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The future of clinical cancer genomics

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ABSTRACT

The current and future applications of genomics to the practice of preventive oncology are being impacted by a number of challenges. These include rapid advances in genomic science and technology that allow massively parallel sequencing of both tumors and the germline, a diminishing of intellectual property restrictions on diagnostic genetic applications, rapid expansion of access to the internet which includes mobile access to both genomic data and tools to communicate and interpret genetic data in a medical context, the expansion of for-profit diagnostic companies seeking to monetize genetic information, and a simultaneous effort to depict medical professionals as barriers to rather than facilitators of understanding one's genome. Addressing each of these issues will be required to bring "personalized" germline genomics to cancer prevention and care. A profound future challenge will be whether clinical cancer genomics will be "de-medicalized" by commercial interests and their advocates, or whether the future course of this field can be modulated in a responsible way that protects the public health while implementing powerful new medical tools for cancer prevention and early detection.

1. Introduction

Whether or not it was first said by atom-splitter Niels Bohr or splitter-ball catcher Yogi Berra, we all agree "it's tough to make predictions—especially about the future." In the concluding section of this monograph on the current status of predictive cancer genomics, it is appropriate to ponder the future of this translational field of medical science. As will also be addressed here, it is particularly instructive for the providers and consumers of the rapid advances in genomics and medicine to make their own predictions of the impact of "personalized genomics" on preventive oncology.

This effort to encourage introspection is meant to highlight the sea change that is shaping the way genomic predictive markers have been integrated in the practice of "precision medicine." The elements of this sea change are multifold and have constituted a virtual "perfect storm" which is now raining down on the clinical practice of cancer genomics. As will be discussed here, these factors include the rapid advances in genomic science and technology that allow massively parallel sequencing of both tumors and the germline [1,2], a landmark shift in interpretation of statutes bearing on intellectual property and diagnostic applications of germline genetic discoveries [3], rapid expansion of access to the internet, including mobile access to both genomic data and tools to interpret these data in a medical context, the expansion of for-profit genomic diagnostics—some masquerading as "recreational genomics," and a potentially worrisome effort to depict medical professionals as barriers to rather than facilitators of understanding one's genome. Each of these factors will impact how the discipline of predictive and preventive oncology is able to shape the translation of genomic technologies in the most responsive and responsible way. Here, the challenges and potential conflicts in bringing "personalized genomics" to oncology will constitute the primary focus. I will build on a framework developed in a prior essay on this topic [4], updating and expanding these observations based on recent developments in the clinic, in translational research, in the courts, and in the economic and social infrastructure that impact how cancer patients and those at risk for cancer have access to and can benefit from genomic information.

2. Shifting paradigms in cancer genomics

2.1. Causative events, consequences, and emerging strategies

In his classic monograph "The Structure of Scientific Revolutions" [5], the historian of science Thomas Kuhn coined the term "paradigm shift" to characterize periods of sudden departure from

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"normal science" when "unprecedented" discoveries shift the very practice of science in a fundamental, revolutionary way. To a real extent the rapid pace of the "genetic revolution" has impacted medicine. Perhaps in no other area has this change been more dramatically felt than clinical cancer genomics.

The preceding chapters of this monograph have updated our current knowledge of inherited mechanisms of cancer susceptibility. They have presented new information about genotype and phenotype, risk prediction, and targeted intervention. However, this monograph can only give hints at what lies ahead, since the major forces that will drive changes in clinical genomics are only now coming into focus. Thomas Kuhn stated that to meet the bar of a paradigm shift, the new advances must be "sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity." He predicted that a true paradigm shift would be "sufficiently open-ended to leave all sorts of problems for the redefined group of practitioners to resolve." Here, we will argue that the factors driving the paradigm shift in cancer genomics are not only on the verge of changing the medical model for delivering cancer genetic information but of replacing it entirely.

