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The Promise and Pitfalls of Genomics-Driven Cancer Medicine

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Mrs. J is a 45-year-old woman with metastatic breast cancer. Her cancer has proved resistant to several standard chemotherapy treatments. Her doctor has become aware of a new clinical trial, which offers whole genome sequencing of the patient's tumor to select treatment based on specific mutations found in the cancer. To properly interpret somatic mutations found in the tumor, the study also requires a sample of germline DNA. Mrs. J agrees to participate in the trial. Several weeks later, testing reveals a PTEN mutation in her breast cancer that qualifies her for targeted chemotherapy based on this finding. However, germline DNA sequencing incidentally reveals a PSEN1 mutation, which is known to cause a heritable form of early-onset Alzheimer dementia. Mrs. J presents to clinic to find out the results of her testing. With her 21-year-old daughter by her side, she asks, "Doctor, what did my tests show?"

Over the last decade, the field of cancer medicine has witnessed an explosion in technological advances, now allowing rapid and inexpensive sequencing of the entire human genome. These advances hold great promise in our ability to understand and treat cancer and to develop true "genomics-driven cancer medicine" based on a patient's individual tumor profile. However, with these advances come significant challenges, both technical and ethical. As the case illustrates, while so-called "next-generation sequencing" (NGS) can successfully guide therapy, it can also reveal significant incidental findings that patients, families, and physicians may not be prepared to handle and may not want to know. In this article, we aim to provide an overview of NGS and its role in cancer medicine. We then highlight some of the technical issues and ethical challenges we must face as we use this technology in real-time oncologic care.

Genomics-Driven Cancer Medicine

Defined as the study of genes and their functions, the field of genomics addresses the interrelationships of all genes and their combined influence on the development and growth of an organism [1]. This discipline applies sophisticated laboratory technology and bioinformatics to analyze the sequence, broader structure, and function of genomes. Whereas the field of genetics focuses on single genes, genomics seeks to understand an organism's entire complement of DNA [1, 2].

Cancer is inherently a genomic disease. In other words, most cancers accumulate an array of mutated genes that interact over time to initiate neoplasia and fuel its progression [3]. The introduction of high-throughput, massively parallel ("next-

generation") sequencing to evaluate all of the bases in the human genome has revolutionized our ability to study and understand the cancer genome. Although methodology varies among NGS platforms, all are designed in such a way that an extremely large number of DNA molecules are spatially arranged onto a solid matrix. The many thousands to millions of DNA strands are then sequenced simultaneously. All NGS sequencing results in a huge volume of raw data, generating hundreds of millions to even trillions of data points, in a single instrument run [4]. These data must then be processed and interpreted by comparison with a reference genome (e.g., the human genome in the case of medical genomics) requiring complex biostatistical and bioinformatics analysis [5].

To put the impact of NGS in context, sequencing of the first human genome was completed in 2001 after more than two decades of work and at the cost of $2.7 billion [4, 6]. With the introduction of NGS in 2005 and continued improvement in NGS instrumentation, we can now sequence a human genome within days at a cost of approximately $5,000 [7]. This dramatic drop in cost and turnaround time has allowed for broad use of NGS for cancer research and advanced clinical diagnostics. With the potential to quickly detect all mutations in a tumor and an expanding library of targeted anticancer agents, oncology is serving as a proving ground, unique among medical specialties, for genomics-driven therapy [3].

The application of NGS to oncology, or "genomics-driven cancer medicine," is conceptually logical and simple: First, the genome of a patient's tumor is sequenced, and all genetic differences from the standard human reference genome are identified. Because all human beings have many normal genetic variants that differ from the reference genome, the tumor sequence is compared with the patient's constitutional ("germline") genome to determine which alterations in the tumor are somatic (and therefore potentially pathogenic) and which are germline (and probably not cancer-related). Next, the somatic mutation list is filtered through a database of mutations that may render tumors sensitive to established and emerging anticancer drugs. Finally, an annotated list is provided to the treating physician to be used in clinical decision making and clinical research design [3, 8]. However, several technical and ethical challenges must be addressed before real-time application of NGS can become a reality in cancer medicine.

Technical Challenges

Though the advantages of NGS for cancer medicine seem obvious, clinicians and researchers alike must be wary of several potential pitfalls when applying this technology to patient care. First, the quality of the data generated depends heavily on the quality of the sample provided. The percentage of tumor cells within a given sample can vary widely, and furthermore one tumor may harbor different genetic changes in different geographic regions ("tumor heterogeneity") [4, 5]. Availability of ample, representative, high-quality biospecimens may prove scarce in real-time oncology NGS diagnostics.

