Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis*

Vivek Subbiah, MD[1,2] and Razelle Kurzrock, MD[3,4]

Advances in the genomic era have led to identification of cancer-causing genes and unprecedented progress in the development of gene-targeted therapies and agents that can unleash the immune system. These advances have improved the outlook for patients with lethal malignancies.

Cancer is a genomic disease in that gene alterations drive the cellular growth and immune surveillance perturbations that enable malignant cells to take hold and to metastasize. Hereditary genetic factors play a key role in cancer predisposition, initiation, prognosis, and therapy. In a previous viewpoint, we posited that we need universal (somatic) genomic testing to win the war against cancer.[1] Currently, given the rapidly emerging evidence, we update our view to state that universal germline, in addition to tumor somatic, genomic testing is needed to win the war against cancer.[1]

Germline genomic testing has important implications for patient diagnosis, prognosis, treatment (type of surgery, chemotherapy, radiotherapy, and novel therapeutics), screening, and for offering risk-reducing interventions, determining eligibility for clinical trials of novel agents and cascading to genetic counseling/testing of affected patients and families. Currently, most next-generation sequencing (NGS) panels involve only tumor somatic analysis. Previous guidelines for germline genome testing have been restricted to patients with known hereditary cancer syndromes thought to be at highest risk for pathogenic germline variants (PGVs) and did not favor testing all patients. Although the groups of patients indicated for germline testing has incrementally expanded, a legacy thought process remains, and stems from several perceived notions: Hereditary cancers are a rare event, high testing cost (lack of reimbursement), dearth of therapeutic options, medicolegal/ethical challenges including preexisting condition coverage, as well as lack of awareness of clinical utility, absent clear management pathways once a variant is found, discomfort in counseling patients appropriately about their risk profiles, shortage of genetic counselors, and unknown implications for approved therapies.

Currently, National Comprehensive Cancer Network recommendations include universal multigene germline testing for patients with pancreatic and ovarian cancer, as well as for those with metastatic prostate cancer[2] and those younger than 50 years with colorectal cancer. For other cancers, different professional societies (and various payers) have divergent guidelines, including the genes to be tested. Importantly, restricted guideline-based testing may miss significant numbers of patients with cancer harboring germline mutations, and testing even in subsets of patients with breast cancer where guidelines are established has a low uptake in the real world, perhaps because restricted guideline-based testing leads to complexity, confusion, and practice variability. In fact, a study showed that testing all patients with breast cancer (versus guideline-based testing) doubles the number of patients identified as having an actionable germline genetic result,[3] consistent with a report suggesting that restrictive testing may deny data-informed clinical management to patients with breast cancer.[4] Even in other cancers with clear testing guidelines such as ovarian, pancreatic, and metastatic prostate cancers, there is significant testing underutilization, perhaps because of the complexity of guidelines between cancers.[5] There is ample evidence that broad-based reflex testing of germline (providing the patient agrees) is necessary for individuals with a cancer diagnosis.

With somatic genomic alteration testing alone, we are likely missing an opportunity for screening, prevention, and offering risk reduction to close relatives of patients with cancer.[6] Moreover, relatives who are not carriers need not have the apprehension about cancer risk. Furthermore, a combined tumor and germline multigene testing strategy expands our understanding of both the tumor and host. Genomics is the diagnosis, and the most powerful argument for its universal use is that every patient afflicted with cancer deserves a full diagnosis.

Where Is the Evidence?

There are multiple studies in both adults and children that support the implementation of universal genomic

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germline testing. In a pan-cancer study (>50 cancer types) of 11,947 patients,[7] 17% (n = 2,037) harbored a germline likely pathogenic or pathogenic variant; 9% (n = 1,042) had an actionable PGV.[7] A prospective study of 2,984 patients with cancer examined the prevalence of PGVs using a universal germline versus target-only test on the basis of clinical guidelines, in addition to the uptake of cascade family variant testing[8]; one in eight patients had a PGV, one-half of which would not have been detected using a guideline-based approach. Moreover, about one-third of patients with a high-penetrance variant had revisions in their clinical management on the basis of the findings. Another study demonstrated that approximately 55% of patients with actionable PGVs would have failed to be tested under conventional guidelines.[9] A recent review further showed that PGVs were found in 3.9%-56.2% of patients with common solid tumors who were unselected for family history or other putative risk factors.[5] Similar data have been demonstrated in hematological malignancies as well.[10] Germline mutations in cancer-predisposing genes were also identified in 8.5%-13% of multiple pan-cancer pediatric studies,[11,12] and family history did not predict the underlying predisposition syndrome in most patients.[11] Taken together, these data have important implications for the management of patients with cancer and their family members.

Are There Treatments?

There is an expanding armamentarium of US Food and Drug Administration (FDA)–approved precision medicines as therapeutic options, both as histology-specific and tissue-agnostic indications for many germline-aberrant cancers[13]: PARP inhibitors (olaparib, rucaparib, and niraparib) for treatment of germline or sporadic *BRCA*-mutated or homologous recombination–deficient breast, ovarian, prostate, and pancreas cancer[13]; immune checkpoint inhibitors (pembrolizumab and dostarlimab) for patients with germline or sporadic high microsatellite instability/mismatch repair-deficient solid tumors; nivolumab ± ipilimumab for the treatment of high microsatellite instability/mismatch repair-deficient colorectal cancers; hypoxia inducible factor 2α inhibitor belzutifan for patients with germline Von Hippel-Lindau–associated cancers; RET inhibitors for *RET* germline-positive medullary thyroid cancers; selumetinib for neurofibromatosis type 1 with symptomatic, inoperable plexiform neurofibromas; and everolimus for *TSC1/2*-associated cancers (Subependymal Giant-Cell Astrocytomas, renal angiomyolipoma and seizures).[14]

What About the Cost?

