomic alterations and variants of unknown significance. Our study reported a number of important findings. First, with existing technology, more mutations were detected in tissue as compared to cfDNA. Second, while concordance across all genes (including wild type/wild type genes) was high (>90%), concordance when genomic alterations were actually detected in either technique ranged from 11.8-17.1%. This has important

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clinical implications because one of the main goals of cfDNA assays is to detect specific resistance mutations. Third, unique mutations were discovered using both techniques with over 50% of mutations detected in one technique that were not detected using the other method. Potential reasons for our findings include tumor heterogeneity, inability to capture cfDNA at very low detection thresholds, fewer cfDNA variants released into the peripheral blood, our inclusion of a heterogeneous group of solid tumors, or different sequencing and detection techniques.

While our results were initially surprising, they highlight the complex biology of advanced solid tumors, which has served as both a challenge and an opportunity in personalized oncology. While the current gold standard for NGS is tissue, limitations exist with respect to taking a single biopsy from either a primary or metastatic site to capture the spatial heterogeneity and an evolving molecular profile of a tumor. There are also inevitable risks associated with repeat invasive biopsies.(6) In contrast, non-invasive emerging technologies including cfDNA, RNA sequencing, microRNA, circulating tumor cells (CTCs), and single cell proteomics and metabolomics have promising potential. These assays may enable monitoring genomic profile at various time intervals, non-invasively.

For cfDNA liquid biopsies, optimal timeframe regarding when and at what time intervals these assays should be performed remains unknown. In our retrospective study, median time interval between tissue and blood biopsies was approximately 90 days, but with a considerable range. While we hypothesized that concordance would be higher based on shorter time interval between tissue and blood biopsies, our study was unable to support this hypothesis. Previous work has reported that biopsies with at least one concordant mutation have a shorter timeframe between biopsies, but to our knowledge no studies have supported this consistently across many genes.(7) Future studies are needed to examine concordance at various intervals between biopsies and to monitor cfDNA over time.

While cfDNA assays theoretically have the potential to better represent tumor heterogeneity by capturing tumor DNA from multiple metastatic sites, the technique is predicated on the ability to detect circulating tumor DNA that is shed into the blood. The mechanism of tumor DNA being released into the blood is likely to occur via apoptosis and necrosis.(8) As a result, a hypothesis that needs to be tested is whether circulating tumor DNA preferentially represents therapy-sensitive tumor cells. While potentially advantageous for particular targeted therapies, a biological challenge would be to identify whether tumor DNA shed into the blood may not identify some resistant clones or subclones.(9) In many circumstances, therapy resistance is likely driven by these resistant clones, which may best be analyzed via other invasive techniques (repeat tissue biopsy, if feasible) or other non-invasive techniques (such as circulating tumor cells that are intact and have not undergone apoptosis).

Recently, there have been two prominent editorial pieces in the *New England Journal of Medicine* and *Nature* pointing out how personalized oncology has failed to realize clinical benefits in many instances.(10,11) In the articles, the authors identified real challenges with regard to cost, tremendous individual tumor heterogeneity, and lack of data in randomized control trials that these approaches improve survival outcomes. Our study clearly supports the genetic tumor heterogeneity seen in tissue and blood. However, we envision the combination of tissue and non-invasive monitoring of peripheral blood cfDNA, RNA, CTCs, etc. will one-day enable more precise and dynamic monitoring for therapy to change in conjunction with tumor molecular evolution (Figure 1). In regards to the cost debate, an effort directed towards providing the right treatment to the right patient for the right duration of time based on the non-invasive assays discussed above may actually improve the value and cost-effectiveness of each therapy.

Clearly, prospective trials examining whether utilizing circulating tumor cfDNA to guide treatment decisions can improve progression free or overall survival are needed. While our initial study compared concordance across a heterogeneous group of advanced solid tumors, we are currently examining concordance for particular histologies and at various time intervals between