A second major technical pitfall relates to the ability to accurately interpret genomic data. Bioinformatics and computational biology are rapidly evolving, but considerable risk remains of false positive results, false negative results, and misinterpretation of gene mutations [4, 9]. Because almost all malignancies are genetically unstable, tumors accumulate a large number of random genetic alterations not related to their pathogenesis. The causative or so-called "driver" mutations seen in tumor DNA can be difficult to distinguish from the more common random, "passenger" mutations that do not contribute to disease [5]. Even among somatic alterations in genes known to cause cancer, many are variants of uncertain significance (VUS), in which the effect of the DNA change on protein function cannot be predicted using current informatics tools [9]. To select a cancer therapy based on a mutation that does not truly "drive" the given cancer would likely lead to ineffective treatment for the patient.

A third possible pitfall of using NGS in real-time oncology is that, even when we can correctly identify a driver, treatments that target it may not exist. Indeed, the pace of sequencing technology has far exceeded our ability to develop and use targeted drugs in the research and clinical settings. In fact, fewer than 30 percent of all cancer patients screened with NGS receive a genomically directed therapy [5]. This phenomenon calls into question the cost-benefit ratio of NGS in the cancer setting, where most patients are not seeing "clinically actionable" results from their testing [3].

Ethical Challenges

The ethical challenges raised by the use of genome-scale sequencing in guiding cancer therapy relate to germline variants detected in the process of comparing tumor DNA to constitutional DNA. The great majority of patients undergoing genome sequencing will be found to carry a handful of deleterious autosomal recessive alleles [10]. These recessive genes result in a phenotype only when present in the homozygous state and do not cause symptoms in heterozygous carriers. While potentially relevant to offspring and other relatives, autosomal recessive genes generally don't have much impact on the cancer patient. Of greater concern are X-linked recessive diseases in males and autosomal-dominant diseases in males or females, as in the hypothetical case described above. These mutations are much rarer than autosomal recessive mutations but still are present in a substantial fraction of patients [11]. So-called "incidental findings" that are unintentionally discovered when NGS is used for cancer genome testing can pose a significant ethical problem for patients, their families, and their physicians.

It has been recognized for some time that even targeted genetic testing for somatic mutations in cancer can identify germline mutations that indicate the presence of hereditary cancer predisposition. Identifying a BRCA mutation in a breast tumor, when testing the tumor for sensitivity to PARP inhibitors, simultaneously predicts that the patient has a hereditary cancer syndrome since virtually all tumor BRCA mutations are also present in the germline [12-14]. The possibility of finding a mutation that predicts hereditary cancer predisposition can be discussed ahead of

time with patients undergoing tumor testing because results of this nature are not unanticipated. In the context of colorectal cancer, some groups advocate specifically including hereditary cancer genes when testing tumors for mutations in order to identify patients with genetic cancer predisposition [15].

However, genetic diagnoses not closely related to the disease for which testing was originally ordered are more problematic. Which incidental findings to report and whether to report incidental findings at all have been fiercely debated among genetic researchers, clinical laboratories, and direct patient care providers. The American College of Medical Genetics recently published guidelines recommending mandatory reporting of incidental findings in 57 genes that lead to "actionable" genetic disease [11], but quickly revised its guidelines after an outcry from the genetics community over what was felt to represent major violations of informed consent [16].

Though a consensus has yet to be found, most agree that there is, at a minimum and in certain contexts, a "duty to warn" a patient when results that indicate predisposition to a life-threatening disease are found [17]. Incidental findings from genomic testing have been compared to incidental findings in medical imaging, where case law suggests that clinicians may face liability for failing to disclose information that would have offered an opportunity to improve health outcomes [18]. On the other hand, results that predict the presence of or predilection to an untreatable disease, as in the present case, would seem to have limited personal utility or clinical value. Nevertheless, the lay public expresses concern about health care professionals filtering data and failing to provide complete information [19].

To prevent the ethical dilemmas associated with "incidentalomes," clinical laboratories and those in direct patient care relationships should make explicit decisions, in advance of testing, about what in the genome will be queried and reported [20]. Choosing a selected set of genes to analyze would reduce the risk of false positives and incidental findings. It would also theoretically allow for the patient to better understand what results may stem from a given test and to provide informed consent for testing. However, obtaining true informed consent for testing for a single gene mutation is already complicated and lengthy; NGS has exponentially multiplied the difficulty in ensuring that a patient truly understands the implications of testing. A patient's "right not to know" is a widely held value in medicine and has been a thorny issue in NGS testing [21]. Some have suggested a tiered approach to result reporting as a solution to this issue, in which patients can choose which results will be disclosed based on clinical utility, disease implications, and potential for heredity [17, 20, 22]. It remains to be seen whether this ostensible patient consent would protect a health care provider who fails to reveal actionable information.

Conclusions

Modern sequencing technologies have dramatically changed the face of cancer medicine in recent years, and the future holds great promise. NGS has made

genomic-driven cancer medicine a reality, with hopes of tailoring cancer therapy to individual patients. To be sure, NGS is not without its challenges. But with foresight, careful planning, collaboration among researchers, clinicians and patients, and adequate funding, NGS may very well lead us to the end of cancer as we know it.

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