Many arguments against testing are centered around the cost. Yet, the cost of germline testing (and NGS in general) has markedly decreased over the past decade. Furthermore, patients get repeat routine prevention testing (mammograms, computed tomography scans for lung cancer, colonoscopies, or laboratory tests), which are quite expensive, compared with one time hereditary testing cost, which may be invaluable for the patient over an entire lifetime and informative for their family.[3] In addition, the cost of the test must be weighed against the cost of expensive (and possibly futile) therapy the patient will be subjected to because this genetic information was not available in a timely manner.

What About Implementation and Legal Issues?

We acknowledge that implementation of universal genomic (somatic and germline) testing is not without challenges, including testing, coverage, reimbursement, education (including for genetic counsellors and for physicians in training and ongoing education for those in practice), and a need for more well-trained and qualified genetic counsellors.[15] However, the requirement of genomic testing and services will only continue to increase, especially as universal germline testing is deployed, with the need to test and counsel family members, and the health care system needs to be ready to meet the demand, especially with access to genetic counselors who are best equipped to provide family member testing and counseling.[15]

As with everything in medicine and in rapidly evolving areas of science, there is no one-size-fits-all approach. Personalized medicine is focused delivering the right medicine to the right patient at the right time, and this entails the right testing for the right treatment at the right time. There are many different approaches one could envision in implementation and every clinic, hospital, health system, state, professional society, and patient advocacy group will need to find way to apply this to their population. Innovative solutions such as outlined in the ASCO educational handbook[15] including telegenetics, group genetic counseling, collaboration with nongenetics heath care professionals, genetic counselor extenders, and modifications of traditional models may be required.

Because emergence of genomics has caused rapid changes to established law, the National Institutes of Health (NIH) has funded a project LawSeq^{SM}: Building a Sound Legal Foundation for Translating Genomics into Clinical Application.[16] This project seeks to address the legal challenges including how the law of liability for all stakeholders from health care professionals to industry should adjust to meet the challenge of genomics. Since the law underlying application science is ambiguous, the LawSeq^{SM} project has convened a national Working Group of top legal and scientific experts to compile, collect, and analyze current US federal and state law and regulation on translational genomics including liability from failure to test.[17-19]

Current restrictive guideline-based testing misses many patients with germline alterations, especially in underserved populations (with African-American, Asian/Pacific Islander, and Hispanic populations) typically underrepresented in germline testing[20] which in turn denies data-driven care to patients and amplifies disparities. A

recent review of 84,297 oncology clinical trials from the Trialtrove database revealed that 887 (1.1%) trials used germline data for inclusion/exclusion, and most trials using germline data were conducted in the United States, Canada, and Europe versus other countries, mirroring disparities in cancer genomics data globally.[21,22] In addition, immune checkpoint inhibitor pembrolizumab is US FDA-approved for solid tumors with high tumor mutational burden (TMB-high; ≥10 mutations/megabase) or microsatellite instability (which itself leads to a high TMB).[23] It was shown recently that TMB is affected by an individual's genetic ancestry and race.[24] Tumor-only sequencing overestimates TMBs especially in people of non-European ancestry, exacerbating disparities in precision medicine.[24] Calibration of tumor-only TMB using paired tumor/normal TMB and/or algorithmic strategies may improve ancestral biases.[25]

Universal germline testing may not only transform the outlook for those with traditional hereditary cancer syndromes but also identify a wider range of associations and penetrance for germline variants. If we are serious about winning the war against cancer, we need to have every bit of intelligence about it, both to treat cancer and to detect it early. The potential impact of the host should be considered in every patient with cancer. Applying universal germline testing to patients with cancer routinely is one of the major opportunities that can revolutionize precision medicine practice and is needed to win the war against cancer (and possibly many other diseases).

AFFILIATIONS

[1]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
[2]Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX
[3]Department of Medicine, Medical College of Wisconsin Cancer Center and Genome Sciences and Precision Medicine Center, Milwaukee, WI
[4]WIN Consortium, Paris, France

CORRESPONDING AUTHOR

Vivek Subbiah, MD, Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), Unit 455, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; Twitter: @VivekSubbiah; e-mail: vsubbiah@mdanderson.org.

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Vivek Subbiah
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Travel, Accommodations, Expenses: PharmaMar, Bayer, Novartis, Helsinn Therapeutics, Foundation Medicine
Other Relationship: Medscape

Razelle Kurzrock
Leadership: CureMatch, CureMetrix
Stock and Other Ownership Interests: CureMatch, IDbyDNA, CureMetrix
Honoraria: Roche, EUSA Pharma, NeoGenomics Laboratories, Biocom, NeoMed, LEK, AACR, Chugai Pharma USA, Wiley, Merck, Pfizer, Foundation Medicine, Turning Point Therapeutics, Bicara Therapeutics
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