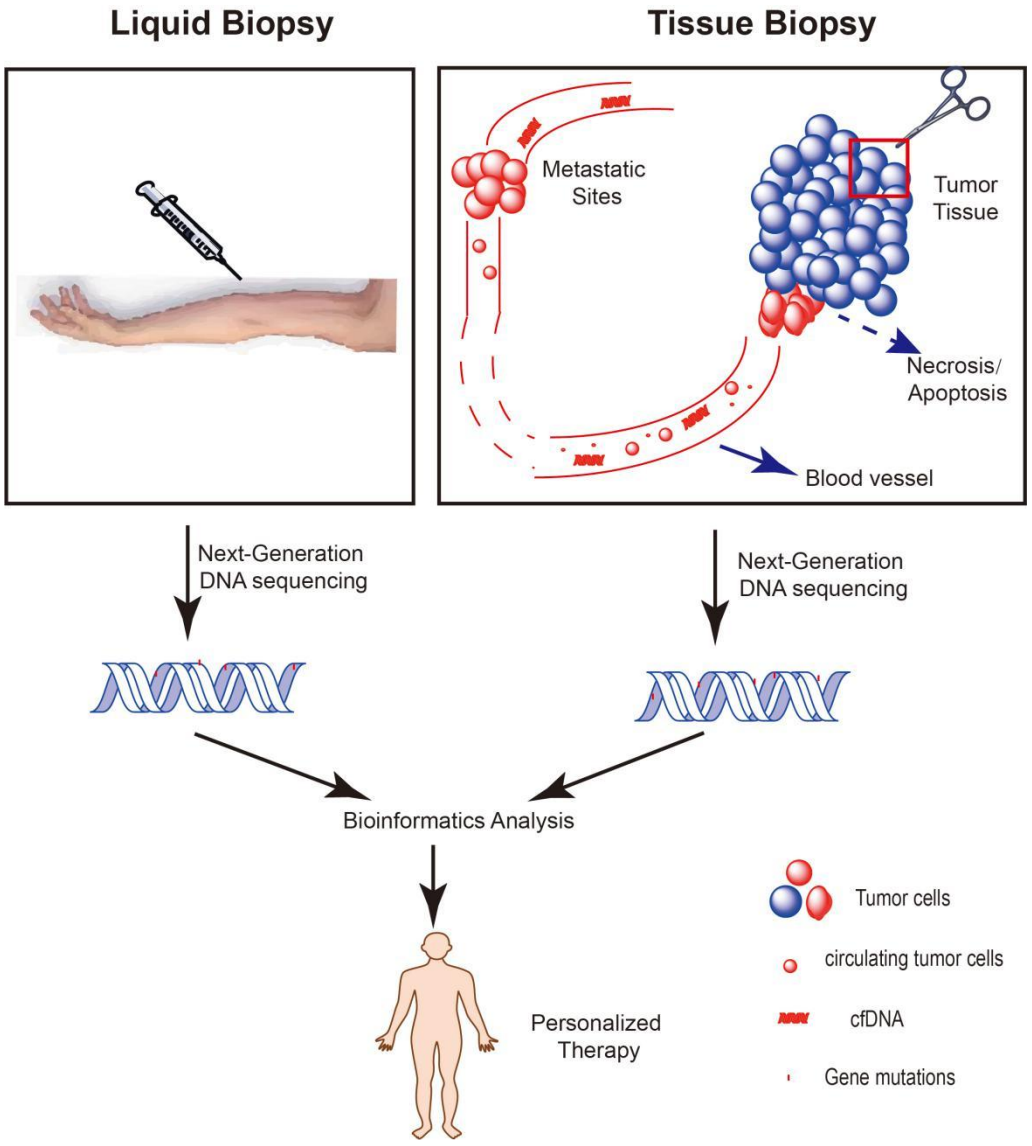

Figure 1. Model of DNA sequencing and comparison of cfDNA and tissue DNA.

biopsy sampling and treatment, which may affect the degree with which cfDNA is shed into peripheral blood. Previous studies have demonstrated that different tumor types release DNA to different degrees in blood.(12) Therefore, we would expect concordance to vary as a result for certain tumor types. For now, there are emerging examples of circulating tumor cfDNA being capable of detecting resistance mutations, such as EGFR T790M in lung cancer or ESR1 in breast cancer.(13,14) To our knowledge, no prospective studies have identified whether detecting these alterations early in blood improves patient outcomes. However, certainly the potential exists.

Collectively, our study and many others highlight the substantial challenge and opportunity in personalized oncology. Given the considerable spatial and temporal heterogeneity of tumors, we

must use a sophisticated combination of invasive and non-invasive techniques to monitor tumor evolution. We envision two exciting ways that non-invasive biopsies could change clinical practice. First, we suspect that the number of cfDNA clones and subclones, as well as somatic mutation frequency, may change prior to radiographic disease progression. In the future, this could enable changing therapy earlier based on an evolving genetic profile, rather than waiting for radiographic disease progression. Second, a long-term goal and incredible opportunity to improve survival would be for even earlier detection—detecting some marker of tumor cells, expression, or DNA in blood prior to metastatic disease. Certainly, there are tremendous challenges with respect to cost and when these non-invasive biopsies would be performed, but without further research into personalized oncology, these ambitious goals will never be achieved.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

None

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