2.1.1. Consequences of current generation DNA sequencing

Compared to Sanger capillary-based sequencing, massively parallel sequencing, touted as "next-generation sequencing" (NGS), is now part of current generation practice. NGS employs simultaneous sequencing reactions detected automatically, producing millions of sequence calls per instrument run, at a significantly lower expense. Recent advances have increased the number of nucleotides per sequence read (or read lengths) and lower cost and greater base-calling accuracy [1]. These technologies have been applied to sequencing of exomes, entire genomes, and exons and splice region sequences of selected genes. The research impact of NGS technologies on the pace of new syndrome identification has been remarkable. By sequencing relatively few members of families with recurrent and unexplained malignancies it has been possible over just the past few years to identify over a dozen new cancer syndromes (Table 1). Only some of these new syndromes have been included in the preceding sections of this monograph, as these discoveries are so recent that precise genotype–phenotype correlations have yet to be established. As an example of the challenges of clinical translation posed by these NGS discoveries, we described two new syndromes of predisposition to childhood acute lymphoblastic leukemia [6,7], both caused by inherited mutations of transcription factors. While there was compelling functional biological evidence of "causation" behind the association of these germline mutations and the familial occurrences of leukemia, both syndromes demonstrated incomplete penetrance, and for both there was no proven preventive intervention other than pre-implantation genetics to halt transmission of the trait. In contrast, we have recently employed NGS to discover a novel mechanism of susceptibility to breast cancer due to a mutation in the nucleotide excision repair pathway, which does provide a potential rationale for targeted therapy [8].

In addition to their role powering whole genome discovery, NGS technologies have also impacted the rapid diagnosis of known syndromes by utilizing "capture" of exons and exon–intron splice regions of dozens of cancer predisposition genes, all analyzed simultaneously, as part of a new wave of multiplexed diagnostic panels [9]. As will be discussed, this technological innovation has stimulated the appetite of both providers and consumers of genetic tests, in favor of "prix fixe" menus of multiple gene tests at costs lower than that of the old "a la carte" one-at-a-time menu of phenotype-directed genetic analysis.

2.1.2. Fallout of the end of gene patenting

Just as NGS technologies began to generate novel syndromic discoveries of potential diagnostic value, the US Supreme Court ruled that isolated genomic DNA was not patent-eligible under section 101 of the Patent Act. The court, however, let stand patents for cDNA, an approach which some of us accurately predicted before the decision, and which we argued would have a gradual impact on the practice of preventive oncology [3]. The opinion written by Justice Thomas was unanimous and brief. The oral argument, was notable for the apparent and very limited understanding of the Justices and the US Solicitor General of basic concepts of genetics (eg, the difference between DNA and RNA), and the use of nonscientific metaphors, involving trees, baseball bats, etc. The late Justice Scalia wrote that he agreed with the majority opinion even though he admitted he did not feel educated enough on the topic to sign the recitation of "the details of molecular biology." Within a few days of the decision, as *NY Times* reporter Andrew Pollack sought confirmation from many of us that it would be a very short time before academic and for-profit genetic testing companies would make available NGS for panels including *BRCA1/2* [10], many also expressed concern that broad deployment of these multigene panels was premature in the absence of regulatory oversight of quality of testing, evidence of clinical utility, and strategies to interpret genetic variation [9].

2.1.3. Awash in variants of familiar and novel genes

Despite the warnings, the rush to multigene panels left clinicians coping with interpretations of reports of variants of unknown significance (VUS), with such findings as frequent as 10%–90% depending on gene and panel [11]. Of more concern, anecdotal experience revealed some not ideally educated health practitioners recommending preventive surgeries following VUS detection. And even more challenging, the multiplex panels included genes for which mutations were only known to be associated with low to intermediate penetrance, and genes for which mutations had unclear clinical utility and were previously not recommended for clinical testing. For example *CHEK2,* recommended as of unclear clinical utility in the era of single gene testing [12], was now routinely included in multigene panels. Valiant efforts were made to catalogue current knowledge of disease specific gene of varying penetrance [13]. As new genes came to be discovered by NGS strategies (represented in Table 1), they often were added to existing panels, even in the absence of data on associated phenotypes and penetrance.

2.1.4. Initial response of federal agencies and the academy to the genomic tsunami

Just as the "tsunami" from the perfect storm of NGS breakthroughs, internet marketing, and the lifting of intellectual property restrictions hit clinical oncology, one federally supported body charged with interpreting the evidence basis for genomic diagnostics, including those for cancer susceptibility, experienced a 95% budget reduction. This group, called The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative, funded largely by the Center for Disease Control, had produced a number of evidence reviews bearing on cancer [14–17]. However, EGAPP was not to be fully available for the sudden commercial proliferation of multigene panels in cancer risk testing. To address the most pressing need for cross-sectional databases, to document genetic variation and curation, and in the absence of a unified strategy from the for-profit laboratories to address the consequences of premature deployment of multigene panels, spontaneous initiatives were launched by other stakeholders. The *BRCA* Global Challenge was organized by a combination of governmental, commercial, and academic groups to seek to